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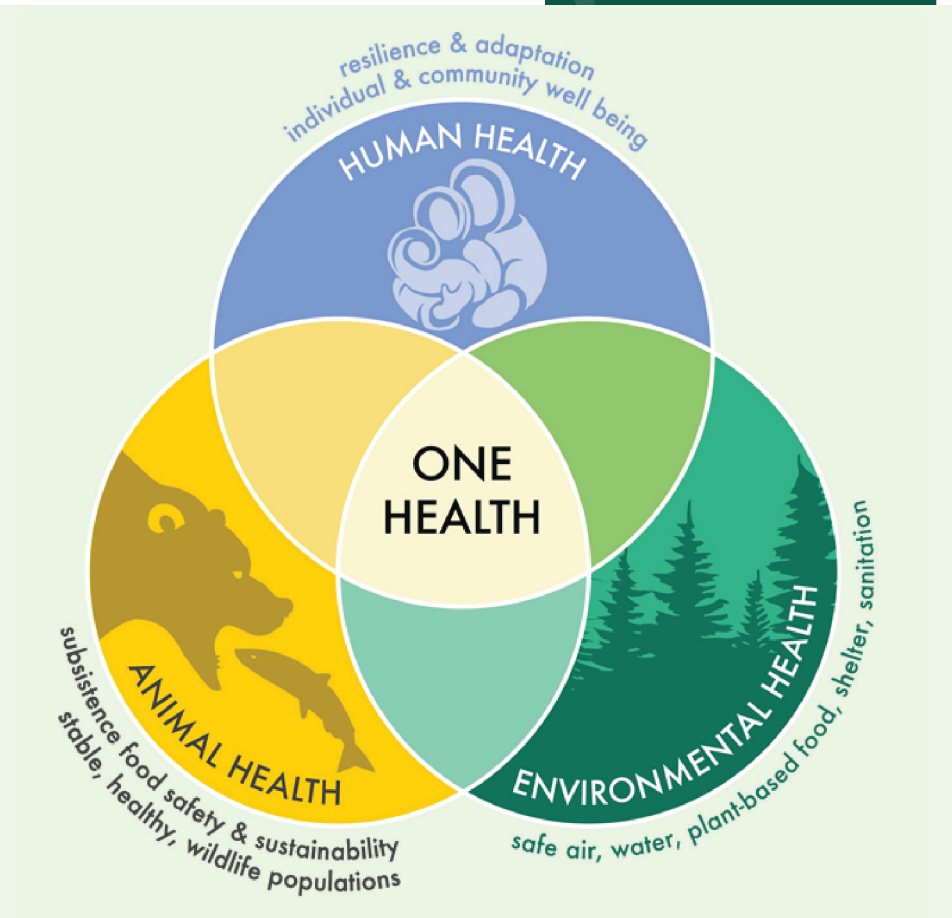
Editors' Choice



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MEDICC Review

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An Urgent Call to Make One Health Work for People and Our Planet

January 2020 begins a new decade, a chance for the international health community to take a hard look at where we are, where we stand, what we stand for and why we need to stand up. Staring us down are two concurrent global health emergencies: the coronavirus epidemic originating in Wuhan, China and climate change. As you read this, the trove of articles and assessments published on both is growing faster than most can absorb.

What does it all mean for us, as publicly engaged scientists? Like separate streams flowing into the more powerful ocean, several currents of thought and action are poised for the first time to mutually enhance their potential influence, for the sake of people and our planet. First is the well-established attention to social determinants of health matched by the multi-sector action-oriented 'health in all policies' approach, also reflected in the UN Agenda 2030 for Sustainable Development and its ambitious benchmarks.

Of note is that the 2030 Sustainable Development Goals (SDGs) were built on the underlying recognition that good health depends on integrated strategies; on cooperation not only between teams dedicated to different fields within health care and health promotion (mental health, maternal health, etc.), but between groups dedicated to causes integral to human health and wellbeing, such as the eradication and amelioration of poverty and the fight for climate justice.

This leads us to the second current: the public and scientific push to effectively address climate change, as the world hurtles along unsustainable, uneven and inequitable paths of consumption, emissions and economic/social development. More explicitly, nearly upon us are both the deadline for the 2030 SDGs and the point of no return for keeping global warming below the 2K target.[1]

The climate crisis is the game changer for One Health

The climate crisis is in fact the game changer for the third current: One Health, a concept that traditionally has viewed human health through the lens of veterinary medicine, focusing primarily on zoonoses and food-borne diseases, with environmental concern as a less-prominent element. However, we agree with Paul Gibbs who argues that (while) "in the first decade of the One Health era, the concept provided the initiative, coordination, and drive to control and prevent disease in animals and people; now in the second decade, One Health needs to recognise the broader issue of Planetary Health…" [2] That is, when viewed synergistically with the more recent notion of Planetary Health (see the new journal in *The Lancet* family), One Health simply brings it all together, providing new momentum for interdisciplinary research and action.

To contribute to this movement, we have decided to expand the journal's purview to include research and perspectives on health in all policies and One Health in particular. In so doing, we extend a ***MEDICC Review*** invitation to scientists and professionals who focus on climate change; the links between environment and health; food security and poverty; disaster mitigation; health impact of economic/social injustice, conflict and crisis; human migration and demography; equality in access to health and health care; and all related endeavors of research and action. As always, ***MEDICC Review*** remains dedicated to our mission of incorporating and elevating voices and research from the Global South, from Latin America and the Caribbean in particular; those for whom these issues have hit, and will continue to hit, the hardest.

> The One Health concept is a worldwide strategy for expanding interdisciplinary collaborations and communications in all aspects of health care for humans, animals and the environment.
> —**One Health Initiative**
> http://www.onehealthinitiative.com/about.php

Taking a look inside this issue: Much like the UN and climate researchers globally, WHO has agreed that 2020–2030 must be a "decade of action,"[3] and to that end has published a list of "urgent health challenges" for the next ten years.[4] Articles in this ***MEDICC Review*** tackle some of these.

Worldwide, access to WHO-defined "essential medicines"[5]—medications necessary for treating conditions and disorders that primarily affect the world's poor—remains inadequate. A full third of the world's population lacks access to many of them, and for patients in developing countries who do, medicines represent 50%–90% of their out-of-pocket spending on health care.[5]

Cuba's burgeoning biotech industry has played a key role in increasing access to both novel medicines and biosimilars for Cuban and other patients in the Global South[6] and is poised to do so for years to come. Yet, as Blanco-García's article in this issue points out, reframing of global biotech's financial underpinnings is bound to present new challenges for Cuban biotechnology, which has thus far operated much on its own terms.

Investing in health equity means identifying those populations who are often left out of the conversation and understanding them well enough to address their needs in ways that acknowledge the relation between social and physical aspects of human health. In this context, the transition from working life to retirement can be precarious, and Cuba has one of the most rapidly-aging populations in Latin America and the Caribbean.[7] Ponce-Laguardia's paper describes the design and development of a community-wide (soon to be region-wide) program to help individuals prepare for and navigate this major life transition, putting emphasis on their mental health, social inclusion and overall wellbeing.

This year, as part of its "decade of action", WHO will issue new guidelines for health care providers and policymakers entitled

Helping Adolescents Thrive. Among the issues addressed is the fact that teens worldwide are disproportionately affected by sexually-transmitted infections.[8] In this issue, we publish pioneering research that identifies the most prevalent HPV genotypes circulating among Cuban women. Guilarte-García and colleagues provide evidence supporting inclusion of an HPV vaccine into the public health system's national immunization program to help prevent cervical cancer, the fourth most frequent cancer and the fifth cause of cancer mortality in the female population.[9]

February 11 marks the International Day of Women and Girls in Science,[10] an excellent opportunity to draw attention to our regular column, *Cuba's Women of Science*. This time, we highlight the life and work of Dr Herminia Palenzuela, a founder of the Children's Heart Center at Havana's William Soler Pediatric University Hospital.

MEDICC Review also takes this opportunity to extend a warm welcome to Dr Caitlin Baird, a medical anthropologist and Mesoamericanist who has joined our team as Senior Editor, English Edition. Her experience, editorial skill and perspectives enrich us all.

And finally, we offer sincere gratitude to the scholars who provided peer reviews in 2019. Our work would not be possible without the generous donation of their time and effort.

We hope you will join us in tackling the challenges of the new decade—as readers, contributing authors, peer reviewers, in your letters to the editor, as interviewees, and as friends and colleagues. Decidedly, we are all in this together, and the "cost of doing nothing is one we cannot afford".[4]

The Editors

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Unilateral Optic Neuritis in Cuban Patients with a History of Arbovirus Infection

To the Editors:

Seven patients with clinical signs consistent with optic neuritis were diagnosed and treated in the neuro-ophthalmology service of the Hermanos Ameijeiras Clinical-Surgical Teaching Hospital in Havana, Cuba from August 6 through November 16, 2018. Clinically, optic neuritis should be distinguished from epidemic optic neuropathy, which occurred in Cuba in the 1990s, as described in a 2011 ***MEDICC Review*** article.[1]

Four of the patients were men, three women; and average age was 33 (23–44) years. All were from the western provinces of Havana and Matanzas, and three lived in the Ciénaga de Zapata area, a wetland ecosystem in southern Matanzas. Four patients reported signs and symptoms suggesting that they had recently suffered from arbovirus infection (dengue or chikungunya)[2] and one confirmed a dengue infection the previous month. All patients reported sudden, painless and unilateral vision loss one or two weeks after recovering from fever. The neuro-ophthalmological examination showed severe impairment of both visual acuity and color vision. Centrocecal scotoma was the most frequently observed campimetric defect.

All patients were hospitalized and given intravenous methylprednisolone and B-complex vitamins. Treatment was considered satisfactory if 15 days after completion patients presented improvement of at least two lines on the Snellen chart. We observed that treatment effectiveness depended largely on time elapsed between symptom onset, initial diagnosis and treatment initiation. Patients who received treatment during the first seven days of the condition's evolution recovered satisfactorily, but those who received treatment after this period did not.

We wish to alert family doctors, clinicians, ophthalmologists and epidemiologists of the circumstances that make these cases particularly interesting from a clinical-epidemiological perspective: that is, their relative spatial concentration as well as temporal concentration (noting that, historically, only one to two optic neuritis cases are usually treated in our service annually), and above all, the clinical history suggestive of arbovirus infection, whose relationship with the occurrence of parainfectious optic neuritis has been established.[3] The alert also includes the recommendation to begin treatment immediately for patients presenting with vision loss. It is noteworthy that in a similar time span (September–November 2019) we have received three new patients presenting with optic neuritis and a history of arbovirus infection, two of whom delayed seeking medical attention and whose vision loss is now irreversible, due to signs of partial optic atrophy.

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Research and Scientific Publishing: Essential Ingredients to Health Sciences Training

To the Editors:

A paper published in ***MEDICC Review*** by Ibraín Corrales-Reyes and colleagues concludes that Cuban health sciences universities' curricula should include subjects related to scientific writing and publishing as a way to inspire students to generate scientifically valuable research projects.[1] Diabetes, to which the authors make specific reference, is followed in Cuba at the primary care level, where ideally its behavior should be a source of information to update local physicians who have close ties with the communities where they work. As future actors in the global health arena, medical students should learn the necessary strategies and acquire the necessary motivation to in time develop a medical practice based on information obtained through their own experiences, which could also serve as reference points for other countries in the region and the world.

In the Dominican Republic, scientific research and publication are subjects scarcely addressed by most medical schools. Although the basic principles of research methodology are included in the medical curriculum, few students opt to pursue postgraduate studies in research or to collaborate in local research projects. As medical students, we believe that this is simply the result of inadequate training—dating back years—that considers scientific publication as a nearly unreachable goal, if not impossible altogether. In addition, we find professors who do little to foment critical analysis or to provide students with more modern, creative views of research itself.

Thus, we agree that any agenda for scientific development demands changes in health sciences curricula, in which research practice must be included, to usher in an era of "research, teaching and learning."[2] Scientific research should be incorporated into all Latin American health sciences curricula, to be taught by instructors capable of inspiring and motivating students to follow research paths in their respective professions. This could be accomplished in several ways: one might be to revamp already existing programs on research techniques and benefits; another might be to include workshops and seminars on scientific writing and publication.

Perhaps as an extreme alternative, publication of at least one scientific paper should be required for medical students to earn their degrees. These recommendations share the common objective of ensuring that universities prepare physicians in particular to carry out research on key aspects of population health.

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"Retirement, what?"
Herminia Palenzuela MD PhD
Coordinator, National Pediatric Cardiology Network
William Soler Children's Heart Center, Havana

Gail Reed MS

"Our family wasn't rich, but we didn't want for anything," says Dr Palenzuela by way of introduction. In 1950s Cuba, her father drove a taxi and her mother was a homemaker, raising two daughters—one now an economist and the other a top pediatric cardiologist. In many ways, Dr Palenzuela's career rode the wave of social change that swept Cuba beginning in 1959. Like many others, time and again she stepped up to the plate, and in 1986, she became a founder of one of the Cuban health system's premier institutions: the William Soler Children's Heart Center, a tertiary facility in Havana. There, to this day, she balances multiple responsibilities—as coordinator of the National Pediatric Cardiology Network, head of the Center's Quality Assurance Program and lead professor of the annual National Certificate Course in Pediatric Cardiology. ***MEDICC Review*** spoke with her between phone calls, meetings and patient consults.

MEDICC Review: **Let's start with the early 1960s, a fast-paced time in Cuba. How old were you then?**

Herminia Palenzuela: I was 12 in 1959, enrolled in a Catholic secondary school, the tuition covered by an uncle. Two years later, I went on to high school and also joined the national literacy campaign. Teens like me were volunteering to head across the country, especially to rural areas, to teach people to read and write. But my dad wouldn't have any of it: "You're going *where*? To do *what*?." I was determined to participate but wasn't ready to cross him by running away. So I ended up teaching some of my own neighbors who were illiterate, five altogether.

MEDICC Review: **Growing up, did you have any female role models?**

Herminia Palenzuela: No, none. In one sense, my role models were mainly negative since there were no professional women in my family back then. What led me to medicine was the call the government made for more young people to become doctors. We had only about 6000 physicians for the whole country to begin with, and then half of them migrated after the revolution, mainly to the United States.

