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Global South Contributions to Universal Health Coverage: The Case of Cuba

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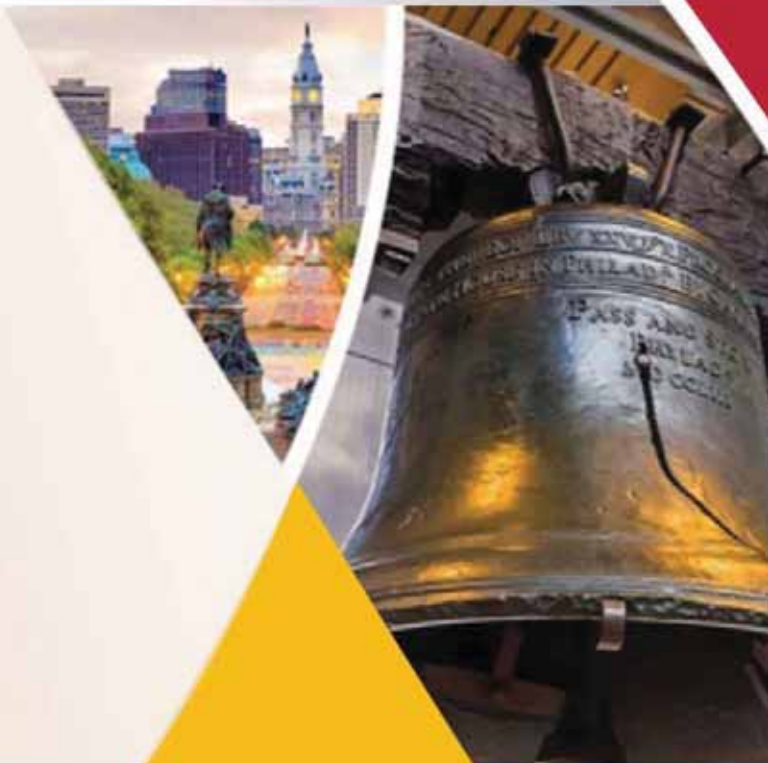
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The Right to Health: The Devil is in the Doing

Addressing the world's injustices in all forms is the only way to breathe life into the "health for all" principle and aspiration expressed so eloquently in the 1978 Alma-Ata Declaration. The first of these injustices is more evident than it was 41 years ago: the international economic order has concentrated vast wealth in ever-fewer pockets, while half the world's people go without essential health services . . . and most certainly without the economic, social, political and cultural conditions and empowerment needed to otherwise thrive.

This massive violation of rights can only be addressed by governments acting in concert—defended and demanded by progressive civil society participation—to take responsibility for ensuring that the likes of health and education are public goods, available and accessible to all without discrimination. This is a tall order for a growing number of global leaders who seem hell-bent to run in the opposite direction, unwavering in corporate commitments but unwilling to confront the alarming consequences of climate change; epidemics old and new; or gender, age, socioeconomic, racial, ethnic, religious and geographic inequities. They have contributed to the causes, not the solutions, for millions of people for whom death is simply a relief from suffering.

In this context, it is no wonder that scant attention is paid to efforts by the low- and middle-income countries to address inequities within and across borders. In fact, the attention that does go their way tends to depict one humanitarian crisis after another, and to demand that governments in Africa, Asia, Latin America and the Caribbean simply step up and do a better job with the scarce resources at hand. Such "bootstrap economics," coupled with minimal, strings-attached foreign aid, is somehow expected to make a real difference . . . or perhaps not.

Lost in the global shell game of resources in any case are the innovations emerging from the Global South itself, often times necessity being the mother of invention. But undoubtedly, the different approaches and strategies some are implementing can make key contributions to solving problems of equity and equality faced by this (for better or worse) globalized world. Such is the case of Cuba, a country of 11.2 million, which took a new path 60 years ago, and now by all accounts has one of the world's healthiest and most educated populations. Whatever one's political inclinations, these facts merit further study.

Thus, as representatives of nearly 200 countries gather at the first UN High-level Meeting on Universal Health Coverage, **MEDICC Review** takes the opportunity to share with readers both the results and challenges of several Cuban programs and strategies that have extended the right to health in Cuba and abroad.

This issue is intended as a followup to the *Pan American Journal of Public Health's* 2018 special issue on Cuba's health system,[1] which painted in broad scientific strokes the evolution, practice and transformations in areas such as maternal-child health, prevention and control of communicable diseases, climate change mitigation, and human resource training; as well as challenges ranging from the economic to the demographic, including rapid population aging. Most importantly, it described and analyzed a fundamental

pillar of Cuba's single, universal public health system: the strategy of primary health care, which involves health professionals with their communities in protecting and constructing health, informs other levels of care and decisionmaking, and generates greater attention to the social determinants of health.

We introduce our own special issue with another pillar undergirding Cuban public health: the political will to make health a priority, despite resource constraints. In his paper, Dr Lage-Dávila presents the paradox of impressive health outcomes achieved within limited resources, compounded by global economic vicissitudes and US economic sanctions, and illustrated in a biotechnology sector at the service of public health. He challenges new generations globally to use scientific approaches for tackling society-wide problems lest rapidly changing technologies outpace abilities to harness them for the public good, allowing profit-making to reign over social development.

While most of the articles that follow focus on Cuban public health programs and research implementation, two look at broader experiences and their relation to "leave no one behind" and critically, to "leave no one behind while moving forward." The first of these is by Dr Castell-Florit, who refers to the constitutional and legal framework in Cuba providing for the right to health, as well as health as a component of overall policymaking and the intersectoral imperative . . . "health in all policies," looking ahead to "one health."

Dr Álvarez, Distinguished Member and Secretary of the Cuban Academy of Sciences, provides the perspective of an activist determined to incorporate a gender perspective into policy formulation and practice. She shares thoughts on factors affecting women's presence in Cuban and global science, and what can be done to enhance it. Cuba's Academy has the highest percentage of women of any in the world (34% in 2018). But, as she reflects, there is much more to be done in this country where women still do 14 more hours a week of household chores than men, no matter their professional or leadership roles. This gender discussion is pertinent to health for all in the context of social goals—as Dr Álvarez quite cogently puts it: "to reap development, you must sow science," and that means liberating the full potential of women and girls.

The health of women and children is the focus of one of Cuba's national public health programs, the others devoted to older adult health, communicable diseases, chronic non-communicable diseases, and natural and traditional medicines. Four manuscripts bring the Maternal-Child Health Program into clearer focus as it relates to ensuring health for all, the most vulnerable first. Dr Rojas-Ochoa chronicles Cuba's almost six-decade experience with maternity homes for at-risk pregnant women, an institution that also represents the health system's flexibility in meeting different challenges through time. He also cautions that health equity must remain a central emphasis as the system as a whole seeks greater efficiency, advice worth heeding well beyond his own country, as trends in infant and maternal mortality are revealing indicators, especially when disaggregated.[2]

Also in the domain of maternal-child health, Dr Abreu-Suárez writes of challenges faced by Cuban efforts to eliminate childhood

tuberculosis; and Dr Esquivel-Lauzurique describes the use of growth and development studies to follow the health of Cuban children over decades.

Finally, Dr Marcheco-Teruel recounts the principles, practice and results of Cuba's national sickle-cell anemia program, relating it to ethics, reproductive rights, and the rights and treatment of children born with this genetic condition.

The difficult process of putting science to work for the most vulnerable is reflected in two more papers in this **MEDICC Review** issue: Dr Rodríguez-Labrada recounts the determination of scientists to establish in Holguín, a city in eastern Cuba, a top-flight institution dedicated to research and rehabilitation for rare hereditary ataxias. While no cure has been discovered for the condition, which is fatal, the center has developed considerable scientific potential and its results with patients and families are encouraging.

The experience of Cuban biotechnology in lifesaving vaccines is the focus of an article by Dr Sierra-González concerning the Finlay Institute's VA-MENGO-BC, the world's first vaccine proven effective against serogroup B meningococcal infection. Developed in response to an epidemic among youngsters that was declared Cuba's number one public health problem in the 1980s, the vaccine was successful and was later used to combat outbreaks in other countries. It is disconcerting to recall that, despite the vaccine's existence and disposition of Cuban scientists, collaboration with US researchers in this area stalled. One wonders if such cooperation might have given a better chance to the 100 youngsters who lost their lives to serogroup B meningitis in Washington state alone (1989–2007) or to the university students stricken in other states during the 2013 outbreaks. (It was not until 2014 that another fast-tracked serogroup B vaccine was licensed in the USA.)[3,4]

In a related article, Dr Galindo-Santana provides a Cuban perspective on the antivaxer movement and its now ubiquitous social media attacks on childhood vaccination. She also proposes ways to maintain public trust in vaccine safety, with a view to sustaining Cuba's high immunization coverage (>99%). Her voice, urging health professionals to keep science front and center and engage in broad public education, is important for Cuba and other latitudes as well. WHO recently announced retraction of measles-free status from four European countries, including the UK, where antivaxer misinformation campaigns have caused immunization rates to plummet. In 2018, there were 991 confirmed cases in England and Wales, up from 284 in 2017, and 230 in just the first quarter of 2019.[5]

Prioritizing health and putting science to work for public health are joined in Cuba's case with a third essential element: global health cooperation. This issue carries four papers offering an inside look at the principle and Cuban practice, particularly South–South collaboration: Dr Peix relates cooperation with the International Atomic Energy Agency to assist in developing human resources and standardized protocols in nuclear cardiology throughout Latin America and the Caribbean, to ensure more equitable access to lifesaving technologies.


Dr Herrera-Valdés describes experiences in intersectoral action and South–South cooperation to tackle the epidemic of chronic

kidney disease of nontraditional etiology in El Salvador, first observed among subsistence farmers in that Central American nation, but now found throughout the region and elsewhere. Scientists hypothesize that labor conditions plus agrochemicals may play roles in the disease, which has already felled 20,000 in El Salvador alone.

Dr Pérez-Ávila's article is one of the first publications describing the work of the 256 Cuban health professionals who cared for Ebola patients in West Africa during the epidemic in Liberia, Sierra Leone and Guinea. The reference is tragically relevant now, as Ebola once again threatens the lives of people in the Democratic Republic of the Congo, neighboring African countries and worldwide.

Senior Editor Gorry has written a comprehensive article that reviews six decades of Cuban global health cooperation, in which over 400,000 Cuban health professionals have served abroad, primarily in disaster zones or in marginalized communities and remote settings, providing care for the world's most vulnerable. Gorry's feature brings health for all full circle in the Cuban context, as global health cooperation and relations—whether health services, technology transfer or biotech collaboration and exports—hold the key to sustainability for Cuba's single, universal health system, with care free to patients.

The economic and demographic road ahead is undoubtedly a difficult one, and not only for Cuba. Without minimizing the value of global debates on universal health, health care or health coverage, we venture that the urgency faced by low- and middle-income countries—and by marginalized populations everywhere—demands action towards greater health equity and in the form of practical, working models. In such circumstances, the advice of Cuban independence hero José Martí is as compelling now as it was over a century ago: "The best way to say . . . is to do."

In making this issue possible, we are grateful for the cooperation and support provided by PAHO/WHO's representation in Havana, The Atlantic Philanthropies, Ford Foundation and The Christopher Reynolds Foundation. 

The Editors

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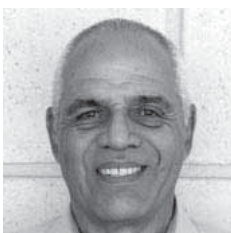
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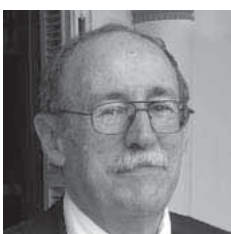
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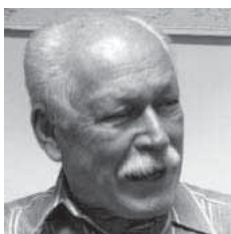
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Science and Challenges for Cuban Public Health in the 21st Century

Agustín Lage MD PhD

ABSTRACT

Cuba's public health outcomes are rooted in political and social phenomena that have favored achievement of health indicators well above expectations for an economy of its size. A less studied causal component of Cuba's development in health is the creation, from early in the 1960s, of scientific research capacity throughout the health system, including use of science to launch a domestic industry for manufacturing high-tech products. This component should play an even greater role in meeting Cuba's 21st century health challenges, especially the demographic and epidemiological transitions, increasing prevalence of chronic diseases, rapid emergence of a complex-product biotechnology pharmacopoeia, greater molecular stratification of diseases, rising health costs, and the need to maintain communicable diseases under control in a global context of climate change and more population mobility.

Tackling these challenges will demand greater scientific influence in the health system, application of a scientific approach in all activities and at all levels, and integration with scientific endeavors of other sectors such as agriculture, industry and education.

KEYWORDS Public health, science, health care costs, health workforce, chronic disease, biotechnology, immunology, aging, Cuba

INTRODUCTION

Although public health is a complex, multifactorial phenomenon requiring qualitative evaluation that cannot be reduced to a series of statistics, some of its aggregate indicators are universally accepted as expressions of the quality and impact of health interventions. Life expectancy at birth and mortality are two of these emblematic indicators.

Public health outcomes in Cuba since the 1959 revolution are recognized worldwide, supported by sound data. Life expectancy at birth is over 79 years—7 years longer than the world average and 3 years more than in Latin America.[1] Infant mortality in 2017 was 4 per 1000 live births, the lowest in the country's history and lower than the US rate. Cuba's physician–population ratio (81.9/10,000) is one of the highest in the world. The country has eliminated 14 infectious diseases, and 9 others are no longer public health problems, as their rates are under 0.1 per 100,000 population.[1] In 2010, Save the Children rated Cuba the best country in Latin America in which to be a mother.[2] Cuba has one of the lowest HIV infection rates in Latin America (0.4% of the population aged 15–24),[3] and in 2015 was certified by WHO as the first country to eliminate mother-to-child transmission of HIV and syphilis.[4] The Bloomberg Report of February 2019 ranked

IMPORTANCE This article highlights the little-explored phenomenon of the early introduction, following the 1959 revolution, of a science-based approach to knowledge construction, inherent in the strategies leading to Cuba's public health achievements.

Cuba 30th among the healthiest countries in the world—higher than all Latin American countries and the USA.[5] The list of such hard facts and indicators could be much longer.

Cuba's results offer an encouraging exception to the usual correlation between health indicators and size of GDP. In this regard, two interrelated characteristics of trends in Cuban health indicators deserve special mention. The first is that changes in the health picture happened rapidly. Life expectancy at birth in 1960 was estimated at 63 and the country had less than one tenth of the physicians it has today.[6] Infant mortality prior to 1960 is hard to determine due to incomplete data, but is estimated at 34.8 per 1000 live births, almost ten times the current rate.[7] The second characteristic worth noting is that not only were the changes rapid, but they preceded economic growth, meaning that they were achieved with limited material resources and in a context of external economic hostility and even aggression.[8–10]

After 1990, this dissociation became evident once again in a longitudinal analysis derived from an “undesirable experiment,” when the Cuban economy contracted by 35% upon the loss of its advantageous economic relations with the European socialist countries and the tightening of the economic embargo imposed by the US government—an era known in Cuba as the “special period.”[8–10] Conventional wisdom and models describing the association between economics and health[11] predicted that Cuba's health indicators would deteriorate (as they did in Russia and Eastern European countries). However, they did not decline to the degree anticipated.[12] Infant mortality, for example, continued to improve during the 1990s, despite a GDP that did not return to its 1989 level until 2003, a trend that continued through the next decade (Figure 1).

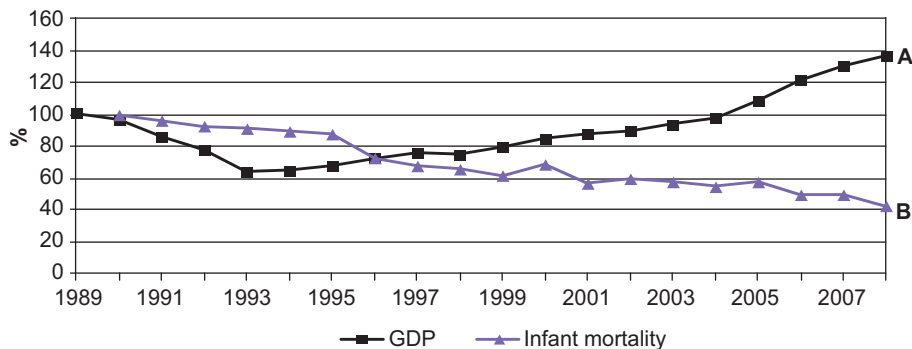
Later in the current century, Cuba's positive deviation from the association between material wealth and health indicators has become evident once again in a cross-sectional analysis by country of the relation between GDP and these indicators. The point corresponding to Cuba in these figures deviates from the line of best fit between GDP and life expectancy and shows that life expectancy is five years longer than would be expected, given the size of the economy. Something similar happens with infant mortality, which also deviates positively from predictions based on economic indicators.[11]

This counterintuitive phenomenon (in which wealth and health are not bound together) in post-1959 Cuban public health merits deeper study, as it can provide insights for other countries as they develop strategies to achieve universal health.

Roots of the paradox

The main explanations for Cuba's health outcomes are political in nature.[4,13] These are reflected in principles resulting in: the priority that Cuban socialism has always given to public health; the single, free and universal character of the health system; an economic order that provided the state with resources for health programs; the capacity for mobilization of human resources; and the social cohesion developed around these policies. As a result,

Figure 1: GDP and infant mortality trends in Cuba



Source: Secondary data, GAPMINDER[11]

A: 1989 GDP, in constant dollars B: % of 1990 rate per 1000 live births (10.7 in 1990; 4.7 in 2008)

GDP: gross domestic product

health promotion and disease prevention, a robust primary care strategy and human resource training have become the cornerstones of Cuban public health.

In this context, it is noteworthy that Cuba's scientific approach to public health policies and programs, coupled with an emphasis on knowledge construction, have played an important causal role in the country's health achievements and will continue to do so. They also help explain why the health status of the Cuban population has advanced beyond predictions based on economic indicators alone.

Human health is not a simple biological attribute. Both the classic definition adopted by WHO in its constitution of 1946 (*Health is a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity*)[14] and other more recent documents that object to the concept of "complete well-being"[15,16] point to other factors that shape health throughout the life course.

Since the 1970s, and from different points along the ideological spectrum, the scientific literature reflects growing recognition of health's social determinants.[17,18] In fact, WHO recognizes that most of the global burden of disease and the principal causes of health inequities found in all countries stem from the conditions in which people are born, live, work and age. These social determinants of health represent a shift in focus that encompasses not only determinants that are social *per se* but also economic, political, cultural and environmental.[19]

The obvious corollary of this definition is that if there are social determinants of the burden of disease and death, there also must be social determinants of improvement in health indicators. Worthy of mention in this regard are Cuba's organized social response since the 1960s and the country's capacity to resist despite economic pressures, particularly those stemming from the US embargo imposed since 1962.[20]

A related factor explaining Cuba's early health improvements was the simultaneous attention, development and priority accorded to health and education—the latter considered an important social determinant of health. Health programs began in 1960 with the creation of the Rural Social Medical Service, while educational programs began in 1961 with the National Literacy Campaign. These two arenas of social endeavor were mutually reinforcing, an example of the close structural correlation between health and education.[21]

Thus, social policies that prioritized both universal public health system development and attention to social determinants contributed to improved health outcomes in Cuba, as did a third, less-studied component of Cuba's health strategy, the subject of this paper: its scientific approach closely connected to the processes of knowledge construction.

SCIENCE'S ROLE IN PUBLIC HEALTH

Superficially, science tends to be identified with laboratories full of complicated instruments, but this is not its essence. Science is primarily a way of thinking, a structured method for obtaining and creating new, generalizable and objectively verifiable knowledge.[22]

The ability to make verifiable predictions and the refutability of hypotheses are the hallmarks of scientific thinking. Its tools are objective measurement of phenomena, identification of associations between data and evaluation of interventions.

This definition is independent of the complexity of the instruments used. These may be simple (e.g., a survey), or very complicated and expensive (e.g., a DNA sequencer or positron emission tomography scanner), depending on the problem studied. The essential thing is not the data collection instrument, but rather the capacity to discern what data should be collected and how to interpret them.

The scientific method is a cultural triumph of the 18th century Enlightenment in Europe. Born of physics, it spread rapidly to the biological sciences and medicine, and more recently, with particular characteristics, to the social sciences. In medicine, it gave rise to "evidence-based medicine" and clinical research methodology. In population health, it gave rise to the epidemiological method and scientific assessment of the impact of collective health interventions.[22]

Public health practice is at once a series of specific actions to improve health and also a continuous process of knowledge construction and dissemination. Knowledge dissemination by itself can alter health indicators through a complex process of mediating variables, among which higher risk perception, a greater culture of health, and conscious lifestyle changes play a key role. Also of interest to science are the ways knowledge is disseminated, incorporated into the thinking of its intended public and subsequently transformed into behavioral and lifestyle changes.

Production of scientific knowledge rapidly accelerated in the 20th century, with two momentous consequences for public health. The first is that the time it takes knowledge and medical technologies to become obsolete became shorter than the working life of a health professional.

While 19th century physicians could practice for 40 years using what they had learned in medical school, today's physicians must update their arsenal of knowledge and technologies several times in their lifetime. Much of what they learned in medical school will probably be obsolete in less than 20 years. Thus, curriculum designers find it ever harder to predict what knowledge and skills students will need 20 years after graduation. And the assumption that education also means "teaching how to learn"—that is,

to interpret and apply new scientific knowledge—becomes all the more central.

The second consequence is that new knowledge and technologies appear and are replaced before there is time to fully evaluate them. Thus, health professionals often will be working with a degree of uncertainty with emerging and inadequately vetted technologies. This means they must know how to distinguish between different levels of evidence supporting each new proposal and to participate themselves in validating the health technologies they use in their specific context.

Both phenomena require all health professionals to conduct scientific research and be proficient in its methods.

