MEDICC Review

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On COVID-19

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MEDICC Review

July 2020, Vol 22, No 3

MEDICC
Medical Education Cooperation with Cuba

MEDICC Review is a unique open-access platform for Latin American and Caribbean praxis addressing today's critical interactions between human health, development of sustainable societies, and the health of our planet. Drawing upon the contributions of the region in social medicine, social movements, rich diversity and scientific prowess, Latin America and Caribbean authors published in the journal can help fill gaps in thinking and evidence sorely needed to build a sustainable future and a hopeful legacy for future generations.We look forward to contributing to increased visibility for their work and to its positive impact on both regional integration and worldwide solutions.

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MEDICC Review

Editorial Board

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MEDICC Review

A Call for Papers

To Latin American & Caribbean Health & Related Professionals

- ***MEDICC Review*** welcomes papers from Latin American and Caribbean authors, addressing today's critical interactions between human health, development of sustainable societies, and the health of our planet.

- In the era of the COVID-19 pandemic, ***MEDICC Review*** editors are fast-tracking peer review of papers that provide results of regional, national or local experiences with prevention, control, diagnosis, and therapies, as well as development of medications and vaccines. See Author Guidelines at **www.mediccreview.org** for **Short Article**, **Lessons From the Field**, and **Original Research** sections.

- Your evidence-, experience-based commentaries are also welcome for our **Perspective** and **Viewpoint** sections.

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We consider submissions in Spanish, English and Portuguese for publication in English. No author fees are charged.

Send questions and submissions to
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COVID-19 in the Americas: Strategies that Mark the Difference

Four months after COVID-19 was declared a pandemic, it has found a new epicenter: the Americas. With over four million cases and nearly half a million deaths at this writing, the United States is providing the best example of a failed response to a crisis in which GDP is not proving the best predictor of success. Zero coordinated national strategy combined with unnecessary delays in testing, confusing and often contradictory messaging, and politicization of even the most elementary measures to combat the virus have led some US states to surpass infection and death rates in even the most hard-hit countries. Brazil, where government finally resumed reporting, is second only to the USA, its authorities admitting 2.4 million cases and over 300,000 deaths thus far. And by all counts, as in many countries, numbers are vastly underestimated.

However, some countries are doing better: Canada, with 24.07 deaths per 100,000 population, compared to the USA at 44.11/100,000; and Uruguay (0.99/100,000), which borders Brazil (40.14/100,000). Cuba is also doing well at 0.77/100,000. We know what doesn't work—many of us are living with the consequences—but what *does*?

In this issue, we interview Cristian Morales, PAHO/WHO's Permanent Representative in Mexico, who insists that any successful containment of "the multi-system threat of COVID-19" will depend on "social cohesion, a united effort among the different sectors, and collaborative participation from public, non-governmental and private sectors." And he stresses what he considers another key factor: those countries with universal health care and strong primary healthcare subsystems are simply in a better position to face the challenges of COVID-19.

One example is Cuba, which managed to flatten its curve relatively early, bringing deaths to a total of 87 as of this writing, despite toughened US sanctions by the Trump administration, which have blocked donations and access to medicines and essential equipment. In the following pages, ***MEDICC Review*** continues to document Cuban approaches to COVID-19 and publish scientific results and reflections on their application. Some aspects already merit particular attention (see details in *Cuba's COVID-19 Strategy: Updated Epidemic Control and Recovery Measures* this issue):

- A single, coordinated national strategy, prioritizing health in an intersectoral framework
- Quick action, organizing a national plan months before the country's first cases were diagnosed
- Massive public health messaging coupled with daily televised briefings for domestic and international press on the status of the epidemic, detailing cases and deaths
- Early reliance on Cuban and international science to guide epidemiological measures, as well as treatment protocols (See *Cuba's Women of Science* interview with Iramis Alonso for the importance of popular science in separating fact from fiction.)
- Implementation of key public health measures, including closing international travel (with few exceptions), cancellation of large public gatherings, mandatory use of masks in public, physical distancing and special attention to risk groups
- Use of thousands of primary healthcare professionals to conduct door-to-door active screening for symptomatic persons, referring them for testing
- Hospitalization of ALL confirmed cases, and isolation (and testing) of suspected cases or contacts in specially established centers
- Tracing of contacts of all confirmed cases
- Constant updating of treatment protocols, including use of both imported and domestically produced biopharmaceuticals like Biomodulina T, whose role as an immunomodulator is considered in this issue of ***MEDICC Review***.
- Hospital release dependent on negative RT-PCR, patients followed by family doctors once home, including additional testing
- Selective use of quarantine for local COVID-19 clusters of community transmission
- Retooling of some biotech and other industries to produce ventilators, masks, diagnostics

To date, the Cuban COVID-19 strategy has continued to flatten the curve (see Medina-Mendieta on mathematical forecasts for the country in this issue), with less than 3000 cases thus far, only about 100 active. However, these results have received scant attention in international media, a lack of coverage with origins that are likely more political than scientific. This is the same political logic that hammers Cuba with tougher sanctions as the economy attempts to rebound from the crisis…clearly, Cuba's biggest challenge ahead. This is the same logic that denigrates the contribution of Cuban physicians and nurses to the global fight to stem the pandemic in over 30 countries. And such bias has also kept Cuban biopharmaceuticals from the US market for physicians and their patients.

These include COVID-19 vaccine candidates, Biomodulina T (used in Cuban nursing homes during the epidemic to preventively boost immunity), Itolizumab (a monoclonal antibody approved in Cuba for emergency use vs. the cytokine storm in serious and critical COVID-19 patients) and Heberprot-P, a drug shown to reduce by 70% the risk of amputation from diabetic foot ulcers. The latter is the subject of the Berlanga-Acosta article in this ***MEDICC Review***.

We take this opportunity to pay tribute to Editorial Board member Dr Francisco Rojas Ochoa, who passed away on May 30. He was a physician, teacher, health system builder and editor… and always a defender of scientific rigor in favor of health for all. We continue to draw on his critical thinking, generous spirit, devotion to science and extraordinary example as a tireless fighter for global health equity.

Finally, ***MEDICC Review*** stands with WHO in its call for global cooperation and repudiates the US administration's attempt to withdraw from the world's most important collaborative health organization. As COVID-19 engulfs humanity and challenges our dedication to building a more sustainable and resilient future, we must have the humility to learn from all quarters. To move ahead, multilateralism and solidarity are the only viable strategies.

The Editors

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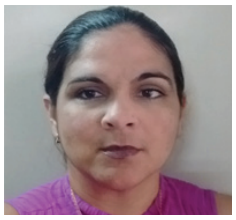

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NOTE: The remaining authors in the following pages are members of the journal's editorial team, and we are grateful for the extra effort they expended to make this issue possible.

Strategies Needed to Ensure Higher Immunization Rates in the Americas

To the Editors:

In their ***MEDICC Review*** Perspective, Galindo-Santana and colleagues highlight the challenges presented by anti-vaccination groups, stressing that immunization is an essential cost-effective preventive measure that promotes population health.[1] In 2019, WHO identified vaccine hesitancy, fragile and vulnerable settings and weak primary health care as 3 of 10 main global health threats. Close attention to these threats can detect potential areas of missed opportunities for immunization across populations and mitigate risk of preventable diseases.

In recent decades, expanding immunization coverage to reduce child morbidity and mortality from preventable communicable diseases has been an international priority: WHO developed the Expanded Programme on Immunization in 1974, established the Strategic Advisory Group of Experts on Immunization in 1999, and accepted the Global Vaccine Action Plan 2011–2020 in 2012. Regional efforts in the Americas have successfully eliminated polio, rubella and neonatal tetanus, aiming to eliminate hepatitis B by 2020.[2] These goals require robust coordination efforts to strengthen global health workforce capacity, support educational outreach about adherence to vaccination schedules and expand service delivery to all communities. With recent resurgence of vaccine-preventable diseases like measles, however, nations must identify gaps and challenges in immunization programs and explore opportunities to maintain high immunization coverage.

To strengthen immunization efforts in the Americas, we propose that leaders in ministries of health prioritize three actions. First, community-based research using quantitative and qualitative approaches can examine the determinants of health that influence community understanding of and adherence to recommended vaccination schedules. Second, capacity building for nurses and health promoters can offer accurate, up-to-date vaccination recommendations and reinforce competencies. Third, primary health care centers can promote holistic health through the One Health concept, which describes the interconnectedness of human, animal, and environmental health, while dispelling myths and fostering provider–patient rapport and acceptance of evidence-based vaccination schedules.

Regional action for widespread adoption of evidence-based vaccination schedules is essential to safeguard population health. By prioritizing community-based research, health capacity building and the One Health concept, nations can accelerate progress to achieving high immunization coverage through Sustainable Development Goal targets 3.8 and 3.b.

1. Galindo-Santana BM, Cruz-Rodríguez E, López-Ambrón L. A Cuban perspective on the antivaccination movement. MEDICC Rev. 2019 Oct;21(4):64–9.
2. Pan American Health Organization. Basic indicators 2019: Health trends in the Americas [Internet]. Washington, D.C.: Pan American Health Organization; 2019 [cited 2020 Jul 5]. Available at: http://iris.paho.org/xmlui/handle/123456789/51543
3. World Health Organization [Internet]. Geneva: World Health Organization; c2020. SDG 3: Ensure healthy lives and promote wellbeing for all at all ages. The goals within a goal: Health targets for SDG 3; [cited 2020 Jul 5]; [about 1 screen]. Available at: https://www.who.int/sdg/targets/en/

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CUBA'S COVID-19 STRATEGY: UPDATED EPIDEMIC CONTROL AND RECOVERY MEASURES

MEDICC Review continues documentation of Cuba's COVID-19 Prevention and Control Plan and its implementation, begun with our April issue (see https://mediccreview.org/cubas-covid-19-strategy-main-actions-through-april-23-2020). This time, we present two tables: the first refers to measures taken to confront the epidemic, and the second, to the phased recovery process that is expected to lead to changes in many, if not all, sectors of Cuban society. In both cases, we have indicated the source of the information provided.

Timeline of COVID-19 Measures in Cuba (April 24–July 20, 2020)

Date	Actions
April	
	Cuban Center for State Control of Medicines and Medical Devices (CECMED) **approves expanded compassionate use of Cuban monoclonal antibody Itolizumab** (Anti CD6) for seriously ill patients with pneumonia resulting from COVID-19. https://www.cecmed.cu/covid-19/aprobaciones/itolizumab-anti-cd6-0
	CECMED approves the **Esperanza study, a controlled clinical trial, to evaluate safety and efficacy of Heberferón vs. Heberón alpha 2b** (interferons produced by the Genetic Engineering and Biotechnology Center, CIGB, Havana) for patients infected with SARS-CoV-2. https://www.cecmed.cu/covid-19/aprobaciones/esperanza-heberferon-heberon
25	Health authorities inaugurate a **650-bed hospital-clinic at the Informatics Sciences University** in Havana for potential COVID-19 patients. https://www.biocubafarma.cu/noticias/noticia-post.php?id=6
25	Public Health Minister announces **comprehensive program to provide psychological care** for the general population, health workers, those in isolation centers and patients hospitalized for COVID-19, to assist them in addressing the mental health effects of the epidemic. http://www.granma.cu/cuba-covid-19/2020-04-25/diaz-canel-sobre-la-organizacion-hospitalaria-se-debe-evitar-la-sobrecarga-con-pacientes-sin-confirmacion
May	
4	Council of Ministers approves adjustments to the **2020 National Economic Plan**, considering the impact of the epidemic. https://www.presidencia.gob.cu/es/noticias/ajustarse-a-la-realidad-e-imponerse-a-ella-con-el-trabajo/?fbclid=IwAR1sXpxGRno0bSdH90BKIAxNClDKO2ITynRmDrpW5um0C5C3DoWPuL5fqJ8
7	Cuban Immunoassay Center **develops a rapid-test kit for COVID-19**, Umelisa SARS COV-2 IgG, based on Ultramicroanalytic System (SUMA) technology. http://www.cubadebate.cu/noticias/2020/05/07/desarrollan-en-cuba-sistema-diagnostico-para-detectar-anticuerpos-de-la-covid-19/comentarios/pagina-2/
11	Over 5000 older adults treated since April 3 to date with **Biomodulina T**, **a Cuban immunoregulator** approved for use in respiratory infections, as part of prevention protocol for COVID-19. Among those treated are persons living in nursing homes. http://www.granma.cu/cuba-covid-19/2020-05-11/biomodulina-t-otro-eficaz-farmaco-cubano-contra-la-covid-19-11-05-2020-00-05-53
12	National study begins in 1400 families (4000 persons) nationwide to **discover extent of COVID-19 circulation**, using real-time polimerase chain reaction (RT-PCR) tests to detect cases. http://www.sld.cu/noticia/2020/05/12/comienza-estudio-poblacional-en-cuba-para-identificar-posibles-casos-de-la-covid-
21	Cuba is using **plasma from recovered COVID-19 patients** to treat serious cases. http://www.acn.cu/salud/65068-cuba-apuesta-tambien-por-la-terapia-con-plasma-hiperinmune-ante-la-covid-19
June	
2	**Study begins on genetic implications of severe COVID-19 cases.** http://www.giron.cu/realizan-en-cuba-estudios-sobre-la-genetica-y-su-implicacion-en-la-covid-19-infografia/
11	Government announces three-phased, gradual **post-epidemic recovery program**. http://www.cubadebate.cu/noticias/2020/06/11/gobierno-cubano-informa-medidas-para-la-recuperacion-tras-la-epidemia-de-la-covid-19/#anexo-1381187
12	Phase-2 clinical trial begins for **CIGB 2020 vaccine candidate, for COVID-19 and other acute respiratory infections. Developed by CIGB.** http://www.cubadebate.cu/noticias/2020/06/12/salud-y-ciencia-la-respuesta-integrada-de-cuba-ante-la-covid-19-video/
17	**CECMED authorizes emergency use of Jusvinza** to treat serious or critically ill COVID-19 patients affected or potentially affected by hyperinflammation ("cytokine storm"); produced by the CIGB. https://www.cecmed.cu/covid-19/aprobaciones/jusvinza-cigb-258-1

June	
18	**Phase One of recovery begins in 13 of 15 provinces**, plus the Isle of Youth Special Municipality. Havana and Matanzas Provinces have yet to enter Phase One. https://www.presidencia.gob.cu/es/noticias/nota-informativa-sobre-el-inicio-de-la-primera-etapa-y-fase-1-de-la-recuperacion-pos-covid-19/?fbclid=IwAR1DgJBm3m4vShpeu1lZa68GP31q26EW2zljS4CLdmcnbYKbhdNv258_i6U
18	**Cuba opens to domestic tourism** in provinces already in **Phase One** of recovery, with added precautions at hotels and resorts. http://www.cubadebate.cu/noticias/2020/06/17/comercio-interior-transporte-turismo-y-la-aduana-informan-sobre-las-medidas-de-la-etapa-pos-covid-19/
22	Council of Ministers approves **detailed Three-phase Recovery Program,** plus indicators for each phase. http://www.cubadebate.cu/noticias/2020/06/22/medidas-a-implementar-en-las-tres-fases-de-la-primera-etapa-de-recuperacion-pos-covid-19-pdf/
23	**Matanzas Province enters Phase One of recovery.** http://www.granma.cu/cuba-covid-19/2020-06-22/pasa-matanzas-a-la-primera-fase-de-la-recuperacion-pos-covid-19-22-06-2020-20-06-33
26	Prototype of low-cost **emergency pulmonary ventilator successfully developed in Cuba**, as well as non-invasive ventilator (requiring no intubation); 250 of each expected to be completed before year's end. Participating: Cuban Neuroscience Center and the Immunoassay Center. On April 11, usual foreign suppliers of ventilators indicated they could no longer supply them, since these companies were acquired by US corporations that conform to US sanctions on Cuba. http://www.cubadebate.cu/especiales/2020/06/26/cneuro-ventiladores-pulmonares-made-in-cuba-fotos-y-video/
July	
1	**Cuba re-opens international tourism to several of its keys**, with extra precautions, including at airports. https://www.prensa-latina.cu/index.php?o=rn&id=378158&SEO=reabre-cuba-sus-puertas-al-turismo-internacional
3	**Havana Province enters Phase One of recovery**. http://www.cubadebate.cu/noticias/2020/07/01/la-habana-pasa-a-la-primera-fase-de-recuperacion-a-partir-del-3-de-julio-el-resto-del-pais-excepto-matanzas-a-la-segunda/
3	**Phase Two of recovery begins for 13 of 15 provinces** plus the Isle of Youth Special Municipality. http://www.cubadebate.cu/especiales/2020/07/03/el-programa-de-medicamentos-en-el-pais-una-prioridad-del-gobierno-cubano/#.Xx87t-cpDIU
8	**Matanzas Province enters Phase Two of recovery.** http://www.granma.cu/cuba-covid-19/2020-07-08/matanzas-a-la-segunda-fase-en-la-habana-se-refuerzan-las-medidas-de-la-primera-08-07-2020-00-07-37
16	**New economic measures announced for recovery period** related to increased food production, greater autonomy for state companies, design of micro-, small and medium enterprises (PIMES), possibilities extended for private businesses to import and export, greater incentives for direct foreign investment, improvements for work in non-state sectors, separation of retail and wholesale markets, and elimination of 10% tax on US dollar, among others. http://www.cubadebate.cu/noticias/2020/07/16/gobierno-cubano-informa-nuevas-medidas-economicas-video/
20	**Phase Three of recovery begins in 13 of 15 provinces** plus the Isle of Youth Special Municipality. Havana and Mayabeque Provinces remain in Phase Two. http://www.cubadebate.cu/noticias/2020/07/16/a-partir-del-20-de-julio-avanzan-a-la-tercera-fase-todas-las-provincias-del-pais-con-excepcion-de-la-habana-y-mayabeque/

POST-EPIDEMIC RECOVERY PROGRAM

Of Cuba's 15 provinces, 13 and the Isle of Youth Special Municipality entered Phase-One COVID-19 recovery on June 18, 2020; Matanzas Province on June 22; Havana on July 3. Entrance into each phase is determined by analyzing the following five COVID-19 indicators in each territory, established by the Ministry of Public Health, with thresholds for each indicator (see http://www.cubadebate.cu/especiales/2020/07/03/el-programa-de-medicamentos-en-el-pais-una-prioridad-del-gobierno-cubano/#.Xx87t-cpDIU):

1. Incidence rate
2. Reproductive number/ratio
3. Number of active cases
4. Number of positive cases with known route of infection in the past 15 days
5. Existence and number of local transmission events

Main Actions During Three Phases of Cuba's COVID-19 Recovery Program

Phase One	Phase Two	Phase Three
General measures for all phases		
Ensure physical distancing in all public areas, prohibiting large public gatherings		
Save electricity by staggering shifts in production plants and other workplaces		
Prohibit symptomatic employees from entering workplaces, and guarantee their immediate referral to health centers		
Obligate hand disinfecting at all institution entrances, as well as systematic disinfecting of surfaces therein		
Strengthen communication with home renters in zones where tourism has re-opened, as well as epidemiological control of all international visitors who rent		

Use primary health care to carry out active surveillance and case detection of patients with respiratory symptoms		
Take temperatures of all Cuban and international travelers upon leaving or entering the country, to or from any destination		
Maintain strict protection for workers in areas where they are at risk of contagion		
Establish multidisciplinary teams to provide 24-hour care in hotels, including on-site presence in each of a doctor, nurse and trained hygiene and epidemiology specialists		
Health sector hygiene and epidemiology measures		
Physical distancing: mandate at least one meter between persons; mandate use of face masks in public places; restrict locales' capacities for meetings and gatherings; restrict numbers in outdoor gatherings	Mandate use of face masks only in public places that may be crowded (buses, beaches, stores, etc.) Limit numbers of persons in meetings or gatherings	
Screening: active daily screening by primary health care personnel in the entire population to identify symptomatic persons who are referred for evaluation	Systematize targeted active screening to identify symptomatic persons, priority afforded to those living or staying in institutions, as well as vulnerable groups	
Carry out RT-PCR on all travelers arriving in Cuba	Adjust traveler measures according to the country's epidemiological situation	
Mandate that a sworn declaration of health status be completed by every traveler upon entry		
Hospital biosafety: Maintain suspension of visitors for hospitalized patients, but permit one companion during hospital stay. Maintain protections for hospital staffs.		Permit family members to visit hospitalized patients
Hospital services: Gradually re-open hospital activities, outpatient services and other ambulatory care, up to 50% of capacities	Re-open activities up to 75% of institutional capacities	Completely re-open hospitals for all patient care services
Labor and employment		
Pay public-sector workers affected by the epidemic (in isolation or hospitalized) 100% of basic salaries during this period		
Guarantee unpaid leave (in addition to normal paid leave under law) to mothers unable to return to work, their jobs guaranteed		
Continue to provide special attention to most vulnerable families, in particular disabled persons, older adults and those living alone		
Encourage telecommuting when justified and conditions permit	Improve telecommuting implementation and supervision	
Guarantee 100% of salaries to musicians, actors and others whose performances were cancelled due to the epidemic		
In eventuality of workplace shutdown, transfer employees to other workplaces, and if not possible, guarantee them 60% of salary until shutdown ends		When transfer impossible, suspend pay after first month of shutdown, according to Decree Law 326
Pay caregivers for children 60% of basic salaries unable to return to work because primary and special schools are closed		Eliminate this guarantee once schools re-open
Social activities		
Allow religious institutions to gradually re-open, ensuring physical distancing and other hygiene measures		
Resume visits to penitentiaries, normalizing these in Phase Two, limiting numbers of visitors		
Services, Taxes, Commerce		
Maintain priority for vulnerable groups sales of high-demand basic goods		
Guarantee availability of items included in the basic family basket		
Maintain postponement of billing for electricity, water, telephone land lines and cooking gas, except for those who can pay electronically	Resume billing for electricity, water, telephone land lines and cooking gas, establishing payment timetables for accumulated debt	
Maintain postponement of billing for individual taxes, taxes on sales and services, and others, as well as those on personal income of artists and artisans	Resume billing for payment of these taxes	
Resume gastronomical services, limiting patron capacities to 30%–50%, with tables separated by at least 1.5 meters		Resume gastronomical services of all types, guaranteeing physical distancing
Re-open at 50% capacity amusement parks, zoos, botanical gardens, libraries, museums, aquariums, clubs, fairs and others. Pools at 30%.	Expand capacities up to 80%	Return to full capacity

Transportation		
Maintain isolation areas at all airports and ports		
Maintain medical staff in national bus and train stations, as well as airport terminals for domestic flights		
Discourage foreign delegation visits to Cuba, and consult on those that may require an exception, due to their high priority for the country		
Permit only residents of Cuba to enter the country, on the condition that they receive RT-PCR upon entry and remain in preventive isolation for a period of 14 days in centers established for that purpose		Permit entry to international visitors and residents of Cuba, with precautionary measures (rapid test upon entry and home or hotel quarantine followed by family doctors/nurses)
Re-establish limited transportation (urban public, intermunicipal, rural, government and private); buses limited to full seating capacity, 50% standing	Expand urban public transportation; buses limited to 60% standing capacity	Fully resume urban public transportation
Continue suspension of commercial and charter flights, except for emergencies and those carrying persons collaborating abroad, cargo, donations, or stranded foreign visitors	Continue suspension of international flights; charter flights authorized for international tourism to authorized destinations	Authorize regular commercial flight operations
Education		
Keep schools closed	In September, begin completing the 2019–2020 academic year, assuming all provinces in Phase Two; physical distancing, disinfecting, no entrance for symptomatic students or staff, teachers, daily active screening.	Guarantee the 2020-2021 academic year in the new conditions faced by the country.
Sports		
Continue suspension of international sports events and activities at training camps involving foreigners	Resume training	
Keep gyms closed	Resume open-air gym activities, depending on their conditions and the country's epidemiological situation	
Culture		
Resume theater, music and dance rehearsals. Performances permitted without audiences, broadcast on social media, radio and TV	Resume activities at cultural centers and theaters, maintaining physical distancing measures	
Recreation		
Re-open beaches, limiting numbers of people to avoid crowds	Limit crowds at beaches, all open	
Tourism		
Resume tourism, limited to domestic market	Resume international tourism to the northern and southern keys, ensuring tourists are separated from the general population	Begin opening all remaining resorts and tourism destinations
Resume all hotel services, occupancy limited to 60%	Permit hotels to apply various alternatives to expand services	

Source: http://media.cubadebate.cu/wp-content/uploads/2020/06/Etapa-de-recuperaci%C3%B3n-pos-COVID-19-medidas-a-implementar-en-sus-tres-fases.pdf

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Science as a Social Good: Iramis Alonso-Porro
Director, *Juventud Técnica*

Conner Gorry MA

Science journalism was little known in Cuba when Iramis Alonso wrote her thesis on the specialized field in 1990. That year, journalism degree from the University of Havana in hand, she set off to Cuba's eastern countryside to complete two years of social service reporting for local, regional and national print media. Living in the mountains of Holguín, a typical day for the cub reporter took her to caves, forests and fields for stories on the intersection of science, culture and the environment. Alonso credits this formative experience with igniting her passion for investigative and science journalism, setting her on a unique career path as a journalist and editor specializing in the sciences writ large: climate change, astronomy, mathematics and other hard sciences, engineering, information technologies and social sciences, among others.

After finishing her social service, Alonso became a news analyst, parsing national and international print, radio and TV reports—this experience would prove indispensable in a future when misinformation can go viral. In 1994, Alonso began reporting on scientific issues for the national daily newspaper *Juventud Rebelde* where she spent five years broadening her knowledge and contacts and co-founding the paper's monthly scientific supplement, *En Red*, still published today. After eight years there, she jumped to *Bohemia*, Cuba's oldest and most respected magazine, where a culture of investigative journalism and 'pushing the envelope' prevails. She has worked with various international agencies, including the UN Development Programme (UNDP) and Oxfam, and was professor of science journalism at the University of Havana for six years (2011-2017). She is a regular lecturer on science journalism at the Jose Martí International Institute of Journalism in Havana. In 2007, Alonso became director of the national popular science magazine *Juventud Técnica*. In March, 2020, just two days after the first COVID-19 cases were confirmed in Cuba, she switched roles from journalist to interviewee.

***MEDICC Review:* Cubans revere *Juventud Técnica* (*JT*) as an entertaining and educational resource. But many *MEDICC Review* readers may never have heard of it. Can you talk a bit about the magazine's editorial mission?**

Iramis Alonso: *Juventud Técnica* covers all fields of science—astronomy, engineering, biotech and pharmaceutical development, the environment, mathematics and more—with the specific purpose of exploring the social applications of science. How can we get science out of the ivory tower and put it at the service of people to help improve their lives? That's our mission and vision. When considering editorial content, we focus on science as a social good and the magazine's contribution to moving that idea forward. So *Juventud Técnica* is not about science for the sake of science. Instead, we want to spark debate by covering polemical issues and digging deeper. So rather than report 'there's a novel vaccine and this is what it does' or 'new technology is available and these are its applications,' we explore the antecedents, process and setbacks. With a new vaccine for example, we investigate the history of the vaccine, why it's needed, who developed it and other similar vaccines that are available. We'll look into the R&D process: what problems were encountered? How were they overcome? What did the learning curve look like?

Sometimes there is this sense that science is always right and free of contradictions. But that's not how it works; scientific discovery is rarely linear and never static. I often say that science commits suicide with every new discovery. It's about testing and re-testing theories and disproving them until they can't be disproven. Today's accumulated scientific knowledge is built upon previous research—the advances and shortcomings. It's important to understand that process and context.

MEDICC Review: **You helped spearhead science journalism and editing in Cuba as a specialized profession. Can you talk about how that happened and why it's important?**

Iramis Alonso: Environmental reporting didn't become part of the University of Havana's journalism curriculum until 1992, following the Rio de Janeiro Earth Summit—so I didn't learn about it in the classroom, I learned about it in the field. During my social service, I was riding horses into the mountains to report on coffee yields or traveling to isolated coastal keys to write about beach erosion. I'll be honest: I miss field reporting.

When I became a science correspondent for *Juventud Rebelde*, I immediately became a part of the science and environment journalism section of the National Journalists Union. At the time, they had a really helpful system whereby once a month, we were invited on a site visit to different scientific institutions and research centers. We weren't expected to generate stories from these visits; they were meant for us to learn about the research happening and meet the scientists involved. One month we'd go to the Institute for Food Industry Research, the next to the Center for Applied Nuclear Technology Development and so on. This was an incredible learning experience and I wrote on just about every field of science while I was at the paper.

When I moved to *Bohemia*, where they employ specialist writers and editors for each section—culture, sports, science—I became convinced this is the ideal model. I firmly believe that scientific reporting and publishing requires a team of specialists, which is complex because science encompasses everything from computer technology and the environment to biotech and physics. We use the specialized journalism model at *Juventud Técnica* because readers need to know we've fact-checked and filtered the real from the bogus. It helps build and maintain credibility.

MEDICC Review: **One of the issues tackled in your magazine and which you've written about falls under the social sciences umbrella—gender. How do you view the status of Cuban women in science today?**

Iramis Alonso: Despite everything Cuba has achieved in gender parity and advancement of women in all senses, including science—the majority of scientists in Cuba are women!—we are still the minority in math and physics. There's a persistent sociocultural attitude that these fields are difficult, and more difficult endeavors are for men, while biology and chemistry are 'easier' and so somehow more 'appropriate' for women.

Of course we know that there is absolutely no evidence supporting this idea that biologically one gender is more intellectually suited or predisposed to one field over another. This bias is part of the machista construct and culture of our society. Stratifying social phenomena, instead of viewing them together as part of a diverse spectrum, also plays a part: who is to say that if I pursue a literature degree, that I don't also have the intellectual capacity to understand math or physics? This is a fairly generalized perception—that a person can't be drawn to or talented in several fields. When I was younger, I replicated this myth, saying "I'm happy not seeing another mathematical formula ever again." And I was good at math!

Breaking down this societal barrier and prejudice requires an integrated approach—in education, institutions and the media. And it has to start in children's early developmental stages. We need more imagery and media coverage of women in diverse fields; more inclusive messaging starting in elementary school that girls can do anything boys can do; and to celebrate scientists returning from international congresses with press conferences at the airport like we do with athletes. Did you know that in 2017, the first Cuban woman took home 'perfect gold' from the Central American Math Olympics? Probably not, because there's not sufficient media coverage of her achievement—and she's a math superstar [Sofía Albizu-Campos Rodríguez, a 10th grader from Havana, won the gold medal with a perfect score in the 2017 competition—Eds.]

