MEDICC Review

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On COVID-19

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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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Cover photo: *Nurse Xiomara Rodríguez at a community polyclinic vaccination site in Havana for phase 3 clinical trial of COVID-19 vaccine candidate SOBERANA 02.*
Credit: *Jorge Luis Baños, IPS, with permission.*

MEDICC Review

Editorial Board

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COVID-19 Wake-up Call: Equity or Else

COVID-19 is neither the first, last, nor the worst pandemic we will face as a species. Novel zoonoses will continue to develop and spread as the climate shifts, ecosystems contract and habitats overlap. It is entirely possible that history will categorize the COVID-19 pandemic as a 'starter plague.' Our hyper-connected, yet increasingly fragmented world is a petri dish ripe for viral mutation and transmission—international travel happens overnight, mismatched and poorly prioritized health and safety regulations lend themselves more to chaos than cures, and nationalist policies foster both festering global viruses and expanding socioeconomic inequities.

The underlying issue is indeed inequity: too many societies prize wealth and comfort for a few over the health and welfare of the many, or even of the planet itself. It explains why those who are marginalized in society have higher rates of disease and death from COVID-19; why some health systems appear to manage while others become overwhelmed with shortages of personnel, beds and even oxygen; and why entire countries and communities have higher vaccination rates than others.

The epidemiology of COVID-19 does not reflect a consensus that we are 'all in this together,' but rather that some people seem to be predestined targets of the disease. We are living through what several scientists have called a syndemic…in this case, the combined effects of negative social determinants, inadequate or nonexistent access to health services, depleted and pauperized public health facilities, poorly protected and unevenly allocated health workers, and finally scarce vaccine availability. Without a sharp and immediate increase in aid to developing countries, it is estimated that some 150 million more people will be pushed into extreme poverty.

If you take Latin America and the Caribbean as a whole—with the United States, it is the epicenter of the current surge in cases and deaths—you will find a region that not only remains the world's most inequitable, but one that has experienced the most serious economic and social crisis in recorded history, with some economies shrinking by nearly 8%. As a result, last year an *additional* 22 million people in the region were plunged into poverty, a number now exceeding 209 million in total. These people are among those most at risk when it comes to COVID-19; their already precarious lives shortened by lack of health services and slow vaccine rollout.

Like their US neighbor to the north, most of these countries have fragmented health systems, services divided between private and public providers, with private insurers challenging physicians for the 'right' to determine what to prescribe and how to treat. Most, with the exception of Cuba and a few others, invest less than 4% of GDP in health care, and do not ensure medical services for all their people, much less medical care on equal terms. In the context of COVID-19, the universal health imperative looms larger than ever, turning a long-term goal into an urgent, practical matter.

As the global pandemic surge multiplies cases and deaths, the equity of vaccine rollout also looms large. Newly reported evidence suggests that vaccine effectiveness is only half the battle. In fact, a recent study indicates that "a vaccine with 65% and 60% efficacy before and after the variants, respectively, can outperform a vaccine with 95% and 90% efficacy, if its distribution is 46% to 48% faster."[1] And of course the reverse is also true. Unfortunately, COVID-19 vaccine availability now is a byproduct of a big pharma industry that for decades has been more focused on vaccine profitability, thus contributing to vaccine nationalism in both R&D and sales.

> **We are far from the time when Jonas Salk refused to patent his polio discovery, for fear that children's lives would be sacrificed on the altar of profit.**

We are far from the time when Jonas Salk refused to patent his polio discovery, for fear that children's lives would be sacrificed on the altar of profit. Today, vaccine rollout is characterized by a glut of vaccines in some countries… and communities…while others are kept in limbo, left in purgatory for another two to three years before their 'turn' comes around. In the end, the world is billions of vaccines short, and new variants threaten to outpace even the most effective vaccines.

In the case of Cuba, the COVID-19 syndemic has become a 'sandemic,' with the added punitive inequity imposed by US sanctions. Despite the change in administration and despite the annual, overwhelming vote by UN member states against this US embargo (deemed a 'blockade' by Cubans); despite the fact that Cuban scientists have produced at least two promising vaccine candidates that they have pledged to make available to other developing countries, US policy is stuck in the past. Cuba, according to Washington, is 'not a priority.' Granted, police violence against people of color, mass shootings, systemic racism, the flood of immigrants fleeing exacerbated poverty and violence, and COVID-19 itself: all are public health emergencies. But so, we would argue, are the lives of 11 million Cubans currently hanging in the balance, still suffering from the Trump era's 242 additional measures tightening the screws. When will they become a priority? When will US sanctions on Cuba become a public health issue? A human rights issue?

> **When will US sanctions on Cuba become a public health issue? A human rights issue?**

The global clock is ticking, the cases of COVID-19 are mounting, the deaths continue. The pandemic is indeed a moment of reckoning. Rather than punishing a small island country, perhaps we should take a closer look at Cuba, since even in dire circumstances, their rates of illness and death from the pandemic are still a tiny fraction of those in other countries of the region and in the USA itself. Perhaps the takeaway from the Cuban COVID-19 experience is that universal health care may be one of the best investments a society can make.

Which brings us to the journal's current issue. As has been the case for the past year, many of the following pages are devoted to the COVID-19 pandemic. Two articles cover the toll COVID-19 has exerted on mental health and our collective psyche; in Lessons from the Field, Fabelo and colleagues delve into the complications the pandemic has caused for treatment maintenance

in patients undergoing therapy for addiction, while an article by Patricia Áres confronts the strangeness that is 'pandemic time.'

Two Viewpoints warn of COVID-19's aftershocks: the first, by Broche and Medina, addresses the neurological and cognitive sequelae of the disease, using preliminary evidence to call for longitudinal studies of patients suffering from persistent, or 'long-haul' illness. The second, by Ley, alerts pediatricians the world over, suggesting that cardiovascular damage in children afflicted by the SARS-COV-2 virus is likely under-reported—an issue of undeniable importance as new variants affect more children worldwide.

Of increasing clinical import, a systemic review by Suárez and Villegas examines the links among aging, chronic disease and the immunopathological progression of the SARS-CoV-2 virus, associating severe clinical manifestations of COVID-19 to low-grade chronic inflammation.

MEDICC Review reiterates our call to Latin American and Caribbean population health, medical and planetary health authors to consider submitting their work to our journal, in English or Spanish. You are the reason we publish.

—The Editors

1. Kim D, Keskinocak P, Pekgün P, Yildrim I. The balancing role of distribution Speed against varying efficacy levels of COVID-19 vaccines under variants. medRxiv [Preprint]. 2021 Apr 13 [cited 2021 Apr 20]. Available at: https://www.medrxiv.org/content/10.1101/2021.04.09.21255217v1

In Memoriam

***MEDICC Review* dedicates this issue to**

V. Gustavo Sierra-González MD PhD

(1952–2021)

A loss for Cuba, Latin America and the world: immunologist and biotechnology pioneer Dr Gustavo Sierra has died from complications of COVID-19. An initiator of Cuba's biotechnology takeoff in the late 1980s, he was a founder of the Finlay Vaccine Institute and the Genetic Engineering and Biotechnology Center, as well as among the first leaders of the BioCubaFarma conglomerate and the first President of the Cuban Society of Immunology. At the time of his death, he chaired the Expert Committee of Cuba's National Immunization Program and served as Advisor to the President of BioCubaFarma.

Credited to Dr Sierra is authorship of the world's first effective vaccine against serogroup B meningococcal disease in 1989, a patent for which his team won the World Intellectual Property Organization's Gold Medal. Earlier, he was among the researchers who obtained Cuba's first interferons.

These accomplishments, together with his later work on a host of other vaccines, earned him the country's highest award, the Carlos J. Finlay Order, as well as honors from the Health and Science Workers Union and distinguished membership in the Cuban Academy of Sciences.

He was advisor to some 45 doctoral dissertations, among his responsibilities as teacher, mentor and guide to generations of physicians, scientists and scholars.

Dr Sierra was a peer reviewer and author for ***MEDICC Review***, his most recent manuscript published in 2019 recounting the history and use of the meningitis B vaccine in Cuba and the world (*Cuban Meningococcal Vaccine VA-MENGOC-BC: 30 Years of Use and Future Potential*).

He was appreciated and loved by his family and so many others for his modesty, wisdom, good humor and boundless solidarity.

Our editors have lost a friend and colleague. The world has lost a vaccine hero.

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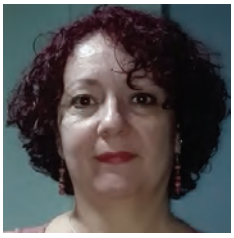

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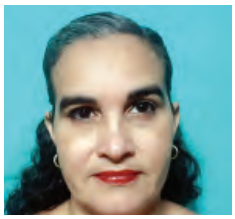

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The remaining authors in the following pages are members of the journal's editorial team.

AN EXPERIENCE WITH CUBAN BIOTECH'S NASALFERON TO PREVENT SARS-COV-2 INFECTIONS IN INTERNATIONAL TRAVELERS AND THEIR CONTACTS

To the Editors:

The COVID-19 pandemic has led to collapse of national health systems across the globe, overwhelmed by the imbalance between health care needs and availability of human and material resources. To control and prevent further transmission, Cuba has developed intersectoral strategies in which the biotech industry has been deeply involved.[1,2]

One of several products destined for COVID-19 control is Nasalferon, a nasally administered recombinant alfa 2b interferon that acts against viral replication.[3,4] Its use is recommended as a complement to public health measures to reinforce the first line of defense against the virus in the oropharyngeal tract.

From January 14 to 24, 2021, 103 international adult travelers arriving in Cárdenas, Matanzas Province, as well as their 317 close adult contacts—all with initial PCR tests negative for SARS-CoV-2—received Nasaferon.[3] Each was visited daily for 15 days, to determine SARS-CoV-2 infection and observe any adverse events potentially related to the medication. At 15 days, PCR results and clinical examination indicated that no travelers or contacts had become infected.

Headache (73/420; 17.4%) and weakness (13/420; 3.1%) were the only adverse events notified. All events were mild, transient and limited. No one had to stop using the medication (applied twice daily) because of potentially drug-related adverse events.

Based on our experience, we strongly recommend the use of Nasalferon as an additional tool to prevent SARS-CoV-2 infection in travelers and their close contacts.

This study was part of a larger intervention in Matanzas Province during January and February 2021. Along with the Cárdenas travelers and contacts, workers from three hotels in Varadero Beach—Sol Palmeras, Meliá International and Royalton Hicacos—and from the Las Morlas campsite were also included.

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Submitted: February 10, 2021
Disclosures: None

BEST WISHES FROM A FOUNDING EDITORIAL BOARD MEMBER

Dear Dr Keck and Ms Reed,

I regretfully submit this letter of resignation from the Editorial Board on account of my retired status and my age—I turn 82 this year.

It has been an absolute privilege to witness the innovative transformation and tremendous progress ***MEDICC Review*** has made over the years, and I was honored to have served on the Board for all the years during which the journal has made such significant contributions to the body of knowledge and influenced health care globally.

I am absolutely confident that it will continue to do for many more years to come. Kudos to you for your dedication and commitment.

With collegial regards,

Daniel J. Ncayiyana MD FACOG
Emeritus Professor, University of Cape Town
Emeritus Editor, *South African Medical Journal*

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Submitted: February 21, 2021
Disclosures: None

COVID-19 Requires Innovation, Regulation and Rigor: Amaylid Arteaga-García MD MS

Director, National Clinical Trials Coordinating Center (CENCEC)

Tania L. Aguilar-Guerra MD MS and Conner Gorry MA

The effects and implications of COVID-19 are global, comprehensive and long-term. The pandemic has exposed inequities, the fragility of economic and political systems, and in many cases, skewed priorities. Population health, not to mention planetary health, is suffering as a result. Nevertheless, the global health crisis in which we are embroiled has provided opportunities for effective collaboration, scientific innovation and real dialog around health and equity.

Dr Amaylid Arteaga-García, director of Cuba's National Clinical Trials Coordinating Center (CENCEC), emphasized these opportunities when discussing Cuba's clinical trials in times of COVID-19. Founded in 1991 in response to the groundbreaking research emerging from the country's biopharmaceutical sector—including the first safe, effective vaccine against serogroup B meningococcal disease, VA-MENGOC-BC in 1989 and a recombinant vaccine against hepatitis B, Heberbiovac in 1990—CENCEC now coordinates some 100 clinical trials annually, many of them multi-site trials involving thousands of volunteers. Little did Dr Arteaga García know what problems lurked when she became CENCEC director in 2019.


E. Añé

In February 2020, Cuba implemented its National COVID-19 Prevention & Control Plan. This included a scientific Innovation Committee tasked with evaluating promising projects, products and research that might be used in the health system to control and treat COVID-19. This approach taps into two of Cuba's strengths: biotechnology and primary health care. Given the volume and complexity of COVID-19 clinical trials, Dr Arteaga-García's background as a family doctor with a master's degree in primary health care and a passion for research, augured well for marshaling these strengths. She is also a professor at the Medical University of Havana. Dr Arteaga-García spoke to ***MEDICC Review*** about Cuba's regulatory framework and clinical trials currently underway to detect, treat and control COVID-19.

MEDICC Review: **Multi-center research is your area of expertise. Can you describe your professional journey from family doctor to CENCEC director?**

Amaylid Arteaga: Scientific research fascinates me—it has since I was a medical student. I find primary care-level research more fascinating still; it's why I specialized and sought out opportunities in this area. I realized the allure of research and the impact it can have on population health when I was asked to coordinate a study across 75 community polyclinics. This was in 2005–2006, a transformative moment in our medical education and primary care systems when in-classroom instruction was complemented by teaching at academically-accredited 'university polyclinics.' Our study looked at how this hands-on learning in the community affected the delivery of health services and patient satisfaction.

The study spanned more than two years, during which I was director of the Héroes de Girón Polyclinic in Havana's Cerro municipality. Subsequently I was offered a position at the Ministry of Public Health (MINSAP), but I didn't want it. I sought more on-the-ground experience. What convinced me to accept the job was the prospect of conducting more community-based participatory research. The study that made me fall in love with my work and set me on my definitive career path looked at the introduction and use of six domestically-produced biotech products into the primary health care system. I directed the Health Technologies Innovation Department within MINSAP by this time, driven by a passion for research. When I began at CENCEC two years ago and immersed myself in the world of clinical trials, I found my life's work; I hope to spend the rest of my career here.

MEDICC Review: **Can you explain CENCEC's role in the clinical trial process?**

Amaylid Arteaga: CENCEC was formed to conduct clinical trials for our nascent biotech industry, working closely with products developed by the Molecular Immunology Center (CIM) and the Genetic Engineering and Biotechnology Center (CIGB). As time

went on and Cuban researchers made more scientific innovations, Cuba's regulatory framework was overhauled to create a national clinical trials system and our role expanded.

Today, our clinical trials system is designed as a unified, integrated network where we serve as the link between Cuba's national regulatory authority, the Center for State Control of Medicines and Medical Devices (CECMED), the biotech industry and the health system. While we used to coordinate individual trials, today we coordinate Cuba's entire clinical trial system, monitoring each trial in that system from conception to execution, ensuring adherence to best practices and design protocols. Our trial control and oversight mechanisms are designed and evaluated together with MINSAP.

CENCEC offers all the services necessary to conduct clinical trials: trial design analysis; data collection and management; pre-certification evaluation of clinical sites; problem solving within clinical trials, etc. It's a mix-and-match model where institutions can contract all or some of our services, similar to Contract Research Organizations (CROs) typically used by pharmaceutical companies elsewhere. Any foreign entity wishing to conduct clinical trials in Cuba must contract CENCEC—the only entity authorized to control trials within our health system.

MEDICC Review: **Cuban clinical trials are officially registered, correct?**

Amaylid Arteaga: That's right. All clinical trials need to be published in a public registry to comply with best practices related to transparency, patient recruitment and other fundamental principles. The Cuban Public Registry of Clinical Trials (https://rpcec.sld.cu/) was launched in 2007—the first in Latin America—and in 2011 was accredited as a WHO Primary Registry. Today, all Cuban clinical trials are registered on this platform.

MEDICC Review: **How about training and other 'behind the scenes' work necessary for clinical trials coordination?**

Amaylid Arteaga: CENCEC is also the national coordinating center for ethics in health research. Every clinical trial must be approved by an independent ethics committee. As the coordinating center, we participate in the composition of all the ethics committees related to vaccine production in Cuba.

A large part of our work is also related to organizing multi-center clinical trials in terms of guaranteeing compliance with trial protocols, designing proper patient flow at vaccination sites and training our professionals in clinical best practices. CENCEC coordinates certification of vaccination sites and nurses administering the vaccines, as well.

MEDICC Review: **Scores of clinical trials were underway when you became director of CENCEC. Then the COVID-19 pandemic hit, generating many more trials. How was the work organized to incorporate new trials?**

Amaylid Arteaga: By February 2020, we had a national, intersectoral plan in place. In terms of clinical trials for treatments, vaccines and diagnostics, our most urgent endeavor was to identify Cuban research and products that might be useful in addressing the pandemic. Two scientific taskforces were convened as part of the national plan to achieve this: the Science Group and the Innovation Committee. It is led by the Director of Science and Technology Innovation at MINSAP and her counterpart at BioCubaFarma (Cuba's biotech conglomerate), and includes specialists from individual biotech institutions, CENCEC and CECMED. It is responsible for evaluating which Cuban biotech products might be used in our COVID-19 response. The Science Group, meanwhile, is tasked with analyzing research that might be useful. Together, these groups developed national, pandemic-specific protocols.

By the time we detected our first cases here in Cuba in March 2020, these protocols were in place. But within a month, the global epidemiological situation worsened considerably, with rapid increases in transmission and mortality. This was a dramatically different panorama, making our search for solutions more urgent still. Our imperative at this point was to adjust regulatory mechanisms for the global health emergency, while maintaining standardized best practices required for new products.

MEDICC Review: **Regulatory authorities worldwide made adjustments in response to COVID-19. What did Cuba do in this regard?**

Amaylid Arteaga: We streamlined our clinical trial process, making it more efficient, without compromising scientific and ethical quality. We went from a silo model, where each step was conducted independently by the corresponding entity—CENCEC, CECMED, Independent Ethics Committees for Scientific Research, CEI—to an integrated, collaborative model coordinated by the Innovation Committee. Under this new model, the Innovation Committee vets and recommends the most promising products, with CENCEC, CECMED and the CEI analyzing the proposed trial together according to established guidelines; CECMED does not green light any clinical trial before receiving MINSAP and CEI authorization. The transition was arduous. We worked around the clock organizing this new process.

The products currently used in our national COVID-19 treatment protocols were authorized according to this streamlined model. The new process has been quite a revelation…it's more dynamic and innovative, while maintaining the same scientific and methodological rigor. Like many national regulatory authorities, CECMED can also issue emergency use authorization (EUA) and we're using this mechanism as well.

MEDICC Review: **Which brings us to Cuba's vaccine candidates…**

Amaylid Arteaga: All trials for our COVID-19 vaccine candidates—SOBERANA 01, 02 and Plus; Abdala and Mambisa—were authorized according to this streamlined model. Today we have over 10 regulatory-approved clinical trials testing these five candidates; all five have concluded phase 1, plus we have a pair—Abdala and SOBERANA 02—that have concluded phase 2 and are now in phase 3 trials. These two candidates are also in parallel intervention trials vaccinating frontline health workers in Havana that will eventually be broadened to include most adults in the province.

Conducting concurrent phase 3 trials and intervention studies allows us to test and reaffirm efficacy and gather preliminary data on effectiveness by approximating real-world conditions

Conducting concurrent phase 3 trials and intervention studies allows us to test and reaffirm efficacy and gather preliminary data on effectiveness by approximating real-world conditions. Hopefully these trials will provide the evidence we need for EUA approval for these most advanced vaccine candidates, and we will be able to begin mass vaccination of our population. We should know soon.

Other candidates in different stages of evaluation include SOBERANA Plus, currently in phase 2 trials to evaluate safety, reactogenicity and immunogenicity in COVID-19 convalescent patients. Initial results from this trial are encouraging, with the vaccine generating impressive levels of neutralizing antibody titers. Pending further results, we may be able to immunize all our convalescent patients with SOBERANA Plus.

MEDICC Review: **Can you talk specifically about CENCEC's responsibilities around Cuba's COVID-19 vaccines?**

Amaylid Arteaga: As I mentioned, CENCEC oversees the entire clinical trial process from conception to conclusion, but also can be contracted by research centers to assume individual steps in that process. All the SOBERANA candidates are products of the Finlay Vaccine Institute (IFV); the institute's in-house specialists authored the trial design. Once that design was approved by CECMED, IFV contracted us to conduct all trial phases for SOBERANA 01, 02 and Plus.

Our role was more limited with phases 1 and 2 of Abdala and Mambisa, both Cuba's Genetic Engineering and Biotechnology Center (CIGB) products, but now is intensifying as the number and types of clinical trials multiply. Which is another challenge because we're reaching our limit. Although we haven't had to decline any new contracts, we're trying to figure out ways to increase our output without affecting service quality. One solution is a push for new hires at CENCEC to increase our workforce; we're working on that initiative right now.

In preparation for the phase 3 trials and intervention studies, we designed and implemented a standardized methodology all vaccine sites across the country must follow. This includes but is not limited to: a waiting area, a vaccination room, an area for one-hour post-vaccination observation and another area for attending any adverse events that may arise. Each person to be vaccinated must receive a pre-vaccination consult and another after the one-hour observation period.

Finally, we have a monitoring role, performing site visits to ensure trial design, documentation and data collection protocols are being followed. This is fundamental: we cannot have the quality of a trial compromised by faulty documentation. Due to the magnitude of our intervention study, during which 1.7 million people will be vaccinated, we've trained facilitator-monitors—mostly university professors with backgrounds in research. CENCEC just doesn't have enough monitors for all the clinical sites.

MEDICC Review: **You mentioned the intervention study—which has been anxiously awaited in Havana, Cuba's COVID-19 epicenter. Can you explain how this works?**

Amaylid Arteaga: This is a 'real-world scenario' study conducted simultaneously with phase 3 trials in a large number of volunteers. The goal is two-fold: to supplement efficacy data gathered from phase 3 trials and to begin demonstrating effectiveness. Due to the gravity of this pandemic and the global health emergency it represents, the scientific community is compelled to conduct parallel studies such as these, with combined phases—an unusual, but necessary, process and only pursued when it is safe to do so. The key is to remain true to the criteria, protocols and schedule established by the national regulatory authority. Introducing a more flexible, agile system to provide a faster response to COVID-19 is not unique to Cuba.

MEDICC Review: **How many people work at CENCEC and how are they distributed?**

Amaylid Arteaga: We have 150 people on our team, 60% of whom are women. Each and every one of us is working on the clinical trials—visiting health services and institutions, evaluating vaccination sites, ensuring they meet the criteria necessary for a phase 3 clinical trial, preparing them for certification and establishing conditions for the population intervention study. In the phase 3 trial in Havana alone, there are 35 CENCEC specialists working full time.

We've had to request all hands on deck to prepare for the intervention study. We have the entire institution working on this, including specialists from our quality and regulatory divisions, from our control department…By design, CENCEC is a national network, with specialists working as regional coordinators around the country, including in Santiago de Cuba and Guantánamo in the eastern region where COVID-19 clinical trials are also ongoing.

MEDICC Review: **Has the work generated by the pandemic affected trials that were already underway?**

Amaylid Arteaga: Prior to the pandemic, 40% (nearly 50) of the clinical trials already underway were evaluating innovative treatments for cancer. None of those treatments or trials has been halted even though we're coordinating an additional 25 new COVID-19-related trials. Trials that have been halted or suspended since the pandemic was declared is due to material shortages or lack of eligible candidates, not personnel shortfalls at CENCEC. In summary, we've maintained pre-COVID-19 trials, plus incorporated all the trials related to the pandemic including vaccines, treatments and medical devices.

MEDICC Review: **Your job can't be easy…any final considerations?**

Amaylid Arteaga: The past two years were a steep learning curve for me. But I love working on clinical trials—it consolidates my experience as a family doctor, polyclinic director and researcher. Also, CENCEC has a professional, well-prepared team conducting rigorous research. The work is demanding, but dynamic, the way I like it.

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Monoclonal Antibodies vs COVID-19: Eduardo Ojito-Magaz MS

General Director, Molecular Immunology Center

Tania L. Aguilar-Guerra MD MS and Conner Gorry MA

Cuba has five COVID-19 vaccines in clinical trials and is on track to receive emergency use authorization from the country's regulatory agency to begin mass vaccination with two of those candidates: Abdala and SOBERANA 02. Results from phase 1 and 2 trials of these vaccines, the first developed and produced in Latin America, have been encouraging, both in terms of safety and immunogenicity. The ongoing phase 3 trials will continue to look at safety, together with efficacy; parallel intervention studies involving over a million people in Havana will begin generating data on effectiveness. Coordination between Cuba's biotechnology sector and its public health system—particularly throughout the different levels of primary care—to control and treat COVID-19 is a cornerstone of the Cuban strategy and one that could serve as a blueprint for future pandemics.

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Another Cuban product, itolizumab, is showing positive results mitigating cytokine release syndrome (CRS) in COVID-19 patients with moderate-to-severe acute respiratory distress syndrome (ARDS). Developed in collaboration with Biocon (India), itolizumab is administered under an expanded access program to treat vulnerable populations in Cuba. Marshaling complementary capacities of dozens of institutions belonging to BioCubaFarma—the country's biotech conglomerate—and developing therapies, vaccines and medical technologies together, is another cornerstone of Cuba's strategy to combat COVID-19 and improve population health.

The Molecular Immunology Center (CIM) is a key player in this strategy. Founded in 1992, CIM is a powerhouse in monoclonal antibody research and production, with 6 registered products and 22 in the pipeline. Known for several novel therapeutic cancer treatments, CIM has over two decades' experience producing complex recombinant proteins in mammalian cells on an industrial scale. Once Cuba's Innovation Committee (convened in January 2020 as part of the National COVID-19 Prevention & Control Plan) determined Cuban researchers would pursue protein subunit vaccine candidates, they turned to CIM to produce the required receptor-binding domain (RBD) of the SARS-CoV-2 spike protein, among other responsibilities.

CIM's General Director, Dr Eduardo Ojito-Magaz, is a chemical engineer and holds a master's degree in biotechnology. He spoke with ***MEDICC Review*** just days before 1.7 million Havana residents began participating in the country's largest intervention study with the COVID-19 vaccines his center helped make possible.

MEDICC Review: **Cuba hopes to vaccinate its entire population this year with COVID-19 vaccines developed on the island. Can you tell us about CIM's role in producing the SOBERANA line?**

Eduardo Ojito: CIM, together with the Genetic Engineering and Biotechnology Center (CIGB), are Cuba's leading institutions when it comes to immunology and cancer technologies. We're the brain trust so to speak—of all the research centers under the BioCubaFarma umbrella, CIM and CIGB are the main repositories of knowledge about these technologies and immune response. Our institution has over 25 years' experience producing monoclonal antibodies (mAbs) and currently provides the national health system with several products using these proteins, including erythropoietin-stimulating agents, granulocyte colony-stimulating factor and human growth hormone. Recognizing this expertise, the Finlay Vaccine Institute (IFV) approached us to produce the proteins used in our country's first COVID-19 candidates, SOBERANA 01 and SOBERANA 02.

Our collaboration focused mainly on two areas: 1) developing the recombinant RBD and 2) producing enough recombinant RBD for the vaccine, using CIM technology based on mammalian cell cultures.

MEDICC Review: **Most of the world has no idea about Cuba's history producing vaccines for use in its public health system, including a national regulatory authority that serves as a Regional Reference Authority for PAHO/WHO…**

Eduardo Ojito: Cuba has over 30 years' vaccinology experience and proven safety profiles for the vaccines we produce, distribute and market abroad. This includes CIGB's pentavalent vaccine that protects children against pertussis, diphtheria, tetanus, hepatitis B and *Haemophilus influenzae* type b, and the VA-MENGOC-BC vaccine developed by IFV in 1989—the world's first safe, effective vaccine against serogroup B meningococcal disease. In addition to administering these through our own health system, Cuba exports these vaccines to dozens of other countries. In short, several million people around the world are immunized with Cuban vaccines.

Several million people around the world are immunized with Cuban vaccines

Such experience, coupled with a technological platform and evidence base spanning decades, allowed us to modify our processes quickly and confidently for a new vaccine—in this case, for COVID-19. It's no coincidence that SOBERANA 02 couples recombinant RBD with tetanus toxoid, which is used in all the vaccines in our national health system. Starting with a proven technology provides an added layer of confidence for our COVID-19 candidates.

It helps, too, that CIM's production technologies are certified by our national regulatory authority, the Center for State Control of Medicines and Medical Devices (CECMED), but also foreign authorities around the world. Any vaccine must be approved by the importing country's regulatory agency before it can be used in their health system. In Mexico, vaccines have to be approved by the Federal Committee for Protection from Sanitary Risks (COFEPRIS); the National Health Surveillance Agency, ANVISA, is the regulatory authority in Brazil; in Argentina, it's the National Administration of Drugs, Foods and Medical Devices (ANMAT); and so on. People trust our products because our vaccines have proven safe and effective according to independent regulatory authorities in individual countries for over 20 years.

MEDICC Review: **It's clear Cuba has the brain power. But does it have the manufacturing power to produce enough doses of the COVID-19 vaccines?**

Eduardo Ojito: Without a doubt we've shown our capacity for generating ideas—it's one of our strengths. Cuban science is intense; we generate knowledge at an incredible pace. What I mean by that is we are adept at identifying a scientific problem, generating a hypothesis to research that problem, and defining what scientific method is most appropriate for investigating it. The question is: how do you convert that knowledge, that scientific method, into a viable product? This has proven extraordinarily challenging with COVID-19 vaccines.

Organizationally, we've faced substantial hurdles. In just one year, we've had to conceive, develop and produce vaccine candidates, plus ramp up our technology, design and conduct clinical trials, and comply with all necessary requisites for any new pharmaceutical product like toxicology and stability studies. In order to achieve all this in such a short time, we innovated, by shifting our production capacity to the spike RBD for use in the SOBERANA candidates.

CIM's production capacity of monoclonal antibodies is on par with the biggest pharmaceutical manufacturers in Latin America and we have successfully produced enough doses for the ongoing phase 3 trials and intervention studies. To comply with our national vaccination plans, we will need 30–35 million vaccine doses to cover our entire population, meaning CIM has to produce 100 grams of spike RBD monthly. We have that capacity right now and will continue at this pace to be able to produce the 15 million doses needed over the next few months to begin vaccinating our population.

MEDICC Review: **What implications has the push for a COVID-19 vaccine had for production of other therapies and treatments in CIM's portfolio?**

Eduardo Ojito: To tell you the truth, this pandemic steamrolled us: initially, we thought our 500-liter bioreactor would be sufficient to produce the necessary quantities of antigen without affecting other products. But it quickly became clear that we had to speed up pharmaceutical and clinical development of our vaccine candidates, that time was of the essence and that CIM would have to switch over its entire production capacity to manufacture the proteins needed for COVID-19 vaccines. This represented a significant organizational and technological challenge for us.

As a result, we made the difficult decision to pause production of nimotuzumab, an anti-epidermal growth factor therapeutic monoclonal antibody used to treat head, neck and pancreatic cancers and astrocytoma tumors. We always maintain a three-month supply surplus to guarantee this treatment for our patients in case of any unforeseen event and are supplementing supplies with imported nimotuzumab. Cuba has joint venture production facilities in Bangkok and Beijing that manufacture our products for the Asian market; we're finalizing details now to receive nimotuzumab from our Beijing plant.

MEDICC Review: **What about material resources? Has CIM faced problems acquiring the inputs it needs to produce the spike RBD?**

Eduardo Ojito: We've had fewer challenges on this front because the same materials used to produce monoclonal antibodies for other vaccines in our portfolio are used in SOBERANA. For example, the inputs for erythropoietin—which we acquire from Latin America and Europe—are the same, so we didn't have to procure more materials; it was more a question of retooling our production lines and ramping up production. This was simpler than the organizational challenges, which were quite complex.

MEDICC Review: **Shifting from vaccines, is CIM producing treatments for COVID-19 patients?**

Eduardo Ojito: Yes. It's called itolizumab, and I'll admit it's one of my favorite products. Itolizumab was originally developed to treat cutaneous T-cell lymphoma and severe psoriasis; CIM founders tell

me it was the first mAb produced here. Researchers subsequently discovered that itolizumab moderated cytokines associated with inflammatory response in certain autoimmune diseases and could be used to treat rheumatoid arthritis, for example.

In March 2020, Dr Tania Crombet (Clinical Research Director, CIM; see *MEDICC Review's* Cuba's Women of Science Collection for an exclusive interview, Eds.) proposed using itolizumab to mitigate inflammatory response in COVID-19 patients. This was one of those 'aha! moments' provided by the pandemic: it forced us to look at science from a different perspective and take an innovative approach. From that moment, we began considering the possibility of repurposing itolizumab for COVID-19 treatment—a strategy that is gaining global traction as scientists repurpose existing drugs in an effort to find effective treatments. In the case of itolizumab, new findings were just published and oncologist researchers in the USA are investigating possible new applications of the drug. It's an amazing product; the evidence speaks for itself.

MEDICC Review: **How is Cuba contributing to that evidence base?**

Eduardo Ojito: Clinical trials evaluating the safety and efficacy of itolizumab in COVID-19 patients with acute respiratory distress syndrome (ARDS) are currently underway at the Manuel Piti Fajardo Military Hospital in the central city of Santa Clara. Trial protocols and design are registered with the Cuban Public Registry of Clinical Trials (https://rpcec.sld.cu). More than a dozen clinical sites in the central and western part of the country are participating in the trial but it is coordinated at the Santa Clara hospital because they have the most clinical experience applying itolizumab in patients with severe SARS-CoV-2 pneumonia, including appropriate administration for ICU patients and evaluating adverse reactions. The professionals at the Manuel Fajardo Hospital are in the forefront of this initiative and are researching applications of itolizumab to treat other acute respiratory infections, as well; treatment protocols for these additional applications are being designed now.

MEDICC Review: **Our readers may recall another CIM product making headlines prior to COVID-19. Can you update us on the CIMAvax clinical trials being conducted at Roswell Park in the United States?**

Eduardo Ojito: In 2018, Cuba and Roswell Park Comprehensive Cancer Center entered into a research and development partnership to produce innovative cancer therapies. CIMAvax, a CIM therapy for non-small cell lung cancer approved for Cuba's Basic Drug List in 2012, is currently in clinical trials at the Roswell Park campus in Buffalo, New York. This is a strategic, but also historic alliance: receiving FDA approval for trials using a Cuban product is groundbreaking and the joint venture agreement to produce CIMAvax in Cuba for the US market is *sui generis*.

Three dozen patients—well shy of the 100 required—are currently enrolled in the CIMAvax trials being conducted at Roswell Park. Ultimately, the goal is to complete phase 3 trials in the United States, gain FDA approval for the treatment and make it available to US patients.

The trials recently incorporated off-campus cancer patients from the surrounding community. This is extraordinarily important in my view. Here in Cuba, CIMAvax is administered to patients at the primary care level, not in oncology hospitals or other tertiary institutions. That Cuba's community-based approach is being adapted to a US context, using a Cuban-produced therapy, is an endorsement of our biopharmaceutical products, but also our organizational know-how, and Cuban science in general.

MEDICC Review: **A Cuban biopharmaceutical product with FDA approval…that is groundbreaking. Were there hurdles?**

Eduardo Ojito: As you know, any pharmaceutical product has to adhere to regulatory standards, best practices and other parameters set by the country where it will be used. The FDA has approved CIMAvax for phase 1/2 use and we've had no problems to date. The plan to produce CIMAvax for the US market at a manufacturing plant in Cuba's Mariel Economic Development Zone is more challenging. Regulatory standards for phase 3 and commercial use in the US are very high. Ours are too, but compliance for the US market implies making certain upgrades, technological updates, and auxiliary-system improvements. So the plan is on hold for now—at least until the required number of candidates for the clinical trials at Roswell Park is reached and that depends on the epidemiological situation created by COVID-19.

MEDICC Review: **Are other monoclonal antibodies in production or in the pipeline at CIM?**

Eduardo Ojito: The only mAb commercially available at the moment is nimotuzumab. Meanwhile, itolizumab, another monoclonal antibody, has received conditional registration from CECMED for treating COVID-19 patients and is currently in clinical trials, as I mentioned. Another product we have in the pipeline and which has already received Cuban registration is Ac CD20, used to treat B-cell malignancies. We had to pause production temporarily on this product due to limited manufacturing capacity. Other mAbs in different stages of development include the PD-L1 molecule for certain cancerous cells and the 14F7 molecule, used to treat solid tumors. The latter is in clinical trials here in Cuba.

We're taking advantage of evolving technology to complement our mAb products with others, especially antibody-cytokine fusion proteins known as immunocytokines. One molecule showing great promise in clinical development is interleukin-2 (IL-2) mutein, as well as another fusion protein, IL-2 Fc.

We're also working with bispecific antibodies (bsAbs), molecules that can bind to two different antigens simultaneously. We acquired this technology overseas and are positioning CIM to remain on the cutting edge of science and technology moving forward.