Since I really hadn't decided what I wanted to do, I took a chance and signed up for the 15-month pre-med course. After that, I was all in and with good grades, I went on to medical school and graduated at 22. Today, not too many graduate at that age!

MEDICC Review: **And then you went into pediatrics.**

Herminia Palenzuela: Yes, I did my residency at a Havana pediatric hospital and then went on to do postgraduate work in eastern Cuba in the small rural town of Banes, now in Holguín Province. My husband (also a recent graduate) and I went for two years, which turned into four because of the tremendous need for doctors there. We were still facing a lot of childhood malnutrition and parasites, and ramping up the national vaccination program.

After Banes, where my mother-in-law helped us at home with—by then—our two children, we spent another seven years on the Isle of Youth, south of the main island. As its name implies, the Isle was full of young people—thousands of Cubans and also foreigners, mainly Africans, who were on scholarship in boarding schools there.

MEDICC Review: **From those early years, are there children, parents, faces . . . that you particularly recall?**

Herminia Palenzuela: I remember most the children who died, not the ones we were able to save. They and their families stay with me, like the little boy who died of meningitis . . . like others. I'm forever

grateful for the children we successfully treated, who survived, but they aren't the ones I think of most.

MEDICC Review: **For over 35 years, you've dedicated yourself to pediatric cardiology. How did you decide on that specialty?**

Herminia Palenzuela: (*laughing*) I decided, like I did almost everything else: because it was needed at the time and there was a place for me. In the effort to reduce Cuba's infant mortality, it had become clear that congenital malformations were playing an outsized role in infant deaths—about 3 per 1000 live births for congenital cardiopathies in the early 1980s.

At the time, such infants and children had nowhere to go in Cuba for treatment. So, in 1983, the government decided to establish the Children's Heart Center at Havana's William Soler Pediatric Hospital and with it, the National Pediatric Cardiology Network. The first would become a tertiary care, research and teaching institute, and the Network would offer us an organized way to locate, treat and follow our patients throughout the country.

As a founder of the Center, I joined other specialists in a year of preparatory training in Prague, (then) Czechoslovakia prior to the Center's opening. Later, I also trained in Britain and France.

MEDICC Review: **If we fast forward, what would you say are the Center's main results?**

Herminia Palenzuela: We have managed to reduce the part congenital cardiopathies play in infant mortality from 3 per 1000 live births to less than 0.5 per 1000 live births today. We carry out some 120 to 150 interventionist catheterizations and 250 to 300 surgeries per year, including open-heart or cardiopulmonary bypass. Our surgical survival rate has increased to 91% in 2019, despite the fact that there are more newborns as a share of the total, younger patients in general, and the reality that they come to us with more complicated pathologies.

One thing that has helped greatly is our ability to use the National Network to detect abnormalities during pregnancy, so we are aware what the baby may need even before birth.

MEDICC Review: **Nevertheless, this must be a scary time for parents and families. How do you approach them?**

Herminia Palenzuela: We've always been very transparent, very direct with parents. We explain each procedure's risks and benefits, reviewing in detail chances for survival, recovery and for living a normal or close-to-normal life. Especially in the early years, more parents were afraid of the surgeries. But as we gained a reputation and as parents' educational levels also increased over time, fewer of them would simply say, "Well, we have our child for as long as he/she lasts . . ." Now, they ask more informed questions, often researching the problem on internet. The key is that they are always the ones who make the decisions, and so we do our best to make sure they have the information they need.

MEDICC Review: **You coordinate the National Pediatric Cardiology Network.**

Herminia Palenzuela: Ah, yes. That's my pride and joy. In each of the country's 15 provinces, we have a team headed by a pediatric cardiologist who has received training here at our Center. He or she is joined by other specialists and together they link with provincial and municipal hospitals that, in turn, link to community polyclinic pediatricians and neighborhood family doctors.

Through the Network, we screen for and identify cardiopathies before birth, decide treatment options with specialists and parents, and assure followup for life. Truly, we have patients who are now 20, 30 and 40 years old! The Network also allows us to provide postgraduate training in pediatric cardiology throughout the country, constantly updating professionals and involving newly minted specialists.

MEDICC Review: **I know that the Children's Heart Center, like all health care in Cuba, faced particularly difficult challenges during the economic crisis of the nineties, known as the Special Period. What were some of the toughest and which ones persist today?**

Herminia Palenzuela: It was a terrible time, and when I look back, I think the Center was kept open by the sheer will of our leadership and our professionals. One thing that made it especially problematic, and does so today, is the tightening of US sanctions on Cuba starting in 1992. There were and are medications very specific to these patients that remain under US patent, and others whose manufacturers have been absorbed by US companies. While supposedly licenses can be obtained by these firms to sell to Cuba, most have been unwilling to even apply or are apparently afraid to do so. As a result for example, medications such as prostaglandin E (used to keep 'blue babies' arteries open before surgery) became very difficult to obtain at one point, and supplies were severely limited.

And that doesn't take into account the broader effects of what we call the US blockade: the fact that US-patented drugs and equipment purchased through intermediaries come at a higher price and are sent from further away and thus sometimes delayed.

As we emerged from the worst of the Special Period, early in the new millennium we decided to take a national census to see how many patients had accumulated during the most resource-scarce period . . . and to see which cases were by then the most urgent. During the Special Period, with the tightening of US sanctions, children became victims, and certainly some died as a result, despite all our efforts.

MEDICC Review: **Turning to women in your profession, what is the status of women in pediatric cardiology today?**

Herminia Palenzuela: A significant portion of our specialists on the clinical side are women, perhaps even most. But this isn't true on the surgical side, where men still prevail. I really don't have an explanation for why this is so, especially since the doors are open to women and in fact, right now women are the majority of physicians. So, it's a good question, worth looking into.

MEDICC Review: **After so many years of constant activity, any thoughts of retirement?**

Herminia Palenzuela: Retirement, what? No, none at all, even though I'm 73. We now have a good pipeline of younger leaders here at the Center, so this doesn't worry me. As a consulting professor, I teach, continue my research on pulmonary hypertension and I weigh in on the most complex cases. This keeps me hopping. But I also have a flexible schedule that suits me. So, as long as I'm in good health, I'll be right here for some time to come.

Role of Business Models in Funding the Biotech Industry: Global Trends and Challenges for Cuban Biotechnology

Einard Blanco-García MS

ABSTRACT

Forty-three years after it was founded, with billions of dollars invested, the global biotech industry is still not positioned as a mature low-risk sector for the international investor community. Despite the clear commercial success of a number of leading companies and overall growth of the industry's revenues, most biotech companies are not profitable and many fail to overcome the formidable barrier constituted by the high cost of the sector's research and development. However, over the last four years, visible signs of change have appeared, which could be harbingers of an approaching turning point in this trend.

This article analyzes the historic background of the biotech industry's business models and corporate structures, as well as their impact on the industry's financial framework. It examines recent changes implemented by the sector's main actors—including young startups, venture capital funds and big pharma companies—to mitigate financial risk associated with development of new biotechnology products.

Finally, it discusses the challenges and opportunities that these tendencies entail for Cuban biotechnology development and proposes adoption of business policies more tolerant of the financial risk inherent in this sector, as a condition for attracting venture capital.

KEYWORDS Biotechnology, fund raising, risk management, entrepreneurship, Cuba

INTRODUCTION

With global sales of US$188 billion in 2017 and 316 commercially licensed products in the United States and Europe by mid-2018, biotechnology is one of the world's fastest growing industries today.[1]

The biotech industry has had a significant impact on biomedical sciences innovation, diagnosis and treatment of chronic noncommunicable diseases, evolution of government health policies, and the risk-management model for financial operations in capital markets.[2]

Despite this progress, the biopharmaceutical industry still shows signs of organizational immaturity, hampering its definitive economic takeoff. Indications of this sluggish trajectory are the high indices of uncertainty and financial volatility compared to more established sectors (such as the pharmaceutical industry itself).[3] Over the last four years, however, significant changes have been emerging in the corporate architecture and business models in which the industry's key actors operate, making it possible to envision a path toward higher performance levels.

This article examines the basic determinants of these changes and discusses the challenges and opportunities they present for development of Cuba's biotech industry.

The global biotech boom: science as business According to Pisano,[4] the concept of science as business arose in 1976 when young, up-and-coming investor Robert Swanson joined University of California professor Herbert Boyer to found Genentech, the world's first biotech firm. Pisano posed that, in addition to demonstrating that recombinant DNA could be applied successfully to industrial-scale *in-vitro* production of human proteins for use as medicines, Genentech created a model to monetize intellectual property that enabled expansion of the biotech industry's potentialities, situating it by the late 1990s as one of the world's fastest-growing economic sectors.

IMPORTANCE This paper presents an overview of the evolution of the biotech industry's financial framework. It also proposes strategic guidelines to reformulate Cuban research and development (R&D) programs in the sector to minimize risk and facilitate access to sources of capital.

Pisano posited that this new model was based on three interrelated pillars:

- technology transfer from universities to the private sector, creating new firms instead of licensing technologies to traditional pharmaceutical companies;
- access to capital markets (public or private) to finance the technology's initial development phases, mainly clinical research, and to compensate incubator company founders for the initial risk they assumed; and
- a know-how market in which, once clinical efficacy was demonstrated, young firms license or sell their intellectual property to established pharmaceutical firms in exchange for additional financing to once again enable reimbursement for founders and venture capital investors.[4]

The model's structure was largely based on the Silicon Valley paradigm, which had worked so well to commercially channel the burgeoning innovative wave of the informatics/communications sector (software, computers, semiconductors, cellphones, Internet, online services, etc.).

Prior to founding Genentech, science and business operated in separate spheres of influence. Basic medical sciences were the exclusive pursuit of universities and research centers, while pharmaceutical companies invested only in incremental improve-

ments in the innovations acquired from those institutions. In 1978, Genentech licensed the rights to manufacture and market recombinant insulin to the company Eli Lilly. Under the agreement, Eli Lilly would finance product development and pay Genentech royalties on sales.[5] This was the first time a big pharma transnational acquired technology protected as intellectual property of another for-profit company.

Genentech's successful public offering in 1980 also showed for the first time that a company with no products in the market, no income and no earnings was capable of attracting investment capital based on expectation of future growth. This was the start of the market's recognition of the potential of intangible assets (patents and know-how) to generate future earnings in the legal context provided by guarantees of commercial exclusivity for patent-protected products. This success fostered the market's perception that biotechnology was capable of converting science into business.

In the 1980s and 1990s, the biotech sector appeared to offer a solution to the scientific productivity crisis suffered by the large transnational pharmaceutical companies. In the late 1990s, big pharma tried in vain to recuperate from the financial imbalance caused by income lost from blockbuster products (often products with annual sales in the billions of dollars) due to patent expiration and new products entering the market sustained by increased R&D spending.[2] Biotech firms offered presumed advantage in new product development, given their smaller size and greater scientific specializations, as compared to the significant bureaucracy and vertical structuring inherent to big pharma.

Inspired by Genentech's success, pharmaceutical firms enthusiastically invested in biotechnology, facilitating emergence of firms such as Amgen, Biogen, Cetus, Chiron, Genzyme and Idec.[2]

Perception of superior scientific productivity expected from the biotech sector, compared with that of the pharmaceutical industry, was reinforced by the significant advances in genomics, proteomics and combinatorial chemistry starting in the 1990s, predictors of greater efficacy in candidate products' development and selection. Finally, the indisputable commercial success of hormone replacement therapies (insulin, human growth hormone, coagulation factors and erythropoietin)[2] appeared to validate the idea that biotechnology would increase R&D projects' probability of success with less risk to investors, and that these elements together would unleash the industry's economic potential.

Once biotech's "paradigm of promise" was introduced, it appeared that funding sources would not pose a problem. It may be useful at this point to review the financing mechanisms for biotech's intensive R&D spending.

The industry's financial engine and death valley Emergence of biotech firms as centers for innovative product development, outside of universities, limited access to government funding. Young prototypical entrepreneurs were forced to seek alternative sources in the capital market, laying the groundwork for a new paradigm in which venture capital investors covered the growing financial needs of product clinical development.[6] Figure 1 summarizes biotech's capital sources according to each R&D project's development stage in the product portfolio.

These funds invest in biotech firms with promising R&D projects (already demonstrated in initial trials) whose significant innovations could make a big splash in the market. In exchange, investors participate as shareholders in the firms, with the expectation of increased stock values, permitting subsequent sales of their shares at higher prices. In 2014, Ford and Nelsen[7] identified the following main sources of biotech capital:

- *Family and friends*: Typically, these include members of the founding entrepreneurs' inner circle. They provide seed capital to establish incubator companies. They do not seek to generate profits, but rather are motivated simply by the desire to help a relative or friend starting up a new high-risk business venture. Usually, these investments are only in the tens of thousands of US dollars.

- *Angels:* Angel investors and super-angel investors invest in companies in very early product development stages, usually in the preclinical research phase. Since this is a highly risky stage, appearance of a fund interested in investing is perceived as a gift from heaven, hence the name "angel." Angels may invest hundreds of thousands of dollars, but they decide their investments based on considerable scientific and business acumen, in addition to connections that enable them to contribute more to the target company's growth than the precise amount invested. Many are successful entrepreneurs themselves with experience funding other incubators.

- *Foundations and patient groups:* These nonprofit organizations that promote advances in the fight against specific diseases, commonly invest in early development phases. Accessing these funds requires a clear connection between the organization's area of interest and the innovation promoted by the incubator.