MEDICC Review: **Are there specific strategies *Juventud Técnica* uses to promote women in science?**

Iramis Alonso: Absolutely. We are especially pro-active when it comes to scientific citations. The thesis by a *JT* journalist examining the diversity of scientific citations in Cuban publications found that almost all references cited were by white men in their mid-50s or older. Given that most scientists in Cuba are women, we intuited that there must be women doing similar research in whatever field being cited. This led to a study we conducted on the h-index of Cuban scientists, which found that the two most-cited Cubans at that time were women—Dr María Guadalupe Guzmán and Dr Susana Vázquez, both of the Pedro Kourí Tropical Medicine Institute (IPK) in Havana. The Secretary of the Cuban Academy of Sciences, Dr Lilliam Álvarez, has made a point of trying to get more Cuban female scientists 'seen,' nominated for awards and recognized for their work, but the fact is, male scientists are more visible.

So citing references, we consult our colleagues at the Cuban Academy of Sciences and scientific institutions to see if there is an appropriate reference by a woman or person of color we might substitute for the older white male citation. We consciously look for these alternatives. It goes without saying that first and foremost, the reference must be valid and meet the scientific criteria—no personal characteristics can supersede that.

In our interview section, we consciously strike a balance by interviewing as many women as men, and people of different skin color and ages: our goal is to represent the reality of Cuban science and that includes all types of people. By publishing interviews with younger scientists we also hope to stimulate the new generation to pursue scientific careers.

We are conscious about the language we use in our articles as well. Instead of saying 'science in the service of man,' we say 'science in the service of the human race,' which is more accurate anyway. And because Spanish uses grammatical gender [with gendered nouns and defaulting to the masculine when pluralized—Eds.] we look for gender-neutral alternatives.

MEDICC Review: **The title of your publication includes 'youth.' Is it difficult attracting young people to scientific fields in Cuba?**

Iramis Alonso: This is extraordinarily complex given Cuba's context. On the one hand, our education system graduates high-caliber professionals—despite resource scarcity and brain drain of professors to other countries and the private sector. On the

other hand, we don't have the economy to match, so it's difficult to attract young people into science. In short, Cuba has a first-world professional capacity within a developing-world economy, compounded by the US embargo of course.

So how do we reconcile the younger generation's social and professional commitment with their individual goals given the country's tenuous economic circumstances? This is no small challenge since we need their energy and creativity to develop sustainably.

The network of scientific and technological campuses cropping up across the country is a very interesting advance in this regard. These act as incubators for innovation, linking businesses, research institutes and universities to spark scientific and technological solutions to societal problems, while generating revenue for the country and the professionals forging those solutions. Supported by financial mechanisms and incentives, this model presents the possibility for more efficient implementation of applied research, greater student participation, and more passion in general for science and technology as young people see their ideas put into practice. The earning potential of this intersectoral approach is also much faster than traditional scientific research and development.

MEDICC Review: **Undoubtedly, human resources are one of Cuba's strengths….**

Iramis Alonso: Cuba doesn't have significant natural resource deposits or export market possibilities. And while I don't particularly like the term 'human resources'—we're talking about people!—it is shorthand for where we excel: a highly educated and trained professional and technical workforce. But it's not only about providing good jobs for this workforce, because one of the challenges we're facing is related to the perceived value of science. This is more intangible but no less important. It boils down to what value does science have for Cuba and for humanity? Doing more to impassion our society about science is needed. Going to the theater or movies, listening to music—these are popular pastimes. Imagine if looking at the stars and identifying constellations like I used to do with my grandfather or going to the natural sciences museum or aquarium became as popular…All the things we're talking about need to spring from a strong scientific culture.

MEDICC Review: **Speaking of passions, what are you most passionate about in your work?**

Iramis Alonso: I feel like my mission in life—aside from raising my kids, one of whom is a physicist, so I'm doing my part for science there as well!—is to mentor young journalists. I want to nurture their interest in scientific reporting, editing and publishing so the field continues to thrive and grow. *JT* is the only publication of its kind and we function as a forge for the next generation of scientific journalists and editors. This type of training and experience is important since we'll need to pass the torch to them at some point.

My other passion is to continue learning for my personal and professional edification. I've had no shortage of opportunities in this regard since I'm not a digital native and *JT* is very much in the thick of new technologies, with new multimedia platforms and initiatives.

MEDICC Review: **What are some of these new initiatives?**

Iramis Alonso: Despite challenges we've faced with the digital version of *JT*—streaming audio and video was problematic given our limited bandwidth—we are getting ready to launch *JT* 4.0. This is a multimedia platform with audiovisual components that incorporates a more user friendly and attractive interface without sacrificing scientific rigor. And this is both the driving force and biggest hurdle with new media and technologies for us as a publication: how do we design a social media and online strategy that pulls in young readers but maintains quality reporting? Too much of what's published online these days defaults to sensationalism just to get as many clicks as possible. And while we understand that remaining relevant to younger generations, who *are* digital natives, means having shorter, snappier headlines, using eye-catching graphics and being more agile in our reporting and response to readers, we still need to maintain the evidence-based and scientific standards for which we're known.

Doing this successfully requires us to adapt and learn new skills; a print publication is a different animal—slower, more in-depth—but we've developed a strategy and are about to hire a digital community manager to help us maximize the potential of the medium. This is especially important since we began our digital fact-checking initiative #*VerificaJT.*

MEDICC Review: **This project was mentioned in *MEDICC Review's* April 2020 issue in relation to coronavirus misinformation and disinformation. Can you explain what this is and why it's necessary?**

Iramis Alonso: We launched #*VerificaJT* to combat false news in science, technology, health and the environment. It's reader-generated and designed to fact check rumors and disinformation in these fields. Readers tag us with #*VerificaJT* about items or reports they think be false or need accuracy checked and our journalists begin to research the news in question to determine whether it's true or not.

Specialized science publishing helps filter out the real and valid news from the partially true or outright fabricated

The glut of information today is astounding; there's more information out there than human beings can process and then there's the question of *how* to process it, to filter it. So this, too, is a function of specialized science editing and publishing: it helps filter out the real and valid news from the partially true or outright fabricated. This is incredibly basic for me as a journalist—our job is to root out and verify facts, the credibility of sources, always going to the original source. When was it published? Where? What type of publication is it? Is their editorial process rigorous? These are the questions we ask when we get a reader request via #*VerificaJT*.

This is where our social media strategy comes in. Since we follow so many scientists and specialists on Twitter, for example, they can be consulted speedily to help verify news in their field. Twitter has proven an extraordinary tool for us in this regard, but also because you can tag who you want to see your content—if we're writing about gender violence, we tag the Cuban Women's Federation or Oxfam, both of which have campaigns against gender violence. Facebook is more like a crowded apartment building where all the neighbors are giving their opinion, so its less useful, but in Cuba you have to be on Facebook since its where the overwhelming majority of Cubans are online and provides the most visibility. We have strategies for both, plus Instagram and Telegram, too.

MEDICC Review: **Can you give some examples of items readers have sent in to #*VerificaJT*?**

Iramis Alonso: First, let me say that there is so much fabricated news flying around on the internet, we could dedicate our entire work day to just this. So we prioritize the fields I mentioned and serious inquiries only. We aren't interested in those queries sent by people determined to provoke or stir the pot.

So while we've received a lot of requests, we've only addressed a handful. One was a rumor that was making the rounds about contaminated Arcor food products [Arcor is an Argentina-based food company with 40 industrial plants in Latin America; their products are sold in Cuba—Eds]. We began researching reports and after consulting a similar fact-checking project in Argentina called Chequeado, learned that this was a two-year old rumor that started in that country and was completely false. We also addressed a rumor in Cuba about bananas being injected with HIV-contaminated blood. Also false. We had a reader request about a tornado that touched down in Mayabeque Province, not far from Havana. This was easy to verify as true, since journalists from the regional newspaper in Mayabeque reported on it.

More recently, we debunked a rumor about the first coronavirus cases in Cuba. On February 27, 2020, news began circulating on social media that there were three tourists with coronavirus hospitalized at the IPK. Since we have a large network of contacts at that hospital and research institute, it was an easy and quick process to verify that this was false news [the first three conf rmed cases of coronavirus in Cuba were diagnosed on March 11, 2020, Italian tourists who had arrived March 9—Eds]. Having contacts such as these and at the Cuban Academy of Sciences and other research institutes is a tremendous resource for quick and accurate verification.

MEDICC Review: **Cuba's National COVID Prevention and Control Plan was adopted over a month before the first cases were detected. How might the pandemic and the control measures affect your work?**

Iramis Alonso: One of the hundreds of measures put into place here relates to telecommuting, something we've been doing at *JT* for some time. Actually, I came in today just to talk to you; usually, we're only in the office once a week for our editorial planning meeting. We meet each week to design our work plan, divvy up editorial assignments and responsibilities and then work online from home. We've had to adapt this to our context and connectivity challenges, with low-data usage workarounds to send documents back and forth for example, but it's effective. This work-from-home model has advantages, especially since some of our team members live far away. While telecommuting for us pre-dates COVID, it will become important for many different sectors as transportation and physical contact becomes more restricted.

I foresee a lot of requests via #*VerificaJT*—social media is dominated by COVID-content content right now, not all fact-based, as we know. We've also been generating a constant stream of infographics and launched a COVID-19 dashboard, *Covid19CubaData*, with all the latest data, available online (https://covid19cubadata.github.io/) and as a mobile app (https://www.apklis.cu/application/ club.postdata.covid19cuba).

What I can tell you is our work is about to become a lot more intense!

Editors' Note: *In follow-up emails through early July, 2020, Iramis Alonso indicated that work at JT had indeed intensified and showed no signs of slowing, but noted the positive progress made in controlling COVID-19 in Cuba. As of this writing, the entire country has entered Phase 2 of the re-opening plan, except Havana which continues in Phase 1; the capital cannot pass to Phase 2 until the 5 established epidemiological criteria are met.*

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Economic Packages for COVID-19 Recovery Must Invest in More Resilient Health Systems

Cristian Morales MS MPH
PAHO/WHO Permanent Representative, Mexico

Gail Reed MS

Cristian Morales, an economist by training, has dedicated his career to improving health and health equity in the Americas through his work with PAHO/WHO. This has taken him from hurricanes, earthquakes and epidemics in Haiti to PAHO's Washington DC offices, where he was instrumental in achieving consensus on a resolution aiming for universal health—coverage plus access—approved by all governments in the Americas. In 2015, he was appointed PAHO/WHO Permanent Representative in Cuba, and in 2018 to the same post in Mexico.

MEDICC Review interviewed Mr Morales in Mexico City on June 19, 2020, when the region was already the COVID-19 epicenter with half the world's confirmed cases and deaths. Cases in Mexico are now expected to peak in August; then comes the question of how to rebuild. Leaders around the globe are grappling with the same question and in Latin America, it is challenging the status quo of health systems, economies and the very underpinnings of society. Mexico alone is now expected to suffer a 6% reduction in GDP, accompanied by rising poverty (to 47.8%) and extreme poverty (to 15.9%). Projections for many other countries in the region are similar. This implies, as Mr Morales emphasizes, that other actions must accompany the fight to bring the pandemic under control.

Courtesy C Morales

MEDICC Review: **Mexico is facing an increasingly complex COVID-19 situation, as are several other countries in the Americas. What measures are vital going forward to stem the viral spread and move towards a recovery that takes into account the most vulnerable people?**

Cristian Morales: The moment is complex for two essential reasons: first, the epidemic's intrinsic dynamic, where the overwhelming majority of Mexican states are confronting increasing community transmission in terms of both number of cases and deaths. This is particularly problematic in Mexico City and the State of Mexico—the so-called Valley of Mexico—where although we're seeing a certain plateau in case numbers, there is still considerable epidemic activity. This puts the area in the orange category in the alert system used here to express levels of epidemic threat, which goes from red (maximum threat) to orange, yellow, and finally, green (a new normal). In fact, all of Mexico's state-level authorities have posted red or orange, indicating a serious epidemic situation.

The second factor contributing to the complexity is that this epidemiologic picture co-exists with the reopening process, compounded by the country's sheer expanse and its geographic, cultural, economic and social diversity. So you can't really speak of one 'Mexican epidemic'—you have to look at the epidemic and reopening economic, social and cultural activities through all these lenses. The truth is, half the Mexican population has to go out to work every day in order to eat, and after 110 or 115 days of restrictive measures in terms of social interaction and physical distancing, people are exhausted and facing the possibility of a collapsing economy. The greatest danger right now is diminished risk perception, compounded by economic necessity, which could lead to a contagious spike.

What measures need to be maintained? Once the "safe distancing period" finished on May 31, the color-coded alert system was introduced. This involves specific measures for each threat level, permitting decentralized epidemic management according to regional and local conditions. These include home sheltering, safe physical distancing, hand cleansing and use of masks when safe distancing isn't possible, in order to contain the disease.

MEDICC Reivew: **Can you walk us through the measures Mexican authorities have taken and their results thus far?**

Cristian Morales: Mexico took measures quite early, much earlier than other countries. It was the first country in the region to operationalize real-time polymerase chain reaction (RT-PCR) technology following WHO protocols, and it was here in Mexico that personnel were trained from labs in Cuba, the Dominican Republic and all the Central American countries. It's important to have these capabilities—an adequate system for efficient epidemiological surveillance—to be able to apply data-informed public health measures.

Afterwards, and since March, explicit public health measures were taken in an effort to cut the person-to-person chain of transmission. On March 14, it was announced that schools would close the following week. At that time, Mexico had just over 100 cases, and if you recall, Italy closed its schools when it already had more than 2000 cases.

The main result has been to postpone the timing of the curve's peak. If these measures hadn't been implemented, we probably would have seen a significant spike in April, which would have overwhelmed the capacities of the health system, resulting in collapse. That didn't happen. We're still in an extremely dangerous situation, but the health system has general COVID-19 hospital-bed occupancy (with and without ventilation) of under 80%. That is, 20% to 25% of the beds dedicated to these patients are still available at the highest level, and nationally, this is 50% to 55%. Postponing the peak of the curve allowed time to purchase extra equipment, train human resources and better prepare the health system.

Does this guarantee that the system won't collapse? No, absolutely not. We could envision a case where the population doesn't adhere to the public health measures dictated by the color codes, with infection rates spinning out of control, as we have unfortunately seen in other countries, and in our own region in particular, in some South American countries.

MEDICC Review: **What is PAHO's role in Mexico during the pandemic?**

Cristian Morales: Our work here, like in other countries in the region, is based on four main pillars. The first is to reinforce and support Mexico's epidemiological surveillance system and diagnostic capacities—that is the RT-PCR, the only test with sufficient sensitivity and specificity to confirm diagnosis.

Second is decreasing person-to-person transmission. This has to do mainly with communicating risk, and communicating the public health measures such as safe physical distancing, which—with others such as handwashing, use of face masks when safe distancing isn't possible—are the main tools that the whole population can use to cut the chain of transmission. That means reaching communities and all the various sectors: public and private, social and economic.

Third is protecting health workers, which includes everything to do with correct use of personal protective equipment (PPE) and its accessibility for those who most need it, that is, those on the front lines fighting COVID-19. In Mexico as of June 17, of the some 160,000 hospitalized cases, 22% (32,000 to 35,000) were health workers. This is of grave concern. To decrease cases, health workers also need adequate training and preparation to confront COVID-19 to minimize the risk of contagion, another area where PAHO is collaborating.

Fourth is saving lives. This involves developing guidelines and technical recommendations, as well as providing support to ensure adequate supply of medical equipment and devices to address COVID-19. This implies knowing the WHO technical norms for respirators and ventilators and PPE, as well as the guidelines concerning hospital transformation to expand the health system's response capabilities.

MEDICC Review: **So over 20% of confirmed cases in Mexico are health workers, and most are in serious condition?**

Cristian Morales: Yes. In Mexico, confirmed cases are mainly those that have been hospitalized. That is, when we're talking about 160,000 cases, these are primarily people who have a serious case and have had to be hospitalized. Of those, between 32,000 and 35,000 have been seriously ill health workers, and nearly 500 have died.

We have lost some of the most experienced health workers from the frontline fight against COVID-19. They have to be replaced by others who first need to acquire the necessary competencies for these jobs. The losses have been great, and thus too the need for actions to protect these workers—not only providing PPE, which is fundamental, but also training them specifically to address COVID-19.

MEDICC Review: **We see complex COVID-19 scenarios in Mexico, Peru and Chile—and worse yet, in Brazil, where case numbers are second only to the USA. Yet, countries such as Costa Rica, Cuba, Uruguay, as well as Jamaica and several other Caribbean islands, are having more impact on the pandemic. Are there common denominators among those beginning to control the disease?**

> **Universal health systems are better prepared to confront the pandemic**

Cristian Morales: I'm convinced that universal health systems are better prepared to confront the pandemic. But also better prepared to confront a number of health problems that affect our populations, such as degenerative chronic diseases, other communicable infections and so on. One of the characteristics of the countries you mention is a focus on primary health care and strong primary care in general. This is fundamental for facing COVID-19 and a host of other health issues.

Last year, as part of the movement for health system transformation, PAHO/WHO organized a regional meeting in Mexico City to draw lessons to help achieve universal health. The gathering was a watershed as it clearly articulated recommendations for health systems to move more aggressively towards strengthening primary health care, but not limited to that. It noted the need to increase capabilities to resolve health problems at the primary care level, and at the same time to develop integrated service networks, emphasizing the classic component of health promotion and disease prevention, as well as patient care. These key elements must also be at the heart of the COVID-19 response.

MEDICC Review: **Interviewed for our April issue, ECLAC Executive Secretary Alicia Bárcena warned of a serious economic recession in Latin America and the Caribbean, already the world's most unequal region. She predicted a contraction of 5.3%, a figure unprecedented in recent times, but also said this presented a unique opportunity for economies and health systems to change direction towards more equity, more solidarity.**

Cristian Morales: We're facing an epidemic with economic, social, cultural, sports and recreational, sanitation and environmental consequences, just to name a few. So it has to be addressed from an intersectoral perspective, taking into account a recovery that could ensure more resilient societies—to COVID-19 and other health problems.

We have to set our sights on the medium and long term, and avoid lapsing into simplistic reductionism that pits public health measures against those for economic revitalization. That's a serious mistake we can't afford to make, since a healthy economy is only possible when the society enjoys good health and well-being. We don't get anywhere hurrying short-term recovery, because we'll have recurrent COVID-19 outbreaks that will undo economic recovery. Health and the economy must go hand-in-hand, and there are many positive symbiotic actions that can be taken for sustainable human development.

Nobody can ignore the fact that health systems have been overrun, and even when they haven't collapsed, they're under severe pressure. Mexico has been able to achieve adequate hospital reconversion that maintained bed availability—a key indicator during community transmission—but this hasn't been for free. It has required investments. In addition, if Mexico and other hard-hit countries had started with more developed health systems, already more geared towards primary health care, they would be better able to confront COVID-19.

So the first way the economy and health can work together is for economic recovery packages to invest in health systems, to bolster their capacities, make them more resilient and get them on course to becoming universal. This would also allow for more attention to COVID-19 prevention, and the most appropriate and timely use of services at every level for affected populations as well as those at risk.

PAHO's member countries have unanimously recommended that public investments in health should be at least 6% of GDP. For most countries in the region, that investment has stalled at around 3%, even below 3%, for the last 10 years. Now we have an opportunity to reverse this situation.

A second area where health and economics meet is in our ability to rethink the health of workers and companies as we reopen. There's much that can be done to protect the health of workers in the workplace and their families. Examples range from reimagining the physical space along production lines and finding ways to ensure safe distancing between workers, to palliative measures that can be taken until investments create such conditions. These include guaranteeing more breaks for handwashing, making alcohol gels readily available, requiring face masks where appropriate, and management decisions that make it possible for symptomatic workers to stay home without fear of losing their jobs. To the extent that these investments protect workers, they also protect the companies they work for.

So if we move in directions that imply health and the economy go hand-in-hand, then I think we'll be making a fundamental contribution to a resilient recovery, even when it may be interrupted by new outbreaks. Because if we do the right things and build more resilient societies and health systems, these outbreaks will be ever fewer, smaller and more readily controlled, with less multidimensional impact. And that means we are better prepared to face medium- and long-term challenges, because it's doubtful we'll have a vaccine on hand for at least another 18 to 24 months. Even if one were invented tomorrow, scaling up manufacturing to produce the doses needed, and for the vaccine to reach those who most need it in the Americas, is something that unfortunately is not going to happen quickly.

Lockdown alone isn't going to solve the problem in the long run. Because the informal sector, the precarious work and the fragile lives of millions of people in our region and the world aren't going to hold on. We need health systems that better attend to whole-population needs and economies that better protect their workers, jobs, and production itself, in order to emerge from the unprecedented recession that ECLAC speaks of, and in which most countries of the region are already immersed.

MEDICC Review: **Poor people and those working in the informal sector are most in need of the approaches you mention—more equitable, more inclusive health systems and economies. Yet, this implies that during a severe recession, more funds have to be found to finance these changes. We see in Mexico and Latin America sectors such as pharma and biotech, the health sector more broadly, that could serve as engines of economic recovery.**

Cristian Morales: Absolutely. It's clear that it will be hard to resolve the situation created by COVID-19 in the midst of the pandemic. Yet, we have to begin decreasing inequities—including inequities in access to such basic services as water and sanitation, also fundamental to controlling the disease. Employment is uneven, precarious, and the quality of jobs is not the same in different regions of Mexico and other countries of Latin America. And thus I'm convinced, and PAHO is convinced, that the health sector needs to be understood as an economic sector as well, one that can contribute to growth, and not only to growth.

First, remember that investments in health broadly speaking have an impact on the capacity to offer timely access to those suffering from a particular disease. And if we achieve adequate access to quality services, then we are probably going to improve productivity in general, as the sector continues to contribute economically, decreasing hospital stays, saving lives.

Second, health sector jobs, despite the generally precarious nature of the region's health systems, tend to be better jobs than many others. Thus, we're contributing to an important Sustainable Development Goal, number 8, promoting economic growth and decent employment. And moreover, an investment in health and expanded system capacities can also help diminish

gender disparities, since we know that the health sector is primarily composed of women. So an investment in better quality jobs, an expanded health system, will also improve women's employment. I also think you need to consider the possibility of developing other economic engines and expanding the green economy.

We must consider technological innovation, in this case technologies that can help protect us from COVID-19. These come from economically more developed countries, arriving late to those with lesser development, generating even greater inequities among countries and punishing those most in need, the most vulnerable groups that are found mainly in countries with the least economic development. Building our own pharmaceutical industry capacities to be able to innovate and produce within the region, is a commitment that I think would put us in a better position to confront other epidemics and future health problems in general.

MEDICC Review: **What about collaborative efforts among sectors within Latin American countries?**

Cristian Morales: I'm convinced that in Mexico and the rest of our region, if we can contain COVID-19, it will be because of social cohesion, a united effort among the different sectors, and collaborative participation from the public, non-governmental and private sectors. Without that, and without support from society at large—academia, scientific societies and so on—it will be very difficult to overcome the challenges presented by the multi-system threat of COVID-19. Especially since this is not a classic threat that stresses, disappears, and then allows us to recover. No, we're going to be living with outbreak after outbreak, as we're already seeing in China.

MEDICC Review: **And collaboration among countries?**

> **Multilateralism: the most important strategy that countries can adopt together to confront COVID-19**

Cristian Morales: There are some important initiatives among countries. One is the Mexican resolution recently presented to the UN General Assembly, which was adopted overwhelmingly. The resolution takes aim at the practice of stockpiling technologies and medical equipment for COVID-19, as well as price speculation. It's not simply a suggestion, but rather a mandate to the Secretary-General, to intervene through the various UN bodies, to guarantee just and equitable access to medicines and medical equipment throughout the world. It calls into action the most important strategy that countries can adopt together to confront COVID-19: multilateralism. This is why it is so significant and I hope that the mandate can be operationalized via the different UN agencies, including WHO, the World Food Program, UNICEF and others in the UN system.

Right now, we don't have medicines that can change the natural course of the disease; we don't have the vaccine we are all waiting for that will protect us and provide acquired immunity to the general population…in this world where people are sick in at least 215 countries and territories, at least half these cases in the Americas and half the deaths as well.

So we need more collaborative initiatives, such as the one guaranteeing access to innovative technologies for COVID-19, launched by WHO in association with various governments and foundations. This is the kind of thing we need to deepen the public-private alliances that can deliver quickly the tools to combat and contain COVID-19.

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Health Must Be Recognized as the Human Right It Is: Héctor Javier Sánchez MD MS

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He has been a member of the National System of Researchers since 2000, belongs to the Health Research Group for Africa and Latin America (GRAAL), and is technical secretary of the Latin American Forum of Health Research Ethics Committee (FLACEIS). ***MEDICC Review*** interviewed Dr Sánchez by e-mail on COVID-19 and its impact on Chiapas, indigenous populations and Mexico's health system.

Dr Sánchez appears on Rompeviento TV's program Mirada Crítica (Critical Look).

MEDICC Review: **What structural and health challenges do indigenous populations face—in Chiapas where you work and elsewhere—during the current pandemic?**

Héctor Javier Sánchez: Several fundamental aspects need to be considered when analyzing the health and economies of indigenous populations. First, indigenous peoples often live in conditions of extreme poverty. Second, native populations, who are among the poorest and most marginalized sectors of society, have notable difficulties in accessing and navigating the public health system. And third, Chiapas, sharing more than 600 kilometers of unpatrolled border with Guatemala, is a transit site for migrants traveling to the United States. Recently, thousands of migrants fleeing their countries have been held in detention facilities in this region—facilities that open the door to infectious disease transmission.

It is highly probable that the COVID-19 pandemic will have adverse consequences not only on the health sector, but contribute to higher levels of poverty among indigenous populations as well. This is, of course, due to the structural violence under which these populations have suffered for generations.

MEDICC Review: **Specialists predict a serious economic recession as a consequence of COVID-19. What would a recession mean for these indigenous populations in Chiapas? What social and economic conditions do they face?**

Héctor Javier Sánchez: Before the emergence of COVID-19, the UN Economic Commission for Latin America and the Caribbean (ECLAC) estimated that Latin American and Caribbean (LAC) economies would be facing a period of minimal growth, predicting just 0.1% in 2019 and 1.3% in 2020. Indeed, the entire LAC region, including Mexico, has shown six consecutive years of slowed growth.[1] Along with this general economic decline, there was sustained deterioration in the quality of employment—regionally, the largest source of new jobs is in the informal sector, characterized by low and unstable income, precarious social conditions and weak worker protections.[2] Given these circumstances, policies need adopting that stimulate growth and reduce inequality.

Chiapas is the Mexican state with the highest levels of poverty, 76.2%.[3] While 10.1% of the Mexican population are indigenous,[4] in Chiapas, at least 27% of the more than 5 million people are indigenous and speak indigenous languages

(Tseltal, Tsotsil, Chol, Zoque, Tojolabal and Lacandón, among others); 14% of them are monolingual, and do not speak Spanish.[5] Economic, educational, and health conditions are worse in indigenous populations than in non-indigenous populations: illiteracy rates are higher (17.8% vs. 5.5%), average years of education are lower (3.7 years vs. 9.4 years), rates of extreme poverty are higher (31.8% vs. 7.1%), lack of social security is higher (79.4% vs. 56%), and so is lack of income sufficient to ensure basic nutrition (44% vs. 18%).[4]

MEDICC Review: **Can you talk a little about health care for indigenous peoples in Mexico?**

Héctor Javier Sánchez: According to the National Human Rights Commission (CNDH), indigenous peoples in Mexico suffer from denial of services; inadequate provision of public health services, including medical negligence, discrimination, forced contraception, shortage of medications, confidentiality violations, irregular record keeping and failure to provide information on the patient's state of health; as well as insufficient infrastructure to provide health care.[6] What's more, the conditions under which these services are provided are even more precarious. PAHO/WHO recommends a minimum investment in health equivalent to 6% of GDP. In 2018, Mexico barely allocated 2.81%.[7]

Additionally, in Mexico, out-of-pocket expenses as a percentage of total healthcare spending is very high, above 40%. In other countries in the region, such as Cuba and Uruguay, this is only 10.3% and 17.4%, respectively.[8] This is an important indicator because the vast majority of indigenous populations have high indirect healthcare costs (transport, lodging, food, medicines) when they receive care in urban centers due to the scarcity of services in their communities.

MEDICC Review: **Clearly, these factors do not bode well for the health of indigenous communities beyond the pandemic…**

> **...other health problems of indigenous people in Mexico could be exacerbated during the critical stage of the pandemic**

Héctor Javier Sánchez: If more health resources are not made available, other health problems could be exacerbated during the critical stage of the pandemic and beyond, including:

1. A rise in infectious disease rates such as tuberculosis, HIV/AIDS, other respiratory infections, and vaccine-preventable diseases (like whooping cough in children). This increase would not be adequately addressed if there is a shortage of health resources, including well-equipped health units, trained personnel and supplies of necessary medications and vaccines.
2. Increased maternal mortality. Chiapas has the highest maternal mortality of any state in our country. According to figures from the Maternal Mortality Observatory in Mexico, more than half of maternal-mortality deaths occur among indigenous women, despite the fact that they represent less than 28% of the female population.[9]
3. Increase in nutritional disorders—both those due to deficiency (mainly chronic infant malnutrition) as well as overweight/obesity. In turn, all three of these conditions are strongly linked to diabetes mellitus.
4. Increase in mental and social disorders including fear, post-traumatic stress, suicidal ideation (and suicides) and social violence. These conditions can be exacerbated by the recession (or depression) expected to follow the pandemic, and can lead to higher levels of poverty, insecurity and social unrest.

In addition to these concerns, aspects that deserve special attention in indigenous areas include violence against women, ranging from physical and psychological abuse to femicide; living conditions of migrants who return to their communities; health status of the incarcerated; and accountability for use of health resources.

MEDICC Review: **This is a dire state of affairs. Do you foresee any positive outcomes from the pandemic for the health of indigenous people?**

Héctor Javier Sánchez: Once the pandemic is controlled, and taking into account the conditions of poverty, marginalization, exclusion and lack of basic health services addressing their needs in culturally- and linguistically-appropriate ways, indigenous communities could see positive economic and health effects post-COVID-19. These include:

1. Some mechanical ventilators acquired during the pandemic will remain available locally.
2. Perhaps, although less likely, the pandemic could bring greater awareness of and sensitivity to the unmet health needs of indigenous communities, and the government and health system may respond accordingly. Consider that the lack of personal protective equipment (PPE) for health personnel during the pandemic has been so great that doctors in indigenous communities have had to make 'protective' suits out of plastic garbage bags.[10]
3. We may see greater recognition of the importance of community health workers, particularly midwives—not just in care during pregnancy and low-risk deliveries, but as true community health workers at the primary care level. Unfortunately, government policies in Mexico in recent years have devalued and excluded midwives from their work in indigenous communities.