MEDICC Review: **How does it feel to have your entire country watching your work and awaiting results while the pandemic rages? It must be an anxious mix of stress, pride, and accomplishment.**

Eduardo Ojito: I'm 49 years old, born, raised and inculcated with the ideals of the Revolution—ethical, humble, unpretentious. I honestly don't feel as if I'm doing anything special. I'm just trying to make good on our commitment to our citizens, our country, to have a safe, effective vaccine that can cover our entire population by year's end.

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Clinical–Epidemiological Characteristics of the First Patients Diagnosed with COVID-19 in Cuba

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ABSTRACT

INTRODUCTION COVID-19 is caused by the novel coronavirus SARS-CoV-2 and was declared a pandemic on March 11, 2020, the same day that the first cases in Cuba were diagnosed. In Cuba, all confirmed cases of COVID-19 were hospitalized from this point forward.

OBJECTIVE Characterize the first patients diagnosed with COVID-19 in Cuba.

METHODS We carried out a descriptive, cross-sectional study of 415 suspected cases of COVID-19 admitted to the Pedro Kourí Tropical Medicine Institute in Havana, Cuba, from March 11, 2020 through April 10, 2020. (In Cuba, all patients suspected of being COVID-19–positive were admitted to hospitals or isolation centers for observation and treatment.) Of these 415 individuals, 63 (15.2%) tested positive for SARS-CoV-2. Information was obtained from the Institute's databases as well as a standardized interview form for cases confirmed or suspected as infected with the novel coronavirus. We considered the following variables: age, sex, occupation at the time of interview, national origin, personal health history, time elapsed between symptom onset and hospital admission, signs and symptoms, diagnosis and status at discharge. We based our analysis on frequency distributions and double-entry contingency tables.

RESULTS The mean age was 50 years (range: 16–94 years). The 45–54 age group represented the largest share of cases (25.4%; 16/63); persons aged ≥65 years were 20.6% (13/63); there were more men than women (55.6% vs. 44.4%). Cubans represented 52.4% (33/63) of patients while 47.6% (30/63) were from 14 countries where COVID-19 had already been identified. All foreigners and Cubans who arrived from abroad were considered imported cases (54.0%; 34/63). Health personnel (10 doctors and 1 nurse) represented 17.5% (11/63) of cases. Cough (50.8%), fever (46.0%), sore throat (22.2%) and headache (19.0%) were the most frequently reported symptoms. Asymptomatic patients represented 25.4% (16/63) of cases. Hypertension was the most frequently associated chronic disease (28.6%), followed by asthma (25.0%) and diabetes (17.9%). Patients who were admitted to hospital ≥3 days after symptom onset represented 66.7% (42/63) of cases. Mean hospital stay was 13.7 days (range: 1–27 days).

Factors associated with a higher risk of contracting the disease included occupation as a healthcare worker (OR: 1.85; 95%, CI: 0.88–3.87) and aged ≥65 years (OR: 1.68; 95% CI: 0.85–3.34).

Five individuals died, for a fatality rate of 7.9% (three foreigners and two Cubans; four men and one woman). Four of these patients were infected outside of Cuba and one was identified as a contact of a confirmed case. All patients who died had significant comorbidities (diabetes, asthma and hypertension). Age of deceased patients ranged from 54 to 87 years.

CONCLUSION The first patients diagnosed with COVID-19 in Cuba were admitted to the Pedro Kourí Tropical Medicine Institute in Havana. They share characteristics with those reported by other countries: more men than women were affected, and comorbidities including hypertension, diabetes and asthma were all important risk factors, as was age ≥65 years. More than half of all cases were imported, and autochthonous patients were all contacts of confirmed cases.

KEYWORDS Pandemics, COVID-19, SARS-CoV-2, Cuba

INTRODUCTION

The current pandemic has resulted from COVID-19, an infectious respiratory disease caused by the SARS-CoV-2 virus, and is characterized by rapid spread and high fatality. [1,2] Clinically, COVID-19 has been accompanied most often by fever, cough, dyspnea and pneumonic changes on chest radiography.[3,4]

WHO declared the novel coronavirus a pandemic on March 11, 2020, due to its spread by that month to 58 other countries in different regions of the world, including the Americas.[1] The pandemic's evolution, in terms of incidence rates, mortality and rapid expansion, constitutes a challenge for countries' health and epidemiological surveillance systems, which must improve their capacity to detect cases and analyze the massive amounts of data generated. At the time this article was written the number of infected individuals has exceeded 88 million worldwide, with more than 1 million deaths to date in 218 countries and territories.[5–7]

IMPORTANCE
We describe the main demographic and clinical–epidemiological characteristics of the first patients diagnosed with COVID-19 in Cuba, providing a reference for the history of the pandemic there.

COVID-19 surveillance began in Cuba in January 2020. The first cases, three Italian tourists, were confirmed at the Pedro Kourí Tropical Medicine Institute (IPK) in Havana, Cuba, on March 11, 2020. The pre-epidemic phase was declared in the country on March 27, beginning with a local transmission event in Matanzas province. During a pre-epidemic phase confirmed cases are travelers from affected countries and their local contacts. The limited autochthonous transmission phase was declared on April 7, 2020.[8] In this phase, cases in which it is not possible to establish a link with travelers from affected areas are confirmed, reported, and contact tracing is initiated.

The objective of this study is to describe the first patients admitted to IPK with suspected COVID-19, who were confirmed COVID-19–positive between March 11 and April 10,, three days

after the limited autochthonous transmission phase was declared. This paper aims to encourage current working groups' efforts to analyze the beginning of the pandemic and provide a historical reference for studying the pandemic's evolution in Cuba.

METHODS

Study type and participants We carried out a descriptive, cross-sectional study whose universe consisted of all persons suspected of having COVID-19 (n = 415) who were admitted to IPK from the beginning of the pandemic on March 11, 2020—following identification of the first cases in Cuba, which occurred on the same date—until April 10, 2020. The study group consisted of 63 patients who were diagnosed as COVID-19–positive (15.2%).

Variables

Age The sample was split into the following age groups: 15–24, 25–34, 35–44, 45–54, 55–64 and ≥65 years.

Sex Male, female.

Occupation at time of COVID-19 diagnosis Employment, activity or profession.

National origin From Cuba or from abroad (including Cuban nationals living abroad).

Personal health history Coded dichotomously, the category was 'yes' if the patient had a history of respiratory disease (bronchial asthma, chronic obstructive pulmonary disease); cardiovascular disease (hypertension, ischemic heart disease); diabetes or other comorbidities referenced in the anamnesis of the patient's medical history. The category was marked as 'no' if no pre-existing conditions were mentioned.

Signs and symptoms Also coded dichotomously: 'yes' for presence of fever, cough, shortness of breath (dyspnea), headache, myalgia, arthralgia, asthenia, vomiting, diarrhea or other symptoms; and 'no' if the patient was asymptomatic at the time of admission.

Time elapsed between symptom onset and first medical visit ≤24 hours, 1 day, 2 days, 3 days, 4–6 days, ≥7 days.

Diagnosis

Suspected case: if patient presented with fever, acute respiratory disease, a history of travel to countries with local COVID-19 transmission, or had contact with a confirmed case or a case under investigation up to 14 days before symptom onset. Also considered suspected cases were those who died from a severe acute respiratory infection of unknown etiology.

Confirmed case: if patient met the operational definition of a suspected case and had had SARS-CoV-2 infection confirmed by real-time polymerase chain reaction (RT-PCR) at the IPK National Reference Laboratory.

Severity

Severe: confirmed positive for SARS-CoV-2 (by RT-PCR) and presenting with acute respiratory distress syndrome, septic shock, metabolic acidosis or coagulation disorders (prognosis varied from recovery, in many cases, to torpid evolution and death).

Not severe: confirmed positive for SARS-CoV-2 (by RT-PCR), either asymptomatic or mildly symptomatic, with non-specific signs such as fever, cough, sore throat, nasal congestion, mild headache or general malaise, without signs of dehydration, dyspnea or sepsis. Patients may have presented with polypnea, with humid rales (crackles), or with atypical pneumonia, but without signs of severity and with an SPO_2 (either pressure or partial oxygen saturation) of >90%. There must have been no signs of respiratory failure or severe respiratory distress.

Status at discharge Alive or deceased.

Data collection and processing All information was obtained through document review of primary sources; namely IPK's form for investigating suspected and confirmed SARS-CoV-2 cases, and IPK databases.

In order to characterize patients according to sociodemographic, clinical and epidemiological variables, the 415 cases admitted to IPK suspected of being COVID-19–positive from March 11, 2020 through April 10, 2020 were selected from the institution's database.

We constructed double-entry tables and obtained 95% confidence intervals for odds ratios (OR) used to measure association between COVID-19 and age, sex, patient occupation and medical history.

In calculating ORs, we considered the following groups to be at increased risk of infection: people who were aged ≥65 years, male sex, healthcare workers or had pre-existing comorbidities (underlying respiratory disorders, cardiovascular disease, diabetes mellitus, immunodeficiencies, cancer, kidney disease, neurological disorders, allergies, etc.).

Ethics This study was approved by the Specialized Scientific Commission on Epidemiology of the IPK Ethics Committee. Patient anonymity was guaranteed. Informed consent was deemed unnecessary as researchers only interacted with IPK database information.

RESULTS

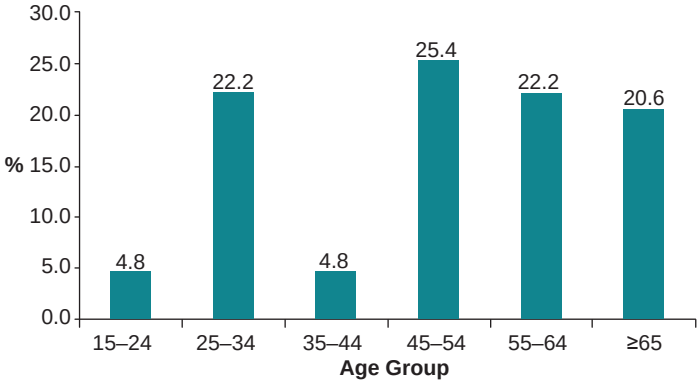
Of the 415 suspected cases, 63 patients were confirmed to be COVID-19–positive. This was a rate from one to five cases confirmed per day, with an average of two cases per day. Male patients predominated over female at 55.6% (35/63).

Patients' mean age was 50.6 years (range: 16–94 years), with the largest number concentrated in the 45–54 age group (25.4%; 16/63). Patients ≥65 years represented 20.6% (13/63) of the total (Figure 1). There was one pediatric case, aged 16 years (1.5%).

At the time of diagnosis, patient occupations included actors, construction workers, athletes, drivers, teachers, students, self-employed, retirees and public administration employees, but the highest proportion of cases were healthcare workers in direct patient care (17.5%; 11/63; 10 doctors and 1 nurse). Foreign travelers made up 12.7% (8/63); 6 of the 8 were tourists (Figure 2).

Cuban citizens made up 52.4% (33/63) of cases, and were from 7 of the country's provinces. The highest number of positives were from Havana Province (87.9%), followed by Artemisa (6.0%), Villa Clara (6.3%) and Sancti Spíritus (3.2%), and then Santiago de Cuba,

Figure 1: Confirmed COVID-19 cases (n = 63) by age group, Havana, Cuba (March 11–April 10, 2020)



Source: COVID-19 Surveillance Database, IPK 2020

Figure 2: Confirmed COVID-19 cases (n = 63), by patient employment, activity or profession at diagnosis, Havana, Cuba (March 11–April 10, 2020)

Other: driver, secretary, civil servant, actor, construction worker, self-employed, athlete, student, electrician, engineer, cook, teacher, student, government official
Source: COVID-19 Surveillance Database, IPK 2020

Matanzas and Pinar del Río (at 1.6% each). Source of infection could be identified in 100% of Cuban patients, as they either had a history of travel to countries where COVID-19 was present or had had contact with travelers (mainly from Spain, the United States, Mexico, Italy and Russia), with symptom onset that either preceded their arrival in Cuba or began ≥48 hours after their arrival.

Of the 30 non-Cuban citizens, 5 were from Italy, 5 from Spain, 4 from Canada, 3 each from Russia and China, and 1 each from 10 other countries (Belgium, Bolivia, Colombia, Panama, Ecuador, France, Peru, Tanzania, United States and Mexico).

Patients traveling from abroad were admitted to IPK <72 hours after arrival in Cuba. Since they came from countries where the SARS-CoV-2 virus was already present, theirs were considered 'imported cases' (54.0%; 34/63).

Pre-existing comorbidities were present in 44.4% (28/63) of patients; the most frequent were hypertension, asthma, diabetes mellitus and ischemic heart disease (Figure 3).

Symptoms were present in 74.6% (47/63) of patients at the time of admission; the most common were cough and fever. The remaining 25.4% (16/63) were asymptomatic (Figure 4).

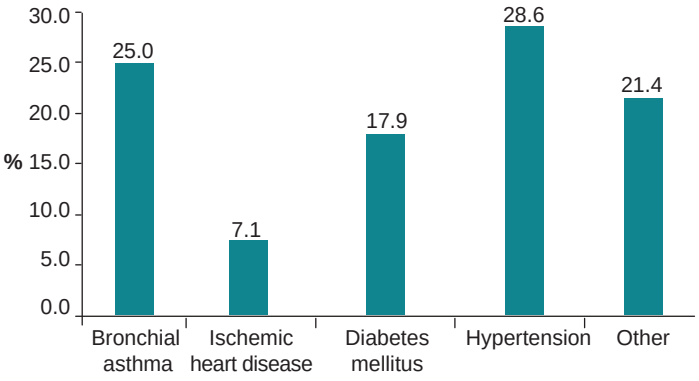
Of symptomatic patients, 53% (25/47) were admitted within the first 72 hours of symptom onset; 47% (22/47) were admitted later (Figure 5).

Mean hospital stay was 13.7 days (range: 1–27 days). Most patients (92%; 58/63) recovered completely and were discharged, remaining under epidemiological surveillance at the primary care level for 14 days. Two foreign travelers were evacuated to their countries of origin (Canada and the United States).

Five patients died, for an initial fatality rate of 7.9%: three non-Cubans (one each from Italy, Spain and Russia) and two Cubans. Among the deceased, 80% were men aged between 54 and 87 years, all of whom had pre-existing comorbidities (diabetes mellitus, asthma and hypertension). These patients presented with a cough and a sore throat, 60% were admitted ≥72 hours after symptom onset, 4 were infected outside Cuba, and 1 was a contact of a previously confirmed case.

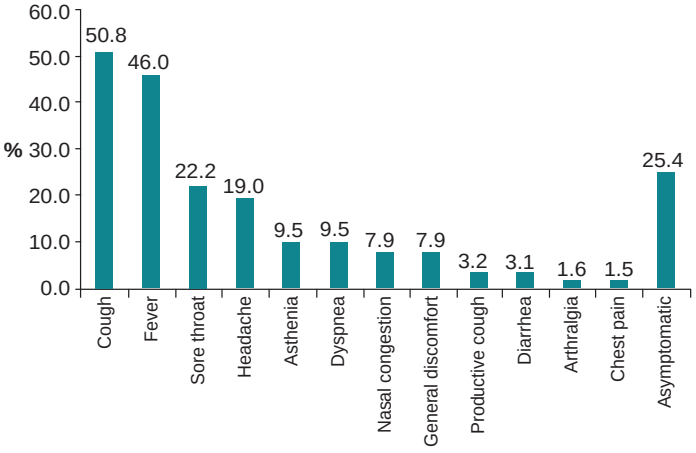
Wide confidence intervals did not allow for conclusive inferences, but age of ≥65 years, male sex, occupation in the health professions working in direct patient care, asthma and diabetes mellitus showed striking correlations with COVID-19–positivity (Table 1).

Figure 3: Confirmed COVID-19 cases (n = 63) by associated comorbidities, Havana, Cuba (March 11–April 10, 2020)



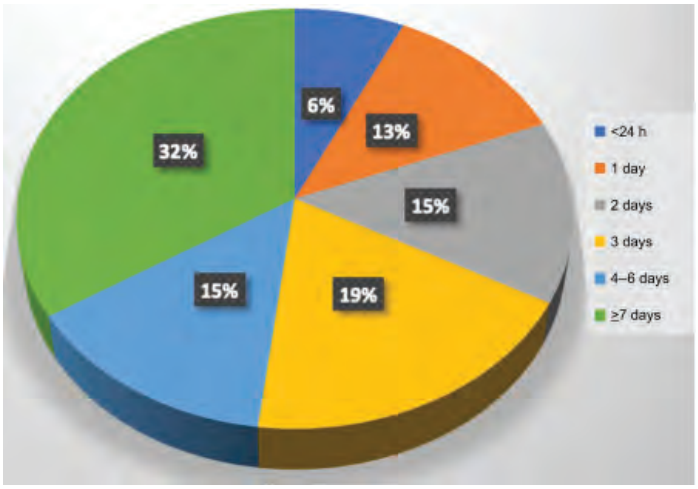
Other: HIV, cancers, epilepsy, arthritis, hypothyroidism, kidney disease, etc.
Source: COVID-19 Surveillance Database, IPK 2020

Figure 4: Confirmed COVID-19 cases (n = 63) by signs and symptoms, Havana, Cuba (March 11–April 10, 2020)



Source: COVID-19 Surveillance Database, IPK 2020

Figure 5: Confirmed COVID-19 cases (n = 63) by time elapsed between symptom onset and hospital admission, Havana, Cuba (March 11–April 10, 2020)



Source: COVID-19 Surveillance Database, IPK 2020

DISCUSSION

Results for sex and age variables showed similarities with other studies of confirmed COVID-19 cases. Male sex was slightly more frequent in this study, in agreement with other studies of COVID-19 conducted in Cuba.[10,11] In a press report by Carmona and Fariñas, men accounted for 50.7% of the 564 cases confirmed by the end of the first month of the epidemic in Cuba.[12] However, the Carmona–Fariñas press report showed that 13.9% of those affected were children,[12] while the IPK sample of 415 cases had only one pediatric patient (a 16-year old).

Age distributions have been variable, with a general trend of fewer cases among those <45 years of age, as was observed in our study, and more cases occurring in those ≥45 years. Li found a similar result in Wuhan, China, in the first 425 confirmed COVID-19 cases; a median age of 59 years, 56% male, and no initial cases <15 years of age.[13] Sun found an average age of 46 years, 55% male, and 3% <15 years old in the first 507 cases confirmed in China between January 13 and January 31, 2020.[14] The WHO mission in China examined 55,924 confirmed COVID-19 cases, finding 51% male, with a median age of 51 years and cases concentrated in the age range of 30–69 years.[15] A report by Spain's National Epidemiology Center examining 18,608 cases found age and sex profiles similar to those observed in China: a median age of 58 years (with an interquartile range of 43–74 years), 51% of whom were male.[16]

Given that both SARS-CoV-1 and MERS-CoV showed high intra-hospital transmission, health personnel involved in direct patient care were considered a high risk group.[17] In our study, medicine and nursing were the most common occupations among COVID-19–positive patients. By February 14, 2020, WHO had already reported 1716 confirmed cases among health workers in China (3.4% of all cases) and 6 deaths.[18] On April 17, 2020, the Cuban Minister of Public Health reported that 92 health workers had tested positive for SARS-CoV-2; 47 (51%) physicians and 30 (32.6%) nurses (no deaths).[19] As health workers face the highest risk of infectious disease in the course of their professional duties, precautions must be taken at both the individual level (personal protective equipment, or PPE) and the institutional level to minimize risk of intra-hospital spread and to protect health workers and those around them.[20]

Persons with pre-existing comorbidities are at increased risk for developing severe forms of COVID-19. In this study, 44% of confirmed cases and 100% of deceased individuals had pre-existing comorbidities, the most frequent being hypertension, asthma and diabetes mellitus. Yang found similar results in a systematic review of 8 studies involving 46,248 COVID-19 patients in Wuhan, China. Hypertension was the most common comorbidity (95% CI: 14–22), followed by diabetes mellitus (95% CI: 6–11), cardiovascular disease (95% CI: 4–7) and respiratory disease (95% CI: 1–3).[21]

SARS-CoV-2 patients present a wide array of clinical symptoms, ranging from asymptomatic or oligosymptomatic to severe and sometimes fatal pneumonia.[22] In our study, 75% of confirmed cases presented clinical manifestations at the time of admission, with cough and fever the most common, followed by sore throat, headache, asthenia and shortness of breath. The remaining 25% were asymptomatic. Yang's systematic review of COVID-19 patients in Wuhan, China, found similar results: the most common clinical manifestation was fever (95% CI: 21–40), followed by cough (95% CI: 59–76), fatigue (95% CI: 34–68) and dyspnea (95% CI: 21–40).[21] Another study, this one of patients admitted to the Wuhan University's Zhongnan Hospital between December 24, 2019 and February 24, 2020, found only 57.7% of patients were symptomatic, with the most common symptoms being fever, fatigue and a dry cough.[22]

Research involving the first 76 patients studied in Mexico in February 2020 found only 20% of confirmed patients to be asymptomatic (the remainder had mild symptoms).[17] The Diamond Princess cruise ship, long quarantined in Japan, screened 3700 passengers, finding that 50% (96) of the 192 patients who tested positive were initially asymptomatic.[23] After 14 days of observation, most COVID-19–positive passengers developed symptoms, reducing the share of truly asymptomatic patients to 18% (95% CI: 15.5–20.2). These results differ from

Table 1: Demographic and clinical variables for patients confirmed and suspected of COVID-19, Havana, Cuba (March 11–April 10, 2020)

Variable	Group	Confirmed cases (n = 63) n (%)	Suspected cases (n = 352) n (%)	Total (n = 415) n (%)	OR	95% CI LL–HL
Age	≥65 years	13 (20.6)	47 (13.4)	60 (14.5)	1.68	0.85–3.34
	<65 years	50 (79.4)	305 (86.6)	355 (85.5)		
Sex	Male	35 (55.6)	179 (50.9)	214 (51.6)	1.20	0.70–2.07
	Female	28 (44.4)	173 (49.1)	201 (48.4)		
Occupation at time of diagnosis	Health worker	11 (17.5)	36 (10.2)	47 (11.3)	1.85	0.88–3.87
	Other	52 (82.5)	316 (89.8)	368 (88.7)		
Pre-existing comorbidities	Yes	21 (33.3)	99 (28.1)	120 (28.9)	1.27	0.72–2.26
	No	42 (66.7)	253 (71.9)	295 (71.1)		

CI: confidence interval HL: higher limit LL: lower limit
Source: COVID-19 Surveillance Database, IPK 2020

those published by China's Center for Disease Control of 72,314 cases, of which only 1.2% were asymptomatic.[24] Spain's Health Awareness Agency stresses the importance of accounting for asymptomatic COVID-19–positive individuals in designing and implementing infection prevention and control measures, given their impact on disease transmission. The Agency developed guidelines based on a systematic review of 24 studies.[25]

Cereda's study in Lombardy, Italy, found no statistically significant difference in viral loads taken from nasal swabs of asymptomatic and symptomatic patients, suggesting both groups had the same potential for transmitting the virus. However, contact tracing identified limited numbers of asymptomatic-infected patients, suggesting they may play a minor role in the overall spread of infection.[26] Additional research, including seroprevalence studies in the general population, will be necessary to accurately assess the role asymptomatic individuals play in SARS-CoV-2 transmission.

Epidemiologically, identifying and notifying suspected cases is an essential component of any disease surveillance system, as it demonstrates the transmissibility of infectious disease and can lead to a decrease in serious cases and deaths. In this study, 47% of suspected cases were admitted to health services more than 72 hours after symptom onset, despite media campaigns requesting that individuals seek out care in a timely manner and the existence of free universal health care. These findings are consistent with a retrospective study of 249 patients admitted to a hospital in Shanghai, 94.3% (235) of whom experienced symptom onset an average of 4 days prior to hospitalization (range: 2–7 days).[27]

The case fatality rate in this study (7.9%) was higher than that reported later in the whole country during the beginning of the epidemic (2.6%).[12] However, this was much lower than the rate recorded during a similar period in the largest study of hospitalized COVID-19 patients in the USA, which was roughly 25%.[28] High case fatality rates may imply undetected transmission and an underestimation of the epidemic, indicating a need to improve epidemiological surveillance systems.[29] However, the underestimated value could be used to estimate the real number of infected individuals.[29]

In summary, this study showed the presence of disease in these first cases in Cuba was related to age ≥65 years, male sex, occupation as a health worker engaged in direct patient care, and pre-existing comorbidities including hypertension, bronchial asthma and diabetes mellitus. This is in keeping with Wynant's systematic review, where significant correlates of infection included older age, male sex, pre-existing comorbidities, previous hospital admissions and negative social determinants of health.[30]

As this study includes only those patients admitted to IPK, the sample size is not very large, and the conclusions we can draw are limited. However, despite this and the fact that the study was limited to a single institution, the study's value lies in its examination of the first diagnosed cases of COVID-19 in Cuba, which can serve as a reference for the history of the disease in Cuba, the Caribbean and Latin America.

CONCLUSIONS

The first individuals diagnosed with COVID-19, who were admitted to Pedro Kourí Tropical Medicine Institute in Havana, Cuba, were mostly imported cases and adult men with pre-existing comorbidities that put them at higher risk of severe manifestations of the disease. These results contribute to knowledge of the history of the COVID-19 pandemic in Cuba and the region.

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Adverse Reactions to Antiretrovirals in Cuban Patients Living with HIV/AIDS

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ABSTRACT

INTRODUCTION Disease and deaths from HIV/AIDS have decreased since antiretroviral treatment was introduced in 1996. Since 2005, as treatment availability has increased worldwide, deaths from HIV/AIDS have declined 48%. As of November 2019, 26,952 cases have been reported in Cuba, of which 5159 (19.1%) are deceased. The country has experienced a reduction in mortality rates since 2002, when antiretroviral treatment became available. Although there are clearly benefits to treatment, it is important to understand antiretroviral safety profiles as their toxicity may lower treatment adherence.

OBJECTIVE Describe adverse reactions attributable to antiretrovirals used in Cuban patients living with HIV/AIDS.

METHODS I studied notifications of adverse reactions to antiretrovirals used in Cuban patients with HIV/AIDS from January 2003 to December 2017. The sample consisted of 352 notifications in the National Pharmacovigilance Database regarding adverse reactions attributed to antiretrovirals. The variables considered were sex, notification year, antiretroviral drug, and number, type, frequency and severity of adverse reactions, whether or not they were preventable, and the reasons for categorizing them as they were.

RESULTS Antiretrovirals reported an average adverse reaction rate of 2.1 per million population per year, representing 24.2% of adverse reactions produced by the antiviral drug group in that period. Adult males represented 75% (264/352) of patients who had adverse reactions to antiretrovirals. Most adverse reactions were in response to nevirapine (29.0%; 102/352) and zidovudine (26.7%; 94/352). The most frequent reactions were hypersensitivity (24.4%; 86/352), digestive disorders (15.9%; 56/352) and anemia (15.6%; 55/352). Reactions were common (62.5%; 220/352) and moderate in severity (70.4%; 248/352). Preventable reactions made up 52.6% (185/352) of adverse reactions. Of preventable reactions, 68.1% (126/185) were associated with drug interactions and 16.2% (30/185) with improper dosage or prescription errors.

CONCLUSIONS Adverse reactions to antiretrovirals in Cuban patients are common and moderate in severity. The drug with the most notifications was nevirapine, and the most common adverse reaction was hypersensitivity. More than half of adverse reactions are considered preventable, and their main causes are prescription errors.

KEYWORDS Drug-related side effects and adverse reactions, antiretroviral agents, secondary prevention, tertiary prevention, Cuba

INTRODUCTION

HIV is a major global health problem. By the end of 2019, 75.7 million people had contracted HIV since the beginning of the epidemic, and 32.7 million died of AIDS-related causes. In 2019, 1.7 million persons were infected with the virus, despite global campaigns to reduce transmission. The introduction of antiretroviral therapy has reduced deaths and contributed to the perception of HIV/AIDS as a chronic disease.[1]

Effective treatment to achieve maximum, prolonged plasma viral load suppression is based on early individualized use of a combination of antiretroviral drugs administered sequentially.[1] Therapy should include at least three antiretrovirals with at least two different mechanisms of action. Introduction of this treatment regime led to radical changes in the infection's natural history, although over time it became clear that the main limitation of antiretrovirals was their toxicity.[2] Because they are taken indefinitely, long-term toxicity increases, adherence decreases, and patients leave treatment, which fosters both the appearance and transmission of resistant strains.[3]

IMPORTANCE

This study updates the safety profile of antiretrovirals used in Cuban patients living with HIV/AIDS, children of seropositive mothers, and those accidentally exposed to the virus. Profiles are important for improving treatment regimens by reconfiguring the therapeutic combinations recommended in international standards for specific patients. Safety profiles also provide information for personalized treatment.

Timely detection of HIV infection allows early treatment, which reduces illness and death from AIDS. Starting antiretroviral treatment upon diagnosis reduces deaths,[4] gives infected persons a life expectancy similar to that of uninfected persons, and lowers transmission rates in couples with one uninfected person. One of the main obstacles to effective response to the HIV/AIDS epidemic is late diagnosis.[4,5]

From 2010 to 2019, new HIV infections worldwide decreased by 23% in adults and 52% in children. Antiretrovirals capable of reducing viral loads to zero played an essential role in this reduction, as did increased protective measures. Until June 2020, only 26 million infected people had access to antiretroviral therapy, or about 68% of HIV-positive individuals worldwide. Since their 2004 peak, deaths from the virus have dropped more than 60%. However, many people in low- and middle-income nations cannot access antiretrovirals, although WHO and the UN have proposed 2030 as the year of zero AIDS-related deaths, zero new infections and zero discrimination against people living with HIV/AIDS.[5–8]

As of November 2019, 26,952 cases of HIV had been reported in Cuba. By the end of that year, prevalence was 0.4% in people aged 15–49 years, the lowest in the region, and one of the lowest in the world. AIDS was responsible for 89.9% of the 5159 deaths from HIV.[9]

Treatment with domestically-produced generic antiretrovirals began in mid-2001 as part of a national strategy to ensure full

treatment access for HIV/AIDS patients. Cuban Therapeutic Guidelines were updated in 2002.[9] These advised that treatment should begin as soon as a person is diagnosed as seropositive, based on clinical, immunologic and virologic criteria established by the scientific community.[9] When Cuban generics were introduced, infection-related health indicators changed because of the clinical efficacy of antiretrovirals.[10] The number of deaths and opportunistic infections greatly decreased, survival increased, treatment became more accessible, and patient quality of life improved.[11] By 2003, the Cuban health system guaranteed access and free treatment to 100% of HIV-positive patients. Manufacturing generic drugs in-country that replaced imports increased therapeutic benefits and allowed potential savings of US$46 million in the first decade that they were produced.[12,13]

The antiretrovirals currently used are divided into several subgroups: nucleoside reverse transcriptase inhibitors (NRTIs: stavudine, lamivudine, zidovudine, abacavir), non-nucleoside reverse transcriptase inhibitors (NNRTIs: nevirapine, efavirenz), protease inhibitors (indinavir, ritonavir, saquinavir), entry inhibitors (also called fusion inhibitors: enfuvirtide), integrase inhibitors (raltegravir, elvitegravir, dolutegravir), and coreceptor antagonists (maraviroc).

Most adverse reactions to these drugs are tolerable, although some may be serious and show drug group effects common to antiretrovirals with the same mechanism of action. Nucleoside reverse transcriptase inhibitors produce mitochondrial damage and protease inhibitors cause metabolic changes, while non-nucleoside reverse transcriptase inhibitors do not have these effects. Adverse reactions in nonnucleoside reverse transcriptase inhibitors are drug-specific and can range from variable-intensity hypersensitivity reactions to neurological disorders. Hypersensitivity is caused by an immune response to some element of the drug and can provoke reactions as varied as skin lesions, to Stevens–Johnson syndrome, epidermal necrolysis, eosinophilia and other systemic reactions.[14,15] In general, treatment benefits outweigh the risk of adverse reactions. As understanding of drug safety profiles increases, treatment protocols improve, and as treatment options improve, patients are less likely to experience adverse reactions.[14,15]

Drug interactions are common because of the idiosyncrasy of these drugs (many are enzyme inductors or inhibitors), and other drugs prescribed to patients. Several studies describe clinically significant drug interactions that could cause adverse reactions in 20%–30% of patients. We do know that protease inhibitors and non-nucleoside reverse transcriptase inhibitors are the antiretroviral subgroups with the most potential interactions.[1,9]

Cuba's antiretroviral pharmacovigilance program offers a model of active drug surveillance. Latin America and Caribbean nations are making efforts to document these adverse reactions. In Mexico, this documentation is relatively new, with most issues reported reflecting notification quality and patients abandoning treatment due to adverse reactions, leading to an assumption of under-reporting. Although Cuba has an established, globally recognized pharmacovigilance program, under-reporting still exists because of various factors influencing notifications and their quality.[16] According to annual pharmacovigilance reports in Cuba, adverse drug reactions (ADRs) to antiretrovirals represent 0.09% of total notifications about antimicrobials.[17] Among all ADR reports, antimicrobials as a drug group are responsible for the most reports.[18]

Cuban studies on this topic have been limited to one institution or region of the country, and have not considered whether the ADRs were preventable.[19–21] One previous study examined this problem, but included all groups of antivirals, not specifically antiretrovirals.[17] The goal of this study is to describe adverse reactions to antiretrovirals reported in Cuba from 2003 to 2017.

METHODS

Study type A pharmacovigilance study was performed using a case series design. The sample consisted of 352 antiretroviral-drug ADR notifications entered into the National Pharmacovigilance Database (FarmaVigiC) of the National Pharmacovigilance Coordinating Unit (UCNFv)[22] from January 2003 to December 2017.

Study variables The variables were:

- Adverse reaction identified as the main adverse effect, specifying the condition of the patient. We used Uppsala Monitoring Centre adverse reaction terminology.[23]
- Notification year
- Age of children (0–17 years), adults (18–59 years) and persons aged ≥60 years.[22]
- Sex
- Antiretroviral drug
- Frequency: common, uncommon, rare, undescribed. Classified according to the criteria of the Cuban Pharmacovigilance System,[22] which uses the categories and events within each category established for each drug in the National Drug Formulary. The total number of occasional, rare and undescribed adverse reactions were coded together as low-frequency adverse reactions.
- Severity: mild, moderate, severe and fatal. Minor reactions that did not require an antidote, treatment or hospitalization, with easily tolerated symptoms or signs, were classified as mild. Reactions were considered moderate if they required a change in drug treatment or increased observation and caused malaise that interfered with regular activities. They were considered severe when they were life-threatening or caused disability. They were considered fatal when they contributed directly or indirectly to the cause of death.
- Preventable adverse reaction: yes or no, depending on the answer from the Schumock and Thornton preventability algorithm, modified by Otero.[24,25]
- Preventable ADR causes: A cause was considered preventable when there were improper drug instructions, dose, route of administration, intervals of administration or treatment length, a history of adverse effects or allergic reactions to the drug, a drug interaction, or self-medication.

Causality was not among the variables assessed. It was used only as an inclusion criterion for the filters to select the study sample and establish whether ADRs were preventable.

Data collection The information was obtained from FarmaVigiC, which receives spontaneous ADR reports. The database stores information contained in the official template from suspected adverse reaction reports electronically submitted to UCNFv from different levels of the national health system. Reports are made by physicians, nurses and pharmacists caring for patients who take these medications and experience ADRs.

The database was filtered for the field "drug class," and the term "antiretroviral" and the "suspected drug" was used as the inclu-

sion criterion, which included all drugs classified as antiretrovirals in the Cuban National Drug Formulary and international literature. The database was also filtered for "causality," where the categories "definite," "possible" or "probable" were used because they indicate a positive cause-effect relationship between the drug and the ADR. This was done to determine if the ADR was preventable, and was used only as a filter to define the sample. An Excel database was created with the results and named "primary database." This database stored the remaining fields in FarmaVigiC. The study universe comprised adverse reactions contained in the primary database.

After selecting the ADRs contained in the primary database, the Schumock and Thornton algorithm,[24] modified by Otero,[25] was used to identify preventable ADRs. A "yes" answer to the preventability question indicated that the ADR could have been prevented. Using these databases, a new database was created ("secondary database"), which stored all FarmaVigiC fields. An expert from the UCNFv created both databases without changing variable classifications or assessments.

Potentially preventable reactions were determined based on the information contained in FarmaVigiC, which is validated and verified by trained pharmacovigilance experts. Quality of FarmaVigiC notifications is ensured by regular data review and standardization using different levels of filters according to the quality standards of the Uppsala Monitoring Centre (UMC), the governing body of the WHO Programme for International Drug Monitoring.[22,23] Professionals in Cuban municipalities and provinces receive annual pharmacovigilance training and are supervised by UCNFv specialists.[22]

Data analysis Absolute and relative frequencies and reporting rates of ADRs for antiretrovirals were estimated per year and per million population, by sex and using the population data reported by the National Health Statistics Yearbook.[26] Proportions of patients treated with each antiretroviral were not calculated because the data were not available. The frequency distribution for each drug was estimated based on the total number of notifications.