SCIENCE IN CUBAN PUBLIC HEALTH'S INSTITUTIONAL EVOLUTION

Scientific development is a two-term equation. One of them, quantitative, is expressed in terms of the number of scientists, institutions and articles published; the other, conceptual and strategic, lies in the strength of the connections between science and other spheres of human endeavor—among them the promotion, preservation and improvement of health, and the prevention of disease.

Health programs in Cuba embraced these ideas in the early 1960s, just after the creation of the new Ministry of Public Health (MINSAP) in August 1961, replacing the former Ministry of Health and Social Assistance. By integrating medical care, teaching and scientific research into all health institutions, they have become centers for knowledge construction and dissemination, adding to their value as service providers.

Also dating from the 1960s is the Statistical Information System, which began by improving vital statistics. The 1960s also saw the first programs for vaccination and infant mortality reduction incorporating a scientific design and objective evaluation criteria, as well as greater attention to epidemiology with the first national forum in this field held in 1963. In 1965, the National Scientific Research Center, including an important biomedicine division, was founded under the Ministry of Higher Education. Its scientific personnel were trained from the ranks of medical students (at the time, the majority of university students), particularly those enrolled in the Victoria de Girón Institute of Basic and Preclinical Sciences, created in Havana in 1962.[23]

In 1966, the first eight MINSAP research institutes were created (Oncology and Radiobiology, Cardiology and Cardiovascular Surgery, Gastroenterology, Hematology and Immunology, Angiology and Vascular Surgery, Neurology and Neurosurgery, Nephrology, and Endocrinology). These were followed by the establishment of the Institutes of Nutrition and Occupational Health. During this period, the Hygiene, Epidemiology and Microbiology Institute, created before 1959, reached full scientific and technical development, as did the newly baptized Pedro Kouri Tropical Medicine Institute, named after the scientist who founded it in 1937. This made a total of 12 institutes.[24] In 1973 came the founding of the Health Development Institute (IDS), which conducted major studies such as the Growth and Development Survey of the Cuban population.[25] These institutes, each in its own field, integrated basic research and technology assimilation, as well as epidemiological projects and those devoted to health systems and services evaluation.

For example, as early as 1981, the National Oncology and Radiobiology Institute housed the laboratories that produced the first monoclonal antibodies in Cuba; the original technology had been developed in 1975.[26] This institute was also the gateway for the technological assimilation of radiotherapy and nuclear medicine, including the first radiation protection service; it was the incubator for the first specialized clinical trials unit, the National Cancer Registry[27] and the initial versions of the National Program for Reduction of Cancer Mortality.[28] Each of these scientific institutions has a similar story. Science was part of virtually all actions at all levels that changed Cuba's health picture.

In summary: In 1959, Cuba had only one institution devoted to higher education in medicine—the University of Havana Medical School. By 2018, it had 25 medical faculties in 13 medical universities throughout the country. This human resource capacity has been supplemented today by 37 Science and Technological Innovation Units,[13] over 4300 researchers and more than 1000 PhDs in the national health system. Strengthening this community is Infomed, the system's national online platform for communication, knowledge sharing and knowledge creation, established in 1992 from the embryonic National and Provincial Medical Sciences Information Centers set up nearly two decades earlier.[29]

CUBAN SCIENCE AND THE INDUSTRY OF HEALTH

Biotechnology took off in the 1980s with the creation of the Biological Front (directly overseen by the highest level of government) and the launch of the Biological Research Center in 1981, the Genetic Engineering and Biotechnology Center in 1986, the Immunoassay Center in 1987, and the other institutions that by 1992 were included in the Western Havana Scientific Pole, with more than 10,000 employees.[30]

In 2012, these institutions merged with the enterprises of the pharmaceutical industry, and together gave rise to the umbrella company BioCubaFarma, which at this writing includes 34 enterprises, supplies the health system with more than 1000 products (including 62% of the essential medicines list), holds 182 patents, conducts over 100 simultaneous clinical trials with its products at 200 clinical sites, and exports to 49 countries.[31]

Behind these figures lie concepts. With the advent of biotechnology in Cuba arose the concept of the “research and production center,” where scientific research, production and export activities take place under the same management in a closed financial loop,[30] the precursor of the high-tech socialist state enterprise. These institutions embody a trend that emerged in the industrial sectors of the more technologically developed world in the mid-20th century, whereby scientific research became an integral part of the activities of corporations, which *ipso facto*, shouldered the burden of their financing. An original concept emerged in Cuba, however, that did not replicate the global biotechnology scheme: the integration of industry and health programs.[13,30]

Several examples illustrate this. The first major success of Cuba's nascent biotechnology sector was the meningococcal meningitis B vaccine, the first achieved globally, which halted an epidemic of this disease in the 1980s. The Finlay Institute not only created the vaccine but was an active participant in confronting the epidemic. Later, the recombinant hepatitis B vaccine brought the incidence of that disease down to zero in children under 15.[13,30]

The Molecular Immunology Center achieved 100% coverage of chronic kidney failure patients with recombinant erythropoietin and today plays a leading role in the country's cancer control program. Several of its projects (such as the one in Villa Clara Province for access by lung cancer patients to immunotherapy) are complex health interventions aimed at assessing the population impact of supplying advanced biotech products to all cancer patients in a given territory.

Possibly the most outstanding example of the synergy between cutting-edge technology and primary health care lies in the Immunoassay Center (CIE). This research and production institution was created in 1987, but its founding team had been working throughout the previous decade on immunoenzyme diagnostic techniques and computerized equipment to enable inexpensive implementation of these techniques on a massive scale. In its 30 years of operation, CIE has developed 26 diagnostic reagent kits for 19 diseases, as well as 15 types of diagnostic equipment and 25 software packages. It has 1562 laboratories in Cuba and 546 abroad.[32]

The most interesting aspect of CIE's experience is that virtually all its products have emerged as part of a public health program, and their integration into these programs has shaped product design. Thus, CIE products are part and parcel of programs such as maternal and child health; certification of blood, placenta and organs; epidemiological surveillance; cancer and diabetes control; and minimally invasive neurosurgery—all products used in the national health system.[13,30,32]

What often happens in countries with major pharmaceutical and biotechnology industries is that the industry's strategy (which seeks to maximize profits) and the health system's strategy (which seeks to maximize coverage and impact on population indicators) are at variance and often mutually exclusive.

In contrast, Cuba's biotechnology sector is already shaping an industry model that takes responsibility for its products' coverage and impact on population indicators, designs population health interventions and participates in their evaluation and financing. This strategy may drive up costs in the short term, but in the medium term, it reinforces the "proof of concept" of its products' impacts, and hence, its competitive position. The full cycle is completed by the twin means of exports and health impacts, mutually reinforcing.

THE 21ST CENTURY BRINGS NEW CHALLENGES

The Cuban health system has successfully responded to the challenges of the 20th century in which the main challenges were achieving full health service coverage, improving maternal and child health, and controlling infectious diseases. These challenges were tackled essentially with firm political will supported by parallel successes in education and the strong cohesion and public mobilization generated by Cuba's social project. The first point

of this essay is to underscore the role of science in achieving these results. The second is that the role of science should be expanded further to meet the health challenges of the 21st century.

Disregarding the inevitable exhaustion of reserves to maintain it indefinitely, the past decade's trend toward stabilization of life expectancy (about 80 for women and 76 for men) and infant mortality (about 4 per 1000 live births)[1] suggests the emergence of new barriers to steady improvement in health benchmarks, the nature of which needs to be understood. Apart from climate change, the global effects of migration and the phenomenon of multidrug resistance, this article proposes to highlight five major challenges to health improvement, namely: (1) population aging; (2) non-communicable chronic diseases; (3) the biological pharmacopoeia and molecular stratification of diseases; (4) rising costs of medical services and drugs, and the distorting effects of the market; and (5) emerging and reemerging diseases.

Population aging The Cuban population has experienced a steady increase in life expectancy for years, coupled with a steady decline in birth rates, resulting in an aging population. The percentage of older adults (aged ≥ 60 years) grew from 12.9% in 2000 to 20.1% in 2017.[1]

Population aging is not limited to the quantitative fact of longer life expectancy, which demands social actions to ensure health care in older age and adaptation of institutions and work processes; rather, it also involves a qualitative change in human biology, which has come about as a result of evolution, as people live decades in the postreproductive stage, while the human genome has been selected over the course of thousands of years to maintain homeostasis and species survival in the prereproductive stage.

One of the consequences of this disconnect between the genome and the current conditions of life is "inflamm-aging," a state of chronic, low-grade inflammation that accompanies aging, even in the absence of disease,[33,34] for which health systems currently have no defined strategies.

Non-communicable chronic diseases Accompanying population aging is an increase in non-communicable chronic diseases: atherosclerosis, hypertension, diabetes, cancer, arthritis, Alzheimer's disease and others, which also involve a qualitative change. Table 1 summarizes essential features that differentiate chronic diseases of adults from infectious diseases and

Table 1: Differences between acute and non-communicable chronic diseases

Attribute	Acute	Chronic
Conditions	Infections, injuries, poisoning, etc.	Cardiovascular diseases, cancer, chronic kidney disease, diabetes, degenerative diseases of the central nervous system, etc.
Onset	Sudden	Insidious over time
Causes	Single primary factor	Multiple
Clinical progression	Generally rapid	Slow
Treatment	Single targeted interventions	Multiple, complex interventions
Aim of medical intervention	Health restoration	Long-term control, treatment of complications
Life stage affected	Throughout life course	Mainly postreproductive: relaxed homeostatic controls, no protective genes selected through evolution

Source: Author

accidental injuries in terms of their onset, progression, causality, treatment aims, stage of life in which they appear and their underlying mechanisms.

Modern health systems emerged in many countries in the 20th century and evolved in an era in which the essential tasks, largely successful, were infectious disease control and improved maternal and child health. These systems were developed to address single primary causes, basically external, through targeted and public health interventions. However, the structure and functioning of those health systems are not well adapted to the era of chronic diseases. Reconfiguring them for this purpose will require research not only on new diagnostic and treatment products, but also on the workings of the health systems themselves, as well as social and intersectoral action to improve the quality of life of older adults and people with disabling chronic diseases.

Another important transformation required of health systems will be adaptation to the modern “life course” paradigm, which has broadened the temporal horizons of causality and included transgenerational effects. The causes of today’s diseases do not lie solely or even mainly in exposure to risk factors in the immediate term, but in a complex pattern of contextual influences present throughout the life course, in prenatal life, and even in previous generations. The contribution of scientific research across its spectrum of specialties—from basic sciences to health administration, stretching from clinical to epidemiologic, public health, and the social sciences—has been and must be pivotal.[35]

The biological pharmacopoeia and molecular stratification of diseases New products will also be necessary. Many will derive from the so-called “biotechnology revolution,” which is essentially the ability to identify and clone genes and re-express them in suitable vectors on an industrial scale. This revolution is still in its infancy. Its first significant product was recombinant human insulin, registered in the USA in 1982.[36] Before then, the vast majority of drugs were chemical products, but since then, the fraction of the pharmaceutical market corresponding to biological products has grown and currently stands at 25%. The fact that today, more than 900 biotech products are in clinical trials and 40% of all drugs in the research pipeline are biological products leads to the prediction that these products will soon represent more than half the pharmaceutical market (Figure 2).[37] For example, current predictions indicate that by the 2020s, more than 60% of cancer patients will receive some form of immunotherapy.[38]

Biological pharmaceuticals will increase specificity of treatments. This good news, however, implies the challenge of identifying the molecular targets of each biopharmaceutical and the genes that predict the sensitivity to each treatment. Each known disease will likely be stratified into many subtypes and variants, each with a different treatment, in what is now known as “precision medicine.” This will require physicians to interpret many biochemical and genetic data simultaneously to guide therapy decision-making.

The rising cost of medical services and drugs and the distorting effects of the market All these changes already have—and will continue to have—a substantial impact on the cost of medicines and medical services, threatening the collapse of health systems forced to shift from a chemical pharmacopoeia based on widely used, more affordable generic drugs to a biological pharmacopoeia consisting of expensive products targeting a small niche market of patients.

Part of this cost increase is due to technical components: more complex processes associated with production of biological substances, and wider molecular variability, adding to costs of quality control systems. At some point, though, technology development is expected to lower the cost of these processes.

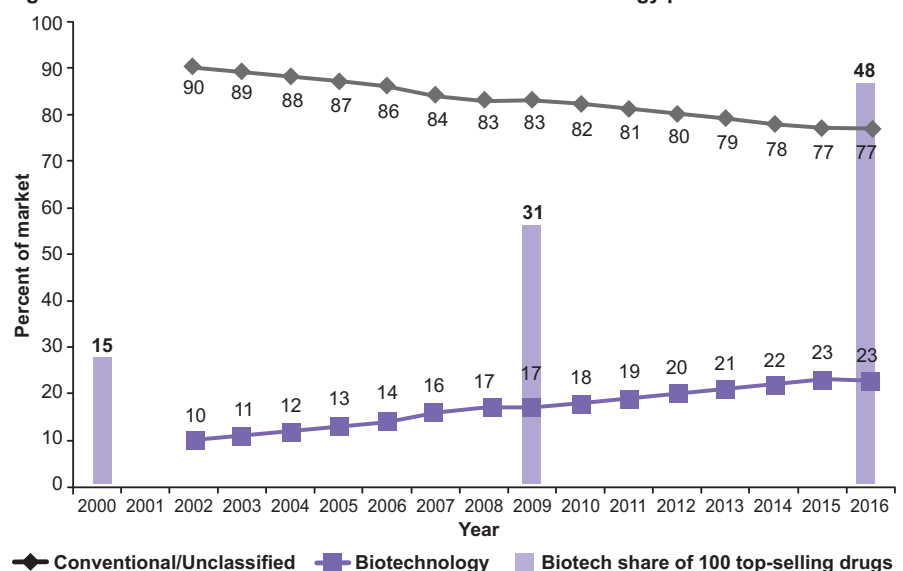
But another cost component is derived from the distorting effects of the market. Pharmaceutical research funding changed in the second half of the 20th century. As late as the 1970s, less than 5% of clinical trials were funded by private industry. In 2004, that percentage was already 57%; today it is higher.[39]

This change puts scientific decision-making in the hands of industry, which in turn is subordinate to market interests in most contexts. The result is the search for small, incremental improvements to reduce the risk of clinical trials, making for only minor differences in previous treatments that are nevertheless sufficient to patent and sell at a higher price. This, in turn, finances aggressive marketing to ensure that new products are financed by health systems. This is not a technical but a political component and has been explored elsewhere.[40,41]

The arrival of many biotech products also has implications for science’s impact on health systems, since it will require deployment of national productive capacity, as well as capacity to assess population impact of each potential new technology. Some countries have created institutions specifically to conduct cost-benefit analyses.[42]

The problems described in the preceding paragraphs have increased hand in hand with the rising incidence of non-communicable chronic diseases.

Figure 2: World market share of conventional and biotechnology pharmaceuticals



Source: Lage[40] with data from Evaluate Pharma,[37] used with permission

Emerging and reemerging diseases Infectious diseases have not disappeared; there are new ones and some that had disappeared are reappearing. This phenomenon not only has biological, but socioeconomic and political components. Suffice it to mention, for example, the antivaccination movement, which is growing even in the middle and upper classes of wealthy countries, posing a serious threat to public health and constituting a retreat to eras of underdevelopment that the world believed it had definitively left behind.[43]

Climate change, growing urbanization and population mobility are creating the conditions for this reemergence of infectious diseases, which now is occurring in aging populations.

THE RESPONSE AND ITS DEMAND FOR KNOWLEDGE CONSTRUCTION

The first message of this article is that while the political will, priority and role of the state (and not the market) in health, interdisciplinarity and social cohesion are at the root of post-1959 Cuban public health outcomes, less studied but also important has been the role of an early focus on scientific methodology and research practice.

Measuring phenomena, describing associations and objectively evaluating interventions are the three basic functions of health research promoted since the founding years of Cuban public health. Added to this was the role of science in building an industrial sector for biotechnology and the pharmaceutical industry, supporting the effort with a scientific approach to technology evaluation and adoption, and the capacity to generate innovative products.[22,30]

The second message is that the role of science in health must be expanded in the immediate future, included in all stages of knowledge construction from basic research to health care delivery (also with a scientific approach), and encompassing development of products and production processes.

History teaches us that decades may pass before a scientific discovery (even a well-validated one) has an impact on population health. By way of example, the smallpox vaccine was discovered in 1798, but it took almost 200 years (until 1980) to eradicate the disease.[44] Although the polio vaccine was developed in 1955, wild-strain cases are still being reported.[45] These intervals could be reduced through a scientific approach to research on barriers to application of advances and on health intervention implementation processes that takes into account factors such as patient, family and community education—all vital as well to the much-needed shift from the concept of preserving health to that of constructing health.

In the face of a health situation marked by a growing predominance of non-communicable chronic diseases, significant impacts are unlikely to be obtained with straightforward measures as occurred with vaccines to combat infectious diseases. More than discrete measures, the greater need will be for policies and programs designed to consider context and its influences on individual and population health at multiple levels over extended periods, with special emphasis on critical points in the life course.[35] Introducing new products and technologies proposed by scientists into the health system will be more complicated and multifactorial, and their evaluation more complex.

The first step in preparing our science system to tackle the challenges of the 21st century will be to explicitly develop and modernize a “demand for knowledge.” What knowledge, skills and technologies do we need for this new stage, given our material conditions?

- We will have an older population, demanding more scientific research specifically targeting this stage of life. We will have a disease landscape in which non-communicable chronic conditions will play a key role and for which control strategies must address biological problems not yet solved by science, as well as complex interventions targeting both the individual and other critical actors (family, community, school and workplace).
- The system’s center of gravity will increasingly shift towards the primary care level, where more scientific research must be directed. Institutions must also be strengthened to permit greater scientific activity at this level.
- A more intersectoral approach in health programs and scientific research will demand greater participation by professionals outside the health system (for example, in nonmedical universities). It will be especially important to improve communication between the health and social sciences as attention migrates from the study of disease to the study of risk, and from there, to positive health indicators; and from the concept of “preserving health” to “constructing health,” which considers people not as passive beneficiaries of services but instead as active agents in the health-building process.
- In the global context created by market-driven industry, replete with costly medicines and equipment whose health impacts are not always sufficiently validated, substantial scientific capacity will be needed to decide what new items to assimilate and also how to continue developing our own industries.

Although high-priority, centrally directed scientific projects will continue to be necessary, the scientific challenges of the 21st century call for a response distributed across the system, where all professionals involved in health are proficient in scientific methodology (regardless of the complexity of the equipment they can access in each location) and embrace a culture in which they measure and evaluate what they do. It will be increasingly necessary to have a health system armed with a scientific culture expressed in day-to-day decision-making, which implies data-driven reasoning, alternatives designed based on verifiable hypotheses, decisions submitted to impartial critique, impact assessment. This also means rejection of improvisation, pseudoscience (which, like infections, often reemerges), uncritical imitation and superficiality.

All of this is possible. It will be necessary to overcome the economic constraints faced by all health systems, exacerbated in Cuba by the US economic and trade embargo that persists and is reinforced despite its overwhelming worldwide moral rejection.


Nevertheless, there are favorable conditions:

- Human capital, since Cuba has one of the highest densities of health professionals in the world, armed with knowledge and values;
- Universal coverage and access to the services of a single and public health system and the strength of its primary care;

- A national industry that is not in private hands, with capacity to assimilate cutting-edge technology and generate innovative products;
- A medical sciences university system covering all provinces and actively participating in scientific research;
- An educated, well-informed and engaged population, especially in health-related activities;
- Intersectoralism and political will, key premises determining the health of the Cuban population;
- Half a century of experience in health development, including constructing knowledge in the biological, clinical, epidemiological and operational spheres.

How far we advance in public health in the 21st century will depend on intelligently leveraging these conditions, and on the volume and quality of messages drawing on the Cuban experience that we can communicate to the international health community.

CONCLUSIONS

Scientific research has been an important component of Cuban health achievements and must serve as a basic resource for tackling current challenges and those already visible on the horizon. This endeavor does not exclude any sector of society or branch of science and relies on the basic synergy among science, education and development, a distinctive Cuban hallmark in the field of health. 

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Cuba's Women of Science Of Glass Ceilings, Velvet Circles and Pink-Collar Ghettos: Lilliam Álvarez MS PhD Secretary, Cuban Academy of Sciences

Gail Reed MS

She was a country girl from the northeastern Cuban province of Holguín, her father a farmer, her mother a teacher. Fast forward a few decades: Dr Lilliam Álvarez mastered mathematics, physics and nuclear science, finally specializing in numeric solutions to differential equations. She spent 20 years at the Cybernetics and Physics Institute in Havana, half that time as deputy director. For another eight years, she served as director of science in the Ministry of Science, Technology and the Environment. Full professor and senior researcher at the University of Havana, she is a member of the national academic authority that awards doctoral degrees in math and is Cuba's ambassador to the International Mathematical Union. In 2000, she was inducted into the Caribbean Academy of Sciences, and in 2008, was elected a full member of the Third World Academy of Science (now The World Academy of Sciences).



E. Añé

But over time, her rich bibliography, with titles the likes of *A numerical technique to solve linear and non-linear singularly perturbed problems* began to be peppered with other provocative gender-informed work: *Women doing hard sciences in the Caribbean*, *Are Women Good for Math?* and her 2011 book *Ser mujer científica o morir en el intento* (Be a Woman Scientist or Die Trying). Her focus on women in science—and their rights to belong in its leadership as well as its ranks—is also reflected in her activist approach internationally and in Cuba.

She is a member of the Organization for Women in Science for the Developing World and heads its Cuban chapter. After her designation as a Distinguished Member of the Cuban Academy of Sciences, she was elected Secretary in 2010 and also chairs its Commission on Women in Science.

The Cuban Academy of Sciences was the right place to hear her story and to explore the way she sees women scientists in today's Cuba—and the country she would like to see in the future.

MEDICC Review: Let's start from the beginning: what drew you to science, and to math and physics in particular, as a young girl in small-town Cuba?

Lilliam Álvarez: Although my parents weren't highly educated, my mother was a teacher. She had 14 brothers and sisters and all of them were teachers! And one of them, an uncle, taught physics. So, studying was a way of life in our household and I also got exposed to the hard sciences through him, and became what they called a "class monitor" in the subject. Monitors were supposed to keep up their grades, and even to teach a class now and then.