MEDICC Review: **Given these circumstances, how does Mexico move forward towards universal health care that meets the needs of indigenous populations of Chiapas and elsewhere?**

Héctor Javier Sánchez: First, health must be recognized as the human right that it is. The capitalist vision of health as merchandise has to be discarded—the paradigm where the doctor-patient relationship is a provider-client relationship. In these circumstances, collective health is viewed disparagingly, and importance is afforded only to clinical specialties. Doctors choosing to be epidemiologists, primary healthcare professionals or public health specialists are viewed pejoratively, as practicing 'inferior' specialties. This view must change drastically to acknowledge the full value of specialties like family medicine, public health, community health and epidemiology.

Who would be opposed to health care for all, universal health? I think the great majority of people would favor it, but not broken down into ´basic packages´, but rather truly comprehensive health care, considering and meeting the needs of different populations. Three major aspects stand out in this regard:

1. Financing must ensure sufficient budget for the organization, operation, supervision and accountability of health services, and must be provided through either general or sales taxes.
2. A larger number of interventions related to a broader range of diseases must be covered universally. The previous government tried to implement universality of health services, but only for a limited number of listed conditions and interventions under the so-called 'Popular Insurance' program (created in 2003; dissolved in 2020 and replaced by the Institute for Health and Well-being, INSABI). Popular Insurance operated as public health insurance for that portion of the population not participating in social security. People had to take out 'complementary' private insurance for conditions not covered under this program, such as chronic kidney disease. In fact, as a result, the burden of most illnesses was shifted from government to the population itself, and care depended on each person's ability to pay for private services. The private sector, needless to say, supported this scheme.
3. Thus, as a population we must still mobilize to demand true universal health with comprehensive, not partial, coverage. And we must also continue to fight to improve the social determinants of health. COVID-19 raises the question: how do we proceed after the pandemic? If the population doesn't assume a collaborative stance based on solidarity and collectivity, we will be stuck with the vision imposed until now. Let's not forget that immobilizing social movements could be collateral damage from measures taken to stem the epidemic, such as physical and social distancing. So coordination between and within communities, in addition to mobilizing social movements, will be very important in defining changes shaping the health sector and in fulfilling the unmet needs of indigenous peoples, whether in Chiapas or elsewhere in Mexico.

MEDICC Review: **Are there examples of this type of collaboration during the pandemic?**

Héctor Javier Sánchez: In Los Altos de Chiapas, an indigenous region where there is greater community coordination and the Zapatista National Liberation Army still has influence, various communities quarantined returning migrants and suspended public transportation to some areas to prevent possible transmission. This region lacks information in indigenous languages, has insufficient health services and few protocols based on an intercultural approach providing for the protection and medical care of the population.

Concerning social mobilization, the creation of social observatories like those dedicated to maternal death, HIV and tuberculosis may serve as pressure mechanisms to protect the health sector against government 'adjustment measures' or budget cuts. They can also provide guidance regarding resource allocation to ensure basic health services and those related to new COVID-19 outbreaks (or other epidemics). Additionally, they can provide disease surveillance and serve as a source of accountability to society.

Government responsibility cannot be reduced to minimum health service packages, especially for the most vulnerable populations such as indigenous peoples

Structurally, constitutional reforms and corresponding laws must be promoted and implemented that guarantee the right to health. Government responsibility cannot be reduced to minimum health service packages,[11] especially for the most vulnerable populations, such as indigenous peoples.

MEDICC Review: **How might the pandemic affect health inequalities in the future, especially for vulnerable populations?**

Héctor Javier Sánchez: COVID-19 has displaced all other diseases from the spotlight and revealed governments' poor preparation to face a new infectious agent. Moreover, the pandemic laid bare the social, health, psychological, political and economic problems plaguing the planet. At the health level, it exposed the frail hospital and laboratory infrastructure, and shortage of equipment and properly prepared and protected human resources. It also exposed the lack of intersectoral policies needed to face such a pandemic.

In Chiapas, as in other regions, COVID-19 is monopolizing resources of all kinds, leaving other health problems without due coverage, neglected. When the COVID-19 curve flattens, it will leave a clearer picture of the state of these neglected diseases, like tuberculosis. Even before the pandemic, TB was underdiagnosed, had high dropout rates for treatment in areas of socioeconomic marginalization, and widely documented multidrug–resistant cases, resulting in high levels of mortality. This is particularly true for disadvantaged areas like Chiapas and other regions with large indigenous populations, characterized by low human development indices.[12–14]

Likewise, there are various diseases that especially affect indigenous and rural areas, and which have been poorly attended by health services. These include dengue, Chagas disease, Zika and chikungunya; although the extent of chikungunya's prevalence in the area remains uncertain.

This situation illustrates the challenges faced by Chiapas and other regions with the twin conditions of high socioeconomic marginalization and social exclusion. In summary, COVID-19 will have a much greater negative impact if actions are not taken that reinforce universal access to, and the quality of, health services and address the social determinants of health.

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Epidermal Growth Factor in Healing Diabetic Foot Ulcers: From Gene Expression to Tissue Healing and Systemic Biomarker Circulation

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ABSTRACT

Lower-extremity diabetic ulcers are responsible for 80% of annual worldwide nontraumatic amputations. Epidermal growth factor (EGF) reduction is one of the molecular pillars of diabetic ulcer chronicity, thus EGF administration may be considered a type of replacement therapy. Topical EGF administration to improve and speed wound healing began in 1989 on burn patients as part of an acute-healing therapy. Further clinical studies based on topically administering EGF to different chronic wounds resulted in disappointing outcomes. An analysis of the literature on unsuccessful clinical trials identified a lack of knowledge concerning: (I) molecular and cellular foundations of wound chronicity and (II) the pharmacodynamic requisites governing EGF interaction with its receptor to promote cell response. Yet, EGF intra- and perilesional infiltration were shown to circumvent the pharmacodynamic limitations of topical application. Since the first studies, the following decades of basic and clinical research on EGF therapy for problem wounds have shed light on potential uses of growth factors in regenerative medicine. EGF's molecular and biochemical effects at both local and systemic levels are diverse: (1) downregulation of genes encoding inflammation mediators and increased expression of genes involved in cell proliferation, angiogenesis and matrix secretion; (2) EGF intervention positively impacts both mesenchymal and epithelial cells, reducing inflammation and stimulating the recruitment of precursor circulating cells that promote the formation of new blood vessels; (3) at the subcellular level, upregulation of the EGF receptor with subsequent intracellular trafficking, including mitochondrial allocation along with restored morphology of multiple organelles; and (4) local EGF infiltration resulting in a systemic, organismal repercussion, thus contributing to attenuation of circulating inflammatory and catabolic reactants, restored reduction-oxidation balance, and decreased toxic glycation products and soluble apoptogenic effectors. It is likely that EGF treatment may rearrange critical epigenetic drivers of diabetic metabolic memory.

KEYWORDS Epidermal Growth Factor, diabetes, diabetes complications, wound healing, diabetic foot, amputation, ulcer, Cuba

INTRODUCTION

Diabetic foot ulcers (DFU) are one of the most feared complications of diabetes. It is a common cause of nontraumatic amputation, resulting in significant disability, morbidity and mortality.[1] An ulcer is the distal expression of an impaired healing process with a high rate of recurrence, so that patients who have temporarily achieved wound closure are considered to be remission rather than healed.[1]

The glycemic imbalance and other diabetes-related factors contribute to sculpt an epigenetic blueprint that results in a sort of "stagnant transcriptome"[2,3] in which precocious senescence, proliferative refractoriness, and apoptosis appear to be critical drivers resulting in wound chronicity.[4] These biological deterrents have been related to a substantial reduction in availability and activity of several growth factors, as major players of internal and peripheral tissue repair.[5,6]

IMPORTANCE

This article describes the molecular mechanisms of epidermal growth factor (EGF) pharmacological activity, and links gene response to organ system homeostasis. The depicted cascade of events may underlie the clinical efficacy of locally-infiltrated EGF in restoring the healing response of high-grade diabetic foot ulcers. To our knowledge, this is the first comprehensive description of how EGF reverts the chronic wound phenotype in a meaningful clinical scenario when properly delivered to responsive cells.

The diabetic wound microenvironment is hostile to the chemical integrity and bioavailability of local growth factors (GF) and ultimately, to their role in the healing process. Examples of these growth factors include EGF, Platelet-Derived Growth Factor (PDGF), Transforming Growth Factor beta-1 (TGF-β 1), and Insulin-Like Growth Factor I (IGF-1).[7–9] The expression and transduction signaling of EGF and PDGF receptors are also impaired within the diabetic environment.[9] Accordingly, as described for the molecular mechanisms operating in peripheral insulin resistance, it may be that diabetic wound cells exhibit reduced tyrosine kinase activity, accounting for loss of function of the growth factor receptor, which predisposes cells to proliferative arrest and senescence.[10]

In 1962, Stanley Cohen announced EGF isolation and purification from salivary glands. EGF was shown to induce precocious development and maturation of epidermal tissue and its appendages when injected into newborn mice. In other words, EGF induced maturational reprogramming of chronologically imprinted events. This is the most studied growth factor in wound healing, given its ability to promote epithelial and mesenchymal cell proliferation.[11] Yet, circulating EGF levels are reduced by

diabetes,[12] contributing to development of local and systemic complications.[13,14] Consequently, EGF and other deficient growth factors are exogenously administered as a replacement therapy in diabetes, as an attempt to restore physiological healing processes.[13,14]

Topical administration of recombinant human EGF dates back more than 30 years. Initially, it was thought to be an encouraging alternative to combat the torpid healing of problem wounds.[15] However, the history of GF pharmacology in wound healing suggests that EGF's clinical introduction was rather precocious, at a time when basic knowledge on the biology of chronic wounds remained elusive. Initial clinical trials proved disappointing, as topical EGF administration failed to enhance a healing response in chronic wounds,[16] even in acute, experimentally induced wounds in healthy volunteers.[17]

In line with the notion that EGF reverses the proliferative arrest that characterizes chronic wounds,[18,19] we introduced EGF administration through local infiltration to treat high grade DFU (for review see [18]). It was our hypothesis that intralesional infiltration could circumvent the limitations confronted during years of topical EGF administration.

The infiltration protocol calls for an EGF liquid formulation to be injected locally in the wound, at a depth of 6 mm to 10 mm, 3 times a week for 5 to 8 weeks, targeting the wound bottom and dermo-epidermal junction. The decision to use this delivery mode resulted from insights accumulated from animal models and *ex vivo* and *in vitro* experiments, further enriched by valuable conclusions obtained by others.[18,20–22] These studies were possible given the availability of high-purity recombinant human EGF manufactured at the Genetic Engineering and Biotechnology Center, Havana, Cuba.[23]

A nationwide clinical development program started in Cuba in 2001,[24] which ultimately included pharmacovigilance studies that confirmed the safety and efficacy of EGF delivery by intralesional infiltration. Almost 20 years of clinical practice have shown a 75% probability of complete granulation response, 61% of complete healing; 16% absolute and 71% relative reduction of amputation risk. Furthermore, recurrences were reported as an exceptional event upon a 12-month follow-up period.[25,26]

Despite years of international research, GF prescription for healing problem wounds remains controversial.[27] Although GF therapy is not yet included in International Working Group on the Diabetic Foot (IWGDF) recommendations, (www.iwgdfguidelines.org), EGF intralesional infiltration has nevertheless been internationally validated and recommended as adjuvant therapy for high-grade DFU, considering its benefits in resuming a normal healing process with reduction of amputation rates.[28–32]

This article summarizes the major molecular, cellular and biochemical findings supporting the clinical efficacy of EGF intralesional infiltration for DFU in the commercially available pharmaceutical formulation Heberprot-P. The drug is included in the Cuban national medication registry since June 2008 and has offered the only pharmacological alternative for the treatment of high-grade, complex diabetic ulcers.

EGF INFILTRATIVE INTERVENTION: IMPACT ON GENE EXPRESSION, TISSUE REPAIR AND CIRCULATING BIOMARKERS

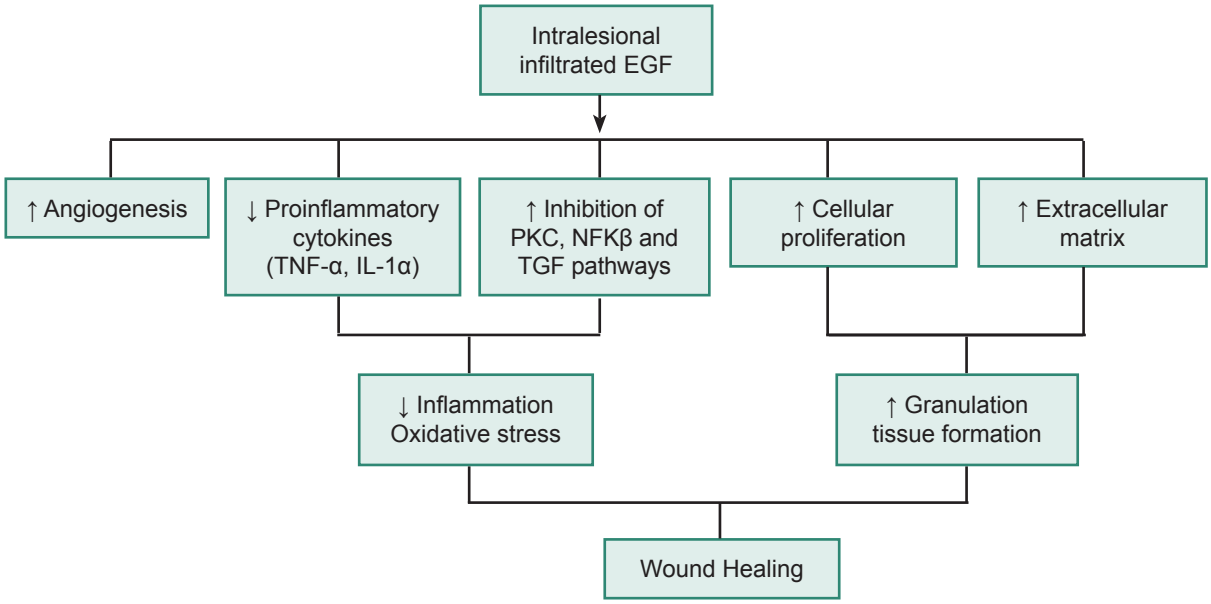
Gene transcriptional response in granulation cells Although not found on hematopoietic cells, the EGF receptor is widely expressed in mammals and has been implicated in the expression of a myriad of genes during various stages of embryonic development of both epithelial and mesenchymal tissues.[33–37] Accordingly, EGF administration modifies the course of the cutaneous healing process by promoting migration and proliferation of both epithelial and mesenchymal skin cells where its receptor expression is enhanced.[15,38]

Camacho and colleagues[39] described changes in the expression of several genes encoding proteins involved in wound healing. The investigation was part of a clinical trial (IG/FCEI/PD/0911 in the Cuban Public Registry of Clinical Trials, http://registroclinico.sld.cu/en/trials/RPCEC00000117-En) and included paired granulation tissue biopsies from 29 patients meeting the following criteria: Wagner grade 3–4 lesions, clinical responders with complete re-epithelialization at the end of treatment, and high-quality RNA samples for differential expression studies. Of the 29 patients, 10 were randomly chosen as the minimum sample size able to detect a 1.5-fold RNA expression difference relative to the basal constitutive value (paired control) just before treatment (biopsy identified as T0). EGF (75 µg dose) was infiltrated intralesionally 3 times/week. A second biopsy (T1) was collected at the end of treatment week 2. Paired comparisons between T1 and T0 biopsies revealed a significant increase in cell proliferation modulators Cyclin-Dependent Kinase 4 (CDK4), P21 and TP53, in collagen synthesis and Extracellular Matrix remodeling gene products (Collagen type I, alpha 1 chain, Matrix Metalloproteinase 2 and TIMP2), and a concomitant reduction of some inflammation markers, including NFKB, Tumor-Necrosis Factor-alpha (TNF-α) and interleukin 1 alpha (IL-1α). Local cell proliferation, synthesis and secretion of wound matrix proteins, and downregulation of inflammation mediators such as TNF-α, are critical events for physiological healing.[10]

The authors concluded that the observed increase in P21 and TP53 is a cellular feedback mechanism limiting the intensity and duration of the EGF-induced proliferative signal. A molecular action mechanism was postulated from these findings (Figure 1).[39] Irrespective of the differences between samples collected from diabetic ulcers and neonatal keratinocytes cultured from healthy donors, the data from Blumenberg[40] on EGF effects on transcriptomes validate the induction of keratinocyte proliferation and motility associated with feedback mechanisms controlling EGF effects. In concurrence with Blumenberg's study, our data indicate that EGF effects are modular and multifaceted rather than all-or-nothing events. This is the first clinical study addressing the transcriptomic effect of EGF in a model of human diabetic ischemic ulcers.

EGF intervention to ameliorate the histological aspect of neuropathic and ischemic lesions Ischemic diabetic lesions are characterized by a hyaline aspect matrix and paucity of functional neovessels, as well as angiogenesis defects (Figure 2A). In sharp contrast, neuropathic lesions appear to granulate earlier, exhibiting a poor collagen matrix deposition, an image similar to a spider web of thin collagen fibers, which react weakly to Mallory

Figure 1: Changes in gene expression upon EGF infiltrations



Patients who responded to EGF intralesional infiltrations exhibited gene expression changes that assisted in resuming and sustaining wound healing, and a reversion of the chronic phenotype. The clinical response was mediated by an elevation of angiogenesis, cell proliferation, and matrix fibrogenic ingredients coding genes and a reduction in inflammation related genes, stimulating the tissue repair process. (Reproduced from [39] under CC4 license).

staining. Additionally, reduced density of extracellular matrix-producing cells has also been noted (Figure 2B). As opposed to ischemic ulcers, small capillaries are observed, often surrounded by peripheral fibrin cuffs, suggesting hyperpermeability.[41] Following 9 to 12 EGF infiltration sessions (third/fourth week of treatment), granulation tissue of both ischemic and neuropathic origins exhibited substantial clinical amendment, with a consistent increase of functional small-caliber vessels across the ischemic tissue (Figure 2C). The granulation tissue matrix of neuropathic lesions becomes densely indurated by thicker and compact collagen bundles accompanied by increased productive cellularity (Figure 2D). In both scenarios, the inflammatory infiltrate appears substantially reduced.[42] Therefore, EGF positively impacts the local microenvironment of both pathogenic classifications of DFU.

It is of relevant therapeutic significance that EGF infiltration changes the biology of ischemic ulcers. Given its angiogenic effect, in addition to creating *de novo* vessels,[43] EGF acts as a cytoprotective agent, enhancing cell and tissue survival in otherwise lethal episodes like ischemia/reperfusion and hypoxia.[21,44–47] This drives a hypothesis that agonistic stimulation of EGF receptor (EGFR) triggers survival signals that may depend on translational modifications, with tyrosine phosphorylation being the most common.[48,49]

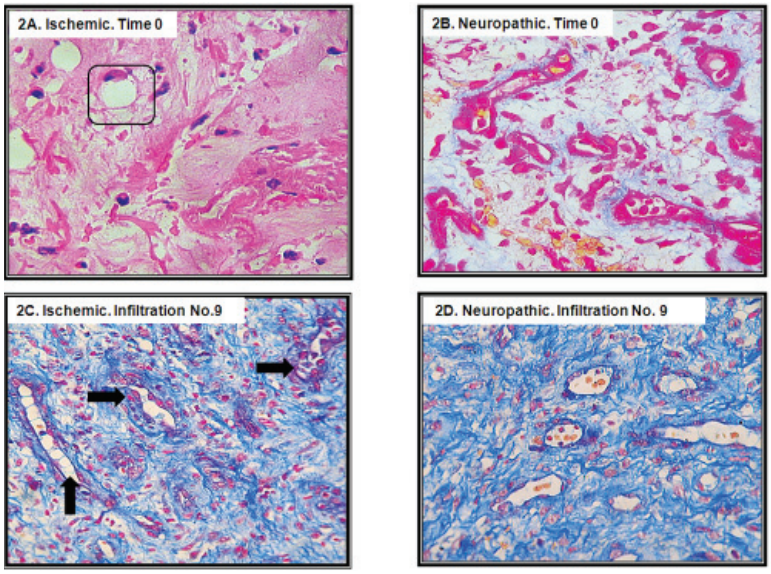
Zhang and colleagues recently conducted a thorough characterization of molecular mechanisms underlying EGF's effect on diabetic wounds.[50] The authors implemented a full-thickness wound model in type-2 diabetic rabbits. The EGF-induced effect after one month of daily dermal delivery is reminiscent of the microscopic outcomes identified in patient biopsies: (1) increased granulation tissue with elevation of clustered fibroblasts, (2) abundant extracellular matrix, indurated by dense and ordered collagen bundles, (3) increased active vessels and (4) attenuation of the inflammatory infiltrate. Interestingly, and aside from the histological findings, EGF treatment induced the transcription of its own gene with an increased EGF-mRNA accumulation.[50]

The EGF-induced modifications in problem wounds with different pathogenic ingredients suggest that locally-infiltrated EGF stimulates both mesenchymal and ectodermal cell responses, expressed by proliferation, migration, secretion, angiogenesis and survival. Accordingly, EGF infiltration is a DFU-specific therapy that may synchronize local cellular behaviors, thus reversing the chronicity phenotype.[51]

EGFR intracellular trafficking: EGF induces its own receptor expression in granulation tissue fibroblasts By means of immunoelectron microscopy of ulcer fibroblasts, Falcón-Cama[52] characterized EGFR time-point kinetic intracellular trafficking. EGF locally infiltrated into Wagner's 3 and 4 neuropathic ulcers translated into:

(a) Significant increase of EGFR membrane expression 15 minutes after EGF infiltration as compared to T0;
(b) Immediate EGFR endocytosis;
(c) Translocation and biodistribution to different cytoplasmic organelles from 15 minutes to 24 hours after infiltration;
d) Nuclear translocation of EGFR and its binding to DNA, which appeared to last from minute 45 to 24 hours after treatment;
(e) Concomitant activation of proliferating cell nuclear antigen (PCNA) gene transcription which appeared to last for about 24 hours after treatment;
(f) Substantial EGFR accumulation in mitochondria, which peaked between hours 6 and 24 after infiltration; and
(g) EGFR accumulation bound to extracellular matrix-secreted collagen fibers, along with abundant appearance of exosomal extracellular vesicles.

Figure 2: Wound matrix transformation by locally infiltrated EGF



Source: Jorge Berlanga-Acosta. Archives of the laboratory of experimental pathology. Center for Genetic Engineering and Biotechnology, Havana. Cuba.

Histological images of granulation tissue biopsies collected prior to the initial EGF infiltrative intervention and after the 9th intervention. Images are representative of the two major etiopathogenic forms of diabetic lower extremity disease: ischemic and neuropathic. 2A: Representative of a clean, ischemic diabetic granulation tissue bed before the first local EGF infiltration. Granulation tissue exhibits a "hardened" hyaline matrix with a general scarceness of functional neovessels. Nonfunctional capillaries are seen since early stages (enclosed). 2B: Representative of an early granulation tissue matrix, collected from a neuropathic lesion exhibiting poor extracellular matrix accumulation, scarce collagen deposition and a limited productive cellularity before EGF treatment. These are all histological hallmarks of protracted, poor healing of neuropathic wounds. 2C: Image showing the transformation of the wound matrix composition, with substantial angiogenic response induced by the local EGF infiltration with patent large vessels (arrows) across the microscopic field of an ischemic lesion. 2D: Accumulation and organization of a substantial amount of new extracellular matrix material is conspicuous. There are functional vessels across the wound area after EGF infiltration. Biopsies from 2C and 2D were collected upon the 9th EGF infiltration session. Figure 2 conclusively denotes that EGF infiltration may positively impact on the healing biology of both ischemic and neuropathic wounds. All samples are 5 µm sections and Mallory stained X 40. Original unpublished images.

Most importantly, ultrastructural characterization of the fibroblast-like cells 24 hours after EGF exposure revealed significant changes, suggesting organelle repair as compared to T0.[52] Figures 3A and 3B reflect how EGF resulted in effective treatment for control of the rough endoplasmic reticulum (RER) dilation. At 24 hours after EGF intervention, RER tubules and cisternae appeared far less dilated as compared to T0. Similarly, mitochondria were also a target of EGF effect (Figures 3C and 3D). The latter show a far less dilated organelle in which matrix cristae are observed. The presence of two adjacent organelles may suggest an active process of mitochondrial fission.

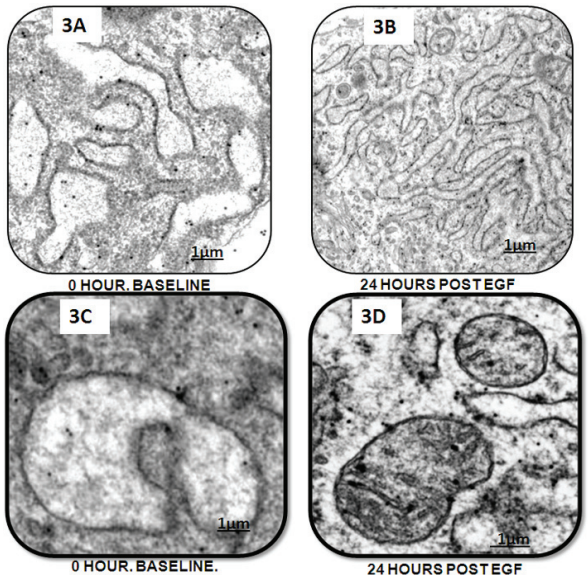
Although prior evidence had indicated that EGF can induce the expression of its own receptor,[53] current research provides the first evidence concerning EGFR transcriptional induction, internalization and intracellular trafficking kinetics in response to a therapeutic intervention with an EGFR ligand in a clinical setting.[52] This intense EGF-induced cellular response is consistent with its broad biological activity. *In vitro* models have documented that EGFR activation upon EGF binding induces the phosphorylation of 2244 proteins at 6600 catalytic sites,[54] the expression of 3172 genes and 596 proteins which are significantly altered in epithelial cells.[55]

In vitro evidence shows that full length EGFR translocates to the cell nucleus after ligand binding,[29,56] where several functions are performed.[57] First, EGFR operates as a co-transcription factor regulating the expression of cyclin D1, a proximal driver of cell proliferation.[58,59] EGFR interacts with DNA-dependent protein kinase, leading to the repair of DNA double-strand breaks.[60] Furthermore, nuclear EGFR phosphorylates chromatin-bound PCNA, thus increasing its stability and eventually enhancing cell proliferation.[61] Intracellular PCNA is related to anti-apoptotic activity, which may act as one of the multiple mechanisms mediating EGF pro-survival effects in a variety of cell populations.[62] Supporting this notion is the identification of the mitochondrion as another EGFR translocation compartment. Mitochondria are the hub of cellular metabolism, survival and death; they modulate not only apoptosis, but also autophagy. EGFR translocates to mitochondria where it phosphorylates cytochrome c oxidase subunit II , resulting in decreased cyclooxygenase activity, thus eventually preventing apoptosis.[63] EGF is also involved in mitochondrial fission,[64] fusion[65] and ultimately, in control of cellular response to stress, where it plays a pro-survival role.[37]

EGF infiltration sequentially activates EGFR in dormant ulcers, fibroblasts, and in its intracellular trafficking, promotes fibroblast proliferation, migration and survival.[59,66,67] The fact that EGF may reduce RER dilation, ameliorate mitochondrial damages, and stimulate proliferation of fibroblasts in DFU drives speculation that EGFR stimulation may mitigate senescence-related traits. Although this hypothesis has yet to be experimentally verified, evidence from our group and others support this possibility.[68,69]

Locally infiltrated EGF reduces diabetic dyshomeostasis Oxidative stress not only promotes the onset of diabetes but also exacerbates the disease and its complications. Brownlee[70] proposed oxidative stress as a major operator in the pathophysiology of diabetes and its complications.[71] Hyperglycemia has been invoked to promote oxidative stress through free radical generation and ensuing deterioration of antioxidant defense systems.[71] Chronic wounds are considered a pro-oxidative organ superimposed upon a preexisting dysmetabolic host (the diabetic patient).[18,72] In a small cohort of diabetic neuropathic ulcers, García-Ojalvo and colleagues addressed whether an improved systemic reduction-oxidation (redox) balance is associated with healing response in patients infiltrated with EGF.[72] The rationale for the above study was supported by previous experiments demonstrating that EGF reduced levels of oxidative stress biomarkers, ultimately attenuating cytotoxic damage.[73–76] After 3 to 4 weeks of EGF treatment (9 to 12 infiltration sessions), 4 circulating biomarkers (erythrocyte sedimentation rate, IL-6, soluble FAS and pentosidine) were significantly reduced, while antioxidant parameters increased.

Figure 3: Impact of EGF treatment on ulcer-fibroblasts organelle repair



3A. Electron microscopy image of the rough endoplasmic reticulum (RER) at time 0. Sample collected before EGF infiltration. The dilation and distortion of the RER cisternae is evident.

3B. Effect of EGF intervention after reverting cisternae dilation and ameliorating the preexisting distortion after 24 hours of treatment.

3C. Electron microscopy image of a ballooned mitochondria showing its notable dilation and disappearance of internal cristae before the first EGF intervention. A fine granulation is dispersed within the mitochondrial matrix.

3D. Twenty four hours after the EGF treatment, it is noticeable the substantial transformation of the mitochondria. Mitochondria are far less ballooned with matrix content and exhibiting some cristae.

Source: Falcón-Cama V, et al.[52]

Notably, at least 50% of patients showed a favorable response for each evaluated marker. EGF's molecular effect was simultaneously associated with a positive clinical response in terms of granulation, contraction and re-epithelialization. This was the first clinical validation of *in vitro* and animal data indicating that EGF's cytoprotective effect is at least partially mediated by correcting the redox balance.[18,73,76–78]

A more recent study by García-Ojalvo and colleagues[79] confirmed previous observations concerning the systemic impact of locally-infiltrated EGF on reestablishment of a physiological redox balance. Moreover, the new data indicates that EGF's effect extends to reduction of diabetic endovascular pro-inflammatory markers. Within three weeks of treatment, patients showed significant reduction of: erythrocyte sedimentation rate, IL-6 circulating levels, soluble FAS and the glycoxidation product pentosidine, as well as a significant reduction of oxidative and nitrosilative stress markers (Table 1).