Ethics The Cuban Ministry of Public Health's National Drug Division authorized the use of information in FarmaVigiC. Privacy was respected, and no patients who reported antiretroviral ADRs were identified.

RESULTS

During 2003–2017, the new, primary database (filtered FarmaVigiC data) included 352 antiretroviral ADRs. This figure is equivalent to an average reporting rate of 2.09 per million population annually, representing 24.2% of all adverse reactions produced by the antiviral drug class during this period.

Most ADRs were reported from 2009 to 2016, with the greatest share in the final year (85/352; 24.1%). From 2003 to 2005 and in 2007, no antiretroviral ADRs were reported.

Male patients accounted for 77.3% (272/352) and female patients for 22.7% (80/352) of total ADRs notified in the study period. ADR notifications were more common in adults, with higher proportions in men (272/352; 77.3%) than in women (80/352; 22.7%). A single report in children was made, and there were no reports in persons aged >60 years.

Of the antiretrovirals, nevirapine had the highest number of reports, followed by zidovudine (Table 1).

Formulations containing combinations of antiretrovirals from different groups at fixed doses (Kaletra, Atripla, Truvada, etc.) were responsible for 4.3% (15/352) of reports.

Hypersensitivity reactions accounted for the greatest number of ADRs, followed by digestive disorders and anemia, in which the number of reports differed by a single report. Although hepatotoxicity is not one of the most common ADRs (8.2%; 29/352),it needs to be considered because of its severity (Table 2).

There were 9.1% (32/352) of ADR notifications grouped as "other reactions" because of their infrequent occurrence. Among these were psychiatric and sleep abnormalities and metabolic, hematologic and vascular disorders, as well as headache and conditions caused by hydroelectrolyte imbalances.

Antiretroviral ADRs were common (62.5%; 220/352). The most common were those of moderate severity (Table 3). Some ADRs, 5.4% (19/352), are not described in the Cuban National Drug Formulary. Any ADRs recorded in the system that do not appear in the National Formulary are reported to the pharmaceutical industry to be evaluated for inclusion in the formulary, depending on their frequency and importance.

No fatal ADRs were reported.

Preventable ADRs made up 52.5% (185/352) of all notifications. Main causes were drug interactions (with drugs in the same drug class or any other that the patient was taking), inappropriate dosage, and a history of ADRs to the suspected drug. Drug interactions alone made up nearly 70% of preventable reactions (Table 4).

DISCUSSION

In Cuba, HIV infection is more common in men than women, in a ratio of 4:1. Men are therefore the largest group of antiretroviral consumers in the country, which would explain the higher percentage of ADRs in males.[9] These results were similar to those obtained in Paraguay, where 62.2% of antiretroviral ADRs were reported in men.[27] A study conducted in Cuba showed that ADRs were more common in adult males.[28]

Table 1: Adverse reactions to antiretrovirals, by medication

Antiretroviral	Total (%)
Nevirapine	102 (29.0)
Zidovudine	94 (26.7)
Stavudine	46 (13.1)
Efavirenz	29 (8.2)
Lamivudine	19 (5.4)
Indinavir	18 (5.1)
Fixed-dose combinations	15 (4.3)
Ritonavir	8 (2.3)
Abacavir	7 (2.0)
Atazanavir	6 (1.7)
Tenofovir	5 (1.4)
Saquinavir	3 (0.9)
Total	352 (100.0)

Source: FarmaVigiC database

Table 2: Adverse reactions to antiretrovirals, by type

Reaction type	Total (%)
Hypersensitivity reactions	86 (24.4)
Digestive disorders	56 (15.9)
Anemia	55 (15.6)
Polyneuritis	42 (11.9)
Other reactions*	32 (9.1)
Lipodystrophy	30 (8.5)
Hepatotoxicity	29 (8.2)
Stevens–Johnson syndrome	9 (2.6)
Renal lithiasis	6 (1.7)
Nephrotoxicity	4 (1.1)
Fever	3 (0.9)
Total	352 (100.0)

*psychiatric and sleep abnormalities; metabolic, hematologic and vascular disorders; headache and conditions caused by hydroelectrolyte imbalances
Source: FarmaVigiC database

Table 3: Adverse reactions to antiretrovirals, by severity and frequency

Frequency	Severity			Total (%*)
	Mild	Moderate	Severe	
Common	47 (13.4)	163 (46.3)	10 (2.8)	220 (62.5)
Uncommon	14 (4.0)	52 (14.8)	5 (1.4)	71 (20.2)
Rare	12 (3.4)	20 (5.7)	10 (2.8)	42 (11.9)
Undescribed	3 (0.9)	13 (3.7)	3 (0.9)	19 (5.5)
Total (%)	76 (21.6)	248 (70.5)	28 (8.0)	352 (100.0)

*All percentages were calculated using the grand total (n = 352)
Source: FarmaVigiC database

Table 4: Adverse reactions to antiretrovirals, by preventable cause

Causes	Total (%)
Drug interaction	126 (68.1)
Improper dose	30 (16.2)
History of adverse reactions	28 (15.1)
Improper length of treatment	1 (0.5)
Total	185 (100.0)

Source: FarmaVigiC database

Antiretroviral nevirapine had the highest proportion of ADRs. According to the literature, this drug is well-tolerated long term, although during treatment initiation, 15%–20% of patients may experience allergic reactions.[12] This could explain some of the ADRs attributed to nevirapine despite its reported good tolerance. According to reports on Cuban treatment protocols, in 2006, 66% of patients followed a regimen that included nevirapine.[11] Recent studies show sex-dependent variations in biotransformation of this drug that induce reactive metabolite formation in women,[29–32] so toxicity should be greater in female patients. However, available information does not specify sex distribution of the ADRs for nevirapine. Treatment regimens have now changed, and nevirapine is used only as an alternative drug in second-line treatment, due to ADR frequency.[12]

In a 2011–2013 study in Cuba, nevirapine had the most ADR notifications,[19] but in another study conducted at the same site in 2015, its notifications ranked third. At that time, zidovudine and efavirenz had higher adverse reaction frequencies, but the authors did not explain the possible causes.[20] Data from that study show that in Cuba, antiretroviral-related ADRs are mainly associated with nucleoside reverse transcriptase inhibitors (NRTIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs), which are the subgroups most often used in combination treatment regimens.

According to a study by Bastida,[32] polymedication due to the combined use of NNRTI antiretrovirals with medications for comorbidities is four times more common than in the general population because non-communicable chronic diseases appear sooner in patients living with HIV. This increases the risk of interactions and toxicity. The benefits from synergy among the active ingredients of antiretrovirals justify their combined use, and although ADRs are reported, interactions are more common with protease inhibitors, so NRTIs and NNRTIs are considered a safer alternative.

All antiretrovirals can cause hypersensitivity reactions, but NNRTIs are the ones most often linked to ADRs. Nevirapine is a common cause, as is, to a lesser extent, efavirenz. Most patients who develop a skin rash with nevirapine do so with efavirenz, but if the reverse occurs and the rash is caused by efavirenz, use of nevirapine is not recommended.[33] This should be made clear in patient treatment protocols.

Digestive disorders were the second-most common ADR, followed by anemia, lipodystrophy and hepatotoxicity, findings similar to those of other studies conducted in Cuba, although not always in this order of frequency.[19,20,28] In other nations such as Ecuador, the most common adverse effects are gastrointestinal disorders, and lipodystrophy is the most common chronic effect following antiretroviral therapy. Lipodystrophy is a pathological change in adipose tissue distribution, associated with metabolic complications from the effect of antiretrovirals on adipocytes. It is a characteristic reaction to drugs such as stavudine, lamivudine, zidovudine and emtricitabine, among others, which are in the NRTI subgroup and still among the drugs used in first-line treatment.[29] Because of their conditions and comorbidities, persons living with HIV are polymedicated. This may increase toxicity from interactions among antiretrovirals or with other drugs to treat associated pathologies, thus increasing the number of ADR reports.[34]

No ADRs were reported in persons aged >60 years, understandable since in Cuba ADRs are concentrated in those aged 40–49, 25–29, and 20–24 years. Chronicity and increased survival lead to a higher average age of infected persons, but HIV incidence in older adults is low, which explains why interactions with drugs for comorbidities occurring in these age groups are uncommon. Interactions described in this study as the cause of ADRs occur more commonly with other antiretrovirals than with antiretrovirals and other drugs.[11]

New treatment strategies with fixed-dose combinations of antiretrovirals are based on the premise that combining these drugs simplifies treatment and improves adherence and compliance. These combinations also improve quality of life and decrease the risk of medication errors and drug resistance.[35]

By and large, preventable ADR causes were prescription errors. Prescription errors were related to the fact that antiretrovirals were administered in fixed-dose combinations and all patients did not tolerate them equally. This is important because treat-

ment is based on positive synergy of two or more antiretrovirals and is governed by established protocols.[12,38] These results could be useful for helping health system decisionmakers find safer treatment options to prevent this type of error. It is important for patients to receive proper doses of the different antiretrovirals used in combination therapy. The interactions among these drugs can lead to better results because a stronger effect can be obtained with lower doses. Nevertheless, individual differences and genetic polymorphisms in ABC superfamily membrane transporters contribute to resistance and predispose patients to toxicity.[12]

Nine clinical trials conducted in the United States and Europe during 2000–2013 discovered increased transmission of mutations linked to antiretroviral resistance. For NNRTIs specifically, this resistance increased from 0.3% to 2.7%, because this drug subgroup is inexpensive and frequently used, especially in low-income countries.[30,36] The emergence of resistance from prolonged exposure is one of the current challenges in the global response to the HIV/AIDS pandemic. ABC superfamily transporters are essential proteins for drug absorption and elimination in the body, and polymorphisms in the genes that code these proteins may cause a loss of response to certain drugs, even at therapeutic concentrations.[37] Genetic polymorphisms found in the ABCB1 subfamily are involved in cellular resistance to the protease inhibitor drug subclass (indinavir, ritonavir, adefovir). The overexpression of multidrug resistance protein 4 (Mrp4) is associated with drug resistance to nucleoside reverse transcriptase inhibitors.[37]

HIV's mutation potential generates variants that bind to the viral genome and are transmitted to new virions that emerge from virus-replicating infected cells and create new viral populations resistant to one or more antiretroviral drugs. In 2019, WHO reported increased prevalence of simultaneous resistance to several antiretroviral groups, which means that possible changes to established, validated treatment protocols need to be assessed.[38] This phenomenon, known as triple resistance, increased more than 10% in low- and middle-income countries.[39–40] In mid-2020 the world's first case of pandrug resistance was reported in a patient infected with HIV-1 subtype B, who showed resistance to five oral antiretroviral groups.[41]

Among the limitations of working with FarmaVigiC is that it does not allow evaluation of treatment adherence, which is negatively related to toxicity. Toxicity influences treatment adherence because the more adverse reactions or signs of toxicity patients experience, the less likely they are to adhere to treatment regimens. ADR reports sent to the database are based on spontaneous patient declarations, which favors under-reporting and does not distinguish between noncumulative and cumulative effects. The latter occur when a certain threshold is reached, beyond which the drug can produce ADRs. The spontaneous notification system does not allow ADR frequency to be determined in the total number of patients who took the drugs, because the exact number of persons using them is unknown. In this case, these are not only patients living with HIV/AIDS, but also infants born to seropositive mothers and those who had accidental contact with the virus (medical and paramedical staff, and researchers). Despite these limitations, this record system is the most complete and reliable source of data available for information about pharmacovigilance in Cuba.

CONCLUSIONS

In Cuba, ADR reports for antiretrovirals are rare, classified as frequent and of moderate severity, and are mainly hypersensitivity reactions. The antiretrovirals that most often cause them are nevirapine and zidovudine. Most ADRs occur in adult males, and more than half are considered preventable. The most common causes of preventable ADRs are prescription errors.

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Spatiotemporal Distribution of Non-syndromic Orofacial Clefts in Villa Clara Province, Cuba, 2013–2018

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ABSTRACT

INTRODUCTION To discern environmental factors that, along with genes influencing susceptibility, drive the occurrence of non-syndromic congenital disorders, it is important to identify clusters of these abnormalities.

OBJECTIVE Determine the adjusted prevalence of orofacial clefts in Villa Clara Province, Cuba, and identify and describe their spatiotemporal variability during January 2013–December 2018.

METHODS Cases were selected from a total of 46,007 births that took place in the province's four maternity hospitals during the study period. Of these, 36 cases of newborns with either prenatal or postnatal non-syndromic orofacial cleft diagnoses were obtained from hospital and community registries. We applied spatial statistical analysis techniques with the aim of identifying areas within the province with the highest prevalence.

RESULTS Adjusted prevalence was 0.78 per 1000 births. The most common non-syndromic orofacial congenital abnormality was cleft lip with or without cleft palate. Frequency of congenital abnormalities increased during the first two years of the study and decreased during the last two years. A primary spatiotemporal cluster was identified in two contiguous municipalities in 2017 and a secondary one in two other neighboring municipalities between 2014 and 2016.

CONCLUSIONS Spatiotemporal analysis of non-syndromic orofacial clefts in Villa Clara Province, Cuba, identified two spatiotemporal clusters, constituting an opportunity to better understand the etiology of orofacial clefts.

KEYWORDS Cleft lip, cleft palate, congenital abnormalities, disease hotspot, spatial analysis, Cuba

INTRODUCTION

Non-syndromic orofacial cleft (NSOFC) refers to a congenital abnormality of multifactorial origin attributed to a combination of genetic and environmental factors, in which a monogenic or chromosomal cause has not been identified, characterized by a cleft lip with or without palate involvement. Its Online Mendelian Inheritance in Man (OMIM) designation is 119530.[1–3]

NSOFC results when structures that give rise to the upper lip and secondary bone palate fail to fuse during fetal development. Its clinical phenotype varies from small abnormalities on the vermillion border of the lip (bilaterally, unilaterally or centrally) to large spreading clefts reaching toward the nostril floor through the maxilla's alveolar portion, which can cause complete palatal clefts encompassing the secondary or posterior palate, extending over the entire soft palate and reaching the anterior incisive fossa.[4,5]

In 1942, Fogh-Anderson classified NSOFCs as cleft lip with cleft palate (CL with CP), cleft palate (CP) and cleft lip (CL). Early in the 21st century, NSOFCs were already being classified into two groups: either CL, with or without non-syndromic CP; or non-syndromic CP according to different embryological and environmental factors and genetic studies. The CL group with or without non-syndromic CP includes both persons with CL only (unilateral or bilateral) and those with CL accompanied by CP. Cases with non-syndromic CP show a separation in either the hard palate, soft palate or uvula without lip involvement, pointing to the highly variable phenotypic expression of this kind of congenital abnormality.[1,2,6]

IMPORTANCE

Detecting spatio-temporal orofacial cleft clusters allows the planning of more targeted investigations aimed at identifying genetic, epigenetic, or environmental factors related to the origin of these congenital abnormalities.

The most serious morphological abnormality among NSOFCs is bilateral CL and total CP (10% of cases) and the most frequent is unilateral CL with total CP (40%). Syndromic abnormalities have dysmorphic patterns which are associated with other congenital abnormalities; more than 300 different syndromes associated with NSOFCs have been identified. However, most cases present as non-syndromic abnormalities (70%).[7–10]

Although practically all types of Mendelian inheritance have been considered for these congenital abnormalities, many of their characteristics are those of a classic multifactorial threshold trait, where complex interactions between genetic and environmental factors influence phenotypes. Evidence of genetic contributions to phenotypic expression are supported, for example, by variations in frequency between ethnic groups, an increased risk of recurrence of the most severe phenotypes within families (from 4.0% in unilateral CL without CP to 8.0% in cases with both CL and bilateral CP), a greater concordance between monozygotic or identical twins (25%–40%) than between dizygotic or fraternal twins (3%–6%), a greater risk of recurrence in first-degree relatives and a 76% heritability rate.[1,7]

On the other hand, various environmental risk factors have been identified in NSOFC etiology, many of which are both preventable and tend to vary depending on the specific congenital defect. Among these are maternal alcohol consumption, habitual smoking, maternal comorbidities like diabetes and obesity, use of certain medications, exposure to environmental pollutants and pesticides, and deficiencies in folic acid and other micronutrients in the first trimester.[1,2,11–15]

The consideration of space is implicit when calculating incidence and prevalence rates. Statistical techniques for detecting spa-

tial, temporal or spatiotemporal clusters provide opportunities to quantify aspects related to the abnormalities' spatial and temporal distributions. Variability patterns in the timing and geographic distribution of health events are essential for understanding exposure and preventing future events, whether the underlying process is contagious, environmental or related to genotypic variability.

Information about spatial patterns is just as useful as information about demographic or temporal patterns, allowing deeper exploration of the interactions among people, time and space.[16]

Villa Clara Province is in central Cuba, and at 8411.81 km^2 is the fourth-largest Cuban province, representing 7.6% of the country's total landmass. It is divided into 13 municipalities and has a population of 780,749. From January 2013 through December 2018, a total of 46,007 births occurred in the province.[17]

Malformations involving orofacial structures account for three-quarters of all congenital abnormalities, which can be attributed to the intricate genetic and epigenetic mechanisms involved in assembling the orofacial region.[18,19] NSOFCs affect approximately 135,000 newborns annually worldwide, with prevalence ranging from 1 in 2500 to 1 in 500 births. Average prevalence worldwide is 1 in 700 newborns, although there is considerable geographic, ethnic and sociocultural variation.[6,7,8,20,21]

The most commonly-treated congenital abnormalities in Cuban pediatric maxillofacial surgery services are labial and palatal fissures.[22,23] Herrera,[24] in a 2009–2013 cohort study of congenital malformations and cognitive disability in Villa Clara Province, found a frequency of 1 in 1115 newborns, with an adjusted prevalence of 1.7 per 1000 births.

There are no studies analyzing the spatiotemporal variability of these congenital disorders in Cuba. Our research was carried out to determine the adjusted prevalence of NSOFCs in Villa Clara Province, and identify and describe their spatiotemporal variability in the years 2013–2018.

METHODS

Study type We carried out a retrospective descriptive observational study using data from 2013–2018 obtained from the Cuban Congenital Malformation Registry (RECUMAC) and the Cuban Congenital Malformation Prenatal Registry (RECUPREMAC). Both RECUMAC and RECUPREMAC are hospital-based registries in operation since 1985, allowing for clinical and epidemiological surveillance of congenital abnormalities in Cuba. These registries include all live newborns, stillbirths and elective abortions after 20 weeks' gestation, weighing ≥500 grams who presented with one or more major congenital abnormalities upon physical examination during the first few hours after delivery.

Data collection RECUMAC data were compiled using results of physical and dysmorphological examinations performed at one month and three months of age by genetic counselors as part of the National Program for the Diagnosis, Management and Prevention of Genetic Diseases and Congenital Disorders. This program was first implemented in the 1980s and provides community-based information from all medical genetics departments in all Cuban municipalities.[25]

Congenital abnormalities were coded according to the ICD-10.[26] All cases with syndromic NSOFC were excluded from the study. In all cases, diagnosis was confirmed by clinical genetics specialists at the Villa Clara Provincial Medical Genetics Center.

Statistical analysis Prevalence rates adjusted at birth were calculated by dividing the numerator (NSOFC live births, stillbirths or elective terminations among 2013–2018) by the denominator (total live births and stillbirths in the same period). Prevalence rates were expressed as the number of cases per 1000 births. Adjusted prevalence rates were calculated for each of the spatial analysis units (municipalities) based on the number of births (live or stillbirths) that occurred in each municipality during the study period. Temporal units of analysis were divided by year.

To detect spatiotemporal NSOFC clusters, we used specific statistical techniques for spatiotemporal analysis available in the freeware SaTScanv7.01. Probability of clusters in each spatial analysis unit was compared with the probability of clusters occurring outside the unit, and we estimated maximum likelihood ratios using the Kulldorff method[27] to check if the number of cases observed in each municipality exceeded the number of cases that would have been expected for the year. Areas with statistically significant maximum values were considered primary clusters, where case frequency could not be attributed to chance. In all other cases, they were considered secondary clusters. We set the significance level at $\alpha = 0.005$.

Expected case number in each municipality was calculated using the following expression:

$$E(c) = p \times {}^{C}/_{P}$$

…where c is the observed number of NSOFC cases in each spatial unit; p is the reference population (live births, stillbirths, and elective pregnancy terminations) in each municipality; and C and P correspond to the total number of NSOFC and births (live births and stillbirths), respectively.

Relative risk (RR) for each spatial unit was calculated by dividing the observed number of cases by the expected number of cases, using the following formula:

$$RR = \frac{c/E(c)}{(C-c)/[C-E(c)]}$$

…where c is the observed number of NSOFC cases, E is the expected number of cases, and C is the total number of cases within the cluster.[28] Cartographic representations were made using MapInfo v. 8.5 by exporting statistical results to the program's geographic information system. Primary and secondary clusters were represented via red-to-pink color degradation.

Ethics This study is based on data analysis of records from which all identifying information had been removed, guaranteeing complete patient anonymity. Additionally, all mothers of newborns (live births and stillbirths) included in the study gave written informed consent, in accordance with the Helsinki Declaration's ethical standards for human research.[29,30] The study was approved by the Ethics Committee of Villa Clara Medical University's Biomedical Research Unit, as part of the project entitled *Interrelation of genetic and environmental factors in con-*

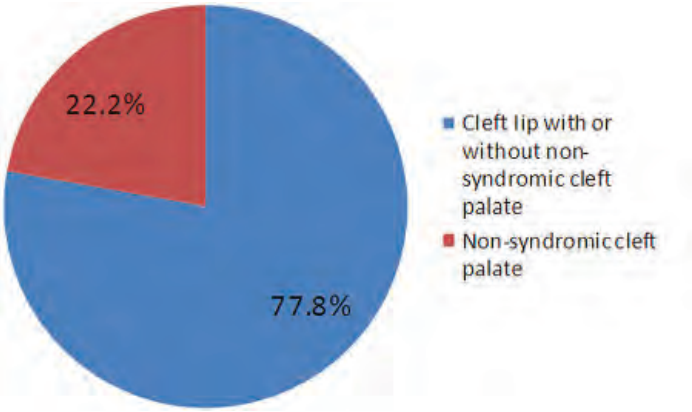
genital malformations with probable association to folic acid and other micronutrient deficiencies in Villa Clara Province.

RESULTS

A total of 36 NSOFC cases were registered and included in this study from January 2013 through December 2018. Live births accounted for 30 (83.3%) of congenital abnormalities and 6 (16.7%) were elective pregnancy terminations (in all cases, combined with cardiovascular congenital abnormalities, without evidence of underlying syndromic etiology). No NSOFC were observed in stillbirths. Other congenital abnormalities were observed in 8 cases (22.2%). CL with or without CP was observed in 28 cases (77.8%) (Figure 1).

There were 46,007 births during the study period (45,692 live births and 315 stillbirths), for an adjusted NSOFC prevalence of 0.78 per 1000 births, and an overall prevalence of 1 per 1277 newborns (Table 1). In general, NSOFC prevalence increased until 2016 and then decreased between 2016 and 2018 in cases of CL with or without CP, while adjusted prevalence of non-syndromic CP varied little, save for two peaks in the curve in 2014 and 2016 (Figure 2).

Figure 1: NSOFC relative frequency, Villa Clara Province, Cuba, 2013–2018



NSOFC: Non-syndromic orofacial clefts

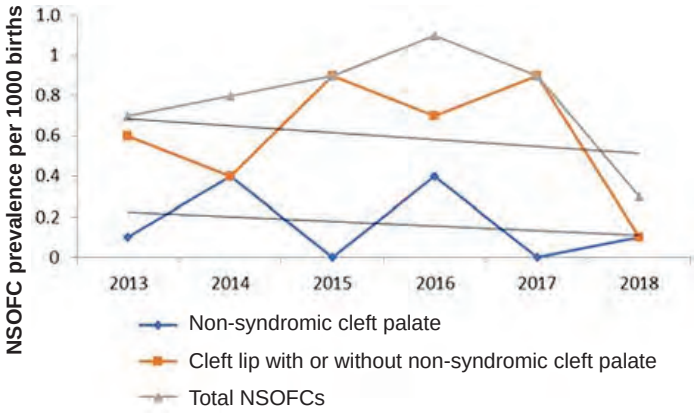
Table 1: Adjusted NSOFC rates, Villa Clara Province, Cuba, 2013–2018

Congenital abnormality	Cases	Adjusted prevalence per 1000 births	ICD-10 codes
CL with or without CP	28	0.61	Q36, Q36.0, Q36.1, Q36.9, Q37, Q37.0, Q37.1, Q37.2, Q37.3, Q37.4, Q37.5, Q37.8, Q37.9
Non-syndromic CP	8	0.17	Q35, Q35.1, Q35.3, Q35.5, Q35.9
Total NSOFC	36	0.78	Q35–Q37 (except Q35.7: bifid uvula)

CL: cleft lip CP: cleft palate ICD-10[26] NSOFC: Non-syndromic orofacial cleft

Both primary and secondary spatiotemporal NSOFC clusters were observed in Villa Clara from 2014 through 2016 (Figure 3), and we collected information on these clusters (municipalities, observed and expected case numbers, statistical analysis results related to relative risk, p-values) (Table 2).

Figure 2: Annual adjusted NSOFC prevalence, Villa Clara Province, Cuba, 2013–2018



NSOFC: Non-syndromic orofacial clefts

DISCUSSION

Other associated congenital abnormalities were observed in 8 (22.2%) NSOFC cases. Congenital heart disease (CHD) was the most common. In six of these infants, the abnormalities were detected in utero and the couple requested termination. Prenatal fetal health monitoring provides information necessary for detecting congenital abnormalities and in estimating their effects on postnatal life.[31]

CHD frequency in our study coincides with that observed by Jamalian in their work in Iran, who found that CHD, at 38%, was the most frequent congenital abnormality co-occurring with orofacial clefts, while CHD was only observed in 2% of cases without orofacial clefts.[32]

However, a 22-year longitudinal hospital-based series carried out in the Manzanillo municipality (Granma Province, Cuba) found that the congenital abnormalities most frequently associated with lip-palatal clefts were those of the osteomyoarticular system (5.4%), followed by CHD (3.9%).[33]

CL frequency with or without non-syndromic CP in the present study (77.8% of cases) was 3.5 times higher than that of non-syndromic CP, similar to rates observed in Brazil (78.6% of cases, 2.6 times the frequency).[2] Aggregate data from 9 South American countries in the Latin American Collaborative Congenital Malformation Study (ECLAMC) found CL frequency with or without non-syndromic CP (82.7% of cases) to be 4.7 times higher than non-syndromic CP.[20]

In Villa Clara Province, CL case frequency, with or without CP, was higher than rates in the eastern province of Santiago de Cuba from 2000 to 2009 (71.4% of cases, 2.5 times higher than CP frequency).[34] A US population-based study conducted from 1989 to 2010 in 8 California counties found an overall frequency of CL with or without CP of 65%, 1.9 times higher than the frequency of isolated CP, although this study was limited by its failure to include stillbirths or elective terminations.[35]

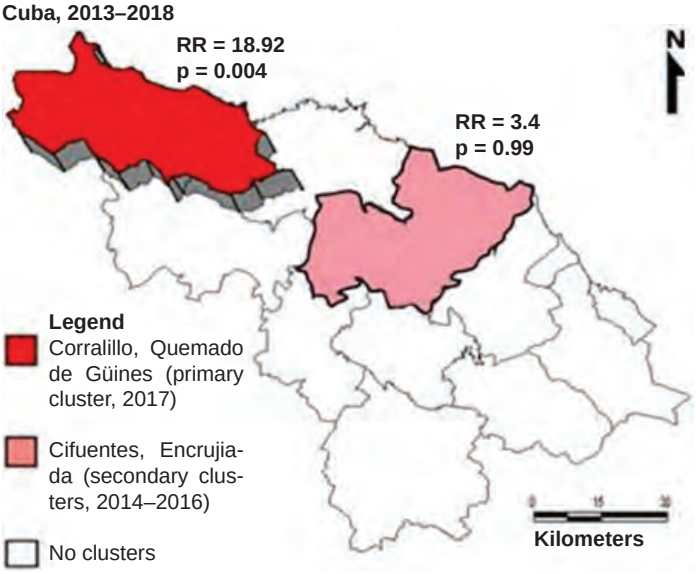
As CP is less evident upon external examination, non-syndromic CP prevalence could be underestimated in studies basing their data on initial newborn inspection.[8] However, this is unlikely to be the case in our study, as all live births are evaluated before dis-

Table 2: Spatiotemporal NSOFC rates, Villa Clara Province, Cuba, 2013–2018

Cluster	Municipality	Years	Observed cases	Expected cases	RR	p-value
Primary	Corralillo, Quemado de Güines	2017	5	0.31	18.93	0.004
Secondary	Cifuentes, Encrucijada	2014–2016	4	1.28	3.41	0.965

NSOFC: Non-syndromic orofacial cleft RR: Relative risk

Figure 3: Spatiotemporal NSOFC clusters, Villa Clara Province, Cuba, 2013–2018



charge in neonatology services, at one month and three months of life in community genetics services, and all elective pregnancy terminations are carried out at the provincial maternity hospital, where all fetuses undergo an exhaustive morphological study by pathology services.

In several national and international studies, isolated CP represents only a third to a half of all observed NSOFC cases.[8,24,34,36] Other studies show even lower frequencies, including one carried out in Villa Clara Province in the 1990s at the José L. Miranda Pediatric University Hospital's orthodontic service, where isolated CP represented only 11.4% of all NSOFC cases.[37]

One possible explanation for this difference is that hard-palate fissures are frequently accompanied by fissures in the lips.[8] Additionally, the lip and palate have different embryological origins: the palate is derived from the endodermal lamina, while the lips are derived from the ectodermal lamina.[2]

Adjusted NSOFC prevalence at birth in Villa Clara Province (0.78 per 1000 births) is within the range described both in Cuba and worldwide (0.7–1.5 per 1000 newborns).[2,22,29] This frequency is slightly higher than that found in research on congenital disorders in newborns carried out in Havana from 2000 to 2003, in which CL with or without CP NSOFC represented 5.4% of all isolated congenital abnormalities, at a prevalence of 0.71 per 1000 births.[38] This coincides with that observed by Cisneros in Santiago de Cuba, who diagnosed 98 NSOFC cases in 138,381 births over a period of 10 years.[34]

However, over a five-year period (2007–2011), researchers in Havana found an adjusted CL (with or without CP) prevalence rate of 1.1 per 1000 births in Arroyo Naranjo municipality,[39] lower than observed frequencies in the years 1998 and 2000 in Octavio de la Concepción de la Pedraja Pediatric University Hospital in Holguín, a province in eastern Cuba, at 1.22 and 1.26 per 1000 live births, respectively.[40]

Frequency of congenital malformations varies greatly by ethnicity: populations of African ancestry have the lowest prevalence, followed by those of European descent, and then populations of Native American and Asian ancestry, who have the highest prevalence.[6–8,10]

A descriptive analysis using ECLAMC clinical-epidemiological data from 9 South American countries for 1995–2012, identified 2773 newborns with NSOFC (2293 with CL with or without CP, and 480 with isolated cleft palate), for an overall prevalence of 1.08 per 1000 newborns.[20]

In Guadalajara, Mexico, which has a large indigenous population, a 2009–2016 study found a high prevalence of NSOFCs (2.79 per 1000).[41] Other authors studying NSOFC rates in Mexico have estimated overall frequencies between 0.6–0.9 per 1000 live births.[28] In the USA, NSOFC rates vary considerably among different ethnic groups, with higher frequencies among Asian Americans and Native Americans (2 per 1000), followed by non-Hispanic whites and Hispanics (1–1.43 per 1000), and with lowest frequencies among African Americans (0.4 per 1000).[7]

In addition to genetic factors that influence NSOFC-frequency differences among ethnic groups, economic and sociocultural factors play a role in NSOFC spatial variation. For example, NSOFC rates vary within ethnic groups and nationalities in Africa, from 0.5 per 1000 in Ghana and Nigeria (the latter the most populous African country and the nation with the largest Black population worldwide, at >160 million people); 0.7 per 1000 in Malawi; 1.4 per 1000 in Ethiopia; and up to 1.65 per 1000 in Kenya.[21,42]

A recent meta-analysis estimated NSOFC prevalence at 1.38 per 1000 births in low- and middle-income countries.[35] Risk factors are often interrelated; for example, Chileans with higher NSOFC rates are in the lowest socioeconomic strata and are also more likely to be of indigenous ancestry.[5] Possible explanations for differences in prevalence among geographic regions and socioeconomic statuses include environmental factors like vitamin intake, nutrition, access to health care and education and lifestyle-related factors, like smoking and alcohol abuse.[36,43] The decrease in cases after 2016 in our study could be attributed, in part, to increasing consumption of folic acid. In mid-2015, Villa Clara province implemented a program promoting preconceptive use of folic acid supplements in all women of childbearing age.

Spatiotemporal variability analysis using spatial epidemiology techniques can offer important clues as to environmental disease etiologies. Numerous geospatial cluster studies have been conducted examining the effect of environmental factors on different congenital abnormalities.[16,20,28]

A primary spatiotemporal NSOFC cluster was identified in two municipalities in the extreme northwest corner of Villa Clara Province in 2017. Secondary spatiotemporal clusters were observed in the northern municipalities of Cifuentes and Encrucijada between 2013 and 2016, which merits further study.

These findings are similar to others that have identified geospatial variations for this type of congenital abnormality. For example, there are significant differences in NSOFC prevalence in different regions of China, with higher prevalence in the country's interior (frequencies of 3.0–4.7 per 1000) compared to coastal areas (at frequencies of 0.98–1.29 per 1000).

Researchers believe that environmental pollution, economic conditions, health service coverage and diagnostic capacity could contribute to geographic variation.[8] Even within the same Chinese province, great spatial variability has been reported; as an example, NSOFC prevalence in Jiayuguan (3.9 per 1000) and Dingxi (2.71 per 1000) were higher than other cities in Gansu Province. In that case, researchers did not observe significant correlations between economic conditions and NSOFC prevalence.[44]

Descriptive analysis of high NSOFC prevalence in South America found a spatial NSOFC cluster encompassing two cities in southern Ecuador (Cañar and Azogues). Different genetic and environmental risk factors were associated with NSOFCs in this area, including advanced maternal and paternal age, parental consanguinity, low maternal education level and use of drugs such as antimicrobials in the first trimester of pregnancy.[20]

Other NSOFC risk factors are low serum zinc concentrations and inadequate maternal levels of folic acid and other vitamins. In fact, according to WHO, 94% of congenital abnormalities occur in developing countries, where mothers are more vulnerable to malnutrition. In particular, micronutrients have a decisive influence on the health of pregnant women and normal fetal and placental development.[15,45,46] Zinc is an important micronutrient in embryo-fetal development and zinc deficiency is linked to nonsyndromic CP and other congenital abnormalities in animal studies.[21]

An exploratory ecological study of NSOFC spatial variability in the metropolitan area of Monterrey, Mexico, showed a marked concentration of cases in the urban periphery that resulted in several spatial clusters in the northeast territory showing a strong spatiotemporal association with environmental pollution.[28]

Although NSOFC spatiotemporal analyses do not offer causal explanations for identified clusters, they often generate working hypotheses that can be tested in future research. More targeted research designs, such as population-based case-control studies, should be used to explore potential causes of NSOFC clusters in Villa Clara Province. This study lays the foundation for future studies of specific NSOFC risk factors, including alcoholic beverage consumption; smoking; nutritional disorders, including deficiencies in zinc, folic acid, or other micronutrients; and heavy metal and nitrate levels in the soil and in drinking water in the territories under study.

Identifying NSOFC causal factors is the first step to NSOFC primary prevention. This study's strength is the high reliability and coverage level of the Cuban prenatal and postnatal records of congenital abnormalities, as well as absence of unregistered NSOFCs due to the network of community genetics services located in every municipality, whose counselors evaluate all newborns at one and three months of age. This study's limitations are similar to those of all spatial analysis research, including biases related to extrapolating aggregate-level associations to the individual scale, as well as expected limitations of spatiotemporal analyses, namely the inability to provide causal explanations for the study's results.

CONCLUSIONS

NSOFC frequency in Villa Clara Province, Cuba from 2013–2018 fell within expected Cuban and worldwide prevalence ranges. NSOFCs increased during the first four years of the study and began decreasing in 2016. Our research identified primary and secondary spatiotemporal NSOFC clusters in several geographically close municipalities. Although the underlying cause of this clustering remains unknown, identification of these clusters allows for more targeted investigations aimed at pinpointing factors related to NSOFC etiology.

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Genodermatoses in Las Tunas Province, Cuba, 1989–2019

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ABSTRACT

INTRODUCTION Genodermatoses are a group of genetic diseases that affect the skin and adjoining tissues. They represent 15% of genetic diseases worldwide. Cuba established a National Program for the Diagnosis, Care and Prevention of Genetic Diseases and Congenital Abnormalities in 1980, which was implemented in Las Tunas in 1989. In 2010, a specialized multidisciplinary provincial service for genodermatoses patients was established in Las Tunas province. Several studies in Las Tunas show that genodermatoses represent 22.2% of genetic diseases; the most common are ichthyosis (16.7%), mastocytosis (11.7%), and neurofibromatosis (8.3%). Children aged <12 years are the most affected (61.6%).