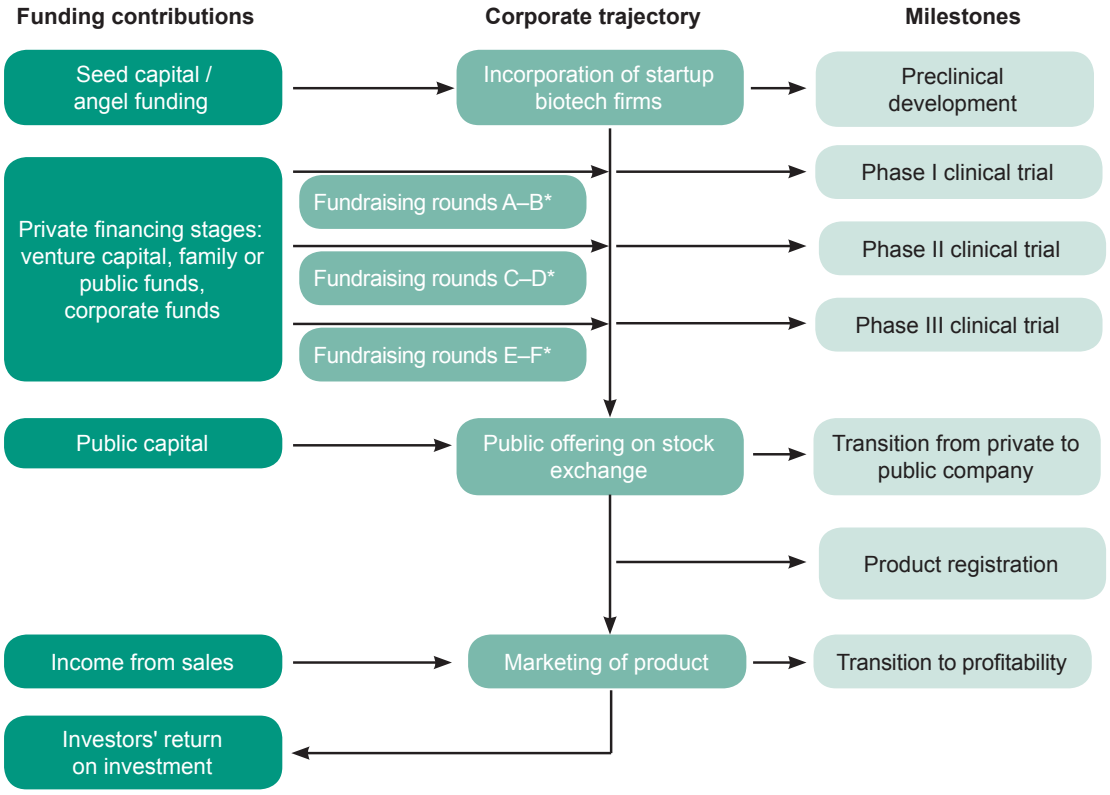
- *Venture capitalists:* These companies specialize in financial management of funds from different sources (personal, business, banks, pensions, etc.). They may invest in a wide range of economic sectors to diversify risk, but some specialize in biotechnology. They invest in startup companies in early development phases when stock market indicators are favorable. They move investments toward later-stage companies (with less risk) in times of financial crisis. They invest tens of millions of dollars per company.

- *Federal government agencies:* These include a wide range of agencies that foster public policies through investment in development programs (local, national and international).

- *Family funds:* These are companies that manage funds of wealthy individuals and families, usually including contributions of US$100 million or more per member. They invest in all stages of a biotech firm's development.

- *Corporate venture capital:* These are investment funds created by pharma giants mainly since the late 1990s. They emerged after the wave of patent expirations resulting in a crisis of low scientific productivity that intensified in the early 2000s. The new investments enabled big pharma companies to extend their options of control over young biotech firms' portfolios of innovative products, thus avoiding costs associated with expansion of their own R&D programs and the corresponding burden of their internal bureaucracies.

Figure 1: Sources of capital for biotechnology, by R&D project development phase



*A–B: fundraising rounds for Phase I clinical trials; C–D: fundraising rounds for Phase II clinical trials; E–F: fundraising rounds for Phase III clinical trials

Biotech firms' bold approach to securing alternative funding sources, as occurred in Silicon Valley, enabled several to take off, including Amgen, Genentech (now part of Roche), Biogen and Genzyme (now part of Sanofi). They now have several products with sales above US$1 billion and can afford the luxury of financing their own growing R&D project portfolio.[2]

Just over 40 years after the biotech industry's founding, however, only a small fraction of its companies have become profitable and as a whole the sector operates with negative profitability indicators.[1] Moreover, globally, about 50% of biotech companies operate with liquidity levels sufficient for less than two years of survival.[8]

In its first 20 years, the biotech sector appeared to successfully apply the Silicon Valley model for attracting funding sources to bring its innovations to market. Unlike the information and communications technology (ICT) sector, however, with its 2- to 3-year development cycles, the biotech product cycle is 10 to 12 years and—according to various sources—requires investments that range from almost US$650 million to US$1.8 billion.[9,10] The lion's share of these considerable development expenses is explained by the high cost of conducting clinical trials required to prove product efficacy and safety for human use.

In addition, government regulatory agencies continually tighten the requirements for approving registrations and conducting clinical trials, further boosting costs. The high cost of clinical development has created an insurmountable hurdle for the majority of biotech companies. They must often sacrifice potential candidates from their project portfolio due to the difficulty of financing them. A leading project's failure to demonstrate clinical efficacy and/or safety can send a business into bankruptcy. Both the highest costs and the highest probability of failure are concentrated in this product development phase, when substantial resources and time have already been invested in the project. This phase is referred to as "death valley." So then, what factors determine profitability in biotechnology?

Innovation and uncertainty: financial risk in development of biotech products Venture capital investors usually operate with a three- to four-year timeline from initial investment to return of capital with earnings. In the case of clinical development, the more extended timeline does not allow for balancing investors' interest in short-term profits with biotech companies' goal of getting their products to the marketing phase, especially when the financial costs are so high and the likelihood of success so uncertain.

Two of the most rigorous recent studies[11,12] estimated that less than one in ten products manage to pass all phases of clinical development and to reach market (9.6% and 6.9% in the studies). The greatest likelihood of failure occurs in Phase II clinical trials: approximately one in three products succumbs in this stage (30.7% and 38.2%, according to the studies) when products must first prove their efficacy in humans (Phase I trials demonstrate product safety, while Phase III confirm safety/efficacy in a larger population).

Despite the scientific and technological advances made in biotechnology, data confirm that lingering uncertainties hinder the capacity to predict a product's success in its interaction with complex biological systems. The primary challenge lies in designing diagnostic and classification systems that can better identify patients who can potentially benefit from a given treatment (as occurs in personalized medicine).

The additional risk factor associated with the greater volatility of investing in biotechnology as compared to other sectors[3] has propelled venture capital funding toward greater specialization in selecting assets in which to invest and greater diversification of investments as a way to compensate for po-

tential failures. Fortunately, the capital market's perception of biotechnology's potential to generate high rates of return on investments remains high, especially for the most specialized investors.[13]

Assessing 40 years of biotechnology development: the risk does not justify the investment A study of economic performance of all publicly traded biotech companies (627) in 2017 concluded that these companies generated revenues of US$160.6 billion (85% of total sales in the sector) and R&D spending of US$49.3 billion (30.7% of total income). These figures confirm the aforementioned intensity of R&D spending.[13] However, the top 30 companies account for more than 80% of revenues (US$134 billion), illustrating the high concentration of earnings in the industry. By the close of 2017, these 30 companies employed over 145,000 workers worldwide, more than the 101,000 workers employed by the remaining (public) biotech firms.[13] Compilation of data from all public companies (large and small) confirms that the sector operated with a negative rate of return during 2017 (total loss of almost US$ 2.7 billion).[13] As reported by *Nature Biotechnology*, globally the industry did not turn a profit until 2018, with a total net revenue of US$345 million.[14]

These data reinforce the hypothesis set forth by Pisano in 2006[4] on the flawed structure of the industry. According to Pisano, the prevailing organizational structure has constrained it and prevented biotech from untying the Gordian knots keeping it from maturing as an industry:

- *High risk*: As an industry, biotechnology operates under high levels of inherent risk, due to the deep and systematic uncertainty rooted in the limited knowledge of human biological processes and systems.
- *Poor integration*: A medication's development process cannot be broken down into its components; the disciplines involved must coordinate and work closely together. The structure of small and highly specialized incubator companies presents an obstacle to this principle.
- *Limited learning*: A good portion of the knowledge generated by the disciplines involved in the biotech sector is implicit and intuitive, which complicates the necessary task of coordinating collective learning.

Pisano argues that for most industries' R&D, basic technological feasibility is not a problem, since efforts and resources are invested in developing primary concepts of known technical feasibility. Industrial designers, for example, can address engineering problems concerning car parts, confident that the car will run when the process is complete. In biotechnology, however, the industry faces an added challenge: to attain confidence involves a long and uncertain trial-and-error process in which instinct and individual experience continue to carry considerable weight.

Will it be possible, then, to tip the balance toward greater certainty in the development of this burgeoning but risky industry?

New emerging model: mitigating the risk In the three-year period from 2015 to 2018, biotechnology took a major leap forward in its capacity to attract venture capital. For the first time in its history, overall venture capital investments in 2015 surpassed the barrier of US$6 billion, reaching over US$10 billion, and not falling below US$8 billion in more recent years.[15]

Although fluctuations in capital markets are the rule and not the exception, the shift in the industry's capacity to convert science into business does not appear to be circumstantial. There is evidence of improved interactions between key stakeholders in the industry's value chain that may offer responses to the contradictions outlined by Pisano.[4] These indications are summarized as follows:

The biotech company Progress in the field of personalized medicine has helped optimize the patient selection process for new therapies,[16] resulting in increased benefits exhibited by these products in early clinical phases, thus reducing time, development costs and risk to investors. For 20 years, from 1995 to 2014, the number of biological products in the USA and Europe (registered in average 5-year periods) hovered around 54 to 60. In the 3.5 years from January 2015 to July 2018, 112 new biological products were registered.[1] True, this period coincided with the emergence of biosimilars, which increased the number of registrations by 59% compared to the previous 5-year period (2010–2014), but novel products saw similar growth (52%). Examples of this new reality include the drugs Keytruda, Opdivo, Kymriah and Yescarta (all approved by the FDA and EMA with Phase II clinical results). The first two, registered in 2017, achieved global sales the same year of US$3.8 billion and US$.79 billion, respectively.[1]

An analysis of all drugs registered between 2006 and 2015 illustrates the importance of appropriate patient selection, based on personalized medicine research, to mitigate the risk of failures in clinical development.[11] Data show that from the preclinical research stage, use of biomarkers during clinical development can triple the likelihood of a product's entry into the market (from 8.4% to 25%).[11] Recent advances in big data management and artificial intelligence can further reinforce this trend.

Venture capital funds In 2013, nine of the ten companies that raised the most capital in their initial public offerings had products in Phase III clinical trials already on the market. In 2017, six of the first ten had products in Phase I or Phase II.[15] In stark contrast with the past, these figures show the market's perception of the increasing value of companies with portfolios of innovative, early-stage development projects. They also reveal a capacity to ensure attractive returns for shareholders.

Greater investor interest in exploring businesses in early development stages is proof of the growing maturity of investment funds, which now often have executives from the biotech sector who have deeper scientific knowledge and are more capable of evaluating investment risks.

Several of these funds (including Third Rock Ventures, ARCH Venture Partners, Flagship Pioneering and Fidelity Biosciences) have abandoned the traditional pattern of investing in preexisting incubator companies, deciding instead to launch their own, relying on meticulous and exhaustive selection of their intellectual property assets, management teams and business plans.[15] With these steps, the funds have been able to accumulate a significant number of success stories, in which they have been

able to sell the companies at exorbitant prices after increasing their value with partial clinical advances. Examples include Denali Therapeutics, Jounce Therapeutics, Delinia Pharmaceuticals and Kite Pharma. In August 2018, Kite Pharma was sold to Gilead for US$11.9 billion after having absorbed repeated investments from various venture capital funds.[13]

Big pharma companies have learned from their bureaucratic limitations in order to coordinate disruptive development programs and have fine-tuned their business models for a more effective approach to biotech firms. To this end, they have set up corporate venture capital funds from which they invest in innovative biotech companies of interest given the complementarity of their intellectual property assets.[17] All in all, they have managed to nurture and coordinate a decentralized, agile development program outside the influence of internal vertical structures.

Three of these funds were established from 1970 to 2000 (Johnson & Johnson, Glaxo SmithKline, and Novartis),[17] but many more began to spring up in the new millennium. Through 2011 another nine were founded (by Astra Zeneca, Roche, Pfizer, Novartis, Boehringer Ingelheim, Merck, and three by Eli Lilly), with US$100 to 500 million invested in each case.[17]

Another resource successfully explored by big pharma is the creation of what is known as quasi-public institutions, which involves pharma industry acquisition of the majority of public shares (listed on a stock exchange) of successful medium- to large-sized biotech firms with several profitable products on the market. In this way, a pharmaceutical giant can control the most important companies in the emerging biotech sector without purchasing them outright or constraining their autonomy, therefore preserving their robust scientific productivity. One example is Genentech-Roche, where Genentech's corporate independence has survived the purchase of all its shares by Roche.[18]

Resilience, adaptation and change: challenges and opportunities for Cuba's biotechnology sector While the current context for the industry's global development poses challenges for the future of biotechnology in Cuba, it also provides opportunities, given the strengths demonstrated by this sector in the country.

Cuba's biotech industry was launched in 1981, just a few years after the first biotech company in the USA (Genentech, 1976). From the start, the fledgling industry has enjoyed strong financial support from government, which bet on the rigor and audacity of its innovation, as well as its ability to contribute to population health in Cuba. The sector is characterized by early dedication to completing the product development cycle, taking a product from laboratory to market, thus converting science into business while responding to health problems through prompt introduction of results in the country's national health service.

All this fostered the relatively rapid advance toward overall profitability of Cuba's biotech system as a set of companies, generating exports and positively impacting various health indicators in the country. Today, a total of 34 research/production/marketing facilities employing more than 20,000 workers are brought together under the BioCubaFarma holding company. More than 700 products have been registered in Cuba and abroad, exports are sold to 49 countries, and more than 400 products are in various stages of the R&D pipeline. Chronic as well as infectious diseases are targeted for novel product development as well as biosimilars for domestic use.[19]

Another of Cuban biotech's strengths continues to be integration with the country's universities, public health system and informatics/telecommunications industries, which can accelerate early development of R&D programs and reduce costs. At the same time, Cuban firms have experience interacting with pharmaceutical companies and entering into intellectual property licensing agreements abroad.

Yet, challenges abound, beginning with the external context, involving changes identified earlier in the financing arrangements for the industry globally, as well as in the particular context faced by Cuba's biotechnology and economy at this juncture.