The fact that EGF infiltration reduced circulating levels of IL-6 is highly significant in diabetes. IL-6 is perhaps the best-reputed bona fide cytokine, pathogenically involved in the primary event of insulin resistance, in the morbidity caused by multiorgan complications, and in the onset of a poor healing

Table 1. Systemic effects of locally infiltrated EGF in patients with diabetic foot ulcers

System	Systemic effect
Redox balance	↓ Total oxidative capacity ↓ MDA ↓ AOPP ↓ Total organoperoxides ↓ Nitrite/Nitrate ratio ↑ Total antioxidant capacity ↑ SH groups
Anti-inflamatory mechanism	↓ Erythrosedimentation ↓ C Reactive Protein ↓ IL-6 ↓ MIP1-α ↓ sFAS
AGE pathway	↓ Pentosidine ↑ sRAGE
Extracellular matrix	↓ MMP-9 ↓ TIMP-1

Diabetic patients with lower limb wounds were treated with intralesional infiltrations of EGF (75 µg), three times per week during 3-4 weeks [72, 79]. *Systemic antioxidant effects*: decrease of circulating levels of total oxidative capacity, malondialdehyde (MDA), advanced oxidation protein products (AOPP), total organoperoxides, and nitrite/nitrate ratio; increase of total antioxidant capacity and sulfhydryl (SH) groups. *Anti-inflammatory effects:* reduction in erythrosedimentation, C reactive protein, interleukin-6 (IL-6), macrophage inflammatory protein 1-alpha (MIP1-a), and soluble FAS (sFAS). *Systemic attenuation of the advanced glycation end (AGE) pathway*: decrease in pentosidine, increase in the soluble receptor for AGE (RAGE) circulating levels. *Extracellular matrix elements modulated at the systemic level:* reduction of matrix metalloprotease 9 (MMP-9) and tissue inhibitor of MMP 1 (TIMP-1).

response. *In vitro* studies by our group reproducibly show that DFU-derived fibroblasts exposed to lipopolysaccharides exhibit a highly significant increase of IL-6, which returned to basal levels, similar to those of untreated cells, after adding EGF (Yssel Mendoza-Marí, manuscript in preparation. April 2020). Simply said, dampening IL-6 circulating levels could contribute to restoration of metabolic homeostasis in diabetic patients.[80–82] Aside from IL-6, EGF intervention also reduced serum levels of soluble FAS and the chemokine Macrophage Inflammatory Protein (MIP1-α). Although further studies are clearly needed, collectively this evidence suggests that EGF may have assisted in reduction of insulin resistance, attenuation of endovascular inflammation and reduction of apoptotic rates; thus attenuating premature diabetic organ senescence.[83] Conclusively, EGF treatment exhibits broad systemic pharmacodynamics that go beyond the reestablishment of redox balance.

CONCLUSIONS

The discovery of growth factors initiated a new era in wound healing biology and held out hope for recalcitrant wound treatment. EGF, the prototypic and founding member of the EGFR ligand family, led to use of topical administration of growth factors for wound healing. Evidence suggests its role in tissue repair was already apparent in the early 1960s in Stanley Cohen's work subjecting rabbits to corneal burns followed by treatment with homemade natural EGF eye drops.[11] Despite the initial promise and years of research, growth factors have not garnered a definitive acceptance in the

clinical toolbox for wound management. Lessons learned over the past decades reinforce the importance of growth factor stability, which allows for sufficient residence time within the wound matrix to achieve the expected pharmacodynamic response. Cleverly engineered formulations are emerging that may yet vindicate growth factors' intrinsic biological potential. The intralesional infiltrative procedure, despite its simplicity, safeguards EGF bioactivity for prolonged periods, thus emphasizing the concept that spatio-temporal control of EGF availability is fundamental for clinical success.

This pioneer growth factor has proved to modify gene and protein expression, phosphorylate catalytic sites, modulate organelle homeostasis and, at an organismal level, reverse changes in inflammatoxic markers involved in progression of diabetic complications. The latter may represent the systemic effects of EGF, accompanied by amelioration of the wound chronicity phenotype. Again, wound-host bidirectional communication is underscored.

A research challenge is elucidation of the molecular foundations that may explain the unusual EGF trait of helping to prevent ulcer recurrence over the long term.[25,26] We hypothesize that infiltrated EGF exerts a local 'rejuvenating' effect by replacing senescent cells or by dismounting or reversing the fibroblasts' epigenetic senescence program. Thus, EGF may potentially act as a senolytic agent for diabetic wounds, promoting neodermal resilience and tolerance to physical and mechanical stress.

In conclusion, two decades of clinical and basic research on EGF therapy for problem wounds have shed light on the utility of growth factors with broad pharmacological potential in regenerative medicine; the time has come to focus on how, when and where to deliver their messages to their targets.

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COVID-19 Forecasts for Cuba Using Logistic Regression and Gompertz Curves

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ABSTRACT

INTRODUCTION On March 11, 2020, WHO declared COVID-19 a pandemic and called on governments to impose drastic measures to fight it. It is vitally important for government health authorities and leaders to have reliable estimates of infected cases and deaths in order to apply the necessary measures with the resources at their disposal.

OBJECTIVE Test the validity of the logistic regression and Gompertz curve to forecast peaks of confirmed cases and deaths in Cuba, as well as total number of cases.

METHODS An inferential, predictive study was conducted using logistic and Gompertz growth curves, adjusted with the least squares method and informatics tools for analysis and prediction of growth in COVID-19 cases and deaths. Italy and Spain—countries that have passed the initial peak of infection rates—were studied, and it was inferred from the results of these countries that their models were applicable to Cuba. This hypothesis was tested by applying goodness-of-fit and significance tests on its parameters.

RESULTS Both models showed good fit, low mean square errors, and all parameters were highly significant.

CONCLUSIONS The validity of models was confirmed based on logistic regression and the Gompertz curve to forecast the dates of peak infections and deaths, as well as total number of cases in Cuba.

KEYWORDS COVID-19, SARS-CoV-2, logistic models, pandemic, mortality, Cuba

INTRODUCTION

The COVID-19 pandemic and the characteristics of the SARS-Cov-2 viral agent[1] have led many governments to restrict social contact in order to cut the chain of transmission and thus reduce cases and deaths. The measures include some variation of lockdown, which in various countries has proven effective at curbing disease spread, flattening the curve and avoiding health system saturation.[2] Thus, it is vitally important for decision-makers to be able to approximate the maximum number of infections and deaths expected, as well as when caseload peaks will occur.

In Cuba, many measures have been implemented to mitigate COVID-19 spread and to limit the severity of cases and deaths.[3] However, until April 22, 2020, the increase in confirmed case numbers was approximately exponential. Going forward, reliable estimates are needed to inform decision-making in the context of limited resources.

Many such forecasts are made using mathematical modeling. A classic epidemiological model is SIR (Susceptible, Infectious, Recovered), based on ordinary differential equations. This modeling has been used successfully for the COVID-19 pandemic in some regions.[4,5] In Cuba, several authors have also applied it to the COVID-19 pandemic.[6–8]

Other techniques that have been used for modeling COVID-19 are:

- Statistical time-series models to predict the number of infections and/or deaths[9]
- Data processing to obtain forecasting models using the internet[10]
- Models based on artificial intelligence and machine learning[11,12]

These approaches are based on parameters that describe different characteristics of the pandemic. The estimation of these guiding parameters is complex, requiring controlled study of samples or use of approximations. Interpreting the models themselves is also complex.

Among the statistical models are logistic population growth models and the Gompertz growth model.[13] These models have been used in the COVID-19 pandemic and are less complex than those previously mentioned. But they are limited to short-term forecasts since they incorporate few parameters related to changes in epidemic dynamics, such as those that are sensitive to actions of a clinical nature, or to transmission-mitigation measures. To estimate the parameters of these models, the nonlinear least squares method is used. This modeling has been applied worldwide to forecast for incidence and prevalence rates.

Various studies have used logistic models to make predictions regarding COVID-19's epidemiologic dynamics and the disease's effects. Batista used the logistic regression model to study the magnitude of the pandemic in China through February 25, 2020;[14] Morais used it in forecasting deaths in China, Iran, Italy, South Korea and Spain;[15] Tátrai and Várallyay applied the model to predict the peaks in various countries affected by COVID-19 and assessed the quality of its fit with data from various regions in China affected by COVID-19.[16] Wu used a logistic model to estimate the peak in confirmed cases for Europe and the United States, and evaluated goodness-of-fit using a sample of 29 provinces in China and 19 countries that had passed the peak.[17] Qaedan used a logarithmic-logistic model to obtain predictions for the state of Utah in the United States and assessed its fit based on adjustments made in South Korea and Italy.[18]

IMPORTANCE

This study confirms the validity of an analytical tool that can be used to forecast the total number of COVID-19 cases and deaths in Cuba at different points in time, allowing health authorities and government to make more informed decisions on use of available resources to stem the pandemic and organize recovery phases.

Some studies have implemented the Gompertz model. Mazurek and Nenickova applied it to predict the pandemic's peaks in the United States.[19] Mazurek took a similar approach to study data for the United Kingdom, the Russian Federation, Turkey and the world as a whole;[20] and Razzak applied the model to predict the course of the pandemic in New Zealand.[21]

Other studies have used both models simultaneously to obtain forecasts for COVID-19. Jia used Gompertz, Bertalanffy, and logistic models to predict COVID-19 case numbers in various regions in China. These authors first studied the models' goodness-of-fit using data from SARS-CoV-1 confirmed cases in China in 2003.[22] Similarly, based on the goodness-of-fit of the logistic model and the Gompertz model for the data from China and South Korea, Villalobos presented predictions for Costa Rica.[23] Milhinhos and Costa adjusted logarithmic-logistic models and logarithmic-Gaussian models to obtain forecasts for Portugal based on their goodness-of-fit for distribution of COVID-19 data in South Korea.[24]

Dattoli used a three-parameter logistic model and the Gompertz model to make estimates for Italy.[25] Bauckhage used the logistic and Gompertz models to obtain predictions for Germany for mid-April 2020,[26] while Rodrigues-Silva used these models to obtain predictions for the state of Goias in Brazil[27] and Dutra used them to estimate the number of persons affected by COVID-19 for various US states and the whole country.[28] Attanyake fitted logistic, Gompertz and other exponential models to data corresponding to the impact of COVID-19 in Sri Lanka, Italy and Hubei, a province in central China.[29] Ahmadi adjusted the Gompertz, Bertalanffy and cubic polynomial models to forecast pandemic dynamics for April 2020 in Iran.[30]

The ordinary differential equations presented in Equation 1 and Equation 2 are known as the logistic differential equation (or Verhulst equation) and Gompertz equation, respectively.[31]

$$\frac{dP(t)}{dt} = r \cdot P(t) \cdot \left(1 - \frac{P(t)}{K}\right)$$

Equation 1: Logistic differential equation

$$\frac{dP(t)}{dt} = r \cdot P(t) \cdot \ln\left(\frac{K}{P(t)}\right)$$

Equation 2: Gompertz differential equation

Both describe the growth of populations where: *P(t)* represents the number of organisms or the size of a population at a given moment in time, *r* represents the instantaneous rate of increase and *K* corresponds to the carrying capacity of the environment or the maximum number of individuals that the population can sustain. *K* and *r* are positive real numbers and the function *P(t)* is positive, monotonically increasing and suitable for representing epidemiological models, as it presents a rapid initial growth that is approximately exponential and as the number of infections increases, the number of non-infected individuals in the population decreases. As a result, the relative growth rate within the population decreases until growth stops when there are no individuals left to infect.

Both models present an explicit solution provided by Equations 3 and 4 for the logistic model and Gompertz models, respectively.

$$P(t) = \frac{P_0 \cdot K}{P_0 + (K - P_0)e^{-rt}} = \frac{K}{1 + e^{b - rt}}$$

Equation 3: Logistic model (b >0)

$$P(t) = K \cdot e^{-\ln\left(\frac{K}{P_0}\right) \cdot e^{-rt}} = K \cdot e^{-b \cdot e^{-rt}}$$

Equation 4: Gompertz model (b > 0)

P_0 represents the population *(P)* at the start of the growth process ($0 < P_0 < K$). The *b* parameter is found to be associated with displacement on the abscissa axis for both sigmoid models. This is obtained through changes in variables (in Equation 3, algebraic transformations were applied before implementing the variable change).

The inflection point for these population growth models is of interest, as it represents the moment at which the rate of growth is highest, which can be interpreted as the peak of the pandemic. The inflection point for the logistic model is presented in Equation 5 while the inflection point for the Gompertz curve is presented in Equation 6. In the logistic model, this point is at 50% of population growth (the logistic function is symmetrical with regard to this point) while this point on the Gompertz model is approximately located between 35% and 40% of population growth.[31]

$$t = \frac{b}{r}$$

Equation 5: Inflection point of the logistic model

$$t = \frac{\ln(b)}{r}$$

Equation 6: Inflection point of the Gompertz model

The relative rate of population growth is linear in the logistic process (Equation 7) and logarithmic in the Gompertz process (Equation 8). The latter growth process develops more slowly with respect to the logistic model process.[31]

$$TC_{|P} = \frac{\frac{dP(t)}{dt}}{P(t)} = r \cdot \left(1 - \frac{P(t)}{K}\right)$$

Equation 7: Relative population growth rate in the logistic model

$$TC_{|P} = \frac{\frac{dP(t)}{dt}}{P(t)} = r \cdot \ln\left(\frac{K}{P(t)}\right)$$

Equation 8: Relative population growth rate in the Gompertz model

This study aims to fit logistic and Gompertz models to the distribution of COVID-19 in Cuba for confirmed and deceased cases, to demonstrate the fit of these models for these distributions in such a way that they can be generalized as predictive models and to make forecasts for the peak dates of confirmed cases and deaths due to COVID-19 in Cuba.

The first aspect studied was the fit of the models used for the distribution of COVID-19 confirmed cases and deaths in Spain and Italy, countries that had passed the peak of the pandemic. The good fit of these models in those countries and their comparative simplicity in relation to other models has piqued interest in applying them to forecasting in Cuba. The adequacy of the models in estimating distribution of confirmed cases and deaths in Cuba was assessed by analyzing the parameters for goodness of fit and testing the models themselves for statistical significance.

METHODS

Design and participants This is an inferential and predictive study using the logistic model and the Gompertz growth curve. The curve fitting method was used by applying the least squares technique for non-linear models with respect to their parameters.

This study was conducted from March 16 to April 22, 2020, while Cuba was experiencing the impact of COVID-19, by a group of professors from the Mathematics Department at the Carlos Rafael Rodriguez University of Cienfuegos in collaboration with the Department of Educational Technology at the same institution.

Official data on the number of confirmed cases and deaths from COVID-19 reported by the governments of different countries were studied as summarized by WHO and recorded and published by Johns Hopkins University. These data are updated daily and show cumulative confirmed cases, deaths and recoveries from the disease for different countries and territories. The first record in this database is from January 22, 2020.[32] Data was collected until April 22, 2020.

For the countries studied, documentation began with the date of the first recorded confirmed cases or deaths in the territory (Table 1). The daily cumulative cases were recorded in both analyses. In Cuba, the first cases were confirmed on March 11, 2020, but they were recorded in the database the following day.

Table 1: First recorded date of confirmed cases and deaths by country

First date recorded	Recorded cumulative data	
	Cases	Deaths
Italy	January 31, 2020	February 21, 2020
Spain	February 1, 2020	March 3, 2020
Cuba	March 12, 2020	March 18, 2020

Study variables The variables analyzed in this investigation are discrete quantitative variables, specifically:

- Number of days elapsed since the first positive cases of COVID-19 were confirmed. Each data point for this variable is recorded on a daily basis: for example, in the case of Cuba, the first day corresponds to March 12, 2020 and the second corresponds to March 13.
- Number of days elapsed since the first confirmed deaths of patients diagnosed with COVID-19. These values are recorded in a similar way to the previous variable, but using the database corresponding to deaths.
- Number of confirmed daily cumulative cases for COVID-19.
- Number of daily cumulative deaths for patients diagnosed with COVID-19.

Data Management and Processing Downloaded daily as .csv files, data were decoded using programmed scripts for that purpose.

The Maxima 5.41.0[33] symbolic software programs and R 3.6.1[34] programming language for number processing were used to process the data.

To use the least squares method, the lsquare.mac (version 5.41.0) package was used in the Maxima program and for the commands for R; nls, SSlogis and SSgompertz from the stat package (version 3.6.1) and drm from the drc package (version 3.0-1) were used. To study the Root Mean Square Error (RMSE) and the significance of the parameters of the model, the summary command from the stat package (version 3.6.1) was used and the adjusted R^2 was calculated using rSquared from the miscTools package (version 0.6-22). To determine the goodness-of-fit for the model, the command neill.test from the drc package (version 3.0-1) was used.

Analysis The logistic and Gompertz models were fitted to the data published for COVID-19 for confirmed cases and deaths in Spain and Italy. Italy had its peak of confirmed cases on March 26, 2020 and its peak deaths on March 27, 2020.[35] Spain had its peaks of confirmed cases and deaths on March 31, 2020 and April 2, 2020, respectively.[36] As of April 22, 2020, according to the Johns Hopkins database, Italy had reported a total of 187,327 confirmed cases due to COVID-19 with 25,085 deaths, while Spain had recorded 208,389 confirmed cases and 21,717 deaths. As these countries had passed the peak of the pandemic, the official published data on the peaks was compared to the forecasts obtained using the models.

The RMSE and the R^2 adjusted coefficient of determination were calculated to study the goodness-of-fit of the models, while keeping in mind that, for both models, values close to 1 for R^2 and lower values for RMSE indicate a better fit.

The models were adjusted to the data published for COVID-19 for confirmed cases and deaths in Cuba. Goodness-of-fit was determined using the analyses of R^2 and RMSE. Significance of the models' adjusted coefficients was determined using the t test. Goodness-of-fit was verified using the Neill test, which is suitable for non-linear models with respect to the established parameters, and which utilizes grouping techniques in the event that there are no replicates.[37] The significance threshold selected *a priori* was alpha = 0.05.

Once the models' statistical significance had been demonstrated for distributions of confirmed COVID-19 cases and deaths in Cuba, these models were used to forecast the same.

RESULTS

Confirmed cases of COVID-19

Case Study, Italy The first case was recorded on January 31, 2020. However, it was not until February 21 that exponential growth of the pandemic was officially reported. Figure 1 presents the geometric representation of cumulative confirmed cases and the logistic model (Equation 3) and Gompertz curve (Equation 4). Table 2 presents the adjusted coefficients for each model, R^2, the RMSE values obtained for each, and the forecasted peaks. Both models show an R^2 greater than 0.99 with a notably lower RMSE in the Gompertz model. Using the logistic model, the peak was forecast at 60 days (March 30) after first case, while the Gompertz model forecast it at 57 days (March 27).

Case Study, Spain The first case was recorded on February 1, 2020. However, it was not until February 25 that the pandemic's exponential growth was officially reported. Figure 2 shows the geometric representation of cumulative confirmed cases, according to the logistic model (Equation 3) and Gompertz model (Equation 4).

Table 2 shows R^2 greater than 0.99 for both models. The Gompertz model shows a lower RMSE than the logistic model, which suggests a better fit. The estimated peak, according to the logistic model, is calculated at 62 days (April 2); while the estimated peak for the Gompertz model is estimated at 59 days (March 30).

Figure 1: Logistic model and Gompertz curve: confirmed COVID-19 cases in Italy

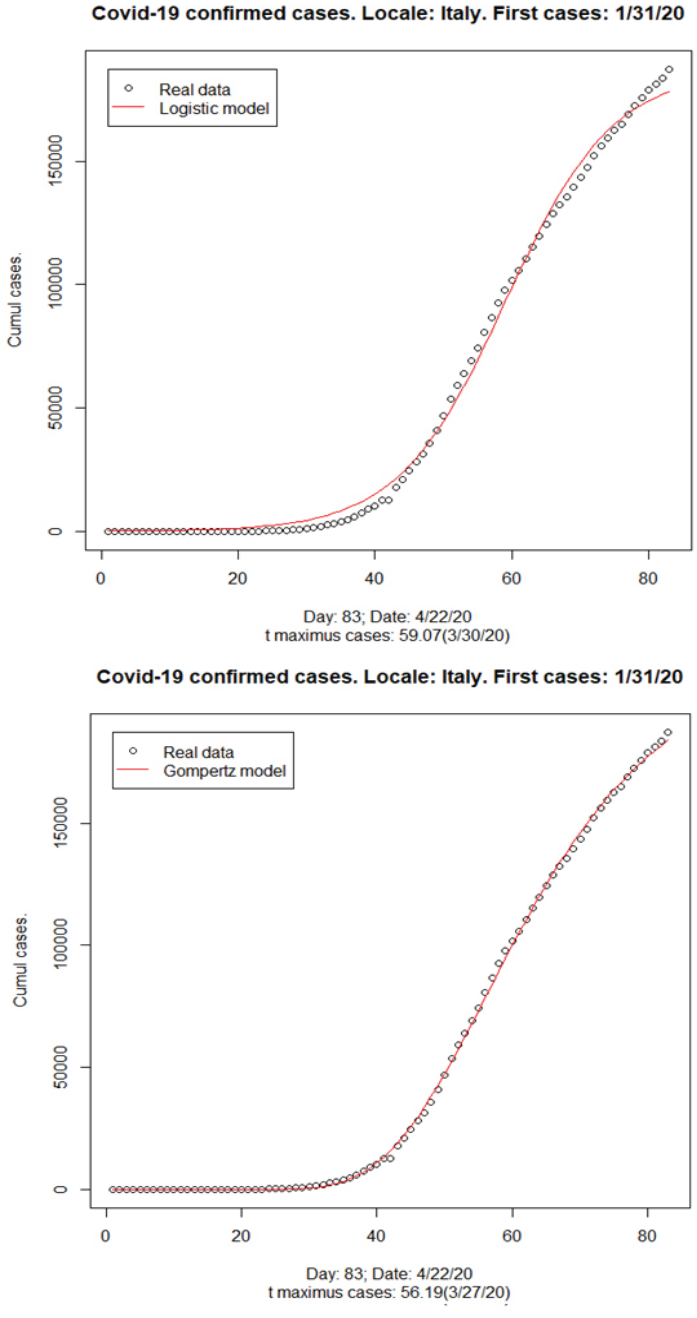


Figure 2: Logistic model and Gompertz curve: confirmed COVID-19 cases in Spain

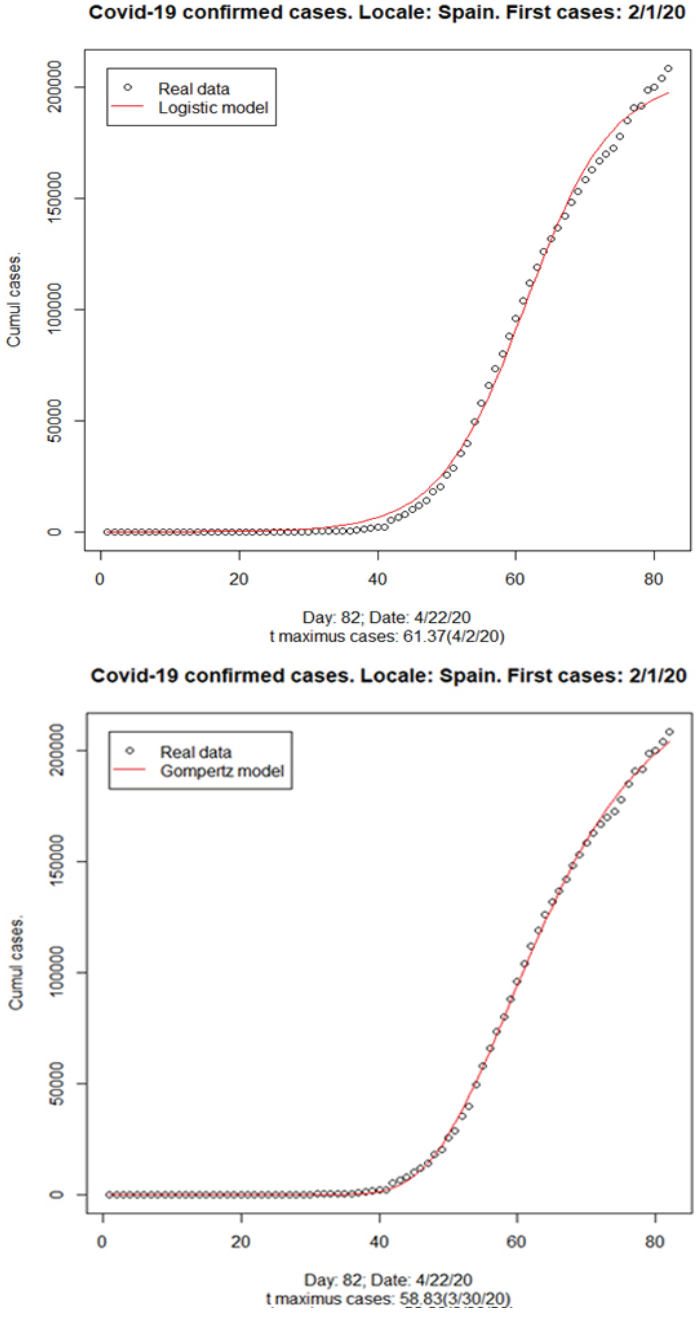
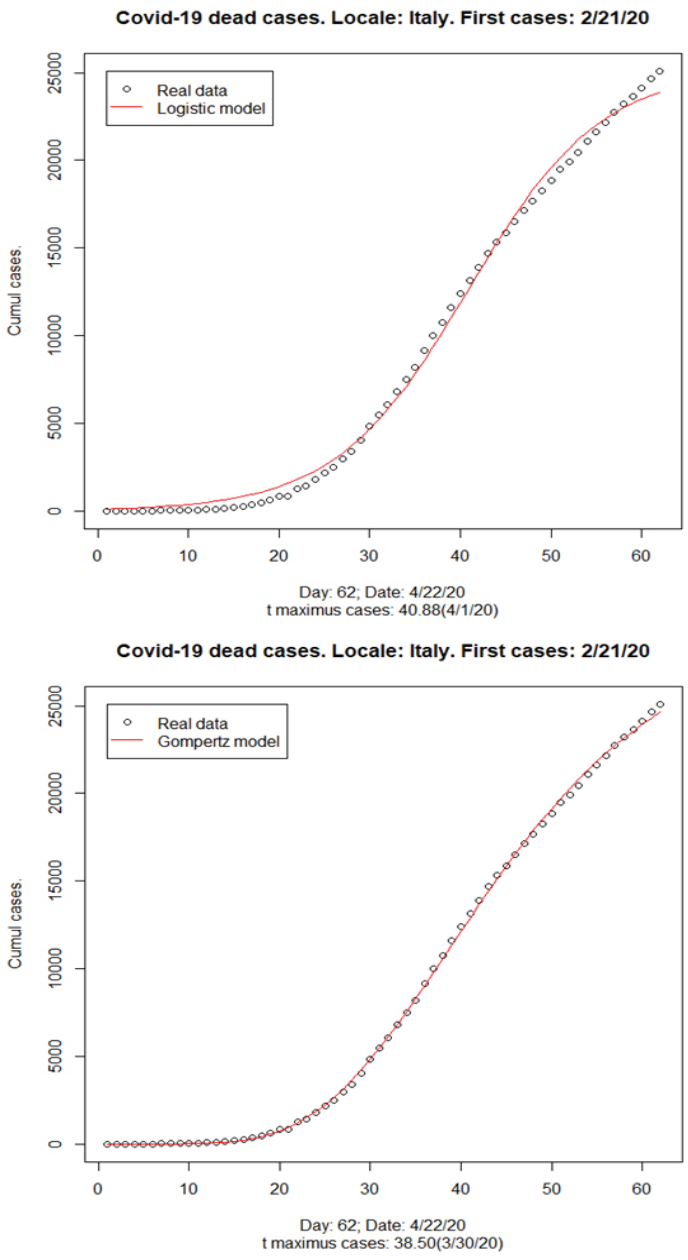


Table 2: Comparison of models fit with real data for confirmed cases of COVID-19 in Italy and Spain

Estimate of confirmed cases		Coefficients (model)	R^2	RMSE	Maximum cases (forecasted)	Peak (forecasted)	Real peak
Italy	Logistic Model	K = 186,701 r = 0.13 b = 7.54	>0.99	3537	186,701 (cumulative)	March 30	March 26 (6203 cases recorded)
	Gompertz Model	K = 216,522 r = 0.07 b = 44.97	>0.99	1291	216,522 (cumulative)	March 27	
Spain	Logistic Model	K = 204,499 r = 0.16 b = 9.85	>0.99	3644	204,499 (cumulative)	April 2	March 31 (9222 cases recorded)
	Gompertz Model	K = 232,770 r = 0.09 b = 168.46	>0.99	1712	232,770 (cumulative)	March 30	

RMSE: Root Mean Square Error R^2: coefficient of determination K: maximum number of individuals a population can sustain
r: instantaneous rate of increase b: a measure of the displacement of the abscissa axis

Figure 3: Logistic model and Gompertz curve: COVID-19 deaths in Italy



COVID-19 DEATHS

Case Study, Italy The first death was reported on February 21. The graph in Figure 3 shows the geometric representation of observed cumulative deaths and the estimations by the logistic model (Equation 3) and Gompertz curve (Equation 4). Both models have an R^2 greater than 0.99, however, the Gompertz model has a lower RMSE than the logistic model (Table 3). The logistic model has a forecasted peak at 41 days (April 1), while the forecasted peak for the Gompertz model is 39 days (March 30) after the appearance of the first case in the country (February 1).

Case Study, Spain The first death was reported on March 3. Figure 4 shows the geometric representation of observed and predicted cases and deaths by the logistic model (Equation 3) and Gompertz model (Equation 4). Both models had an R^2 higher than 0.99, however the Gompertz model had a smaller RMSE (Table 3). The logistic model had a projected peak at 33 days (April 4) while the projected peak for the Gompertz model is estimated at 30 days (April 1) after the reporting of the first death in the country.