Another person influenced me a lot: math professor Dr Matilde Camayd, who was an important role model. You can imagine that in those days, the 1960s, there weren't many women in

math and science. Then there was a chemistry teacher, and my own sisters, one of whom became a chemical engineer. I was literally surrounded by women university graduates. But my father wouldn't let me enroll in high school in the capital; I had to wait until 1967, when I took off to enroll in the University of Havana.

By that time, university education had become totally free to students, and they hadn't yet instituted the rigorous entrance requirements they have now: you simply had to show up, climb those tall stairs to the statue of the Alma Mater, and matriculate. You were also automatically given dormitory space if you were from the provinces. For the first time, you were seeing young people from the countryside, women, black and mestizo students, filling the halls of the university. It was quite something, and a little intimidating for me.

MEDICC Review: How many students enrolled in math and physics your year, and how many finished?

Lilliam Álvarez: About 100 enrolled with me that first year, only 15 or 20 of us were women; and only 25 ended up graduating, of whom only 6 or 7 were women. It was clear that the university was open to all, but to graduate you had to study very hard. And that was tough, because it was a time of enormous cultural activity, music festivals, folksinging, dancing . . . big temptations.

But that was when I also began to realize that without science, no country can develop. The industrialized nations have known that for a long time. You have to sow science to reap development: a critical mass of university-trained scientists is an important indicator of social and economic development for every country, a key factor for sustainability.

At that time, we weren't yet using words or concepts like "gender equality" or "social inclusion," but in fact, that's what was happening at universities and in the Cuban workforce as a whole. The potential was enormous: women constitute 50% of human potential, half the potential of societies worldwide, half the potential of our own country, and we certainly couldn't afford to lose it.

MEDICC Review: If we look at the facts today, how are Cuban women represented in the sciences? How many are there? And where do you find them?

Lilliam Álvarez: Women constitute over 40% of the labor force in Cuba. We are over 60% of university graduates and approximately 49% of the country's scientists (that is, those with higher academic degrees). Interestingly, Cuba's Academy of Sciences has the highest percentage of women of any academy in the world, revealed in a 2015 study by the InterAcademy Partnership (The Global Network of Science Academies): at that time it was 27% (as compared to the world average of 12%) and in 2018, it had climbed to 34% of our over 400 members. We have a commission that I chair, which works to promote women's leadership in the sciences, and right now half the leaders in the Academy are women. Every six years, we renew membership, add new members, and now are turning special attention to incorporating younger people as associate members as well. In order to become a member, you have to be nominated by the scientific council of the institution where you work, and then there is a formal and quite thorough process for final consideration.

I also work to attract young people to the sciences as career paths, particularly young women, through the Academy's Science Promotion team that goes to secondary and high schools, organizes science fairs, and is now participating in establishing the first interactive "scientific park" here in Havana.

Nevertheless, there are challenges: you asked where the women scientists can be found. The truth is that they are still located more at the bottom of the leadership pyramid than at the top. Today, we have the first woman rector at the University of Havana, an institution that is over 300 years old!

MEDICC Review: What are the barriers? You mention several in your book . . . are these applicable to Cuba today?

Lilliam Álvarez: Certainly. I think the most important barrier is imposed by the realities of daily life. We made lots of headway through the 1980s, both through efforts of government and the Federation of Cuban Women. Women began to study, to work, and this was supported by child care centers available to youngsters of working mothers, as well as school lunch programs and other facilities, and salaries that went a lot further than they do now.

However, then as well as now, the double and triple shift is a huge burden for working women, more so for women aspiring to career development and leadership. Studies show that Cuban women do 14 more hours of chores weekly than men. Economic crises complicated by the ever-tighter US economic sanctions on Cuba make daily life even more difficult today. And of course many households are home to multiple generations, with a tendency to replicate patriarchal divisions of labor and situate working women as caretakers of both the elderly and the children (we are the "sandwich generation"!).

As with issues of skin color and sexual orientation, changing consciousness is the key to battling inherited cultural biases and stereotypes. This has to be active, constant and vigilant. For example, I found myself replicating traditional gender roles with my own children: I had my son taking out the garbage, lugging home produce from the farmers' market, and my daughter helping me with the cleaning and dishwashing!

MEDICC Review: You refer in your book to the glass ceiling, "velvet circles" and pink-collar ghettos. I'll include a graphic here on those subjects. But can you give us some examples that may be global but also pertain to Cuba?

Lilliam Álvarez: Ah, yes. I borrowed some terms from the global movement for women's empowerment, and invented a few of my own, for example the "velvet circle." The basic idea behind the book was to compile results of gender-based studies, but not entirely focused on the social sciences. Why are there so few women mathematicians in the world? Physicists? What is happening with women of color, who research shows must work three to four times harder to make it into their professions, and even harder to be recognized for leadership?

First, there are the stereotypes. If women study science, the machista version goes, then they should stay in the social sciences, which are more attuned to their "vocation" for service. So we find women in the pink-collar ghettos of social sciences, health, teaching. In Cuba, it is also true that, historically, medicine has been a very prestigious calling, so that's another reason explaining women's choices. But take a look at the literature in math and physics: if you have any pictures in the textbooks, they're of old, bald white men with glasses, and the problem-solving always starts with "Pepe had five apples . . .", never "Lucy" or "María."

And here I have a criticism of scientific journals in general: the norm is to list only the first initial of an author in the references, making it almost impossible to carry out studies on the presence of women scientists in the literature. You need to help us change that!

Then there is the infamous glass ceiling, which goes along with the pyramid concept. Women become scientists, but they

Barriers to Women in Science and Leadership

Descriptor	Meaning
The Scissor Effect, the Pipette or the Pyramid	Reduced percentages of women with higher academic degrees and promotions, as compared to male colleagues, even though more women may have started in university or become university graduates
Pink-collar Ghetto	Overrepresentation of women in health and education, the more service-oriented and social sciences; and underrepresentation in natural or “hard” sciences, considered the purview of men
Glass Ceilings and Walls	Limited empowerment to reach important decision-making levels of leadership, and horizontally, to explore fields in addition to those where a woman has achieved expertise
Sticky Floors	Women bound to the lower ranks of their professions by the burden of family: the good wife, mother, daughter, caretaker, homemaker, lacking enough time to advance or take on leadership
Slippery Stairs	Women undervalued by male supervisors, unwilling to recognize their potential for advancement in their fields or promotion to greater responsibilities
The Velvet Circle	Relegation of women to particular leadership roles to which patriarchy assumes them best “suited” so as not to “overburden” them: the director of communications, but never the director
The Good Girl	Gender stereotyping that begins in the home and schools, in which girls are to be exemplary in all things but never outspoken
Super Woman	Expectations held out by society of women who have earned leadership or distinction in their field, “liberated but overburdened, enslaved by daily second or third shifts”
Peak to Plains	The duty of women in the sciences and in leadership to pass on their experiences and learning, particularly about barriers to empowerment, to help transform society and ease the way for women at the base, “on the plains”

Source: Álvarez L. *Ser mujer científica o morir en el intento*. La Habana: Editorial Academia; 2010. 95p. Spanish.

simply aren't promoted at the same rate as men. That is a global phenomenon, perhaps less present in Cuba, but certainly present. And here it is also influenced by the household burden: not every capable woman professional wants to be a leader in her field or director of a program or institution, if it means taking her to the point of exhaustion.

There is also the concept of the “good girl,” which needs to be tackled in the schools. Girls are supposed to excel, get good grades, and be exemplary . . . but not to be outspoken or have the courage to defend their ideas. As a result, you get adult women who will say they don't really believe in “this thing” called gender roles, that all you have to be is good at what you do and you will succeed, be a “good girl.” I have heard this in Cuba quite a lot.

Finally, there is what I call “from the peak to the plains”, a reminder to all those women who have climbed to the top not to forget the women behind them, where they come from. As Dr Rosa Elena Simeón, an extraordinary Cuban scientist, once said, “when a woman plays a leadership role, she promotes other women in the process,” as an encouraging role model and inspiration. And she can also bring to that role different styles of leadership.


MEDICC Review: The future for Cuba's women scientists? For Cuban science?

Lilliam Álvarez: We need to build a future for the planet and for our country that is sustainable, in harmony with nature, that develops high standards of health and education, prevents vulnerabilities and above all does this by using the benefits of science. Through education and science, both governmental and nongovernmental actors can make better and more rational, informed decisions.

All of this requires a gender perspective, which has to be present in all spaces of society. In the schools, in workplaces, in neighborhoods. As activists, we have to promote debate on these

issues, from the ground up, across disciplines, geographies and in all contexts, including social media. We need to move to greater equity in our socialist context, further opening the doors for the new generation of women.

MEDICC Review: You mentioned that you are working on a new book about Cuban women scientists, past and present. If there were one, now gone, whom you would have liked to meet, who would it be? And why?

Lilliam Álvarez: Dr Laura Martínez Carvajal, Cuba's first woman physician. You know, she studied physics first, which took her to ophthalmology, through the study of lenses. She was an extraordinary thinker, woman and scientist. I discovered her story right here, in the Academy of Sciences. Why? Because she is the first one to come out of the shadows, out of anonymity. But there are so many, many more. 

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Cuban Meningococcal Vaccine VA-MENGOC-BC: 30 Years of Use and Future Potential

V. Gustavo Sierra-González MD PhD

ABSTRACT

Every year, meningococcal infection by *Neisseria meningitidis* causes over 500,000 cases and 85,000 deaths in the world, with 20% of survivors suffering sequelae. In Cuba its incidence in 1980 reached 5.9 cases per 100,000 population; about 80% of cases were serogroup B, prompting health authorities to declare meningococcal disease the country's main public health problem.

Several provinces reported over 120 cases per 100,000 children aged <1 year, overwhelmingly serogroup B. At that time, no vaccines existed with proven efficacy against *N. meningitidis* serogroup B, nor was there a vaccine candidate that could be successful in the short term. By 1989, researchers in Havana had developed a Cuban meningococcal B and C vaccine, VA-MENGOC-BC, the world's first against serogroup B meningococcal disease. Its efficacy of 83% was demonstrated in a prospective, randomized, double-blind, placebo-controlled field study. Vaccine production used vesicle or proteoliposome technology for the first time. The same year, the World Intellectual Property Organization awarded its gold medal to the main authors of the VA-MENGOC-BC patent.

The vaccine was used in a mass vaccination campaign and later included in Cuba's National Immunization Program, with a cumulative impact on incidence of serogroup B meningococcal disease greater than 95% (93%–98%). Mass, systematic vaccination shifted the spectrum of meningococcal strains in healthy asymptomatic carriers and strains circulating among population groups toward nonvirulent phenotypes. The disease ceased to be a public health problem in the country. VA-MENGOC-BC is the most widely applied vaccine against serogroup B meningococcal disease in the world. Over 60 million doses have been administered in Latin America. In several countries where it has been applied, in which strains other than the vaccine-targeted strains circulate, VA-MENGOC-BC has demonstrated effectiveness against all (55%–98% in children aged ≤4 years and 73%–100% in children aged >4 years). The vaccine and its proteoliposome technology have had an impact and continue to have potential, not only for meningococcal disease, but also for development of other vaccines and adjuvants.

KEYWORDS *Neisseria meningitidis*, meningococcal disease, meningococcal vaccine, biotechnology, pharmaceutical industry, bacterial meningitis, meningococcal meningitis, immunization, vaccination, Cuba

INTRODUCTION

Meningococcal disease, caused by infection with *Neisseria meningitidis*, has been greatly feared since the 19th century[1] and is still a global public health problem. Its main variants are meningitis and septicemia, both severe conditions and leading causes of invasive bacterial infection.[2]

Worldwide, annual incidence ranges from 1 to 27.5 per 100,000 population. During epidemics in the “meningitis belt” (Sub-Saharan African countries from The Gambia to Sudan), up to 1% of the population might become ill.[3,4] Overall case fatality is 5.3%–26.2%, with an average of 14.4%. During an epidemic in Africa, case fatality can exceed 30%.[5] Despite underreporting in many areas, it is estimated that there are over 500,000 cases and over 85,000 deaths every year. Twenty percent of survivors have sequelae, with risk in Africa triple that of the USA or Europe.[6]

There are millions of asymptomatic nasopharyngeal carriers of *N. meningitidis* in the world who can transmit the disease to others. Reported frequency is greatest in young adults (10%–35%).[7]

IMPORTANCE This article reviews development, characteristics, trials and use of the Cuban vaccine VA-MENGOC-BC, the world's first effective vaccine against serogroup B meningococcal infection, 30 years after its efficacy was demonstrated. The paper also describes its impact on population health in Cuba and other countries, especially in children and young people, as well as the contributions of its production technology to scientific and technological advances in the biotechnology industry.

In the 1960s, meningococcal disease was considered a public health problem only in tropical countries, but in the 1970s, this view changed with the appearance of outbreaks in Europe and North America. Since World War II, the main epidemics have been in Sub-Saharan African countries, including the meningitis belt, where 60% to 65% of all meningitis cases are meningococcal meningitis. However, meningococcal disease now occurs on every continent. Meningococcal disease caused by serogroup B meningococci occurs mainly in the countries of North America, central and southern Europe, southern and northeastern Africa, the Middle East, Russia, China, Japan, Australia and New Zealand.[3] During the early 1980's, when Cuba was just beginning vaccine development for later preclinical and clinical assessment, production and use, the country was a hot spot on the map of worldwide meningococcal disease burden, reaching an all-ages incidence of 14.4 cases per 100,000 population by 1984. After mass vaccination was instituted, beginning in 1989, meningococcal disease ceased to be a public health problem and Cuba no longer appears among the hot spots still found in other regions.

This article assesses the importance and current relevance of meningococcal disease in the world, its status in Cuba and results of the Cuban meningococcal BC vaccine, VA-MENGOC-BC, since its development. It analyzes, among other aspects, the impact of the vaccine's application, its current usefulness, relevance of its pioneering technology and its contribution to Cuban and global scientific development.

MENINGOCOCCAL DISEASE IN CUBA, VACCINE DEVELOPMENT AND USE

Meningococcal disease, characteristics and burden in Cuba: confronting and solving the problem From 1916 to the mid-

1970s, Cuba experienced only sporadic cases of meningococcal disease. In 1976, outbreaks began to occur that ballooned into epidemics. In 1978, incidence was 1.5 per 100,000 population and by 1979 it had reached 5.6 per 100,000 population. Over 50% of cases were caused by serogroup C and close to 35% by serogroup B. Most affected were children aged 10–14 years, followed by those aged <1 year.[8]

In 1979, Cuba undertook a vaccination campaign to control the disease; 3,245,046 people aged 3 months–19 years were vaccinated with meningococcal AC vaccine (Merieux, FR), for over 80% coverage. Incidence due to serogroup C decreased, but meningococcal disease continued to increase, and in 1980 reached 5.9 per 100,000 population; case fatality was 10%–25%.[8,9] and about 80% of cases were due to serogroup B. That year, meningococcal disease was declared the country's main public health problem. By 1984, overall incidence had risen to 14.4 per 100,000 population. Several provinces reported >120 cases per 100,000 children aged <1 year.[8]

At that time, no vaccine existed in the world with proven efficacy against serogroup B *N. meningitidis*, nor was there a vaccine candidate that could be successful in the short term. The highest development achieved by the most advanced groups was a serotype-specific antigen vaccine; its characteristics are summarized in Box 1 and compared with the Cuban vaccine.[9–12]

From 1980 to 1986, Cuban scientists at the National Center for Meningococcal Vaccine Development in Havana (precursor to the Finlay Vaccine Institute, founded in 1991), developed a vaccine candidate based on outer membrane vesicles (OMVs or proteoliposomes). Its clinical efficacy was field tested from 1987 to 1989. Developing this vaccine candidate involved creating a scalable and integrated production system with complex know-how for initial culture, fermentation, extraction, purification, formulation, adjuvantation, bottling and packaging. Stable OMVs were obtained, with a lipopolysaccharide composition apt for administration in humans without toxicity while conserving contribution to immunogenicity (Box 1).

With technological innovations in the development of VA-MENGOC-BC, patents were registered[13,14] that obtained licenses in Cuba[18] and, through the Patent Cooperation Treaty, in Australia and countries of the Americas, Europe, Asia and Africa. In 1989, the World Intellectual Property Organization awarded its gold medal to the main authors of the VA-MENGOC-BC patent. Their most important scientific achievements were obtaining immunogenic and stable OMVs or proteoliposomes from serogroup B meningococcus; the development process; and the product, whose composition, formulation and efficacy differed from existing vaccine candidates. Proteoliposomes or OMVs constitute the fundamental structure that ensures vaccine's immunogenicity and protective capacity. OMV characteristics are shown in Figure 1, and Box 2 describes the vaccine's formulation, as well as functions of the mixture and of several of the molecules formed.

Studies of the vaccine before licensing and mass administration From 1987 to 1989, a prospective, randomized, double-blind, placebo-controlled efficacy study was carried out in 7 provinces, involving 106,251 youngsters aged 10–16 years.

Box 1: Meningococcal B Vaccines Characteristics

Serotype-specific antigen vaccines (1970–1978)

Vaccines based on purified serotype-specific antigens, with adjuvants and without outer membrane vesicles (OMVs). Experimental formulations included capsular polysaccharides from other groups for better solubility. Lipopolysaccharide was mainly free or formed part of blebs or membrane fragments and had to be eliminated to the extent possible, due to its toxicity.

These were laboratory-scale efforts, lacking established technologies and good manufacturing practices. There was no demonstrated correlate of protection in controlled efficacy tests in humans. The few vaccines that were subject to trials in humans were discontinued. They required use of aluminum hydroxide as an adjuvant and to reduce toxicity.[9–12]

Cuban Vaccine VA-MENGOC-BC (1982–1989)

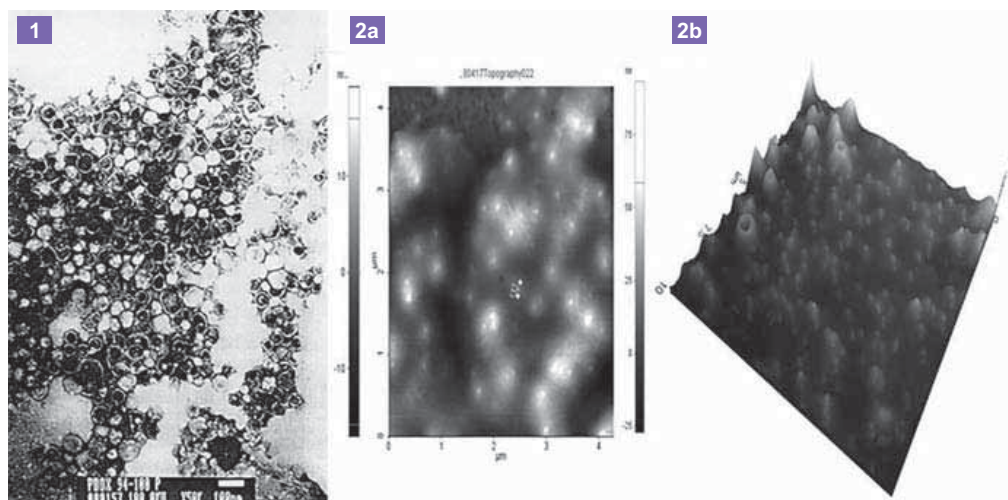
This is an OMV or proteoliposome vaccine. Its serological and overall efficacy is related to OMV presence, stability and consistency. The vesicular structure gives adjuvant and immunostimulating properties. OMVs provide the polysaccharide and other low immunogenic antigens with some degree of thymus dependence and enhance immune response to them.

Lipopolysaccharide is integrated into OMVs and may or may not adsorb to $Al(OH)_3$ gel. VA-MENGOC-BC's adjuvant capacity does not depend on $Al(OH)_3$, but instead on OMVs, which also contain the proteins necessary for protection against a broad spectrum of heterologous strains.[13–16] The main role of $Al(OH)_3$ in VA-MENGOC-BC is to achieve pharmaceutical stability, which is supported by results with new formulations without aluminum hydroxide in preclinical development.[17]

Researchers from the Finlay Vaccine Institute, Cuba's Ministry of Public Health, Cuba's Center for State Control of Medicines and Medical Devices, PAHO/WHO, and the US CDC participated in discussion of the final trial protocol and its evaluation.

The field study lasted 16 months, during which 25 cases of meningococcal disease occurred. Once concluded, the blinding code was broken, revealing whether cases were in the placebo or vaccinated group: there were 4 cases among the 52,966 who received the vaccine, and 21 among the 53,285 who received the placebo. Estimated efficacy was 83% ($p = 0.0019$).[16] VA-MENGOC-BC thus became the world's first vaccine against serogroup B meningococcus found effective in a prospective, double-blind, placebo-controlled field trial.

In 1989, preclinical studies and phase I, II and III clinical trials required by national and international regulatory authorities were completed, and Cuba's Center for State Control of Medicines and Medical Devices—the Cuban regulatory agency—licensed VA-MENGOC-BC for marketing.[18]

Figure 1: Characteristics of VA-MENGOC-BC

Outer membrane vesicles of strain CU-B385/3 of serogroup B *Neisseria meningitidis*, basic core of VA-MENGOC-BC. Electron micrographs of proteoliposomes or outer membrane vesicles (OMVs). Vesicles 50–80 nm in diameter can be seen. Well-defined and chemically and physically stable OMVs or proteoliposomes are the heart of VA-MENGOC-BC and ensure its immunogenicity and protective capacity.

1) transmission electron microscopy

2a) two-dimensional atomic force microscopy

2b) three-dimensional atomic force microscopy. Digital Nanoscope III AFM (Santa Barbara, CA) coupled to scanner (J-Scanner) of 125 μm, Software used UTHSCSA Image Trial (USA).