For example, from 2005 to 2015, the country's biotech export capacity was reinforced through complementary economic agreements between Cuba and various Latin American governments.[20] However, regional changes in recent years have undermined the industry's self-financing capacity, and Latin America's unstable political context has had a negative impact on the natural market for Cuban biotech products. This has been exacerbated by the US administration's escalation of economic sanctions and hostilities towards Cuba, aimed at torpedoing investment, trade and financial operations.[21] Cuba's minimal economic growth during the period has shifted government financial priorities toward shorter-term investments such as real estate and tourism.

Further complicating this situation is the proliferation of barriers to development and registration of new products due to growing data requirements for regional regulatory filing.[22,23] Altogether these factors make it essential for the Cuban biotech sector to adapt to the new environment: engaging alternative financing sources for innovation, and new product development is of strategic importance for the sector's future.

To accomplish this, a number of steps must be taken. One is for Cuban biotechnology to redesign its R&D programs to mitigate risk and facilitate access to funding sources. This means it should set priorities in its projects portfolio, sacrificing some projects to reserve funds for those most likely to succeed, and should also hold off on negotiations until more advanced stages when products have gained greater value.

These changes will require new policies that favor the ability to rapidly identify and seize marketplace opportunities, which will both attract capital and stimulate innovation within the high-tech sector, in addition to allowing more freedom in assuming risk to compete in the international marketplace. After all, the best way to mitigate risk is not to avoid it at all costs, but to try to understand and navigate it as intelligently as possible. Recently, new business models are being explored that should allow more dynamic access to foreign capital for developing innovative biotech projects and achieving their insertion in more competitive markets.

Historically, several Cuban biotech companies have been able to move toward profitability based on exports to the Global South.[20] While income is insufficient to finance clinical development of their products in high-income countries, the operational profitability in the South can offer the financial guarantees necessary to attract venture capital.

The new context requires adopting flexible business models and adapting the industry's discourse to attract new interest from venture capital funds, since these usually invest in companies rather than projects or technologies.[24]

One example demonstrates the feasibility of attracting such capital for Cuba's intangible biotech assets. In October, 2018, the US company Equillium earned US$65 million in revenues when it offered a portion of its shares for sale on Nasdaq. At that time, Equillium had a single intangible asset: marketing rights in the USA and Canada for Itolizumab, developed and patented by Cuba's Molecular Immunology Center (CIM) and sublicensed to Equillium by Biocon, CIM's Indian licensee.[25]

Indirect investment, including venture capital, could be transformed into direct investment in Cuban biotech companies if a more flexible and less risk-averse legal framework were put in place for the sector, reflecting policies aimed at longer-term profitability. All of these changes are necessary to foster a successful and sustainable future for Cuban biotechnology, building upon nearly 40 years of experience, intellectual capacity, business acumen and scientific innovation.

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Circulation of Human Papillomavirus and *Chlamydia trachomatis* in Cuban Women

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ABSTRACT

INTRODUCTION Human papillomaviruses and *Chlamydia trachomatis* are the most frequent causes of sexually transmitted infections. Although the association between some human papillomavirus genotypes and cervical cancer has been demonstrated and *Chlamydia trachomatis* infection is the most common cause of female infertility, Cuba has no national baseline studies on the circulation and co-circulation of these agents, the synergistic effect of which may be a risk factor for occurrence and development of precancerous cervical lesions. Additionally, few local studies have examined risk factors for infection.

OBJECTIVE Determine the frequency of infection by human papillomavirus and *Chlamydia trachomatis* and their association with sociodemographic, clinical and epidemiological variables in women seeking routine Pap smears or other medical services at the primary care level in Cuba.

METHODS A cross-sectional study was conducted among 500 women aged 16–67 years (100 from Havana, 200 from Villa Clara and 200 from Holguín Provinces, Cuba), from August through December 2015. *Chlamydia trachomatis* infection was detected by real-time polymerase chain reaction and 35 genotypes of human papillomavirus by low-density microarray. We then examined the association of infection with sociodemographic, clinical and epidemiological variables.

RESULTS Human papillomavirus was detected in 14.8% (74/500) of the women. Of the 29 genotypes identified, 79.7% (59/74) were oncogenic high-risk types. Type 16 was the most frequently identified (23%; 17/74), followed by type 31 (10.8%; 8/74) and then by types 33, 53, 61 and 66 in equal proportions (8.1%; 6/74). Infection frequency was greater in women aged ≤25 years (38.8%; 31/80), students (46.7% 7/15), single women (23.0%; 40/174) and among those who reported having more than 3 sexual partners in the last 2 years (41.5%; 17/41). Differences were found among provinces for circulating genotypes and infection-related variables. Human papillomavirus infection from genotypes 16, 31, 33, 53, 61, 66, 68 and 89 was associated with the 7.9% (30/382) of women who had positive Pap tests. Infection from *Chlamydia trachomatis* was positive in 1% (5/500) of women, all aged ≤25 years. Coinfection by *Chlamydia trachomatis* and HPV was found in one woman infected with human papillomavirus genotype 61.

CONCLUSIONS Frequency of human papillomavirus is high in the three Cuban provinces studied, with greater frequency of genotype 16 and other oncogenic high-risk types. For both agents, infection is more frequent in young women and adolescents. Positive Pap tests are frequently associated with HPV infection. Prevalence findings from this study could be used as a baseline for future research or interventions.

KEYWORDS Human papillomavirus, genotypes, *Chlamydia trachomatis*, neoplasms, sexually transmitted diseases, cervix Uteri, infection, real-time polymerase chain reaction, women, Cuba

INTRODUCTION

Human papillomavirus (HPV) and *Chlamydia trachomatis* are among the most frequent causes of sexually transmitted infections (STI) in the world. WHO estimates that close to 290 million women have HPV, and approximately 131 million chlamydia cases are reported annually. The latter is the most frequent bacterial STI. Despite advances in STI diagnosis, treatment and prevention, these two infections still constitute a global health problem.[1]

HPV infection is a necessary but not sufficient condition for appearance and development of cervical cancer, which is the main cause of anogenital neoplasms.[2] Cervical cancer ranks fourth in cancer incidence in the world.[3] Close to 200 HPV genotypes have been described, and approximately 15 to 19 are high-risk HPV based on their oncogenic potential.[4] HPV types 16 and 18 are the high-risk HPV genotypes most frequently associated with precancerous lesions and cervical cancer.[5]

IMPORTANCE This paper characterizes frequency of HPV and *Chlamydia trachomatis* infection in women of three Cuban provinces and highlights the need to study chlamydia infection in young and adolescent women. It supports the need to include HPV vaccination in the National Immunization Program and contributes knowledge about HPV genotypes in Cuba potentially useful for considering vaccine candidates for domestic production.

Since 1968, Cuba has implemented a cervical cancer early diagnosis program,[6] now carried out through the national network of neighborhood family doctor-and-nurse offices. The program screens sexually active women aged 25 to 59 years, for whom protocols indicate a Pap test every 3 years. The program may have contributed to the decline in cervical cancer mortality rates from above 20 per 100,000 women in 1965 to 7.7 per 100,000 in 2010. However, since then, this rate has increased. In 2016, it reached 9.1 per 100,000 and in 2018, 9.7 per 100,000. Although these rates are among the lowest in Latin America, the increases are cause for concern.[7]

Countries report different HPV prevalences by age group: in some, infection is concentrated in women aged <24 or <35 years, while in others, prevalence is also high in older women.[8] Several studies in Cuba have included populations considered at risk due to positive Pap tests or age >30 years with a positive or negative Pap. Prevalence was 94.3% in women with a positive Pap,

and 41.4% in those with a negative Pap, with high frequency of oncogenic genotypes (>80%), particularly HPV 16, 18, 31, 45, 52 and 58. The factors most commonly associated with infection were low educational level, smoking, alcohol use and perimenopausal status. The factors associated with precancerous cervical lesions in these HPV-infected women were oral contraceptive use for over five years and a history of positive Pap tests or colposcopies.[9,10]

Despite these findings and the known relationship between HPV and cervical cancer, at the time of this writing, no national baseline studies have been conducted on HPV prevalence and circulating genotypes in Cuba's female population. Due to shortcomings in prior research, limited to risk groups in a single city, it is of interest to learn frequency of HPV circulation and behavior of sociodemographic and epidemiological variables associated with infection in open populations in several regions of the country.

Most chlamydia infections are asymptomatic and frequently are neither diagnosed nor treated, leading to persistent infections that can cause pelvic inflammation, ectopic pregnancy and tubal factor infertility.[11] Infertility in Cuba is estimated at 12%–14% of couples, in which 40%–50% of causes are associated with the female partner. Tubal defects are one of the most frequent causes of female infertility,[12–14] making this infection an important health problem in Cuba.

For the past several years, the Cuban public health system has been using rapid chlamydia tests for diagnosis. However, due to the their lack of specificity, false positives occur from cross-reactions with antigens from other micro-organisms, and frequencies of up to 80% have been reported in women with lower abdominal pain.[15] Nucleic acid amplification testing has greater sensitivity and specificity for chlamydia diagnosis, but the cost is prohibitive for broad use in clinical diagnosis in low- and middle-income countries. In Cuba, these tests have been used in a few studies to estimate frequency of chlamydia infections, either by use of polymerase chain reaction (PCR) or real-time PCR. A small number are also reserved for patients with a history of infertility, those who are HIV positive, or who have symptoms of a genitourinary system disease in which prevalence fluctuates from 1% to 6%.[15–17] Thus, only a few Havana hospitals use these methods, which is why there is no data on chlamydia circulation in open populations.

The objective of this study was to determine the frequency of HPV and chlamydia infections in sexually active Cuban women with no genitourinary symptoms who sought routine services at the primary care level, as well as co-circulation of both agents and their association with relevant sociodemographic, clinical and epidemiological variables.

METHODS

Design and subjects A cross-sectional study was conducted from August through December 2015 of 500 women in 3 Cuban provinces: 100 in Havana (western Cuba), 200 in Villa Clara (central) and 200 in Holguín (eastern), with ages ranging from 16 to 67 years (mean: 38; median: 40). The provincial capital cities were chosen to include representation from the country's three geographical regions (west, central and east) and to identify possible differences among them.

Women were included who sought primary care services: 382 for the routine Pap test included in the cervical cancer screening program and 118 outside the program's age range of 25–59 years who sought services for other reasons, were sexually active, and who expressed interest in being tested for HPV and chlamydia.

Women were excluded if they were pregnant, HIV positive or if they had been diagnosed with any cervical disease.

After agreeing to participate by providing written informed consent, participants completed a questionnaire containing the study variables: age, educational level, occupational status, marital status, smoking status, parity and number of sexual partners in the past two years, age of onset of sexual activity, history of STIs, regular condom use, and use of intrauterine devices (IUDs) and oral contraceptives.

Two age groups were established: ≤25 and >25 years. Educational level was stratified according to Cuba's national education system: primary, secondary, high school or vocational school, and university. Marital status was classified as either single or married/with stable partner. Age of onset of sexual activity was divided into three categories: ≤15 years, 16–20 years and >20 years, and number of sexual partners was categorized as 0, 1, 2 and ≥3.

Pap tests were done on 382 women. Those aged <25 years (80) or >59 years (38) were excluded because they were outside the age range of the national cervical cancer screening program.

Sampling Cervical cells were obtained for the Pap test.[18] Following this, an endocervical brush (Digene Inc., USA) was inserted into the endocervical canal and after extracting it, brushed around the exocervical region to obtain endo- and exo-cervical cells and extract DNA. Cells were kept in a preservation solution (Digene Inc., USA) and stored at -20 °C until processing by the virology department's STI Laboratory at the Pedro Kourí Tropical Medicine Institute, where DNA extraction and HPV and chlamydia detection were carried out.

DNA extraction Cell suspensions were homogenized through vigorous vortex mixing (Vortex Mixer VM-10, DAIHAN Scientific Co., Ltd., South Korea) and 200 µL were taken to extract DNA using the commercial QIAamp DNA Mini Kit (QIAGEN, Germany), following manufacturer's instructions. From 50 to 100 ng/mL of DNA was obtained from the 200 µL of homogenized cervical cell suspension. DNA was diluted in 100 µL of elution buffer and stored at -20 ºC until detection of HPV and chlamydia were carried out.

HPV detection and genotyping Using low-density microarrays, HPV detection and determination of genotypes was done with the commercial CLART HPV 2 kit (Genómica, Spain), following manufacturer's instructions. A 450-base pair fragment in the virus's L1 region was amplified via PCR (AERIS BG096, ESCO Micro Pte., Ltd., Singapore) and hybridization was done with specific probes for each viral genotype. Ten µL of purified DNA from each clinical sample were used in the amplification reactions. Each microarray included an internal DNA control from the clinical sample, an external amplification control and a control for marking and visualization of the amplified products. Analytic sensitivity of the assay was calibrated by the manufacturer using commercial plasmids cloned from each viral genotype. Probes

were used to identify the 35 HPV genotypes of greatest clinical importance: low-risk HPV (6, 11, 40, 42, 43, 44, 54, 61, 62, 71, 72, 81, 83, 84, 85 and 89) and high-risk HPV (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 70, 73 and 82). High or low risk of genotypes was established in accordance with the criteria of the International Agency for Research on Cancer (IARC).[19]

***Chlamydia trachomatis* detection using real-time PCR** Chlamydia detection was done with real-time PCR at the Pedro Kourí Tropical Medicine Institute (IPK), following the Wei protocol.[20] A pair of primers that amplify a preserved fragment within the tryptophan synthetase gene of the chlamydia genome and a TaqMan (ThermoFisher Scientific, USA) probe were used. Ten µL of purified DNA were taken from each clinical sample and from the positive control, which consisted of a *Chlamydia trachomatis* reference strain, LGV Serovar II (ATCC VR-902BD). Negative controls consisted of 10µL of molecular-biology–grade sterile water and 10 µL of human fibroblast DNA (ATCC, CCL 171).

Data collection and handling During sampling, personal and epidemiological data were also collected, through a questionnaire designed for this purpose. Each patient's laboratory test results were added, and all information was stored in an Excel database. Each patient was assigned a unique identification number to protect confidentiality.

Statistical analysis A database for variable analysis was developed in the SPSS statistical package version 19.0 (IBM Inc., USA). Absolute and relative frequencies of HPV and chlamydia were calculated, along with the specific HPV genotypes detected and the multiple infections diagnosed in study participants.