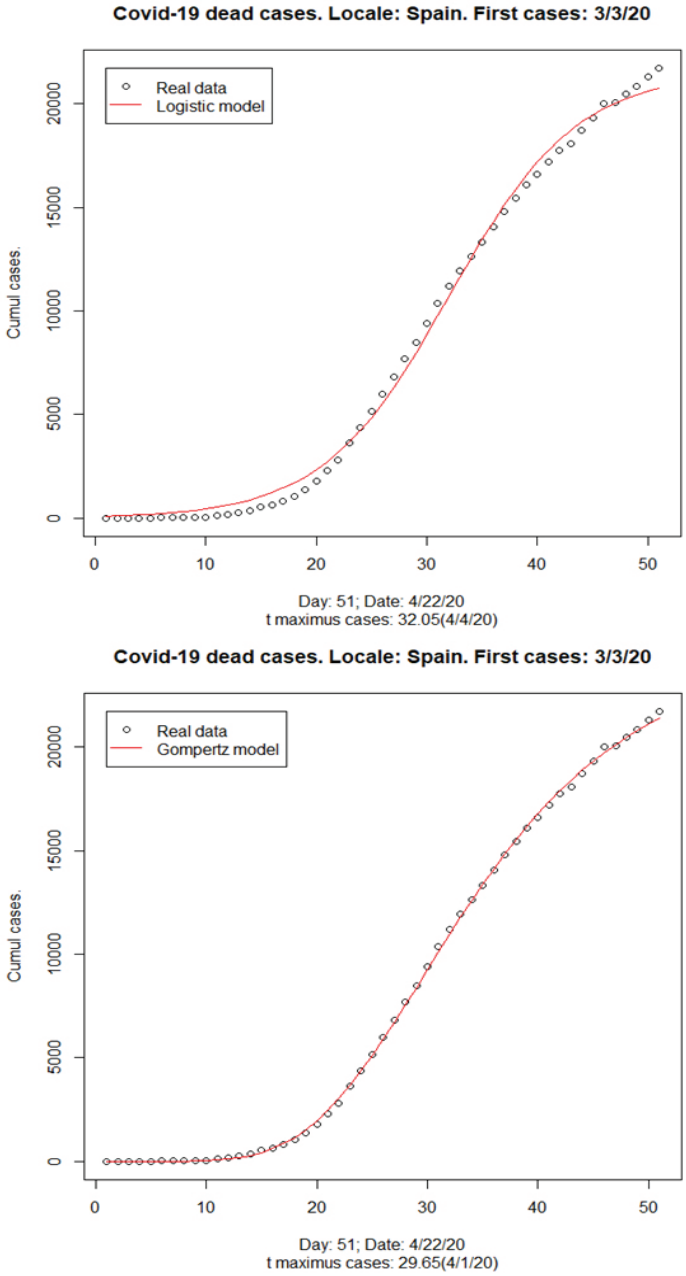
Estimation for Cuba The first cases were diagnosed on March 11, recorded on March 12, and the first death was on March 18. As of April 22, it had been 42 days since the first report of infection and 36 days since the first death. Figure 5 presents the geometric representation of observed cumulative confirmed cases and deaths using the logistic model (Equation 3) and Gompertz curve model (Equation 4). On the graph, it can be observed that the models were correctly fitted to the data and the increase in the data is within the prediction interval of 95%.

The model-generated forecasts for Cuba provide a projected peak of infection between 34 and 39 days after first report of COVID-19 cases (March 12) and put the peak of deaths between 32 and 49 days after confirmation of the first death in the country (March 18). As with Spain and Italy, the Gompertz model forecast a greater total number of confirmed cases and deaths than the logistic model. Table 4 shows the coefficients corresponding to the logistic models and Gompertz models fitted to the reported Cuban data for confirmed COVID-19 cases and deaths. The criteria for the goodness-of-fit were similar for both models; they are slightly better in the Gompertz model for the distribution of confirmed cases and in the logistic model for the distribution of deaths.

Associated p values for the significance tests for the coefficients were all less than 0.05, indicating that the models were acceptable. Goodness-of-fit was demonstrated using the Neill test, which presents levels of significance higher than 0.05 for each model in each of the applied distributions (confirmed cases and deaths). This also demonstrates an acceptable fit for the models and thus their suitability for prognostic purposes.

Forecasts for the days with the highest numbers of infection and deaths were obtained using the calculation of the inflection point

Figure 4: Logistic model and Gompertz curve: COVID-19 deaths in Spain



in each adjusted model and the cumulative totals corresponding to the K parameter (Table 4).

DISCUSSION

The logistic growth and Gompertz models provided good forecasts for Italy and Spain. For both countries, the Gompertz model had better estimates for the peak in confirmed cases and deaths. In the case of Italy, this model provided forecasts with an error of one day later and three days later for the peaks of infection and deaths respectively in comparison to the real peaks presented for that country. For Spain, the Gompertz model presented the forecasts for the peaks in infection and death with one day of error earlier than the real dates on which these peaks occurred. The Gompertz model forecast a higher total number of cases and deaths than the logistic model in both countries.

Figure 5: Logistic model and Gompertz curve: confirmed COVID-19 cases and deaths in Cuba

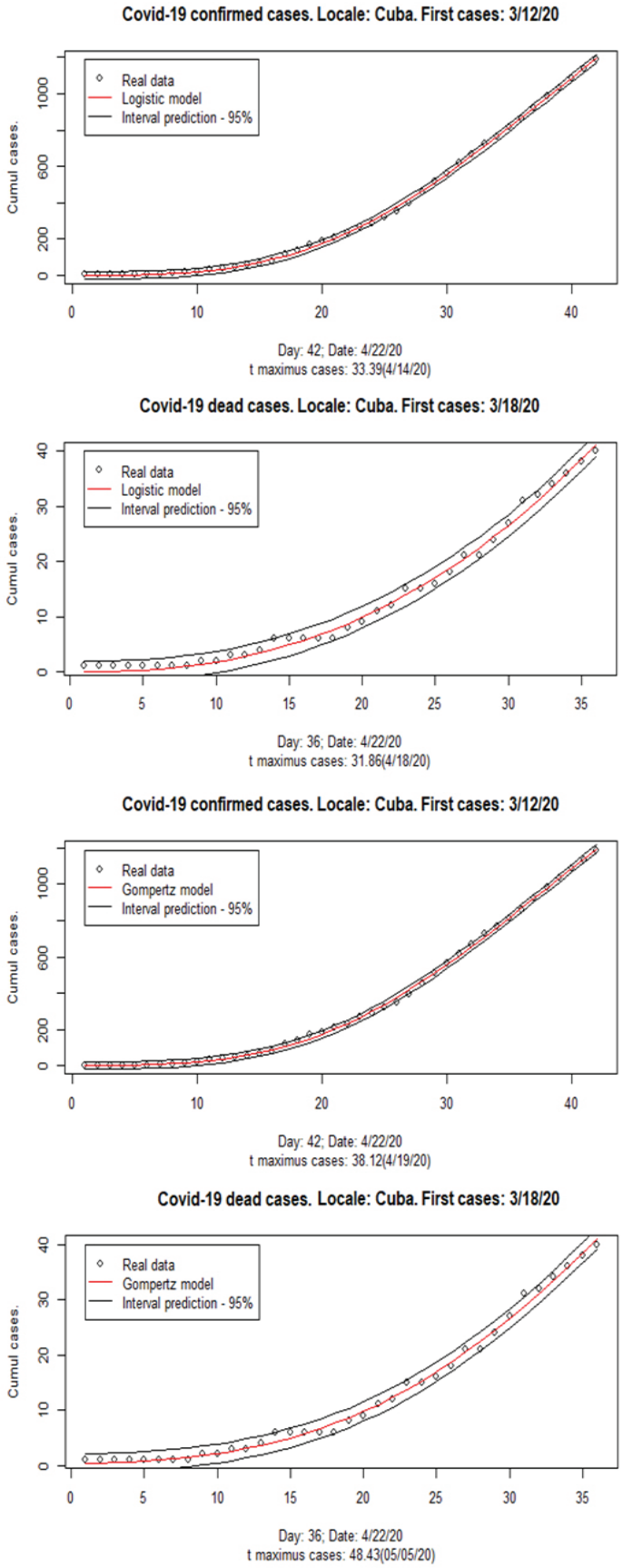


Table 3: Comparison of models fit with real data for deaths from COVID-19 in Italy and Spain

Estimate of deaths		Coefficients (model)	R^2	RMSE	Maximum cases (forecasted)	Peak (forecasted)	Real peak
Italy	Logistic Model	K = 25,223 r = 0.14 b = 5.58	>0.99	500.3	25,223 (cumulative)	April 1	March 27 (919 cases recorded)
	Gompertz Model	K = 29,826 r = 0.07 b = 15.11	>0.99	169.5	29,826 (cumulative)	March 30	
Spain	Logistic Model	K = 21,494 r = 0.17 b = 5.60	>0.99	454.5	21,494 (cumulative)	April 4	April 2 (961 cases recorded)
	Gompertz Model	K = 24,356 r = 0.10 b = 16.97	>0.99	137.3	24,356 (cumulative)	April 1	

RMSE: Root Mean Square Error K: maximum number of individuals a population can sustain
r: instantaneous rate of increase b: a measure of the displacement of the abscissa axis

Table 4: Fitted models and their statistical significance for reported data of confirmed cases and deaths due to COVID-19 in Cuba. Forecast of peak days of confirmed cases and deaths and cumulative total

Models and forecasts for Cuba	Confirmed cases		Deaths	
	Logistic Model	Gompertz Model	Logistic Model	Gompertz Model
Model parameters and p-value	K = 1482 <0.001 r = 0.15 <0.001 b = 5.09 <0.001	K = 2678 <0.001 r = 0.055 <0.001 b = 8.27 <0.001	K = 63 <0.001 r = 0.146 < 0.001 b = 4.66 <0.001	K = 211 <0.001 r = 0.039 <0.001 b = 6.77 <0.001
Quality of fit	R^2 = 0.999 RMSE = 14.43	R^2 = 0.999 RMSE = 9.96	R^2 = 0.997 RMSE = 0.75	R^2 = 0.996 RMSE = 0.83
Neill goodness-of-fit test F (p-value)	1.69 (0.199)	1.28 (0.290)	1.86 (0.189)	1.93 (0.174)
Forecast peak (day)	April 14	April 19	April 18	May 5
Total amount forecast	1482	2678	63	211

RMSE: Root Mean Square Error K: maximum number of individuals a population can sustain
r: instantaneous rate of increase b: a measure of the displacement of the abscissa axis

The authors hypothesized that if the models provided good forecasts for Spain and Italy, they would also do so for Cuba. Various authors[16–18,22–24] have used this subjective principle of plausibility and have anticipated goodness-of-fit in territories that had not yet passed the peak of the pandemic, based on adequate fit in other territories that had passed their peaks.

To test this hypothesis, the models were fitted to the distribution of confirmed cases and deaths recorded in Cuba and goodness-of-fit was assessed. Significance testing for the models' coefficients demonstrated their validity. Each of the models passed the Neill goodness-of-fit test, which makes it possible to generalize these models to mathematically describe the dynamics of the pandemic.

CONCLUSIONS

The logistic and Gompertz population growth models used to predict peaks and total numbers of infected cases and deaths due to COVID-19 have been statistically validated with the usual analytical resources, which confirmed the initial hypothesis that these models could be extrapolated and applied in Cuba. This provides two additional options that are methodologically viable to model epidemiological processes over time, especially for short-term forecasting and when the aim is not to include the influence of a large number of external factors.

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Antimicrobial Resistance in Bacteria Isolated from Foods in Cuba

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ABSTRACT

INTRODUCTION Antimicrobial drug resistance constitutes a health risk of increasing concern worldwide. One of the most common avenues for the acquisition of clinically-relevant antimicrobial resistance can be traced back to the food supply, where resistance is acquired through the ingestion of antimicrobial resistant microorganisms present in food. Antimicrobial resistance constitutes a health risk, leading to production losses and negative consequences for livelihood and food safety.

OBJECTIVE Determine whether resistant bacteria are present in foods in Cuba.

METHODS A descriptive observational study was conducted in the Microbiology Laboratory of Cuba's National Institute of Hygiene, Epidemiology and Microbiology from September 2004 through December 2018. Researchers analyzed 1178 bacterial isolates from food samples. The isolates were identified as *Escherichia coli, Salmonella, Vibrio cholerae* and coagulase-positive *Staphylococcus*. The antimicrobial susceptibility study was performed using the Bauer-Kirby disk diffusion method, following procedures outlined by the Clinical and Laboratory Standards Institute. The data were analyzed using WHONET version 5.6.

RESULTS Of the total isolates, 62.1% were resistant to at least one antibiotic. Within each group, >50% of isolates showed some type of resistance. *E. coli* and *V. cholerae* exceeded 50% resistance to tetracycline and ampicillin, respectively. *Staphylococcus* showed the highest resistance to penicillin, and *Salmonella* to tetracycline, nalidixic acid and ampicillin. The highest percentages of non-susceptible microorganisms were identified in meats and meat products.

CONCLUSIONS These results serve as an alert to the dangers of acquiring antibiotic-resistant bacteria from food and demonstrate the need to establish a surveillance system and institute measures bacterial control in food products.

KEYWORDS Microbial drug resistance, bacteria, food, foodborne disease, Cuba

INTRODUCTION

Antimicrobial resistance (AMR) is a health risk worldwide, leading to production losses and negative effects on livelihood, food safety and the economy,[1] including in Cuba. Statistics from the national program for prevention and control of healthcare-associated infections show an increase in resistance to the most commonly used hospital antibiotics in the last few years, as well as longer hospitalizations and higher spending on these infections.[2] The public health sector is acting to promote the rational prescription and use of antimicrobials, and is conducting various susceptibility studies on clinically-obtained isolates.[3] However, there are few reports on antimicrobial-resistant foodborne bacteria.

Quantitatively, foodborne AMR is the most common route for the spread of antibiotic-resistant bacteria. The presence of these microorganisms in the food chain, the environment and water can lead to their appearance in the human intestinal microbiome, turning it into a major reservoir for resistant genes in the body. It also increases the risk of their dissemination among commensal bacteria and pathogens that cause intra- and extraintestinal infections.[4]

Among the most clinically important foodborne pathogenic bacteria in AMR are strains of *Salmonella* and *E. coli,* which carry extended-spectrum beta lactamases, fluoroquinolone-resistant *Campylobacter* and *Salmonella*, and methicillin-resistant *Staphylococcus aureus*.[5] However, commensal bacteria also found in foods play a key role in AMR evolution and spread. They predominate in the environment and show greater genetic diversity and host variety in nature, which makes them a potential indicator for AMR. Thus, studying these agents can provide early warning of emerging AMR.[6]

IMPORTANCE This paper highlights the importance of antimicrobial resistance surveillance in foods commonly consumed in Cuba.

WHO suggests regular, periodic surveillance to address the problem of AMR, with permanent monitoring of changes in its prevalence in humans, animals, foods and the environment.[7] Clearly, it is important to discover foodborne AMR as quickly as possible. This includes studying risks by identifying dangers: antimicrobial-resistant microorganisms, the antimicrobials to which they are resistant, and the food products in which this resistance is found. Cuba has no program dedicated to ongoing surveillance of this problem. For these reasons, this study was performed with the aim of assessing antimicrobial resistance in clinically relevant bacteria isolated from foods in Cuba.

METHODS

A descriptive observational study was conducted from September 2004 through December 2018 on 1178 isolates identified in foods (381 isolates of *E. coli*, 402 of *Salmonella*, 113 of *V. cholerae* and 282 of coagulase-positive *Staphylococcus*). The isolates were performed at the Provincial Hygiene, Epidemiology and Microbiology Centers in 13 Cuban provinces and in the Microbiology Laboratory of the National Hygiene, Epidemiology and Microbiology Institute (INHEM) in Havana, following current standards in Cuba.[8–11]

The microorganisms were identified in a variety of 146 foods subject to microbiological surveillance in the study of foodborne disease outbreaks and health inspections of foods before sale. These were categorized in 14 groups, according to Cuban microbiological criteria standard NC 585, 2017.[12] The food types were:

- Ready-to-eat foods
- Beverages (juices and soft drinks)
- Broths, soups and creams
- Meats and meat products—processed fresh meats sold in pieces and fresh ground meats (poultry, pork, beef); semiprocessed meat products: protein mix, hamburger, sausages, chorizos; processed meat products: mortadella, bologna, smoked products
- Cocao derivatives
- Spices and condiments
- Nutritional supplements of vegetable origin
- Fruits and vegetables
- Eggs and derivatives—prepared eggs: omelets, scrambled eggs and other products; pastry products and egg-based creams
- Milk and dairy products—pasteurized liquid milk, ice cream, cheeses, yogurt
- Fish, seafood and fish products
- Grain-based products

Antimicrobial susceptibility was determined using the Bauer-Kirby disk diffusion method, strictly adhering to procedures established for this purpose by the Clinical and Laboratory Standards Institute (CLSI).[13] The antimicrobial disks (CPM-SCIENTIFICA, Italy) contained the following loads:

Antimicrobial disk	Antibiotic load (µg)
Nalidixic acid	30
Amikacin	30
Ampicillin	10
Azithromycin	15
Carbenicillin	100
Cefotaxime	30
Ceftazidime	30
Ceftriaxone	30
Ciprofloxacin	5
Chloramphenicol	30
Doxycycline	30
Erythromycin	15
Streptomycin	10
Gentamicin	10
Kanamycin	30
Oxacillin	5
Penicillin	10 IU
Sulfamethoxazole/trimethoprim	1.25/23.75
Tetracycline	30

IU: International Units

As part of quality control, *Staphylococcus aureus* ATCC 25923, *E. coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 reference strains were used.

Antimicrobials were selected according to bacterial species. For *Salmonella* and *E. coli:* nalidixic acid, amikacin, ampicillin, carbenicillin, cefotaxime, ceftriaxone, ceftazidime, ciprofloxacin, chloramphenicol, streptomycin, gentamicin, kanamycin, sulfamethoxazole/trimethoprim and tetracycline were chosen. For *Staphylococcus:* amikacin, cefotaxime, ceftriaxone, chloramphenicol, ciprofloxacin, erythromycin, gentamicin, kanamycin, penicillin, oxacillin, sulfamethoxazole/trimethoprim and tetracycline were selected. For *V. cholerae*: ampicillin, ciprofloxacin, sulfamethoxazole/trimethoprim, tetracycline, doxycycline and azithromycin were chosen.

Extended-spectrum beta lactamase (ESβL) detection was performed on 97 *E. coli* isolates from fresh meats. Isolates with inhibition halos equal to or less than the following diameters were classified as presumptive carriers: cefotaxime ≤27 mm, ceftazidime ≤22 mm, and ceftriaxone ≤25 mm. The disk combination method (CLSI, 2015) and ETEST strips (BioMérieux, France) containing the following combinations were used for confirmation: ceftazidime (0.5–32 µg/mL) and ceftazidime/clavulanic acid (0.064–4 µg/mL) (Liofichem, Italy). Results were interpreted following the manufacturer's criteria. *E. coli* ATCC 25922 strains were tested as a negative control, with ESβL *Klebsiella pneumoniae* ATCC 700603 strains tested as a positive control.

Results were analyzed using a database created in WHONET version 5.6, a WHO digital platform for surveillance of antimicrobial resistance and infection control.[14] The antibiogram interpretation criteria cutoff points were updated according to CLSI standards. Susceptibility was analyzed by isolate source, for which contingency tables were established, and the chi-square test was applied with a significance level of 0.05%. The data were processed using the EPIDAT program (EpiData Association, Denmark) for epidemiological analysis of tabular data, version 3.0 of 2004.[15]

Results of the *in vitro* susceptibility tests were expressed as absolute frequencies and percentages. Isolates with full growth around the antibiotic disk or those in which growth inhibition did not reach the diameter established for the CLSI susceptibility criterion (reduced susceptibility) were considered resistant. Otherwise, they were considered sensitive to the antibiotic.

Ethical considerations No clinical assays were performed on persons or animals in this study, and the study was authorized by INHEM's scientific council. This document contains no company, institution or brand names of foods from which the isolates were obtained.

RESULTS

AMR was analyzed according to the microorganisms retrieved from different food types (Table 1). Of all isolates, 62.1% (731/1178) were antibiotic-resistant; of all bacteria studied, AMR was observed in 32.3% (236/731) of *Salmonella* isolates, 30.1% (220/731) of *E. coli*, 29.9% (212/731) of *Staphylococcus* and 8.6% (63/731) of *V. cholerae*. Resistant microorganisms were most often identified in meats and meat products, with *Salmonella* and *E. coli* isolates predominating.

Resistance was detected less frequently in bacteria isolated from milk and dairy products, with *Staphylococcus* and *E. coli* the most common. In egg-based products, *Salmonella* and *Staphylococcus* isolates predominated. A low frequency of isolates was found in all other foods.

V. cholerae was isolated in fruits and vegetables, and in fish, seafood and fishery products, which had the highest percentage of resistant isolates at 69.3%.

Table 1: Antimicrobial resistance of microorganisms according to food type from which they were recovered. INHEM 2004–2018

Food Type	*Escherichia coli*			*Salmonella*			*Staphylococcus*			*Vibrio cholerae*			Total		
	No.	AMR	%[a]	No.	AMR	%[a]	No.	AMR	%[a]	No.	AMR	%[a]	No.	AMR	%[b]
Meats and meat products	215	141	36.7	284	173	45.1	132	70	18.2	0	0	0.0	631	384	52.5
Milk and dairy products	85	35	36.5	4	4	4.2	62	57	59.4	0	0	0.0	151	96	13.1
Eggs and derivatives	27	14	17.7	67	37	46.8	28	28	35.4	0	0	0.0	122	79	10.8
Fish, seafood and fish products	8	5	6.7	16	2	2.7	28	16	21.3	98	52	69.3	150	75	10.3
Ready-to-eat foods	22	20	30.3	29	19	28.8	27	18	27.3	0	0	0.0	69	66	9.0
Fruits and vegetables	5	0	0.0	0	0	0.0	4	4	26.7	15	11	73.3	24	15	2.1
Nutritional supplements	0	0	0.0	1	0	0.0	8	8	100.0	0	0	0.0	9	8	1.1
Beverages (juices and soft drinks)	13	4	100.0	0	0	0.0	0	0	0.0	0	0	0.0	13	4	0.5
Cocao derivatives	1	1	33.3	0	0	0.0	2	2	66.7	0	0	0.0	3	3	0.4
Spices and condiments	0	0	0.0	1	1	100.0	0	0	0.0	0	0	0.0	1	1	0.1
Grain-based products	2	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	2	0	0.0
Broths, soups and cream-based soups	3	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	3	0	0.0
Total %	381	220	30.1	402	236	32.3	282	212	29.0	113	63	8.6	1178	731	100.0

[a] Percentage refers to total number of isolates in category [b] Percentage refers to total number of foods analyzed per microorganism
AMR: Antimicrobial resistance INHEM: National Institute of Hygiene, Epidemiology and Microbiology

Table 2 shows the relation between AMR in *Salmonella, E. coli* and *Staphylococcus* and their isolate sources. *Salmonella* was not associated with any specific food type. The highest percentage of resistant isolates was found in meats and meat products. *E. coli* had a higher proportion of resistant isolates compared to subgroup size in meats and meat products. Additionally, *Staphylococcus* had a higher proportion of resistant isolates found in meat and dairy products.

Table 2: Relation between antibiotic resistance of *Escherichia coli, Salmonella* and *Staphylococcus* and food type from which isolates were recovered (n = 1065). INHEM 2004–2018

Susceptibility	By Isolate Source			p Value
	Escherichia coli (n = 381)			
	Meats and meat products	Milk and dairy products	Other	
Sensitive %[a]	74 (34.4)	50 (58.8)	37 (45.7)	0.0000
Resistant %[a]	141 (65.6)	35 (41.2)	44 (54.3)	
Total %[b]	215 (56.4)	85 (22.3)	81 (21.3)	
X^2 22.7709				
Susceptibility	*Salmonella* (n = 402)			
	Meats and meat products	Eggs and derivatives	Other	
Sensitive %[a]	111 (39.1)	30 (44.8)	25 (49.0)	0.3397
Resistant %[a]	173 (60.9)	37 (55.2)	26 (51.0)	
Total %[b]	284 (70.6)	67 (16.7)	51 (12.7)	
X^2 2.1666				
Susceptibility	*Staphylococcus* (n = 282)			
	Meats and meat products	Milk and dairy products	Other	
Sensitive %[a]	52 (42.6)	5 (8.1)	13 (13.3)	0.0003
Resistant %[a]	70 (57.4)	57 (91.9)	85 (86.7)	
Total %[b]	122 (43.3)	62 (22.0)	98 (34.8)	
X^2 16.7991				

[a] Percentage refers to total number of isolates in category
[b] Percentage refers to total number of foods analyzed per microorganism
INHEM: National Institute of Hygiene, Epidemiology and Microbiology

Resistance by antibiotic type was low overall, except for tetracycline in *E. coli* and ampicillin in *V. cholerae*, for which resistance was over 50% (Table 3). Of the 19 antibiotic agents analyzed (14 for *Salmonella* and *E. coli*, 12 for *Staphylococcus* and 6 for *V. cholerae*) *Salmonella* expressed in vitro resistance to 12, and *E. coli*, to 14. Tetracycline, nalidixic acid and ampicillin showed the highest resistance levels. More than 75% of *Staphylococcus* isolates were resistant, mainly against penicillin, erythromicin and tetracycline, in decreasing order. *V. cholerae* was resistant to three antibiotics, namely tetracycline,

Table 3: Percentage of resistance by antibiotic and microorganism. INHEM 2004–2018

Antibiotic	*Salmonella* n = 236		*E. coli* n = 220		*Staphylococcus* n = 212		*V. cholerae* n = 63	
	No.	%	No.	%	No.	%	No.	%
Tetracycline	140	59.3	91	41.4	44	20.8	3	4.8
Nalidixic acid	70	29.7	102	46.4	-	-	-	-
Ampicillin	55	23.3	117	53.2	-	-	54	85.7
Carbenicillin	31	13.1	27	12.3	-	-	-	-
Ceftriaxone	14	5.9	23	10.5	59	27.8	-	-
Ceftazidime	16	6.8	13	5.9	-	-	-	-
Streptomycin	8	3.4	12	5.5	-	-	-	-
Cefotaxime	7	3.0	13	5.9	0	0	-	-
Sulfamethoxazole/ trimethoprim	4	1.7	40	18.2	0	0	6	9.5
Chloramphenicol	2	0.8	38	17.3	0	0	-	-
Kanamycin	2	0.8	15	6.8	6	2.8	-	-
Ciprofloxacin	2	0.8	19	8.6	8	3.8	0	0
Amikacin	0	0	11	5.0	2	0.9	-	-
Gentamicin	0	0	12	5.5	1	0.5	-	-
Penicillin	-	-	-	-	88	41.5	-	-
Oxacillin	-	-	-	-	43	20.3	-	-
Erythromycin	-	-	-	-	52	24.5	-	-
Azithromycin	-	-	-	-	-	-	0	0
Doxycycline	-	-	-	-	-	-	0	0

INHEM: National Institute of Hygiene, Epidemiology and Microbiology

Table 4: Isolates studied, by microorganism and province where identified. INHEM 2004–2018

Province	*E. coli*		*Salmonella*		*Staphylococcus*		*V. cholerae*		Total	
	No.	%[a]	No.	%[a]	No.	%[a]	No.	%[a]	No.	%[b]
Havana (INHEM)	263	42.4	98	15.8	250	40.3	10	1.6	621	52.7
Pinar del Río	64	82.1	10	12.8	4	5.1	0	0.0	78	6.6
Santiago de Cuba	39	30.0	67	51.5	9	6.9	15	11.5	130	11.0
Las Tunas	10	15.4	49	75.4	6	9.2	0	0.0	65	5.5
Sancti Spíritus	2	16.7	10	83.3	0	0.0	0	0.0	12	1.0
Villa Clara	2	3.0	65	97.0	0	0.0	0	0.0	67	5.7
Granma	1	1.1	6	6.9	0	0.0	80	92.0	87	7.4
Ciego de Ávila	0	0.0	14	51.9	7	25.9	6	22.2	27	2.3
Camagüey	0	0.0	27	96.4	0	0.0	1	3.6	28	2.4
Cienfuegos	0	0.0	4	66.7	2	33.3	0	0.0	6	0.5
Guantánamo	0	0.0	12	92.3	0	0.0	1	7.7	13	1.1
Holguín	0	0.0	21	100.0	0	0.0	0	0.0	21	1.8
Isla de la Juventud*	0	0.0	1	100.0	0	0.0	0	0.0	1	0.1
Matanzas	0	0.0	18	81.8	4	18.2	0	0.0	22	1.9
Total	381	32.3	402	34.1	282	23.9	113	9.6	1178	100.0

[a] Percentage refers to total number of isolates for province, [b] Percentage refers to total number of isolates
INHEM: National Institute of Hygiene, Epidemiology and Microbiology * Special Municipality

ampicillin and sulfamethoxazole/trimethoprim (Table 3). A low percentage (2.8%) of ESβL enzyme was detected in 97 *E. coli* isolates obtained from fresh meats.

Geographical distribution of isolates (Table 4) showed that the highest percentage, 52.7% of the total, was identified in Havana Province at INHEM's laboratory. The percentage of isolates sent from provinces outside Havana was low. The highest percentage came from Santiago de Cuba (11.0%); the rest were less than 10.0%.

DISCUSSION

More than half of the bacterial isolates recovered from foods were resistant to at least one of the drugs tested. The most clinically important isolates were *E. coli* and *Salmonella,* since they often cause gastrointestinal disease or extraintestinal infections requiring treatment. The least effective antibiotics administered *in vitro* were tetracycline, ampicillin, nalidixic acid and penicillin, as also found in international studies.[16–20]

For WHO-classified antibiotics,[18] specifically those appropriate for only limited use in humans (including ciprofloxacin, cefotaxime, ceftriaxone and ceftazidime), resistance was low and observed more often in *E. coli* and *Staphylococcus.* The international literature reports resistance percentages higher than those in this study.[19–21] The foods that most often contained resistant isolates were meats and meat products; for *Salmonella,* this result is consistent with those of other researchers, which show that these products are among the main sources of resistant bacteria in this genus.[22,23]

The 173 *Salmonella* isolates from meats and meat products were obtained from 31 different foods. Hamburger showed the highest number of resistant isolates. Among fresh meats, resistance was most often found in poultry, where isolates from ground turkey were predominant, followed by those from ground chicken and mechanically deboned meat. These results agree with international reports, which found that in ground meats, the *Salmonella* detected often presents with high virulence and high levels of AMR.[24,25] Since most poultry meats in Cuba are imported,[26] this could be considered a route for spreading resistance, in addition to antibiotics found in imported meat that are not used in domestic animal production, such as cefotaxime, ceftriaxone and ceftazidime.

Resistant *E. coli* isolates were most often found in pork, mortadella and smoked pork loin. Three isolates carrying ESβL were found in imported poultry meat and beef, and in domestically produced pork, at a lower percentage than has been reported in other countries.[27,28]

Globally, antimicrobial susceptibility of *E. coli* is studied in different foods depending on geographic region. In the European Union and the United States, emphasis is on meats and antibiotics such as cephalosporins and fluoroquinolones.[29,30] In Asia and Latin America, there are more studies on ready-to-eat foods.[31,32] This could be due to greater availability of industrially processed ready-to-eat foods in developed countries, while in developing nations there are more prepared foods sold by small-scale manufacturers who generally do not monitor product preparation, potentially allowing bacterial contaminants to survive and multiply. In this study, which analyzed meats and ready-to-eat foods, antibiotic resistance was frequent regardless of food type.