Vaccination results from 1989 to 2019 With the vaccine registered, Phase IV (postmarketing surveillance) began. In 1989 and 1990, a national campaign was carried out, in which more than 3 million people aged 3 months–24 years were vaccinated, for over 95% coverage. High-risk groups were also included, mainly workers and students living in dormitories, prisoners, health personnel, etc., regardless of age, prioritized by province according to disease incidence.[8,16]

In 1991, VA-MENGOC-BC was added to the National Immunization Program, where it has remained without interruption or essential changes, using a 2-dose schedule, the first at age 3 months and the second at age 5 months. This universal and systematic immunization in infancy maintained coverage for those who were born after the mass vaccination campaign.

Annual incidence of meningococcal disease in Cuba before vaccination averaged 14.4 per 100,000 population. Following vaccination, the rate decreased to ≤ 1 per 100,000 population in 1993 and has remained below 0.1 per 100,000 population since 2008. In children aged ≤ 6 years, average annual incidence before vaccination was 38–120 per 100,000, and this dropped to 0.01–1.8 per 100,000 population in the following two decades. The reduction was an estimated 95% (93%–98%) and meningococcal disease has been eliminated as a public health problem in Cuba. [8,16,21–23]

Impact of mass vaccination on strain patterns in carriers and patients In the prevaccination epidemic stage, a cumulatively total of 96.8% of strains isolated from patients were from serogroup B, 1.4% from C, and 1.8% were not groupable. In carriers, 67.3% were from serogroup B, and 32.7% were not groupable. The vaccination campaign changed strain distribution: 100% of patients were now from serogroup B. In healthy carriers, strain distribution shifted to 26.7% from serogroup B and 70.8% from nongroupable

strains, while serogroup W-135 appeared in 2.5% of cases.[24] Selective pressure by the vaccine, which was over 95% effective against group B (demonstrated by decreased incidence and reduced B capsule expression in healthy carriers from 67.3% to 26.7%) had not been previously described for any meningococcal B vaccine.

Changes in serotypes and subtypes in postvaccination patients and carriers can be interpreted as an expression of broad-spectrum vaccine-induced immune response, as epidemic serotypes and subtypes were eliminated or decreased and nontypable and nonsubtypable serotypes and subtypes increased in patients and carriers. Serotypes and subtypes different from the vaccine strain did not increase in patients or carriers. The vaccine was effective against homologous

strains and also against heterologous strains.[24] Frequency and diversity of hypervirulent clonal complexes (ST-32 and ST-41/44) in patients and carriers decreased after vaccination and were replaced by the ST-53 complex, which represents a positive change. [25] After 2008, four serotype B:17 strains, never before reported in Cuba, appeared. Before this, between October 2004 and March 2005, strain B:17:P1.19, belonging to a new circulating clone (ST-269), was reported in Canada.[26]

These changes are favorable because two of the most important hypervirulent clones in the cause and expansion of Cuba's

Box 2: Additional characteristics of VA-MENGOC-BC

VA-MENGOC-BC is a bivalent vaccine of serogroups B and C meningococcal antigens, which forms a stable mixture adsorbed to $Al(OH)_3$ gel. Each dose contains 50 μg of membrane proteins, with 2 μg of serogroup B lipopolysaccharide, integrated in the OMVs, and 50 μg of serogroup C polysaccharide, as well as 2 mg of $Al(OH)_3$ gel, a formulation buffered with phosphates and sodium chloride at physiological pH; this mixture allows stable adsorption of the protein-polysaccharide-lipopolysaccharide complex, suitable for immune system delivery.

Proteomics has demonstrated the basis of its broad protective spectrum. Integration into the vesicles and adsorption to the gel detoxifies the lipopolysaccharide and assures conservation of its adjuvant properties, necessary in the formulation. OMVs constitute the fundamental adjuvant capable of provoking a potent Th-1 type immune response pattern.[18–20]

epidemic and others in the world were eliminated, in addition to the change in carrier phenotypes to nonvirulent variants and the transformation of epidemic strains in patients. However, it is necessary to carefully assess the possible importance of the appearance, although very limited, of clone ST-53, and whether the B:17 strains found are of the ST-269 type, as in Canada, as well as the levels of protection conferred by the Cuban vaccine against these strains.

Importance of immunization schedule and coverage in VA-MENGOC-BC's effectiveness Despite the 95% impact and protection achieved by the National Immunization Program's high coverage, as demonstrated over the past 30 years, there are indications that duration of postimmunization protection has decreased with the two-dose VA-MENGOC-BC schedule used in Cuba, particularly in children up to age one year. Although protection decreases over time, it was demonstrated that the vaccine was effective with the two-dose schedule and that it provides better protection against meningococemia, which is more severe and lethal, than against the meningial form.[27]

Decreased protection time with the program's schedule is due to the fact that bacterial vaccines' lower immunogenicity requires primary schedules of more than two doses, with boosters in the initial schedule[27] and even booster doses after a certain period or when the immune system is stressed. The superiority of a three-dose schedule for VA-MENGOC-BC has been demonstrated in studies conducted in Cuba and other countries.[16,28–30]

In conclusion, the vaccine could offer higher protection in infants and against the clinical meningial form if an initial immunization schedule with three or more doses, along with a booster (which improves maturation of the immune response) were instituted; this should therefore be considered. However, even if the number of doses is increased, it is advisable to maintain the high coverage that has demonstrated effectiveness and sustained impact, and that will contribute to elimination of the disease.

ADMINISTRATION OF MENINGOCOCCAL HYPERIMMUNE GAMMAGLOBULIN (HGG) IN SEVERELY ILL CHILDREN

Participants in the vaccine registration clinical trials donated blood to obtain plasma, where vaccine-induced antibodies were in high concentrations. Globulins[31,32] were purified, their composition and concentrations characterized, and basic preclinical and toxicological studies performed.[32,33] Several lots of meningococcal HGG were produced and released by the national regulatory authority for experimental use in sick children whose lives were at risk.

Meningococcal HGG was used to conduct a clinical trial that included 123 children diagnosed with meningococcal disease in 21 intensive care units in 9 provinces.[31,32] For ethical reasons, results from the historical series were used as a comparison and meningococcal HGG was administered to all children in the trial.

Cases were stratified according to number of poor prognostic factors (PPFs). PPFs were established based on clinical assessment and disease course of patients in the epidemic's historical series. To evaluate effectiveness of meningococcal HGG administration, survival results in the clinical trial were

compared with those with the same number of PPFs reported in the historical series.

Treatment followed established standards for patients with given numbers of PPFs, along with meningococcal HGG. In children with up to 2 PPFs, conventional treatment plus meningococcal HGG achieved 100% survival. With 3 or 4 PPFs, the respective survival percentages with conventional treatment were 86% and 78.5%, while in both cases survival was 100% with meningococcal HGG. Patients with 5 PPFs (serious, in clinical status terminology) had 53% survival with conventional treatment and 88.9% survival when meningococcal HGG was added. Children with 6 PPFs (classified as critical) had 21.4% survival with conventional treatment and 62.5% when meningococcal HGG was added. With 7 or 8 PPFs, administration of meningococcal HGG did not improve survival.

Certain combinations of PPFs had high case fatality and very low survival (20%) with conventional treatment, such as cases with a platelet count <150,000, + shock, + acidosis (pH <7.3). When meningococcal HGG was administered, survival increased to 62.5%. These results provided new evidence supporting the protective capacity of vaccine-induced antibodies.[31,32]

POTENTIAL OF VA-MENGOC-BC IN PREVENTION OF GONORRHEA

Two bacterial species of the genus *Neisseria*, *N. meningitidis* and *N. gonorrhoeae*, are antigenically related commensals and pathogens exclusive to humans. The first causes meningococcal disease and the second causes gonorrhea, a sexually transmitted infection. Gonococci have become resistant superbacteria and are a growing problem, with no vaccine to prevent them.[34,35]

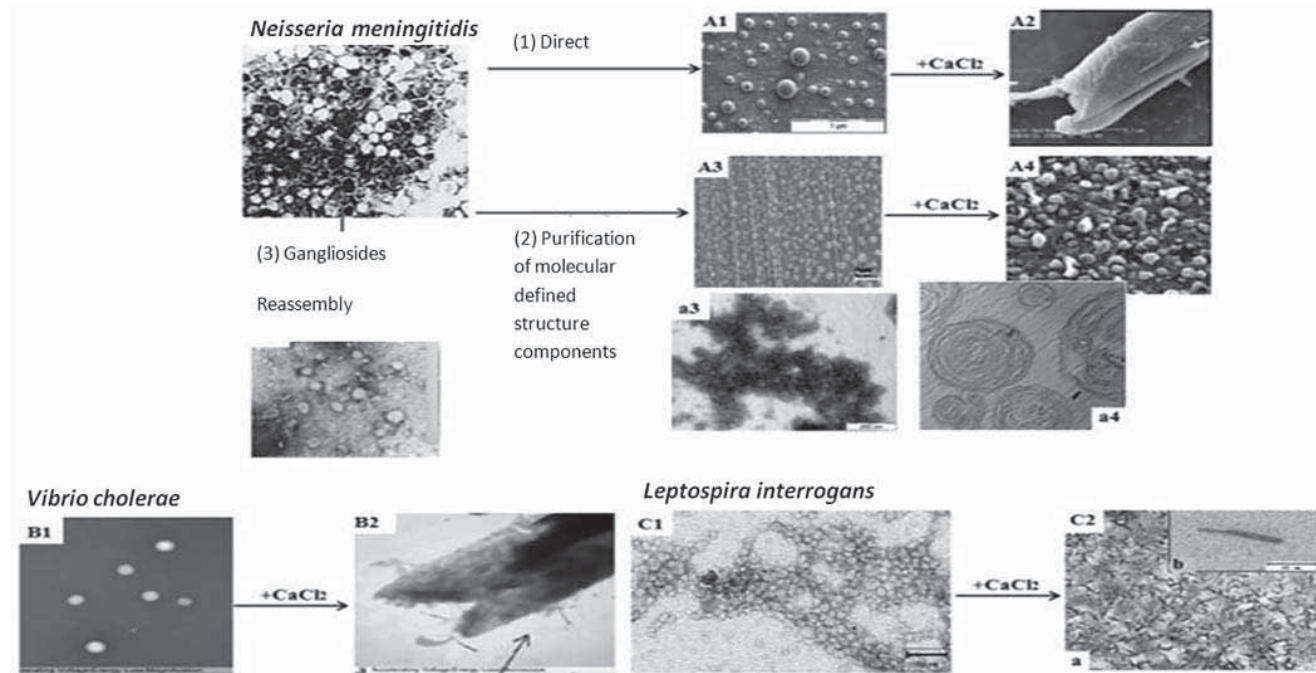
Laboratory studies conducted in Havana at the Finlay Vaccine Institute and the Pedro Kourí Tropical Medicine Institute (IPK) demonstrated cross reactions among *Neisseria* species antibodies in serum and secretions when VA-MENGOC-BC was administered to mice. Elements of a cellular response induced by VA-MENGOC-BC against gonococci were also identified, which could have contributed to the reduction of gonorrhea incidence after mass campaigns with this vaccine (at the time, there were also public health campaigns specifically directed at reducing sexually transmitted infections).[36]

In a case–control study conducted in New Zealand, those who received the meningococcal vaccine had a significantly lower risk of gonorrhea than those who were not vaccinated (OR 0.69, $p < 0.001$).[37] Another New Zealand study with the same vaccine reported an overall effectiveness of 31% and a 47% effectiveness against hospitalization attributable to gonorrhea in one cohort.[38]

ADVANCES IN THE FIELD OF ADJUVANTS FOR HUMAN VACCINES: TECHNOLOGICAL PACKAGE AND PATENTS

The most widely used technological platform in Cuba for human vaccine adjuvants is based on proteoliposome technology to obtain OMVs from *N. meningitidis* strain CU-B385/3. This technology, which was used to manufacture more than 70 million doses of meningococcal vaccine, produced a family of patents, new vaccines and opportunities for biomedical and biotechnology development.

Figure 2: Platform developed using vesicular or proteoliposome technology



Electron micrographs of the adjuvant formulation platform with proteoliposome and cochlear structure, developed using technology from the Finlay Vaccine Institute, to obtain *N. meningitidis* B outer membrane vesicles (OMVs)

- 1) A,A1,A2 new OMVs and cochleates obtained directly from originals
- 2) A,A3,A4,a3,a4 a new generation of nano-OMVs and nanocochleates
- 3) very small size proteoliposomes with gangliosides, obtained directly from OMVs

The four photos in the lower block represent application of vesicular technology to cholera (B1,B2) and leptospirosis (C1,C2) vaccines.[39]

Table 1: Technology package. Know-how for new adjuvants and vaccines based on vesicular VA-MENGOC-BC technology

Document	Patent	PP	Biotechnology product(s)	Reference
CU 21888A1	X	—	Vaccine against <i>N. meningitidis</i> B	[13]
EP 0301992B1	X	—	Vaccine, gammaglobulin and transfer factor, <i>N. meningitidis</i>	[14]
WO 2004/047805A1	X	—	Cochleate-based vaccines and adjuvants	[40]
WO 2003/094964A1	X	—	Allergy vaccines and treatments	[41]
WO 2010/057447A1	X	—	Vaccines and types of administration	[42]
WO 2011/137876A2	X	—	Tolerogenic, malaria vaccines	[43]
WO 2002/45746A2	X	—	Poorly immunogenic antigen adjuvant (cancer)	[44]
Vaccine (1999)	—	X	Poorly immunogenic antigen adjuvant (cancer)	[45]
VacciMonitor (2012)	—	X	<i>Leptospira</i> nanocochleates and proteoliposomes	[46]
BMC Immunol (2013)	—	X	New <i>N. meningitidis</i> B vaccine, without Al(OH) ₃	[17]
J Sci Tot Env (2019)	—	X	Meningococcal nanocochleates, nano-proteoliposomes	[19]
Rev Chim (2019)	—	X	Immunotoxicological evaluation vaccine without aluminum hydroxide	[20]
Methods (2009)	—	X	Proteoliposome & cochleates from <i>Vibrio cholerae</i> O1	[47]
BMV Immunol (2013)	—	X	<i>Bordetella pertussis</i> acellular vaccine	[48]

PP: primary publication

A new therapeutic allergy vaccine currently in clinical trials uses proteoliposome technology as an adjuvant. Therapeutic vaccines under development against several types of cancer also use variants of proteoliposome vesicular technology as adjuvants. The new generations of experimental meningococcal, leptospirosis, cholera and pertussis vaccines also use OMV technology in their production.[39] Figure 2 and Table 1 summarize these aspects.

OTHER SCIENTIFIC AND TECHNOLOGICAL ADVANCES MADE IN THE MENINGOCOCCAL VACCINE MACROPROJECT

Scientific and technological package, selected patents and publications Genetic engineering technologies were used to clone and obtain important proteins for new generations of serogroup B meningococcal vaccines: PorA, PorB, OpcA, NadA, Tbp, NspA, NlpB, IpdA, and others, and variants of some of these.[49,50]

Serogroup B polysaccharide peptide mimotopes were obtained and characterized by phage display technology, which opened new vaccine potential based on B polysaccharide and prevented possible development of autoimmunity.[51]

Table 2: Scientific technological package. Meningococcal vaccine macroproject's selected patents and primary publications

Document (year)	Patent	PP	Biotechnology Products	Reference
EP 0474313A2	X	—	P64k protein-r, carrier (cancer, infectious diseases)	[55]
WO 2009/003425A1	X	—	CIMAvax- EGF (cancer therapeutic vaccine)	[56]
CU 2006/0020	X	—	Mimetic peptides of <i>N. meningitidis</i> polysaccharide B	[57]
USP 5747653A	X	—	Hyperimmune gammaglobulin and its method	[58]
Int J Med Micro (2011)	—	X	Mimetic peptides of <i>N. meningitidis</i> polysaccharide B	[51]
Exp Rev Vaccines (2015)	—	X	CIMAvax-EGF-P64K (lung cancer therapeutic vaccine)	[59]
BBRC 308 (2003)	—	X	Dengue virus-P64k protein-r	[60]
Doctoral thesis (2006)	—	X	Human meningococcal immunoglobulin	[32]
Proteomics (2006)	—	X	Characterization of vesicles of VA-MENGOC-BC	[52]
Hum Vaccine (2009)	—	X	Characterization of vesicles of VA-MENGOC-BC	[53]
Microb Pathogen (1997)	—	X	Acquisition of <i>N. meningitidis</i> iron-regulated proteins	[49]
Biología Aplicada (2008)	—	X	Genetic and immunological properties NlpB antigen	[50]

PP: primary publication

Table 3: Efficacy/effectiveness of VA-MENGOC-BC in populations and age groups of various countries

Place	Date	Age group	Efficacy /effectiveness by age group (%)		Reference
			≤4 years	>4 years	
Cuba (7 provinces)	1987–1989	10–16 years	—	83 ^a	[16]
Cuba (12 provinces)	1988–1990	3 months–4 years	93	—	[61,62]
Cuba (14 provinces)	1989–1994	3 months–4 years	81	—	[62]
Cuba	1997–2008	<1 year	84	—	[27]
Brazil (Sta. Catarina)	1990–1992	3 months–7 years	66	88	[63]
Brazil (Rio de Janeiro)	1990–1992	6 months–9 years	64	82	[64]
Brazil (Sao Paulo)	1990–1991	3 months–6 years	55 ^b	73	[65,66]
Colombia (Antioquia)	1991–1994	3 months–4 years	98	—	[67]
Uruguay (Canelones)	2002–2003	4–19 years	—	100	[68]
Uruguay (Montevideo)	2002–2003	4–19 years	—	88	[68]

^aefficacy with placebo and vaccine in prospective, randomized double-blind design

^beffectiveness in the prospective arm of study

Monoclonal antibodies against *N. meningitidis* were produced and are used for diagnostic purposes, in analytical techniques and in purification processes. Proteomics was used to study the CU-B385/3 strain, which contains in its OMVs all the proteins essential for protection against *N. meningitidis* with immunomodulatory power.[15,52,53]

Ultramicroanalytic ELISA-type assays were carried out—using small amounts of reagents and biological samples—for serologi-

cal diagnosis of VA-MENGOC-BC–induced immune response in field studies, to evaluate population immunity, and to quantify concentrations of meningococcal immunoglobulin G from hyperimmune plasmas used in production of meningococcal HGG.[32]

The genetically engineered recombinant protein of *N. meningitidis* P64K was used as a carrier for vaccines, and its N-terminal is part of genetic constructs that enable high levels of fusion-protein expression. It is included in the structure of dengue vaccine candidates under development, and in therapeutic vaccines against cancer and autoimmune diseases. It is the carrier protein of CIMAvax-EGF, a therapeutic vaccine used in treatment of patients with lung cancer.[54] Table 2 summarizes patents and publications of this technological package.

VA-MENGOC-BC USE IN OTHER COUNTRIES

In several Latin American countries, strains different from VA-MENGOC-BC circulate, and VA-MENGOC-BC has shown a high percentage of effectiveness against all, in the range of 55%–98% in children aged ≤4 years and 73%–100% in children aged >4 years. Table 3 shows results of effectiveness evaluation in several countries, including Cuba.


In 1989–1990, 2.4 million children in the state of Sao Paulo, Brazil were given two doses of VA-MENGOC-BC. Effectiveness was lower than seen in Cuba, probably because isolated interventions were carried out without the rigor or systematic coverage of a campaign or program, in a state with more than 40 million inhabitants. Subsequently, other countries and regions within countries were incorporated, using two-dose vaccination schedules restricted to certain age groups, also with lower coverage than in Cuba, and where there was greater heterogeneity in circulating strains. In general, children from states, provinces or localities with high incidence rates were vaccinated in single interventions not included in a national immunization program, leaving children from neighboring localities and at-risk age groups unvaccinated.

Several reviews including studies of the efficacy of VA-MENGOC-BC against heterologous *N. meningitidis* strains in children aged ≤4 years demonstrate the effectiveness of the vaccine in these conditions.[69–71]

CONCLUSIONS

Meningococcal disease is no longer a public health problem in Cuba after the introduction of VA-MENGOC-BC vaccine, due to its structure (based on presence, stability and consistency

of proteoliposomes that confer immunogenicity and protective capacity) and administration strategy. VA-MENGOC-BC is the first vaccine of proven efficacy against *N. meningitidis* serogroup B and is also effective against C and a wide spectrum of heterologous serogroup B strains. It has cross reactivity against *N. gonorrhoeae*, which broadens the possible prevention spectrum for this infection. The vaccine's systematic application with wide coverage in Cuba's National Immunization Program keeps incidence of meningococcal disease low. Vaccination changes patterns of strains in asymptomatic carriers

and circulating strains, which is important for the epidemiology of the disease. Greater survival in children with severe meningococcal disease treated with meningococcal hyperimmune gammaglobulin evidences the protective capacity of vaccine-induced antibodies. VA-MENGOC-BC production technology contributes to the development of the Cuban biotechnology and pharmaceutical industry, obtaining important technological advances, backed by a family of patents and primary publications in the field of vaccines and adjuvants, for current and future benefit. 

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Cuba's Maternity Homes, 1962–2017: History, Evolution, Challenges

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ABSTRACT

Cuba's maternity homes were founded in 1962 as part of the general movement to extend health services to the whole population in the context of the post-1959 social transformations. The overarching goal of the homes was to improve the health of pregnant women, mothers and newborns. Hence, in the beginning when there were few hospitals in Cuba's rural areas, their initial purpose was to increase institutional births by providing pregnant women a homelike environment closer to hospitals. There, they lived during the final weeks before delivery, where they received medical care, room and board free of charge. Over time, and with expanded access to community and hospital health facilities across Cuba, the numbers, activities, modalities and criteria for admission also changed. In particular, in addition to geographical considerations, expectant mothers with defined risk factors were prioritized. For example, during the 1990s economic crisis, the maternity homes' role in healthy nutrition became paramount. The purpose of this essay is to provide a historical perspective of this process, describe the changes and results during the 55 years examined, and take a critical look at the challenges to successful implementation of this model, a mainstay at the primary healthcare level of the public health system's Maternal–Child Health Program.