Ethics The project was approved by IPK's Research Ethics Committee. Study participants provided written informed consent per the Declaration of Helsinki[21] and guidelines of the Council for International Organizations of Medical Sciences.[22] The signed document contained the necessary information about the research study, including possible benefits and risks. Participants were informed that they could withdraw from the study at any time without penalty or any effect on their care and treatment. Data were saved following the principle of confidentiality and individual identities were not revealed. Sampling was done by a trained clinician, taking the necessary care to minimize risks in accordance with good clinical practice standards. Laboratory methods were chosen according to principles of maximum beneficence and non-maleficence according to good laboratory practice standards.

RESULTS

Of the 500 women examined, 14.8% (74/500) were infected by one or more HPV genotypes. A total of 29 genotypes were identified, of which 79.7% (59/74) were high-risk HPV. Genotype 16 was the most frequent, followed by 31, and then 33, 53, 61 and 66, in equal proportions (Figure 1). Low-risk HPV genotypes were found in 27% (20/74) of positive cases, with coinfection with high-risk HPV in 6.7% (5/74) Coinfections with several HPV genotypes were identified in 3.4% (17/500) of all women in the sample and in 23% (17/74) of infected women (Figure 1).

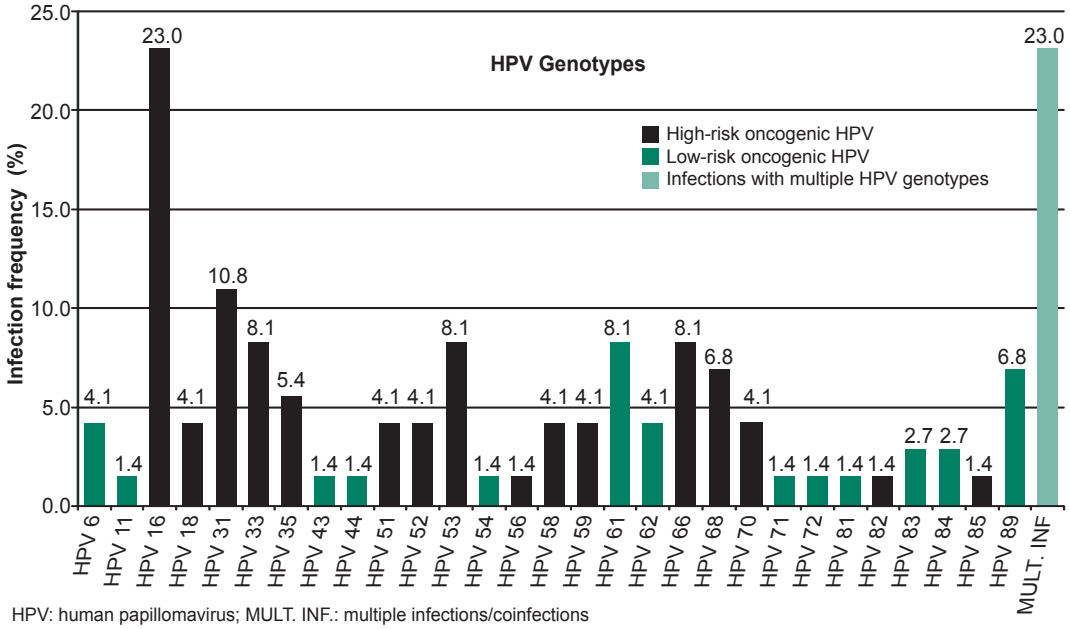
Women with multiple infections were positive for at least one high-risk HPV type. Among coinfected women, 58.8% (10/17) had 2 genotypes, 35.3% (6/17) 3 genotypes, and 5.9% (1/17) >3 HPV genotypes. No particular combinations were seen in these infections, although genotypes 16, 68, 53 and 31 were the most frequent in the coinfections identified: 35.3% (6/17); 29.4% (5/17); 23.5% (4/17), and 23.5% (4/17).

Small differences were found among provinces concerning HPV infection prevalence: Havana, 18% (18/100); Holguín 15% (30/200); and Villa Clara 13% (26/200).

Figure 2 shows frequencies of different genotypes by province. In Havana residents, 14 genotypes were identified and, of them, 10 (71.4%) were high-risk HPV. The proportion of women infected by HPV 16 was greater in Havana (Figure 2A). For high-risk HPV 35 and 68, differences were also found between Havana and the other provinces. These genotypes were detected in equal proportion in Havana residents (Figure 2A).

In Villa Clara Province, 20 HPV genotypes were identified, of which 12 (60%) were high-risk HPV. Figure 2B shows frequency of diagnosis for the different genotypes in this province. Prevalence of HPV 31 and 33 were greater in women in Villa Clara compared with the other provinces studied.

Figure 1: Genotype frequency among HPV-positive cases in Cuban women living in three of the country's provinces



HPV: human papillomavirus; MULT. INF.: multiple infections/coinfections

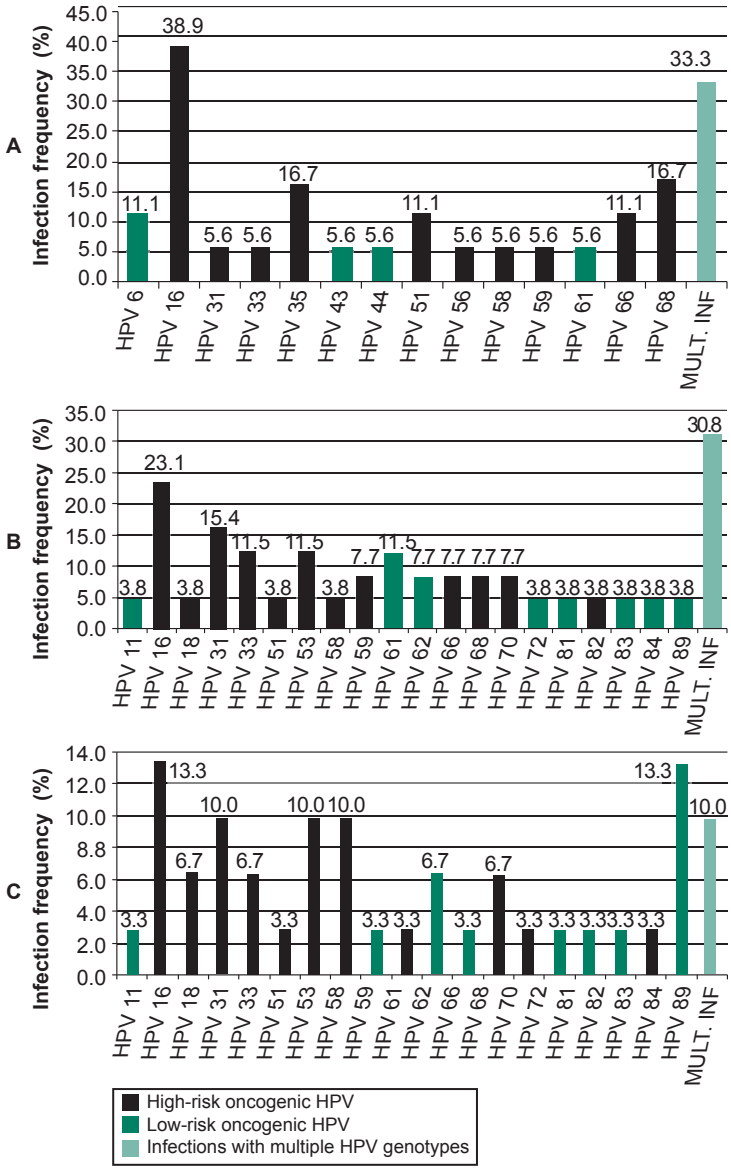
In Holguín Province, 19 viral genotypes were detected, of which 11 (57.9%) were high-risk HPV. Frequencies of the different genotypes in this province are shown in Figure 2C. Genotype 15 was less frequent in women in Holguín than those in Havana and Villa Clara.

HPV coinfections in women were more frequent in Havana than in Villa Clara and Holguín (Figure 2). In comparing coinfection frequencies among provinces, differences were found between women residing in Havana and Holguín: 6/18 (33.3%) vs. 3/30 (10%).

Table 1 shows infection frequencies by sociodemographic variables. Note that infection was almost 4 times greater in women aged ≤25 years than in women over this age. The proportion of infected women with only a primary-level education was twice that of university-educated women. Greater frequencies are concentrated in students, single women, smokers and in oral contraceptive users. The percentages of those who tested positive increased as the number of sexual partners in the last two years increased and the earlier women started having sexual relations. Although women with a history of STIs had the greatest frequency, there were only small differences between them and those with no STI history. We also found only a small difference related to IUD use, but women who reported regular condom use had slightly greater frequencies than women who did not (Table 1).

HPV-positive frequencies differed little among the provinces, with 18%, 13% and 15% in Havana, Villa Clara and Holguín, respectively. Infection frequencies according to sociodemographic variables by province are shown in Table 2 and generally reproduce the countrywide pattern for variables that represent the greatest risk of infection.

Figure 2: Genotype frequency among HPV-positive cases, in Cuban women living in (A) Havana, (B) Villa Clara and (C) Holguín Provinces



HPV: human papillomavirus; MULT. INF.: multiple infections/coinfections

The data indicate differences in sociodemographic patterns by province, and show that, especially for women in Havana, the variables most closely associated with infection are single status, a high number of sexual partners, history of STIs, early onset of sexual activity, smoking and use of oral contraceptives (Table 2).

Coinfections with several HPV genotypes were more frequent in women aged 15 to 25 years and were detected in 10% (8/80) of positive cases and in 6.3% (11/174) of single women. No relationship was found between presence of coinfections and other variables associated with higher risk of infection.

Cervical lesions were detected in 7.9% of the women who received a Pap test (30/382) and HPV infection was found in a high percentage of positive Pap smears (60%, 18/30). For intraepithelial lesions, 30% (9/30) had high-grade lesions and 70% (21/30) had low-grade lesions. Table 3 shows the association between lesions of both grades with high- and low-risk genotypes. High-risk HPV 16 and 66 were more frequently associated with positive Pap tests. HPV 16 was the most frequent in both types of lesions.

Among high-risk genotypes, genotypes 16 and 66 were the most frequent in high-grade lesions, and low-risk genotypes 61 and 89 were identified in greater proportions in low-grade lesions (Table 3).

Chlamydia was diagnosed in 1% (5/500) of women studied. All (100%, 5/5) were aged ≤25 years, and represented 6.3% (5/80) of that age group. Of these five women, two lived in Havana, two in Holguín and one in Villa Clara.

Eighty percent (4/5) of those infected had a secondary educational level (secondary, high school or vocational), 60% (3/5) were single and 60% (3/5) were homemakers. No association was found between chlamydia infection and these sociodemographic variables. Presence of chlamydia was associated exclusively with age (age ≤25 years). Coinfection with chlamydia and HPV was found in one (20%) woman infected with genotype 61.

Table 1: Frequency of HPV infection among Cuban women in three provinces, by sociodemographic and epidemiological variables

Variable	Groups or Ranges	HPV Positive		
		n	%	Total
Age in years	≤25	31	38.8	80
	>25	43	10.2	420
Educational level	Primary	3	25.0	12
	Secondary	13	14.8	88
	High school or vocational	37	16.4	225
	University	21	12.0	175
Occupational status	Student	7	46.7	15
	Homemaker	24	13.3	180
	Worker or technician	25	16.0	156
	Professional	18	12.1	149
Marital status	Married/stable partner	34	10.4	326
	Single	40	23.0	174
Parity	0–2	67	15.0	446
	3	6	12.2	49
	≥4	1	20.0	5
Number of reported sexual partners in the last 2 years	0	3	8.1	37
	1	39	11.2	349
	2	15	20.5	73
	≥3	17	41.5	41
Regular cigarette use	No	66	14.3	462
	Yes	8	21.1	38
Age at onset of sexual activity	≤15	31	17.3	179
	16–20	40	13.8	289
	>20	3	9.4	32
History of STI	No	57	14.5	393
	Yes	17	15.9	107
Regular condom use	No	50	13.7	364
	Yes	24	17.6	136
Intrauterine device use	No	60	14.8	405
	Yes	14	14.7	95
Oral contraceptive use	No	60	13.7	437
	Yes	14	22.2	63

HPV: human papillomavirus, STI: sexually transmitted infection

DISCUSSION

Anogenital HPV is the most frequent STI in the world, given that close to 90% of the sexually active population has the virus.[23] The infection is common in adolescents and young adults, who acquire it when they first become sexually active,[24,25] which concurs with the finding in this study that the greatest frequency of infection is in women aged ≤25 years.

HPV infection is a necessary condition for the appearance and development of cervical cancer, but in women aged <25 years, the worldwide incidence of invasive cervical cancer is very low (1.7 per 100,000 women per year). In these women, infection with high-risk HPV and low-grade intraepithelial cervical lesions tend to be transitory phenomena. The mean age of women with high-grade intraepithelial cervical lesions is 30 years, but these may result from infections acquired before that. After this age, it is more difficult for the immune system to clear primary high-risk HPV infection, leaving women at greater risk for developing persistent infections that cause precancerous lesions and invasive cervical cancer.[26]

In some geographic areas, the behavior of cervical cancer has changed due to the increasingly early age of onset of sexual activity and to contagion with high-risk HPV. The consequence of this is appearance of premalignant cervical lesions before the age of 25 years.[27] This change in behavior justifies prevalence or baseline studies for HPV infection in open populations to define the epidemiological situation and the circulation of oncogenic genotypes in different age groups and in different geographical regions of each country.

A meta-analysis that included 1 million women with normal Pap tests from 59 countries and 5 continents reported a prevalence of cervical infection between 1.6% and 25%, with differences among geographic regions, and an overall prevalence of 11.7%. HPV prevalence was 24% in Sub-Saharan Africa, 21.4% in Eastern Europe and 16.1% in Latin America. The lowest prevalence values were found in North America (4.7%) and Western Asia (1.7%).[28] These differences are related to sociodemographic, cultural, epidemiological and clinical aspects.[28] Another meta-analysis, which included 1425 women with normal Pap tests from Australia, Brazil, Canada, Mexico, Saudi Arabia, South Africa, Sweden, Tanzania, Thailand and the USA, found a 12.4% HPV prevalence.[29] We obtained prevalences similar to those in Latin America for women with normal Pap tests, which could be explained by the fact that they are in the same geographical region and share certain sociocultural and epidemiological characteristics.