Currently, AMR in commensal bacteria such as *E. coli* is cause for growing concern because resistant genes can be replaced with bacteria that are pathogenic to humans. The scientific literature has demonstrated transfer of multidrug resistance through *E. coli* plasmids to other enterobacteria such as *Salmonella*.[33]

Most antibiotic-resistant *Staphylococcus* isolates were identified in meats and meat products such as sausages, ground meats and hamburger. In milk and dairy products, most isolates were found in cheese, mainly artisanal cheeses. This last food group was shown to be associated with resistant isolates. Other countries report varying percentages of AMR to at least one of the antibiotics tested, among which *S. aureus* was the most prevalent in meats and cheeses.[21,34]

It should be noted that foodborne staphylococcal intoxication does not require antibiotic treatment, and there is no evidence that consuming foods contaminated with this bacteria is associated with infection in humans.[35] However, there is now special interest in antimicrobial susceptibility studies because of the possible transfer of resistant genes between microorganisms, and thus from the environment to humans.[7]

V. cholerae is a species endemic to aquatic environments, and thus may be an indicator of antibiotic resistance in bacteria found in these ecosystems. In this study, it was mainly found in fish, seafood and other fish products. Its expressed resistance was low except to ampicillin, to which resistance was seen in >50% of isolates. No resistance was found to ciprofloxacin, azithromycin

or doxycycline, which are often used as first-line treatments for infections of toxigenic agents of this species. For *V. cholerae*, the international literature reports AMR usually higher than that found in this study.[36,37]

The highest percentage of isolates analyzed came from foods inspected at INHEM as part of the institution's responsibilities in sanitary registration including imported products and those domestically produced by various Cuban companies. Foods that do not meet the bacterial limits in the standard[11] are not approved for sale. However, there are currently no trade regulations that address antibacterial resistance, which is why studies focusing on risk are needed to accurately determine the scope of the problem.[38]

We observed an unequal distribution in both the number and geographic origin of isolates received from laboratories in other provinces participating in the study, as well as in numbers of isolates of each bacteria type received. There were low percentages of *E. coli*, *Staphylococcus* and *V. cholerae*, which made it impossible to analyze antibiotic resistance for each region of the country. This would be possible if a national antimicrobial resistance surveillance system were established to obtain standardized information that would allow comparisons by region and over time.

One of the study's main limitations was the unequal numbers of bacterial isolates sent from each province. The study was based on the isolates received, which did not allow nationally based analysis of a resistant bacterial load for each food. In addition, the information presented was obtained more than a year ago, which makes it invalid for immediate surveillance purposes, but does not affect its usefulness as a resource for illustrating a problem that demands surveillance and control. Despite these limitations, a broad range of antibiotics were analyzed, including most classes used in human and veterinary treatment, and the number of isolates studied for each bacterial genus was sufficient for making preliminary estimates of AMR prevalence in each case, although without claims as to their representativity.

CONCLUSIONS

Resistant phenotypes were identified in more than half the bacteria isolated from foods, with a higher percentage found in animal products such as meat, dairy, eggs and foods made from these ingredients. Low percentages of AMR were found for antibiotics classified as critical for human use. These results may serve as an alert to the dangers of acquiring foodborne antibiotic-resistant bacteria and demonstrate the need to establish a surveillance system and institute related control in Cuba.

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Prognostic Scale to Stratify Risk of Intrahospital Death in Patients with Acute Myocardial Infarction with ST-Segment Elevation

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ABSTRACT

INTRODUCTION The scales available to predict death and complications after acute coronary syndrome include angiographic studies and serum biomarkers that are not within reach of services with limited resources. Such services need specific and sensitive instruments to evaluate risk using accessible resources and information.

OBJECTIVE Develop a scale to estimate and stratify the risk of intrahospital death in patients with acute ST-segment elevation myocardial infarction.

METHODS An analytical observational study was conducted in a universe of 769 patients with acute ST-segment elevation myocardial infarction who were admitted consecutively to the Camilo Cienfuegos Provincial Hospital in Sancti Spíritus Province, Cuba, from January 2013 to March 2018. The final study cohort included 667 patients, excluding 102 due to branch blocks, atrial fibrillation, drugs that prolong the QT interval, low life expectancy or history of myocardial infarction. The demographic variables of age, sex, skin color, classic cardiovascular risk factors, blood pressure, heart rate, blood glucose level, in addition to duration and dispersion of the QT interval with and without correction, left ventricular ejection fraction, and glomerular filtration rate were included in the analysis. Patients were categorized according to the Killip-Kimball Classification for degree of heart failure. A risk scale was constructed, the predictive ability of which was evaluated using the detectability index associated with an receiver-operator curve.

RESULTS Seventy-seven patients died (11.5%). Mean blood glucose levels were higher among the deceased, while their systolic and diastolic blood pressure, left ventricular ejection fraction, and glomerular filtration rate were lower than those participants discharged alive. Relevant variables included in the scale were systolic blood pressure, Killip-Kimball class, cardiorespiratory arrest, glomerular filtration rate, corrected QT interval dispersion, left ventricular ejection fraction, and blood glucose levels. The variable with the best predictive ability was cardiorespiratory arrest, followed by a blood glucose level higher than 11.1 mmol/L. The scale demonstrated a great predictive ability with a detectability index of 0.92.

CONCLUSIONS The numeric scale we designed estimates and stratifies risk of death during hospitalization for patients with ST-segment elevation myocardial infarction and has good metric properties for predictive ability and calibration.

KEYWORDS ST-segment elevation myocardial infarction, mortality, risk assessment, Cuba

INTRODUCTION

Cardiovascular disease is a global health problem. According to WHO, 17.8 million people worldwide died from cardiovascular disease in 2016, with 52.8% of these deaths attributable to ischemic heart disease.[1] Ischemic cardiopathy is the cardiovascular disease with the highest morbidity and mortality, and acute myocardial infarction (AMI) is the most serious and causes the most deaths.[2,3] According to a report from the American Heart Association, every 40 seconds, a US person suffers an AMI, although mortality from this cause decreased by 14.6% between 2006 and 2016 in the United States; however, approximately 550,000 first episodes and 200,000 recurrent episodes of acute myocardial infarction occur annually.[4]

In Europe, national records of countries in the European Society of Cardiology reveal intrahospital mortality at 4%–12%, while annual AMI mortality is approximately 10%.[2]

Eighty percent of deaths from AMI occur in low- and middle-income countries, where there is scarcity of therapeutic resources that meet international treatment guidelines.[5] The ability to predict the risks of complications and death with a scale that does not require angiography or serum biomarkers is an attractive prospect for these countries.

IMPORTANCE

The scale designed permits estimation and stratification of intrahospital death risk for patients with ST-segment elevation myocardial infarction, using conventional clinical tools without the need to obtain angiographic studies or serum biomarkers in cardiac care units with limited resources.

In Cuba, the mortality rate from heart disease in 2018 was 228.6 deaths per 100,000 population, with 63.3% of these deaths due to ischemic heart disease. For AMI, the mortality rate was 65.3 deaths per 100,000 population, of which 45.2% of deaths were due to ischemic heart disease. In Sancti Spíritus Province, in the center of the country, heart disease is also a health issue with a crude death rate of 237.9 deaths per 100,000 population and an age-adjusted death rate of 109.7 deaths per 100,000 population.[6]

Ischemic heart disease can be classified as an acute coronary syndrome, with or without ST-segment elevation, depending on the recording of at least two contiguous leads of the surface electrocardiogram (ECG).[5] In acute ST-segment elevation myocardial infarction (STEMI), risk of complications and death is high despite advances in diagnosis and treatment of the condition. Prognosis for STEMI patients is related to the probability of developing short- or long-term complications and depends more on the state of the patient at the time of admission than on prior coronary risk factors.[2,5]

Efforts to develop models to quantify risk of complications or death for a patient with AMI using a scoring system started in the early 1950s,[7] and expanded as specialized coronary care units began to appear. In recent years, prediction models or

algorithms have been developed that use serum biomarkers and clinical, electrocardiographic and angiographic variables to evaluate risk with greater precision and accuracy.[8] Despite the wide variety of proposed models[9,10] and the simplicity of some of them,[11,12] their use in clinical practice is limited, as they are highly dependent on availability of resources, primarily those relying on serum biomarkers.

High-income countries implement international treatment guidelines for AMI treatment[2,3] but these guidelines have limited applicability in low- and middle-income countries due to difficulty accessing more modern therapeutic resources. A 2014 study by Shimony[13] revealed that patients in low- and middle-income countries are less likely to receive treatment with percutaneous transluminal coronary angioplasty (PTCA) than those in high-income countries (4.9% compared to 45.6%), and that thrombolytic therapy was more common in low- and middle-income countries (72.5% compared to 38.9%). These disparities in AMI treatment are reflected in mortality rates that are higher in low- and middle-income countries.[5] A study evaluating regional differences in AMI mortality at two years showed that the highest rates were reported in Latin America (7.4%) and the lowest in northern Europe (2.5%).[14] The differences in therapeutic options for these patients force low- and middle-income countries to look for risk stratification alternatives that allow them to decrease mortality while optimizing resources.

Risk estimation and stratification usually rely on analytical resources that combine the effects of different variables.[15] All risk scores designed thus far have their strengths and weaknesses, and their application is limited to the populations that served as the basis for their construction. The Global Registry of Acute Coronary Events (GRACE)[16] is the best-studied and validated instrument in the world,[17] but it contains elements that are not accessible for many low- and middle-income countries, such as measuring serum troponins.[7] The Thrombolysis in Myocardial Infarction (TIMI) Risk Score is an easy model to apply, but it was designed in the course of clinical trials, which has led its usefulness in daily practice to be called into question.[7,12] A meta-analysis that included 42 validated studies on 31,625 patients recognized TIMI and GRACE as the only duly validated scores. The TIMI score has lower predictive ability (C = 0.77) than the GRACE (C = 0.82).[17]

Advances in AMI treatment allow providers to offer patients multiple therapeutic options depending on the severity of the disease and its prognosis. For this reason, there is still interest in determining the risks of complications and mortality with precision and accuracy. Considering the limitations of current algorithms and their application in coronary care units with limited resources, sensitive prognostic models must be developed to concentrate efforts and expenses on higher-risk patients, thereby improving risk-benefit and cost-effectiveness indicators.

The hospital where this research was conducted does not have the resources needed to perform modern reperfusion techniques, such as PTCA and use of fibrin-specific thrombolytic agents.[2] This further supports the need to more accurately estimate and stratify the initial risk of complications and death in STEMI patients in the days following AMI.

The objective of this study was to create a scale to estimate and stratify risk of intrahospital mortality for STEMI patients.

METHODS

Design and population An observational analytical study was conducted on STEMI patients admitted consecutively to the coronary care unit at the Camilo Cienfuegos Provincial Hospital (HPCC) in Sancti Spíritus Province, Cuba, between January 1, 2013 and March 31, 2018. A total of 769 patients were registered, with 667 included and 102 excluded for the following reasons: 31 due to left bundle branch block of His, 19 due to prior atrial fibrillation, and 14 with medications that prolong the QT interval. These are all conditions that may make it difficult to take electrocardiographic measurements. Patients with conditions unrelated to the current ischemic event that considerably worsen prognosis were excluded from the study, including 23 patients with a history of myocardial infarction. Another 15 patients who were excluded due to a life expectancy of less than one year from non-cardiac conditions. Average age was 67.4 years (SD = 12.8). Of all participating patients, 441 (66.1%) were men and 226 (33.9%) were women.

In the absence of left ventricular hypertrophy and left bundle branch block, STEMI requires ≥2 mm of ST elevation (measured at J point) in two contiguous ECG leads in men ≥40 years old according to the ACC/AHA definition. A total of ≥2.5 mm is required in men <40 years old, and only 1.5 mm required in women of any age in the V_2– V_3 leads, or ≥1.0 mm in other leads.[2]

Study variables Age, sex, and skin color (white, brown, or black), were recorded, the latter variable determined by observers trained in this type of study. The following were considered cardiovascular risk factors: arterial hypertension (>140/90 mmHg), prior ischemic heart disease, hypercholesterolemia (cholesterol >6.71 mmol/L, according to established reference values), tobacco use, obesity (body mass index >30 kg/m^2), history of diabetes mellitus and history of chronic obstructive pulmonary disease (COPD).[18] Systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) upon admission were considered clinical variables.

The degree of acute heart failure was evaluated using the Killip-Kimball classification[19] based on the following criteria:

Class I: No heart failure (no clinical signs of cardiac decompensation)
Class II: Heart failure: (rales in the lower half of lung fields, S3 gallop, and pulmonary venous hypertension)
Class III: Severe heart failure (frank pulmonary edema with crackling rales in all lung fields)
Class IV: Cardiogenic shock: (hypotension defined as systolic blood pressure <90 mmHg and evidence of peripheral vasoconstriction, such as oliguria, cyanosis and diaphoresis)

Values for blood glucose, leukocytes, creatinine, uric acid and total cholesterol were determined. Blood was drawn from the antecubital vein within 24 hours of the patient's admission and was processed using a Hitachi High-Technologies Corporation Cobas C311 Analyzer (Tokyo, Japan).

When possible, pharmacological thrombolysis was performed as a reperfusion procedure with 1,500,000 IU of Heberkinasa (recombinant streptokinase, Centro de Ingeniería Genética y Biotecnología, Cuba) administered intravenously.[20] This procedure was not performed on 307 patients for the following reasons: 127 (41.4%) due to long ischemic time (lapse from symptom onset to hospital arrival) >12 hours; 82 (26.7%) without precise initial diagnosis of AMI; 37 (12.1%) in cardiogenic shock; 21 (6.8%) with hemorrhagic stroke; 14 (4.6%) in prolonged cardiac arrest; 11 (3.6%) with known hemorrhagic disorders; 9 (2.9%) reporting a transient ischemic attack in the previous 6 months; and 6 (2.0%) with a history of gastrointestinal hemorrhaging in the last month.

The infarction was localized via ECG performed on admission and classified according to the Bayés de Luna criteria (extensive anterior, mid-anterior, apical-anterior, septal, inferior, infero-lateral, and lateral).[21] Among the complications studied were newly detected atrial fibrillation confirmed via surface ECG upon admission, high-grade and grade III atrioventricular blockage, recurring infarction (when signs and symptoms of acute coronary failure were repeated during admission after the first infarction)[22] and death.

The left ventricular ejection fraction (LVEF) was estimated using the Simpson biplane method[23] using a transthoracic echocardiogram with Aloka Alpha 5 equipment (Tokyo, Japan). The echocardiogram was performed when patients were hemodynamically stable with no signs of arterial hypotension, extreme bradycardia or arrhythmias.

Renal glomerular filtration rate (GFR) was calculated with the Cockcroft-Gault formula[24] using the obtained creatinine values.

GFR [mL/min] = (140 - age [years]) x weight [kg] / Serum creatinine [mmol/L] x 0.81

For women, the expression above is multiplied by 0.85.

Electrocardiogram variables A 12-lead ECG was performed upon admission, before thrombolysis, and was repeated at 90 minutes. Electrocardiographic variables were taken from the first ECG and with patients who underwent thrombolysis, reperfusion signs were analyzed from the 90-minute ECG. ECGs were performed at a sweep speed of 25 mm/s with standardization set at 10 mm/mV, using a Cardiocid BB electrocardiograghy (Central Institute for Digital Research, Cuba)[25] with a bandpass filter restricting spectrum frequencies to 0.05–150 Hz and a comb filter for electrical hum at 60 Hz. Two observers used a magnifying glass to manually and independently measure the following parameters in all ECG leads:

QT interval (QTi): time in milliseconds from the start of QRS complex to the end of the T wave, defined as the point of ventricular repolarization of the T wave to the isoelectric line or the nadir between the T wave and the U wave if present.[26] This was measured in all the leads and the average calculated. Corrected QTi (QTc), estimated using the Bazett's formula.[27] QT dispersion (QTd): QTi measured in the 12 ECG leads, calculating difference between maximum and minimum values. Rate-corrected QTd (QTcd): QTi measured in the 12 ECG leads corrected with Bazett's formula,[27] the difference calculated between maximum and minimum values.
ST elevation >1mV: Measured in all ECG leads in which ST elevation is observed from the baseline to the J point, and the TP segment is considered more isoelectric.
ST depression >1mV: Measured in all ECG leads in which the ST depression is observed from the baseline to the point of greatest ST-segment depression and the TP segment is considered more isodiphasic.
ST elevation in the aVR lead: ST-segment elevation is recorded at ≥1mm in this lead.

Data collection, processing and management Cardiologists performed initial patient evaluations and clinical followup. The hospital stay lasted five to seven days. Data was collected via hospital registration forms for the variables being studied.

A database was created using the SPSS statistical package version 21.0 for Windows (IBM). Continuous data were summarized with mean (m) and standard deviations (SD). For categorical data, absolute numbers and percentages were used. These descriptive statistics were calculated for both the living and deceased patients.

The heuristic for the creation of the scale is based on application of a classification model (classification tree) and a prediction model (binary logistic regression), the results of which were used to select the set of variables for later use in creating the scale, along with a criterion of parsimony to avoid information redundancy. The tree would provide evidence for choosing the optimal intercepts for each variable, and the regression model would be used to provide quantitative approximations the appropriate weights.

The number of categories (2 for cardiac arrest and 4 for the other variables) and the values on the scale were determined and assigned considering the criteria from the literature.[2,3,5,28,29] Categories were assigned between 0 and 3, except for cardiac arrest, which, due to its severity, was categorized as 0 (no) or 3 (yes). These categories and their significance are summarized below:

Cardiac arrest: 0, no; 3, yes
Blood glucose level: 0, ≤6.1 mmol/L; 1, 6.2–7.7 mmol/L; 2, 7.8–11.1 mmol/L; 3, >11.1 mmol/L
SBP: 0, >100 mmHg; 1, 90–100 mmHg; 2, 60–89 mmHg; 3, <60 mmHg
GFR: 0, ≥90 mL/min; 1, 60–89 mL/min; 2, 30–59 mL/min; 3, <30 mL/min
QTcd: 0, <40 ms; 1, 40–59 ms; 2, 60–79 ms; 3, ≥80 ms
Killip-Kimball class: 0, Class I; 3, Class IV
LVEF: 0, ≥55%; 1, 45–54%; 2, 30–44%; 3, <30%

The adjusted odds ratios (OR) were chosen as weights for the scale categories, rounding the results of the binary logistic regression model to the nearest whole number (except for the Killip-Kimball class which is rounded to the next highest whole number). Thus, the ORs are as follows: of QTcd = 2.18 ≈ 2; of GFR = 1.87 ≈ 2; of cardiac arrest = 3.17 ≈ 3; of SBP = 1.65 ≈ 2; of blood glucose level = 2.62 ≈ 3; of LVEF = 1.92 ≈ 2 and of Killip-Kimball class = 1.27 ≈ 2. The total score was obtained as a scalar product of the values of the variables, organized by their

weights. The result is a scale we named EERIAM-HCC (in Spanish 'Escala de Estratificación de Riesgo para el Infarto Agudo del Miocardio del Hospital Camilo Cienfuegos'), the Camilo Cienfuegos Hospital's risk stratification scale for the AMI. It uses values between 0 (for a patient in the most favorable condition for all variables) and 48 (for a patient in the most unfavorable condition). After calculating their 10th, 25th, 50th, 75th, and 90th percentiles, this scale was then transformed into an ordinal scale with four levels:

Low risk: <25th percentile
Moderate risk: 25th–74th percentiles
High risk: 75th–89th percentiles
Extreme risk: ≥90th percentile

The discriminatory power of the EERIAM-HCC scale for intrahospital mortality is estimated using the receiver-operator curve (ROC) using estimates and the 95% confidence interval (CI) area under the curve. Calibration (the relationship between the observed and expected risk) was evaluated using the Hosmer-Lemeshow chi-square goodness-of-fit test. Traditionally, a value of p >0.05 associated with this test suggests an acceptable calibration of the model.

Ethics The study was approved by the hospital's Research Ethics Committee. The design respected the principles of the Declaration of Helsinki,[30] the Norms of the Council of International Organizations of Medical Sciences (WHO-CIOMS),[31] and the principles of good clinical practices. Each patient received a description of the research, including its risks and benefits. Written informed consent was obtained from patients, or from an immediate family member when patients were in extremely critical condition or had lost consciousness. The study design did not include manipulation of variables and followed the protocol established at the hospital for AMI treatment. The tests and interventions were conducted by qualified personnel, with the necessary care taken to minimize risks in accordance with good clinical practice guidelines. Selection of laboratory methods followed the principles of maximum beneficence and non-maleficence in accordance with good laboratory practice guidelines.

Data were encrypted and names were not included in the databases, nor was any other information that could be used to identify participating patients, in order to respect their privacy and confidentiality.

RESULTS

Case fatality was 11.5% with 77 deceased patients, of which 49 (63.6%) were men. The average age was similar in both groups, as was distribution by sex (Table 1).

Results (Table 1) that distinguish the deceased patients from those who survived were notably higher values for the duration and dispersion of measured and corrected QTi, of the QRS complex and of blood glucose levels, as well as notably lower values of GFR and LVEF (Table 1).

Also notable are the differences between the two groups in frequency of cardiac arrest, atrial fibrillation, infarction

Table 1: Baseline characteristics of patients included in the study

Variables	Deaths 77 (11.5%)	Alive 590 (88.5%)
Demographic variables		
Age	68.9 (SD = 11.9)	67.2 (SD = 12.9)
Female	28 (36.4%)	198 (33.6%)
Male	49 (63.6%)	392 (66.4%)
White skin color	55 (71.4%)	437 (74.1%)
Brown skin color	14 (18.2%)	102 (17.3%)
Black skin color	8 (10.4%)	51 (8.6%)
Risk factors		
Arterial hypertension	60 (77.9%)	469 (79.5%)
Diabetes mellitus	35 (45.5%)	165 (28.5%)
Hypercholesterolemia	13 (16.9%)	83 (14.1%)
Tobacco use	36 (46.8%)	344 (58.3%)
Prior ischemic cardiomyopathy	39 (50.6%)	258 (43.7%)
Obesity	18 (23.4%)	165 (28.0%)
COPD	16 (20.8%)	138 (23.4%)
Clinical variables on admission		
Heart rate (beats/min)	86.8 (SD = 24.5)	80.8 (SD = 24.3)
Systolic blood pressure (mmHg)	88.5 (SD = 33.1)	116.2 (SD = 38.7)
Diastolic blood pressure (mmHg)	51.7 (SD = 23.2)	69.7 (SD = 24.8)
Topography of infarction		
Apical-anterior	15 (19.5%)	61 (10.3%)
Extensive anterior	26 (33.8%)	76 (12.9%)
Mid-anterior	14 (18.2%)	119 (20.2%)
Inferior	12 (15.6%)	265 (44.9%)
Inferior plus right ventricle	2 (2.6%)	11 (1.9%)
Infero-lateral	3 (3.9%)	38 (6.4%)
Lateral	5 (6.5%)	16 (2.7%)
Septal	0 (0.0 %)	4 (0.7%)
Electrocardiogram variables		
Duration of measured QTi (ms)	434.7 (SD = 51.0)	397.4 (SD = 50.6)
Duration of corrected QTi (ms)	510.1 (SD = 90.1)	450.8 (SD = 85.5)
Dispersion of measured QTi (ms)	77.8 (SD = 19.9)	56.2 (SD = 25.5)
Dispersion of corrected QTi (ms)	91.4 (SD = 27.3)	63.9 (SD = 30.9)
Duration of QRS (ms)	103.0 (SD = 8.7)	97.1 (SD = 8.2)
Dispersion of QRS (ms)	41.6 (SD = 13.0)	35.7 (SD = 12.2)
ST elevation of >1mV	20 (26.0%)	167 (28.3%)
ST depression of >1mV	21 (27.3%)	155 (26.3%)
ST elevation in the aVR lead	8 (10.4%)	12 (2.0%)
Reperfusion therapy		
Thrombolysis	45 (58.4%)	315 (53.4%)
Reperfusion*	8 (17.8%)	62 (19.7%)
Ischemic time (minutes)	248.0 (SD = 184.9)	235.6 (SD = 149.1)
Blood chemistry		
Blood glucose levels mmol/L	8.6 (SD = 2.8)	7.0 (SD = 1.7)
Creatinine µmol/L	112.2 (SD = 34.8)	88.5 (SD = 20.8)
Uric acid mmol/L	367.4 (SD = 105.6)	370.1 (SD = 100.3)
Cholesterol mmol/L	4.8 (SD = 1.6)	4.8 (SD = 1.5)
Hematic biometrics		
Absolute leukocyte values (x 10^9/L)		
Complications		
Newly detected atrial fibrillation	22 (28.6%)	59 (10.0%)
Recurring AMI	20 (26.0%)	46 (7.8%)
ECG upon admission	48 (62.3%)	44 (7.5%)
Atrioventricular block	4 (5.2%)	44 (7.5%)
MACE	77 (100%)	85 (14.4%)
Killip-Kimball Case		
Class I	25 (32.5%)	290 (49.2%)
Class II	11 (14.3%)	131 (22.2%)
Class III	13 (16.9%)	105 (17.8%)
Class IV	28 (36.4%)	64 (10.8%)
Other variables		
GFR mL/min	70.9 (SD = 26.2)	84.2 (SD = 26.1)
LVEF	39.4 (SD = 11.2)	47.3 (SD = 10.7)

*Percentage in relation to total thrombolyzed patients.
COPD: chronic obstructive pulmonary disease GFR: glomerular filtration rate
LVEF: left ventricular ejection fraction QTi: QT interval
AMI: acute myocardial infarction
MACE: major adverse cardiovascular events

Table 2: Intrahospital deaths per ordinal categories of the EERIAM-HCC Scale (predictive ability and calibration)

Risk level	N	Deaths	%
Low (0–9 points)	146	0	0.0
Moderate (10–19 points)	347	11	3.2
High (20–25 points)	101	19	18.8
Extreme (≥26 points)	73	47	64.4

Predictive ability C = 0.93 Calibration (Hosmer-Lemeshow) p = 0.85
EERIAM-HCC: Escala de Estratificacion de Riesgo en el Infarto Agudo del Miocardio Hospital Camilo Cienfuegos

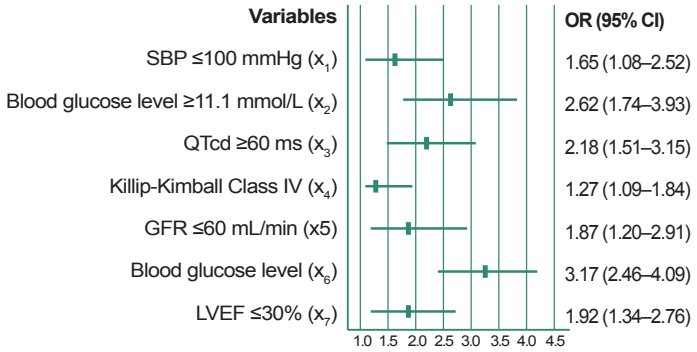
recurrence, atrioventricular block, and diabetes, with this last factor being particularly high among the deceased.

Previous extensive apical myocardial infarction was much more frequent in the deceased patients, as was the number of cases in Killip-Kimball class IV (Table 1).

Proceeding through the nodes and branches of the regression tree (Figure 1), we see the following notable results:

Cardiac arrest is the event with the worst prognosis and the one that most distinguishes the response variable (alive or deceased). The risk ratio of death associated with cardiac arrest is >10 (52.2% for those with cardiac arrest and only 5% for those without cardiac arrest). In patients who did not suffer cardiac arrest (node 1) the risk increased 5% to 45.8% if initial blood glucose level was >11.1 mmol/L.

Figure 2: Logistic regression with the main mortality predictors obtained from the classification tree

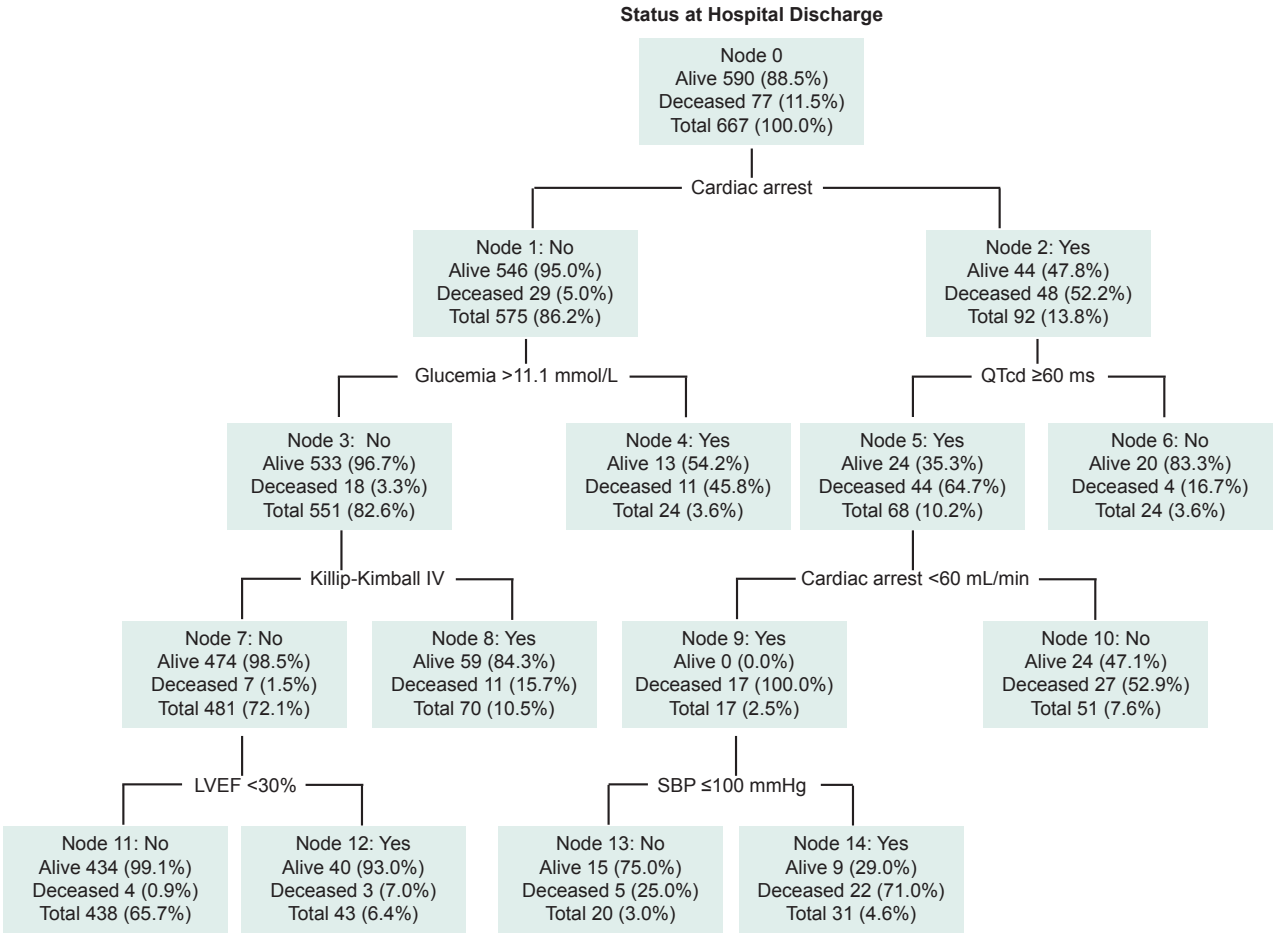


SPB: systolic blood pressure QTc: corrected QTi
Qtd: difference between maximum and minimum values
GFR: renal glomerular filtration rate LVEF: left ventricular ejection fraction

Only 3.3% of patients who did not suffer from cardiac arrest and whose blood glucose levels were <11.1 mmol/L died, but that risk quintupled if the patient was in Killip-Kimball class IV. If the patient was not in the Killip-Kimball class IV and their LVEF was >30%, risk of death was reduced to <1%.