OBJECTIVE Describe genodermatoses in Las Tunas Province, Cuba, since the implementation of the National Program for the Diagnosis, Care, and Prevention of Genetic Diseases and Congenital Abnormalities, and after the creation of a specialized multidisciplinary provincial service for genodermatoses patients.

METHODS We conducted an observational, descriptive, retrospective study in 249 patients diagnosed with some type of genodermatosis who received care in Las Tunas during 1989–2019. Variables considered were: type of genodermatosis, complications, deaths and geographic location by municipality. We studied prevalence rates (1989–2019), incidence rates (2010–2019), proportion of complications, survival rates, and types of genodermatosis diagnosed by municipality in two periods (1989–2009 and 2010–2019) one before, and one after the implementation of a targeted multidisciplinary provincial care service.

RESULTS The general prevalence rate of genodermatoses in Las Tunas Province was 46.51 per 100,000 population. The forms with the highest prevalence rates were neurofibromatosis type 1 (13.6 per 100,000 population), classical Ehlers-Danlos syndrome (7.1 per 100,000), ichthyosis vulgaris (5.0 per 100,000) and cutaneous mastocytosis (2.4 per 100,000). The highest incidence rates coincided with the conditions with the highest prevalence: neurofibromatosis type 1 (81.5 per 1000 cases in 2013), classical Ehlers-Danlos syndrome (44.4 per 1000 cases in 2013) and ichthyosis vulgaris (52 per 1000 cases in 2010). From 1989–2009, patients presented a greater frequency of complications, at 40% (22/55) than from 2010–2019 at 21.1% (41/194). Pyodermitis was the most common during the study period (1989–2019), with 29.1% (16/55). Survival was high, at 98.0% (only 5 deaths in 2009, 2010, 2011, 2012, and 2015, and were no deaths during other years) in the study period. The greatest share of genodermatosis cases was registered in the municipality of Majibacoa (0.07%), and consanguinity was found in cases of epidermolysis bullosa, Herlitz type and xeroderma pigmentosum.

CONCLUSION In Las Tunas Province, Cuba, genodermatoses as a whole are not rare diseases. Those with the highest prevalence and incidence rates are neurofibromatosis type 1, classical Ehlers-Danlos syndrome and ichthyosis vulgaris. After implementation of the specialized multidisciplinary provincial service for genodermatoses patients within Cuba's National Program for the Diagnosis, Care, and Prevention of Genetic Diseases and Congenital Abnormalities, in addition to the active screening implemented by this Program, more cases were diagnosed, and a lower proportion of complications and a higher survival rates were recorded.

KEYWORDS Dermatology; skin diseases, genetic; genetic diseases, inborn; neurofibromatoses; Cuba

INTRODUCTION

In general, most dermatological diseases are genetic in origin; almost all cases involve a genetic predisposition to skin diseases.[1]

Individual immune response to infectious processes is modulated by epigenetics. The infectious dermatosis that best exemplifies this phenomenon is Hansen's disease.[2] However, '*genodermatosis*' refers to the process in which genetic anomalies (generally mutations of a single gene) play a predominant role in the origin of the disease and lead to clinical symptoms, which then manifest in the skin and adjoining tissues (adnexa). Their common characteristic is that they are all inherited.[3]

IMPORTANCE

This study updates understanding of genodermatoses in Las Tunas Province, after the implementation of the National Program for the Diagnosis, Care, and Prevention of Genetic Diseases and Congenital Abnormalities and the specialized multidisciplinary service that provides specialized care to patients affected with these genetic diseases.

Individually, genodermatoses are rare, but together they comprise a large group that is difficult to diagnose, treat and monitor due to their diversity in presentation and inheritance, even within the same disease.[4] Neurofibromatosis, Leopard syndrome, Ehlers-Danlos syndrome and tuberous sclerosis are diagnosed via clinical exam,[5,6] while ichthyosis, Darier disease, epidermolysis bullosa and mastocytosis are confirmed through histopathology.[5] In other cases, such as xeroderma pigmentosum (XP), supplemental studies are not conclusive. To diagnose the aforementioned conditions, Cuba uses histopathology, which is not conclusive, and single gel electrophoresis (SCGE) on isolated lymphocytes from peripheral blood to evaluate DNA's ability to repair itself after damage is induced by ultraviolet light, a test which is not 100% specific to XP.[7] In general, there are no genetic tests available for mass screening of these conditions.

Genodermatosis lesions can be very visible and have a psychological impact on patients, and can result in social stigma, negatively impacting their quality of life. Many genodermatoses lead to chronic disability, others to death.[4]

It is difficult to gather precise data on the prevalence of genodermatoses (especially in developing countries), due to the diversity

of diseases that are grouped under this common name, many of which go undiagnosed. In the most studied diseases, the results vary from one country to the next. Worldwide, the incidence of hypomelanosis of Ito is 1 per 7540–10,000 live births;[8] ectodermal dysplasia, 1 per 100,000 births;[9] oculocutaneous albinism, 1 per 18,000 births;[10] incontinentia pigmenti, 1 per 40,000–50,000 births;[11] tuberous sclerosis, 1–5 per 10,000 live births;[12] epidermolysis bullosa, 1 per 500,000 live births;[13] and Waardenburg syndrome, 1 per 42,000 births.[14]

Few population studies on genodermatoses have been conducted in Cuba. Dorticós conducted research to characterize them in a study involving 10 hospitals in Havana from 1980 to 1986, in which ichthyosis (37.7%) and neurofibromatosis (18.8%) were the most common genodermatoses.[15] Campo Díaz published a study on Ehlers-Danlos syndrome type III conducted in Pinar del Río Province in 2010–2011, finding 100% with manifestations on the skin and 59.3% with associated bleeding disorders.[16] Orraca also made a genetic, clinical and epidemiological characterization of neurofibromatosis type 1 in Pinar del Río Province, finding a prevalence of 1 per 1141 in pediatric patients, above rates reported globally for this disease.[17] One study performed in 2015 in Las Tunas, an eastern Cuban province, suggested that 85% of genetic diseases treated at the Provincial Medical Genetics Department (PMGD) were diagnosed in pediatric patients; of those, 22% were dermatological.[18]

WHO estimates that there are approximately 10,000 genetic diseases affecting 7% of the world population.[19] Genetic diseases make up 25% of pediatric hospital admissions, with 15% of cases affecting the skin and adnexa.[20]

Since 1963, WHO has urged member states to focus on the control and prevention of genetic diseases (through early diagnosis, access to care, genetic counseling, etc.).[21] In developed countries, there are numerous foundations dedicated to the treatment of specific genetic diseases, but there is no unifying vision that involves all levels of health care. In 1980, Cuba's national health system implemented the National Program for the Diagnosis, Care, and Prevention of Genetic Diseases and Congenital Abnormalities,[22] which we will identify below as NGP (National Genetics Program). This program is supported by a network of Genetics Counseling Service comprising 172 Medical Genetics Municipal Departments (in every municipality in the country), 16 PMGD (located in all Cuban provinces), and the National Medical Genetics Center (CNGM), a lead institution that provides coverage to the entire population. CNGM is a collaborative center focused on genetic developments that help promote health worldwide.[22]

NGP's work is guided by the Manual of Regulations and Procedures for medical genetics services in Cuba,[23] which offers standards for mass screening for some genetic diseases via specialized screening. NGP not only offers specialized medical care, but also conducts preventive prenatal, perinatal, and postnatal services (at the three levels of prevention: primary, secondary, and tertiary) for early detection of congenital diseases and abnormalities; supports research aimed at designing education strategies for patients, their families, and the general public; and works to promote social inclusion of affected persons and improve their quality of life.[22] Masters and specialists in clinical genetics regularly conduct exchanges for diagnostics and patient follow-up with those in other fields (gynecology and obstetrics, ophthalmology, endocrinology, orthopedics, otorhinolaryngology, neonatology, immunology, molecular biology, dermatology, pediatrics, psychology, neurology, cardiology, oral medicine, pathology and imaging, etc.).[23]

NGP was established in Las Tunas Province in 1989. In 2010, a specialized multidisciplinary provincial service was established to care for genodermatosis patients. This bi-weekly service is managed by specialists in clinical medical genetics and dermatology, the service's main specialties, with support from psychologists, immunologists, pediatricians and others, depending on patient characteristics and symptoms. From 2010 to 2012, the most common genodermatoses were ichthyosis (16.7%), mastocytosis (11.7%), and neurofibromatosis (8.3%). The most affected were patients <12 years of age (61.6%).[24]

The objective of this study was to describe genodermatoses in Las Tunas Province, Cuba, since the establishment of NGP, and after the creation of a specialized multidisciplinary provincial service for genodermatosis patients.

METHODS

Study type and participants A descriptive observational study was performed, with cross-sectional and retrospective components. It was conducted at the PMGD's specialized multidisciplinary provincial genodermatoses service in Las Tunas Province, Cuba, and comprised the years 1989–2019. The universe was composed of 942 patients with genetic disease diagnoses, registered in the PMGD database and, for non-probability sampling, 249 patients who met the diagnostic criteria of genodermatoses.

Inclusion criteria Patients seen at the service, who met genodermatosis diagnostic criteria, and who gave written informed consent to participate in the study (in the case of minors, parents or guardians authorized patient participation).

Exclusion criteria Patients seen at the service, but whose medical records did not contain all data necessary for the study, or who had psychiatric conditions that would prevent necessary data collection.

Diagnostic criteria Genodermatoses are considered clinical conditions whose primary phenotypic manifestations involve the skin and adnexa and that have a genetic component. Patient genealogy was examined to determine genetic history, inheritance patterns and the diagnosis of new cases in the family since the proband case.[23] In all cases the diagnosis was confirmed by a clinical geneticist.

Supplemental studies were performed to corroborate the diagnosis or presence of complications. These studies were: hematological (liver transaminases, eosinophil count, peripheral blood smears to explore the presence of mast cells in peripheral blood);[25] histopathological (skin biopsy for microscopic diagnosis of aplasia cutis, cutis laxa, cutis verticis gyrata, congenital ectodermal dysplasia, Darier disease, Hailey-Hailey disease, epidermolysis bullosa, hypomelanosis of Ito, ichthyosis,

incontenencia pigmenti, mastocytosis, pityriasis rubra pilaris, porokeratosis of Mibelli, palmoplantar keratoderma, Netherton syndrome, Proteus syndrome, and Rothmund-Thomson syndrome);[1,2] imaging (ultrasonography, computed tomography, and magnetic resonance imaging; fundamental in diagnosing neurofibromatosis, tuberous sclerosis and Sturge-Weber syndrome);[23] genetic, to corroborate genodermatosis diagnoses whose clinical presentations were not conclusive on their own or to differentiate them from other clinically similar conditions, such as SGCE on isolated lymphocytes XP diagnosis;[7] indirectly using five markers: four microsatellite markers (IVS27AAAT2.1, IVS38GT53.0, IV27AC28.4 and Mfd15) and one restriction fragment length polymorphism (Rsa I NF1 exon 5) to diagnose neurofibromatosis type 1;[17] and other studies required to diagnose infectious complications, such as bacterial and fungal cultures.[2]

The foundation of all diagnoses in the study were initial clinical exam and personalized physician–patient relationships, the fundamental pillars of diagnostics in general, especially when advanced technology is not available to corroborate the suspected clinical condition.[26]

Variables

Diagnosed genodermatoses (based on diagnostic criteria) The following were considered: Oculocutaneous albinism (OCA) [OMIM 203100 203200 203290 606574 615312 113750 615179 606952 ORPHA 55 GARD 10958], aplasia cutis [OMIM 107600 600360 ORPHA 1114 GARD 5835], cutis laxa [OMIM 123700 6144434 616603 219100 ORPHA 90348 90349 GARD 1639 8480], *cutis verticis gyrata* (CvsG) [OMIM 123790 ORPHA 671 GARD 1643], autosomal dominant hypohidrotic ectodermal dysplasia (HED-AD) [OMIM 129490 224900 614940 617337 ORPHA 238468 GARD 76], Darier disease (Darier) [OMIM 124200 ORPHA 218 GARD 6243], Hailey-Hailey disease (Hailey-H) [OMIM 169600 ORPHA 2841 GARD 6559], Niemann-Pick disease (Nieman P) [OMIM 257200 607616 257220 607625 ORPHA 77292 77293 646 GARD 7206 10729], generalized epidermolysis bullosa simplex (EB simplex) [OMIM 131900 ORPHA 79399 GARD 2147], junctional epidermolysis bullosa, Herlitz type (EB Herlitz) [OMIM 226700 ORPHANET 79404 GARD 2153], tuberous sclerosis (TS) [OMIM 191100 613254 ORPHA 805 GARD 7830 946], hypomelanosis of Ito (H. Ito) [OMIM 300337], ichthyosis vulgaris (Ichthyosis V) [OMIM 146700] Lamellar ichthyosis (Ichthyosis L) [OMIM 615024 ORPHA 313], incontinencia pigmenti (I.Pigmenti) [OMIM 161000 ORPHA 69087 GARD 3912], cutaneous mastocytosis [OMIM 154800 ORPHA 66646 GARD 7842], neurofibromatosis type 1 (NF-1) [OMIM 162200 ORPHANET 636 GARD 7866], segmental neurofibromatosis (Segmental NF) [OMIM 162200], piebaldism [OMIM 172800 ORPHA 2884 GARD 4344], pityriasis rubra pilaris (PRP) [OMIM 173200 ORPHA 2897 GARD 7401], classic porokeratosis of Mibelli (PM) [OMIM 175800 ORPHA 735 GARD 4438], epidermolytic palmoplantar keratoderma (PPK) [OMIM 144200 600962 ORPHA 2199 496 GARD 2826 5186], Albright syndrome (S. Albright) [OMIM 174800 ORPHA 562 GARD 6995], occipital horn syndrome (OH) [OMIM 304150 ORPHA 198 GARD 4017], classical Ehlers-Danlos syndrome (ED) [OMIM 130000 130010 ORPHA 98249 GARD 6322], LEOPARD syndrome (LEOPARD) [OMIM 151100 611554 613707 ORPHA 500 GARD 1100], Netherton syndrome (Netherton) [OMIM 256500 ORPHANET 634 GARD 7182], Noonan syndrome (Noonan) [OMIM 163950 605275 609942 610733 611553 613224 613706 615355 616559 616564 618499 618624 ORPHA 648 GARD 10955], Proteus syndrome (Proteus) [OMIM 176920 ORPHA 744 GARD 7475], Rothmund-Thomson syndrome (R-T) [OMIM 618625 ORPHANET 2909 GARD 4392], Sturge-Weber syndrome (S-W) [OMIM 185300 ORPHA 3205 GARD 7706], Waardenburg syndrome type I (W-I) [OMIM 193500 ORPHA 3440 GARD 5525] and xeroderma pigmentosum (XP) [OMIM 278700 278720 278730 278740 278760 278780 610651 ORPHA 910 GARD 7910].

New cases New cases diagnosed per year, for each genodermatosis.

Complications We considered complications secondary to skin abnormalities due to genodermatosis, such as secondary pyoderma (Bacterial I),[2] superficial cutaneous mycoses (Fungal I) and within these, dermatophytosis and mucocutaneous candidiasis, erythroderma, sun damage (sun burns, sun freckles, elastosis, premalignant lesions, skin cancer) and systemic inflammatory response syndrome (SIRS). The number of patients with each complication were considered.

Number of deaths and diagnosis Deceased patients with genodermatosis and genodermatosis diagnosis at death.

Geographic location by municipality All municipalities of the province were considered: Amancio Rodríguez, Colombia, Jesús Menéndez, Jobabo, Las Tunas, Majibacoa, Manatí, and Puerto Padre. This variable provides important epidemiological elements pertaining to inheritance patterns, potential consanguinity and prevalence of specific genodermatoses within particular regions.

Data collection and analysis Information was collected using primary sources consisting of patients of legal age and parents or guardians of patients who were minors, and secondary sources consisting of the patient's medical record and records from PMGD and specialized multidisciplinary provincial service for patients with genodermatoses. Techniques used to obtain information included participatory structured observation, face-to-face medical interviews, and general and more targeted physical examinations, as well as a review of secondary sources. All information was gathered in a Microsoft Excel database and was processed using the SPSS Version 18 for Windows.

Prevalence rates were calculated per 100,000 population, taking into consideration the population of Las Tunas Province in 2019 (535,335 inhabitants), according to the Cuban National Statistics and Information Bureau (ONEI).[27]

The annual incidence rate of genodermatosis was calculated for 2010–2019 (the period following the implementation of the specialized multidisciplinary provincial service for patients with genodermatoses), as was the proportion of complications. Two periods of time were compared, from the start of the National Genetics Program in 1989 to implementation of the specialized multidisciplinary provincial service for patients with genodermatoses in 2009, and during the service's operation in 2010–2019. We also calculated the survival index (100 x number of survivors annually/total patients), fatality rate (100 x number of deaths per year/total patients), and number of genodermato-

ses diagnosed per municipality (number of patients/municipality population) x 100) for each genodermatosis.

To compare results among municipalities, the population of each was taken into consideration (according to ONEI data): 37,695 inhabitants in Amancio; 32,167 in Colombia; 48,208 in Jesús Menéndez; 42,603 in Jobabo; 211,596 in the municipality of Las Tunas; 41,287 in Majibacoa; 29,930 in Manatí, and 91,879 in Puerto Padre.[27]

Ethical considerations The research protocol was approved by the research ethics committee and scientific council at Mártires de las Tunas Provincial Pediatric Hospital and research was conducted in accordance with the Declaration of Helsinki.[28] To participate in the study, written informed consent was obtained from patients (or parents or guardians of patients who were minors). The written information provided explained the importance of participation, the risks and benefits, participants' rights and study characteristics. Data was coded to protect patient identity.

RESULTS

From 1989 through 2019, general prevalence rate of genodermatoses in Las Tunas Province was 46.5 per 100,000 population. Neurofibromatosis type 1 was predominant at 13.6 cases per 100,000 population, followed by classical Ehlers-Danlos syndrome at 7.1 per 100,000, ichthyosis vulgaris at 5 per 100,000 and cutaneous mastocytosis at 2.4 per 100,000 (Figure 1).

From 2010 through 2019 highest recorded incidence rates were for neurofibromatosis type 1 at 81.5 per 1000 (2013), 50.6 per 1000 (2016), and 40.6 per 1000 (2017). The next highest rates were for ichthyosis vulgaris at 52 per 1000 (2010) and classical Ehlers-Danlos syndrome at 44.4 per 1000 (2013). During this time, all rates decreased and the lowest were observed in 2019, the last year of the study (Table 1).

Complications for 1989–2009 (Figure 2) represented 40% (22 of 55 diagnosed with genodermatosis); higher than during 2010–2019, when it was 21.1% (41 of 194 diagnosed). In both periods, pyodermitis was predominant at 29.1% (16/55) in 1989–2009 and 13.4% (26/194) in 2010–2019, followed by sun damage at 9.1% (5/55) in 1989–2009 and 4.1% (8/194) in 2010–2019.

General survival (1989–2019) was high at 98% (only 5 deaths of 249 diagnosed). Deaths occurred in the years 2009, 2010, 2011, 2012, and 2015 (one in each year). There were no deaths during the other years in the study period.

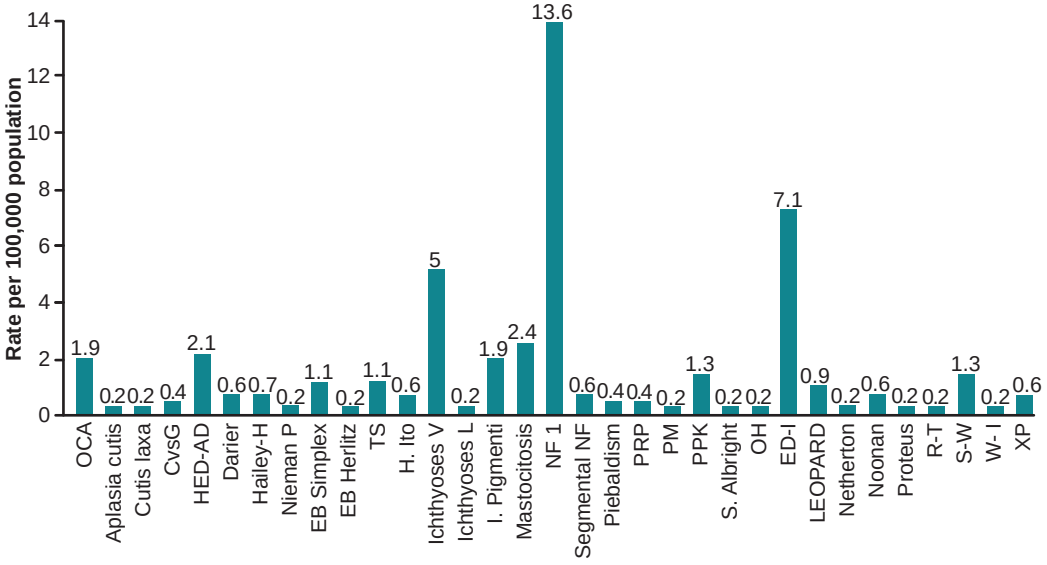
The municipality with the highest proportion of genodermatosis cases was Majibacoa (0.07%), followed by Las Tunas (0.06%) and Colombia and Jobabo, both at 0.05%. The municipalities with the lowest prevalence were Amancio and Puerto Padre, both at 0.02%. There was consanguinity in the municipality of Manatí, with a case of junctional epidermolysis bullosa, Herlitz type; in the municipality of Colombia there were two cases of XP.

DISCUSSION

The most predominant inheritance patterns of genodermatoses in Las Tunas are those with autosomal dominant Mendelian inheritance, such as neurofibromatosis type 1, classical Ehlers-Danlos syndrome, ichthyosis vulgaris, and cutaneous mastocytosis.[29] In this type of inheritance, traits or conditions are present in all generations, even if the individual is heterozygous; it affects both sexes, with a 50% probability of transmitting the affected allele to their offspring,[29] and accordingly, the proportion of affected individuals in a population will be higher. These conditions often present low fatality, which contributes to increasing prevalence.

According to WHO, rare diseases are those that affect less than 5 persons per 100,000 population.[30,31] Other authors internationally have reported prevalence rate of neurofibromatosis type 1 at 1 per 2500–3000 population,[32] classical Ehlers-Danlos syndrome at 1 per 5000 births,[33,34] ichthyosis vulgaris at 1 per 250–1000 population,[35] and cutaneous mastocytosis at 2 per 300,000 births.[36] Considering the results of our study, these diseases, as a group, and by this definition, are not rare in Las Tunas Province; neither are neurofibromatosis type 1, classical Ehlers-Danlos syndrome,

Figure 1: Genodermatoses prevalence (per 100,000 population). Las Tunas, Cuba, 1989–2019



OCA: occulocutneous albinism; CvsG: cutis verticis gyrata; HED-AD: hypohidrotic ectodermal dysplasia congenita autosomal dominant; Darier: Darier disease; Hailey-H: Hailey-Hailey disease; Nieman P: Nieman Pick disease; EB simplex: epidermolysis bullosa simplex; EB Herlitz: junctional epidermolysis bullosa type Herlitz; TS: tuberous sclerosis; H. Ito: hypomelanosis of Ito; Ichthyosis V: ichthyosis vulgaris; Ichthyosis L: lamellar ichthyosis; I.Pigmenti: incontinentia pigmenti; NF-1: neurofibromatosis type 1; Segmental NF: segmental neurofibromatosis; PRP: pityriasis rubra pilaris; PM: porokeratosis of Mibelli; PPK: palmoplantar keratoderma; S. Albright: Albright síndrome; OH: occipital horn síndrome; ED: Ehlers-Danlos syndrome type classic; LEOPARD síndrome; Netherton: Netherton síndrome; Noonan: Noonan síndrome; Proteus: Proteus síndrome; R-T: Rothmund-Thomson síndrome; S-W: Sturge Weber síndrome; W-I: Waardenbur syndrome type I; XP: xeroderma pigmentosum

Table 1: Annual incidence of genodermatoses (per 1000 population). Las Tunas province, Cuba, 2010–2019

genodermatoses	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
OCA	0	0	0	7.4	13.8	0	0	0	4.4	0
Aplasia cutis	0	0	9.3	0	0	0	0	0	0	0
Cutis laxa	13	0	0	0	0	0	0	0	0	0
CvsG	13	11.8	0	0	0	0	0	0	0	0
HED-AD	26	0	9.3	7.4	0	0	0	5.1	0	8
Darier	0	0	0	0	0	0	0	0	13.2	4
Hailey-H	0	0	9.3	0	0	0	0	5.1	0	0
EB Simplex	13	11.8	0	0	0	0	11.2	0	4.4	0
EB Herlitz	0	11.8	0	0	0	0	0	0	0	0
TS	13	11.8	0	0	6.9	6.3	0	0	0	4
H. Ito	0	0	0	0	0	0	0	0	8.8	0
Ichthyosis V	52	11.8	46.3	29.6	13.8	6.3	5.6	0	26.4	0
I.Pigmenti	13	0	9.3	22.2	6.9	0	0	10.2	0	0
Mastocytosis	4	0	27.8	7.4	0	6.3	5.6	5.1	4.4	4
NF-1	26	23.5	0	81.5	6.9	44.3	50.6	40.6	35.2	16.1
Segmental NF	0	0	9.3	0	0	0	0	0	4.4	4
Piebaldism	13	0	0	0	0	0	0	0	4.4	0
PRP	0	0	18.5	0	0	0	0	0	0	0
PM	0	0	9.3	0	0	0	0	0	0	0
PPK	13	11.8	9.3	0	6.9	6.3	0	0	4.4	0
OH	13	0	0	0	0	0	0	0	0	0
ED	0	0	18.5	44.4	6.9	12.7	28.1	30.5	13.2	0
LEOPARD	0	0	0	0	0	0	11.2	0	4.4	4
Noonan	0	0	0	0	6.9	0	0	0	0	8
Proteus	0	0	0	0	0	0	0	0	0	4
R-T	0	0	9.3	0	0	0	0	0	0	0
S-W	13	0	27.8	0	6.9	0	0	0	0	4
W-I	0	0	0	0	0	0	0	0	0	4
XP	13	0	0	0	0	0	0	0	8.8	0

OCA: occulocutneous albinism; CvsG: cutis verticis gyrata; HED-AD: hypohidrotic ectodermal dysplasia congenita autosomal dominant; Darier: Darier disease; Hailey-H: Hailey-Hailey disease; EB simplex: epidermolysis bullosa simplex; EB Herlitz: junctional epidermolysis bullosa type Herlitz; TS: tuberous sclerosis; H. Ito: hypomelanosis of Ito; Ichthyosis V: ichthyosis vulgaris; I.Pigmenti: incontinentia pigmenti; NF-1: neurofibromatosis type 1; Segmental NF: segmental neurofibromatosis; PRP: pityriasis rubra pilaris; PM: porokeratosis of Mibelli; PPK: palmoplantar keratoderma; OH: occipital horn syndrome; ED: Ehlers-Danlos syndrome type classic; LEOPARD síndrome; Noonan: Noonan síndrome; Proteus: Proteus síndrome; R-T: Rothmund-Thomson síndrome; S-W: Sturge Weber síndrome; W-I: Waardenbur syndrome type I; XP: Xeroderma pigmentosum

and ichthyosis vulgaris. However, cutaneous mastocytoses have lower rates in the province than those reported at globally.

The multidisciplinary service offers genetics counseling for families including a discussion of reproductive options. While not all families perceive risk the same way, genetic counseling has increased the birth rate of individuals with conditions that are not lethal or whose life expectancy is higher. High prevalence rates may be due in part to increased treatment effectiveness and genetics counseling availability in the province.

In many genodermatoses, including neurofibromatosis type 1, classical Ehlers-Danlos syndrome, and ichthyosis vulgaris, among others,[5] patients do not manifest signs and symptoms in the first year after birth, which makes it very difficult to determine prevalence rates at birth. However, when incidence rates are studied in relation to specific genodermatoses diagnosed per year, the most commonly-diagnosed genodermatoses in any one year can be identified. For genodermatoses whose manifestations begin in the first year, like congenital ectodermal dysplasia, oculocutaneous albinism, epidermolysis bullosa, and incontinentia pigmenti,[5] incidence rates coincide with prevalence rates at birth.

The fact that annual rates are higher for genodermatoses that do not present symptoms at birth suggests that diagnosis is based on active case screening, identification of affected members of the same family as the proband case, use of genealogical trees and effectiveness of the risk counseling process. This is possible thanks to NGP working at all three levels of care, both for the patient and their family, facilitating better control of these diseases.[23]

When skin is damaged, as occurs in most genodermatoses, it loses its barrier-protective function, which allows bacteria and fungi to colonize the skin.[37] Comparing the most common complications in both periods, we found fewer during the second period, which coincides with the 2010 implementation of the specialized multidisciplinary provincial service for patients with genodermatoses, the multidisciplinary work between the geneticist and dermatologist, and the application of treatments to improve the clinical status of the patient with consequent complication prevention.

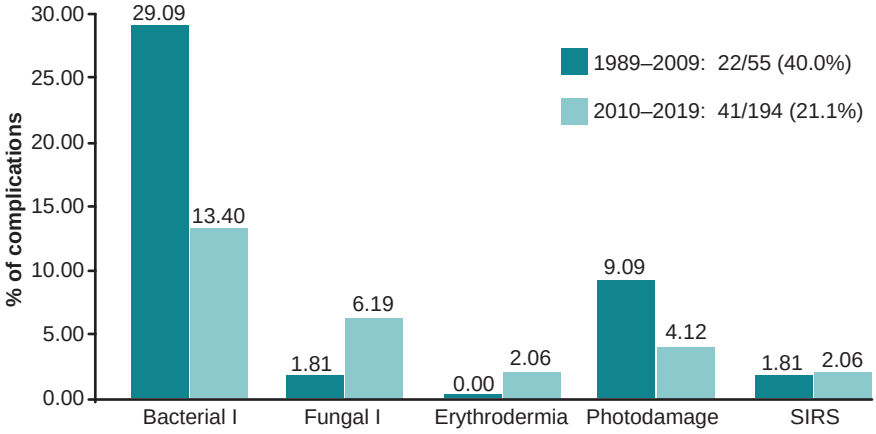
General orientations provided by the service included hygiene, sun protection, skin self-examination, a balanced diet rich in fruits and vegetables (vitamin therapy), adequate skin hydration and use of emollients for xerodermic or ichthyosiform skin.[2] Preventive therapeutic measures included emollient and antibiotic creams used in combination for diseases with high risk of damage to skin integrity, such as ichthyosis, Darier disease, epidermolysis bullosa and pityriasis rubra,[2] as well as antifungals, since fungal infections such as palmoplantar keratoderma and epidermolytic hyperkeratosis may occur.[2]

For pyodermitis, antibiotics such as penicillins and cephalosporins were employed, as these are effective against *Staphylococcus aureus* and group A beta-hemolytic *Streptococcus*, bacteria that commonly colonize the skin and may even lead to systemic complications.[1]

While patient survival was high, five deaths occurred, all due to complications, described as follows:

One patient had junctional Herlitz-type epidermolysis bullosa.[38] This patient presented symptoms of generalized blistering from birth that left atrophic scars, with marked epidermal detachment, presence of the Nikolsky sign (except the palms of the hands and soles of the feet) and nail dystrophy, with no tooth development and madarosis. Skin lesions were poten-

Figure 2: Most frequent complications (percentages) in genodermatosis. Las Tunas, Cuba, 1989–2009 and 2010–2019



Bacterial I: Bacterial infections; Fungal I: Fungal infections: SIRS: systemic inflammatory response syndrome
Note: A patient may present with more than one complication.

tial entry points, which led to symptoms of sepsis, immunodeficiency, delayed psychomotor development, protein-energy undernutrition,[38] and finally, multiorgan failure, with death at 11 months.

A patient with occipital horn syndrome presented hypotonia, with frequent symptoms of diarrhea, cutis laxa, joint hypermobility, coarse hair, clotting disorder, and an aortic aneurysm,[39] which led to his death at eight months. This syndrome, formerly known as type IX Ehlers-Danlos syndrome, was excluded from the classification of variants of Ehlers-Danlos syndrome established by an international expert consortium in 2017,[40] and is currently classified in the connective tissue disorder group caused by abnormalities in copper metabolism.

Another patient with a Rothmund–Thomson syndrome presented with typical features of the disease, such as xeroderma, poikiloderma of the face, congenital cataracts, photophobia, delayed physical growth, immunodeficiency and sepsis[41,42] and died at under five months of age.

One patient presented with Netherton syndrome, a rare disease transmitted through autosomal recessive inheritance and defined by the characteristic triad of congenital ichthyosiform erythroderma, hair shaft abnormalities and immunological disorders.[43,44] From birth, this patient had symptoms of erythroderma accompanied by frequent skin infections, leading to repeated admissions to intensive care units and ultimately death from sepsis at two years of age.

Another patient had neurofibromatosis type 1 associated with congenital cardiovascular malformations that led to cardiogenic complications and death. Neurofibromatosis type 1 is a multisystem disease, considered a neuroectodermal syndrome (currently called neurocristopathy), transmitted through autosomal dominance through the nf1 gene located at locus 17q11.2 and affecting mainly the skin and nervous system. It produces melanic manifestations of the skin and tumors, but is often not lethal.[45] In this patient, more than six cafe-au-lait spots and a genetic family history of the disease were identified, but congenital heart disease led to the patient's death at age two.

The literature considers genodermatoses to be genetic diseases of the skin with high morbidity that, in some cases, present systemic conditions that may be fatal; in most lethal genodermatoses, death often occurs in the first year of life.[5]

This study facilitated identification of geographic distribution (by municipality) and affected families. In general, the number of cases diagnosed was not proportional to the population density of each municipality. The highest proportion of cases was in Majibacoa, which had the fifth highest population density in the province, but a place also characterized by greater involvement of dermatologists in the community. The municipalities with the highest population densities, such as Puerto Padre and Amancio Rodríguez, recorded lower proportions of cases. This may be due to poor screening and less availability of dermatological care. Despite existence of a specialized multidisciplinary provincial service for genodermatoses patients that includes both clinical geneticists and dermatologists, the latter are in the highest demand for these patients, and their greater participation in the NGP is needed.[24]

A case of epidermolysis bullosa (Herlitz type) was diagnosed in Manatí municipality. The patient had a family history of the disease, including a maternal uncle who died of it, and parental consanguinity. In Colombia municipality, a case was confirmed of xeroderma pigmentosum with familial ties to an affected family from another province (Ciego de Avila) in which consanguinity was determined. Consanguinity is the genetic union of two people descended from common ancestors, (second-degree cousins or closer). Currently, over 1.2 billion people worldwide are in consanguineous marriages and it is estimated that 10.4% of the world population is married to a biological relative or is the offspring of a consanguineous union.[46] A consanguineous marriage increases the risk of autosomal recessive diseases transmission by 25%–50% because it increases the probability of two affected alleles being combined and thus the birth of an affected child.[46]

CONCLUSIONS

In Las Tunas Province, Cuba, genodermatoses as a whole are not rare diseases according to WHO definitions. Those with the highest prevalence and incidence rates are neurofibromatosis type 1, classical Ehlers-Danlos syndrome and ichthyosis vulgaris. After implementation of the specialized multidisciplinary provincial service for genodermatoses patients within Cuba's NGP, in addition to active screening, more cases were diagnosed, and a lower proportion of complications and a higher survival index were recorded. However, improving the quality of care for patients with genodermatosis is necessary with the implementation of a methodology protocolizing their care and establishing follow-up algorithms.

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Implications of Low-grade Inflammation in SARS-CoV-2 Immunopathology

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ABSTRACT

INTRODUCTION Advanced age and chronic disease comorbidities are indicators of poor prognosis in COVID-19 clinical progression. Fatal outcomes in patients with these characteristics are due to a dysfunctional immune response. Understanding COVID-19's immunopathogenesis helps in designing strategies to prevent and mitigate complications during treatment.

OBJECTIVE Describe the main immunopathogenic alterations of COVID-19 in patients of advanced age or with chronic non-communicable diseases.

DATA ACQUISITION We carried out a bibliographic search of primary references in PubMed, Elsevier, Science Direct and SciELO. A total of 270 articles met our initial search criteria. Duplicate articles or those unrelated to at least one chronic comorbidity, senescence or inflammation and those that studied only patient clinical characteristics, laboratory tests or treatments were excluded. Finally, our selection included 124 articles for analysis: 10 meta-analyses, 24 original research articles, 67 review articles, 9 editorials, 9 comments, 3 books and 2 websites.

DEVELOPMENT Hypertension and diabetes mellitus are the most common comorbidities in COVID-19 patients. Risk of developing severe manifestations of the disease, including death, is increased in senescent and obese patients and those with cardiovascular disease, cancer or chronic obstructive pulmonary disease. Low-grade chronic inflammation is characteristic of all these conditions, reflected in a pro-inflammatory state, endothelial dysfunction, and changes to innate immunity; mainly of the monocyte-macrophage system with changes in polarization, inflammation, cytotoxicity and altered antigenic presentation. In the case of SARS-CoV-2 infection, mechanisms involved in acute inflammation overlap with the patient's pro-inflammatory state, causing immune system dysfunction. SARS-CoV-2 infection amplifies already-existing alterations, causing failures in the immune system's control mechanisms. The resulting cytokine storm causes an uncontrolled systemic inflammatory response marked by high serum levels of inflammatory biomarkers and a pro-inflammatory cytokine profile with decompensation of underlying diseases. In asthma, chronic eosinophilic inflammation protects against infection by producing a reduced interferon-mediated response and a reduced number of ACE2 receptors.