KEYWORDS Maternal health, maternal–child health, obstetrics, pregnancy, Cuba

INTRODUCTION

Throughout history and in different parts of the world, the term “maternity home” conjures up a variety of notions and descriptions. These institutions, which nearly always refer to facilities where women live and receive medical attention during some period of their pregnancy, have also been known as “maternal homes,” “maternal waiting homes,” and “centers for protection of rural women.”[1,2] In 1891, the prominent obstetrician Adolphe Pinard founded a shelter for poor Parisian women who were pregnant, and whose delivery and medical services were provided free of charge by Pinard and his colleagues. Similar institutions later sprang up in Sweden, the USA and Latin America, but without notable expansion into the 20th century. It wasn't until the 1950s, faced with alarming maternal mortality, that similar homes appeared near hospitals for women in rural areas of poorer countries.[3,4]

IMPORTANCE This paper describes and analyzes Cuba's 55-year experience with maternity homes for vulnerable and at-risk pregnant women, admitted or day boarders in the weeks and months before giving birth. The institution was founded at the primary care level as part of the nation's implementation of the right to health in the context of limited resources.

In Cuba, as elsewhere, early versions of maternity homes were destined for poor women, and in the 18th century particularly for “disgraced” single women, to hide their shame from society during the last months of pregnancy. Pinard's influence later found disciples on the island, in particular with Dr Eusebio Hernández Pérez, who took the maternity home idea to heart. And while no homes as such were created, a four-bed ward was set aside in Havana's América Arias Maternity Hospital, known as the “maternity home.” The ward was intended for single women who had nowhere to live before or after delivery, since most were domestic workers whose employers fired them prior to giving birth. Supported by charitable donations, such initiative disappeared in the 1920s.[5]

A NEW HOME IN A NEW SOCIETY

The creation of the first maternity home in Cuba was part of the swift and radical transformations of the early 1960s, aimed at creating a more just and inclusive social order, first focusing on the most vulnerable and marginalized populations. Hence, the Agrarian Reform Law of 1959 gave deeds to 150,000 landless farmworkers, generating new economic opportunity; the 1960 Rural Medical Service sent recently graduated physicians to the country's most remote regions, many of whose residents had never seen a doctor; and the 1961 Literacy Campaign (later lauded by UNESCO) sent over 120,000 young volunteers across the island, teaching 700,000 to read and write.[6]

Today, population health experts would say that these programs were aimed at tackling the “social determinants of health,” which they certainly were. A 1956–1957 University Catholic Association study of a representative sample of 1000 rural families had found only 11% of farmworker families had milk to drink; just 2% had eggs; 64% had no latrine; and 84% no place to bathe.[7] Over half the population was undernourished; just 10% of children received pediatric care, while 80% suffered from intestinal parasites; and the first cause of death for all ages was gastroenteritis. Maternal mortality was recorded as 138 per 100,000 live births and infant mortality as 34.8 to 70 per 1000 live births, both certainly underreported (even considering that newborn deaths were not counted in the first 24 hours after birth). Medical services were curative and concentrated in Havana; there was essentially no medical care in the countryside, with only one rural hospital.[8–10]

One rural hospital meant that women throughout the island faced the prospect of home delivery, mainly without skilled birth attendants, or trying to make it to a city hospital kilometers away—if they had the means. This partially explains the low percentage of in-hospital births (20%–60%, according to various authors) in Cuba before 1959.[11,12]

In 1961, noted physician Dr Celestino Álvarez Lajonchere was charged with obstetrical care within the newly unified public health system responsible for all medical services, provided free from this point forward. A main objective was to increase institutional

births as a way to address obstetric complications and thus reduce both maternal and infant mortality. In his interviews with expectant mothers, they referred to distance from hospitals, poor roads and lack of transportation as the main reasons they delivered at home.[13]

This observation led to the creation of the first maternity home in 1962 in eastern Camagüey Province. The home was purposefully located near the province's best-equipped maternity hospital to provide preterm care for apparently healthy pregnant women who nevertheless lived far away, so they could be easily transported to hospital for delivery.[11,14,15] Through 1969, as homes were established primarily in the rural and mountainous eastern provinces, geographic isolation was the main criterion for admission, although poor nutritional status and social conditions contributed to the decision.[16]

In that first period, 15 homes were set up in various provinces. Spacious, vacant houses were usually chosen, adapted to accommodate 15–20 pregnant women. The homes, resembling guest houses, included living and dining rooms (for activities and family visits), several bedrooms, bathrooms, kitchen and laundry, as well as areas that could be converted into nurses' stations and basic exam rooms. Administrators were often midwives (a profession that later disappeared with the training of obstetric nurses), with hospitals providing both budgets and other medical personnel who visited the homes regularly. The result was a relatively inexpensive way to provide care, monitoring and health education to the expectant mothers, as well as to reduce hospital bed occupancy.[16]

CHANGING CONDITIONS, MODELS, PROTOCOLS

Maternity home development in Cuba has been divided into three distinct periods: 1962–1969, 1970–1989 and 1990–2010, to which this essay adds a fourth: 2011–2017. Although the main goal has always been to improve care for pregnant women to ensure healthy mothers and newborns, various aspects of implementation developed with the health system itself.[17]

In the first period, described above, maternity homes functioned essentially as annexes to the hospitals they reported to, without independent budgets, and operated under the guidance of hospital medical staff. Health education of expectant mothers (including care of themselves and their newborns) was informal, recreational activities spontaneous, and meals responded to basic norms of healthy nutrition within limited means. The numbers of homes grew slowly, reaching 15 by 1969 and 24 by the beginning of the second period in 1970. By that year, women in remote areas also had greater access to medical care in general: in addition to improved roads, 53 rural hospitals had been built, and in 1971, the majority of doctors were no longer practicing in the capital, 42% in comparison with 65% in 1958.[18,19]

Over the next two periods, the maternity home concept was adopted and adapted on a national scale, the numbers of homes and beds expanded throughout the country, and more resources were assigned to these institutions. Admissions also grew.[20]

From 1970 to 1989, the numbers of homes and beds multiplied rapidly (the latter reaching 150 by 1989, 10 times the number 20 years earlier), and homes had been established in each

province. Admission criteria were expanded to 22 maternal–fetal risk factors that also considered social determinants and mental health. Among these were insufficient gestational weight gain, prior miscarriage, adolescent pregnancy, macrosomia, risk of low birth weight, anemia, preeclampsia, asthma, history of epilepsy, single women who faced family rejection, depression, stress, domestic violence, low socioeconomic status, and overcrowded or otherwise unhealthy living conditions.[21] In other words, geographic isolation became only one of many factors that could complicate delivery and put mother or infant at risk, and needed to be addressed. In addition to increasing institutional births, a finer point was put on this broader array of risk factors in order to reduce both infant and maternal mortality.

Embedded in this shift was the recognition that maternity homes were also needed in urban areas. In 1972, geographic isolation was the criterion for 1176 admissions, with only 5 the result of maternal–fetal risk factors; 10 years later, 809 admissions were geographic and 225 attributable to other risk factors.[3] In the 1980s, additional risk factors were added, such as jobs requiring heavy labor in agriculture.

At the same time, some of the original premises underwent changes: homes were relocated near community-based multispecialty polyclinics instead of hospitals, sometimes, in fact, far from hospitals; one home had as many as 120 beds, while others were closed, particularly ones that had been established near rural hospitals that no longer provided birthing services; and homes had their own budgets, which raised costs and increased personnel.[3] While most physicians assigned to the homes were still on hospital payrolls, maternity homes now had teams of nurses as well as administrative employees, dieticians, bookkeepers, cooks, housekeepers, launderers and gardeners.[21]

Care during this time was focused on both medical and social aspects, with regular obstetric visits interspersed with those by other specialists. In general, education was enhanced to include information on contraceptives, preparation for labor and delivery, and advice for pregnancy and newborn care, the latter focusing on aspects such as the importance of nursing, vaccination and diet. Noteworthy are two momentous initiatives launched in this period: in 1983, the National Maternal–Child Health Program was established by the Ministry of Public Health (MINSAP), providing both guidelines and benchmarks in this already prioritized sector of the health system. The same year, the Family Doctor-and-Nurse Program was piloted, and soon extended throughout the country, locating a family doctor and nurse in every Cuban neighborhood. These two taken together strengthened the primary health care system, already anchored in the community-based polyclinic, and improved organization of preventive, curative and rehabilitation services. Family doctor-and-nurse offices were handed the main responsibility for regular antenatal visits, well-baby checkups and vaccinations. Patients were also seen by polyclinic obstetricians and pediatricians.

The third period, 1990–2010, saw the fastest growth of homes (153 in 1990 to 336 in 2010), and admission criteria were once again expanded. A new modality was added to the already flexible schedule: that of day boarder—women would spend their days there, returning to their own homes at night. The main purpose was to ensure nutrition, three meals a day, especially for the

growing number of expectant mothers with insufficient weight gain during pregnancy. This modality was critical during the 1990s, when the socialist bloc collapse and tighter US sanctions shrank the Cuban economy by some 35%, making food and other scarcities common. In particular, low birth weight rates—fueled by expectant mothers' poor nutrition, causing intrauterine growth retardation—had begun to creep upward, a sure warning that an increase in infant mortality was not far behind. In 1990, Cuba's low birth weight rate was 7.6%, steadily declining since 1978. But by 1995, after the worst years of the economic crisis, the rate stood at 7.9%. [22]

Many maternity homes had the cooperation of workplace lunchrooms or private farmers, who provided meals and produce free of charge, and novel ideas were implemented in some towns: in Cardenas, Matanzas Province, a restaurant was established catering solely to pregnant women and in other cities, nutrition centers attracted expectant mothers, among others. [3]

Late in this period, the Maternal–Child Health Program issued a series of methodological guides for maternity home aims, organization, evaluation and record-keeping, which are still in place today. By 2007, criteria for admission included multiple pregnancy (>20 weeks), risk of premature birth, fetal growth retardation, maternal age >35 years, anemia, vaginal sepsis, high blood pressure (even if controlled), insufficient weight gain, adolescence, epilepsy, low placental insertion, geographic isolation and social risk (any living conditions that might endanger mother or newborn health). Management of each of these criteria was addressed in the methodological guides, which were quite extensive. They included everything from a questionnaire to ascertain satisfaction with services received, to differential attention to adolescents (since teen pregnancy, although relatively rare, is considered a public health problem) and specific dietary instructions for different recommended levels of calorie intake. [21–23]

The fourth period (2011–2017) coincides with a series of transformations in Cuba's health system as a whole, aiming for both more efficient use of scarce resources and improved quality of care. These transformations were summarized in three dimensions: service reorganization, consolidation and regionalization. In essence, these initiatives were designed to reduce waste and bureaucracy, concentrate high-tech equipment where most often utilized, and locate services and facilities according to need (as defined by use). [24]

This process had specific consequences for the maternity home program: admissions had decreased from 2002 to 2006, when they began increasing once again. But with the 2010 transformations, according to Iñiguez, “the care pregnant women receive in maternity homes is being reorganized based on occupation rate (pregnant women per maternity home), distance to polyclinics with beds, and rapid access to the corresponding obstetrical–gynecological hospital. A reduction of maternity homes is expected, accompanied by a downsizing of maternity care organizational structures.” She noted that consolidation of homes had already begun in some provinces. [25] As a result, the number of homes went from 336 in 2010 to 131 in 2017 (a 61.1% reduction); the number of beds was not cut as drastically, from 4241 to 3413 (a 20.5% reduction); and admissions remained fairly high (67,496 in 2010 and 63,214 in 2017, a reduction of just 6.3%) (Table 1).

Table 1: Maternity homes in Cuba by number, beds, admissions, rate of admission for selected years (1962–2017)

Year	Homes n	Beds n	Admissions* n	Admissions/100 live births*
1962	1	20	NA	NA
1970	24	413	5,167	2.1
1975	56	949	24,629	12.8
1980	75	1219	26,140	19.1
1985	111	1769	36,871	20.3
1990	153	2526	44,840	24.0
1995	208	3132	48,765	33.1
2000	258	NA	57,838	40.3
2005	289	4030	54,054	44.8
2010	336	4241	67,496	52.8
2011	143	3781	58,387	43.9
2012	150	3440	58,103	46.2
2013	142	3344	56,340	44.8
2014	138	3314	58,832	48.0
2015	136	3402	64,239	51.4
2016	131	3370	65,670	56.2
2017	131	3413	63,214	55.0

*Counting readmissions NA: not-available

Source: National Health Statistics and Medical Records Division (CU), National Health Statistics and Medical Records from 1995 to 2017; Gutiérrez Muñiz [17]

While the numbers of live births decreased during the same period (from 127,746 to 114,971, see Table 2), the admission rate per 100 live births actually increased in 2010–2017, from 52.8 to 55. This, along with the reduction in numbers of homes, leaves questions unanswered as to the balance between regionalization and access to needed care, both in terms of increased distance of the homes from women requiring them and in terms of how length of stay may or may not be affected by the new norms—both important to overall health results.

Table 2: Live births in Cuba, selected years (1966–2017)

Year	Live births
1966	264,022
1969	246,005
1989	184,891
2010	127,746
2017	114,971

Source: National Statistics Bureau (ONEI) [26]

RESULTS & OBSERVATIONS

Cuba's improvements in maternal–child health are multifactorial—from women's educational levels and other social determinants, to quality of OB/GYN and pediatric care, the national Maternal–Child Health Program's development and implementation, and in particular the strength gained in primary health care services as pillars of the country's universal health care system (Table 3). It is within the primary care context that maternity homes play a role, and where their results and influence can be described and evaluated.

Evolution tailored to needs Cuba's maternity homes have offered admission to pregnant women at risk due to different factors in different contexts at different times. The institution has shown great flexibility in addressing these needs in terms of location, admission criteria, main activities and personnel. Thus, in the first period (1962–1969), when the main aim was to increase

Table 3: Indicators and resources related to maternal–child health in Cuba, 2018

Indicator/resource	Value
Women's education (level completed, %) (2016)	
• University	16.1
• High school	47.0
• Secondary school	27.6
• Primary school	7.1
• None	2.2
Total hospitals	150
• Of these, general, ob-gyn and maternal–child hospitals*	54
Community-based polyclinics	449
Neighborhood family doctor-and-nurse offices	10,869
Average number of antenatal consults	14
Maternal mortality ratio (per 100,000 live births)	43.8
• Direct	27.5
• Indirect	16.3
Infant mortality rate (per 1,000 live births)	4.0
Low birth weight rate (%)	5.3
Under-five mortality (per 1,000 live births)	5.3
Vaccination rates for 13 childhood diseases (<1 year of age, %)	≥99.0

*does not include pediatric hospitals

Sources: *Health Statistics Yearbook 2018*,[27] *National Survey on Gender Equality 2016*[28]

institutional deliveries for geographically isolated women, the homes contributed to more in-hospital births, a percentage that has dramatically increased, reaching 85% by 1968, and 99.9% in 2018.[21,27] A collateral result was a marked increase in registered births, 100% in 2017.[29] Access to hospitals was also aided by extension of free health services throughout the country as well as building of rural hospitals, as noted above. This was complemented by construction of 27,650 kilometers of new roads between 1959 and 1980. In addition, over time, a greater share of the population was concentrated in urban areas (77% by 2017).[30]

When the economic crisis of the 1990s moved the needle upward on low birthweight rates, the homes' nutritional supplements (assisted by cooperating workplaces and farmers) became a prime objective. Later studies in both urban and rural Cuban settings reveal that maternity homes have played a positive role in gestational weight gain and improved nutritional status, and hence undoubtedly were a factor in bringing down rates of low birth weight (and continued reduction of infant mortality related to this factor).[31–33] For example, in a home in Havana's Cerro Municipality, 71 expectant mothers were studied, most admitted because of insufficient weight gain and 36.9% with anemia; both these factors showed statistically significant improvements, and 69 infants (97.2%) were born with normal birth weight (≥2500 g).[31] This result is consistent with an international review of 36 antenatal interventions, showing that nutritional supplements during pregnancy are one of the few effective ways to address impaired fetal growth.[34]

The educational level of Cuban women (Table 3), as everywhere, is a factor in maternal–child health. Universal education, free through university, has meant ever greater ability of women to understand and implement actions necessary for their own and their children's health. This has assisted health professionals in their maternity-home classes on healthy nutrition, exercise, infant care and medical attention. Certainly, the fact that vaccination

rates for infants under one year are over 99% is one result of combined efforts by such health professionals and the mothers themselves, who are most often the ones to take their children to well-baby doctor visits.

Costs, benefits and satisfaction Although no literature specific to Cuba attests to reduction of hospital stays and associated costs due to use of the more economical maternity homes, the institution's general contribution in this regard is recognized internationally.[4]

The more recent reduction in homes and beds must be assessed in light of maintaining equitable access to quality services, particularly related to issues of transportation. In The 2016 National Survey on Gender Equality, difficulty with transportation was rated by both women and men as one of the three most pressing problems faced, particularly stressful in Havana.[28]

The vast majority of Cuban women express satisfaction with antenatal care in general, with UNICEF data showing 97.8% receiving at least four antenatal consults, with a national average of 14. A 2003 study of pregnant women's attitudes in four developing countries noted that “[Cuban] women expressed a high level of satisfaction about the information they receive during pregnancy. Still, they might be lacking information on how to deal with the emotional and psychological changes occurring during pregnancy.”[35] It is important to recall that maternity home admission is not mandatory, and depends both on a woman's risk perception and her satisfaction with care received, since she can leave at any time.[36] It would be important to conduct research into the level of satisfaction with maternity homes in general, based on the questionnaires that women and their families fill out upon discharge.[22]

Maternity homes' relation to infant and maternal mortality

Both infant and maternal mortality are indicators influenced by multiple factors. In Cuba, where infant mortality has been under 5 per 1000 live births for several years, maternal mortality remains a concern. While steady and sometimes sharp declines were registered from the early 1960s through even the most difficult years of the 1990s,[37] it has since risen slightly, reaching a plateau: maternal mortality ratio (MMR, direct and indirect deaths per 100,000 live births) was 41.9 in 2016, 39.1 in 2017, and 43.8 in 2018.[27]


It is unclear whether maternity homes have greater potential to contribute to lowering MMR at this point, since most causes of direct maternal deaths in recent years are related to postpartum complications, including infections; and hypertension accounted for 3.4 maternal deaths per 100,000 live births in 2018.[27] Focusing more maternity home educational efforts on signs and symptoms related to these causes could be one area worth greater emphasis, as well as exploring paying greater attention to emotional and psychological factors that may contribute to MMR.

Anemia remains a problem for both maternal and newborn health, and excess weight gain and obesity also are on the rise. Maternity homes have a role to play in continuing to address nutritional issues. According to UNICEF, in 2014, 30.9% of pregnant women faced weight problems: 16.3% underweight, 9.8% overweight and 4.7% obese; while over the course of their pregnancies, 71.5% experienced normal weight gain.[38] In addition, one in

five pregnant women suffer mild iron-deficiency anemia in their third trimester.[39] However, according to the same UNICEF survey, of the 31% of pregnant women who are prescribed iron supplements, 93% take their medicines. Since so many women are admitted to a maternity home for at least some time during their pregnancies, monitoring of both nutrition and weight gain can make an important contribution to reduce related risk. It may be worth reviewing both exercise and nutritional regimens for overweight and obese women,

Gender and equity lenses While women's sexual and reproductive rights are explicitly guaranteed under Cuba's Constitution and legal framework, and these rights are further explored and explained in maternity home educational sessions, it is also true that gender inequality has an effect as couples prepare for parenthood.[21] This has several implications for maternity homes: the first is the continued need for these homes, to relieve stress on pregnant women resulting from their greater burden of household responsibilities, estimated at 14 hours

more than men weekly.[28] Second, through the Responsible Parenthood Program, initiated by MINSAP in collaboration with UNICEF,[40] prospective fathers are encouraged to play a greater role in pregnancy, birthing and care for their newborn child. Male partners are asked to attend psycho-physical classes at the maternity homes, preparing for participation when the time comes for delivery, but percentages of men who actually do so are unknown. More attention could be given to this aspect to further support and empower women during and after pregnancy.

A final word Cuban maternity homes were set up first and foremost to improve the health of women, mothers and children in the context of the drive for universal health within limited resources. Key to the continued success and relevance of these institutions will be the degree to which health authorities respond to needs expressed by pregnant women themselves, as participants in the construction of health, and in so doing propose new modifications to the maternity home model that extend equity and improve this vulnerable subpopulation's health and well-being. 

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Sickle Cell Anemia in Cuba: Prevention and Management, 1982–2018

Beatriz Marcheco-Teruel MD PhD

ABSTRACT

Sickle cell anemia is the most common hereditary disease in Cuba. On average, 1 in 33 Cubans is a carrier of this severe hemolytic anemia that can cause early death. In early 1980, its incidence in Cuba was calculated at 1 in 1600 births. In 1982, the Cuban public health system established the Sickle Cell Anemia Prevention Program, which aims to prevent the disease through identification of carrier couples and antenatal diagnosis of fetuses with disease-associated genotypes. In 1982–2018, hemoglobin genotypes were tested in 4,847,239 pregnant women. Of these, 168,865 (3.5%) were found to be carriers or to have sickle cell disease. During the same period, 8180 at-risk couples were identified, of whom 79.2% agreed to an antenatal study for detection of the sickle cell gene in the fetus. Among fetuses diagnosed, 20.1% had the SS genotype, the most clinically severe; 76.2% of the associated couples decided to interrupt the pregnancy. This program has resulted in a 3-fold reduction in prevalence of sickle cell disease in Cuba, a

10-fold reduction in the number of infants born with it each year, and a 16-year average increase in life expectancy of sickle cell disease patients of both sexes. Key contributors to these results have been universal screening of pregnant women in primary care, installation of diagnostic laboratories in every province, genetic counseling for couples, testing of fetal DNA (allowing couples to decide whether to continue the pregnancy if the fetus tests positive for the disease) and guaranteed multidisciplinary clinical care for patients. The Cuban experience shows that a middle-income country can mitigate the impact of a genetic disease through a universal preventive program based in primary care, which also pays particular attention to afflicted patients.