On the right branch of the tree, which corresponds to the patients who suffered cardiac arrest, the risk is always higher than 50%

Figure 1: Classification tree with predictors of death



except for those with QTcd <60 ms, for whom the risk is reduced. The adjusted ORs for covariates provided by the binary logistic regression model (Figure 2) provide an approximate measure of the relative importance of each variable as a predictor of intrahospital death, and are the basis for the creation of the scale established below.

New risk stratification scale for patients with STEMI is a quantitative scale that converts values between 0 and 48 points into an ordinal scale with four categories based on percentile distribution. Factors included in the scale were SBP, Killip-Kimball class, cardiac arrest, GFR, QTcd, LVEF and blood glucose level.

Most patients had between 10 and 19 points, which corresponds to moderate risk. None of the patients had the maximum number of points and only one deceased patient was close, with 44 points. A clear positive association is observed between the points on the scale and case fatality (Table 2).

DISCUSSION

The patients involved in the design of the EERIAM-HCC scale did not undergo PTCA, as established in the international treatment guides for myocardial infarction, as there is no hemodynamic service in the hospital's coronary care unit.[2,3]

The new risk stratification scale for patients with STEMI combines variables that are easily acquired at a patient's bedside, including QTi dispersion, which has been associated with greater severity of coronary artery disease,[32] higher incidence of ventricular arrhythmias,[33,34] and greater recurrence of infarction.[35] No other scale was found in the reviewed literature that included the QTi dispersion; however, QTi prolongation after STEMI was included in the scale designed by Rivera[36] in 2016.

Bordejevic[37] found that SBP <105 mmHg was associated with greater intrahospital mortality, even after PTCA had been performed. [37] SBP <100 mmHg is included as a predictor in both the TIMI[12] and GRACE[16] scales.

The importance of including GFR as a variable is based on indications that patients with chronic kidney disease and diminished kidney function have a greater risk of death and complications in the course of an AMI. Vavalle[38] studied 5244 STEMI patients and found a relationship between worsening renal function after PTCA and renal dysfunction in patients before their AMI. Gutiérrez and Martos Benítez [39] found that Cuban patients who were admitted with AMI and died had worse renal function based on their creatinine and GFR values. Granger[16] found that for every 88 µmol/L increase in creatinine, risk of death increased 19%–29% (95% CI 1.19–1.29) and risk of AMI increased 8%–16% (95% CI 1.08–1.16). Renal function is one of the variables included in the GRACE prognostic score.[16]

High blood glucose levels implies worse prognosis for those with acute coronary syndrome, in both diabetic and non-diabetic patients, and is included in the EPICOR scale.[40] Ding[41] found greater mortality in non-diabetic AMI patients when their blood glucose was >10.0 mmol/L. Stress hyperglycemia is common in AMI patients even without a prior diagnosis of diabetes mellitus.[2,3]

The five-year follow-up for a cohort of STEMI patients who were not diagnosed with diabetes mellitus showed that stress hyperglycemia implied a greater risk of death (relative risk, RR = 1.45; 95% CI 1.06–1.98; p = 0.021) and of readmission for heart failure (RR = 1.48; CI al 95% = 1.04–2.10; p = 0,031); however, in diabetic patients it did not imply a worse prognosis (mortality RR = 1.0; 95% CI 0.68–1.48; p = 0.996 or readmissions due to heart failure RR = 1.31; 95% CI 0.90–1.89; p = 0.154).[42] These findings may suggest a greater tolerance to hyperglycemia in diabetic patients. There are debates regarding what constitutes optimum control of blood sugar levels in AMI patients with acute myocardial ischemia. [43] Lacking sufficient evidence on the matter, the current guidelines recommend starting hypoglycemic treatment with insulin when blood glucose levels reach ≥10 mmol/L and avoiding hypoglycemia at levels <3.9 mmol/L.[2]

Mortality was much higher in patients with cardiac arrest, consistent with studies using the GRACE score[16] and ACTION-GWTG.[10] Cardiac arrest caused by ventricular arrhythmias occurs with greater frequency in patients with an ischemic time >12 hours before receiving medical care, incomplete revascularization, cardiogenic shock, infarctions that affect a large portion of the myocardial tissue, and preexisting arrhythmogenic substrate.[44]

In this study, Killip-Kimball Class I was most common in patients who were discharged alive and Class IV most common in deceased patients. A recent multicenter registry showed an association between heart failure and mortality at 30 days post-AMI in STEMI patients.[45] Cardiogenic shock (Killip-Kimball Class IV) is the main cause of death in myocardial infarction and presents as a complication in 6%–10% of all cases. Early death from cardiogenic shock is higher than 50%.[46] In a cohort of 112,668 survivors of myocardial infarction, 4.9% presented with cardiogenic shock, and a year later, readmissions and deaths from all causes among these patients increased (adjusted OR = 1.1; 95% CI 1.02–1.18).[47]

LVEF is a recognized predictor of long- and short-term complications after myocardial infarction.[29] In a multivariate prediction model for risk based on echocardiographic variables, LVEF was an independent predictor (hazard ratio = 1.45, 95% CI 1.02–2.08; p = 0.040) and the risk prognosis was inversely proportional to LVEF when it was <40%.[48] Schwaiger[49] demonstrated a greater incidence of complications in patients with LVEF <52% (hazard ratio = 2.57; 95% CI 1.1–6.2; p = 0.036) in STEMI patients with topographies that did not involve the anterior face.

The EERIAM-HCC scale developed in our study demonstrated a good discriminative ability (C = 0.92), higher than the C = 0.88 of the ACTION-GWTG score[10], which is consistent with results of this study in the predictive variables of cardiac arrest and the degree of heart failure, GFR and SBP—although this is based on a contemporary record of patients in the United States and includes troponins for estimating prognosis. TIMI,[12] which was used to predict death at 30 days post-AMI, has a C = 0.77 and is consistent with our EERIAM-HCC scale in the SBP and Killip-Kimball class variables. For predicting death at 6 months, GRACE[16] has C = 0.82 and includes among its variables renal function, as does our scale. Conventionally, if the area under the curve has a C value greater than 0.9, the test is considered to have very good predictive power; C values between 0.7–0.9 are considered to have moderate predictive power; and values between 0.5–0.7, are considered to have poor predictive power.[50]

No significant differences were found between the frequency of cases observed and expected according to the Hosmer-Lemeshow goodness-of-fit test, indicating the scale is well calibrated.

One study limitation is that PTCA was never performed on patients in the cohort due to material limitations, and that the percentage of patients who undergo thrombolysis is low, which would explain the high mortality rate of the cohort. However, these results are useful for low- and middle-income countries requiring methods to provide quality medical care with limited resources. Another limitation in this first approximation is that the study did not analyze the outcomes or usefulness of the proposed scale in relation to additional variables such as age, sex and skin color, which should be considered in depth.

CONCLUSIONS

The relevant variables for the EERIAM-HCC scale to predict mortality and complications are cardiac arrest, blood glucose level, LVEF, QTcd, Killip-Kimball class, SBP and GFR.

The scale's predictive ability and good calibration demonstrate its usefulness in stratifying risk of death for AMI patients with ST-segment myocardial infarction during the first seven days of hospitalization in coronary care units in Cuba and other settings where angiography and serum biomarkers are not readily available.

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Biomodulina T May Restore Immunity in Older Adults

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ABSTRACT

Worldwide, there has been a progressive demographic shift over the past 50 years resulting in a larger proportion of older adults in the general population. Aging itself is a complex biological phenomenon characterized in part by changes in the immune system known as "immunosenescence", which makes older adults more susceptible to infectious, cardiovascular and autoimmune diseases, as well as cancers. Several strategies have been proposed in an attempt to reverse immunosenescence, including use of hormones, cytokines and thymic factors. A promising drug in the search to restore the thymic microenvironment (which plays an important role in the regulation and maintenance of the immune system) in older adults is Biomodulina T, a Cuban product registered for use in patients with recurrent respiratory infections. The administration of Biomodulina T increases the number of naïve T-lymphocyte, CD4-positive cells that have recently migrated from the thymus gland (recent thymic emigrants) and memory CD8-positive T lymphocytes, which have characteristics akin to stem cells (stem cell-like memory). Furthermore, the expression of programmed cell death 1 protein in CD4-positive T lymphocytes and CD4-positive T lymphocytes decreases, and the proliferative capacity of CD4-positive T lymphocytes increases, without changes in the frequency of regulatory T lymphocytes. These results suggest that the administration of Biomodulina T could be used to restore immunity in older adults and in other immunocompromised individuals, improve response to other immunotherapies in cancer patients, and increase the efficacy of vaccinations in older adults. Its use has been approved in Cuba for immune system restoration.

KEYWORDS Immunosenescence, aging, immunotherapy, immunomodulation, antineoplastic protocols, Cuba

INTRODUCTION

Since 1950, the proportion of the population aged >60 has steadily increased worldwide. WHO estimates that between 2000 and 2030 the number of people aged >65 will increase to approximately 973 million, representing 6.9%–12.0% of the world's population. By 2045, the number of seniors is projected to exceed the number of children for the first time in recorded history. An increase of 5.5%–11.6% is estimated in Latin America.[1] Cuba has one of the oldest populations in Latin America, with a life expectancy of 78.5 years, and 20.8% of its population aged ≥60 years, a share that could reach 30% by 2030.[2,3]

There is a growing interest in understanding the complex biology of aging with the aim of preventing or delaying the onset of chronic age-related diseases.[4] The age-related changes in the immune system are termed immunosenescence.[5] These changes occur within an inflammatory environment, due to chronic low-grade inflammation known as "inflammaging." A state of mutual dependence is thought to occur, in which immunosenescence is induced by low-grade chronic inflammation, which in turn increases with age and vice versa. Both processes help to explain the particular susceptibility of older adults to new infections and chronic diseases, including cardiovascular, neurodegenerative and metabolic diseases, as well as cancer.[5]

Several strategies have been proposed to reverse the changes that occur in the immune system with age and thus contribute to improving quality of life in older adults. Lang and colleagues defined the "3Rs" of "immune rejuvenation": replacement, by replenishing lost immune function by cells generated *ex vivo*; reprogramming, by regulating telomere length and stability; and restoration, to restore and maintain a normal thymic microenvironment.[6]

IMPORTANCE This article presents the benefits of the use of Biomodulina T as an immunomodulator, and its possible uses to restore immunity in older adults and immunocompromised individuals, and potential to improve the efficacy of immunotherapy in cancer patients.

Recently, our group has demonstrated the capacity of Biomodulina T (BT), a polypeptide fraction derived from the bovine thymus, to expand various cellular subpopulations, contributing to a thymic-environment restorative strategy that could slow the accumulation of exhausted T cells and prevent the decrease in the number of naïve T cells that occurs with aging.[7] In this article, we present suggestions based on our experiences with BT use in older patients with a history of recurrent respiratory infections without associated chronic diseases, which led to the inclusion of this drug among therapeutic options for immune system restoration.

AGING AND THE IMMUNE SYSTEM

Strategies to reverse immunosenescence This phenomenon affects practically all the components of the immune system: however, the changes most often noted in the literature are the decrease in naïve T cells and increase in terminally-differentiated memory T cells, characterized by the loss of surface markers that are frequently found in naïve cells such as CD28.[8,9] The changes are attributed primarily to thymic involution,[10] chronic antigenic stimulation, nutritional impact and dysregulation of some hormonal pathways.[11,12] Immunosenescence studies in Cuba have shown that with age, naïve CD4-positive T lymphocytes (CD4+ T cells) decrease (unpublished author data), as do B lymphocytes, while the number of terminally differentiated CD4+ and CD8-positive T lymphocytes (CD8+ T cells) increases.

The scientific literature documents application of therapeutic strategies to reverse age-associated changes in the immune system.[5] These therapeutic strategies may not only contribute to immunological restoration in older adults, but also to an enhanced immune response to the kinds of attacks that occur in infections and cancer. Regarding cancer,

immunotherapy has opened new therapeutic possibilities in its targeted use against tumor cells.[7]

Various avenues have been suggested to counteract aging's effects on the immune system, including changes in nutrition and lifestyle, dietary supplements with specific micronutrients, modulation of T cell functions, as well as reduction of antigenic load and restoration of thymic function through use of steroids, hormones, growth factors and cytokines such as interleukin-7 (IL-7) and interleukin-22 (IL-22).[13] Reconstitution of the thymic microenvironment is of utmost importance for the maintenance of T cells with adequate repertoire diversity and intact functionality during the aging process.[14] BT is a fraction obtained from the thymus, which restores the normal thymic environment and could compensate for age-associated immune system deficits.

POTENTIAL CONTRIBUTIONS OF CUBAN BIOMODULINA T

BT is a natural immunomodulator formed by polypeptide fractions obtained from the bovine thymus. In Cuba, it is produced by the National Biopreparations Center (BIOCEN) and was registered in 1994 (Health Registration: B-08-038-J05).[15] It comes in 3 mL bulbs containing 3 mg of bovine thymic fraction and is administered either intramuscularly or intravenously. Among the most frequently reported adverse reactions associated with its administration include pain and burning at the site of injection, fever, headache and fatigue.[15]

BT is useful for treating mainly cellular-type immune dysfunction manifesting as recurrent infections in older adults. This use is supported by clinical trials.[15] BT exhibits cellular regeneration and immunomodulatory properties, as it stimulates lymphoblastoid mitosis and thus normalizes the differentiation of T lymphocytes. This activity is detectable up to at least 24 hours after administration.[15] In models of acute inflammation, edema and chronic inflammation, BT demonstrated an anti-inflammatory response associated by modulation of the induced inflammatory response, and inhibited macrophage release of arachidonic acid.[15] BT's anti-inflammatory effect has been shown to operate by inhibiting release of arachidonic acid by macrophages and inflammatory cytokines, a mechanism somewhat similar to that of steroids.[16]

BT permits recovery of thymic mass in children with thymic atrophy or hypoplasia, and a subsequent increase in the release of hormones by thymic epithelial cells, possibly due to the presence of a positive feedback loop of these hormones. Additionally, a decrease in recurrent infections has been observed.[17] In a clinical trial involving patients with relapsing-remitting multiple sclerosis (RRMS), clinical parameters improved and immunological parameters normalized and subsequently remained normal after BT administration, so the use of BT was suggested as a possible therapy for RRMS patients.[16] All of the above clinical studies report that BT is safe and none reported toxicity.[15,18]

BIOMODULINA T PARTIALLY RESTORES CD4+ AND CD8+ T CELL COMPARTMENTS IN OLDER ADULTS

Expansion of naïve and memory T lymphocytes A study recently conducted in 31 patients older than 62 with a history of recurrent respiratory infections (and absent any other previously diagnosed chronic diseases) showed that BT administration temporarily expands naïve CD4+ T-cell production, recent thymic emigrants (RTE) cell production, and stem cell-like memory CD8+ T-cell production.[7] Peripheral production and maintenance of naïve T-cell repertoire is critical to normal immune system function.[6] RTE cells decrease with age[19] and as a consequence of the administration of glucocortoids and cytotoxic drugs during cancer treatment. The population of memory cells with stem cell-like characteristics was only recently identified.[20] These memory T cells have properties similar to those of stem cells in that they are the least differentiated population of memory cells and possess a special capacity for self-renewal.[20] Based on the evidence highlighting the replicative and self-renewing potential of these cells, their expanded presence in older populations could sustain an adequate long-term memory response capable of self-proliferation, and thus could contribute to re-establishing immune system homeostasis.

Exhaustion-resistance and potentiation of the immune system's activation and proliferation capacities In recent years, cancer immunotherapy based on treatment with immune checkpoint inhibitors such as anti programmed cell death receptor-1 (PD-1), anti programmed cell death-ligand 1 (PD-L1) and anti cytotoxic T lymphocyte–associated protein 4 (CTLA-4) has increased survival of patients diagnosed with advanced cancer in different locations.[21]

Blocking the PD-1 receptor allows T cell function to be restored in patients with advanced tumors such as melanoma and lung cancer, suggesting that exhaustion of the immune response is reversible in these patients.[22] BT administration decreased expression of CD4+ PD-1+ and CD8+ PD-1+ T cells, pointing to the BT thymic factor's possible anti-exhaustion value in immune response.[7]

Additionally, BT treatment increased proliferation capacity of CD4+ T cells in older adults (as measured via expression of the Ki67 nuclear marker), as well as intracellular expression of interferon gamma, which shows that BT could constitute a potentiation strategy for increasing immune responses in older adults by contributing to restoration of the Th1 response.[7]

No expansion of regulatory T cells All immune system benefits of BT described above occur in a context absent of the modification of regulatory T cells. Because BT is an extract derived from the bovine thymus, its use could be expected to stimulate thymic production of various cellular subpopulations, including natural regulatory T cells. However, BT administration did not change the frequency of CD4+ regulatory T cells. This result may be suggested as an additional element in favor of BT use, not only in older adults, but in cancer patients as part of a treatment regimen designed to enhance immunotherapy without the danger of increasing regulatory T cells.[7]

CONCLUSIONS

BT intervention contributes to restoration of the normal thymic environment by slowing reduction of the number of naïve T cells that occurs naturally during the aging process and may improve the efficacy of immunotherapy in older adults susceptible to recurrent infections and cancer.

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Why Aren't Cuban Men Healthier?

Ramón Rivero-Pino MS PhD

Analyzing any bio-psycho-social paradigm is complex and requires a comprehensive, integrative approach. Parsing the health picture of individuals, as well as whole populations, is no exception. Considering masculinity as a factor may shed light on health status, especially since traditional ideas of 'manhood' work against health promotion and prevention, as revealed in studies worldwide. In fact, these studies show a direct association between traditional understandings of masculinity and risks, vulnerabilities and the construction of health. In the last decade, such observations have received a bit more attention from international agencies.

This column addresses what it means to be a man in Cuba today and the implications for men's health—and furthermore, what changes might lead to improvements in the situation.

Globally, strides have been made in terms of research and intersectoral policies and practices incorporating a gender perspective. These provide deeper insight into the differing realities of men and women, the effects of inequality and what might be done about it. But gender as a category and its possible associated effects have yet to be fully realized, in part because thus far, it has suffered from a limited and general focus, as well as multicausal resistance to its effective application.

Health services designed for men are often short term, narrowly focused and absent from public policies

The problem is real and the data sobering: women's life expectancy in the Americas is 5.8 years more than men and 1 in 5 men die before they turn 50. Furthermore, many male deaths are preventable, including those related to violence (7 men for every woman); accidents and suicide (3 times the rates of women); and unsafe sex contributing to HIV/AIDS prevalence (more than double that of women). Drug, alcohol and tobacco addiction are more prevalent among men and contribute to a larger share of male deaths: 719 per 100,000 men as compared to 615 per 100,000 women. Data also show that men are much less likely to access health services and follow doctor's orders. Compounding the problem is the fact that health services designed for men are often short term, narrowly focused and absent from public policies.[1]

Data confirm that male gender socialization is more deadly in Cuba as well. Excess mortality is the case for more than 90% of causes of death. Mortality for cirrhosis and other chronic liver diseases is 4 times that of women and intentionally inflicted injury (suicide) almost 4 times as well; men die 1.4, 1.2 and 1.1 times more often than women due to malignant tumors, heart disease and cerebrovascular disease respectively. Figures for influenza and pneumonia, accidents, and chronic lower respiratory disease are similar.

Morbidity data are just as sobering: incidence of gonorrhea among men is double that of women, tuberculosis three times, and HIV/AIDS five times. Years of potential life lost (YPLL) to main causes of death for men between ages 1 and 74 is almost double that of women.[2] This gender health gulf is particularly striking considering that the Cuban public health system has the world's highest doctor-patient ratio (84.8 per 10,000 population), low infant mortality rate (4 per 1,000 live births; 28th globally) and high life expectancy (78 years, average for both sexes, 34th globally).[2]

I believe the problem of Cuban men and their health can be best framed by considering three elements: 1) the effects of hegemonic masculinity on men's health; 2) social representation of masculinity; and 3) health system approaches to men's health.

Hegemonic masculinity refers to traditional roles Cuban men learn and replicate, whose alienating attributes lead them to abdicate responsibility for their own health. We are taught that as providers, our bodies are instruments of labor, that working them to the bone is only natural, minimizing attention to our health. This message is reinforced by society through insufficient criticism to the contrary, resulting in harmful effects on our health and the health of others as well.

This model of masculinity in Cuba manifests itself in several ways, including: attraction to power and drive for leadership; violence; suppressing emotions; scant attention to basic necessities; relegating paternity to a secondary role; homo- and transphobia; misogyny; insufficient participation in household chores; role of "the provider"; promiscuity; self-esteem based on work success; work-related stress; addiction; poor nutrition; sedentary lifestyle; exposure to toxic substances; lack of life skills related to family/married life; and little awareness of necessary lifestyle changes.[3] These manifestations are reinforced throughout our lives, typically first emerging in adolescence when we become irresponsible with our health, deny being sick, find it difficult to seek help (medical or otherwise) and if we do, we don't follow through. We simply don't care for our health.

In terms of **social representations of masculinity**, although Cuban society is known for its humanism, cooperative participation and equitable gender policies, it hasn't been able to rid itself of negative influences on promotion of healthy lifestyles. These include: insufficient intersectoral policies, services and programs focusing on masculinity; unequal resource distribution which aggravate gender inequities among different social groups, including men; a binary gender construct, heteronormativity, and machismo which translate into violence, accidents, homicide, addiction and suicide; inadequate media coverage of problems particular to men, thereby depriving society of health-promoting images; educational institutions ignoring examples of new approaches to masculinity; statements and decisions by lawyers and judges that devalue paternity and sexual diversity; and limited social mechanisms for recognizing best masculine practices such as greater attention to Father's Day and lauding healthy behavior among men.

How the Cuban health system approaches men's health is similar to other countries meaning that health policies with a gender focus lack a relational approach—that is, they don't suf-

ficiently incorporate male or gender-diverse perspectives. While some institutions stand out in this regard including the National Sex Education Center (CENESEX) and the Center for Health Promotion (PROSALUD), their inroads have not been institutionalized, nor incorporated transversally throughout different layers of society. Progress is also slow to incorporate scientific findings about masculinity into university curricula and to implement male-specific health promotion and prevention actions by health institutions. Exerting stronger political will and sparking a transformative process within the health system would help address this, as would learning from civil society, which offers experiences around men's health and wellbeing. Examples include the *Men Against Violence Platform* of the Oscar Arnulfo Romero Center and *Masculinities* of the Cuban Multidisciplinary Sexual Studies Society (SOCUMES).

The link between masculinity and health is almost non-existent in health research and medical training; men's participation in health services is undervalued by health professionals, society-at-large and men themselves; and treatment directed specifically at men focuses principally on HIV/AIDS, violence and addiction. Health programs around sexual health and reproduction are largely directed at women and the national prostate cancer program hasn't had the same impact as the cervical cancer program. Men's mental health is also under-attended due to societal taboos and a lack of targeted services.

In conclusion, I make the following recommendations: 1) implement diagnoses and proposals based on epidemiological factors specific to men's health, with an emphasis on those related to premature death and non-communicable diseases; 2) given the mortality/morbidity evidence, strengthen health policies, programs and services through a more intersectoral and relational gender approach that incorporates men's health; 3) incorporate a more comprehensive focus on gender in all health professional curricula that includes men's health and specific health care needs; and 4) incentivize primary health care actions that deconstruct belief systems related to hegemonic masculinity, underscoring the health costs and consequences of those beliefs. In this way, we can move towards solutions to better controlling mortality and morbidity among men, improve quality of health services delivery and contribute to better population and individual health.

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COVID-19 in East and Southern Africa: Rebuilding Differently and Better Must Start Now

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By June 2020, the cumulative cases and deaths related to COVID-19 in 16 East and Southern African (ESA) countries were still rising, with an average case fatality rate of 1.46%.[1] From its initial presence in cities and regional transport hubs, cases are spreading, including to rural areas, among health workers and as migrants cross borders to return home.[2]

The pandemic has highlighted important public health deficits in the region. While hand washing with soap is a key intervention, in 12 ESA countries fewer than 50% of their populations can access safe water and hand-washing facilities. While many ESA countries implemented early lockdowns, high levels of socioeconomic inequality and precarious employment make them difficult to sustain, as income and food security depend on working daily. Testing for, tracing and quarantining cases work when tests are available and results can be returned quickly. Yet ESA countries have not been able to access sufficient test kits or reagents.[3] Although testing levels in these countries increased to an average of 1800 tests per million people by June 12 (excluding higher levels in Botswana, Mauritius and South Africa), this is well below levels in countries such as South Korea that have effective test and trace strategies.[1]

For ESA countries, COVID-19 has exposed the weakness in being dependent on research and production outside the region of commodities that are needed in good time for communities and services across the region. This not only relates to current demand, like test kits. It forewarns that African countries will be last in the queue when COVID-19 treatments and vaccines are approved. Tariff reductions and reduced protections for domestic industry have suited a global strategy of 'lowest-cost-production' but leave ESA countries vulnerable in the global competition for products. The UN Economic Commission for Africa (UNECA) reports that 94% of Africa's total pharmaceutical stock is imported.[4] With at least 71 countries having imposed limitations or outright bans on exports of certain COVID-19 essential supplies, UNECA observes that this imperils Africa's access to these supplies. ESA countries have thus argued for the policy space to use existing Trade Related Aspects of Intellectual Property Rights (TRIPS) flexibilities for national and regional procurement and production, and for global support for open innovation and manufacturing, to encourage local or regional production to meet the demands related to the pandemic.[3]

COVID-19 has also pointed to resources in the region that could play a more significant role in public health. A high level of literacy, social networking and growing mobile phone uptake are potential assets for community-led social responses to COVID-19, if supported. For example, musicians in Tanzania and Uganda spread COVID-19 messaging, and communities provide solidarity support via South Africa's Together Community Action Network. Meanwhile, innovation by informal enterprises has stimulated the production of face masks, personal protective equipment and other appropriate technologies for health, while formal enterprises, including universities, have repurposed production lines and launched new product lines to supply face shields and ventilation equipment for health services. There are medicine production capacities on the continent, boosted by South-South partnerships. Community health workers (CHWs) are present in all ESA countries and drawing on experience from the Ebola epidemic, CHWs are being trained in some countries as trusted sources of information for community literacy and to support COVID-19 prevention and case detection.[2]

The Ebola experience showed that an effective response demands collaborative work that involves communities and is supported by professionals, governments and accessible, capable public services. This is the same lesson learned from the gains made in health by applying primary health care strategies in the region, despite their being weakened by underfunding of public services.

In contrast, the response to COVID-19 has often generated a self-protective response *across* countries in global trade and a command-and-control response *within* countries. Yet neither are effective strategies for a global pandemic that demands distributed local capacities and action.

> **Building production capacities in the region calls for international collaborations and partnerships that support open innovation and open production**

The existing global model that links R&D to high monopoly prices for new health products does not ensure sufficiently universal or free access to the diagnostics, medicines and vaccines needed to manage COVID-19 as global public goods, notwithstanding the public funding this R&D often receives. It is surely a lesson from COVID-19 that ESA countries cannot continue to rely on importing commodities that are vital for managing epidemics. Building production capacities in the region calls for international collaborations and partnerships that support open innovation and open production, recognizing the mutual health security gained from sharing technical inputs that stimulate a distributed production, while closing the gap between production sites and population need.

Notwithstanding the resources mobilized for the regional response to COVID-19 at all levels, the scale of these responses and the pandemic's economic damage call for deeper and more sustained financing. African ministers of finance have called for an estimated US$44 billion to be released for this by suspending interest payments on debt and sovereign bonds and cancelling debt for the poorest countries, a call also made by UN Secretary-General António Guterres.[3]

There is a sense that our response cannot be 'business as usual.' Opening the 2020 World Health Assembly, UN Secretary-General Guterres described "the recovery from the COVID-19 crisis" as an opportunity "to rebuild differently and

better." This begins with how we respond to COVID-19 today. "Differently and better" includes significantly greater investments in infrastructures, services and pandemic responses within countries that meaningfully engage with communities and address the fundamentals for healthy societies. It includes forms of international cooperation that ensure essential health technologies and capacities for effective pandemic responses can be produced in all regions where they are needed.

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A Cuban Physician on the Front Lines in Barcelona Reflects on COVID-19 Responses in Europe and Cuba

Marià de Delàs

Dr Raúl Herrera Nogueira is a young Cuban physician who completed dual specialties in Cuba in family medicine and cardiology. He is now pursuing a residency in anesthesiology at Bellvitge University Hospital in Barcelona. We publish excerpts from his report as a doctor on the front lines of the pandemic there and his reflections on differences in his home country's approach to medicine, public health and COVID-19. The original article, titled En Cuba, en caso de epidemia, "el personal sanitario sabe inmediatamente dónde tiene que ir y qué tiene que hacer," *was published April 9, 2020, in the Spanish/Catalán publication* ***Público*** *available at https://www.publico.es/sociedad/coronavirus-cuba-caso-epidemia-personal-sanitario-inmediatamente.html*

Several territorial governments in Spain are considering inviting Cuban doctors to participate in the fight against the coronavirus epidemic, just as they have done in Italy and Andorra…Cuba's healthcare culture is different from Europe's, and the response to the epidemic likely would have been different if criteria were used similar to those followed in Cuba.

Dr Raul Herrera Nogueira has been an anesthesiology resident at the Bellvitge University Hospital in Barcelona since May of 2017 after becoming a licensed physician in Cuba and completing a master's degree in Madrid. He explains that as soon as COVID-19 cases began arriving at his hospital, work was reorganized and he was transferred to the ICUs, joining critical care doctors and anesthesiologists on duty there.

Organizational Problems and Lack of Consistent Protocols

He believes, from an organizational perspective, that "the response has been slow and perhaps a bit late." In a telephone interview with ***Público***, he explains: "In terms of health personnel—doctors, nurses, orderlies—it took quite a few days to restructure the work, resulting in delays for optimizing resources and wasteful use of them in the meantime."

But he has also been positively impressed by "everyone's willingness, their desire to do more, to contribute and collaborate, even outside their usual setting or work area." He notes: "I think this has been really positive and compensates somewhat for the lack of order or the Salut [health authorities'] inability to effectively drive, in terms of the hospital where I work, a speedier response to the epidemic."