CONCLUSIONS Low-grade chronic inflammation present in advanced age and chronic diseases—but not in bronchial asthma—produces a pro-inflammatory state that triggers a dysregulated immune response, favoring development of severe forms of COVID-19 and increasing lethality.

KEYWORDS SARS-CoV-2, COVID-19, inflammation, aging, chronic disease, immune system

INTRODUCTION

COVID-19 is caused by the SARS-CoV-2 virus,[1,2] the seventh member of the *Coronaviridae* family capable of infecting humans.[3–6] SARS-CoV-2 genomic modifications affect its pathogenicity,[7,8] which, together with human genetic polymorphisms,[8–10] influence an individual's immune response and susceptibility to the virus.[7–12] Clinical presentations are varied and can affect all systems in the body.[13–15] Worse prognosis is experienced by those aged ≥60 years and those with pre-existing comorbidities.[15–18] Mortality in this age group is especially associated with immunosenescence and the presence of such chronic non-communicable diseases,[19] both of which can increase risk of complications.[13]

Approximately 80% of COVID-19 deaths occur in those aged ≥65 years.[20] These patients are more likely to develop dysfunctional immune response, accompanied by changes in the lung microenvironment, in barrier immunity, macrophage and dendritic cell maturation and migration and T-lymphocyte activation, causing immune system dysregulation.[21]

IMPORTANCE
Comorbidities, age and immunological factors are key in COVID-19 clinical evolution. This review provides an update on immunological factors that influence COVID-19 severity and lethality in older adults and chronic disease patients.

We live in an aging world in which 1 in 11 people are aged ≥65 years,[22] while chronic non-communicable diseases (NCDs) cause 71% of global deaths. Cardiovascular disease, cancer, respiratory disease and diabetes are responsible for >80% of premature death from NCDs.[23] In Cuba, 20.8% of the population is aged ≥60 years, and the NCD mortality rate is the highest among all causes of death at 791.9 deaths per 100,000 population. In this age group, the prevalence rates of hypertension (759.2 and 508.1 per 1000 population in age groups 60–64 years and ≥65 years, respectively) and diabetes mellitus (250.9 and 165.6 per 1000 population in age groups 60–64 years and ≥65 years, respectively) are higher than in other age groups. Asthma has a higher prevalence during adolescence, although in 2019, a rate of 145.9 per 1000 population was reported in patients aged 60–64 years. The incidence of cancer in people aged ≥60 years has increased considerably in the last decade (1910.9 and 1275.3 per 100,000 population for men and women respectively, in 2019).[24]

Due to the worldwide increase in life expectancy, as well as the high NCD prevalence, the pandemic must be faced with a syndemic approach.[25] Studying changes in immune system response helps to better understand the lethality of the disease and improve interventions targeting the modifiable risk factors that can contribute to fatal outcomes and complications, mainly in older adults.

The objective of this review is to describe the main immunopathogenic alterations to COVID-19 progression related to low-grade inflammation in older adults and patients with chronic non-communicable diseases.

DATA ACQUISITION

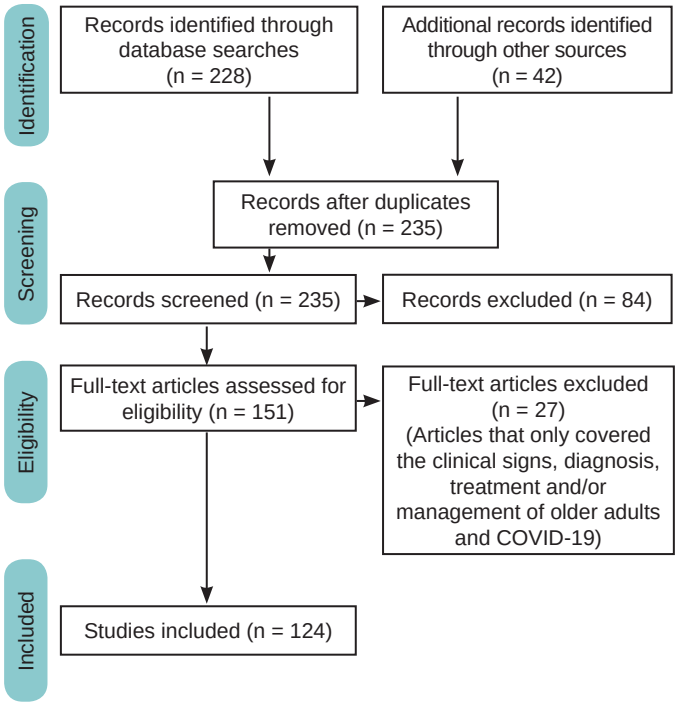
We carried out a bibliographic review of the PubMed, Elsevier, Science Direct and SciELO databases in Spanish and English. We used three search strategies consisting of a combination of descriptors with Boolean operators; a restricted form "AND" for non-homologous terms and an additive form "OR" for homologues:

- "COVID-19" OR "SARS-Cov-2" AND "low-grade inflammation" OR "chronic inflammation"
- "COVID-19" OR "SARS-CoV-2" AND "hypertension" OR "diabetes mellitus" OR "obesity" OR "cancer" OR "asthma" OR "chronic obstructive pulmonary disease"
- "hypertension" OR "diabetes mellitus" OR "obesity" OR "cancer" OR "asthma" OR "chronic obstructive pulmonary disease" AND "low-grade inflammation".

Articles related to COVID-19 were reviewed if published in 2020; articles related to other topics were restricted to the period 2000–2020. Articles published prior to those dates that were cited in the originally selected articles were also included. Demographic and morbidity data were obtained from the official websites of the UN,[22] WHO[23] and the National Health Statistics Yearbook of the Cuban Ministry of Public Health (MINSAP).[24]

Initially, 270 articles met the search criteria. Duplicate articles or articles unrelated to at least one chronic comorbidity, senescence or inflammation and those that studied only patient clinical characteristics, laboratory tests or treatments were excluded (Figure 1). Our final selection included 124 articles: 10 meta-analyses, 24 original research articles, 67 review articles, 9 editorials, 9 comments, 3 books and 2 websites. Preprints were not included in the search.

Figure 1: Literature review process



DEVELOPMENT

Immune system involvement in COVID-19 SARS-CoV-2–infected patients can develop different clinical presentations of COVID-19, and are more likely to die if they have pre-existing comorbidities or are aged ≥60 years.[26] A functional immune system is needed to combat infection and maintain a state of homeostasis; when immune system function is disturbed, the breakdown of this equilibrium can lead to fatal outcomes.[27,28]

The first line of defense in SARS-CoV-2 infection is the innate immune response.[29] The type, quality and efficacy of this response determine the adaptive immune response and influence the course of infection.[30] A failed immune response to severe acute respiratory syndrome is described as being 'trapped' in innate immunity, while progression to adaptive immunity if associated with more favorable outcomes.[31]

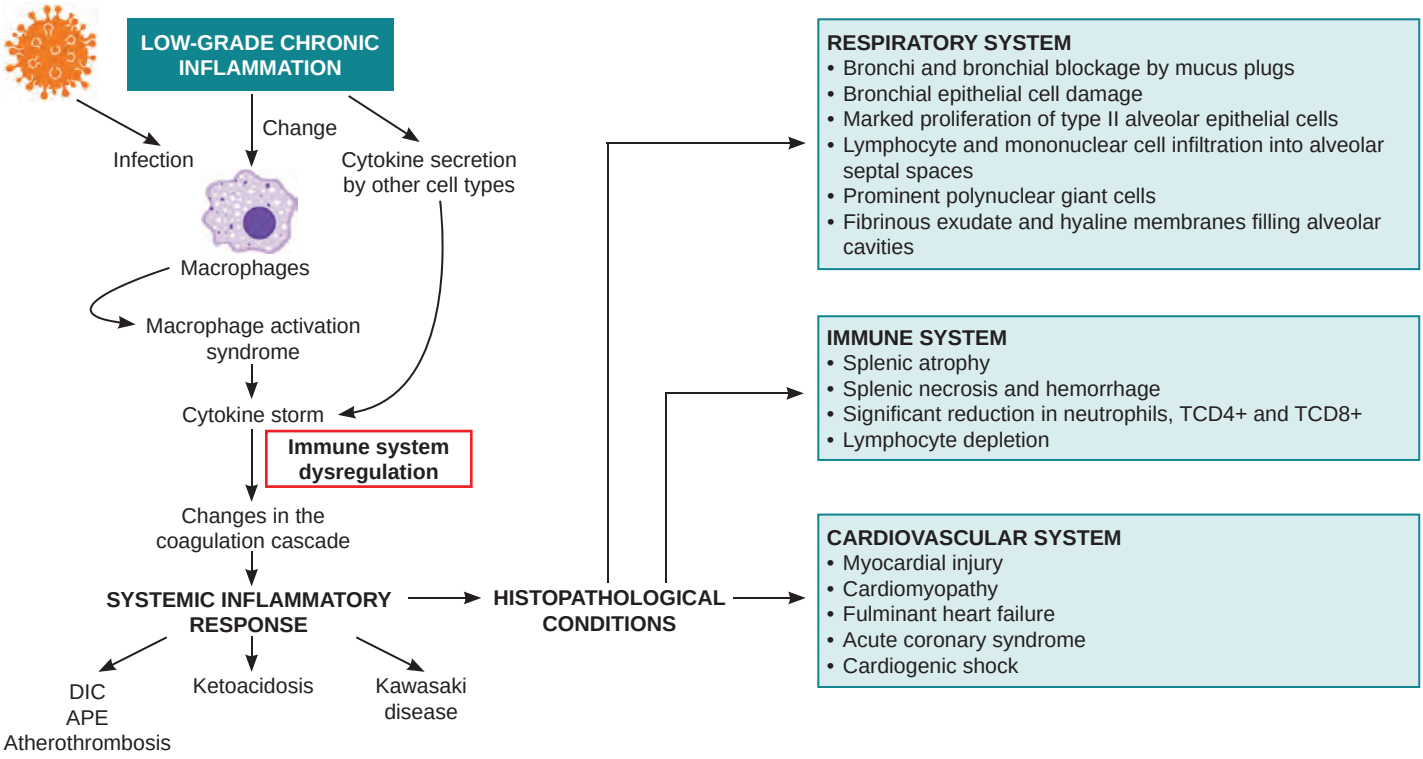
Lung injury in COVID-19 patients occurs either directly, due to destruction of epithelial cells and alterations in the alveolar and bronchial macrophages, or indirectly, through activation of inflammatory mediators released by invariant T lymphocytes associated with respiratory mucosa and Tγδ lymphocytes.[32,33]

COVID-19 patients have larger atypical vacuolated monocytes than normally seen in healthy individuals. Additionally, they present with a decrease of 95.1%–78.7% in the number of classic monocytes in circulation, with an increase of 0.49%–4.34% in the number of intermediate monocytes and a 4.4%–17.0% increase of non-classic monocytes compared to healthy individuals.[34] Both monocytes and macrophages can be infected by SARS-CoV-2, which elicits inflammatory responses and changes in gene expression related to the immune system in cells infected with SARS-C0V-2.[32] Even in the absence of symptomatic infection, monocytes and macrophages can cause viral shedding in the host outside the respiratory system.[35] In COVID-19, Th1 lymphocytes respond by secreting the proinflammatory cytokines IL-6, interferon gamma (IFNγ), interferon gamma-induced protein 10 (IP-10) and monocyte chemoattractant protein-1 (MCP1), which attract monocytes and T lymphocytes to the infected site, resulting in lymphocytopenia and an increase in the neutrophil-lymphocyte ratio (Figure 2).[36]

Pericyte and endothelial cell dysfunction from direct infection or inflammation affects microcirculation.[37] Dysregulated immune responses are involved in thrombosis and endothelial dysfunction,[38] and promote acute inflammation and hypercoagulation, both of which are exacerbated by cytokine storms.[38,39] Increased endothelial dysfunction is also associated with a decrease in physical exercise and an abrupt increase in body weight, both products of social isolation, and both of which cause oxidative stress.[40] Endothelial changes resulting from low-grade inflammation during COVID-19 are considered by some authors to be an epiphenomenon.[38]

Decreased monocyte expression of HLA-DR molecules interferes with the adaptive immune response during acute infection and is associated with progression to severe respiratory failure.[31] An increase in IL-6–producing TCD4+ lymphocytes has been

Figure 2: Implications of low-grade chronic inflammation in seriously ill or deceased SARS-CoV-2 patients



DIC: disseminated intravascular coagulation APE: acute pulmonary embolism.

described, with an accompanying decrease in regulatory T lymphocytes (Treg) and Tγδ lymphocytes,[41] as well as an increase in cytotoxic granule concentrations in TCD8+ lymphocytes.[42] There is evidence of reduced proliferation and differentiation of T and B lymphocytes in the lymph nodes,[31] with alterations in antibody class change and T lymphocyte overactivation,[42] which can cause cell depletion and lymphocytopenia, leading to a fatal outcome.

The immune system is one the most affected bodily systems in COVID-19,[32] and the generated inflammatory response can be protective or harmful. Excessive or aberrant immune responses are ineffective, result in severe lung injury, and can be life-threatening (Figure 2).[43] The entire immune mechanism is compromised in patients with low-grade inflammation, which has negative effects on the course of the disease.

Low-grade inflammation and immune system dysfunction

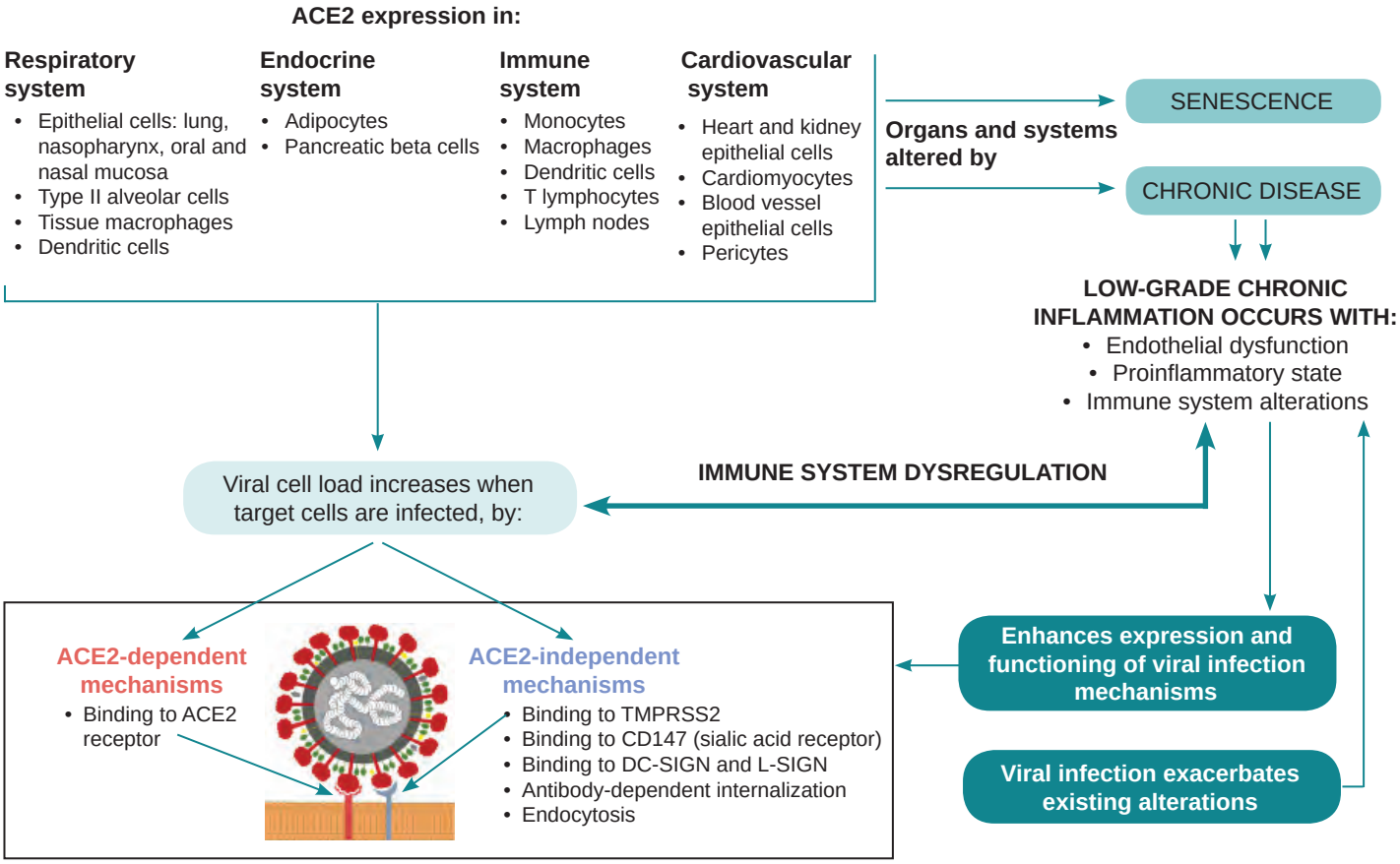
'Low-grade inflammation', an expression coined by Krabbe,[44] must be differentiated from the classical concept of acute inflammation, due to differences in their causes and consequences. Low-grade inflammation is generated by stress and tissue dysfunction while acute inflammation is generated by infections and tissue damage. Low-grade inflammation contributes to chronic non-communicable disease pathogenesis, aging and immunosenescence, while acute inflammation helps to eliminate the noxae that initially caused the inflammation and restore homeostasis.[44] Both involve many common mediators; a persistent increase of these common elements is a predictor of mortality. The term 'low-grade' was given to increases in acute-phase reactants, cytokines and leukocytes that do not reach levels typical of acute inflammation. Low-grade inflammation is systemic, subclinical and chronic.[44,45] In COVID-19 patients, it is associated with a high risk of severe disease and high mortality,[13,14,18] which is again increased in older adults (Figure 3).[20,31]

Low-grade inflammation is associated with changes in cell redox status and in cell-death signaling pathways. It increases over time (years) and causes an accumulation of cellular damage.[46] Low-grade inflammation persists long after the antigenic challenge has passed and continues to damage inflamed tissue, including cells adjacent to inflammatory foci.[44,45] It is perpetuated by positive feedback loops mediated by cytokines, chemokines and sensitized cells.[47] Some of these mediators, such as the pro-inflammatory cytokines IL-1, IL-6, IL-8, IL-13, IL-18, C-reactive protein, tumor necrosis factor alfa (TNF-α), interferon alfa (IFN-α) and interferon beta (IFN-β) are at higher levels in older adults and are predictors of chronic non-communicable diseases (Figure 4).[45,48]

Patients with low-grade inflammation have impaired barrier systems.[28,50] For example, pulmonary surfactant in lung epithelia is affected, one of whose functions is the regulation of macrophage and monocyte actions.[51] Oxidants generated by myeloperoxidase during inflammatory processes interfere with the function of the SP-D (surfactant protein D) in lung surfactant, damaging host defense, innate immunity and surfactant homeostasis.[52]

COVID-19 infection triggers acute inflammation that overlaps with low-grade inflammation. This results in immune system dysfunction in which control mechanisms are no longer effective, mainly due to T lymphocyte depletion and changes in signaling pathways. The immune system's dysfunctional response leads to uncontrolled inflammation and multi-system organ damage.[21] COVID-19 predisposes individuals to a chronic inflammatory state

Figure 3: Immune response dysregulation resulting from chronic low-grade inflammation and SARS-CoV-2 infection



Chronic inflammation increases viral entry and the rate of viral replication. In turn, the viral infection accentuates pre-existing inflammation and causes excessive responses with systemic repercussions and immune response dysregulation.

ACE2: angiotensin converting enzyme 2; CD147: extracellular matrix metalloproteinase inducer; CNCD: chronic non-communicable diseases; DC: dendritic cells; DC-SIGN: dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin; IR: immune response; L-SIGN: liver/lymph node-specific intercellular adhesion molecule-3-grabbing non-integrin type C lectin receptors; TMPRSS2: serine transmembrane protease 2

mediated by innate immune memory.[36] This process occurs mainly in older adults and patients with pre-existing comorbidities.

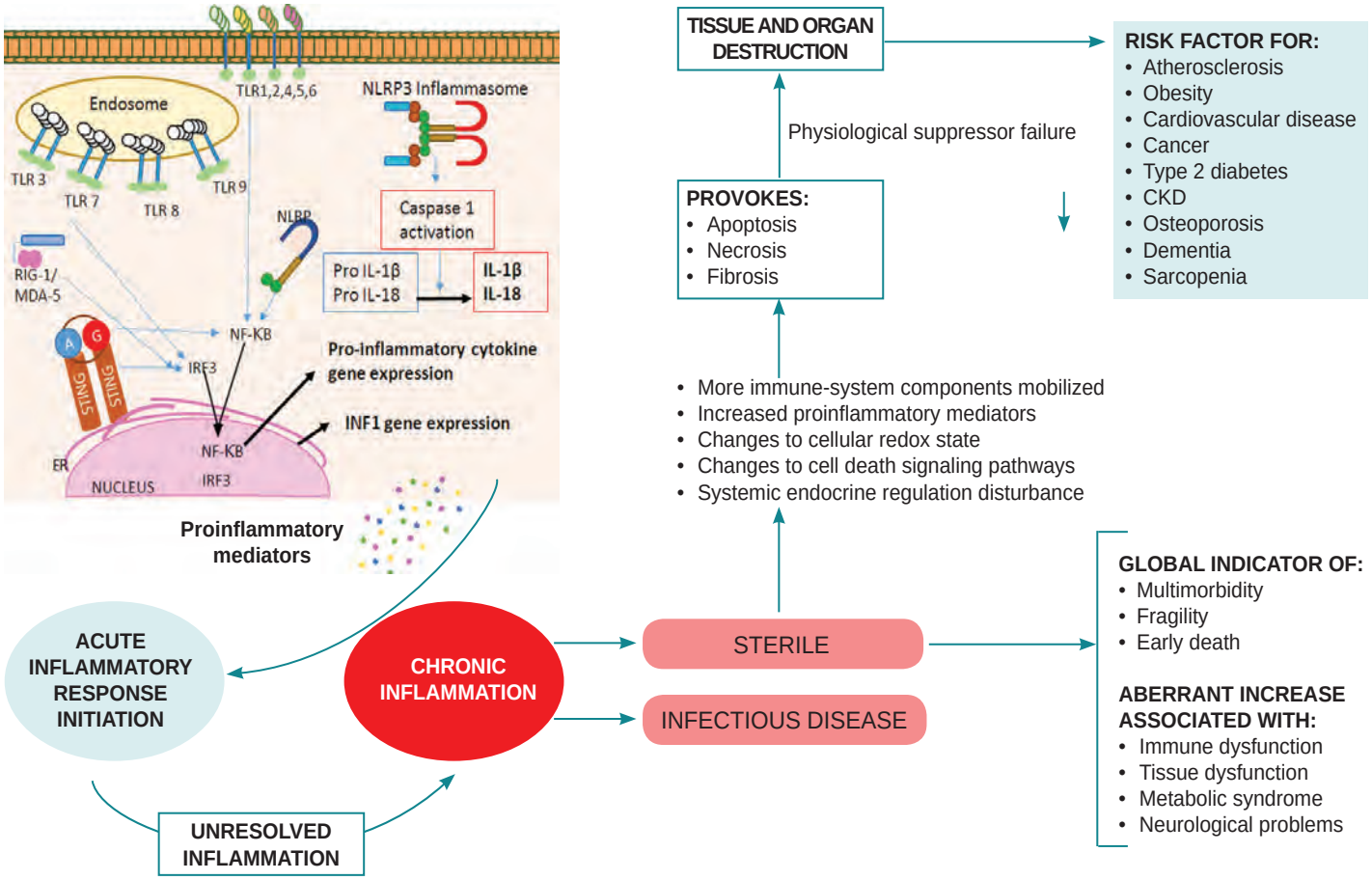
Immunosenescence In one study, the median age of COVID-19 patients admitted to intensive care units was 66 years and 80% of deaths occurred in patients aged ≥65 years, with a case fatality rate of 10%–27% in patients aged ≥85 years. In this study, 69.5% of older adult patients had underlying pre-existing conditions.[53] Another study, conducted in Ireland and Malaysia, of 663 COVID-19 patients found the mean age of seriously ill and critically ill patients to be 61.3 and 67.0 years, respectively, and the mean age of deceased patients was 69.3 years.[54] Another study of 5700 patients hospitalized with COVID-19 reported a mortality rate of 97.2% for patients aged ≥65 years who received mechanical ventilation.[55] These data underscore the importance of understanding the effects of aging processes on the immune system.

Cellular senescence is a regulated process that exhibits marked heterogeneity in the dividing potential of individual cells within the population, and even within subpopulations derived from clones. It is triggered by telomere shortening[56] and factors such as oxidative stress, DNA damage, mitochondrial dysfunction, epigenomic stress, radiation and the expression of certain oncogenes.[56,57] Replicative senescence is the cell's inability to continue dividing after a certain number of divisions due to telomeric shortening.[56–59]

During aging, the immune system undergoes quantitative and qualitative decreases in homeostasis,[59,60] which, to some extent, is considered normal physiology.[59,61] These decreases are due to imbalances in cellular proliferation, survival and apoptosis, in addition to depletion of cellular functions.[62] This phenomenon of immune system readjustment and remodeling is known as 'immunosenescence'[61] and is characterized by thymic involution and atrophy or hypoplasia of lymphoid tissues associated with mucosa and skin.[59] Adaptive immunity is impaired, with a reduction in naïve lymphocytes and T lymphocyte diversity, replaced by antigen-experienced quiescent cells.[63]

In immunosenescence, cells involved in innate immunity remain in a baseline state of activation with increased proinflammatory mediators, decreased receptor signaling and decreased effector function.[64] The most notable cellular inflammatory changes occur in macrophages[28,46] with alterations in M1 (conventional) and M2 (repair-suppressor) polarization,[28] cytotoxicity, intracellular death, antigen presentation[64] and nuclear factor kappa light chain enhancer of activated B cells (NF-κB) signal-

Figure 4: Main inflammatory process generative mechanisms and evolution towards low-grade chronic inflammation



CKD: chronic kidney disease; CVD: cardiovascular disease; DM2: type 2 diabetes mellitus; ER: endoplasmic reticulum; IL: interleukin; IFN-I: type I interferon; IRF3: interferon regulatory factor 3; MDA5: factor or protein 5 associated with melanoma differentiation; NF-κB: nuclear factor enhancing the kappa light chains of activated B cells; NLRP: NOD (nucleotide-binding oligomerization domain) receptors; NLRP3: NOD-like receptor protein 3; RIG-I: retinoic acid inducible gene I (responsible for the response to type 1 interferon); SI: immune system; TING: interferon gene stimulator; TLR: Toll-like receptors

ing, with decreased number and function of Toll-like receptors and antigen-presenting molecules.[46,64] This dysregulation increases the production of pro-inflammatory cytokines such as IL-1 and IL-6, and increases activation levels of NOD-like receptor pyrin domain containing 3 (NLRP3) inflammasomes in alveolar macrophages.[46]

In monocytes, basal cytokine levels are elevated, antigen-presenting molecules are decreased, and phagocytosis changes.[35] In dendritic cells, receptor expression, antigen capture, migratory capacity, functions related to motility, the capacity to activate T cells, and the secretion of cytokines with a decrease in IL-12 and an increase in IL-23 are all affected, while myeloid dendritic cells remain in a semi-activated state that can lead to cytokine secretion even at baseline.[65]

Neutrophils are at the high end of normal limits. Their chemotaxis, respiratory burst resulting in free radical production,[64] microbial functions, phagocytic activity and degranulation capacities are all affected.[66] Neutrophil migration patterns are affected and neutrophil proteinase release occurs, contributing to tissue damage and systemic inflammation.[66] Natural killer (NK) and mature NK cells increase in number,[62] but cytokine secretion decreases[64] (mainly IFN-γ)[67] as does perforin production.[66] Although lytic activity is reduced,[62] its overall activity appears to remain intact and stable.[67]

Changes in the balance of T lymphocyte populations are the result of thymic involution. As part of this alteration, the number of naïve T lymphocytes decreases, memory T lymphocytes accumulate[58] and activated effector cells are dysfunctional and less diverse.[58,63] There is a reduced response to stimulation, and damage to proliferative response with decreased TCD4+ lymphocytes.[62] Functional alterations in Th1 and Th2 lymphocytes produce changes in cytokine secretion with decreases in IL-2 and increases in IL-4 and IL-5.[62] There is also a decrease in naïve TCD8+ lymphocytes and an increase in senescent-memory TCD8+ cells,[68] and therefore a reduction in T cell reserves necessary for protecting the host against novel pathogens.[58,61,69]

Primary antibody responses are weak and short-lived,[67] with lower antibody specificity, affinity and isotype switching.[59] Aging bone marrow has a reduced ability to fully ensure hematopoietic regeneration,[67] which results in peripheral virgin-cell depletion.[63] The spleen suffers a loss of germinal centers and reduction in frequency and size of plasmacytic foci.[67] This results in a decrease in specific antibodies, favoring short-term maintenance of total immunoglobulin levels and serum antibody titers at the

expense of ability to establish fully functional memory B cell levels.[67] All of this leads to increased levels of pro-inflammatory markers and accumulation of activated dysfunctional effector cells with limited repertoires,[48,59] resulting in age-related inflammation.[28] This is a physiologic response to lifelong antigenic stress, altered mitochondrial function, accumulated oxidative stress and compromised antioxidant defense systems.[28,46]

Chronic immune activation, generated in part by persistent antigenic stimulation, contributes to an inflammatory state of multifactorial origin, leading to telomeric erosion and replicative senescence. Replicative senescence, in turn, results in the accumulation of senescent and exhausted T lymphocytes.[28,59] Dysfunctional or hypofunctional cells with terminally differentiated phenotypes express inhibitory molecules such as PD-1 and cytotoxic lymphocyte-associated protein 4 (CTLA-4).[28,58] This depleted phenotype can be also be induced by chronic infections in younger individuals,[70] and can be reversed, at least partially, by therapeutically blocking the immune system's so-called 'checkpoints' (PD-1, CTLA-4, lymphocyte-activation gene 3 or LAG-3, T cell immunoglobulin and mucin domain 3 or TIM-3 and TIMIN).[28]

This knowledge has made it possible to recognize the modifiable nature of some factors involved in immunosenescence. Immunosenescence can be viewed as the result of continuous antigenic challenges[70] induced by inflammatory aging and vice versa,[28] thus understood as two sides of the same coin.[60] The pro-inflammatory state typical of aging is characterized by the accumulation of senescent cells and massive secretion of molecules producing the aptly-named senescence-associated secretory phenotype (SASP).[36] SASP cells produce cytokines, growth factors and proteases that influence neighboring cells, converting them to newly senescent cells through the so-called 'bystander effect.'[56] However, exceptionally successful centenarians are equipped with well-preserved and efficient immune mechanisms, likely through optimal combinations of lifestyle and fortuitous genetics.[61,71]

Healthy centenarians have immune functions similar to those in the young, suggesting that long-lived individuals have less immunosenescence.[70] Keeping chronic low-grade inflammation under tight control is a driving force for longevity due to counter-regulation by anti-inflammatory molecules.[28] Centenarians' survival is associated with immune systems that no longer react strongly to persistent infections.[58]

Centenarians possess trained immune system memories regulated by epigenetic changes, the key to controlling the inflammation characteristic of aging.[28] Their peripheral blood mononuclear cells respond well to chemotactic stimuli, and there is an increase in highly active NK (CD16+CD57-) cells with well-preserved cytotoxicity.[61,71] T lymphocytes show an inverted immune risk profile (a high CD4/CD8 ratio and a lower number of CD8+CD282 cells).[50] There is very little autoimmune response, a marked decrease in B lymphocytes,[61] and an almost complete lack of organ-specific autoantibodies.[61,71] Centenarians also have a well-conserved number of T lymphocytes capable of proliferating, but with delayed maximal responsiveness.[61] This delay could constitute a possible risk factor for more severe manifestations of COVID-19, to which we should also add the deterioration of the immune barrier systems that play an important role in natural resistance to infection.

Chronic noncommunicable diseases Since the beginning of the COVID-19 pandemic, many studies have examined the association between its unfavorable clinical evolution and chronic diseases like metabolic disorders, cardiovascular disorders, oncoproliferative diseases and chronic respiratory illnesses, among others.

A meta-analysis of 24 articles including 10,948 COVID-19 patients found that the presence of chronic disease is related to greater COVID-19 severity (OR 3.50) and greater likelihood of intensive care unit (ICU) admission (OR 3.36). The main comorbidities influencing this increase in severity are diabetes mellitus, hypertension, COPD and cardiovascular disease (OR 2.61, 2.84, 3.83 and 4.18, respectively).[14] Another meta-analysis of 43 studies with 3600 patients reported similar results regarding median prevalences of hypertension (16.0%), diabetes (10.1%) and COPD (2.0%), but did not relate it to the probability of developing severe forms of COVID-19.[15] Yet another meta-analysis of 19 studies involving 656 COVID-19 patients concluded that the disease is accompanied by high morbidity in chronic disease patients (36.8% of patients), among which the most common were hypertension (18.6%), cardiovascular disease (14.4%) and diabetes (11.9%).[16] These data coincide with a study that found that of the total number of COVID-19 cases admitted to ICU, 72.2% had comorbidities, contrasted with only 27.5% of patients who did not require ICU admission.[17]

Jain's meta-analysis, reviewing 7 studies involving a total of 1813 COVID-19 patients, found that despite its rarity, COPD carries a high risk for progression to severity (OR 6.42, 95% CI 2.44–16.9) and the need for ICU admission (OR 17.8, 95% CI 6.56–48.2) and is the comorbidity with the highest predictive capacity for these events.[18] A meta-analysis including 1558 COVID-19 patients in 6 studies[72] also found an association between COPD and poor patient progression (OR 5.97). This association is largely due to changes in innate pulmonary defenses, namely those of immune barriers, that characterize COPD.

Total number of COVID-19 deaths is associated with obesity.[73] In a study by Muscogiuri,[74] obesity and morbid obesity were present in 47.6% and 28.2%, respectively, of patients requiring mechanical ventilation. A meta-analysis by Kumar,[75] including 33 articles and 16,003 patients, showed that diabetics who contract COVID-19 are 2.7 times more likely to develop severe infection and dying than non-diabetics, and that this risk increases with age. Obese or diabetic patients are particularly vulnerable, and the incidence of diabetes mellitus is twice as high in COVID-19 ICU patients than in those who do not require intensive care.[75]

Hu's meta-analysis of 21 studies and 47,344 COVID-19 patients[76] reported a cancer incidence of 1.2%. A similar proportion was reported by El Gohary´s meta-analysis of 22 studies, which found 2.1% of cancer patients among the 11,243 COVID-19 patients involved, of whom 45.4% had serious or critical manifestations of the disease and 21.1% died.[77] In Wang's meta-analysis of 138 hospitalized COVID-19 patients, 7.2% had cancer, 40% of whom required ICU admission, representing 11.1% of all 138 cases admitted to the ICU.[17] Liang's study of 1590 COVID-19 patients found that cancer patients infected with SARS-CoV-2 have a 3.5 times higher risk of serious events, including ICU admission or invasive ventilation, than patients without cancer, among whom age ≥60 years is an aggravating factor.[78] Another analysis (of

6 studies and a total of 1558 patients) failed to find any statistical significance between cancer and severe COVID-19 manifestations ($p = 0.49$), despite an OR of 2.3.[72] This variability may be due to differences in neoplasm location, stage, evolution and treatment, which was not taken into account in these analyses.