KEYWORDS Sickle cell anemia, sickle cell disease, sickle cell disorders, hemolytic anemia, sickle cell trait, sickle cell hemoglobin C disease, HbS disease, prevention, antenatal screening, preventive health services, Cuba

INTRODUCTION

Sickle cell disease (SCD) is a monogenic hereditary disease—a mutation in a single gene is sufficient to cause the disease, which originates in a point mutation in the alleles of the beta-hemoglobin gene. SCD affects most organs, and is characterized by abnormal erythrocytes that lose water and cations under low oxygen conditions due to hemoglobin S polymerization. Changes in the expression of cell adhesion molecules occur, small blood vessels become blocked, and severe hemolytic anemia occurs, characterized by vaso-occlusive crises with tissue ischemia and episodes of severe pain. Crises can be severe and lead to death at an early age.[1]

This recessive autosomal disease is caused by SS, CC and SC homozygotic genotypes. Patients with the SS genotype have the most severe form of SCD. Other allele combinations occur: the AA genotype in healthy individuals, and the AS and AC genotypes in carriers. When both individuals in a couple are asymptomatic carriers, each pregnancy has a 25% chance of producing a child with SCD.[1,2]

The number of children born with SCD in Latin America annually is estimated at about 6000.[3] Caribbean countries have a high SCD prevalence at birth, (0.26–0.65%)[2] second only to that in Sub-Saharan Africa, which had an estimated 230,000 cases at birth in 2010.[4] In Cuba the prevalence of SCD at birth is 0.02%,

the lowest among Caribbean countries.[2] Although there are no substantiating statistics, clinical practice suggests that SCD is the most common monogenic hereditary disease in Cuba.

The genetic ancestry of Cuba's population is a mix, representing—in order of relative frequency—Europeans, Africans and indigenous Americans. A 2014 study showed that on average, 20% of Cubans' genetic information comes from African ancestors. In populations of African origin, the frequency of the S allele is 3%–18%. The magnitude of the African genetic contribution, regardless of skin color, explains the high frequency of the S allele in Cuba's population.[2,5]

By 1982, an average of 100 infants with SCD were being born annually in Cuba. This prompted the Cuban health system to establish an SCD prevention program, operating in a network that included primary care settings, hospitals and research institutions, as well as medical genetics laboratories. The Sickle Cell Anemia Prevention Program was designed to screen pregnant women and couples to detect carriers, and, if detected, to conduct antenatal diagnosis of SCD genotypes in the fetus. In 1982–2006, laboratory testing used hemoglobin electrophoresis on equipment designed and patented by Cuban researchers at the National Medical Genetics Center (CNGM).[6,7] In 2006, this manual technology was replaced with semiautomatic multiparameter electrophoresis, using Hydrasys equipment (Sebia, France), installed in the national medical genetics network's 17 laboratories (1 in each province and 2 in Havana).[8]

In the 37 years since the design and implementation of the Program, CNGM in Havana has coordinated and conducted the national SCD surveillance system (unless otherwise noted, data cited in this article are from the Program's databases). CNGM manages Cuba's hemoglobin electrophoresis laboratories, including purchase and distribution of reagents and supplies for diagnosis. It continually monitors Program operations and

IMPORTANCE This article shows how a middle-income country can reduce sickle cell disease prevalence and increase patient life expectancy through a national, universal preventive program based in primary health care, which also provides multidisciplinary medical followup to children born with the disease.

statistics and performs fetal DNA testing for antenatal diagnosis. Program design follows the population-wide hereditary disease control program model recommended by WHO.[9]

CUBA'S SICKLE CELL ANEMIA PREVENTION PROGRAM

Implementation Begun in Havana in 1982, the Program was rolled out to other provinces through 1986. The first efforts consisted of training staff, purchasing reagents and supplies, manufacturing electrophoresis equipment and developing genetic counseling protocols. Since its inception, the program has used the algorithm described below.

SICKLE CELL ANEMIA PREVENTION PROGRAM ALGORITHM FOR DIAGNOSIS AND GENETIC COUNSELING

At the first antenatal appointment, the woman's family doctor offers to perform the hemoglobin electrophoresis test and suggests she attend a genetic risk assessment interview in the genetic counseling department of her community polyclinic. The test is performed before the end of the first trimester. If she is a carrier or has the disease, the diagnostic test is offered to her partner to identify his disease status (healthy, carrier, or with SCD).

Blood samples are transported from the community polyclinic to the municipal medical genetics department, and from there to the hemoglobin electrophoresis laboratory in the provincial genetics department. Results are sent to the genetic counselor, who shares them with the couple (or with the pregnant woman alone, if necessary). Couples in which both members are carriers of the S or C alleles, or who have the disease (AS, AC, SS, SC and CC genotypes) are offered genetic counseling by a clinical geneticist and antenatal diagnosis of SCD (from week 15 to week 22 of the pregnancy) with a fetal DNA study.

For this study, a sample of amniotic fluid is sent to the molecular genetics laboratory at the National Medical Genetics Center, and the result is returned to the province of origin. The couple attends another genetic counseling session, in which information is provided, including the choice of therapeutic abortion for fetuses who will become sick as infants. For couples who decide to continue the pregnancy, hemoglobin electrophoresis is performed on the newborn to confirm diagnosis, and clinical monitoring in a specialized hematology department is begun, continuing follow-up over time.[10,11]

Genetic counseling provides education about SCD, its causes, consequences, management and prevention, and helps couples make independent choices about their child's future during the pregnancy if the DNA study shows the fetus has an SCD-related genotypes.

In 1987, the Program reached 79% of pregnant women, and in 1989, more than 90%. [6,10,12] In the period 1995–2018, hemoglobin electrophoresis testing was performed on 98% of pregnant women in Cuba.

In 2007, digital databases were introduced to register hemoglobin electrophoresis results in medical genetics departments in community-based polyclinics, municipalities and provinces. This

reduced the number of hemoglobin electrophoresis procedures performed, avoiding repeated tests on multiparous pregnant women whose results were already known. This allowed some pregnant women to avoid uncomfortable blood draws, optimized procedures and reduced costs by decreasing the number of samples drawn, stored, transported and processed. Since 2007, Cuba has saved US\$4 (in reagents and supplies) for each repeat test avoided, thus reducing the annual cost to about US\$500,000 (Program administrative data).

Carrier screening and genetic counseling From January 1982 through December 2018, hemoglobin genotypes were studied in 4,847,239 pregnant women (hemoglobin AA: normal; AS and AC: carriers; SS, SC and CC: SCD). Of these women, 3.5% were diagnosed as carriers or as having SCD because they had one or both variants of hemoglobin S or C (Figure 1). The most common genotype among carriers was AS, with an average frequency of 3.2% in the 37 years since Program inception. Next was the AC genotype, at 0.6%. In pregnant women with SCD, the SS and SC genotypes both occurred at a frequency of 0.02%.

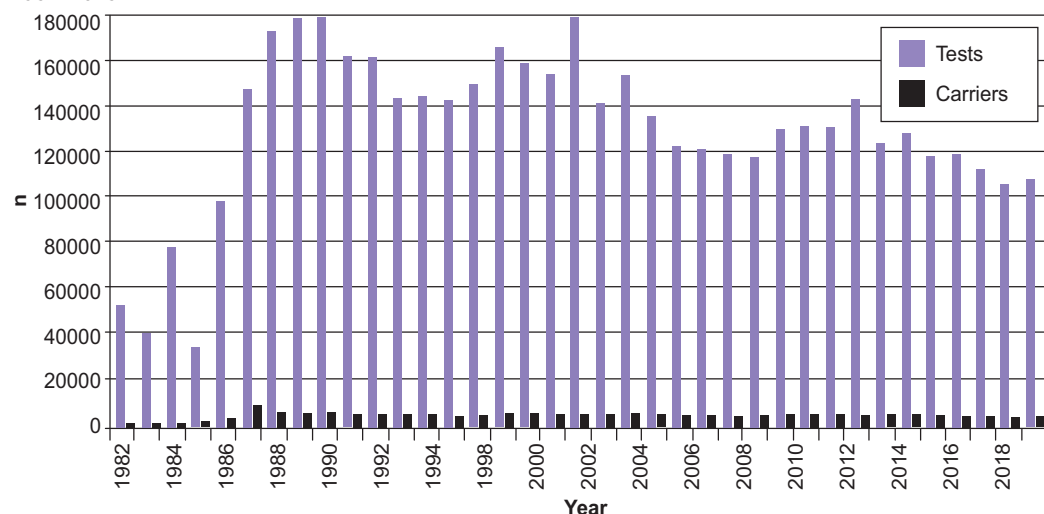
Because SCD has an inherited recessive autosomal pattern, it is important to diagnose carrier status in both parents. The hemoglobin test was conducted on 143,626 men, 85.1% of those who needed to be tested. Holguín Province had the lowest percentage of men tested in Cuba (72.1%), and Havana had the highest (92.3%). The most common reasons why male partners were not tested were: refusal to accept the possibility of being carriers, failure to acknowledge paternity, living apart from the pregnant woman, and lack of interest in being diagnosed. According to standard Program protocols, information about reasons was collected in questionnaires. The data indicate that educational strategies used in genetic counseling to help couples make independent decisions after learning of their diagnosis (as well as SCD causes, consequences, management and prevention) were not fully effective in actively involving male partners in the risk identification program. In 1982–2018, the Program identified 8180 at-risk couples, and of these, 6475 (79.2%) agreed to antenatal diagnosis (Figure 2).

Antenatal diagnosis of SCD by fetal DNA testing Over the life of the Program, antenatal diagnosis using DNA testing identified 1299 fetuses with SCD-associated genotypes (SS, CC or SC), representing 20.1% of all tests. When a fetus tested positive, the couple was offered genetic counseling to help them make an independent decision about whether to continue the pregnancy. Of the couples (or women) facing the most severe forms (SS or SC genotypes), 76.2% chose termination. By contrast, those whose fetuses were CC genotype, which develop less severe forms of SCD, rarely chose to terminate. After birth, all SCD children are monitored and given special care by the Program.

In antenatal DNA studies performed on 3303 fetuses since 2004 through 2018, the most common carrier genotype was AS (1417 cases; 42.9%). Less common were genotypes AA (931 cases; 28.2%), SS (455 cases; 13.8%), AC (270 cases; 8.2%), SC (202 cases; 6.1%) and CC (12 cases; 0.4%).

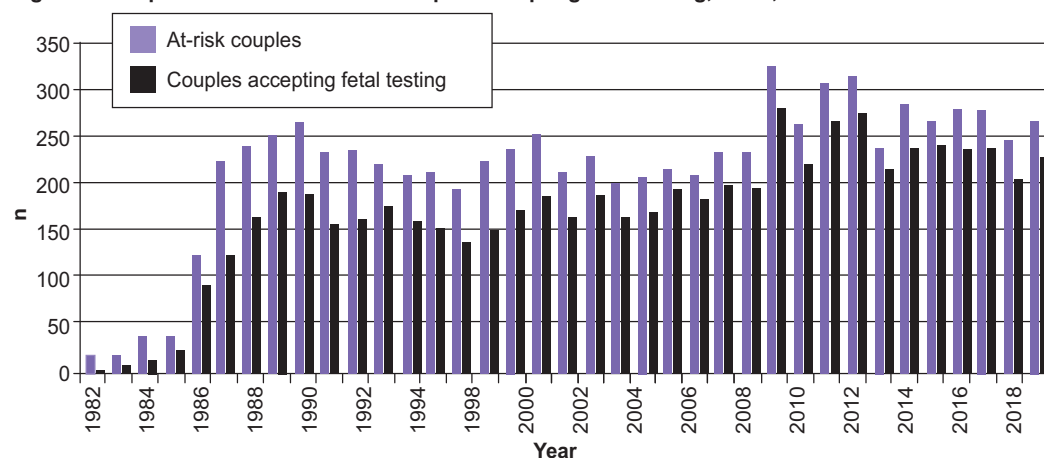
The SS genotype occurred most frequently in the provinces of Cienfuegos (17%), Santiago de Cuba (15.3%), Holguín (14.9%), Havana (14.9%), Sancti Spiritus (14.9%) and Ciego de Ávila

Figure 1: Antenatal hemoglobin electrophoresis for SCD: tests conducted and carriers identified, Cuba, 1982–2018



SCD: sickle cell disease

Figure 2: Couples at risk for SCD and couples accepting fetal testing, Cuba, 1982–2018



SCD: sickle cell disease

(14.8%). The SC genotype occurred most frequently in the provinces of Ciego de Ávila (11.1%), Villa Clara (9.7%), Sancti Spiritus (8.5%), Guantánamo (7.9%), Santiago de Cuba (7.7%) and Matanzas (7.1%).

Since 2014, with the Program testing 99% of pregnant women, an average of 10 infants with SCD have been born each year, most of them due to couples' informed decision to continue the pregnancy. Other reasons for this, which to some extent reveal weaknesses in the Program—but also respect the independence of individuals' decision-making—were the mother's refusal of SCD or carrier-status testing or not knowing the carrier or disease status of the male partner.

SCD carrier prevalence in pregnancy and disease incidence

SCD carrier prevalence was calculated by number of pregnant women tested who had hemoglobin AS or AC. Fetal disease incidence was estimated by number of fetuses with SCD-associated genotypes over total pregnancies tested. Prevalence at birth was taken to be the number of infants born with SCD genotypes among all live births.

Among pregnant women studied in 37 years, 3.5% were diagnosed as SCD carriers, a rate that varied in different provinces, depending on genetic ancestry composition, particularly the percentage of African-origin genes in the population.[5] In regions with greater percentages of black or mestizo residents, the frequency of pregnant carriers and incidence of fetuses with SCD-associated genotypes was also higher. Santiago de Cuba and Guantánamo Provinces had the highest carrier prevalence, 6.3% and 5.3% of pregnant women tested, respectively, while in the central provinces of Villa Clara, Sancti Spiritus and Ciego de Ávila (where European-origin genetic makeup is more frequent), prevalence was 1.7%.

Knowing differences in carrier prevalence and disease incidence permitted the Program to develop priorities and strategies for each territory, including number of genetic counselors needed in each community genetics department, number of multidisciplinary teams for patient care, and cost estimates for maintaining the Program and related health care services.

During the Program's existence, SCD prevalence at birth dropped from 1 in 1600 births in the 1980s to 1 in 5000 in 2018.

The gradual decrease in disease incidence was confirmed through the Program registration system and clinical registry of genetic diseases. Rigorous monitoring was performed at provincial medical genetics centers, which used hemoglobin electrophoresis to detect carrier couples. Quality control of these tests and fetal DNA studies throughout Cuba were performed at CNGM.

SCD mortality in Cuba

From 1987 to 2018, there were 1252 deaths from SCD. Life expectancy since Program implementation has shown a sustained increase. At the end of the 1980s, average age at death for a person with SCD was 28 years; during the 1990s, this rose to 32 years, then to 37 years in 2000–2009 and 44 years in 2010–2018. In Villa Clara Province, survival increased to 53 years in 2010–2018. Average age at death was slightly higher in females, as it was for national all-cause mortality rate. The 16-year increase in survival of patients with SCD (1987–2018) is the result of actions to address SCD through the prevention program, ranging from reducing the number of infants born with the most severe disease genotypes to continuous improvement in clinical attention to patients with SCD. Specialized followup clinical care is provided to children and all those with SCD in every Cuban

province, in teams led by hematologists. This includes folic acid administration throughout life, oral prophylactic penicillin from 3 months through 5 years of age, and a daily dose of hydroxyurea (15 mg/kg).[11,13]

Despite the Program's satisfactory results, deficiencies did occur in primary health care, where detailed, rigorous analysis of data obtained through Program protocols was not always performed. Such analysis would have allowed assessment and improvement of the Program's organizational processes.

In addition, the Program did not achieve a successful communications strategy to increase public awareness of the Program's SCD prevention and management services, and to encourage all pregnant women and their partners to agree to testing and antenatal fetal diagnosis.

CARIBBEAN NETWORK OF RESEARCHERS ON SICKLE CELL DISEASE AND THALASSEMIA (CAREST)

SCD is the genetic disease for which patterns are most similar among Caribbean countries. It was brought to the area through forced migration of more than 12 million Africans during the transatlantic slave trade.[14] The first report of SCD in the medical literature was made in the USA, when a young dental student from Grenada was diagnosed.[15] Carrier prevalence ranges from 13.8% and 13.6% in St. Lucia and Jamaica, respectively, to 10% in Martinique and French Guiana.[1] The country reporting the lowest percentage of carriers is Cuba, with 3.5%.[1]

Cuba was the first Caribbean country to implement nationwide antenatal screening to identify at-risk couples and provide therapeutic abortion upon the couple's request which is not subject to legal exemptions or conditions.[12] Decisions about ending or continuing pregnancy are taken by both prospective parents, but women's decisions are respected and protected.[16]

Jamaica was the first nation to demonstrate feasibility of neonatal screening for SCD and its impact on morbidity and mortality.[17] Neonatal screening programs exist in 7 other Caribbean countries, with coverage of over 96% in Trinidad and Tobago, 98% in Jamaica and Guadeloupe and 99% in Martinique; Grenada and St. Lucia report coverage of 79% and 45%, respectively.[1]

Before 2006, there were no reliable, consistent data on antenatal diagnosis of SCD in the region, with the exception of Jamaica, the French overseas territories, and Cuba. Starting in 2006, collaboration gradually began among research teams in various countries, now organized in the Caribbean Network of Researchers on Sickle Cell Disease and Thalassemia.[1]


As indicated in this paper, antenatal screening coverage in Cuba has been over 98.5% since 1999 and the number of infants born with SCD has decreased, while those living with SCD have increased survival rates. Cuba's strategies have been shared with other CAREST researchers, whose countries nevertheless have adopted their own variants to address SCD, some of them quite different from the Cuban model. Some of these differences are attributable to religious, legal or ethical objections to abortion, or because they do not consider it necessary to offer the option of preventing SCD births, and restrict medical services to prophylactic antibiotic treatment and hydroxyurea to improve patient quality of life. This treatment is also used in Cuba in children with SCD,[11,13] when couples decide not to interrupt pregnancy when faced with an SCD diagnosis.

Notwithstanding differences in program strategies, systematic collaboration among multidisciplinary teams in the CAREST network encourages more detailed analysis of SCD's origins and clinical and epidemiological characteristics, as well as the impact of programs and screening on morbidity, mortality and patient quality of life resulting from interventions carried out in the various countries.

CONCLUSIONS

Cuba's Sickle Cell Anemia Prevention Program has been universally implemented throughout the country and integrated into public health strategies and actions. It has reduced SCD incidence and prevalence and, in followup of SCD children, has increased their survival rates through multidisciplinary clinical care.

Key factors in achieving these results have been universal screening in primary care to identify pregnant women who are carriers, diagnostic laboratories in every province, genetic counseling of at-risk couples and clinical management of SCD patients. The Cuban experience shows how a middle-income nation can mitigate a genetic disease's impact through a national program that is universally implemented, free and accessible, based in primary health care.

The main weaknesses of the Program have been: poorly organized records for pregnant women who were carriers and those with SCD during its first 20 years, which led to unnecessary test repetition on multiparous pregnant women; an inadequate genetic counseling process that did not always motivate the male partner of a carrier to be tested; little analysis and assessment of the Program's operations in polyclinics and municipalities for ongoing improvement of organizational procedures, and lack of a successful communications strategy for educating the general public. 

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Hereditary Ataxias in Cuba: Results and Impact of a Comprehensive, Multidisciplinary Project

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ABSTRACT

Spinocerebellar ataxia type 2 is a degenerative disease that causes physical disability and, ultimately, prostration and death. Globally, reported prevalence is around 3 cases per 100,000 population and Cuba has the world's highest rates of the disease, affecting both patients and their at-risk descendants. In Holguín Province, which has the country's highest concentration of cases, incidence is 4.4 per 100,000 population and prevalence is 40.2 per 100,000 population. In 2000, a specialized research center was established in that province. Supplied with the necessary equipment and human resources, the center conducted national multidisciplinary studies involving molecular biology, clinical care, epidemiology, psychology, clinical neurophysiology, imaging, clinical genetics and community medicine, among others. A training and continuing education program also raised scientific capacity. Priority was given to developing international collaborations for academic exchange and training of Cuban researchers.

Multiple results from research involving clinical and epidemiologic characterization of the disease, identification of biomarkers and

therapeutic targets, genetic association studies, clinical trials and characterization of the disease's preclinical stages have been introduced in care of patients and their at-risk descendants. This has been accomplished through various programs including personalized rehabilitation, predictive diagnosis and social services. These results have also been published in high-impact scientific journals and received national and international awards. Such an experience in the context of Cuba's national health system—which is universal, free, accessible, comprehensive, prevention-oriented and with a record of international cooperation—demonstrates the possibility of providing quality care to affected families. Incorporating research findings into medical practice, with the resulting impact on patients' health and wellbeing, is a practical example of translational medicine in Cuba.

KEYWORDS Spinocerebellar ataxia type 2, health services research, biomedical research, health care delivery, translational medicine, translational research, health equity, Cuba

INTRODUCTION

Spinocerebellar ataxias are hereditary degenerative diseases causing physical disability eventually leading to prostration and death. More than 45 molecular types have been described, most frequently spinocerebellar ataxias types 1, 2, 3 and 6. Fuller understanding of their etiology and pathogenesis requires highly specialized genomic, proteomic and metabolomic studies, as well as research with experimental models.[1,2]

Spinocerebellar ataxia type 2 (SCA2) is a hereditary, neurodegenerative, disabling disease with an autosomal dominant inheritance pattern. It follows a progressive course that affects motor functions related to coordination, gait, postural stability and speech. It produces cognitive and sleep disturbances, as well as dysautonomia. SCA2 inevitably leads to prostration and death, produced by degeneration of the cerebellum and other central and peripheral nervous system structures.[3–5]

SCA2 has low prevalence in most regions of the world, reported globally at 3 per 100,000 population. Cuba has the world's highest concentration of SCA2 patients and at-risk descendants.[6,7] The disease is concentrated in the over one million inhabitants of Holguín Province, northeastern Cuba, where incidence rate is 4.4

and prevalence is 40.2 per 100,000 population. Confronting the disease has been a major challenge for Cuba, requiring enormous efforts by the public health system and government to acquire the necessary technology for molecular diagnosis programs; conduct research with scientific, clinical and social impact; and sustain a presence in the international scientific community. An extra challenge was to develop such advanced science in Holguín, nearly 800 km from Havana.