With regard to genotypes, their distribution may vary among regions within a country, but in general most important is the circulation of high-risk HPV. Depending on which genotypes are circulating, prevention strategies with protective vaccines can be established, taking into account those included in the vaccine formulations available on the market.[30,31] Although genotype distribution was different in the three Cuban provinces, oncogenic genotypes made up the greatest share in all cases, and the most frequent was HPV 16, which is included in commercial vaccines. This result coincides with those for countries in Latin America and throughout the world in women with negative Pap tests, and with cervical lesions of different grades or cervical cancer.[32,33] At least for this genotype, Cuban women would obtain benefits from immunization with imported vaccines until safe and effective vaccine candidates are developed domestically.

Following HPV 16, the next most frequent genotypes differed among the three provinces. Such regional differences are also reported within other countries and geographies. In Brazil;[33] Asia, particularly China;[34,35] and Mexico,[36] the most frequent high-risk HPV genotypes are distinct, which is important both epidemiologically and for vaccine prevention strategies.

Studies in 38 countries (prior to approval and introduction of the Gardasil 9 vaccine) demonstrated that HPV genotypes 16, 18, 31, 33, 45, 52 and 58 contribute considerably to the appearance and development of invasive cervical cancers and other anogenital cancers. Persistent infections with these genotypes are present in approximately 96% of invasive cervical cancer cases and in 70%–90% of all anogenital cancers.[31,37] Concurring with these results, a study of Cuban women in Havana found that HPV genotypes 16, 18, 45 and 58 were associated with presence of high-

Table 2: Sociodemographic and epidemiological variables and HPV infection

Variable	Groups or Ranges	Province						Total
		Havana (n=100) HPV+ (18; 18%)		Villa Clara (n=200) HPV+ (26; 13%)		Holguín (n=200) HPV+ (30; 15%)		
		n (%)	HPV+ n (%)	n (%)	HPV+ n (%)	n (%)	HPV+ n (%)	
Age in years	≤25	20 (20.0)	8 (40.0)	23 (11.5)	9 (39.1)	37 (18.5)	14 (37.8)	80
	>25	80 (80.0)	10 (12.5)	177 (88.5)	17 (9.6)	163 (81.5)	16 (9.8)	420
Occupational status	Student	4 (4.0)	2 (50.0)	7 (3.5)	3 (42.9)	4 (2.0)	2 (50.0)	15
	Homemaker	22 (22.0)	1 (4.5)	63 (31.5)	7 (11.1)	95 47.5)	16 (16.8)	180
	Worker or technician	26 (26.0)	7 (26.9)	65 (32.5)	9 (13.8)	65 (32.5)	9 (13.8)	156
	Professional	48 (48.0)	8 (16.6)	65 (32.5)	7 (10.8)	36 (18.0)	3 (8.3%)	149
Marital status	Married	64 (64.0)	6 (9.4)	141 (70.5)	16 (11.3)	121 (60.5)	12 (9.9)	326
	Single	36 (36.0)	12 (33.3)	59 (29.5)	10 (16.9)	79 (39.5)	18 (22.8)	174
Number of reported sexual partners in the last 2 years	0	0 (0)	0 (0.0)	13 (6.5)	2 (15.4)	24 (12.0)	1 (4.2)	37
	1	58 (58.0)	5 (8.6)	164 (82.0)	19 (11.6)	127 (63.5)	15 (11.8)	349
	2	27 (27.0)	6 (22.2)	18 (9.0)	3 (16.6)	28 (14.0)	6 (21.4)	73
	≥3	15 (15.0)	7 (46.7)	5 (2.5)	2 (40.0)	21 (10.5)	8 (38.1)	41
Age at onset of sexual activity	≤15	36 (36.0)	7(19.4)	59 (29.5)	9 (15.3)	84 (42.0)	15 (17.9)	179
	16–20	56 (56.0)	9 (16.1)	127 (63.5)	16 (12.6)	106 (53.0)	15 (14.2)	289
	>20	8 (8.0)	2 (25.0)	14 (7.0)	1 (7.1)	10 (5.0)	0 (0.0)	32
History of STI	No	64 (64.0)	10 (15.6)	155 (77.5)	19 (12.3)	174 (87.0)	28 (16.1)	393
	Yes	36 (36.0)	8 (22.2)	45 (22.5)	7 (15.6)	26 (13.0)	2 (7.7)	107
Regular cigarette use	No	82 (82.0)	14 (17.1)	193 (96.5)	25 (13.0)	187 (93.5)	27 (14.4)	462
	Yes	18 (18.0)	4 (22.2)	7 (3.5)	1 (14.3)	13 (6.5)	3 (23.1)	38
Oral contraceptive use	No	77 (77.0)	12 (15.6)	181 (90.5)	23 (12.7)	179 (89.5)	25 (14.0)	437
	Yes	23 (23.0)	6 (26.1)	19 (9.5)	3 (15.8)	21 (10.5)	5 (23.8)	63

For each province, the left column shows distribution of sociodemographic and epidemiological variables. Variables shown are only those for which the greatest differences were found with regard to HPV infection frequency for the country as a whole. Likewise, for each province, the right column contains absolute and relative frequencies of HPV infection, for each stratum of sociodemographic and epidemiological variable. HPV: human papillomavirus, STI: sexually transmitted infection

Table 3: HPV genotypes detected among Cuban women living in three provinces who had positive Pap tests

HPV Positive	Positive Pap Smear Cases			Negative Pap test 352 n (%)	Pap test (total) 382
	Total Positive Pap 30 n (%)	High-grade lesion 9 n (%)	Low-grade lesion 21 n (%)		
HPV+	18 (50.0)	11 (61.1)	7 (38.9)	18 (50)	36
HPV 16	8 (61.5)	5 (62.5)	3 (37.5)	5 (38.5)	13
HPV 31	1 (33.3)	1 (100.0)	0 (0.0)	2 (66.7)	3
HPV 33	1 (25.0)	1 (100.0)	0 (0.0)	3 (75.0)	4
HPV 53	1 (33.3)	1 (100.0)	0 (0.0)	2 (66.7)	3
HPV 61	2 (33.3)	0 (0.0)	2 (100.0)	4 (66.7)	6
HPV 66	3 (60.0)	2 (66.7)	1 (33.3)	2 (40.0)	5
HPV 68	1 (33.3)	1 (100.0)	0 (0.0)	2 (66.7)	3
HPV 89	1 (33.3)	0 (0.0)	1 (100.0)	2 (66.7)	3
Multiple infections	6 (60.0)	4 (66.7)	2 (33.3)	4 (40.0)	10

Pap tests were done on 382 women. Women aged <25 years (80) and >59 (38) werenot considered because they are not included in national cervical cancer screening program. The most frequent HPV genotypes were the only ones analyzed. Percentages are added by row , with regard to infection in general and by genotype, including women with positive Pap tests plus women with negative Pap tests. Absolute and relative frequencies of cases with positive Pap, and HPV positive, are distributed by high- and low-grade lesions. PV: human papillomavirus.

grade intraepithelial cervical lesions and cervical cancer in women aged >30 years.[9] Another study of 519 women aged 15–59 years in 4 Havana municipalities found that oncogenic genotypes 16 (41.0%), 31 (11.6%) and 18 (10.2%) were the most frequent and were associated with presence of high-grade intraepithelial lesions.[10] In the women in our study with intraepithelial lesions, two high-risk genotypes (31 and 33) were found, which coincide with the ones most frequently identified in the 38 countries, and one (31), with those in the Cuban study of women living in Havana. Although these genotypes are associated with high-grade lesions, they were also present more often in women with negative Pap tests.

These findings demonstrate that in women with high-grade lesions and cervical cancer, the genotypes of greatest frequency may differ from those identified in the general population and reinforce the positive effect that could result from introduction of commercially-available vaccines in Cuba's National Immunization Program or introduction of another domestically produced vaccine containing them in its formulation.

High- and low-grade intraepithelial lesions found in the women in this study who had no history of positive Pap tests are associated with HPV infection, which coincides with descriptions in other studies.[29,38,39] Among high-grade intraepithelial lesions, two oncogenic genotypes were detected (66 and 68) that are not contained in the HPV vaccine formulations currently in use.[31,37] Taking into account their association with precancerous cervical lesions in Cuban women, these genotypes could be considered for inclusion in Cuban vaccine candidates.

HPV prevalence was similar in the three Cuban provinces, though it was slightly higher in Havana, which could be explained by the sociodemographic profile associated with greater risk of infection. This result differs from those reported by other authors who found greater variations among regions in a single country, as in Brazil and Mexico.[40,41] In-country differences are attributed to social, cultural and economic factors that mediate risk behaviors for acquiring infection.[30,40] Mexico and Brazil, in contrast to Cuba, are countries with diverse ethnic groups and cultural patterns, high rates of poverty, illiteracy and varying levels of health coverage/access, which could influence these quite disparate infection frequencies among states. In comparison, the Cuban population is culturally more homogenous, is covered by a universal health system, and has high literacy and educational levels, facilitating implementation of comparable health promotion and disease prevention actions throughout provinces, although differences between urban and rural areas, for example, cannot be ruled out.

Coinfection with multiple HPV genotypes was more frequent in women living in Havana, probably because this province has the greatest proportion of women aged ≤25 years; HPV infection prevalence studies with broad-spectrum genotyping have demonstrated that multiple infections are more frequent in young women, when they are at the peak of their sexual activity.[33] In coinfection, there is a greater risk of developing precancerous cervical lesions, particularly when viral loads are high (>1000 copies/µL).[42] Coinfection makes it hard to decipher the contribution of individual genotypes to cervical lesion stages, but this is resolved by hierarchically attributing the contribution of each genotype to lesion development, based on the defined prevalence of each genotype in cervical cancer. According to these data, women with cervical cancer who have multiple infections with HPV 16, 18 and 45 may have a poorer disease course and response to treatment.[43,44]

In our study, women aged ≤25 years had greater HPV infection prevalence, which concurs with publications from other countries that report higher infection prevalences in the youngest women, and that infection frequency decreases with increasing age.[45,46] In young women, infection is self-limiting and the histopathological changes are reversible, because at these ages the immune response is efficient and can eliminate the virus from the cells through antiviral effector functions, and tissue repair processes are capable of reversing the cellular changes that produce low-grade lesions.[26]

Although age is important in viral clearing and tissue repair, it is recognized that diverse factors can modify the course of infection, favoring viral persistence and development of cervical cancer. Among these, the most studied are virus-dependent factors, those related to the immune system of infected women and women's lifestyles. Recognized viral factors include integration of high-risk HPV DNA into the host-cell genome, the expression of viral oncoproteins E6 and E7, and complex interactions between these oncoproteins and proteins p53 and pRb of the infected cell.[47] Mechanisms of immune-system dependent viral persistence are related to defects in cellular immune response, inactivation of interferon synthesis, an increase in expression and liberation of anti-inflammatory cytokines, and deficiencies in the maturation and expression of major histocompatibility complex molecules (that introduce viral antigens into the immune system's cytotoxic cells) due to action by high-risk HPV oncoproteins.[48] Among lifestyle factors, it has been demonstrated that smoking contributes to viral persistence when the infection is caused by high-risk HPV.[49] Hormonal contraceptive use has also been associated with viral persistence and with HPV-induced carcinogenesis.[50,51]

HPV infection frequency was greater in students, single or reported having had more than three sexual partners. Student status does not seem to be an independent risk factor in itself, because student status probably coincides with young age, singleness and probably higher-risk sexual behavior. Sexual relations with a large number of partners is a risk factor for HPV and other STIs. It has been described that this behavior is frequent in adolescents and young adults, which is why vaccination strategies have focused on immunizing against HPV at early ages, before the onset of sexual activity,[52] but this can be a frequent practice in women of any age, especially single women.

Frequent changes in partners combined with unprotected sex multiplies the risk of contracting HPV. However, this study observed a greater frequency of infection in women who reported condom use. This finding may seem contradictory as it is known that one of the methods for reducing risk of HPV is protected sex. The problem with questions like these, such as condom use and STI history, is that at times patients' responses do not reflect reality due to social prejudices and perceptions about self-image. For this infection, which is latent and persistent, perhaps the patient uses condoms currently but five or ten years ago did not, or was not using them when she became infected. If condoms had always been used, infection prevalence would most likely be lower.

Although vaccination is the most efficient prophylactic method, because it protects against infection from seven oncogenic HPV genotypes, it is not the only means. Health promotion campaigns in Cuba should more actively promote condom use starting with the onset of sexual relations, because according to the results of this study, oncogenic genotypes that are not included in commercial vaccines are circulating among Cuban women and could infect women exposed to those genotypes, even though it has been reported that cross-protection may exist against some genetically-related genotypes contained in currently available vaccines.[53]

Variables associated with viral infection did not behave equally in the three provinces studied, observing differences primarily in the age of infected women, their occupational status, number of sexual partners in the two years, or smoking and hormonal contraceptive use. The uneven distribution of sociodemographic variables among provinces, particularly those associated with a higher risk of infection, could explain the higher prevalence in Havana as well as the lowest in Villa Clara. For instance, Havana

has the highest percentage of women aged 15–25 years, the same range that concentrates higher rates of infection observed in general. It also has the highest percentage of students, of women who reported having three or more sexual partners in the last two years, women with a history of STIs, smokers and oral contraceptive users. It is also true that Havana does not have the greatest percentage of single women, nor those who began sexual relations at age ≤15 years, although it is where the greatest frequencies of infection are seen within these categories by province.