Metabolic disorders Inflammation stimulated by metabolism, called metainflammation, is an important aspect of metabolic disorders[79] such as obesity, insulin resistance, type 2 diabetes and fatty liver disease.[46] Metabolic imbalances in these diseases coincide with the cellular processes involved in premature aging, suggesting the two may be related.[79]

Obesity Now a global epidemic, obesity involves genetic, epigenetic, hormonal and lifestyle factors,[80] and contributes to development of other metabolic diseases.[74] It is a serious health problem associated with cardiovascular diseases and certain types of cancer,[81] and is accompanied by chronic subclinical inflammatory processes that can affect immune response to infection through direct, indirect and epigenetic mechanisms.[82]

The role adipose tissue physiology plays in the immune system has been understudied.[81] Adipose tissue functions as an endocrine organ that secretes adipokines, growth factors and cytokines,[80] which act in an autocrine or paracrine manner,[46] regulate various metabolic processes[80,81] and modulate inflammation.[48,80] It contains mesenchymal stem cells, stem cells derived from adipocytes, endothelial cells and fibroblasts, which, among others, are responsible for producing extracellular matrices and spontaneous cellular regeneration or induced cell turnover under cellular stress.[79]

Obesity alters the composition, structure and function of adipose tissue,[79] and produces dysfunctional tissue[40,80] whose expansion is accompanied by inflammatory changes that contribute to systemic low-grade inflammation,[80] with inflammatory cell infiltration and endoplasmic reticulum stress production, mitochondrial dysfunction, hypoxia, fibrosis, cell senescence and changes in lipid metabolism.[81] Adipose tissue inflammation initiates systemic inflammation in central (visceral) adiposity.[46] This condition reduces immune cell functionality, results in an imbalance of the intestinal microbiome/virome and induces an inflammatory cytokine phenotype.[82] Macrophages are the main cell type that infiltrate expanding adipose tissue in response to chemokines (MCP-1) produced by hypertrophic adipocytes[80] that increase in number and change location, phenotype and inflammatory characteristics under conditions of obesity.[83] Monocytes, on the other hand, connect low-grade chronic inflammation and altered lipid metabolism through the expression of inflammatory mediators and by modulating intracellular lipid accumulation.[84]

Additionally, TCD4+ and TCD8+ lymphocytes increase, Treg lymphocytes decrease, and this induces a phenotypic shift, recruiting Th1 lymphocytes from the periphery to aid in remodeling the extracellular matrix.[80] This process is associated with fibrosis, insulin resistance and metabolic dysfunction.[79] Th1 lymphocytes secrete interferon, which stimulates production of various chemokines that extend T lymphocyte migration into adipose tissue, including chemokine C-C motif ligand 2 (CCL2), chemokine C-C motif ligand 5 (CCL5), chemokine C-X-C motif ligand 9 (CXCL9) and chemokine C-X-C motif ligand 10 (CXCL10).

Body fat mass increase in children is associated with development of an early immunosenescent profile. Obese children have lower shares of naïve TCD4+ and CD8+ lymphocytes, higher shares of effector memory lymphocytes, and more intermediate TCD8+ lymphocytes and late and senescent TCD4+ lymphocytes; all characteristic of an immunosenescent profile. Obese children also show decreased response to vaccines and increased susceptibility to infection, also characteristic of immunosenescence.[79] Senescence itself impairs normal adipose tissue function and probably contributes directly to the inflammatory characteristics of adipose tissue in obese individuals.[81]

The number of B lymphocytes also increases with body mass index (BMI).[48] The increase in pro-inflammatory B cells is the main driver of the inflammatory profile of T lymphocytes seen in obesity and type 2 diabetes. These cells are characterized by increases in basal secretions of IL-6 and IFN-γ, accompanied by marked decreases in IL-10 secretions, a combination that results in chronic low-grade inflammation.[80] Cytokines released by B cells contribute to phenotypic changes in adipocytes in the abdomen, causing them to release adipokines, other pro-inflammatory markers and cellular debris.[49]

Obese COVID-19 patients experience an interaction between the immune system and adipose tissue, which favors immune system attenuation and chronic inflammation.[82] Proposed mechanisms for the increased severity of the disease in obese patients include reduced end-expiratory volumes, positive end-exhalation pleural pressure, low-grade chronic inflammation and altered immune responses to infection.[53] Barrier mechanisms can become compromised by hypoventilation syndrome, obstructive sleep apnea and other mechanical abnormalities caused by excess thoracic and abdominal fatty mass, leading to respiratory complications.[74] Other factors present in obese patients that potentiate severe forms of COVID-19 are an increase in clearly pro-inflammatory Th17 lymphocytes,[82] vitamin D deficiency,[73,85] and intestinal dysbiosis,[74,85] which can also impact respiratory system mucosa, affecting their function as protective barriers.[28,48.74] These last two risk factors are modifiable and possible points of preventive intervention, including vitamin D therapeutic supplements and consumption of prebiotics and probiotics that can effectively restore healthy gut microbiota. However, as these interventions require long treatment periods before benefits are accrued, they would have little impact during the course of a SARS-CoV-2 infection.

SARS-CoV-2 can infect subcutaneous and visceral adipose tissue, since angiotensin-converting enzyme 2 (ACE2) expression levels are higher in these tissues than in lung tissue.[86,87] Additionally, in obese patients, angiotensin-converting enzyme 1 (ACE1) increases, ACE2 is inhibited, and angiotensin II activates angiotensin I and II receptors, mediating a pro-inflammatory response and a consequent increase in vascular permeability.[82] Adipose tissue may act as a reservoir for the virus and may contribute to viral shedding, increased immune activation and cytokine amplification, explaining obese COVID-19 patients' poor prognoses.[73]

Type 2 diabetes mellitus There has been a parallel increase in the incidences of obesity and diabetes, to the point that diabetes is often considered a comorbidity of obesity.[80] Individuals with this type of diabetes experience both inflammation and metainflammation, most frequently seen in older adults in whom immune dis-

orders overlap with immunosenescence. Type 2 diabetes driven by inflammation is observed at an early age, suggesting that it is a model of premature immunosenescence, as senescent or late-differentiated T lymphocytes predict development of hyperglycemia in humans. Additionally, a feature common to both diabetes and old age is a decrease in naïve TCD4+ lymphocytes, with an increase in memory TCD4+ lymphocytes and effector TCD4+ and TCD8+ lymphocytes.[79]

The immune system is compromised in diabetic patients, especially innate immunity,[88] with phagocytic cell dysfunction and neutrophil chemotaxis inhibition, leading to an uncontrolled inflammatory response, increased levels of enzymes related to tissue damage and states of hypercoagulation, significantly elevated serum levels of inflammatory biomarkers and a proinflammatory cytokine profile.[74] Transient hyperglycemia may temporarily affect the innate immune system's response to infection,[88] as it serves as a trigger for proinflammatory cytokines in innate immune cells, particularly IL-1, IL-6 and TNFα.[79] One mechanism of immune impairment driven by hyperglycemia is the overactivation of the advanced glycosylation end-product pathway and its receptors. Additionally, elevated levels of glycated hemoglobin are associated with decreased phagocytic activity in circulating monocytes and neutrophils.[79] Therefore, maintaining optimal glycemic control in COVID-19–positive diabetics can help to prevent complications and more severe manifestations of the disease.

Factors contributing to disease severity in COVID-19–positive diabetics include hyperglycemia, impaired immune function, suboptimal glycemic control during hospitalization, prothrombic and proinflammatory states,[53,88] and reduced forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) in pulmonary function tests.[88] Fatty liver disease frequency in type 2 diabetics may increase the risk of an exaggerated immune response, including development of a cytokine storm, which is associated with severe lung injury in COVID-19 patients.[53]

Current evidence does not support the conclusion that diabetics are more susceptible to developing SARS-CoV-2 infection, but they are more likely to have more severe clinical manifestations.[88] In turn, COVID-19 can *induce* diabetes by either increasing insulin resistance or by direct damage to the islets of Langerhans,[38] which have abundant viral ACE2 receptors (detectable by immunostaining),[69] whose damage leads to reduced insulin release.[88] ACE2 and dipeptidyl peptidase-4 (DPP4), in addition to acting as receptor proteins for the SARS-CoV-2 virus, are also metabolic signal transducers that participate in pathways that regulate inflammation, renal and cardiovascular physiology and glucose homeostasis.[88] SARS-CoV-2 infection can cause sharp fluctuations in blood glucose levels, and glucose metabolism dysregulation both exacerbates diabetes and increases infection severity.[88] The resulting proinflammatory environment and possible cytokine storm exacerbate existing inflammation and result in systemic inflammation with serious consequences,[74] compounding damage already present in diabetic patients.[38]

Cardiovascular disease Hypertension is one of the most common diseases worldwide, and is considered a silent killer.[89] It is the most common modifiable risk factor in cardiovascular disease,[90] frequently coexisting with other comorbidities and with no apparent cause in 90% of cases.[91]

The immune system plays an important role in hypertension[92] via low-grade inflammation in the kidneys, the arterial wall, the central nervous system,[93] the sympathetic nervous system[91] and the heart,[92] which favor both development and increased severity of hypertension.[93] Low-grade inflammation has been considered both a cause and a consequence of hypertension.[90] In chronic inflammation, innate and adaptive immune cells are activated, cause organ and tissue damage through production of various cytokines and chemokines,[91] contributing to further immune system dysfunction, blood pressure elevation and vascular remodeling.[92]

Other changes in hypertensive individuals include increased pattern recognition receptors; NK cell migration toward the aortic wall; increased serum levels of complement proteins C3a and C5a;[90] increased cyclic dilation of larger vessels; release of IL-6, IL-8, endothelin and other proinflammatory mediators; and increased endothelial expression of VCAM-1, ICAM-1 and cluster of differentiation 40 (CD40).[91] These changes enhance activation of adjacent monocytes, macrophages and dendritic cells. T cell receptors, adregenic receptors and mineralocorticoid receptors on CD8+ cells play important roles in promoting IFN-γ production.[91] The TCD4+ immune response is polarized toward Th1 and Th17 phenotypes, IL-17 secretors and other cytokines involved in hypertensive inflammatory mechanisms.[90]

T lymphocyte polarization—which also occurs in antiviral response—can elicit exaggerated immune responses in hypertensive patients. Poor blood pressure control leads to increased dysregulation of the immune system.[42] Hypertension results in increased blood levels of monocytes, eosinophils and neutrophils.[92] A relationship has been suggested between increased lymphocyte levels and hypertension.[92] CD8+ T lymphocyte dysfunction caused by increased immunosenescent, proinflammatory and cytotoxic CD8+ T lymphocytes has been observed in hypertensive patients.[83,94] These lymphocytes cannot effectively fight viral infections,[42] and increase production of IFN-γ, TNF-α and the cytotoxic molecules granzyme B and perforin,[91,94] contributing to the pathological overproduction of cytokines that occurs in low-grade inflammation.[42]

Animal models suggest that lymphocytic effects may also be modulated by vascular function, blood flow and sympathetic nervous system activation. Endothelial dysfunction favors the recruitment and activation of monocytes and antigen-presenting cells that facilitate inflammation through the release of pro-inflammatory cytokines, which increases endothelial dysfunction, closing a vicious circle in hypertension pathogenesis.[92] Effective antihypertensive treatment is believed to help restore dysregulated immune systems in hypertensive patients.[42] Accordingly, normalizing blood pressure in hypertensive patients can help avoid COVID-19 complications in these patients.

Possible mechanisms of myocardial injury in COVID-19 patients include entrance of the SARS-CoV-2 virus through myocardial ACE2 receptors, hypoxia, and cytokine storm-induced monocyte damage.[88] Cardiac consequences of SARS-CoV-2 infection range from cardiac arrhythmias and hypotension to acute coronary events and heart failure with cardiogenic shock.[42,88] Myocardial injury may be due to viral colonization, cytokine storms,[39] atherosclerotic plaque rupture, hypoxic injury, coronary spasms,

formation of microthrombi, or direct vascular or endothelial injury.[88] Biopsies have shown low-grade myocardial inflammation[39] with interstitial edema[88] and viral particles in and around interstitial cytopathic macrophages but not in cardiomyocytes.[39] COVID-19 can trigger subclinical autoimmune myocarditis, and myocardial damage can cause a *de novo* autoimmune reaction (Figure 2).[42]

SARS-CoV-2 can destabilize or even shed atherosclerotic plaques during profound systemic inflammatory responses, cytokine storms, hemodynamic changes, or the polarization of immune cells toward more unstable phenotypes.[39,42] These processes, in conjunction with cytokine circulation in the heart and reduced oxygen supply, can cause coronary microvasculature dysfunction with inflammatory cardiomyopathy or atherothrombosis, leading to the acute coronary syndrome seen in deceased patients.[39]

Oncoproliferative diseases Oncogenesis is an extremely complex process that involves immune, genetic and exogenous factors.[62] Rudolf Virchow first described the association between cancer and inflammation in 1863.[95] Inflammatory immune responses can be tumorigenic or antitumorigenic, depending on delicate balances between innate and adaptive immune system responses influenced by environmental and microenvironmental conditions.[96–98] A healthy, regulated immune response is considered antitumoral, while uncontrolled and excessive responses can induce chronic inflammation and proto-oncogenic conditions.[97] Low-grade inflammation associated with persistent infection may be carcinogenic.[96,99,100] Genetic and epigenetic factors also play a role in carcinogenesis.[101]

Chronic inflammation can trigger altered oncogene and tumor-suppressor gene expression.[96] This inflammation is associated with environmental factors, which, together with somatic mutations, are responsible for 90% of all cancers.[98] Chronic inflammation leads to structure loss and excessive tissue remodeling and DNA modification due to oxidative stress, increasing cancer risk.[101] Chronic inflammation is also implicated in obesity-related cancers like those of the liver and pancreas,[98,96] and obese patients are 1.6 times more likely to develop these cancers.[98] This inflammation is accompanied by elevated levels of insulin, glucose, leptin, C-reactive protein and IL-6, which can contribute to worse prognoses for overweight or obese COVID-19 patients.[99] Inflammation may also be involved in higher incidences of cancer in older adults. The aging microenvironment, notable within the tumor microenvironment, plays a key role in reprogramming tumor cells toward secretory phenotypes associated with senescence that have tumorigenic effects such as increased malignant phenotypes and tumor induction.[79]

Tumor-associated inflammation develops in tumorigenic microenvironments,[100] in which tumor-promoting immunity and antitumor immunity coexist.[101] In these microenvironments, there are elevated levels of inflammatory mediators, RNOS, microRNAs, and increased cyclooxygenase-2 activity that facilitate inflammation-mediated tumorigenesis.[96,99] The normal processes of cell proliferation, senescence and apoptosis are also affected, as are DNA mutation and methylation rates.[99] Proinflammatory mediators induce several molecular-signaling cascades that promote inflammatory states.[96] IL-23, secreted by Th17 lymphocytes, is a key factor in maintaining and expanding tumorigenic Th17 inflammatory cells, promoting inflammation, angiogenesis and reducing TCD8+ lymphocytes within the tumor microenvironment.[96] All these processes and factors have systemic repercussions, reduce the immune response to SARS-CoV-2 and favor uncontrolled inflammation that can lead to cytokine storms in already immunosuppressed patients.

Cancer patients are more susceptible to SARS-CoV-2 infection due to systemic immunosuppression caused by malignancy and treatment.[78] Cancer patients who have undergone major surgery, chemotherapy, radiation therapy and immunotherapy are at increased risk of contracting COVID-19, and its sequelae,[102] as are patients with lung, hematologic or metastatic cancers.[43,103] Anemia and hypoproteinemia have been found in COVID-19–positive cancer patients, a result of nutritional deterioration that negatively affects immunity and increases susceptibility to respiratory pathogens.[103] Lung cancer patients, who have impaired lung function and resistance, have high probabilities of developing severe anoxia and rapidly progressing to critical condition or death from COVID-19.[43,103] Chronic lung inflammation favors increased proinflammatory cytokines,[43] and poor immune response allows for viral spread, tissue destruction and progression to severe stages of the disease.[33]

Respiratory diseases COPD and asthma are the two most common and dangerous airway diseases.[104] Both are characterized by the presence of chronic inflammation.[105,106] These patients present with changes to lung anatomy and to the blood vessels that feed them.[88]

COPD Chronic obstructive pulmonary disease causes limitations in airflow and is associated with chronic airway and lung inflammation.[51] Other comorbidities are found in 60%–90% of COVID-19–positive COPD patients, aggravating symptoms and worsening disease prognosis.[37]

Defense barrier changes are observed in COPD pathology,[51] mainly failures in mucociliary mechanisms due to hair cell destruction, the presence of dehydrated mucus with changes to normal biophysical properties and mucin hypersecretion.[40] Low-grade inflammation is behind many of the changes caused by COPD, such as destruction of lung parenchyma and parenchymal vasculature, normal tissue repair disruption, small airway fibrosis and alveolar rupture.[51] This inflammation is characterized by an inadequate immune response with increases in neutrophils, macrophages, Th1 lymphocytes, B lymphocytes, vascular endothelial cadherins, platelet endothelial-cell adhesion molecules and E-selectin. These increases are associated with lung destruction and airflow limitation.[51] The protease/antiprotease relationship is altered, causing neurogenic damage and abnormalities in apoptotic, catabolic and senescent mechanisms. Imbalances between oxidizing and antioxidant agents causes activation of kinases and transcription factors, inflammatory mediator release, cell damage and apoptosis. Involved oxidants include reactive oxygen species (ROS) that damage cells, inactivate defense mechanisms, initiate inflammation and increase oxidative stress.[51]

COPD patients have increased ACE2 receptors in small airways,[107] but some authors argue that this may be mediated

in the case of COVID-19 by the use of corticosteroid inhalants, which could limit lung damage in SARS-CoV-2 infection.[108] However, in COVID-19 animal models, ACE2 loss or deficiency is associated with lung injury,[35,109] and causes inflammation,[35] increased vascular permeability and acute respiratory distress syndrome.[109] Pre-existing endothelial damage to pulmonary capillaries is accentuated and leads to lung destruction, cardiovascular disease and cerebrovascular damage.[51] Pulmonary endothelial damage is considered the hallmark of acute respiratory distress syndrome.[38]

Asthma Bronchial asthma is a heterogenous disease characterized by chronic airway inflammation and variable remodeling, with a variety of clinical presentations and responses to treatment.[110] Most viral infections exacerbate asthma,[104,111,112] generally by inducing Th2-mediated responses, and high levels of proinflammatory cytokines and proinflammatory cytokine receptors.[111] Many of these reactions also appear during acute asthma attacks.

Several studies report that SARS-CoV-2 infection does not exacerbate asthma attacks,[111,113,114] and it is not associated with increased risks of hospitalization, severity or mortality, compared to patients without asthma.[114–116] Asthmatic patients generally have more comorbidities; however, greater severity and higher mortality levels have not been seen in COVID-19–positive asthmatics.[88,104,117] This may not be contradictory, as the course of COVID-19 in asthmatics depends on the persistence and severity of the patient's asthma. To avoid or reduce risk of COVID-19 complications in asthmatics, it is important to control both the asthma and its inter-crisis treatment, which prevents structural and functional damage to the tracheobronchial tree.

Different asthma phenotypes show varying susceptibility to and severity of COVID-19.[116] In patients with type 2 asthma, we see chronic eosinophilic type 2 inflammation, the most common form of inflammation in asthma.[104,118] Type 2 asthmatics suffer from bronchial obstruction due to infiltration of innate immunity cells (primarily eosinophils, neutrophils, mast cells and macrophages)[104] and secretion of cytokines by innate immunity cells that shifts the immune response toward production of Th2 lymphocytes, type 2 B lymphocytes and allergen-specific IgE, which, in turn, perpetuates the inflammatory response.[106] Other mechanisms involved in persistent asthma are disruptions in inflammation resolution due to prolonged mast cell and eosinophil survival, decreases in lipoxin A4 in asthmatic airways, responsible for eosinophil apoptosis and for decreasing type 2 innate lymphoid cells (ILC2), and in NK cell activity.[119]

It has been hypothesized that the type 2 inflammatory response in asthmatics behaves differently than those of other pathologies,[10] and that it may act as a protective factor against COVID-19 contraction and progression,[120] due to Th2-biased immunity with cross-regulation between allergic immunity and altered interferon-mediated responses,[118] due to decreased production of bronchial epithelial cells and plasmacytoid dendritic cells.[106] The Th2-dominant environment is capable of regulating the late-phase hyperinflammation that typically marks severe respiratory viral diseases, but immunopathological processes are the hallmark of tissue damage.[118]

There are various schools of thought regarding ACE2 receptor involvement in SARS-CoV-2 infection in asthmatics. Calvielli suggests ACE2 expression is different in different types of asthma.[121] Other researchers suggest that respiratory epithelial cells in asthmatics show decreased ACE2 receptor gene expression,[120,122] and that this decrease overrides the minimal increase in transmembrane protease serine 2 (TMPRSS2) gene expression.[122] The reduced expression of the SARS-CoV-2 receptor could be due to the fact that IL-13 is involved in recruiting eosinophils in bronchial epithelia,[123] which can reduce ACE2 expression in human bronchial tissue (observed *ex vivo*).[120] ACE2 receptor expression is lower in patients with high allergic sensitization.[123,124] In contrast, patients with non-type 2 asthma have inflammatory profiles featuring Th1 and Th17 lymphocytes.[116,119] Non-type 2 asthmatics' molecular phenotype is characterized by metabolic and mitochondrial pathways associated with the inflammasome and is generally accompanied by comorbidities like obesity, type 2 diabetes and hypertension. As they have low blood eosinophil numbers,[116] and ACE2 and TMPRSS2 gene expression levels similar to those in healthy people,[123,124] these asthmatics are susceptible to developing more severe forms of COVID-19.[116]

Scope, limitations and clinical implications of the review COVID-19 research generates such a volume of information that any review article runs the risk of missing important results. Many reviews only include articles written and published in English; this work also includes articles written in Spanish, but not in languages other than Spanish and English. This review focused on intersections of the immune system, low-grade inflammation and COVID-19 immunopathology with chronic diseases and age; other diseases that directly affect the immune system—such as immunodeficiencies or autoimmune diseases—were not included, nor were other chronic diseases such as kidney or neurogenerative diseases.

This review summarizes the main immunopathological alterations of the most frequent comorbidities described in COVID-19 patients, which directly influence the clinical course of the disease. This can aid patient management in clinical practice by identifying possible preventive actions designed to mitigate potential complications or progression to more severe manifestations of the disease.

FINAL CONSIDERATIONS

Low-grade chronic inflammation is characterized by a pro-inflammatory state with endothelial dysfunction and changes to the immune system, mainly in the innate immune response, with increases of proinflammatory mediators that generate pathogenic conditions and prevent elimination of the virus by triggering a dysregulated immune response. Inflammation is a common factor in non-communicable chronic diseases like obesity, type 2 diabetes, hypertension, cancer and COPD, all of which are risk factors for developing severe forms of COVID-19. Such risk is markedly increased when several of these factors occur in persons aged ≥60 years, except for those with type 2 bronchial asthma, where chronic eosinophilic inflammation protects against SARS-CoV-2 infection due to decreased interferon-mediated response and a reduction in ACE2 receptors. The links between immunosenescence, chronic disease and altered immune response in COVID-19 deserves continued attention by researchers.

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Persons with Substance Abuse Disorders and Other Addictions: Coping with the COVID-19 Pandemic

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ABSTRACT

Cuba implemented policies mandating social distancing on March 11, 2020, which were still in place at the time of this study. During such periods of isolation, people with psychoactive substance-related disorders and other addictions may be tempted to reduce tension, stress, uncertainty and possible distress by increasing the use of substances or practices they have abused. This can mean relapses and setbacks for patients undergoing treatment. A multidisciplinary team of health professionals specializing in addiction at the Center for Academic Development in Drug Addiction, in Havana, Cuba, cares for people with these disorders and followed their evolution during the initial period of COVID-19 social isolation.

With the aim of characterizing strategies employed by patients undergoing treatment for substance abuse and addictions, we conducted a qualitative study from April 2020 through May 2020, using a convenience sample of 37 patients (all students) who had been progressing towards recovery from addictive behaviors when face-to-face encounters were suspended due to COVID-19 restrictions. Contact was maintained through information and communication technologies. The research used telepsychology and focused on understanding patient life experiences. Patients were interviewed using a semi-structured survey, which was then transcribed and coded thematically using a grounded-theory approach.

We found that patients' ability to cope successfully with challenges presented by COVID-19 were influenced by: 1) the individual's own methods for maintaining self-control (commitment to studies, projects, and work with therapists) that aided them in their goals concerning abstinence; 2) difficulties faced in addressing specific events and situations (doubts, uncertainties, disagreements, isolation and time use); 3) perpetuation and revivification of myths related to substances and addictive activities (exacerbation of supposed benefits of tobacco, alcohol, marijuana, overuse of social networks); and 4) tendencies toward irrationality and lack of emotional control (fear, sadness, anger, constant worry and self-imposed demands).

Our findings suggest that despite the potential negative psychological impact of preventive social isolation during the COVID-19 pandemic, individual coping mechanisms developed by these patients, aiming at improved self-control, allowed most to avoid setbacks that could have affected their recovery. Nevertheless, patients faced challenges to their recovery that were compounded by difficulties in specific situations, myths related to substances and addictive activities, and tendencies toward irrationality or lack of emotional control.

KEYWORDS COVID-19, substance-related disorders, drug users, alcoholism, tobacco use disorder, psychophysiologic disorders, psychological adaptation, interview, qualitative research, psychological resilience, medical informatics, Cuba

INTRODUCTION

In 2012, researchers at the Medical University of Havana's (UCMH) Center for Academic Development in Drug Addiction (CEDRO) undertook a research project entitled "Implementation and development of a scientific-technological consultancy service specializing in addictions" carried out from January 2013 through December 2017.[1] The CEDRO Consulting Service (SC-CEDRO) was established in 2018 based on the results of that research project.

Individuals requesting advice, guidance and psychotherapy are often referred to SC-CEDRO from UCMH and other institutions of higher education. These referrals include international students enrolled at UCMH who are either paying their own tuition or are hosted on scholarships from their governments or Cuba's. Of particular relevance in this context is follow-up of international students who abuse drugs, referred to SC-CEDRO by the Student Orientation Units of their respective faculties when this abuse poses problems for students or their colleagues.

Historically, the drugs most commonly used in Cuba have been tobacco and alcohol,[2] but the last decade has seen an overall increase in abuse of illegal drugs (marijuana, cocaine, synthetic or 'chemical' marijuana) and prescription medications (tramadol, morphine, carbamazepine).[3,4] Polydrug use, or the use of more than one substance by the same person, is common among people who abuse substances.[5]

IMPORTANCE

The results of this study may be useful in developing preventive and therapeutic strategies in emergency situations applicable to persons with substance use disorders or addictions.

The most frequent non-substance addictions include illicit gambling, technological addictions (video games, internet, mobile phones, online games and social networking) and somatic addictions (compulsive physical exercise, compulsive sexual activity and eating disorders).[6,7]

Preventive social distancing in response to the COVID-19 pandemic began in Cuba on March 11, 2020,[8] and was still in effect at the time of this report (June 2020).[9] Cuban restrictions during this period included the suspension of non-essential work activities, the school year, and sporadic, targeted suspension of public and private transportation. Cuban medical students joined in research related to the COVID-19 pandemic in their communities. International medical students stayed in their student residences and were given the option of voluntarily joining research teams working in nearby areas. Classes (weekly sessions) were held virtually. Only interns (students in their sixth year of medical school) continued their hospital work.[10] These restrictions resulted in drastic changes to SC-CEDRO operations, whose institutional mandate is the diagnosis, treatment and follow-up of patients referred to the service. To this end, SC-CEDRO is comprised of a multidisciplinary team of professors and researchers, including mental health specialists.

As of March 11, 2020, all SC-CEDRO face-to-face activities were suspended.

Nevertheless, the service itself was maintained, turning to remote modes of operation that rely on information and communications technologies (ICT).[11] Telepsychology was incorporated into professional practice, which we define as the provision of psychological services through information processing by electronic means.[12]

During the pandemic, SC-CEDRO has implemented use of telephone, email and social networks (mainly WhatsApp)[13] for therapy and monitoring of individuals requesting the service. These resources are recommended during conditions in which physical distancing is essential,[12] and have been useful in mitigating negative mental health impacts.[14]

During preventive social isolation, patients undergoing treatment for addiction may cohabitate with individuals who may try to avoid stress, tension and uncertainty through social use of alcohol or other drugs. This may favor an increase in consumption or relapse in patients faced with the challenge of organizing their daily lives in a context of pervasive stress and worry.[15]

WHO and PAHO have urged people not to adopt inappropriate response strategies to the pandemic, such as use of tobacco, alcohol or other drugs, since these can damage mental and physical well-being in the long term. Instead, they recommend people adopt strategies they had previously found helpful in managing stress and empowering them in the face of adverse situations.[16]

Current literature suggests that in crises caused by psychological emergencies, interventions should pay close attention to the use of psychoactive substances and other addictive behaviors.[17]

INTERVENTION

To characterize the psychological mechanisms adopted by SC-CEDRO patients in coping with the challenges posed by COVID-19 restrictions, we carried out a qualitative study using a narrative framework aimed at understanding their life experiences during the initial period of preventive social isolation (April–May 2020). As of March 2020, SC-CEDRO served a population of 83 patients who routinely attended appointments with their therapists, and with whom ICT enabled the team to maintain contact thereafter.

We selected a convenience sample of 37 individuals (Cuban and international students) who had been in treatment as of January 2020 and thus had been involved in a routine therapeutic process for at least ten weeks, and who had also made partial progress toward rehabilitation. Selection criteria included attendance at ICT therapy appointments in April and May 2020. Patients' average age was 24.7 years (17.6; 26.4); all were students; and their main sociodemographic and clinical characteristics are specified in Table 1.

Inclusion criteria SC-CEDRO patients who continued to receive psychological care and follow-up services via ICT (telephone, email and social networks, mainly WhatsApp) who agreed to participate in the study.

Table 1: Main sociodemographic and clinical characteristics of study participants (N = 37)

Sociodemographic characteristic	n	%
Region of origin		
Cuban student	14	37.8
International student (Africa)	16	43.2
International student (Americas)	7	18.9
Sex		
Male	30	81.1
Female	7	18.9
Marital status		
Single	24	64.9
Married	8	21.6
Divorced	5	13.5
Current occupation		
University student (undergraduate)	21	56.8
University student (postgraduate)	5	13.5
Allied health professions student (mid-level health technicians)	11	29.7
Type of addictive disorder		
Substance-related	35	94.6
Social/activity-related	2	5.4
Psychoactive substance and addictive social activities		
Alcohol	21	56.8
Tobacco	3	8.1
Cannabis	2	5.4
Polydrug use	8	21.6
Gambling	1	2.7
Addictions to technology	2	5.4
Consumption pattern and addictive social activities		
Excessive consumption (risk)	13	35.1
Abusive use (harmful)	19	51.4
Addictive use (dependence)	2	5.4
Addictive social activities	3	8.1

Exclusion criteria Patients who had been diagnosed with other psychiatric disorders in addition to substance-abuse/addiction-related disorders.

Methodology We used a semi-structured interview developed to explore study participants' experiences during preventive social isolation. We developed a 7-question guide to facilitate open dialogue on how patients were coping psychologically with the restrictions imposed by COVID-19. The guide was developed using theoretical premises obtained from case studies in the field of addiction,[18] and was subsequently evaluated and refined by experts on the subject selected from UCMH faculty in the master's degree program on substance abuse treatment and prevention. Five specialists with recognized expertise on addictive disorders participated in the survey design, all of whom were full professors and PhDs with more than ten years' practice, teaching and research linked to addition issues. Questionnaire topics covered three fundamental areas: 1) behaviors relevant to recovery (time management, therapeutic adherence and addictive temptations); 2) psychological manifestations related to emotional experiences, understanding of the indicated measures and behavior in critical situations; and 3) efficacy in developing personal goals and coping mechanisms (Table 2).

We described the psychological coping mechanisms of these participants during the COVID-19 social isolation period, a situation that called for cognitive and behavioral adaptations in response to challenges that may have exceeded each individual's available resources.[5] Emphasis was placed on individual goals and coping strategies that played a role in preventing or facilitating setbacks or relapses.

Data collection Data were obtained through an interview conducted in Spanish with all patients. Since international students must be fluent in Spanish to access higher education in Cuba, it was not necessary to carry out interviews in other languages. However, some students elected to write reflections in their native language, with the aim of clarifying comments made during their interviews. These reflections were taken into account during data analysis. The interviews were carried out through telepsychology, specifically video calls via WhatsApp. When a participant had difficulty accessing the internet, conventional telephone and email were utilized. The complementary use of voice, video and written communications via internet allowed patients and providers to overcome geographical or temporal barriers, and difficulties caused by limitations and time restrictions placed on transportation.[12]

In the interview, participants described their daily activities and responded to the questionnaire. Interviews were recorded, and duration varied from 21 to 45 minutes (average 34 minutes). Data collection ended when no new themes emerged, suggesting that acceptable information saturation had been reached.[19] Field notes were recorded manually and integrated into interview transcriptions and reflections, which were elaborated upon by participants; most often immediately following the semi-structured interviews, and using the same medium (WhatsApp). In general, reflections complemented question 7 of the semi-structured interview: "Do you have personal coping mechanisms that allow you to overcome difficulties without losing self-control? Please elaborate." The collection of transcripts specific to each patient were ordered and coded by a researcher who obscured personal patient data before submitting them to the research team responsible for their analysis and interpretation.

Table 2: Questions in the study's semi-structured interview

Questions by section
Section 1 (time management, adherence to therapy and addictive temptations)
1. How have you organized your life around the measures put in place to prevent the spread of COVID-19?
2. How has the suspension of face-to-face psychotherapy activities affected your recovery process?
3. How have you managed withdrawal symptoms, addictive temptations, and possible relapses and setbacks?
Section 2 (psychological manifestations—affective, cognitive and behavioral)
4. How have you regulated emotional reactions associated with risk, worry and stress?
5. How have you assessed the COVID-19 control measures implemented in your social and academic spheres?
6. How would you describe your behavior in situations resulting from preventive social isolation?
Section 3 (efficacy of personal coping mechanisms)
7. Do you have personal coping mechanisms that allow you to overcome difficulties without losing self-control? Please elaborate.

Data analysis Researchers who did not conduct interviews analyzed the data and constructed inclusive categories, querying each other to increase reliability of results. Subsequently, we developed a thematic analysis in which illustrative quotes were identified that spoke to larger themes within study participants' experiences.[20] Throughout this process, we kept in mind the psychosocial and mental health considerations pertaining to specific circumstances produced by the COVID-19 pandemic published by WHO/PAHO[16] and by professional psychiatric organizations, both Cuban and international.[21,22]

Ethics The study was approved by the Scientific Council of UCMH's General Calixto García Faculty of Medical Sciences and endorsed by the UCMH Scientific Research Ethics Committee. Each participant received information on study objectives and guarantees as to the confidentiality of their contributions. Patients were assured that their ability to participate in treatment would not be affected if they decided against participating in the study or if they abandoned the study at any point. All participants gave written consent.[23]

Results SC-CEDRO was forced to recess in March 2020 due to the spread of SARS-CoV-2 in Cuba. At that time, patients in this study were in the midst of treatment, the continuation of which during a period of physical distancing implied therapeutic challenges, as it was not possible to verify whether the skills students had been developing were proving useful or to change therapeutic modalities if or when necessary. The psychotherapy and self-help groups in which patients were enrolled had also been suspended and patients were left without direct therapeutic support. In this context, three professionals assumed tele-consulting roles and continued to interact with 65 of 83 patients (78.3%).

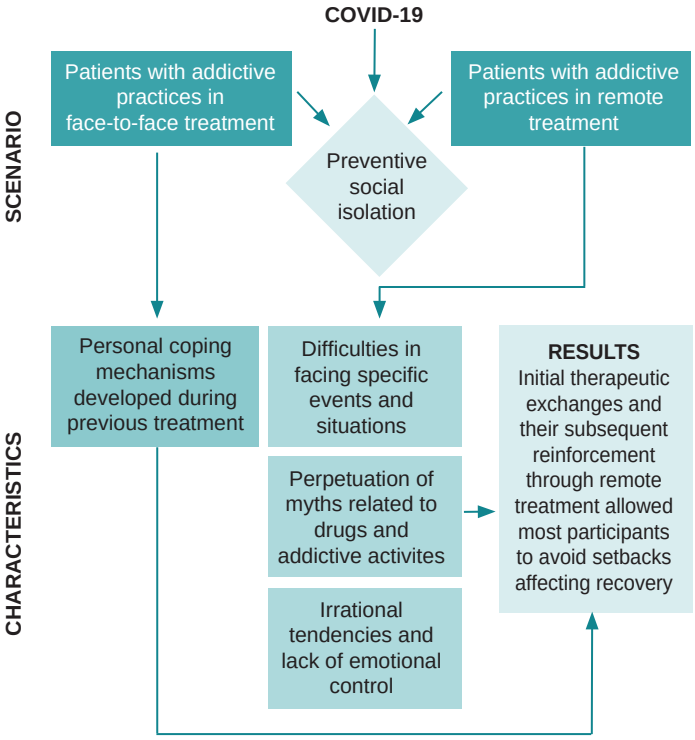
Among the 37 study participants, those who consumed alcohol (22; 59.4%) as their only drug were the most common. Alcohol is easily accessible in Cuba as it is a legal and socially accepted substance. Illicit drug users were predominant in the category of polydrug use, while smoking and social addictions were rare.

We developed a conceptual map of coping mechanisms employed by individuals with disorders related to psychoactive substance abuse or other addictions, demonstrating changes caused by implementation of preventive social distancing (Figure 1).

In this context, we identified the following factors as main influences on psychological coping strategies and their success: 1) personal methods for maintaining self-control; 2) difficulties in dealing with specific events and situations; 3) perpetuation of myths related to drugs and addictive activities; and 4) irrational tendencies or a lack of emotional control.