Cuba's single public health system provides universal, free, accessible, comprehensive, prevention-oriented care, and has a tradition of collaboration with other countries. The system also prioritizes scientific research, technological development and innovation in different fields. It comprises several medical universities and 37 research centers known as Science and Technological Innovation Entities (ECIT).[8]

To meet the SCA2 challenge, the Ministry of Public Health initiated a project for the study of hereditary ataxias and in March 2000, the Center for the Research and Rehabilitation of Hereditary Ataxias (CIRAH) was established in Holguín City, the provincial capital.

From the beginning, CIRAH's primary mission has been to develop scientific research and technological innovations aimed at finding therapies to modify the clinical course and severity of hereditary ataxias. CIRAH also provides medical care to improve the quality of life of patients and their families, and contributes to academic training and continuing education of researchers, technicians and other professionals in the field of hereditary ataxias and other movement disorders.

A little over four years after its founding, CIRAH attained ECIT status in recognition of its research results, accelerated training of human resources, development of scientific projects with

IMPORTANCE This article presents an example of a model for comprehensive management of ataxias that could be useful for other regions of the world. It demonstrates the application of ataxia research in services provided to Cuban patients, their families and descendants, highlighting the value of human resource development as well as international collaboration.

important social impact, and application of specialized health care programs. The latter include comprehensive, personalized rehabilitation; molecular prenatal and presymptomatic diagnosis; and social services for affected families.[9]

The study and treatment of SCA2 have involved basic, clinical, epidemiologic and social research. This article describes and analyzes the program's history, research impacts, medical practices, ethical implications, international cooperation, and family education; as well as public health policies, strategies and practices promoting social welfare and personalized care that have improved quality of life for affected families.

CUBA'S SCA2 PROJECT

In the study of SCA2, Cuba has reached top levels in terms of scientific development and productivity. The text describes how this has come about.

Research history The story begins with the first observations of increased numbers of patients and with various epidemiologic studies conducted since the late 1990s, continuing to the present. Among other aspects, these studies have estimated national SCA2 prevalence and incidence, described the disease's evolution by stage in order of prevalence, and evaluated policy and strategy outcomes.

In the 1960s, Dr Rafael Estrada Pérez, then director of the Cuban Neurology and Neurosurgery Institute in Havana, noticed that most patients with hereditary ataxias came to that institution from Oriente Province, which at the time included the current provinces of Holguín, Las Tunas, Granma, Santiago de Cuba and Guantánamo.[10] In 1978, Vallés reported a prevalence of ataxias in that region of 48.4 per 100,000 population.[10] In 1977, Beguería studied 30 patients with autosomal dominant ataxia and found significant ocular movement alterations.[11]

In the 1980s, a hereditary ataxia study was conducted in the V.I. Lenin University Hospital in Holguín's provincial capital, and collaboration with the University of Düsseldorf, Germany, was initiated. In 1981, Cordovés studied a group of ataxia patients in Tacajó, a health service area in Báguanos, Holguín Province, and as a result, estimated a population of more than 1000 affected individuals for the whole province.[12] In the late 1980s, Nodarse carried out nerve conduction and evoked-potentials studies in families with hereditary ataxias.[13] In 1989, Orozco described the clinical characteristics of patients with autosomal dominant cerebellar ataxia in Holguín and detected a significantly low concentration of dopamine in patients' cerebrospinal fluid, associated with neuronal depletion in the *substantia nigra*. [14]

In 1990, Auburger began to study the "founder effect," which occurs when specific mutations become more prevalent in the population of a determined geographic area, and argued that this phenomenon existed in Holguín, given the high prevalence of SCA2 in that province.[15] In November 1996, scientists mapped the gene associated with SCA2 and the mutation that causes it, which consists of an expanded cytosine-adenine-guanine (CAG) repeat sequence in the 5' end of the ATXN2 gene.[16–18] This discovery led to an important group of molecular, clinical, genetic and neurophysiologic studies that facilitated identification of biomarkers and therapeutic targets, as well as development of clinical trials.

The late 1990s and early months of the year 2000 marked the beginning of a new stage in hereditary ataxia research, with the development of health care programs offering presymptomatic and prenatal diagnosis plus intensive personalized rehabilitation. In 2000, biomarkers were identified and CIRAH was established. A strategy was also initiated for training specialized human resources to develop new research in the fields of molecular biology, clinical epidemiology, neurophysiology and neurochemistry, among others. Major national and international collaboration projects were undertaken, generating increased numbers of publications in high-impact scientific journals.

Cuba is one of the countries contributing most to the body of knowledge about ataxias. Patient studies are ongoing, and characterization of the preclinical phase in at-risk mutation carriers has been completed. Several new studies of early rehabilitation are now under way. All this is particularly important, since identification and characterization of the mutation's preclinical carriers offer early diagnosis and hence the possibility of early disease management through personalized clinical and psychological monitoring. This includes potential to apply various therapeutic options before disease onset, with a view to delaying appearance of the first motor symptoms.

Main health care outcomes and impact Health care services include multidisciplinary consultations at CIRAH and also in the community; personalized rehabilitation; and presymptomatic and prenatal diagnosis programs. The aim is to improve the quality of life of patients and their descendants at risk of becoming ill with the disease by applying medical and social measures that slow progression and onset. In this context, the goal is also to support decision-making and, in the case of predictive diagnosis programs, family planning in particular.

CIRAH's programs are national in scope. Health care and research activities are carried out with patients and their descendants nationwide. Genetic diagnosis includes the molecular forms of spinocerebellar ataxias types 1, 2, 3, 6, 7, 8, and 17, as well as dentatorubral-pallidoluysian atrophy and Friedreich's ataxia.

Programs with highest impact include presymptomatic[19] and prenatal[20] predictive diagnosis. In fact, CIRAH's experience with this type of diagnosis is unique in the field of ataxias. These programs involving different specialists have been applied for more than 15 years. The protocol includes genetic counseling sessions, psychological and psychometric evaluations to determine if an individual is prepared to receive the diagnosis, and subsequent monitoring.[21,22] Research has shown that individuals' levels of anxiety and depression decline considerably after receiving diagnosis, and no severe events (such as suicide) have been reported following ataxia diagnosis (something that occurs frequently with other types of degenerative disorders).[23,24] These outcomes benefited patients, their healthy relatives and asymptomatic carriers of the mutation. Moreover, these programs are distinguished for their ability to manage ethical dilemmas associated with this diagnosis.[25]

Overall, the prenatal diagnosis program has been requested by 201 couples, but has been necessary in only 108 cases of carriers who risked transmitting the mutation to their offspring. The presymptomatic diagnosis program has benefitted 1376

individuals, with 92% adherence and increased demand in the last 10 years (CIRAH administrative data).

Clinical care includes multidisciplinary consultations with neurologists, psychologists, psychiatrists, internists, physiatrists, etc. The number of cases assessed annually has increased, particularly in recent years (Figure 1).

Main research outcomes and impact Various studies have been carried out over CIRAH's nearly 20-year existence, beginning with the first epidemiologic investigations and molecular, neurophysiologic, clinical and neurochemical research. The primary objective of early investigations was identification of biomarkers and target variables for designing clinical trials and generating an SCA2 symptomatic treatment protocol. That strategy began earlier, in 1998, with an epidemiologic study in Holguin Province.[7] Since then, two more national studies have been conducted by CIRAH: one in 2003[6] and the other ongoing since 2017.

These national epidemiologic studies of hereditary ataxias are unprecedented globally: they have identified >160 families affected with some type of autosomal dominant ataxia, involving >700 patients and some 10,000 at-risk relatives. SCA2 is the molecular form with highest incidence and prevalence globally. In Cuba, it affects >100 families and altogether >500 patients, representing a proportion greater than 70% of all dominant ataxias.[6,7]

The findings informed social service provision for affected families, including walkers, canes and wheelchairs; housing and adaptive housing in the neediest cases; and rehabilitation in the community and at municipal and provincial hospitals. More than 800 patients have received physical rehabilitation, 70% of whom have shown improvement in cerebellar functions such as gait, balance, postural stability and speech. Frontal-executive functions, memory, attention and concentration improved in 75% of cases. Followup studies of patients receiving physical rehabilitation for five years showed slowed disease progression.[26–28] The advantages of physical rehabilitation during the disease's preclinical stage has been recently demonstrated, opening the way for early therapeutic protocols to be put into place.[29]

Identification and localization of affected families—patients as well as asymptomatic carriers—enabled characterization of

biomarkers of genetic damage (maximal saccade velocity, REM sleep without atonia, antisaccadic eye movements);[30–32] preclinical biomarkers (amplitude of sensitive evoked potentials, maximal saccade velocity, P40 component latency, central motor conduction time, percentage of REM sleep),[33–36] and progression biomarkers (amplitude of sensitive evoked potentials, periodic leg movements, maximal saccade velocity, percentage of REM sleep, etc.).[31,37,38] This also facilitated identification of therapeutic targets susceptible to eventual treatments or clinical trials.[4]

Identification and characterization of the abovementioned, primarily neurophysiologic, biomarkers enabled evaluation of the nervous system using various techniques. These studies over almost 30 years were conducted in >400 patients, 100 preclinical-stage cases and some 400 controls, and are part of CIRAH's 40 research projects, a number of them with international collaboration. The electrophysiologic studies used most broadly in biomarker descriptions include electronystagmographic investigations. These have identified saccade slowing as a pathognomonic sign of the disease, endophenotypic marker, biomarker of progression and genetic damage, and preclinical biomarker. [30,34,38,39]

Principal study results are the definition and characterization of the prodromal stage of the disease, which precedes onset of the cerebellar syndrome.[33–37,40–42] These findings opened up a new phase, not only from a research point of view but in terms of early intervention as well. Also identified were clinical alterations—such as periodic leg movements during sleep, painful muscle contractions and cognitive disruption—that could be included as response variables in clinical trials. [5,31,32,41–43]

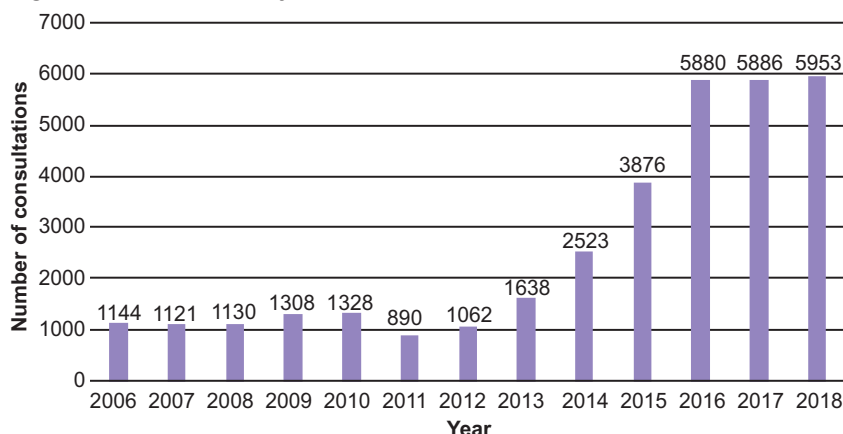
Molecular research was conducted in collaboration with scientists from Germany and the USA. This is the case of the SCA2 genetic modifiers study that identified the alpha 1 calcium channel subunit gene as a modifier of age onset variance and SCA2 severity.[44]

Additional molecular research topics have included a study of other genetic modifiers,[45–47] epigenetic factors, genetic predisposition, founder effect, molecular epidemiology, *de novo* mutations, the pathogenetic role of premutation alleles,[48–51] molecular characterization of Huntington's chorea[52] and SCA3,[53] as well as studies of survival, genetic risk in at-risk descendants, and estimation of age at onset.[54–56]

Development of a transgenic animal model of SCA2 was a major scientific outcome that led to an important collaboration with the Havana-based Genetic Engineering and Biotechnology Center (CIGB).[57] Additional neurochemical research has been conducted on oxidative stress issues.[58,59]

Other clinical trials involving nearly 200 patients and 31 preclinical individuals are shown in Table 1. Several of these results were published in international journals, facilitated doctoral training, and received national and international awards.

Figure 1: Cases assessed by CIRAH, 2006–2018



CIRAH: Center for Research and Rehabilitation of Hereditary Ataxias

Table 1: Clinical trials at CIRAH

Drug	Presentation and dose	Design and sample/year	Main results
Zinc sulphate[60]	50 mg tablets 1 tablet daily for 6 months	Phase II, randomized, placebo-controlled n = 36/2007	Improvement in some cerebellar signs Reduction in cognitive disturbance Reduction of oxidative stress
Zinc sulphate	50 mg tablets 1 tablet daily for 3 months	Phase III n = 50/2009	Reduction in cognitive disturbance
Vimang	300 mg tablets 6 tablets daily for 6 months	Phase II, randomized, placebo-controlled n = 20/2008	No significant outcomes observed
Lisuride[61]	0.1 mg tablets 1 tablet daily for 1 month	Pilot study n = 12/2009	Reduction of involuntary periodic leg movements Improvement in subjective quality of sleep
Creatine	Powder for solution and oral administration 10 g daily for 3 months	Phase II, randomized, placebo-controlled n = 30/2011	Increased muscle strength and muscle mass Stabilization of saccadic slowing
Compvit-B[62]	Intramuscular injection, 2 vials weekly for 1 month, followed by 1 vial weekly for 2 months	Pilot study n = 20/2009	Reduction in signs of peripheral neuropathy Reduction of painful muscle contractions Improvement in cognitive functions
Compvit-B	Intramuscular injection, 2 vials weekly for 1 month, followed by 1 vial weekly for 2 months	Pilot study (preclinical carriers) n = 31/2012	Reduction in signs of peripheral neuropathy Reduction of painful muscle contractions
NeuroEPO	Nasal drops 1 mL daily for 6 months	Phase I–II, randomized, placebo-controlled n = 30/2015	Improvement in cognitive functions Slight improvement in cerebellar signs or coordination

Source: Cuban Public Registry of Clinical Trials (<http://www.rpcec.sld.cu/>) and CIRAH's internal Clinical Trials Registry

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Compvit-B (National Bioproducts Center, Cuba): B-complex vitamin, lyophilized. Each vial contains 100 mg of vitamin B1, 100 mg of vitamin B6 and 5000 µg of vitamin B12

Creatine (Fit Foods Manufacturing Ltd, USA)

Lisuride (Delpharm Lille SAS, France)

NeuroEPO (Molecular Immunology Center, Cuba): human recombinant erythropoetin in solution for nasal use at a 1 mg/mL concentration

Vimang (Reinaldo Gutiérrez Pharmaceutical Laboratory Company and Pharmaceutical Chemical Center, Cuba): tablets with powder from natural extract of *Mangifera indica L.* stem bark

Zinc sulphate (CIDEM, Drug Research and Development Center, Cuba)

The first SCA2 treatment protocol was created, contributing to improvement in the quality of life for patients and preclinical carriers of the mutation.[4,29]

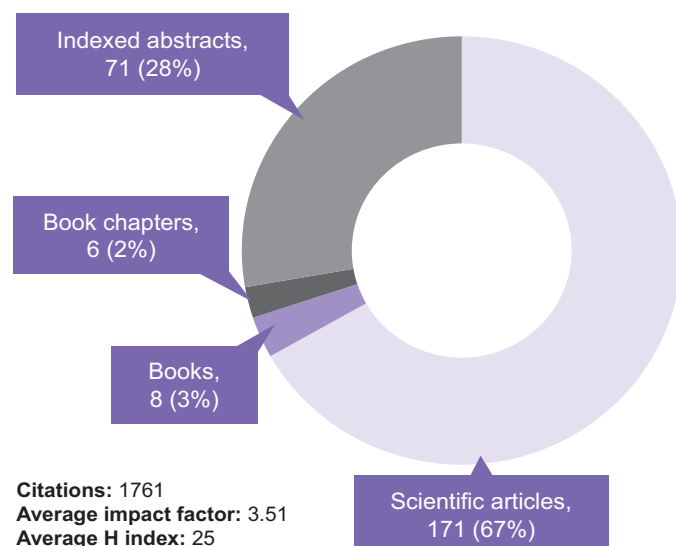
Scientific publications and awards At this writing, CIRAH's work is represented in 256 publications, consisting of 8 books, 6 book chapters, 171 scientific articles and 71 peer-reviewed abstracts. Of these, 67% appear in Web of Science, 80% in SCOPUS and 96% in SciELO. These resulted in 1761 citations, an average publication impact factor of 3.51, and an average H index of 25 (Figure 2).

CIRAH's scientific achievements have been recognized with more than 130 national and international awards. Nationally, CIRAH has won 29 Annual Health Awards from the Ministry of Public Health, 22 of these in the last 5 years, as well as 14 national awards from the Cuban Academy of Sciences. These numbers make CIRAH the Cuban institution with the highest number of awards per researcher and per PhD (1.4/researcher and 2.8/PhD), and the highest number of national awards to an institution located outside the nation's capital.

CIRAH's 57 international prizes include the Alexander von Humboldt Foundation's Georg Forster Research Award (Germany), as well as several awards from the International Parkinson and Movement Disorder Society and the International Brain Research Organization.

Scientific potential and collaboration Some 83% of CIRAH researchers have master's or doctoral degrees, 13 of them PhDs in various fields, including clinical neurophysiology, computer sciences, psychology, biology, microbiology, internal medicine, physical education and dentistry.

Figure 2: CIRAH scientific output, 2000–2019



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Nationally, CIRAH has also collaborated on epidemiologic studies with all of Cuba's medical universities, as well as with the National Laboratory Animal Production Center, CIGB, Cuban Neuroscience Center, Comandante Manuel Fajardo Hospital, Pedro Kouri Tropical Medicine Institute, Neurology and Neurosurgery Institute, Molecular Immunology Center, National Clinical Trials Coordinating Center, Drug Research and Development Center, National Medical Genetics Center, and the Universities of Havana, Santa Clara and Holguín.

CIRAH has collaborated internationally on projects with institutions such as the German universities of Tübingen, Aachen and Frankfurt on electrophysiological and molecular analysis and imaging studies; the National Rehabilitation Institute of Mexico and National Autonomous University of Mexico on neurorehabilitation projects and detection of other molecular types of ataxia, such as SCA7; the National Medical Genetics Center of Venezuela; Neuroscience Center of Antioquia, Medellín, Colombia; and University of Victoria, Canada. In 2017, a research collaboration was established with the University of Chicago, USA.

Challenges and prospects One of CIRAH's principal challenges is sustainability of research, health care and human resource training to deepen knowledge of the mechanisms triggering SCA2 and thus improve prevention and treatment strategies.

Our description of CIRAH as a model for application of scientific research to ataxia characterization and patient care also presents the new challenge of extending strategies to other Cuban institutions, fundamentally those associated with neurosciences and biotechnology. This would allow nationwide harmonization of treatment protocols, leading to a national initiative for early diagnosis and treatment of ataxias. CIRAH's research and development model may be applicable as well in other institutions with similar scientific and health care profiles.

The experience of the Cuban ataxia project offers further evidence of the importance of translational medicine, defined as


clinical application of research outcomes in the shortest possible time. This concept contrasts with the basic research paradigm in which search for and identification of new mutations may proceed without corresponding advances in effective treatments. Promoting such a paradigm shift represents a major challenge for Cuban and other researchers worldwide.

CONCLUSIONS

The fundamental reason for the Cuban SCA2 project led by CIRAH is the application of scientific research towards the goal of better understanding disease for earlier detection and treatment, and to eventually devise more effective treatment protocols. The project offers an example of introducing research results alongside development and application of comprehensive, multidisciplinary intervention programs with positive impacts and improved quality of life for individuals with the disease and those in its preclinical stage.

Over the past two decades, the project has included training and updating of skilled human resources, development of scientific leadership, and financial, material and scientific support obtained through both national and international collaboration.

In particular, the project's and CIRAH's own scientific development was led by researchers' efforts, while international collaboration not only assisted with costly technology, but also provided an effective channel for sharing information and new knowledge. This approach facilitated development of strategies and concrete actions that ultimately made CIRAH a reference institution in the field of ataxias.

Conducting this cutting-edge research in a center far from the Cuban capital is also an indication of the national public health system's priorities and scientists' commitment to bring both scientific research and health care services to the places where health problems are found. 

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Epidemic of Chronic Kidney Disease of Nontraditional Etiology in El Salvador: Integrated Health Sector Action and South–South Cooperation

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ABSTRACT

In El Salvador, chronic kidney disease had reached epidemic proportions towards the end of this century's first decade. In 2011–2012, the Ministry of Health reported it was the leading cause of hospital deaths in men, the fifth in women, and the third overall in adult hospital fatalities. Farming was the most common occupation among men in dialysis (50.7%). By 2017, chronic kidney disease admissions had overwhelmed hospital capacity.

In 2009, El Salvador's Ministry of Health, Cuba's Ministry of Public Health and PAHO launched a cooperative effort to comprehensively tackle the epidemic. The joint investigations revealed a total prevalence of chronic kidney disease in the adult population of farming communities higher than that reported internationally (18% vs. 11%–14.8%), higher in men than in women (23.9% vs 13.9%) and higher in men who were farmers/farmworkers than in men who were not (31.3% vs. 14.8%). The disease was also detected in children. An association was found between chronic kidney disease and exposure to agrochemicals (OR 1.4–2.5). In 51.9% of all chronic kidney disease cases, traditional causes (diabetes, hypertension, glomerulopathies, obstructive nephropathies and cystic diseases)

were ruled out and the existence of a particular form of chronic kidney disease of nontraditional etiology was confirmed (whose initial cases were reported as early as 2002). In the patients studied, functional alterations and histopathologic diagnosis confirmed a chronic tubulointerstitial nephritis; most presented with neurosensory hearing loss, altered tendon reflexes and tibial artery damage.