In addition to differences in HPV prevalence among countries and regions and among provinces and cities,[40–54] differences have been reported in sociodemographic and clinical-epidemiological variables associated with HPV infection and cervical cancer between urban and rural areas in a single country.[55,56] These differences also depend on socioeconomic and cultural aspects that modulate the attitudes and behaviors of women living in each region or city.[30,40] Different lifestyles among urban women may influence their susceptibility to HPV infection and persistence. Habits such as smoking, alcohol and drug use, and treatment with steroidal hormones have been related to behaviors associated with infection.[49,50,55] One possible explanation for the differences found among provinces could be that women living in large urban centers such as Havana experience more stress, smoke and drink alcohol more often, are more independent socially, more isolated from their extended families, and have fewer prejudices and religious taboos, and use hormonal contraceptives rather than other methods.[56]

The effects of smoking on HPV infection have been attributed to the benzopyrene in tobacco smoke, which can modulate the lifecycle of HPV, strengthen the expression of viral oncoprotein mRNA and aid in viral persistence, stimulate carcinogenesis and enhance cancer progression.[49] Cigarette smoking has been related to high viral load values for high-risk HPV, and carcinogens in smoke, synergistically with viral infection, may increase risk of progression to cervical cancer.[57] Although at rates lower than men's, smoking is relatively frequent among Cuban women. In a study of 1959 employees in the education sector, Varona and colleagues found 28.8% of women smoked.[58]

A meta-analysis that studied risk factors for infection and its persistence and for development of cervical cancer reported that long-term oral contraceptive use was an important risk factor.[50] These results are related to the capacity of estrogens to promote virion morphogenesis, viral persistence, tumor growth and positive regulation exercised by estrogens and progesterone on viral oncogenes.[51] In our study, proportions of infection in women who use oral contraceptives were higher than in those who did not, particularly in Havana, but their effect on carcinogenesis was not evaluated because none of the women in the study had cervical cancer lesions.

Chlamydia trachomatis infection was concentrated in women aged ≤25 years, which concurs with worldwide reports of greater prevalence younger women, although figures vary according to region or country: Europe 3.0% to 5.3%, Australia 5.6%, Chile 7.9% and the USA 4.7%.[59–62] In 2012, WHO estimated worldwide chlamydia prevalence in women at 2.4% to 6.9%, highest in the Americas and East Pacific.[63]

Infection prevalence in our study was lower at 1%, which could be due to the fact that mean age of the women was high (38 years) and that the youngest age group was small. Furthermore, this figure does not concur with those from other Cuban studies that assessed chlamydia prevalence in women using molecular techniques, in which values ranged from 6.9% to 8.3%.[15–17] This discrepancy might be attributed to the fact that these studies included women with symptoms of gynecological infections and others who were asymptomatic but who had risk factors associated with HIV infection, while those in our study did not have symptoms, were recruited in primary care when getting a Pap test or other exam, and thus might be considered part of an open population. In most studies globally using these techniques, chlamydia frequencies are significantly greater in symptomatic patients or those who seek care for STIs compared to asymptomatic women and open populations.[64–67]

Chlamydia infection in women is almost always asymptomatic, resulting in late or no diagnosis, which can make transmission easier and also lead to infection chronicity and complications. Thus, we would recommend periodic screening in specific population groups, primarily women aged ≤25 years, those older than 59 years and those with risk factors for infection.[59]

Multiple factors associated with chlamydia infection in women have been described. These include age ≤25 years; being single; and, as with HPV and other STIs, frequent change in sexual partners or having changed partners recently, lack of condom use in recent sexual relations, low socioeconomic level and a history of other STIs. Due to the low frequency of chlamydia infection found, we could not establish associations with the sociodemographic variables in the study design. An important finding was the infrequent circulation of chlamydia in women aged >25 years in the three Cuban provinces, which affirms observations made in daily diagnostic practice of the Pedro Kourí Tropical Medicine Institute's the STI Laboratory.

Despite the low frequency of chlamydia infection, one woman was found to have coinfection with HPV genotype 61. This result, although isolated, is important since it has been reported that HPV is an essential but not sufficient factor in occurrence of malignant lesions[2] and it has been demonstrated that high-risk HPV genotypes have a central role in cervical cancer pathogeny.[68] Among the endogenous and exogenous cofactors explaining the occurrence of malignant lesions in high-risk HPV infections, chlamydia coinfection stands out, since it is the most frequent and most widely distributed bacterial STI, and has been associated with occurrence of malignant or precancerous cervical lesions.[69–72] One biological explanation for the role of coinfection is that chlamydia causes loss of epithelial integrity thus facilitating HPV access to basal epithelial layers, increasing viral persistence and progression of chlamydia infection. It is also postulated that chlamydia infection can induce chronic inflammation, interfere with immune response by decreasing the number of antigen-presenting cells, and reduce cellular immunity to foster HPV persistence.[72]

It is important to underscore that this study is limited to findings related to infection frequency in three regional scenarios, and to describing and evaluating their association with sociodemographic, clinical and epidemiological variables, and that the sampling design used, based on women seen in primary care services, does not allow for inferences to be made at a population scale.

CONCLUSIONS

Women living in three Cuban provinces have a high frequency of HPV infection with proportions higher for high-risk genotypes. HPV 16 is the most frequent genotype. Other circulating genotypes vary by geographic region. Younger women have a greater risk of HPV infection; they have more frequent coinfection with several HPV genotypes, at least one of which is of high oncogenic risk. Although frequency of high-grade cervical lesions is low, these are associated with a high percentage of infection by oncogenic HPV genotypes, but none of the women infected with high-risk HPV had chlamydia. The prevalence of chlamydia infection is low; only the youngest women were infected and, within this study, coinfection with HPV was not associated with presence of cervical lesions.

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Educational Program for Retiring Persons: A Community Experience in Cienfuegos Province, Cuba

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ABSTRACT

Cuba has one of the fastest aging populations in Latin America and the Caribbean (20.4% of the population aged ≥60 years by 2018) and life expectancy has climbed to nearly 79 years. This demographic shift has prompted a number of initiatives to address the needs of older adults and promote active, healthy longevity.

At the community level in Cienfuegos Province, an educational program was implemented designed to foster a more active role in society for older adults and improve their quality of life upon retirement, as well as to reinforce a positive culture of aging. The program ran from June 2010 to June 2018 in the Mental Health Department of the Dr Enrique Barnet Polyclinic in the Santa Isabel de las Lajas Municipality. Twenty-two groups were constituted of 330 older adults who were trained for 10 weeks in techniques of self-awareness, personal growth, development of social skills, use of social support networks, adoption of healthy lifestyles and formulation of retirement plans. Results were assessed for each group one year after program completion and the information summarized.

Participants whose definitions of "older adult" and "retirement" were rooted in nondiscriminatory concepts increased from 53 to 303 and retirees not incorporated into active social/economic life decreased from 228 to 36. At the outset, only 22% had coping mechanisms to manage their new role as retirees and 9% had a life plan for retirement. One year after finishing the program, 318 (96%) reported they were prepared to face this new stage in their lives and 294 (89%) had completed life plans; at the start, 116 (35%) were taking antidepressants and one year later, 103 of them had reduced or eliminated the drugs. The program enriched participants' culture of aging, as well as relationships with their families and their communities.

KEYWORDS Retirement, aging, community health planning, Cuba

INTRODUCTION

Cuba has one of the fastest aging populations in Latin America and the Caribbean. In 1999, 13% of the population was aged ≥60 years, while by 2018, this proportion had climbed to 20.4%. Meanwhile, life expectancy has risen to nearly 79 years.[1–3]

This demographic shift demands attention from all of Cuban society and from the health system in particular, aimed at improving quality of life for older adults. This has prompted initiatives at the community level to address the financial, social and cultural needs of this population; promote their social and family inclusion; foster their active role in society; and continue to ensure their safety, health and wellbeing.

Within the older-adult population, retirees face a particular set of issues, since retirement has major consequences that alter the life course. The change in status from active participant in the labor force to retiree occurs in phases, which begin before retirement and continue well beyond.[4–7] We do know that adjustment to and satisfaction with the retirement process is greater among those who have prepared for this new stage, while those who did not prepare have reported greater dissatisfaction and difficulty adjusting.[8,9]

In Cuba, Social Security Law 24/79 (in effect 1979–2008) set a minimum retirement age at 60 years for men and 55 for women.[10]

IMPORTANCE The Educational Program for Retiring Persons has been under way for nine years in one community setting. Results indicate it has promoted a culture of aging that includes active retirement and improved quality of life in adults aged ≥60 years. As a result, the Program has been extended to several municipalities in Cienfuegos Province, central Cuba.

In 2009, Social Security Law 105/08 increased the minimum retirement age for men to 65 and to 60 for women, with a 5-year transition period, during which the retirement age was gradually increased until reaching those set by the new law.[11] On average, Cubans will live between 13 and 20 years after the set retirement ages (although retirement is not obligatory), taking into consideration the differences in life expectancy between men and women (men at 76.50 years and women at 80.45).[2]

This paper describes a community-based program in the Santa Isabel de las Lajas Municipality in central Cuba's Cienfuegos Province. On the program's start date in 2010, the municipality's working age population was 12,504, 5625 women (45%) and 6879 men (55%); 9581 (76.6%) were employed, of whom 3079 (32.1%) were women. By 2019, the total working age population had risen to 15,111, of whom 6394 (42.3%) were women. Of the 7986 employed (52.8%), 3851 (48.2%) were women. In 2010, there were 4160 adults aged ≥60 years (20.1% of the population); by 2019, this had increased to 5031 (22.7%). Among adults aged ≥60 years, the respective proportions of women for 2010 and 2019 were 50.2% and 50.8%. There were 2488 retirees in the municipality in 2010 and 3532 in 2019 (53% men, 47% women). In 2010, there were 386 actively employed persons aged ≥60 years; in 2019, there were 867.[12]

Intervention universe, design and recruitment The program was designed for persons who either reached retirement age or retired during a one-year period before or after the program's start in 2010 and was implemented in three stages. The first stage, program planning, was carried out in 2010; the second, program implementation, was developed from 2010 to 2017; and the third, program assessment, began one year after the first group concluded the program in 2011 and lasted until 2018, one year after the last group ended the program. It was carried out in the Mental Health Department of the Dr Enrique Barnet Polyclinic in Santa Isabel de las Lajas Municipality, a community-based multi-specialty

health center serving the surrounding health area. The program was authorized by the Santa Isabel de las Lajas Municipal Public Health Department and each retiree provided written informed consent to participate.

The universe consisted of 356 retirees of both sexes, all of them residents of the health area served by the Dr Enrique Barnet Polyclinic, who were organized into 22 groups from June 2010 to June 2018. Of these, 330 completed the program and 26 left for various reasons; of those completing the program, 221 (67%) were women. Each group included 15–20 participants of both sexes. New members were not added to a group once its activities had begun. The program consisted of ten two-hour sessions, held once a week for ten weeks. The Labor and Social Security Office of Santa Isabel de las Lajas supplied the retirees' information and location records, issued in the period from June 2010 to June 2018.

Inclusion criteria Individuals who reached retirement age (according to Social Security Law No. 24/79 and No.105/08) or who had retired within one year before or after each group began its activities, and provided informed consent to participate.

Exclusion criteria Individuals who retired due to total disability (as stipulated in Social Security Law No. 24/1979 and No. 105/08) or partial disability (as stipulated in Resolution 6 of Social Security Law No. 24 /1979); persons with an intellectual disability or severe cognitive impairment who were unable to express their wishes; and individuals who refused to join the study.

Reasons for loss to followup Emigration: 20, death: 6.

Program planning The program was based on a diagnostic study of main factors influencing adjustment to retirement, which included 164 retired seniors. These persons would later enroll in the first of the program's 22 groups. During this stage, participating health professionals learned from the retirees about their problems, how they perceived retirement, and how they wanted to change their lives to approach it more positively. To collect this information, individuals completed a questionnaire after receiving an explanation of program objectives.

This diagnostic tool consisted of 43 sections with closed- and open-ended questions, approved by the Scientific Council and Ethics Committee of the of Santa Isabel de las Lajas Municipal Public Health Department. It was based on an extensive review of the literature on retirement. To evaluate its reliability, the questionnaire was applied to the same group of retirees twice, the second time four weeks after the first, to measure stability over time. This comparison was done using Spearman's rank correlation coefficient, using the usual cutoff point for reliability of 0.80.

Two aspects of the questionnaire's validity were assessed. Its construct validity was evaluated through principal component analysis. When the information collected can be summarized by a few linear combinations of the original variables, the questionnaire is considered consistent. Content validity was evaluated by ten specialists, each with at least two years' experience working with seniors and retirees in three municipalities (Santa Isabel de las Lajas, Cruces and Palmira), all in Cienfuegos Province. The content of each section was rated according to Moriyama's principles.[13]

The validated questionnaire was administered to participants in each of the 22 groups during their first session to learn about their expectations of the program and to eventually adapt the questionnaire to the specific needs of each group. It was readministered during the groups' last session to learn how well the program met expectations.

We assessed the availability of qualified staff and material resources in the municipal Mental Health Department and identified community institutions and social support networks whose directors and employees were willing to help implement the program.

Program implementation The program used therapeutic and participatory techniques, presentations and dramatizations, experiential techniques, audiovisual methods, discussions of cases and situations/problems, and information-sharing and interactive techniques, as well as methods aimed at greater self-control and personal growth. To foster family support and expand retirees' use of social networks to implement their plans for retirement, we held sessions with relatives and visited social institutions. The latter included senior centers (day facilities for older adults, offering lunch, social and recreational activities, etc., supervised by health professionals); senior clubs (often led by family doctors, involving neighborhood seniors in exercises and other activities); and the older-adult university centers (offering continuing education opportunities at the municipal level). In each place, retirees met the institutions' leaders/directors.

Table 1 summarizes activities in each of the program's ten sessions.

One year after each group completed the program, a structured interview was conducted to measure the satisfaction of both participants and their families, lifestyle changes, and how participants had applied what they learned to their plan for retirement.

Participants accessed the program through human resources managers in their workplaces, in coordination with local offices of the Ministry of Labor and Social Security and the National Social Security Institute, or through family doctors, psychologists, geriatricians, social workers, community health activists and older-adult university faculty, as well as other organizations and institutions working with seniors and retirees.[14]

Trained staff, supervised by the program director, implemented the program. A psychologist from either the Mental Health Department or primary health care teams served as the main program facilitator, assisted (depending on the session) by a geriatrician, occupational therapist and social worker affiliated with the Department. All had been trained to work with seniors and retirees, including enrollment in workshops on use of participatory techniques and the Comprehensive Elder Care Course, the latter approved by the Santa Isabel de las Lajas Municipal Public Health Department's Scientific Council.