Personal methods for maintaining self-control Of the 37 participants, 29 (78.4%) had developed methods and goals during initial face-to-face treatment that helped them in maintaining abstinence during preventive isolation and kept them from relapsing into addictive behavior. When initially received at SC-CEDRO,

Figure 1: Conceptual model of psychological coping mechanisms used by study participants during COVID-19 social isolation



most patients were indulging in their addictions uncritically and had already faced various social and academic difficulties. The time they had been in treatment was insufficient to consolidate skills that would help guarantee abstinence and it was entirely foreseeable that relapses and setbacks would occur. However, the resources acquired in the initial stages of treatment appear to have been decisive for many patients in facilitating adequate coping with the challenges posed by the COVID-19 pandemic. The study participants indicated that they made an effort to be consistent with the profession in which they are being trained (medicine, nursing and related fields, dedicated to caring for and assisting people with health problems), consistent with their lifelong goals (usually associated with completing their university studies and being able to practice as health professionals) and respectful of commitments made with their therapists regarding abstinence and reintegration into active social life while exercising self-control and responsibility.

Despite the success of most patients in avoiding recidivism, 8 of the 37 patients (21.6%) relapsed and re-initiated the behaviors for which they had initially began treatment. In these cases, we employed intensive tele-health assistance whenever possible and resumed face-to-face treatment as soon as circumstances allowed. In general, these eight cases were those who had not advanced as far in their treatment plans prior to the pandemic as the rest of their cohort, and those who experienced technical difficulties in accessing remote treatment.

Patient coping mechanisms were revealed in the interviews as well as the participants' written reflections. For example, one international participant stated that he had managed to control his temptation to drink alcohol by keeping in mind that he wanted to become a good doctor and parent. He wrote (edited solely for grammar):

I'm nine months sober and currently I don't feel the temptation to drink alcohol because I keep telling myself what it is I want in life and what I want to achieve. I want to be a good doctor (not a drunk doctor) and a good father (in the future). During my nine months of sobriety, there were challenges, but I defeated them, and I feel good for quitting. Now I am able to see the things I was doing while I was drunk, and my life is no longer the same.

Several participants recognized that despite their initial fear of contracting COVID-19, participating with other medical students in daily active case detection in vulnerable populations had given them a better understanding of the importance of prevention and the need to control their addictive behaviors in order to meet the demands placed on them as healthcare professionals during the pandemic and beyond. To this end, one participant said (edited solely for grammar):

Faced with this complex situation, I have been struggling to maintain the progress made in my treatment and I believe that so far I've succeeded. At first, I felt the stress building and I was surprised that the world had practically fallen apart overnight. However, I've managed to control myself, since I know that as a doctor I must be prepared to face problems like this. It has also helped me participate as a student in the daily COVID-19 case detection efforts (in the community).

Some participants said therapeutic relationships established with professionals caring for them had provided a source of inspiration, helping them control their desire to drink and avoid setbacks. Another international participant wrote:

I have not seen any change with my desire to drink during this pandemic. I am happy with the progress I have made, and I would like to thank my psychotherapist for his professional support and understanding. Many of my fellow students really need someone of your caliber to deal with whatever habit they have developed during their studies in Cuba.

These statements indicate that these participants managed to grow in the face of difficulties they encountered from changes in their personal lives as students and in the general social context. While they spent more time living at home or in the student residence with no face-to-face therapeutic support, they nevertheless were able to overcome stress-induced consumption temptations, retaining some of the progress achieved during their earlier face-to-face therapy sessions. They also adequately addressed challenges posed by the unexpected switch to remote therapy modalities.

Difficulties in dealing with specific events and situations Despite the aforementioned coping mechanisms and strategies, the greatest danger to each patient's continued recovery lay in having to face specific events and situations that exceeded their personal resources. Such difficulties were experienced by 25 participants (67.5%), as stated in interviews. For example, some expressed doubt as to the need for some of the guidelines issued by health authorities. Although they accepted the necessity of hygienic measures and specialized care for infected patients,

they questioned preventive social isolation and the suspension of face-to-face classes and alternative care activities such as psychotherapy and self-help groups.

Other statements reflected participant uncertainty about the efficacy of COVID-19 treatments, expressing critical views of some of the indicated therapies, opinions that relied on sources other than health authorities or healthcare providers. It was also evident that several participants were struggling with time management in their daily lives. 'Time management', for our purposes, is the particular way in which individuals organize their daily activities and implies setting aside time for study, work, family and relationships, childcare, hobbies, rest and relaxation, etc. They said that staying at home or in student residences forced them to give up their usual physical and recreational activities, and some students made little effort to resume these activities.

Some participants referred to the emergence or re-emergence of family or group disagreements. This disruption is common within families of addicts and required negotiating complications like renewed consumption or other situations that are caused or aggravated by social isolation. Likewise, other participants reported difficulties in accepting isolation from family and friends with whom they weren't living. This was a frequent comment among students whose families were either living abroad or in other Cuban provinces.

Participants also described alterations in their sleep–wake cycles generated by the changing circumstances. This was especially evident among students who did not elect to participate in research activities, for whatever reason. Additionally, students expressed worry about the inaccessibility of other sources of complementary professional help, such as psychotherapy and self-help groups (alcoholics anonymous, narcotics anonymous, etc.).

Perpetuation of myths related to drugs and addictive activities These were referred to in 19 participant interviews (51.3%). Such misconceptions increase the likelihood of succumbing to addictive temptations by attributing beneficial qualities to psychoactive substances and addictive behaviors—among these, greater ability to avoid adversity, generate enjoyment and strengthen sociability. The myths relayed in patient interviews referred mainly to use of tobacco, alcohol, marijuana and social networks.

Myths about tobacco. This is a drug with considerable addictive power that can lead to addiction shortly after initiating use. Tobacco's main component, nicotine, is a stimulant. The idea that tobacco is capable of generating peace or relaxation, much less that it conveys a sense of maturity or responsibility, has no basis in fact. Drugs that are smoked also produce damage to the respiratory tract, which can put users at a greater risk for developing severe forms of COVID-19.[24]

Participants expressed misguided ideas about tobacco, even if they did not habitually use the drug. For example, one participant said they had thought they might begin smoking cigarettes to decrease tension, as doing so during quarantine wouldn't result in addiction. Others said smoking during isolation would generate peace and help them relax, and some of the younger participants thought that it might make them look more mature and responsible. A few mid-level students in the allied health professions commented that since the novel coronavirus cannot survive high temperatures, smoking drugs like tobacco and marijuana might contribute to its control. These myths, gathered from participant interviews, could contribute to setbacks and addiction relapses.

Myths about alcohol. Alcohol is a depressant whose consumption in excess can generate or exacerbate problems in work and study, as well with family and other social relationships. Low alcohol concentration per drink does not lessen addictive potential, as any alcoholic beverage consumed in large quantities is capable of generating an addictive response. Alcohol's unquestionable utility in external disinfection does not mean that its consumption constitutes a preventive measure against disease.

Most of the false notions about alcohol expressed in interviews came from participants in therapy for other addictive substances or activities, who believed that alcohol is not a drug and that its consumption helps relaxation. Some participants also stated that beer and wine are not capable of generating addiction, that they are healthy lifestyle choices and useful during social isolation. Some younger students expressed that since alcohol is being used to curtail transmission by using it to disinfect hands and surfaces, then its consumption can destroy the virus in the body. These myths, if acted upon, can result in difficulty controlling alcohol misuse and may even contribute to novel addictions.

Myths about marijuana. Like any other psychoactive substance, marijuana has the potential for medicinal use, but the idea that marijuana is beneficial for health simply because it is 'natural' has no basis in fact. Like tobacco, it can result in respiratory difficulties and can contribute to severe manifestations of COVID-19.[25] Likewise, marijuana does not enhance learning abilities or the assimilation of information; on the contrary, it can have a negative effect on motivation for studying or for self-care.[26]

Some participants expressed beliefs that over-estimated the medicinal benefits of marijuana. They also described it as a 'natural product' whose use is thus beneficial to people's health. Several stated that during preventive social isolation, people in higher education may benefit from marijuana, as its use stimulates learning abilities. A Latin American participant argued that the use of natural medicines containing marijuana is a common practice in his country and that it is beneficial for relieving tension and anxiety symptoms. While we recognize cannabis' medicinal benefits, people who smoke or 'vape' (either tobacco or marijuana) are at elevated risk of severe COVID-19.[25]

Myths about social networks. Social media facilitates information sharing, but indiscriminate use can generate addiction and other problems. During disasters and emergencies such as the COVID-19 pandemic, social media can become a source of confusion and stress if all information is assumed to be factual or objective. Rumors can spread through social networks and can negatively affect people's health and well-being. Spending inordinate blocks of time on social media, including online games, can also be harmful.[27]

Themes related to the indiscriminate use of social networks and techno-addictions in general emerged during analysis. These myths were described by patients currently undergoing treatment for addiction to chemical substances who had also engaged in excessive social media use during the pandemic, often searching

for information about COVID-19 in a compulsive manner. One participant stated that social networks are secure sources of information which only disseminate truthful news; another argued that in order to stay up-to-date regarding the pandemic, one must be aware of the rumors that are constantly generated about the SARS-CoV-2 virus. These notions can lead to indiscriminate acceptance of all manner of unsubstantiated claims made in social media, and to obsessive behaviors. In the case of social media addicts, myths prevailed regarding the habitual use of social networking activities, like the idea that regular participation in online games is a non-dangerous practice that makes social isolation more acceptable.

Irrational tendencies and lack of emotional control Of the 37 participants, 16 (43.2%) expressed difficulty in controlling their emotions in conditions of preventive social isolation. They added that they often engaged in compulsive behaviors. Several participants referred to higher incidences of negative emotions like fear, sadness and anger. One participant commented that in their current circumstances, fear constitutes a frequent and unpleasant emotion, which led to feelings of immobilization, anxiety, panic and insecurity. The constant concerns surrounding not only the very real possibility of getting sick, but also the possibility of infecting family and friends, caused distress and led to feelings of melancholy and depression.

Emotional dysregulation is common during rehabilitation and social integration processes, manifesting with greater intensity during critical or difficult situations. Some participants spoke of frequent and sometimes uncontrollable anger, which was sometimes linked to feelings of resentment toward others. Additionally, several participants from outside Cuba noted that they were very affected by not knowing the current situations of their relatives, which caused them serious worry, leading to a tendency towards feelings of immobilization while waiting for news. One participant expressed frustration and sadness at what was perceived as the unfair fact that reality fails to coincide with one's desires. Many students described negative emotions associated with the belief that it is unacceptable to not be competent and successful in all circumstances one happens to encounter. However, most patients navigated these difficulties without experiencing setbacks in their recovery.

LESSONS LEARNED

Narrative designs are especially useful in social and health sciences, as they encompass attempts to understand the succession of facts, situations, phenomena, processes and events involving thoughts, feelings, emotions and interactions related by the people who experienced them.[28] Participants' statements made it possible to verify that most of them had developed coping strategies for maintaining self-control, which facilitated addressing and overcoming addictive temptations. Their treatment prior to suspension of face-to-face therapy sessions contributed to these strategies, exposing and reinforcing the incongruities of consumption and other addictive practices with the process of their professional training and their lifelong goals. The above arguments and adherence to treatment, fostered in part by commitment to their therapists, facilitated consistent positive changes in many of the patients over a short time, which in turn contributed to effective psychological coping mechanisms, allowing them to face unexpected difficulties imposed by the pandemic without setbacks or relapses.

During circumstances such as social isolation, the risks of initiating, continuing or re-initiating drug use can manifest in various ways. This depends largely on substance type or specific activities and how much treatment each individual patient has already undergone.[29] This last aspect could explain how these patients were able to face the stressful circumstances experienced: that is, they were in an intermediate stage of treatment characterized by partial progress in their rehabilitation, and already possessed a foundational understanding and an appreciation of the negative impacts consumption had on their professional training, their life goals and their interactions with their psychologists.

Participants raised doubts about the need to stop academic activities and treatments not considered to be medical emergencies. Compliance with health authorities' instructions related to social isolation and distancing as well as hygiene minimizes risk of becoming ill with COVID-19. If patients trust that complying with established guidelines will result in greater probabilities of success, they are more likely to adhere to those guidelines.[30] The background literature consulted underscores that success in COVID-19 prevention and management depends on people's behavior and on changes in their usual lifestyle.[31]

The rational use of time has been proposed as a preventive measure against risky behaviors like drug and alcohol abuse, as has attempting to maintain routines as much as possible.[32] During preventive social isolation, perception of time is altered; people often have the impression that days and nights are extremely long, they tend to be more inactive, and they sleep excessively.[33] Their normal routines disrupted, participants often failed to take into account that various activities can be done at home, including individual study, preventive actions within their residential communities and other forms of individual work or collaborative telework.

Living together in limited space can generate or exacerbate disagreements among family members or cohabiting individuals. In this case, appropriate negotiations aimed at fostering an atmosphere of understanding that facilitates continued abstinence should be promoted. One guide for psychological management of confinement during the COVID-19 crisis[34] insists these steps are essential to avoid or ameliorate symptoms of acute stress, exhaustion, irritability and insomnia.

Maintaining connections with family, friends and colleagues with whom one habitually participates in social activities, psychotherapies and self-help groups,[35] and maintaining a 'normal' sleep–wake cycle (which can help patients avoid insomnia, fears or even generalized anxiety and panic attacks) [36] are both practices that can help individuals face novel challenges.

SC-CEDRO provides patients with a care regimen based on planned consultations. However, many patients also seek guidance for challenges arising from specific needs and conflicts through psychotherapy and self-help groups. Study participants referred to the potential negative impact of the suspension of these groups during this period.

Tobacco and rum have traditionally been considered part of Cuban culture. Globally, the purported benefits of marijuana have been disseminated through media campaigns aimed at its legalization and decriminalization.[25] Study participants made reference to myths that were exacerbated during social isolation regarding tobacco, alcohol, marijuana and the indiscriminate use of social networks.

Tobacco use generally leads to addiction.[37] Adolescents often correlate smoking with 'maturity.' Cigarette smoking can cause high blood pressure and other oncological, cardiovascular and respiratory conditions, which can lead to poor disease progression in persons infected by the SARS-CoV-2 virus.[38]

Some so-called 'new myths' were identified during interviews, which erroneously confer protection against the SARS-CoV-2 virus to certain addictive drugs and practices. The false nature of these claims is especially true in the case of drugs that are smoked, like tobacco and marijuana, as COVID-19 mainly affects the respiratory system. The harmful effects of cigarette smoking include a significant reduction in defenses and a progression towards chronic obstructive pulmonary disease, both risk factors for COVID-19.[39]

Alcohol use can also increase an individual's vulnerability to COVID-19, as it is associated with negative health effects including but not limited to a weakened immune system and an increased susceptibility to pneumonia and other acute respiratory infections.[40] Irresponsible alcohol use can lead to a lack of social discipline and a lapse in preventive measures.

WHO has warned that abuse of social media can lead to an increase in anxiety and anguish,[16] which was perceived in our interviews, whether or not participants were addicted to social media. The wave of misinformation available on social networking sites has been called an 'infodemic' and is considered a pandemic parallel to COVID-19.[41] In Cuba, ample information is provided daily on COVID-19, as national and global data are published in daily Ministry of Public Health bulletins, and resources are continually updated via national media and internet. Top Cuban health authorities appear daily in media briefings that address ongoing problems generated by the COVID-19 pandemic, and government authorities provide timely public reports on decisions taken in the national pandemic working group, charged with systematic analysis of the ever-evolving situation.[42]

New terms have also emerged in youth slang and popular parlance: a 'video-drink' of alcohol with friends, 'online sex', or 'sexting' as a compulsive practice.[43] A very real risk is the practice of games linked to alcohol consumption, like the one known as 'Neknomination', or 'Neknominate'. This game involves ingesting a large amount of alcohol, taking a video, uploading it to social media and inviting friends or other people to meet the 'challenge.'[44] Given that patients in this study are young and most have alcohol-related disorders, the rise of such practices constitutes a latent risk.

Lack of emotional control and tendencies toward irrationality were observed in some study participants who had to adapt to different sociocultural environments, most notably living with classmates in student residences while separated from their families. Emotional disorders are common in patients struggling with addiction and are compounded by critical situations like the pandemic. Such situations constitute mental health emergencies.[45] The control of stress-generating compulsive thoughts should be exercised as a prophylactic measure, and attention diverted to rewarding aspects of an individual's personal, family and community life. SC-CEDRO teletherapy is framed around encouraging patients to plan their days well and exercise responsible coping mechanisms when faced with challenges. Psychological interventions are based on the acceptance that reality is independent of individual will, but individuals can adopt resources allowing them to effectively deal with changes in their situations.[46] This is true for both vulnerable populations and for all those affected by the COVID-19 pandemic.

Controlling negative emotions does not constitute their denial, as they are normal in these kinds of situations.[35] Breathing exercises, relaxation, meditation and other activities have been useful in managing the anxiety caused by news about the novel coronavirus.[47] Fear can be handled positively, enhancing the perception of, and allowing individuals to better recognize, risk; and even sadness can grant individuals enriched inner dialogues and deeper self-knowledge.[48] Refusing to acknowledge these emotions can result in inadequate ability to cope with adversity. Even extremely negative reactions like anger and rage can be vehicles in achieving security, confidence and a sense of firmness. The proper management of these emotions can promote individual assertiveness and help prevent uncritical subjection to outside expectations. These emotions foster young people's defensive capacities and, when accompanied by self-control, promote the development of self-confidence and self-esteem.[49] Strengthening one's self-control of emotional states and controlling one's tendencies toward irrationality are essential.[50]

The importance of this study lies in the fact that at the time it was carried out, there was no research in Cuba that considered possible effects of situations generated by COVID-19 on people with addictions. There was concern within the services that attend to these patients, since rehabilitation requires routine therapeutic monitoring for variable time periods, plus subsequent follow-up appointments. The health emergency posed by COVID-19 prevented these therapies from continuing as planned, which could affect therapeutic adherence and recovery. The results of this study are useful in developing corrective strategies and preventive interventions applicable to this situation and other special circumstances related to disasters or other emergencies.

The main study limitation was the application of a qualitative narrative design through telepsychology. This implied difficulties in obtaining data from visual observation and extra-verbal communication. Even after interviews were conducted, coded and interpreted by several researchers independently and then reconciled among all researchers, it was not possible to rule out alternative interpretations. Such a case would be less likely with the use of other resources or with face-to-face interviews.

This study identified the characteristics of psychological coping mechanisms present before the COVID-19 pandemic in a group of people with disorders related to psychoactive substances and other addictions. Our findings suggest that

despite the negative effects of the pandemic, the personal goals and mechanisms for self-control developed by participants during prior therapeutic exchanges and subsequent treatment conducted through telepsychology allowed many patients to face new and unexpected difficulties without compromising their recovery. We also identified circumstances favoring potential relapse, including difficulties in addressing specific events and situations, perpetuation of myths related to drug use and other addictive activities, and a tendency toward irrationality and lack of emotional control.

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Pretreatment HIV Drug-resistance Surveillance as a Tool for Monitoring and Control of the HIV/AIDS Epidemic in Cuba

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ABSTRACT

The HIV/AIDS epidemic is an ongoing threat to public health. Its elimination requires greater efforts to broaden antiretroviral treatment coverage, availability and personalization. HIV drug resistance is currently a global problem due to its continuing increase in recent years, undermining efficacy of antiretroviral therapy. Pretreatment HIV drug-resistance surveillance is part of WHO's strategy for addressing antiretroviral drug resistance.

This paper describes and analyzes pretreatment HIV drug-resistance surveillance in Cuba. It presents a chronology of HIV resistance studies in untreated patients, along with their results and programmatic actions related to first- and second-line treatment regimens. Cuba's incorporation into the Global HIV Drug Resistance Surveillance Laboratories Network and the advantages of having a WHO-designated laboratory in which to conduct periodic studies of HIV drug-resistance surveillance are described.

HIV drug-resistance surveillance in Cuba is a necessary tool in HIV/AIDS monitoring and control, as it obtains population-scale data used to inform programmatic decisions related to optimizing first- and second-line treatments for children and adults, as well as helping meet goals of eliminating HIV transmission.

KEYWORDS HIV; anti-HIV agents; drug resistance, viral; antiretroviral agents; Cuba

INTRODUCTION

Antiretroviral therapy (ART) is one of the most significant advances in battling the HIV/AIDS epidemic. Since ART does not eliminate the virus in individuals, treatment must be lifelong.[1]

Many factors can affect short- or long-term ART success, including poor adherence to treatment, drug intolerance, drug interactions, individual pharmacokinetic variations and preexisting drug resistance due to transmission of a resistant virus. Transmitted HIV drug resistance occurs when a person becomes infected with an antiretroviral (ARV) drug-resistant strain of HIV. This phenomenon may contribute to rising treatment failure rates, undermining long-term effectiveness of recommended first-line regimens.[2]

Faced with grave public health consequences associated with the emergence and transmission of HIV drug resistance, surveillance studies in untreated infected populations are crucial. An understanding of current patterns of pretreatment drug resistance can help clinicians select the most appropriate ART regimens, as well as anticipate trends that may affect optimization of resources allocated for effectively treating HIV-positive persons.[1,2]

IMPORTANCE

Pretreatment HIV drug-resistance surveillance is a vital tool in combatting the HIV/AIDS epidemic. This article describes and analyzes pretreatment HIV drug-resistance surveillance in Cuba, which has enabled identification of the most effective therapeutic combinations for achieving viral suppression and reducing transmission of resistant HIV variants; thus, Cuba expects to surpass 90% treatment adherence, proceeding towards WHO's goal of eliminating AIDS as a health problem by 2030.

Alerted to increasing HIV drug resistance in low- and middle-income countries in recent years, WHO has issued guidelines aimed at minimizing drug resistance and contributing to achieving targets for ending the HIV/AIDS epidemic by 2030.[3]

The Global Action Plan (GAP) on HIV drug resistance, created in 2017, established requirements for providing people living with HIV (PLHIV) with more effective treatments and for preventing drug resistance from undermining efforts to meet global health goals. GAP's strategic goals include increasing laboratory capacities for HIV drug-resistance genotyping, as well as adequate HIV drug-resistance monitoring and surveillance to obtain quality data through studies performed at regular intervals.[4]

Cuba has adopted WHO directives to confront HIV drug resistance. Monitoring and surveillance activities have been specified in several editions of the Cuban Ministry of Public Health's (MINSAP) National Strategic Plan for Sexually Transmitted Infections (STI), HIV/AIDS and Hepatitis.[5,6] Surveillance activities include periodic studies of HIV drug resistance in patients who have not received ART, useful to MINSAP as it evaluates current and potential treatment regimens, since pretreatment resistance to ARVs in use in Cuba can affect patient results and strategies for meeting national and global goals for HIV/AIDS elimination. This paper analyzes the role surveillance of pretreatment HIV drug resistance has had as a tool for monitoring and controlling the HIV/AIDS epidemic in Cuba.

MONITORING PRE-TREATMENT HIV ANTIRETROVIRAL RESISTANCE IN CUBA

HIV drug resistance in untreated Cuban patients Since the first HIV-positive patient was diagnosed in Cuba in 1986, the national health system, through the National Program for the Prevention and Control of HIV/AIDS,[5,6] has designed strategies for the prevention, diagnosis, treatment and epidemiological surveillance of the disease.

Several studies have focused on determining which genetic variants of the virus are circulating in the seropositive Cuban popu-

lation, given their implications for diagnosis, transmissibility and clinical progression.[7–9]

Before ART was initiated in Cuba, a group of Cuban researchers, in collaboration with the Carlos III Health Institute (ISCIII) in Spain, conducted a pilot study to determine HIV drug-resistance prevalence in seropositive patients treated with monotherapeutic or two-drug ARV regimens, as well as in patients not receiving ARV. The results showed a low prevalence of mutations that generate resistance to reverse transcriptase inhibitors (RTI) and protease inhibitors (PI),[10] which aided in selecting ARVs that would later be produced by Cuba's domestic biopharmaceutical industry: zidovudine (AZT), nevirapine (NVP), lamivudine (3TC), stavudine (d4T), indinavir (IDV) and didadosine (DDI) (Table 1).[11]

The introduction of ART in Cuba in 2001 (with domestically-produced generic ARVs) helped reduce the incidence of opportunistic infections and mortality from HIV/AIDS, as well as improve quality of life in PLHIV.[11] By the end of 2018, more than 90% of all PLHIV who initiated treatment in 2007 remained alive.[5,6] However, prolonged ART use in the seropositive population is known to foster emergence of HIV drug-resistant genetic variants in these patients and therefore potential transmission of the resistant strains to the untreated HIV-positive population.[18]

Two years after the introduction of domestically-produced generic ARVs, another group of Cuban researchers in collaboration with the ISCIII in Spain evaluated HIV drug resistance in seropositive Cuban patients. That study included 249 untreated patients and detected a low prevalence (4%) of mutations associated with HIV drug resistance.[12] During 2007–2011 and 2009–2014, researchers at the Pedro Kourí Tropical Medicine Institute (IPK) in Havana studied changes in drug resistance in 152 treated and 342 untreated patients (samples obtained immediately prior to beginning treatment), and results showed moderate resistance prevalence (12.5% and 11.4%, respectively) (Table 1).[13,14]

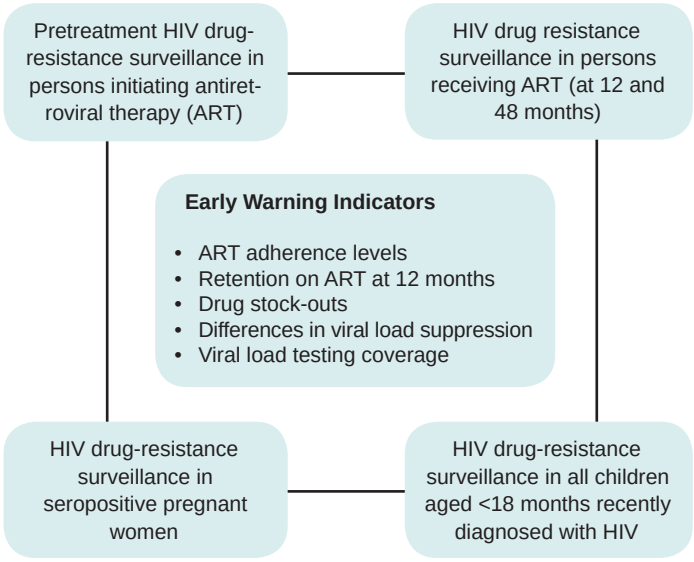
Although several factors interfere with the goal of achieving total ART coverage, Cuba has experienced a sustained increase, reaching approximately 83% of PLHIV.[6] In order to support this goal, and with financial assistance from the Global Fund to Fight AIDS, Tuberculosis and Malaria, HIV drug-resistance genotyping was introduced in 2009.

WHO recommends that countries with ART programs establish sentinel surveillance systems to detect HIV drug resistance and make evidence-based recommendations for preventing drug resistance. Such surveillance is aimed at minimizing the emergence of drug resistance, prolonging the efficacy of first- and second-line therapies, and selecting adequate therapeutic regimens for pre- and post-exposure prophylaxis (Figure 1).[3] In response to those recommendations, MINSAP decided that IPK and the AIDS Research Laboratory (LISIDA) would be in charge of HIV drug-resistance genotyping. Since then, surveillance of HIV drug resistance in a sample of patients with no prior treatment history was undertaken by LISIDA.[5,6]

Once infrastructure was created and staff trained, LISIDA initiated studies of HIV drug resistance in untreated individuals in June 2009. From that date until December 2016, with the permanent collaboration of primary healthcare teams at community polyclinics who were providing care to PLHIV in each province, 469 patients recently diagnosed with HIV infection who had not yet initiated ART were studied. Of those patients, 19% (89) presented a virus with some mutation associated with pretreatment HIV drug resistance: 10.4% (48) to nucleoside reverse-transcriptase inhibitors (NRTI), 12.8% (60) to non-nucleoside reverse-transcriptase inhibitors (NNRTI) and 2.8% (13) to protease inhibitors. The most frequent mutations were K103N/S and Y181C in the NNRTI family, which reduced susceptibility to drugs like NVP and efavirenz (EFV). In the NRTI family, the most frequent mutations were M184V/I (resistance to 3TC) and D67N (resistance to AZT).[15,16] The results showed a high prevalence of pretreatment HIV drug resistance and, consequently, the need to change first- and second-line therapeutic regimens used by the National Program for the Prevention and Control of HIV/AIDS. However, studies conducted in 2009–2016 did not take into account WHO recommendations for sampling and selection of individuals for surveillance of pretreatment drug resistance (Table 1).

In December 2016, LISIDA specialists, in collaboration with the MINSAP's STI, HIV/AIDS and Hepatitis Program and PAHO, designed a national survey of HIV drug resistance in pretreatment patients, following WHO recommendations,[3] aimed at estimating pretreatment HIV drug-resistance prevalence in the seropositive Cuban population.

Figure 1: Cuba's HIV drug-resistance surveillance and monitoring strategy*



*in accordance with WHO recommendations[3,4,6]

The survey was conducted from January to June 2017. Samples from 141 untreated patients from 15 municipalities were studied. Overall prevalence of pretreatment resistance was 29.8% (95% CI: 22.3–38.1). Prevalence for some NRTI was 10.6% (95% CI: 6.07–16.9); for some NNRTI, 23.4% (95% CI: 16.7–31.3); and for some PI, 1.4% (95% CI: 0.17–5.03) (Table 1).[17]

Determination of resistance levels to ARV combinations indicated that treatment would not be effective in 29.7% of patients initiating therapy with the AZT + 3TC + NVP regimen. The ATRIPLA combination of tenofovir (TDF), emtricitabine (FTC) and EFV would not be effective in 27.6% of patients initiating ART. The increase in NNRTI pretreatment drug resistance in Cuban HIV-positive

Table 1: Chronology of pretreatment HIV drug-resistance studies in Cuba

Year of Study	Institution	Patients (n)	First-line ART regimen	% Resistance				Recommendations to health authorities
				Some mutation	NRTI	NNRTI	PI	
1999[10]	LISIDA (collaboration with Carlos III Institute, Spain)	27	Monotherapy, two-drug ART, triple-drug ART	7.4	7.4	-	-	Introduce ART with ARV drugs produced in Cuba
2003[12]	IPK (collaboration with Carlos III Institute, Spain)	249	2 NRTI + 1 NNRTI*[5]	4	4	-	-	Increase HIV drug-resistance studies
2007–2011[13]	IPK	152	2 NRTI + 1 NNRTI*[5]	12.5	3.9	2.0	2.0	Genotyping needed prior to initiating ART
2009–2014[14]	IPK	342	2 NRTI + 1 NNRTI*[5]	11.4	7.9	5.3	2.9	National study needed with WHO representativeness criteria[3]
2009–2016 [15,16]	LISIDA	469	2 NRTI + 1 NNRTI*[5]	19	10.4	12.8	2.8	National study needed with WHO representativeness criteria[3]
2017[17]	LISIDA	141	2 NRTI + 1 NNRTI*[5]	29.8	10.6	23.4	1.4	No NNRTI prescription in first-line ART[6] Incorporate DTG in first-line ART[6]

ART: Antiretroviral therapy; ARV: antiretroviral drugs; DTG: dolutegravir (integrase inhibitor); IPK: Pedro Kourí Tropical Medicine Institute; LISIDA: AIDS Research Laboratory; NNRTI: non-nucleoside reverse transcriptase inhibitors (efavirenz, nevirapine); NRTI: nucleoside reverse transcriptase inhibitors (zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir; PI: protease inhibitors (indinavir, saquinavir, nelfinavir, ritonavir, amprenavir, lopinavir/ritonavir)

*includes combination therapies: AZT + 3TC + NVP; AZT + 3TC + efavirenz (EFV); tenofovir (TDF) + 3TC + NVP; TDF + 3TC + EFV; ATRIPLA: TDF + emtricitabine (FTC) + EFV

patients who participated in the national survey demonstrated the need to evaluate switching to more appropriate and effective ART regimens and strengthening prevention and surveillance of HIV drug resistance.[17]

WHO recommends against NNRTIs in first-line therapy if prevalence of resistance to this family of drugs is >10% and if not possible to eliminate NNRTI, suggests considering HIV drug-resistance genotyping before prescribing treatment.[19] One recommendation suggests incorporating the integrase inhibitor dolutegravir (DTG), which has a high genetic barrier and can rapidly attain undetectable values of plasma viral load.[20] This drug was added to first-line ART combinations in Cuba starting in the last quarter of 2018, one of MINSAP's rapid responses for confronting the high levels of HIV drug resistance detected,[6] thereby obtaining a higher percentage of PLHIV with viral suppression.

Confronting HIV drug resistance should involve educational and preventive interventions with PLHIV on the importance of adhering to treatment along with systematic monitoring of early warning indicators of HIV drug resistance (such as treatment retention, viral load coverage, systematic provision of drugs to pharmacy networks, etc.).

According to WHO criteria, lowering the prevalence of pretreatment HIV drug resistance to <10% will enable Cuba to maintain its achievement as the first country in the world to eliminate mother-to-child HIV transmission[21] and contribute towards its goal of meeting the third 90 in the 90-90-90 treatment targets proposed by the Joint UN Program on HIV/AIDS (UNAIDS) for 2020, which aim to have ≥90% PLHIV on treatment regimens living with undetectable viral loads.[22]

Cuba's incorporation into WHO Global HIV Drug Resistance Network (HIVResNet) laboratories The WHO HIVResNet global laboratory network includes national and regional laboratories, along with specialized international laboratories accredited by WHO, responsible for conducting HIV drug-resistance tests.[23] Depending on their capacity, experience and technical resources, each laboratory carries out specific functions supporting the network's national, regional and global needs.

All national surveys of HIV drug resistance require testing in a WHO-accredited laboratory. The accreditation process is undertaken only by laboratories designated by national authorities to test samples gathered as part of HIV drug-resistance surveys recommended by WHO. Generally, WHO accredits only one laboratory per country, whose primary task is providing high-quality genotyping results, pertinent to national ART programs and supporting public health approaches to ART.[23]

Cuba initiated a national survey to assess variation in pretreatment HIV drug resistance in 2017. MINSAP nominated LISIDA for evaluation and designation by WHO as a National Drug Resistance Laboratory and member of HIVResNet. That same year, WHO experts visited LISIDA, having previously reviewed an accreditation checklist assessing the laboratory's experience and capacity for HIV sequencing, as well as several quality indicators, such as staff competencies, facilities, equipment, management practices, financial security and sustainability, and participation in a WHO External Evaluation Program. The results of the evaluation process were satisfactory and even exceeded criteria for WHO acceptance and designation as a National Reference Laboratory and member of HIVResNet (https:// who.int/temas/global-hiv-hepatitis-and stis-programmes/hiv/treatment/hiv-drug-resistance).

As part of the designation process and as a useful resource for evaluating laboratories' competence in editing and analyzing HIV genetic sequences obtained in HIV drug-resistance genotyping, WHO incorporated dry-panel testing, a novel alternative for quality control, consisting of a group of sequences from HIV protease and reverse transcriptase enzyme regions. This test involved editing and analyzing the sequences, demonstrating competency in quality assurance, data management and reporting.

Since LISIDA's designation as a member of HIVResNet, the laboratory has participated in three dry-panel tests with satisfactory results (94.7–100 points; minimum 85 points required), demonstrating good performance (compliance with Good Laboratory Practices) and competence in data management and reporting.

Results of the 2017 national pretreatment HIV drug-resistance survey were entered into the WHO database and included in its annual HIV Drug Resistance Report in 2019.[24]

LISIDA has played an active role in HIVResNet since joining the network, which has led to the introduction of new methodologies for analyzing HIV drug resistance in Cuba. Its specialists have participated in virtual meetings and seminars, as well as the annual HIVResNet meeting during the 28th International Workshop on HIV Drug Resistance and Treatment Strategies in 2019 (www.hivresistance2019.co.za).

Projections for surveillance of HIV drug resistance in Cuba

Results of the 2017 national HIV drug-resistance survey were presented in different settings (virtual meetings, workshops) to a representative group of doctors caring for PLHIV in Cuba. These exchanges led to National Technical Team approval of new therapeutic regimens accepted in the National Strategic Plan 2018–2023.[6] HIV drug resistance has been a recurring topic in national meetings of the Cuban PLHIV Network, leading to creation of prevention-based strategies to help minimize the emergence of HIV drug resistance through promoting ART adherence and systematic monitoring of early warning indicators. Offering seminars, workshops and conferences for clinicians caring for PLHIV on HIV drug resistance and the use of genotyping in clinical practice is one of the objectives of both MINSAP's STI, HIV/AIDS and Hepatitis Program and laboratory personnel in charge of genotyping in Cuba (LISIDA and IPK).

Incorporating DTG in first-line ART regimens in Cuba involved introducing genotyping to detect HIV resistance to integrase inhibitors, since this is a mandatory requirement for national laboratories accredited by WHO. Having a validated test capable of detecting primary and secondary mutations associated with the emergence of resistance to integrase inhibitors makes it possible to evaluate resistance to these ARV in ART regimens used in Cuba.

LISIDA is working toward validation of HIV drug-resistance genotyping using dry blood on filter paper, given the advantages of this type of sample in terms of transportation and conservation. Incorporation of new technologies for determining HIV drug resistance will strengthen the laboratory by acquiring the Sentosa SQ HIV platform (Vela Diagnostic, Germany), which detects mutations associated with resistance in protease, reverse transcriptase and integrase genes, using next-generation sequencing. In this way, LISIDA will meet one of the HIVResNet goals related to the transition from HIV drug-resistance genotyping based on the Sanger sequencing method,[2] to next-generation sequencing.