"I'm referring especially to the way shifts are structured, the capability to predict needs: while perfectly understandable in such a chaotic situation, this affects organization in some areas such as those for critical patients. So staff are not only overloaded with work and the stress of the situation, but have the added tension of not knowing who each person reports to, who needs to be consulted in certain situations," he adds.

From the technical side, he notes that "every two or three days, protocols change. So this makes providing stable treatment very difficult. There isn't an entity in Spain or in Catalonia that is defining [treatment] protocols. Every hospital issues its own, and these are followed depending on the unit or person in charge."

The Cuban Experience

"In terms of health system organization, and I say this with all modesty, I think we have an advantage, because in Cuba, we're well accustomed to health emergencies related to epidemics because of our experience with dengue. Of course we're not at all talking about the same kind of disease or the same means of transmission, but in Cuba, every two or three years we have dengue epidemics, and the health system response is fairly well structured in these kinds of situations," says Dr Herrera Nogueira. "In a situation like the one we have now, the vast majority of medical staff will immediately know where to go, who they have to report to, and exactly what they have to do," he says.

Dr Raúl Herrera Nogueira (left) and colleague in Barcelona.

Community Care in Cuba

With regards to preparing for emergencies, the physician emphasizes another factor: "the ability to involve large numbers of health personnel in the campaign, resulting from community-based care and specifically, case detection" through "active screening," an information collection system aimed at finding people who may be ill. It means "going door-to-door to find people with respiratory symptoms, while maintaining safety measures and physical distancing to avoid direct contact in their homes with those who may have fever or other symptoms. Thus, people also don't have to go to health centers to be seen," he explains.

The screening means that every 48 hours or so, "a person who could be a medical or nursing student, a doctor or nurse, calls at your door to ask if there is anyone in the household with symptoms, waiting outside to maintain physical distancing," he says. "Then, if there is someone, the family doctor goes to the home to follow up, see how the person is doing," and decide if they need to go to an isolation center or hospital. "In Cuba," he points out, "medical students make up quite a share of personnel, and they are integrated into the campaign to stem the epidemic."

Immediacy and Early Detection

Summarizing two differences between health system behavior in Cuba and Spain when confronting the epidemic: "First, there's the immediacy in terms of organization: I believe it has been slow [here]. I can speak about my own hospital... organizing the shifts and their structure, so that everyone knew which rotation they had, took two weeks. In this kind of situation, that is a lot of time. I think that in Cuba, it would have been done more immediately," he notes. "The second [difference] is the number of personnel dedicated not only to hospital care of patients, but also in the community, directly involved in early case detection, for a more effective response," he adds.

"One thing we are seeing here with our ICU patients is that the time between when they are seen in the emergency room for their symptoms until they are sent to the ICU is about four to five days. Perhaps if they had received more direct follow up care at home first, they might have been sent to hospital earlier, and thus isolation measures for such cases would have been optimized."

Sources consulted by ***Público*** indicate that in Cuba, active screening for cases has been carried out among some 9 million of the country's 11.2 million population.

"I don't know if it's a correct measure in this situation," notes Dr Herrera Nogueira, "but it's being done and it's getting results. I don't want to be overly optimistic—because things could turn the same or worse [than in Spain], because in Cuba's economic situation, it's difficult to maintain isolation—but for right now, after some two weeks in Cuba, the increase in cases and the numbers of patients going to emergency rooms with respiratory symptoms is not overwhelming the health system."

According to the BBC, until this week [April 6], Cuba had detected a total of 396 patients infected with COVID-19, and 11 had died. [As of July 2, 2020, Cuba had accumulated 2361 cases, with 2224 recovered, 94.3%; 86 deaths; and 49 active cases—Eds.]

Western Arrogance

Asked what could have been done to stem such a rapid spread of the virus, Dr Herrera Nogueira criticized the attitude of many governments, including Spain's, in relation to the situation in China. "I think the magnitude of the problem in China was underestimated, as Chinese health and epidemiological authorities were being challenged [by the Europeans], and it seemed as if they were saying that this happened in China because the health system wasn't very organized, because they simply couldn't conceive of the fact that an epidemic of such proportions could happen in Europe."

"The mortality we have in these countries is almost three to four times that of China's. It's an example of a certain arrogance when faced with the situation, and that led to a late response in the first stages, and a level of response below what the situation demanded," he says.

"I think much more rigorous measures should have been taken, and much more urgently than what was done, not waiting for an increase in cases, because when those numbers begin to explode like a chain reaction, then a lot more time is needed to stem that tide. It happened with China, and here in Spain, it happened to us when the same was going on in Italy. In Italy, the hospitals collapsed, the hospitals and the ICUs, and still in Spain, strong measures hadn't been taken to limit travel, promote isolation and physical distancing," he recalls. "I think that we're now paying the price for an arrogant view of experience in other countries."

Was Lockdown Necessary?

Dr Herrera Nogueira has no doubts: "I think it was necessary and much earlier than it was done. I think that a more rigorous and scaled lockdown would have been ideal, even before we were seeing symptoms, before we had symptomatic patients, patients testing positive. The goal in a situation like this isn't to have patients testing positive but controlled; instead it's to have the smallest possible number of positive patients…and in that sense, we have been too slow."

Safety in the ICU

"We have not had sufficient personal protective equipment (PPE) and what we have had is not optimal," he comments. "A critical patient demands a nearly constant presence of nurses and doctors. These are very dynamic patients, who need changes in their medication regimens and in respiratory parameters. Within an hour, there can be changes, a new result, and then the need to change again in a very short window of time. Thus, care for these patients who require isolation is extremely difficult, and I think that we are seeing higher mortality in the ICUs not only due to the disease itself, which can undoubtedly evolve quickly to serious and critical, but also because the care we are providing to these patients isn't that which we would usually give to a critical patient…due to the distancing that is needed," he explains.

To illustrate more clearly, Dr Herrera Nogueira offers an example from personal experience: "I had a patient, a young patient, who got disconnected from the ventilator. This patient

was evolving well, and we were waking them up, and the patient was moving, because even though sedated, they had some responses, and in one of those movements, one of the cables of the ventilator came disconnected. This is something that can happen, but usually you simply need to enter the room and reconnect the ventilator, in a normal situation. But imagine what it was like now."

"You have to get dressed immediately, with all the protective gear, double gloves, mask and so on…ensuring no contact takes time. But just as we were about to enter, we discovered there was no PPE on hand. It was on the way. So we had to go in with protection that wasn't optimal, with a patient disconnected who was releasing into the air their entire viral load, which most probably was high. We had to go in, dressed as we could, to reconnect the ventilator."

Lessons for the Future

One of the most important lessons for the future, says Dr Herrera Nogueira, is the value of public health. "If there is one lesson we have to extract, it's that we need to take care of public health. And not only take care of it, but nurture it to make it more powerful. This doesn't mean no private health care, and in fact the link between public and private should be recognized. But going forward, more value and a greater leadership role needs to be given to public health."

"The capacity for response in this situation has been determined by the public health systems, and if there are weaknesses, then it is because public health itself has been debilitated, because in the last few years, its funding has been significantly cut."

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The Cuban Strategy for Combatting the COVID-19 Pandemic

Amilcar Pérez Riverol PhD

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ABSTRACT

The emerging SARS-CoV-2, a novel human coronavirus, caused the COVID-19 pandemic, with more than 9.5 million cases and 484 000 known fatalities to date (June 24th, 2020). In several regions, healthcare systems have collapsed whereas interventions applied to slow the viral spreading have had major social and economic impacts. After China, Europe, and the United States, Latin America has emerged as the new epicenter of the pandemic. By late-June, the region accounted for roughly 50% of global daily deaths (Gardner, 2020). The evolution of the COVID-19 pandemic in the region has been heterogenous as several countries are currently experiencing exponential growth of their daily cases and fatalities, while others have successfully controlled their corresponding outbreaks. Cuba confirmed its first COVID-19 cases in mid-March. After a three-month outbreak, the country recently began to move to a post-epidemic phase. This dispatch details some relevant aspects of the strategy deployed in Cuba to face the COVID-19 pandemic and to decrease the impact of this emerging disease in the country. In addition, it describes the evolution of some epidemiological variables which allowed the country to de-escalate some of the non-pharmaceutical interventions applied during the outbreak.

Doctors and pedestrian wearing face masks in Havana, Cuba during the COVID-19 pandemic.

1. COVID-19 in Latin America and the Caribbean: early projections and current situation

Early modelling studies suggested that, without the adoption of mitigation/suppression measures to reduce SARS-CoV-2 transmission, by the end of 2020 the COVID-19 pandemic would result in more than 7 billion infections and 4 million deaths (Walker et al., 2020). Under an unmitigated scenario, the study projected more than 566 million cases and 3.1 million deaths for Latin America and the Caribbean. Non-pharmaceutical interventions and policies aimed at controlling the virus' spread include, among others, stay-at-home requirements, social distancing, school closures, bans on gatherings and public events, quarantines, and, in some cases, complete lockdowns. These interventions were commonly combined with travel bans aimed at diminishing the chances that the virus could seed from imported cases. Following the recommendations of several world renowned epidemiologists and the WHO, the European and Asian countries that were the initial epicenters of the pandemic combined several of these strategies to flatten the curve of infections and avoid overwhelming their hospitals and health care systems (Flaxman et al., 2020).

The COVID-19 pandemic has been particularly challenging for Latin America and the Caribbean. Several countries in the region lack strong public healthcare systems and sanitary infrastructures, have a significantly low ratio of medical doctors and hospital beds per million of inhabitants, and face the health crisis created by the emerging virus with limited diagnostic capacity as compared to some Asian and European countries, or the United States. Significant levels of informal employment and the economic difficulties faced by several countries in the region conspire against governments' ability to offer financial stimulus and income support, hampering the implementation of stay-at-home restrictions and social distancing policies. Currently, Latin America and the Caribbean is the region with the highest levels of daily cases and COVID-19-related deaths.

At the time of writing, the region accounts for more than 2.2 million COVID-19 confirmed cases and over 103,000 fatalities (WHO, 2020). Brazil, Mexico, Chile, Peru, and Colombia are among the twelve countries with the highest numbers of daily confirmed cases and fatalities in the last weeks of June (updated June 24th) (WHO, 2020). These numbers are likely undercounted as most Latin American and Caribbean countries show remarkably low testing rates, significantly hampering their national response to the pandemic. Indeed, several independent studies have signaled a potential major under-reporting of death tolls, as fatalities in several territories

and cities are far above of historical averages, even after taking into account the reported COVID-19-related fatalities (Burn-Murdoch, 2020).

2. Cuba before the national outbreak

Early data from China's epidemic showed that COVID-19 has a case fatality rate of around 5.9% among elderly people (>60 years old) (Zhang, 2020). Further studies, including data from Italy, have confirmed the high case fatality rate among patients aged 60 years or older (Onder et al., 2020). Cuba is one of the countries with the highest life expectancy in the region (78.5 years) (MINSAP, 2019) and a major proportion of its population (20.23%) is included in the age group of people who are at higher risk if they get infected by the novel coronavirus. According to official data, the country also has a significant prevalence of diabetes mellitus (64.3/1000 inhabitants) and arterial hypertension (almost one fourth of the population), both identified as risk factors early on (Zhang, 2020). This data, combined with the challenges associated to economic problems and the fact that Cuban economy is highly reliant on tourism, prompted the Cuban political and public health authorities to design a coordinated national strategy to reduce the impact of the emerging virus on the island.

In the context of the Cuban response to the COVID-19 pandemic, it is important to note certain pre-existing conditions that benefitted the implementation of the national strategy. These include universal healthcare, the highest per capita of medical doctors/millions of inhabitants worldwide, a well-structured primary healthcare system, and a previous history of facing emergency situations during the annual hurricane season (Morris and Kelman, 2020). Also—in the context of the response to the pandemic—the existence of a state-controlled economy and public health policies expedited the mobilization of emergency resources and facilitated the rapid isolation of confirmed cases as well as their contacts. It is not the focus of this text to assess the impact of some of the measures implemented in the country (i.e. evacuation to isolation centers, mandatory use of face masks in public places) on individual rights. As a virologist, I will describe these measures' role in controlling the national epidemic and detail some epidemiological data that show the positive outcome of the strategy applied in Cuba.

In the absence of herd immunity, highly efficient antiviral treatment or complementary therapies, or a vaccine, the early application of non-pharmaceutical interventions as well as other epidemiological tools represents the gold standard to face the COVID-19 pandemic. It is important to note that since there is to date no "silver bullet" to stop the spread of the novel coronavirus, several policies must be implemented simultaneously. Cuba started to prepare its national response in late January. The Plan for Prevention and Control of the disease included, among other aspects, the training of the healthcare workers, reinforcement of the National Program for the Surveillance of Acute Respiratory Infections (ARI), and—of particular importance—the preparation and further extension of laboratory infrastructure and facilities for the molecular diagnostic of SARS-CoV-2 infections. On March 11 (coincidentally the same day that the WHO officially declared COVID-19 a pandemic), Cuba confirmed the first cases of its outbreak.

3. The Cuban strategy and its major tools

At the discretion of this author, the Cuban approach to cope with viral spread and to control its epidemic has four major virtues. These are, (i) early, or at least timely, application of mitigation/suppression measures, (ii) massive and reinforced ARI surveillance enabling early detection of suspected cases, (iii) comprehensive contact tracing with rapid isolation of confirmed cases and contacts, and (iv) the development of a rational testing program. In this section, the individual contribution of some of these tools will be briefly discussed.

The course and strength of the non-pharmaceutical interventions implemented by each country can be ranged using the Oxford Stringency Index (Hale et al., 2020). Higher values (%) imply strongest mitigation/suppression measures. An analysis of the Index shows a similar temporal pattern for Cuba, Uruguay, and Costa Rica (Figure 1), which represent some of the Latin American countries that have controlled their initial corresponding outbreaks. Among the measures applied by Cuba were a partial travel ban (22.03.2020, 48 confirmed cases and one fatality), and then a complete international travel ban (01.04.2020)–to prevent viral seeding–, the closure of schools

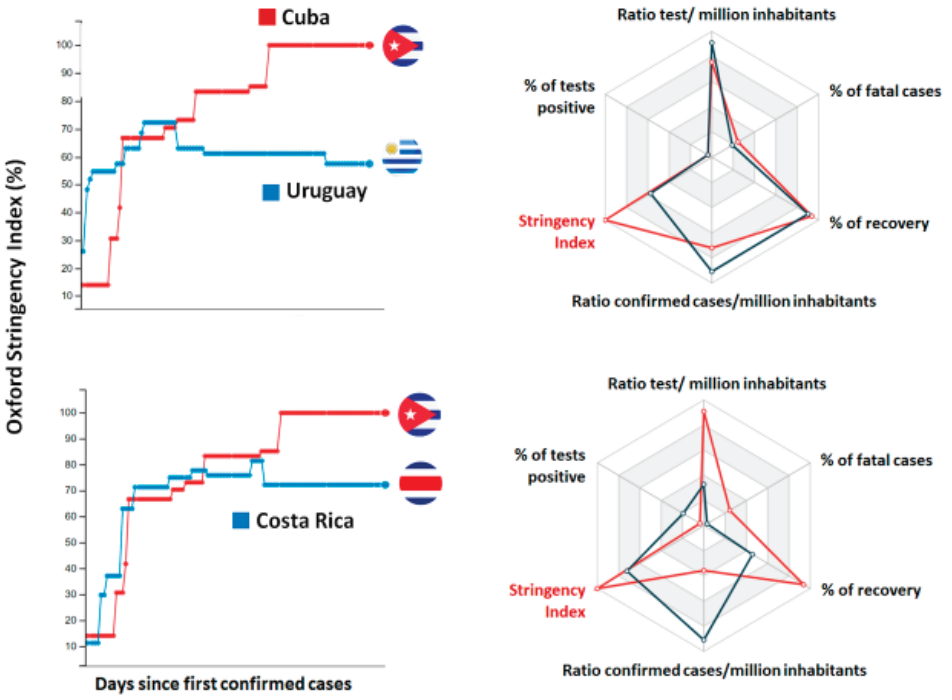


Figure 1. Graph representing the Oxford Stringency Index for Cuba as compared to Costa Rica and Uruguay. [Modified with permission from (COVID19 Cuba Data Dashboard, 2020)].

(24.03.2020, 40 cases, one fatality) and public transportation, restriction of internal movement, public events, and gatherings, as well as selective quarantines or restrictive home isolation in territories with community transmission. Also important is the fact that Cuba mandated the use of face masks in public places as a key tool to reduce transmission (Prather et al., 2020). Similar to Uruguay and Costa Rica, most policies applied in Cuba were implemented in the early phase of the epidemic, thus increasing the probability of a positive outcome. At present, some of the interventions remain active in the island.

3.1 Massive surveillance and contact tracing

Relying on its broad primary health care system and the collaboration of undergraduate medical students, the country deployed a "door-to-door" surveillance of ARI to identify suspected cases and immediately assess whether to recommend home isolation (Acosta and Marsh, 2020; Miranda, 2020). This massive program for the detection of patients with COVID-19-like clinical symptoms, deployed in the pre-pandemic days and particularly during the early phase of the outbreak in Cuba, represented a key tool to control the spread of the virus. According to official data, by March 22nd (40 confirmed cases in total), the Cuban primary health care system was monitoring over 37,000 persons (MINSAP, 2020). The early identified suspected cases that fulfilled epidemiological criteria such as contact with people who had recently travelled to the island from abroad or with confirmed cases, were immediately evacuated to isolation centers and underwent molecular diagnostics. Meanwhile, confirmed cases were hospitalized and treated according to their clinical manifestations. The unique approach significantly reduced the spread of the virus in the early phase of the Cuban epidemic.

Contact tracing and rapid isolation represent critical tools to reduce the basic reproductive number (R0) of the virus and, therefore, stop the outbreak. A recently published modelling study suggested that by detecting and then immediately isolating over 60% of the cases and contacts, countries can reduce and control the COVID-19 pandemic. Cuba is one of the countries in the region that traces all contacts (Figure 2). In contrast to the digital approach implemented by other countries (i.e. South Korea), the Cuban approach of massive manual contact tracing was coordinated by the far-reaching primary healthcare system and the collaboration of thousands of medical students and healthcare workers. In combination with molecular diagnostics, a comprehensive program of contact tracing remarkably reduces the impact of asymptomatic and pre-symptomatic patients in fueling virus transmission. The surveillance and contact tracing models deployed by Cuba were praised by José Moya, representative of the Pan American Health Organization in the island (Miranda, 2020), and have been critical to controlling the spread of the virus.

3.2 Testing program

Molecular diagnostics of SARS-CoV-2 infections represents another key player in controlling the COVID-19 pandemic. The Director of the World Health Organization, Dr. Tedros A. Ghebreyesus, highlighted the importance of testing on March 16th by stating "you cannot fight a fire blindfolded (…) we cannot stop this pandemic if we don't know who is infected." The RT-PCR (reverse transcription polymerase chain reaction) is the gold standard for laboratory testing of COVID-19. This molecular biology technique allows detection of fragments of the viral genome in early and even pre-symptomatic stages of the infection, facilitating the immediate quarantine of confirmed cases and further contact isolation. Yet RT-PCR is an expensive test and requires a complex infrastructure as well as highly qualify and skilled personnel. As noted, several Latin American and Caribbean countries lack the national infrastructure to develop a mass testing program to detect most COVID-19 cases. Global data show that, in general, countries that deployed a mass, or at least rational, testing program in a timely fashion, significantly reduced the impact of the pandemic by efficiently controlling viral transmission.

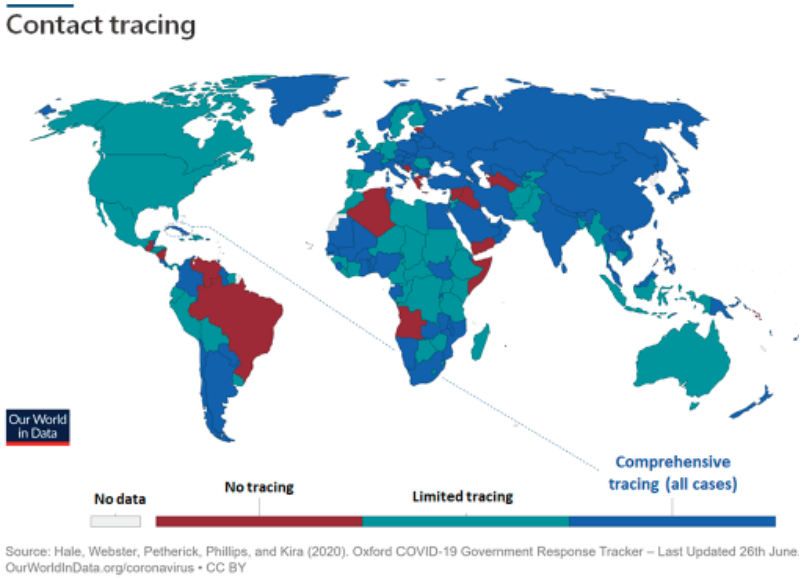


Figure 2. Contact tracing status worldwide. Partially modified and reproduced with permission from the Coronavirus Pandemic (COVID-19), Our World in Data (CC-BY license) (Roser et al., 2020).

Unable to perform mass testing, Cuba used an alternative scheme of molecular testing enabled by outfitting up to seven laboratories in different regions of the country. The Cuban program followed the WHO recommendations of gradually increasing the laboratorial capacity for the molecular diagnostic of SARS-CoV-2 and, more important, to perform daily tests to ensure that no more than 10% of these tests were positive. This is an important criteria that should be addressed by any national testing program. In contrast to the popular belief which suggests the total amount of tests or the per capita test per million of inhabitants is the primary criteria to evaluate a COVID-19 testing program, it is the ratio of total tests for each confirmed case—which takes into account the size of the epidemic—which is the more accurate indicator. An analysis of the official data shows that, throughout its outbreak, the percentage of positive tests in Cuba (except for 27 March) was always under the 10% recommended by the WHO (Figure 3). Overall, during its outbreak, the ratio of total COVID-19 test/confirmed cases in Cuba is 68.8 (Figure 4). Considering only data from June, this value increased to 222.2 tests/confirmed case.

Figure 3. Results of the Cuban molecular testing program for detection of COVID-19 cases. As noted, during its outbreaks, the percentage of positive cases (except March 27) remained under the 10%, as recommended by the WHO. [Data: Ministry of Public Health, Cuba]

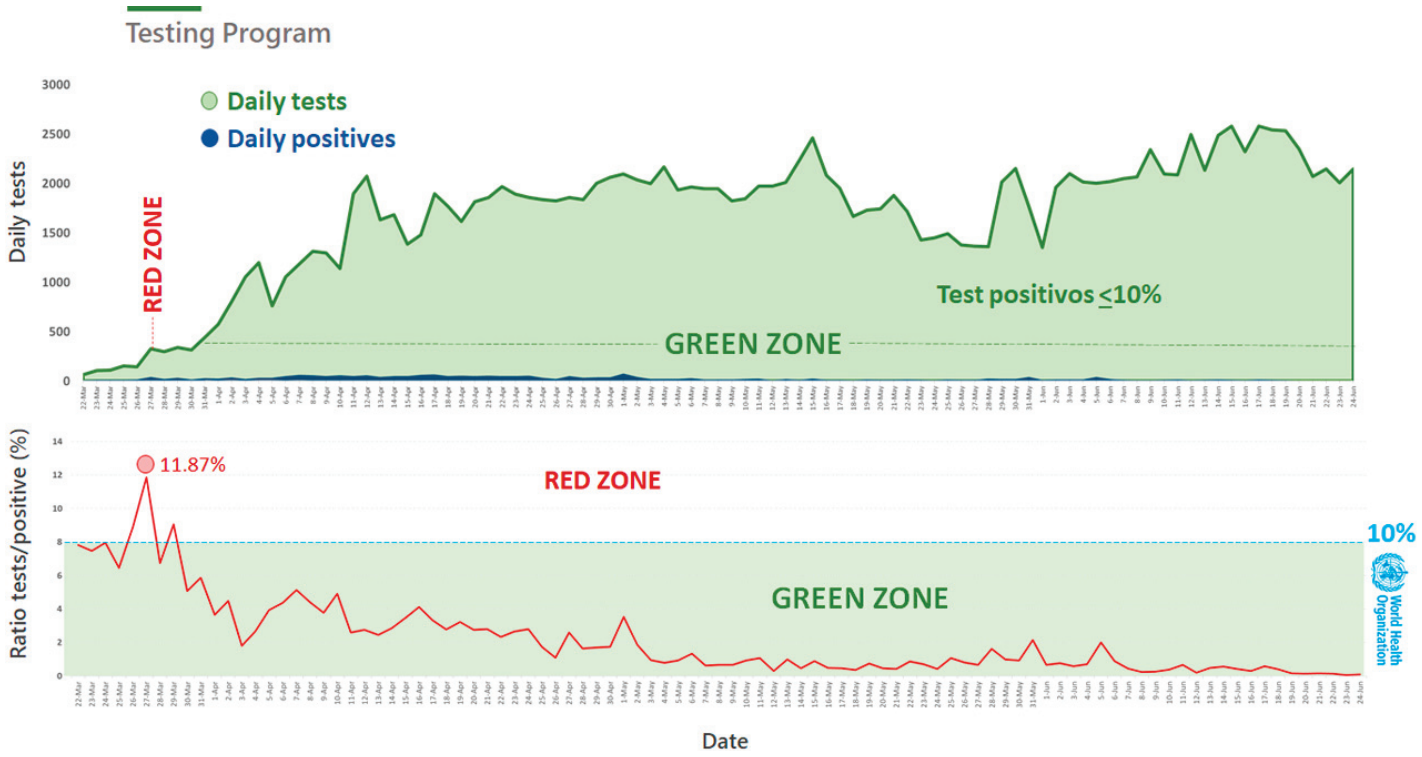
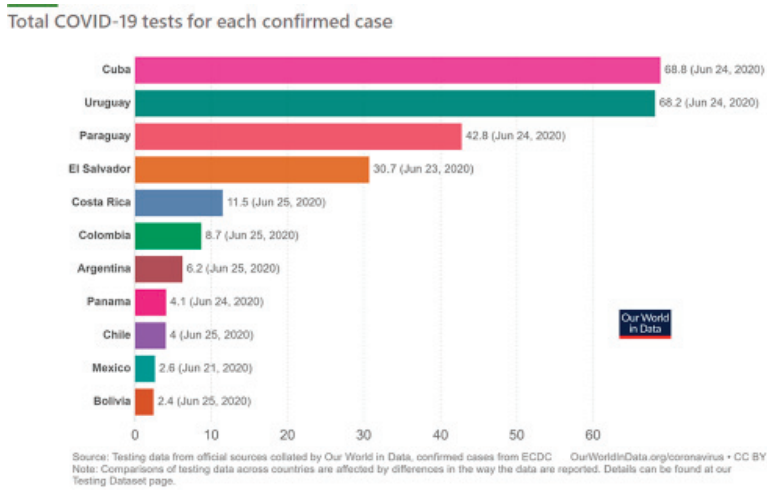


Figure 4. Ratio of COVID-19 test/confirmed cases for some of the countries in Latin America and the Caribbean. Partially modified and reproduced with permission from the Coronavirus Pandemic (COVID-19), Our World in Data (CC-BY license) (Roser et al., 2020).



4. Evolution of the epidemic and final remarks

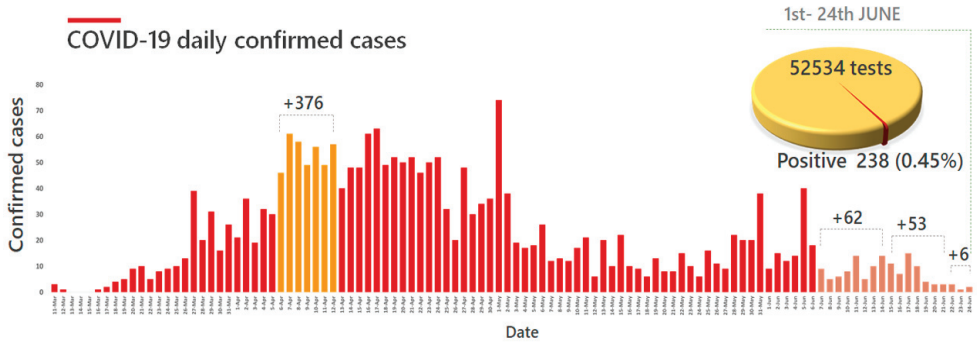
At time of writing (June 24th), Cuba reported a cumulative total of 2,321 COVID-19 confirmed cases and 85 deaths. The island—except Havana—recently moved to Phase 1 of the post-epidemic period, de-escalating several of the mitigation/suppression measures applied during the critical moment of its outbreak. This decision was made considering the positive trends of epidemiological indicators such as daily confirmed cases and fatalities, active cases, patients recovered, and the occurrence of local events with community transmission. In the month of June, Cuba registered two sequential minimums in weekly confirmed cases, an extremely low ratio of positive tests and one biweekly COVID-19-related death (Figure 5). In addition, along with Uruguay, Cuba reported the highest ratio of recovery, as over 93% of the COVID-19 confirmed cases have been already discharged from hospitalization.

To date, the country has only 63 active cases. Most Cuban provinces (as of June 24th) have gone more than two weeks without new COVID-19 confirmed cases, deaths, or local events. Some of them have reported this trend for more than a month. Finally, the number of daily confirmed cases in Havana has dropped significantly during the last week, suggesting that this territory could be entering Phase 1 of de-escalation shortly.

Cuba applied a functional strategy to control its epidemic, based on the timely application of several mitigation/suppression measures, massive surveillance of ARI, and the recently so-called "COVID-19 TETRIS": test, trace, and isolate. In addition, the recommendation to wear face masks in public places contributes to reducing transmission.

Some unique aspects of the Cuban response (massive surveillance, contact tracing, the use of isolation centers) were facilitated by preexisting conditions such as a broad and well-organized primary health care system, the high per capita of medical doctors/millions of inhabitants, and previous experience in rapid evacuations in emergency situations as well as during other epidemics. Remarkably, the massive program of

Figure 5. Evolution of daily confirmed cases in Cuba. Weekly maximum (orange) and sequential minimums (brown) are highlighted. The ratio of test/positive cases for June is also shown. [Data: Ministry of Public Health, Cuba]



ARI surveillance and contact tracing allowed the early detection of pre-symptomatic/asymptomatic patients and their early isolation, thus reducing the rate of transmission. Despite some recent controversies, it has been well documented that pre-symptomatic individuals have a high viral load (He et al., 2020) and represent potential major spreaders of the virus. Finally, the Cuban approach reinforced the epidemiological value of applying a rational testing program for the control of the COVID-19 pandemic.

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