Table 1: Session contents for educational program for retiring persons

Session #, Title	Objectives	Activities
1. Meet friends	a) Create a positive spirit among participants to foster group identification and reflection b) Identify factors influencing adjustment to retirement	a) Participant introductions b) Exercises on expectations c) Program presentation d) Instructions for completing homework
2. Conceptualize "older adult", "retirement" and "retirement plan"	As a group, create collective definitions of "older adult", "retirement" and "retirement plan" based on nondiscriminatory concepts of aging and retirement	a) Homework collected and read, providing comments b) Group construction of definitions for "older adult", "retirement" and "retirement plan" c) Relaxation exercises d) Instructions for completing homework e) Session evaluation report
3. Confront myths and prejudice concerning aging and retirement	Separate retirement and old age from myths, prejudices and stereotypes that hinder adjustment to retirement	a) Homework collected and read, providing comments b) "Myth or Fact" exercise c) Relaxation exercises d) Instructions for completing homework e) Session evaluation report
4. Reflect on retirement	Encourage participants to reflect on adjustment to retirement after viewing a film on the theme	a) How do I perceive myself as a retiree (discussion)? b) Homework collected and read, providing comments c) Film debate d) Relaxation exercises e) Instructions for completing homework f) Session evaluation report
5. Get to know yourself better	Formulate strategies to foster self-awareness and personal growth	a) Homework collected and read, providing comments b) Self-awareness exercise c) Technique: "dissolving negative feelings" d) Technique: "therapeutic poetry" e) Relaxation and breathing exercises f) Instructions for completing homework g) Session evaluation report
6. Improve communication	Encourage communication between retiree and family members	a) Homework collected and read, providing comments b) Psychodrama: communication skit; to be used with a family member present c) Technique: "Ask permission to hug someone" d) Relaxation and breathing exercises e) Instructions for completing homework f) Session evaluation report
7. Enhance social skills	a) Build social skills b) Foster use of social support networks	a) Homework collected and read, providing comments b) Visits to centers that encourage retiree and senior development c) Technique: "Seeking advice" d) Instructions for completing homework e) Session evaluation report
8. Develop a plan for retirement	Train participants to formulate a plan for retirement	a) Homework collected and read, providing comments b) Technique: "Doing something to grow" c) Group discussion techniques d) Technique: "Create a new CV"—based on this, propose a plan for retirement e) Relaxation and breathing exercises f) Instructions for completing homework g) Session evaluation report
9. My plan for retirement	Present retirement plan designs	a) "Here I am, and today I feel…" b) Homework collected and read, providing comments c) Technique: "Problem solving" d) Exercise: "My retirement plan" e) Relaxation and breathing exercises f) Session evaluation report
10. Summary and closing	a) Organize knowledge acquired in the program b) Evaluate individual and group transformations that occurred after completing the program	a) Summary exercise b) Questionnaire administered (same as one given before program) c) Session evaluation report

PROGRAM RESULTS AND LESSONS LEARNED

Although men outnumber women among the municipality's 3532 retirees (in 2019, 53%), most program participants were women (221, 67%). This result bears monitoring in any extension of this program, given potential implications for advancing goals of greater social inclusion and satisfactory aging.

At the program's start, sociocultural, family and individual factors were observed that could adversely affect adjustment to retirement. As sessions developed, retirees worked together in their groups to construct definitions of "older adult" and "retirement" based on nondiscriminatory notions, discussed how to apply these in their daily lives and received training in self-control, relaxation and breathing exercises, among other activities. The structured interview, conducted one year after each group completed the program, assessed participant satisfaction with what they had learned and its application to their plan for retirement. Among the most salient results, as declared in the interview, were:

Participants with nondiscriminatory definitions of "older adult" and "retirement" increased from 53 (16%) to 303 (92%). Retirees with active social participation increased from 102 (32%) to 294 (89%). Of these, 190 (57%) were participating in two or more activities (119 women and 71 men); 104 (32%) were participating in one activity (74 women and 30 men). Stated differently, the number of those who had not changed lifestyles and remained more socially isolated decreased from 228 (69%) to 36 (11%) (28 women and 8 men).

Among the 294 engaged in active social life one year after completing the program, retirees engaged in farming increased from 34 (12%) to 76 (26%); 65 (22%) had returned to work in the education sector, 24 (8%) in the health sector; 85 (29%) were self-employed—food vendors, florists, seamstresses, tobacco selectors, carpenters, craft vendors and caregivers for children and the elderly; 141 (48%) were providing (unpaid) support to family at home by caring for grandchildren and dependent elders; 112 (38%) had joined senior clubs where they practiced physical exercise (data verified with the clubs); 132 (45%) were taking older-adult university classes; 135 (46%) had joined in recreational activities organized by community institutions; 44 (15%) reported a more active social life, visiting friends, family or places of cultural or recreational interest; 32 (11%) were participating in religious activities; and 42 (14%) were involved in sports clubs.

Improved family communications, more balanced division of household work and support for new retirement plans were also reported. Strengthening family relations was aided by participation of 259 (78%) family members invited to specific sessions. Retirees whose families did not participate were enrolled in senior-center programs. Of the 188 retirees who described an overload of household tasks, 115 (61%) reported improvements at year's end—a factor that may have facilitated the greater social incorporation also reported by many participants.

At the program's start, only 22% of participants said they had coping mechanisms in place to address life changes implied by retirement and only 9% had a plan for retirement. One year later, 318 (96%) participants reported feeling motivated and prepared to face this new life stage, and 294 (89%) had a developed a plan for retirement. Among the program aspects contributing most to these changes, 303 (92%) named personal growth and acquisition of social skills to address aging; 294 (89%) mentioned creation of a retirement plan, adoption of healthy lifestyles, such as care for physical well-being, exercising and options for use of free time;[14] and 261 (79%) noted that the program strengthened their social skills for relating to people outside the group and added personal resources to facilitate both self-awareness and personal growth as well as to overcome negative emotional states.

At the program's start, 116 (35%) participants were taking antidepressants; one year later, depression morbidity had decreased and 103 (31%) had appreciably reduced or eliminated their intake of such medications, according to our communication with specialists in geriatrics and psychiatry in the health/catchment area served by the Dr Enrique Barnet Polyclinic in Santa Isabel de las Lajas. We hypothesize that the psychological coping mechanisms and lifestyle changes acquired during the program may have offset more negative biopsychosocial changes characteristic of this life stage.

Table 2 compares a number of self-reported participant variables, before and one year after program completion, illustrating changes perceived.

IMPLICATIONS FOR FURTHER STUDY AND ACTION

The team of health professionals involved in the program gained experience in working with retirees and benefited both professionally and personally. Participating professionals reported that the program spurred actions for community-engaged

Table 2: Participant reports on factors influencing adjustment to retirement that were modified during the program (n = 330)

Factor	Before intervention (Day zero)	After intervention (One year later)
	n (%)	n (%)
Definition of "older adult" and "retirement" based on nondiscriminatory concepts	53 (16)	303 (92)
Knowledge of community social support networks	73 (22)	264 (80)
Use of social support networks	63 (19)	303 (92)
Social/economic incorporation after retirement	102 (31)	294 (89)
Adequate communication between retiree and family members	155 (47)	274 (83)
Overload of family/household tasks	188 (57)	73 (22)
Family support for new post-retirement life plan	188 (57)	277 (84)
Possessing mechanisms to navigate retiree role	73 (22)	318 (96)
Healthy lifestyle	102 (31)	294 (89)
Possessing a plan for retirement	30 (9)	294 (89)

Source: Questionnaires

health promotion and disease prevention, and created a place for retirees to obtain information and guidance about municipal institutions and support networks, as well as their purpose, usefulness and how to access them. They identified the need to find new ways for people to get involved in community social and cultural activities and to create new intergenerational community development projects to pass on craft, culinary and artistic traditions, among others, allowing retirees to become more socially involved.

The program was submitted in response to the 2018 National Call for Health Research and was approved for inclusion in the National Program for Research on Health Determinants, Risks and Prevention in Vulnerable Groups, coordinated by the Ministry of Public Health's National Hygiene, Epidemiology and Microbiology Institute. In January 2019, the program was extended throughout health care institutions in the Santa Isabel de las Lajas and Cruces Municipalities of the province, and in May 2019, it began operating among retiring workers at the Cienfuegos thermoelectric plant and the Dr Gustavo Aldereguía Lima University Hospital, both in Cienfuegos Province.

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Gender Roles in Cuba: Leaving the Kitchen Isn't Enough

Ania Terrero

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The scene: a family doctor-and-nurse office. After the usual well-baby visit for the eight-month-old, the physician poses a question to the young mother that sounds more like a statement: "I suppose you won't be going back to work, right? You'll be staying home to take care of your little girl."

The mother, surprised, responds with a laugh: "Of course not. As soon as she's a year old and walking, she'll be going to day care and I'll be going back to work." The doctor, a look of concern crossing her brow, responds: "But once they start in day care, they catch all kinds of things. They're much safer at home." The mother, now unsmiling, says: "Well, she'll just have to catch antibodies." Attempting a joke, the specialist sighs: "Ah, my friend… and you've been such a good mother!" Silence. How do you respond to this? Two truths are implicit in the commentary, thought the young mother. The first, that the doctor wasn't sure at the outset that she was a good mother. And the other, that once she decides to send her daughter to day care, she stops being one.

Apparently to be a good mother, you have to stay at home. As if there was only one model for motherhood. As if—once again—the father was expected to provide for his children and the mother to raise them. This is a true story, one that hits close to home, from right here in Cuba. And it says a lot.

When Aníbal was little, he played with dolls. This worried the day care teachers, who sent for his mother. "The boy gets here and starts playing house with the girls. Maybe he needs to see a psychologist," they tell her. My mother, flabbergasted, responds: "So why is there a problem? He's used to playing the father to his sisters' dolls."

My brother had cars, whole parking lots, robots, construction tools, even a spinning top…and he loved them all. But with my sister Amanda and me, his main allies come playtime, he had few options. So some days he played the dad in our doll houses and others, he organized the car races. When he entered nursery school, he reproduced these behaviors. He never understood, and in fact never knew, that boys and girls were supposed to play different games. He didn't need that. He was just happy.

Gender roles are assigned to people depending on their sex at birth and, over time, influence the ways established for men and women to act in society. They are transmitted and acquired almost unconsciously through family, teachers, mass media and other avenues. They start with blue for boys and pink for girls, but continue through every stage of personal development.

A couple of years ago, a "compliment" got me thinking. A young guy told me that I was so pretty that he'd take me home with him, so I could also make his house pretty, and thus never have to leave or be bothered by working. In addition to the implicit harassment, I was irritated by the essence of his comment. For him, my place was not out in the world but rather taking care of and adorning his house. And moreover, this should be considered a privilege for me!

Recently, since I've become a mother, more than once walking with my daughter, men have shouted at me things like this: "Don't worry darling, your daughter will always have a daddy to provide for her with a mommy like you!." I know some will say that both kinds of comments have been heard forever, that they're part of "Cubans' witty cultural traditions," an "essential part of our idiosyncrasy."

But besides being examples of harassment, behind them lay the sexist distribution of roles that has accompanied humanity for centuries. Hear this: we women are supposed to be homemakers, to give pride and satisfaction to men, be an asset to their image. And they, in turn, will provide for us and our children.

The worst thing is that we've spent years trying to get rid of these stereotypes [in Cuba] and, after enormous effort, have only made a dent. Those who preceded us managed to get out of the kitchen, began to conquer the world, graduated in science and engineering, gained access to professions historically reserved for men, and reached leadership in politics and in public spaces. You just have to review the statistics to see that women are virtually everywhere. They're in parliament, in Popular Power assemblies at all levels, in research centers, on the bench, in universities, in mass media. In some arenas, they're even the majority.

However, while women leave the house to join the workforce, few men share the work back home. The result: women do a double shift, working outside the home by day and inside by night. Almost always, they have to combine traditional roles as mothers and homemakers with their new professional conquests. In some more advanced scenarios where men have begun to share household work, women still organize family routines. In feminist theory, this is called the "mental burden", that is, when men expect women to assign them household tasks, unconsciously assuming that women are the only ones who understand what, when and how things should get done.

The problem is that when women become organizers, and at the same time carry out part of the chores, in reality they're doing three fourths of the work. They have to be aware of everything and remember everything. And it's work that they generally carry out by themselves, added to all their other responsibilities…invisible, exhausting.

Since my daughter Ainoa arrived, many people have told me that motherhood is now the most important thing in my life, that everything else is secondary and that I should make sacrifices so as to raise her well. In a certain sense, this is true. The problem is that very few people demand the same level of sacrifice from fathers. Yet, motherhood doesn't necessarily mean renouncing everything else when it's accompanied by responsible fatherhood.

When children come along, often gender roles become even more polarized. In Cuba, with parental leave guaranteed for the first year after birth, most postpartum mothers stay at home, sleepless, learning how to care for their babies. The fathers almost always stay at work to bring in more income. Influenced by factors such as breastfeeding and the recuperation needed in the postpartum period, the pattern is repeated unconsciously: mom as caretaker, dad as provider. At least during the first year. In fact, although paternity leave is possible under Cuban law, few men take it.

Everything becomes more complicated when women return to work. At that point, they have to combine the demands of their jobs with those of their households, adding attention to their children, often with little to no participation by their male partners.

But what happens when a father assumes an active role in childrearing and household responsibilities, when tasks are shared equitably? In such cases, men sometimes suffer discrimination from a society not accustomed to finding them in these roles. When fathers are kept from an active role in birthing, when physicians openly ignore them in their offices, when they arrive at hospital with their children and are asked where the mother is, when people are surprised to see them walking alone with their babies, when no media reflect them caring for their children…then, time and again, they are excluded from the whole process. Society is showing them that they aren't part of these activities, that they have no business doing them. And if men aren't taught differently, then later it's very difficult to demand that they act differently.

Our culture, mass media and society show women in their roles as wives and mothers and men as workers or professionals. So we return, then, to the vicious cycle of pink and blue, of those who feel and those who don't cry, those who change diapers and those who bring home the bacon. It's not enough that women have left the kitchen and every day conquer a bit more of the outside world. We have to break the chain, discard the stereotypes, transcend the most arcane versions of our roles and shed their most hidden manifestations.

We need more media reflecting equitable roles, more families that share in all the tasks, more women in all public spaces, more fathers who take paternity leave, more boys who play with dolls, and fewer doctors who think being a good mother means staying at home.

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