As the national reference laboratory for surveillance of HIV resistance and a member of HIVResNet and the national reference laboratory for surveillance of HIV resistance, LISIDA will begin surveying adults receiving ART in 2021 for the purpose of estimating prevalence on a national scale of 1) viral load suppression, and 2) HIV drug resistance in populations that have received ART for 12 months (±3 months) and for ≥48 months. Results of this national survey will contribute fundamental information about the efficacy of the program for achieving maximum viral suppression and document appropriate selection and optimal management of second-line treatments. The National Program can also use the results to detect deficiencies in service provision and implement policies to improve results at individual and population levels.

CONCLUSIONS

In Cuba, pretreatment surveillance has been an efficient tool for detecting high levels of HIV drug resistance to NNRTI, thus prompting adoption of more effective therapeutic combinations to increase viral suppression, lower transmission of HIV drug-resistant variants and thus facilitate ART success. The comprehensive approach, focused research and enhanced laboratory capacity will make substantial contributions to HIV drug-resistance surveillance in PLHIV populations and to achieving WHO goals for eliminating HIV/AIDS as a public health problem by 2030.

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Using Multiple Cause-of-Death Analysis to Estimate Systemic Autoimmune Disease Mortality Burden in Low- and Middle-Income Countries

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ABSTRACT

Autoimmune diseases are not always recognized as urgent health issues, despite a worldwide prevalence of 4%–5%. Most estimates come from high-income countries, as low- and middle-income countries face more issues of under-reporting. Despite this and the lack of recognition under current reporting practices, the role these diseases play in mortality must be acknowledged. In particular, considering multiple causes of death as opposed to a single cause of death results in a 1.5–4.2-fold increase in deaths classified as relating to autoimmune diseases, evidence of their share in overall mortality burden, a factor important for patient care and healthcare policy decision making.

However, formulating such policies and programs for timely, appropriate diagnoses and care is stymied in low- and middle-income countries by the shortage of methodologically sound studies on mortality from systemic autoimmune diseases. This limitation exacerbates inequalities and health gaps among patients in different countries and localities.

Multiple cause-of-death methodology has been validated for research on other diseases and demonstrates the mortality burden of these illnesses in countries where traditional methodological approaches, primarily based on prospective cohort studies, are not feasible. Studying mortality from systemic autoimmune diseases by analyzing multiple causes of death with data from national mortality registries is a low-cost alternative to traditional mortality analysis. The objective of this paper is to demonstrate and defend the usefulness of this approach to estimate mortality burden.

KEYWORDS Autoimmune diseases, mortality, cause of death, Cuba

INTRODUCTION

It is estimated that autoimmune disease prevalence is 4%–5% in high-income countries, and predicted to increase worldwide.[1] In the United States and the United Kingdom, autoimmune diseases are among the 10 main causes of death in women <65 years of age, and are expected to affect 15–20 million people in the coming decades.[2,3]

Within the group of autoimmune diseases are systemic autoimmune diseases (SAD). SAD (as opposed to organ-specific autoimmune diseases) involve pathological processes in which the immune system organizes a response against the host body, causing chronic inflammation and damage to various organs.[1] The most clinically and epidemiologically relevant SAD are systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSc), dermatopolymyositis/polymyositis (DM/PM), and Sjögren's syndrome (SjS), although incidence and prevalence rates vary between countries and regions.[1,4–8]

It is difficult to estimate the burden of SAD disease and mortality in low- and middle-income countries, because they lack services specialized in diagnosing, treating and monitoring SAD patients. Therefore, injuries caused by these diseases often remain undiscovered until an autopsy is performed.[9] RA is the most researched disease; in 2010 it had a global prevalence of 0.24% (95% CI: 0.23%–0.25%) responsible for 4.8 million disability-adjusted life years (DALYs) (95% CI: 3.7–6.1). In 2010, the Global Burden of Diseases study ranked it number 42 among diseases that contributed the most disability of all 291 conditions in the study, just below malaria and just above iodine deficiency.[4] Other SADs were not included as independent entities in the study.

IMPORTANCE

This paper discusses multiple cause-of-death analysis and recommends its use in assessing systemic autoimmune disease mortality in countries where it is difficult to diagnose and monitor autoimmune disease patients using expensive cohort studies, due to resource limitations.

In 2016, SLE global incidence was estimated at 0.3–31.5 per 100,000 person-years, with a prevalence of 3.2–515.5 per 100,000 population. These variations are related to multiple factors, including genetic and geographic differences and methods used in case identification.[5] SSc has an incidence of 0.4–4.3 per 100,000 person-years and a prevalence of 8.8–44.3 per 100,000.[6] DM/PM incidence is 0.11–1.93 per 100,000 person-years, with a prevalence of 2.4–33.8 per 100,000 population.[7] For SjS, the incidence is 6.92 per 100,000 person-years, with a prevalence of 60.82 per 100,000 population.[8] One open-population study performed in Cuba reported an SLE prevalence of 63.3 per 100,000 population and an RA prevalence of 1236 per 100,000 population.[10]

While SAD signs, symptoms and disease progression can be mild, many patients experience severe forms that are refractory to current treatments, and are associated with higher mortality rates than those of the general population, contributing to premature mortality.[11,12]

Mortality is considered the primary and most universal health indicator. Yet, SAD mortality is a topic that has been 'abandoned' by the scientific community; this, despite the fact that RA mortality rates are comparable to those of HIV/AIDS and cardiovascular diseases according to standardized mortality ratios (SMR): 1.47 versus 1.30 and 1.26 respectively.[11,13] SMRs for SLE, SSc, and DM/PM are similar to or greater than those of type 2 diabetes mellitus (SMR: 2.4–4.8 vs. 2.6).[11,14] There are many reasons why SAD mortality receives little attention, but chief among them are:

many patients were unaware of their SAD at time of death as it was never diagnosed; fewer resources are dedicated to researching SAD mortality than to studying deaths from cardiovascular or neoplastic diseases; it is uncommon to find longitudinal databases monitoring SAD patients over 5–20 years; and death certificates do not typically include all rheumatic diseases.[11,15]

In order to recognize the extent of SAD as an important global health problem, and for health systems to design and implement policies that improve medical care quality and healthcare coverage of SAD patients, more data is needed than is currently available.[16] In particular, SAD mortality must be estimated to inform decision makers developing health strategies and facilitate comparisons among health programs in different places.[15–17]

Mortality studies based on the causes of death listed on death certificates are not common in international literature, and those that exist generally only take into account the underlying cause of death.[12,18] Studying the underlying cause of death provides important information, but underestimates the implication of chronic conditions, which undoubtedly are among the many influencing factors in the death. This is especially the case for SAD, which are generally present in patients with multiple comorbidities.[18,19]

Since the mid-20th century, mortality studies that analyze multiple causes of death in chronic disease patients have been considered important for gaining new insights into disease prevention.[19,20] In the last decade, there have been studies that use this methodology in SAD mortality.[18,20–26] However SAD mortality studies in developing countries are scarce, and have not had the impact necessary to impart the importance of SADs as an urgent health issue or to implement health policies designed to reduce mortality.[9,27,28] There are few mortality studies in Cuba that use multiple-cause-of-death analysis, but none of them are related to SADs.[29–31]

In this paper, we discuss the relevance and utility of using multiple-cause-of-death analysis for estimating SAD mortality in Cuba and developing countries with reliable data sources in an effort to encourage healthcare programs and policies to acknowledge the impact of SADs.

DEVELOPMENT

SAD in policy and practice In formulating health policies and programs, decisions must be evidence-based, requiring reliable and timely information to assess the magnitude of the diseases within populations and impacts of the programs designed to eliminate or control them, and to establish research priorities accordingly. Mortality registries are the standardized sources of information most commonly used for these purposes.[16,32]

In high-income countries like the United States and Sweden, cardiovascular diseases are the leading cause of death, followed by cancer. However, deaths from diseases deemed 'rare' are often ignored. Among these diseases are SADs, which are substantial contributors to premature death.[17] In Cuba, cardiovascular diseases have also been the leading cause of death for several years, but reports from the National Medical Records and Health Statistics Bureau in 2008–2010 placed "systemic connective tissue disorders" among the top 10 causes of death for women aged 15–34 years,[33] and the total deaths attributed to these diseases in 2009–2019 were 1419 for both sexes (84% female).[34] The age group in which those deaths were clustered reinforces the importance of properly diagnosing and treating SADs and of addressing them in health system policies.

A few years ago, SAD were not considered 'fatal,' and it was thought that they did not increase short-term mortality, but evidence indicates that mortality may be up to four times higher in SAD patients than in the general population (SMR from 1.44–4.8).[11,12,14,18] One of the reasons low SAD mortality rates are reported in comparison to other diseases is underestimation, since SAD deaths are not reported on death certificates, or at least, not as underlying causes of death—the disease or injury that began the chain of pathological events that directly led to death.[15,16,18,22,35]

Thus, even though these diseases may represent an important burden on individual and population health, they are not recognized as such by many countries when drafting health policies, or determining priorities for research and education.[15,16,22] In response to these deficiencies, WHO promoted 2000–2010 as the 'Bone and Joint Decade' in an effort to raise awareness about SADs and decrease their impact on health.[16,36]

Some countries and regions have adopted health policies addressing SADs, but they are few and far between. In response to WHO's call, the Presidency of the Council of the European Union held a conference in October 2010 on rheumatic and musculoskeletal diseases, where it was recommended that SAD be prioritized in crafting health policy agendas, and that funding for research in EU member countries be increased accordingly. Spain was one of the first countries to design a Comprehensive National Strategy for Rheumatic and Musculoskeletal Diseases,[36] which was supplemented with other regional strategies including the Andalusian Plan for Rheumatic and Musculoskeletal Diseases. It also proposed improving healthcare, increasing SAD awareness and available information, and promoting research and professional training.[36,37]

Several countries have developed SAD-specific policies: for example the National Lupus Public Health Agenda in the United States, which, with 6 priorities, 15 strategies, and 63 recommendations, has achieved both better understanding and management of SLE.[38]

In 2015, the US National Institutes of Health recognized SLE as one of the leading causes of death in young women and increased funding for research into this disease to US$90 million annually. However, despite SLE having an SMR comparable to diabetes mellitus and HIV/AIDS, funding designated for research on diabetes (US$1.01 billion) and HIV/AIDS($US3.17 billion) remains considerably higher.[22]

Countries that already have SAD-specific policies in place relied on information on disease burden, mortality, social determinants of health, the diseases' temporal and geographic trends, and the use of services related to SAD. That data was supplemented with qualitative studies using evaluations of patients and professionals related to their experiences in patient care.[37,38] In low- and middle-income countries, it is more difficult to obtain this information due to the high cost and organizational and infrastructural dif-

ficulties associated with cohort studies and research that provide reliable data on disease burden and mortality, as these countries do not always have services and specialists dedicated to caring for SAD patients.[9,31]

Health authorities in developing countries are hard pressed to fund studies facilitating policy design and implementation for SADs, when forced to dedicate scarce resources to the double burden of diseases that no longer affect high-income countries: communicable diseases plus pressing chronic non-communicable diseases such as diabetes, hypertension, cardiovascular disease, cancer and rheumatic disease.[31,39]

The lack of health policies aimed at improving care for SAD patients in developing countries is evident in the results of a study that analyzed global trends in SAD-related deaths, 2001–2014. In this study, SLE age-standardized mortality rate (ASMR) in Latin America was five times higher than in Europe, and during the 2003–2014 period, there was a significantly increasing trend in SLE ASMRs in Latin America and Asia, while Europe, North America, and Oceania, saw a decreasing trend and ASMRs in Africa remained stable.[1] Hernández Negrín discussed increasing SLE mortality in Latin America and its inverse correlation to country wealth by compiling information from five studies on the topic that obtained their data from mortality registries based on standard WHO death certificates.[27]

Even though health policy deficiencies in recognizing and treating SAD have an important role in SAD severity and high mortality rates, regionalized unfavorable health statistics are due to multiplicity of factors including poverty, malnutrition, low education levels, lack of treatment adherence, adverse perception and non-adaptive behaviors regarding the disease, low clinical suspicion, lack of access to specialized treatments and services, geographic isolation, lack of social support systems, inadequate public policies, and low gross domestic product.[5,9,30,31]

In Cuba, universal health coverage and access provides equitable medical care and epidemiological services to the Cuban population.[40] Yet, despite the existence of rheumatology services designed to diagnose and treat SAD and a Rheumatology Institute conducting research in the field, these diseases are not included in objectives aimed at reducing premature death from select non-communicable chronic diseases (diseases of the arteries and arterioles, cerebrovascular disease, ischemic heart disease, diabetes mellitus, chronic obstructive pulmonary disease, and asthma).[41] Specific public policies for SAD patients are therefore required.

Those policies must be oriented toward improving health professionals' training pertaining to SADs, increasing human resources for diagnosing and treating SAD patients and researching these diseases, developing health models focused on SAD, establishing standardized national guidelines for SAD clinical management, the systematic collection of clinical and epidemiological data to better understand SAD, raising public awareness, creating support groups for SAD patients and their families, improving access to immunological diagnostic testing, and empowering patients to actively participate in disease management.[9,37,38]

SAD mortality study limitations Medical care for SAD patients is tricky due to diverse (but not uncommon) clinical presentation, and because conventional immunological diagnostic methods can provide similar results for several SADs. Clinical studies arising during the course of SAD treatment are occasionally biased and designed inappropriately, and data quality is not optimal,[15] thus contributing little knowledge related to SAD mortality trends within populations, causes of death, or factors influencing prognoses.[1]

Many SAD studies are based on retrospective analyses of clinical histories of hospitalized or prospectively-monitored patients in specialized clinics or patients referred to specialists in hospitals. A select population is seen in these institutions, composed of the most serious cases and cases receiving the most comprehensive medical care, so information that they provide has selection biases that makes it difficult to extrapolate results to other sites, even within in the same country.[12,15]

Many published mortality studies are monocentric, where the cause of death is determined by reviewing clinical histories and autopsy reports, or by contacting the physician who cared for the patient in their final moments. Others use statistics from medical services, disability pensions from institutions and hospital statistics, which are not representative of the general population and are, therefore, often biased.[12,15]

SAD mortality studies conducted in Cuba are the result of case series that summarize the experience of a single doctor or institution (generally at secondary- or tertiary-care levels), with small samples, focused on a single disease. One of their limitations is that they do not capture mortality from SAD over time, nor do they reflect the true burden of these diseases within the general population. Studies that evaluate a single entity are useful in estimating its relevance as a health problem but tend to overestimate the importance of the specific condition on which they are focused.[12,15,42]

SAD mortality using multiple causes-of-death analysis The growing availability of data generated during medical care and monitoring of SAD incidence and clinical progression have transformed the outlook of health research. There was a time that health data collected through routine procedures was considered to be of no investigative interest. But these sources of information (including specific disease registries, primary care databases, administrative databases, archives, cancer registries, mandatory disease-reporting registries and mortality registries) open up opportunities for innovative, efficient, and cost-effective research to aid decisions made in clinical practice; to plan health services, programming and policies; and to improve patient care and healthcare efficiency in various settings and geographic regions worldwide.[43]

Mortality registries have been used as data sources to research mortality in SAD patients, [12,18,20–26] but there are few studies based on these registries despite the fact that they allow for closer examination of population mortality rates, and for inclusion of a greater number of patients over a longer period, which reduces selection bias and sample size problems. They are also more representative of the population than traditional cohort studies conducted among patients who receive specialized care.[15] Moreover, such prospective cohort studies are common for rheumatological research but require close patient monitoring and are expensive, which means that they are not always a viable alternative to research SAD in low-income environments.[9,15,31]

Despite Cuba's high-quality mortality statistics,[33] only one study was conducted in Cuba on the mortality registry that included SAD among the immunopathological conditions considered,[44] which opens up an opportunity for research into a topic that has been understudied in the country.

Death is the result of complex pathological interactions, so the declared underlying cause of death may not entirely reflect causal processes. This aspect is important in SAD patients who often have combinations of diseases with physio-pathological implications and prognoses that are not entirely clear.[12,19] One methodological alternative to resolve this problem is to use multiple cause-of-death analysis. This term identifies an approach to mortality that considers all causes of death reported on the death certificate with no distinction between underlying and circumstantial causes.[18,19,28]

Analyzing multiple causes of death is a powerful epidemiological tool facilitating a more comprehensive understanding of the morbidity process.[18] Often the underlying cause of death is difficult to predict or is diagnosed after the fact. Conversely, the causes or complications derived from underlying causes may be predicted and even expected, which may help in monitoring or even prevention.[19,27]

While multiple cause-of-death analysis has been used since the first half of the 20th century, the last decade has seen an increase in epidemiological research that uses it as a strategy to address death from various health problems such as: opioid use,[45] obesity,[46] cardiovascular diseases,[47] aortic aneurysm dissection,[48] diabetes mellitus,[32] pulmonary embolism,[49] sepsis[50] and hemophilia.[51]

In countries with medium- or high-quality mortality registries representative of the population, these should be used as a source of SAD data, thus reducing patient selection bias and allowing for comparisons between countries as well as study of disease behavior over long periods at a relatively low cost. This potential is revealed in studies carried out in six countries, which show that deaths related to SAD that were identified using multiple-cause-of-death analysis increased 1.5 to 4.2 times compared to those identified using only the underlying cause (Table 1).

When the underlying cause of death is attributed to SAD, associated causes vary depending on the type of disease. In the case of RA, the most frequently associated causes are cardiovascular diseases, infectious diseases and respiratory diseases.[52] In SLE patients, the leading associated causes of death were renal, cardiovascular and infectious,[21] while in SSc patients these causes were infectious, followed by respiratory, cardiovascular and renal.[26] The causes of death most frequently associated with PM/DM were respiratory diseases, infectious diseases and cancer.[20]

Use of data from death certificates is limited by its failure to permit estimation of indicators of importance such as incidence rates and SMR or for life table analysis. The role of SAD disease progression and organ damage cannot be determined. However, perhaps the most important limitation is related to death certificate validity, as a significant percentage of SADs are not declared as either underlying causes or contributing causes of death.[12,15,17]

Despite these limitations, SAD patient mortality profiles could help raise awareness of the need to allocate more material and human resources to manage these diseases, more focused studies on the topic, and more data-driven attention to comparisons between countries and study trends.

CONCLUSIONS

In many countries, SAD is not recognized as an important health issue because the burden of mortality is unknown or has not been properly assessed. This fact makes formulation of policies and programs to monitor SAD difficult, and creates inequalities and health gaps. Studying SAD mortality by analyzing multiple causes of death with data from national mortality registries is a low-cost alternative that offers evidence on mortality burdens in countries where it is not feasible to apply traditional methodological approaches based on prospective cohort studies.

Table 1: SAD mortality studies using multiple causes of death

Reference	Country	Study period	SAD	Number of deaths identified		Ratio Multiple causes of death/ Underlying cause *
				Underlying cause	Multiple causes of death	
Falasinnu T, et al.[53]	USA	2014	SLE	1,180	2,036	1.7
Mitratza M, et al.[42]	Netherlands	2013–2017	SLE	100	251	2.5
Mitratza M, et al.[42]	Netherlands	2013–2017	SSc	268	403	1.5
Mitratza M, et al.[42]	Netherlands	2013–2017	DM/PM	100	212	2.1
Mitratza M, et al.[42]	Netherlands	2013–2017	SjS	48	204	4.2
Poubel Vieira et al.[26]	Brazil	2006–2015	SSc	223	374	1.7
Avouac J, et al.[52]	France	2000–2011	RA	4,597	13,208	2.9
Elhai M, et al.[23]	France	2000–2014	SSc	1,608	2,719	1.7
Thomas G, et al.[25]	France	2000–2009	SLE	637	1,593	2.5
Kiadaliri A et al.[18]	Switzerland	1998–2014	RA	369	1,512	4.1
Pinheiro F, et al.[24]	Brazil	1996–2010	RA	1,095	3,955	3.6
Sato EI, et al.[54]	Brazil	1987–2007	SLE	3,133	4,815	1.5
Santo AH, et al.[20]	Brazil	1985–2007	DM/PM	350	634	1.8

DM/PM: Dermatopolymyositis/polymyositis; RA: Rheumatoid arthritis; SAD: Systemic Autoimmune Disease; SjS: Sjögren's syndrome; SLE: Systemic lupus erythematosus; SSc: Systemic sclerosis

*The ratio between number of cases identified using multiple causes of death and the number of cases identified using the underlying cause of death indicates how many times the number of deaths somehow related to SADs study increased when using the multiple-causes-of-death method.

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Potential Heart Problems in Convalescent COVID-19 Children: Alert from a Cuban Study

Lisset Ley-Vega MD MS

COVID-19, the disease caused by the novel coronavirus SARS-CoV-2, is present in more than 200 countries and regions and is having a devastating impact worldwide. The sheer number of critical and convalescent patients—including pediatric patients—represents a challenge to the global medical community.

Although children with COVID-19 are often asymptomatic or exhibit only mild symptoms, they can transmit the disease and suffer from serious manifestations. In Cuba, 2932 patients ≤18 years old tested positive for COVID-19 between March 2020 and February 1, 2021. Most of these children presented few to no symptoms upon diagnosis. At the time of this writing, 82.8% of those children had recovered,[1] and there had not been a single pediatric death due to the novel coronavirus.

Nevertheless, the world has seen a significant uptick in pediatric infections linked to outbreaks following easing of restrictions designed to control transmission. Cuba is no exception: the island registered 1624 pediatric cases in a single post-holiday month (January 2021) after opening for visitors.[1]

Cuba's COVID-19 Prevention and Control Plan applies national, multidisciplinary and intersectoral protocols to all COVID-19 patients.[2] These define care for suspected, confirmed and convalescent cases, including in pediatric ages. The therapeutic and management protocols for Cubans ≤18 years old according to national case classifications (all medications are produced in Cuba) are contained in the box below.

Pediatric COVID-19 patients tend to evolve more favorably than adults. While individual immune response depends on virus exposure and other factors unique to each patient, a child's immune system differs from an adult's—specifically in the angiotensin-converting enzyme 2 (ACE2), the functional receptor for SARS-CoV-2 to enter into human cells. Children also have fewer comorbidities like hypertension, cardiovascular disease and diabetes mellitus than adults.[3]

One area of growing research interest is cardiovascular damage in children and adolescents recovering from COVID-19. Recent studies indicate that long-term cardiovascular complications from SARS-CoV-2 infection may include arrhythmias, myocarditis, pericarditis, shock, multisystem inflammatory syndrome (MIS) similar to Kawasaki disease, as well as stress-induced cardiomyopathy (Takotsubo syndrome) and sudden death.[3]

Viral infection can damage heart cells in both early and late stages of infection by inducing direct myocardial damage, hyper-inflammation and an immune response causing systemic inflammation and cytokine storm—especially Interleukin-6 that directly affects the QT interval. Other relevant factors may include: vasculitis, vascular microthrombosis, disseminated intravascular coagulation, hypoxia, electrolyte imbalances, myocardial ischemia and ACE2-deficiency disorder—as ACE2 protein expression occurs in various tissues, including heart and lung, with consequences for ion channel function.[4]

Preliminary studies demonstrate myocardial inflammation and injury (without serious symptoms) in recovering COVID-19 patients two months after diagnosis.[5] Although we know that COVID-19 affects both the respiratory system and cardiovascular function over time, the actual prevalence of persistent COVID-19 heart problems is unknown. Furthermore, cardiovascular damage linked to COVID-19 is likely underreported due to low autopsy rates and suspected multi-organ failure based on clinical and radiology exams rather than systematic use of electrocardiograms, echocardiograms, Holter monitors and other measurements. Cardiovascular damage may also go under-detected as a result of low symptomology and insufficient research about subacute (5–20 days after symptom onset), medium- and long-term sequelae of the disease.[4,5] Researchers need more time to study the long-term cardiovascular manifestations of COVID-19, especially in mild pediatric cases.

In 2020, Cuba launched a nationwide study coordinated by the National Genetics Center and carried out by the National

Case classification	Remitted to	Treatment
Contact of confirmed case	Isolation center	PrevengHo-Vir (homeopathic)
Suspected – mild symptoms	Hospital	Oseltamivir/Azithromycin; PrevengHo-Vir
Confirmed – PCR-positive, asymptomatic or mild symptoms w/o risk factors	Hospital	Interferon alfa-2b
Confirmed – PCR-positive, mild symptoms with risk factors	Hospital	Interferon alfa-2b; Lopinavir; Ritonavir
Confirmed – PCR-positive, moderate symptoms without risk factors	Hospital	Lopinavir; Ritonavir; Biomodulina T (immunomodulator)
Confirmed – PCR-positive, moderate symptoms with risk factors, or severe symptoms	Hospital	Steroids; anti-coagulatants; Jusvinza (CIGB 258), used only in those >10 years old
Critical	Hospital	Steroids; anti-coagulants; Jusvinza (CIGB 258); antibiotics (sepsis/septic shock); assisted ventilation as needed. Individualized, according to clinical status
Convalescent – PCR-negative for 14 days	Home	Comprehensive follow-up in local health area by primary healthcare teams

Researchers need more time to study the long-term cardiovascular manifestations of COVID-19, especially in mild pediatric cases

Genetics Network entitled, *Genetic risk factors associated with COVID-19 clinical severity in Cuban patients and their first-degree relatives.* Our study, *Clinical, epidemiological and cardiovascular factors in COVID-19 convalescent patients 18 years and under,* is part of this broader study and was conducted at the children's heart service of the José Luis Miranda Provincial Pediatric University Hospital (Santa Clara, Villa Clara Province).

We studied 110 COVID-19 convalescent patients ≤18 years old, during Cuba's first three epidemiological stages for the disease (March–June 2020; July–October 2020; and November 2020–February 2021). Using retrospective medical interviews to identify antecedents and collect other relevant disease data (symptoms, treatment, length of hospitalization and more), we found all the youngsters participating in the study were asymptomatic or had mild symptoms upon diagnosis. Additionally, they were in good nutritional health and as a group, had a low rate of chronic disease.

We began to actively identify cardiac issues among these convalescent patients using, among others, epidemiological and clinical criteria, electrocardiograms, echocardiograms and chest X-rays. We based our surveillance for cardiac anomalies on a clinical method evaluating mild symptoms that included fatigue after age-appropriate physical activity similar to post-COVID-19 infection asthenia (physical weakness or lack of energy); chest pain; and cardiac rhythm abnormalities. These were complemented by heart rate and blood pressure measurements.

We found cardiovascular abnormalities in 20 patients (18.1%) including myocarditis, pericarditis, arrhythmias and hypertension. These patients evolved satisfactorily following several weeks of monitoring and treatment, after which they received monthly follow-up.

Pediatric COVID-19 patients with heart abnormalities are treated according to national cardiology protocols established for children with congenital and acquired heart problems. This treatment is individualized for each child with or recovering from COVID-19 and approved by a multi-disciplinary team comprised of cardiologists, immunologists, pulmonologists, nephrologists, neurologists and psychiatrists. In our center we have used diuretics, vasodilators, non-steroidal anti-inflammatories (NSAIDs), beta-blockers and immunomodulators to treat pediatric cardiovascular patients, with good results.

Myocardial, pericardial, electrocardiographic and vascular abnormalities are potentially reversible in children recovering from COVID-19. In our opinion, standardizing early detection and timely treatment for these patients can improve their prognosis—however reserved. We continue actively searching for cardiovascular abnormalities in COVID-19 pediatric cases using the methodology described as part of our strategy to minimize the medium- and long-term impact of the pandemic and post-infection complications among children.

It is both urgent and imperative that we continue conducting research about SARS-CoV-2 throughout every stage of the disease, from transmission to recovery and beyond. We recommend cardiovascular studies specifically for convalescent children, based on current evidence and using the latest technology. A cardiology focus should be integrated into the support and follow-up for pediatric patients, monitoring closely for subclinical abnormalities and hidden comorbidities.

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Neuropsychological & Cognitive Sequelae in COVID-19 Patients

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A neuroinvasive respiratory coronavirus, SARS-CoV-2 causes a variety of neurological responses in patients. These include dizziness, headache, myalgias, hypogeusia, hyposmia, polyneuropathy, myositis, cerebrovascular disease, encephalitis and encephalopathy. Such susceptibility of the central nervous system (CNS) to the virus has spurred interest in neuropsychological research in COVID-19 patients and convalescents.

Earlier health crises provide evidence confirming the adverse effects of respiratory diseases on cognitive function. For example, some 15% of patients infected with Severe Acute Respiratory Syndrome (SARS) or Middle East Respiratory Syndrome (MERS) showed deficits in cognitive functions like memory and attention.[1]

Preliminary results from the current pandemic suggest that SARS-CoV-2 infection also negatively impacts neuropsychological function in COVID-19 convalescents.[2] Those processes shown to be adversely affected include sustained attention, memory, working memory, cognitive flexibility and verbal fluency.

People with neurodegenerative diseases are among the most vulnerable for developing cognitive disorders as a result of COVID-19 infection. These include patients with Huntington's disease, amyotrophic lateral sclerosis (ALS), Alzheimer's disease, multiple sclerosis and Parkinson's disease, who will require meticulous cognitive follow-up during COVID-19 convalescence.[3] Furthermore, early evidence suggests that patients who present with metabolic disturbances and test positive for COVID-19 could be at higher risk for cognitive decline and dementia later in life.[4]

Research is still lacking on how COVID-19 infection affects cognitive functioning

Despite these early findings, research is still lacking on how COVID-19 infection affects cognitive functioning. In our opinion, various factors contribute to the dearth of neuropsychological studies among convalescent patients. First and foremost, studies examining SARS-CoV-2 sequelae focus primarily on clinical variables, particularly respiratory and neurological ones—understandable given the gravity of the pandemic declared in 2020. And while the scope of COVID-19 research is expanding, much is still unknown about the disease's medium and long-term complications. Second, confinement measures designed to control transmission have multiplied the pressure on and demand for psychology and neuropsychology services, while making it more difficult to provide face-to-face neuropsychological diagnosis and rehabilitation. Finally, the multiplicity of variables related to COVID-19 that are also linked to cognitive function is another challenge for research. These variables include but are not limited to: disease progression; treatment protocols; patients' emotional response following a positive diagnosis and through convalescence; and physical and psychological complications.

In our work as neuropsychological researchers and clinicians, we measure cognitive function, but also examine variables—direct and indirect—and their effect on higher nervous activity. Increasingly, convalescent COVID-19 patients who access our services complain of deficits in memory, sustained attention and processing speed, among other problems. These patients worry about how these cognitive impairments affect their daily lives and come to us in search of treatment to help them manage these difficulties.

In our daily practice, we have seen that cases can vary widely, from patients with only mild symptoms to others who required mechanical ventilation; some who suffer from severe depression, while fatigue predominates in others; and in several instances, patients stated they have not experienced cognitive decline but clinical evaluation showed otherwise, revealing decreased mental performance in one or more cognitive domains. Given the differences in clinical history and disease progression, each convalescent patient will need meticulous follow-up and individualized neuropsychological treatment.

We cannot overstate the importance of collaboration between neuropsychology researchers and clinicians when attending COVID-19 patients. This type of collaboration is imperative and led us to develop criteria for transversal research taking into account the following variables:

1. Neurological manifestations in COVID-19 patients from diagnosis to hospital discharge, documenting duration and if they continue during convalescence, paying particular attention to neurological changes related to the CNS and peripheral nervous system (PNS);
2. Links between illness severity and level of cognitive impairment—preliminary research indicates that severe COVID-19 patients suffer more serious neurological symptoms and may experience greater neuropsychological changes as a result of infection;[5] and
3. Potential effects of COVID-19 treatment on neuropsychological functioning.

The link between emotional state and cognitive function is another, well-documented, variable that must be considered in future cross-sectional research—specifically manifestations of anxiety and depression. Special attention should be paid to older adults recovering from COVID-19 since depression is linked to significant cognitive decline and is a risk factor for dementia.

Longitudinal studies monitoring cognitive impairment in the short, medium and long term should also be prioritized, bearing in mind that neuropsychological dysfunction can last months or even years after recovery from COVID-19. Documenting the severity of cognitive deficits over time will facilitate design and implementation of appropriate neuropsychological interventions for these patients.

We also recommend conducting baseline studies that examine a minimum of five cognitive domains: attention, memory, executive functions, language and visuospatial functions. These should be monitored and measured using reliable, valid instruments that control for the learning effect. Patients should be evaluated every 3 to 6 months for a minimum of 18 months.

Finally, it's important that future research explore the impact cognitive decline has on daily life over time. Measuring how cognitive and non-cognitive variables affect quality of life, in real-world settings, can help provide ecological validity to these baseline studies. As a tool, we recommend the Post-COVID-19 Functional Status Scale (PCFS) to evaluate how dyspnea, fatigue, memory loss, anxiety, depression and other problems limit daily activities. [6] By measuring and understanding COVID-19 infection's impact on cognitive function, researchers can evaluate the effectiveness of pharmacological (primarily psychoactive drugs) and non-pharmacological (psychotherapy, neuropsychological rehabilitation) interventions for these patients.

In our opinion, thorough, comprehensive control and follow-up incorporating these variables is fundamental for facing the biggest challenge to cognitive health and well-being facing COVID-19 convalescents: neuropsychological rehabilitation.

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The Mysteries of 'Pandemic Time'

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If one thing has changed for everyone everywhere during the pandemic it's our perception of time. We know that besides the objective measures of time marked in seconds, minutes and hours on our watches and in days, months and years on our calendars—in reality, time is lived and felt subjectively and differently, depending on the moment and our experiences.

When these are 'good,' when we're enjoying ourselves, when we like what we're doing, we say time is flying. And when the experiences are bad, or we're feeling despondent, living through loss or anxiously awaiting news, then seconds can seem an eternity.

However, what is novel about the reality we've been living with COVID-19 is that people refer differently to changes in their perception of the passage of time—a 'pandemic time' full of paradoxes and contradictions. The coronavirus, with its peculiar capacity to disrupt all points of reference, makes time appear to go by swiftly and slowly at once. We live through a distorted sort of time that seems slow if taken day-by-day…paused, stalled. But if we look back, then we see time has vanished as if in an instant.

> **The coronavirus, with its peculiar capacity to disrupt all points of reference, makes time appear to go by swiftly and slowly at once**

Thus, people remember 2020 as the year we crossed off with a single pen stroke, the one we're still owed, that shouldn't even count for birthdays. But the pre-pandemic past is perceived as a far-away time that doesn't belong to us anymore, as if we went to sleep in one world and woke up in another.

There's a sensation of 'airplane mode' with an empty cache, without many new experiences accumulated or many new memories stored. Everything indicates that with the shrinking spaces in which we live and work, with so little social contact, time seems to psychologically disappear. As motivations dwindle and the days become more monotonous, for many people time seems to move slower still. Time and space have stepped outside logic and lost their bearings.

As we live through a time where one day resembles the next, the mind works to build memories, but conjures up few details. Carrying out multiple activities in the same place reduces the creation of these memories, since it is harder to attach them to different places or different people. Who hasn't experienced a lapse of memory in the last few months?

Trying to understand the mysteries involved in this new perception of time, I discover that people are living a contradiction: the pandemic gifted us more time for many things that we didn't do in the past, but this 'extra' isn't manifest in daily life. In fact, since there are more things to do than usual in the same amount of time, we perceive greater monotony borne of routines more poorly structured, which then feels like a scarcity of time, as our overloaded schedules run into one another. The day goes by in a perpetual present tense, accompanied by a sensation of strangeness and even at times, surreality.

At the risk of appearing redundant, the truth is that there is no other time than the one we are living in, and we have to learn to accept it as part of reality. It would be a grave error to ruin the present by remembering a past that now has no future. It's real: for us, there is a before and an after. But as Charlie Chaplin said: "Time is the best author. It always writes the perfect ending."

We still have to manage a high degree of uncertainty, especially when it comes to our free time and our social relationships. Time seems to go by waiting for a vaccine, a PCR or for isolation to end. As noted by Juan Carlos Volnovich, an Argentine colleague I admire: "We live in a present that is stuck, refusing to become a past."

So what to do with this disruptive time so that it doesn't disturb us so much?

It won't be enough to just get used to it, resigned, going along darning and mending as time slips by. Nor can we ignore the pandemic, reducing our risk perception: if up to now I haven't gotten sick, then I won't be getting sick, whatever will be will be. But manic euphoria won't help either, the kind that leads us to triumphalism, that the vaccine will solve it and we'll return to life as it was.

The appropriate phrase would be hopeful realism. Keep ourselves occupied, do things that motivate, since there is always time for what matters. Give in to the wisdom of uncertainty, knowing each day's pursuits are enough. Time will go by faster if we pay it less attention, if we dive into what we're doing and do things worth diving into. If we stop keeping score.

If we keep taking care of ourselves, taking care of everyone, then life will begin anew every day—the kind of days we live in now, in 'pandemic time'—monotonous, passing swiftly yet slowly. But this time can still be full of love, the sense that life is worth living. Days when, without realizing it, moments of pleasure can also be found in whatever way we engage: with our work, family, partners, learning, reading, music, or a commitment to the possibility of a better world. Only thus will the future surprise us with new promise.

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