The main results of this cooperation were the epidemiologic, physiopathologic, clinical and histopathologic characterization of chronic kidney disease of nontraditional etiology. This characterization facilitated case definition for the epidemic and led to the hypothesis of systemic toxicity from agrochemicals (e.g., paraquat, glyphosate), which particularly affect the kidneys and to which farmers/farmworkers (who may also become dehydrated in the fields) are most exposed. The research thus also laid the foundations for design of comprehensive intersectoral government actions to reduce cases and put an end to the epidemic.

KEYWORDS Chronic kidney disease; chronic renal failure; tubulointerstitial nephritis; epidemiology; histopathology; international cooperation; agrochemicals; environmental pollutants, noxae, and pesticides; occupational health; PAHO; El Salvador; Cuba

INTRODUCTION

Chronic kidney disease (CKD) mortality has increased worldwide, from an annual adjusted mortality rate of 9.6 per 100,000 population in 1990 to 11.1 per 100,000 in 2010[1] and 18.2 per 100,000 in 2016.[2]

Population-based epidemiologic studies in the USA have shown increased prevalence of CKD from 11% (1988–1994) to 14.8% (2011–2014).[3,4] In 2011–2014, CKD prevalence was higher in US women than men (16.5% vs. 13%) and in the population aged >60 years (32.6%) than in the populations aged 40–59 years (10.6%) and 20–39 years (6.6%).[4] In Cuba, the Isle of Youth Study (ISYS) reported a prevalence of 9.6% in population aged ≥20 years (2004–2008)[5] and in El Salvador, the National Survey of Non-communicable Chronic Diseases in the Adult Population of El Salvador (ENECA-ELS) found 12.6% (2014–2015).[6]

IMPORTANCE This article describes the results of a collaboration among El Salvador's Ministry of Health, Cuba's Ministry of Public Health and PAHO, and its contribution to the characterization of a new epidemic form of chronic kidney disease of nontraditional etiology with high mortality in Salvadoran farming communities. It also suggests an etiological hypothesis and actions to combat the disease, with implications for other affected countries and regions.

ISYS, a population-based epidemiologic study, was conducted in cooperation with the International Society of Nephrology and other international organizations, to assess the CKD situation in Cuba and associated risk factors.[5] The methodology and results of this study served as the foundation for subsequent studies in El Salvador, where in addition to CKD of traditional etiology, a new form of CKD of nontraditional etiology (CKDnT) has emerged, largely found in farming communities.[6]

The purpose of this article is to show how cooperation between Cuba and El Salvador (South–South cooperation) together with PAHO made it possible to conduct epidemiologic and clinical studies on the CKD and CKDnT epidemic in El Salvador's farming communities, and to develop health system capacity to address the epidemic.

EL SALVADOR AND CKD

The principal scientific evidence generated by the joint studies of CKD and CKDnT is summarized below. It includes confirmed prevalence; sociodemographic distribution; social determinants; risk factors; cause; extent of the epidemic; the clinical, physiopathologic and histopathologic patterns of disease; and an etiologic hypothesis for CKDnT. The integrated actions of the Salvadoran health system, South–South cooperation and prospects for future work are also described and analyzed.

Sociodemographic data In 2018, El Salvador had a population of 6,643,359, 11.2% aged ≥60 years, with a life expectancy of

77.6 years for women and 68.6 for men.[7] The World Bank has classified El Salvador as a lower middle income country with a poverty index of 29.2%.[8]

CKD and CKDnT situation The first scientific evidence of a new form of CKD in El Salvador was reported in 2002.[9] It was characterized by lack of association with diabetes mellitus, hypertension or other traditional causes, and by its presence in male farmers/farm workers living in rural communities (Hereafter, “farmer” refers to farm workers hired by landowners or companies, as well as to farmers who may work their own land, usually subsistence farmers in the Salvadoran communities studied).

After becoming Minister of Health in 2009, Dr María Isabel Rodríguez addressed CKD as a serious and complex health problem in the country. In 2011–2012, the Ministry of Health of El Salvador (MINSAL) confirmed that end-stage renal disease was the third leading cause of hospital death in adults, the leading cause in men and the fifth leading cause in women, with a case-fatality rate of 12.6%.[10] One of the main contributing factors was a new type of CKD, unexplained by traditional factors, that primarily affected farming communities.[10]

In order to tackle this health crisis, MINSAL devised and deployed new activities on different fronts. For example, it began new clinical, pathologic and epidemiologic research and strengthened health services (including surveillance systems in primary care) for CKD prevention and control. It also worked to raise international awareness about CKD and took action to address it.[10] MINSAL leadership successfully argued the need to designate CKD an emerging health problem in several international fora, among them PAHO’s 2011 High-Level Regional Consultation of the Americas against NCDs and Obesity;[11] the 34th Regular Session of the Council of Ministers of Health of Central America and the Dominican Republic (COMISCA) in 2011 (resulting in the Antigua Declaration);[12] and the 37th Session of COMISCA in 2012, which adopted Resolution 54/55.[13]

These fora all recognized CKD as a health priority and underscored the need for immediate action. In 2013, as a result of the High-Level Meeting of Ministers of Health (which produced the San Salvador Declaration),[14] the disease was recognized as chronic tubulointerstitial kidney disease of Central America, based on the results of the epidemiologic, clinical and histopathologic studies conducted in El Salvador with CKD patients from farming communities. That same year, at the 52nd Directing Council of PAHO, agreement was reached to recognize CKDnT as a new entity, based on the San Salvador Declaration, and recommendations for action were formulated.[15]

In 2017, progress in implementing these recommendations were reviewed at the 160th Session of the PAHO Executive Committee.[16] The meeting also recognized El Salvador’s progress in conducting and disseminating the results of ENECA-ELS 2015[6] and actions to comprehensively strengthen local capacity to respond to CKDnT in the affected areas. Also recognized were advances in epidemiologic surveillance systems, various intersectoral activities, development of protocols and a dialysis and kidney transplant registry, as well as human resource training.[15]

South–South cooperation In 2009, a technical cooperation agreement among MINSAL, Cuba’s Ministry of Public Health

(MINSAP) and PAHO was implemented, providing the resources for epidemiological, clinical, and health services research for the comprehensive study and management of CKD and CKDnT in El Salvador.

For almost ten years, this cooperation has exemplified integration of professional and technical groups from different institutions and countries: in El Salvador, MINSAL, the National Institute of Health (INS), San Juan de Dios National Hospital of San Miguel, San Juan de Dios National Hospital of Santa Ana, primary care workers and facilities, students from the University of El Salvador Medical School, and Salvadoran farmers’ organizations in the Bajo Lempa region; in Cuba, MINSAP, the National Nephrology Institute (INEF), the National School of Public Health (ENSAP) and Salvadoran students from Havana’s Latin American Medical School (ELAM).

MINSAL oversaw the project led by Dr Rodríguez, during her tenure as Minister of Health and Director of INS, and later as Presidential Advisor for Health and Education. MINSAL furnished all logistical support for project implementation, from primary care to national hospitals. INS planned the project and provided equipment and reagents, coordinated by Dr Carlos Orantes Navarro. Community epidemiological studies were conducted in primary care, with social and farmers’ organizations playing a key role in raising awareness and mobilizing community participation.

Work teams (which carried out research, health promotion and health care activities) were made up of primary care physicians, joined by students from ELAM and El Salvador’s Medical School during vacations, after receiving classroom and field training.

The national hospitals were the setting for clinical, physiopathologic and histopathologic studies, with multidisciplinary participation by 22 biomedical specialties. MINSAP provided a multidisciplinary team of specialists consisting of nephrologists, epidemiologists, nephropathologists, biochemists, toxicologists and biostatisticians from INEF and ENSAP. Cuban team members served as temporary PAHO advisors and were responsible for study methodology and implementation strategy under MINSAL guidance. In this context, the El Salvador research process benefitted from Cuba’s Isle of Youth Study,[5] which provided useful methodological experience for examining CKD in total populations, including its survey forms, physical and laboratory measurement techniques, human resource training and methods for data analysis.

During the research, CKD morbidity and mortality surveillance systems were upgraded, with emphasis on developing human and technical resources through in-service training for professionals and technicians and on building capacity for use of new equipment and diagnostic techniques in all hospitals and health centers conducting the studies. The training was expanded nationwide to primary care.

A new modern facility was also built in the eastern region of the country (Bajo Lempa), the area most affected by CKDnT: the Monsignor Romero Community Family Health Unit, containing a specialized kidney-care section. It was staffed with a nephrologist, nutritionist, psychologist, health educator, laboratory technician and health promoters, and was constructed with funds from the Spanish Agency for International Development Cooperation.

The main results of the joint studies in El Salvador are discussed below.

CKD AND CKDnT: JOINT RESEARCH RESULTS

Epidemiological characterization *Epidemiological research in farming communities* Some epidemiological studies were carried out at different times.[6,17,19–23] In 2009–2013, 11 farming communities in 3 regions of the country were studied, with interviews of 1306 families and 5018 male and female adults aged ≥18 years; almost 90% (4503) were reassessed for CKD with a second measurement of urine albumin and creatinine, 3 (or more) months later.[17] Overall CKD prevalence detected in this adult population was 18%.[17] higher than that reported internationally (11%–14.8%)[18] or domestically (12.8%).[17] The disease was more common in men, in farmers than in nonfarmers, and in male farmers than in female farmers (Table 1).[17,19]

Of total CKD cases in these communities, 51.9% (Table 1) were not diabetic or hypertensive and did not have proteinuria ≥1 g/L (suggestive of glomerular disease), confirming the presence of a particular form of CKD not associated with these traditional risk factors or causes reported internationally. The resulting form was given a presumptive diagnosis of CKDnT.

In the population aged <18 years, CKD prevalence was 3.9% (Table 1). Glomerular hyperfiltration, calculated beginning at age 2 years, was observed in all ages and both sexes. An average glomerular filtration rate (mL/min/1.73 m²) was obtained for ages 2–5 years (male, 174.4; female, 182.5), 6–12 (male, 166.4; female, 175.8) and 13–17 (male, 171.4; female, 160.5). The values obtained were higher than the normal reference values for these age groups and indicative of kidney damage at an early age. [20] These findings revealed that the disease appears in childhood and adolescence, with high prevalence in both sexes.

The environmental and occupational health research found long work hours in a setting marked by high temperatures, intense physical activity and poor hydration. It also revealed use of large quantities of agrochemicals without adequate protection or hygiene and presence of agrochemicals and heavy metals (cadmium and arsenic) in surface and groundwater, wells and sediments, to a greater extent on farmland than in residential areas.[21,22] Direct contact with agrochemicals (46.7%) and use of nonsteroidal anti-inflammatories (NSAIDs) (84.2%) were significant among nontraditional risk factors in this adult population.[17]

Poor housing conditions, deficient water quality, low educational levels, poor nutrition, inadequate health services and a polluted environment (factors associated with poverty) were identified as the most frequent social and environmental determinants. [20,22]

Taken together, these findings suggested that risk factors were associated with farming activity, although they jeopardized the communities at large. It was concluded that attention should focus on the social determinants and environmental factors characterizing the most affected communities.

National Survey of Chronic Non-communicable Diseases in Salvadoran Adult Population ENECA-ELS 2015 This was performed in 2014–2015.[6] It is the most complete and

Table 1: Prevalence of CKD and associated risk factors in El Salvador in joint epidemiological studies

CKD in farming communities, population ≥18 years, 2009–2013[17,19]	Male n = 976	Female n = 1412	Total n = 2388
CKD (%)	23.9	13.9	18.0
CKD in farmers* (%)	31.3	15.8	26.8
CKD in nonfarmers (%)	14.8	13.4	13.8
CKDnT in cases with CKD (%)	45.3	6.6	51.9
CKD in farming communities, population <18 years (n = 2115)[20]			
CKD	3.6	4.1	3.9
National CKD prevalence by sex and location. Population ≥20 years (ENECA-ELS 2015)[6]			
Prevalence	%	CI 95%	
CKD	12.6	11.0–14.4	
Urban	11.3	9.2–13.7	
Rural	14.4	12.1–16.9	
Male	17.8	14.6–20.5	
Female	8.5	7.4–10.5	
**CKDnT	3.8	3.0–4.8	
Urban	3.1	2.2–4.4	
Rural	4.8	3.5–6.4	
Male	6.0	4.6–7.9	
Female	2.1	1.5–2.8	
Agrochemicals as an associated risk factor (≥5 years of exposure) ENECA-ELS case-control study[6]			
Exposure	OR	CI 95%	
Farming	2.0	1.5–2.5	
Handling of agrochemicals	2.5	1.9–3.4	
Storage of spraying equipment and products	1.5	1.2–2.0	
Handling of known nephrotoxic agrochemicals	1.4	0.8–2.2	
Aerial spraying in work or residential areas	2.4	1.7–3.4	
Direct exposure to agrochemicals (occupation sprayer, mixer, formulator or flagman)	1.8	1.4–2.4	
Consumption of river or well water	1.8	1.4–2.3	

*includes both paid farm laborers and farm owners
 CKD: chronic kidney disease (GFR <60 mL/min or GFR ≥60 mL/min with persistent albuminuria >30 mg/g)[6]
 **CKDnT: chronic kidney disease of nontraditional etiology (diagnosis of CKD without history of hypertension, diabetes mellitus or albuminuria >300 mg/g)[6]
 GFR: glomerular filtration rate
 OR: odds ratio

representative dataset available for CKD in El Salvador, characterized for its methodological rigor and use of internationally recommended methods for all measurements.[6,23] Implications of its epidemiological findings were important, as they revealed that the CKD and CKDnT problem was much more serious in rural areas and among men, and confirmed that CKDnT was not a national epidemic but selectively affected residents of farming communities. Concerning nontraditional risk factors, the relative frequency of the general population’s direct exposure to agrochemicals was estimated at 12.6%. As with the 2009–2013 epidemiological studies in farming communities, a nested case–control study conducted with ENECA-ELS survey data showed a strong association between CKD and exposure to agrochemicals for at least five years (OR 1.4–2.5) (Table 1).[6]

Clinical, physiopathologic and histopathologic characterization of potential CKDnT cases A study to identify the clinical and histopathologic characteristics was conducted in 2013 by experts in 22 biomedical specialties.[24,25]

Clinical and physiopathologic characterization The main clinical and physiopathologic findings were: absence of dysmorphic hematuria; proteinuria >1 g; normal kidney ultrasound in all patients; relatively undamaged upper renal arteries, and in contrast, severe damage to tibial arteries, coinciding with the part of the body most exposed to agrochemicals used in spraying; marked electrolyte loss with electrolytic polyuria and positive markers for tubular damage; neurologic damage in the majority of patients, characterized by neurosensorial hearing loss and alteration of the osteotendinous reflexes from the earliest stages of the disease, not attributable to uremia; profuse sweating and inadequate hydration among male farmers due to long periods of intense work in high temperatures. The functional exploration studies were the most complete studies published internationally (Table 2).[24]

Renal histopathology[25] The basic findings were interstitial fibrosis and tubular atrophy, glomerular sclerosis, mild-to-moderate inflammatory interstitial mononuclear cell infiltrates and vascular damage with intimal proliferation, and thickening and vacuolization of the tunica media. The morphologic pattern described corresponds to chronic tubulointerstitial nephritis (Table 2).

Interstitial fibrosis, glomerular sclerosis and vascular damage were higher in men. Interstitial fibrosis and severe tubular atrophy were more marked in sugarcane workers, as was thickening of the arterial wall and vacuolization of the tunica media. These histopathologic findings were present in all cases, male and female, as an expression of common damage, observed from the early lesions of stage 2 of the disease to the advanced lesions of stage 3b. Kidney damage was greater in male farmers and those exposed to greater heat stress.[25]

Electron microscopy revealed myeloid structures and phagolysosomes in the cells of the proximal and distal tubules and in the cytoplasm of the arteriolar vascular smooth muscle cells, which could correspond to chemicals phagocytized by lysosomes.[25]

Inferences and hypothesis Clinical and physiopathologic findings above suggest (1) ruling out primary and secondary glomerular diseases, obstructive nephropathies and cystic diseases; (2) interpreting functional impairments as indicative of interstitial tubular damage and symptoms mentioned by patients as a consequence of electrolyte loss; and (3) a hypothesis of neurotoxicity with concomitant need to explore the possibility of chemically induced vascular damage.[26]

The functional and histopathologic findings support the hypothesis that CKDnT is a chronic tubulointerstitial nephritis, coupled with systemic manifestations of hearing loss, peripheral neuropathy and peripheral vascular damage, which are not traditionally associated with chronic kidney disease.[26]

Summarizing: the etiologic hypothesis is systemic toxicity affecting the kidney, likely from environmental and occupational exposure to toxic substances used in agriculture. Toxic exposure may be greater among farmers, and its effects are likely

Table 2: Characterization of CKDnT patients (n = 46: 36 men, 10 women)

CLINICAL/PHYSIOPATHOLOGIC [24]
CKD progression: stage 2 (32.6%), stage 3a (23.9%), stage 3b (43.5%)
Risk factors
Poverty (100%); exposure to environmental toxins (95.7%); farming occupation (89.1%); male sex (78.3%)
General symptoms
Arthralgia (54.3%), asthenia (52.2%), loss of libido (47.8%), cramps (45.7%)
Kidney symptoms
Nocturia (65.2%), foamy urine (63%), polyuria (52.2%), dysuria (39.1%)
Clinical signs
HT (21.7%), diastolic dysfunction (43.5%), LVH (15.2%), tibial artery damage (65.2%), altered osteotendinous reflexes (43.5%), neurosensorial hearing loss (56.5%), normal fundus of the eye (100%), normal kidney ultrasound (100%)
Kidney function
Markers of kidney damage: no dysmorphic erythrocytes, A3 albuminuria (82.6%), proteinuria >1 g (2.2%), β2 microglobulin (78.2%), N-Gal (26.1%)
Urinary excretion of: magnesium (100%), phosphorus (50%), sodium (45.7%), potassium (23.9%), electrolyte polyuria (43.5%)
In blood: hyponatremia (47.8%), hypocalcemia (39.1%), hypopotassemia (30.4%), metabolic alkalosis (45.7%)
HISTOPATHOLOGIC [25]
Interstitial damage
Interstitial fibrosis: men—mild to moderate (38.9%), severe (33.3%); women—mild to moderate (30%)
Mild chronic inflammatory lymphomonocytic infiltration with <25% of parenchyma affected
Tubular damage
Classic tubular atrophy: 89.1%
Cytoplasmic vacuolization of proximal tubule epithelial cells: 45.6%
Glomerular damage
Glomerulomegaly: 47.8%
Glomerulosclerosis: men: 66.7%; women: 30%
Vascular damage
Fibrointimal proliferation: 19.6%
Thickening of tunica media: 52.2%
Vacuolization of tunica media: 43.5%; C: 55.6%; NC: 41.7%
Immunofluorescence
Negative
Electron microscopy
Phagolysosomes
Myeloid structures
Diagnosis
Chronic tubulointerstitial nephritis
C: sugarcane workers CKD: chronic kidney disease
CKDnT: chronic kidney disease of nontraditional etiology
HT: hypertension LVH: left ventricular hypertrophy
NC: non-sugarcane workers N-Gal: neutrophil gelatinase-associated lipocalin

synergistic with dehydration caused by heat stress during the workday. Within the multifactorial causality of such a complex disease, other risk factors were detected, among them NSAID consumption, a history of malaria, and others that may act as contributing factors.

Health services research in El Salvador Based on the findings of earlier studies, this research was conducted in 2018 to evaluate

service capacity and quality, and links among MINSAL's levels and areas of care needed to comprehensively address the CKD epidemic.

Salvadoran authorities and Cuban researchers examined the country's health statistics, visited facilities at the different levels of care and reviewed their data.[27] Statistical analysis revealed that in overall mortality, CKD ranked fifth among the 10 leading causes of death, with 2710 deaths, for a rate of 41 per 100,000 population. However, when searching for CKD diagnosis under all designations and from multiple causes, CKD mentioned as 'any cause of death' increased by 141%, raising the number of deaths to 3828. Thus, CKD incidence, prevalence and mortality were very high. In 2017, 6951 new cases (93.3 per 100,000 population) were reported, despite possible underreporting in all stages of the disease. CKD was the leading or second leading cause of mortality in the country's main hospitals, with the consequent hospital financial outlays.[28] Mortality in dialysis was also very high (33.8%–42.8%, with possible underreporting). Farming ranked first among dialysis patients' occupations (50.7%).[29]

Despite the development of primary care in the wake of El Salvador's Health Reform,[30] the number of cases exceeded this level's capacity for preventive action, early diagnosis and effective medical attention. At the hospital level, most patients arrived in the terminal stage, and many died before undergoing dialysis; the numbers and seriousness of cases also overwhelmed hospital capacities. The number of nephrologists (eight per million population) and dialysis capacity were insufficient to provide care for the high number of patients.[27]

Rural communities were hardest hit, with double the burden of traditional and nontraditional risk factors. The bulk of patients were in their most productive years (30–59). Cooperative studies with Sri Lanka,[31] one of the Asian countries most affected by CKDnT, also found nontraditional factors, as in other countries where the epidemic is present in farming communities.[23]

In 2017, analysis of national health and hospital statistics revealed other important health problems that may have a bearing on CKD and CKDnT. For example, extreme obstetric morbidity was found to be very high (8%), its increasing trend mainly due to hypertensive disorders (preeclampsia). In 2017, the San Juan de Dios National Hospital (San Miguel), which serves the eastern region (where CKD and CKDnT are most prevalent), extreme obstetric morbidity occurred in 33.8% of births from urban areas and 64.1% of births from rural areas. Other notable indicators were the high rates of low birthweight (8%), prematurity (8%), birth defects (12.6%) and infant mortality (9.2%).[32] The literature reports an association between agrochemical exposure and placental toxicity, presence of agrochemicals in the umbilical cord and preeclampsia,[33] making these findings a topic for special attention in future studies involving CKD and CKDnT.

The high prevalence of obstetric complications[32] and high frequency of kidney dysfunction in children[20] suggest that the disease begins in the preconception period and progresses throughout life. More research is needed on the causes of the high CKD prevalence in children and adolescents and its possible link to the epidemic of chronic tubulointerstitial nephritis in farming

communities in El Salvador, exposure to agrochemicals, NSAIDs, hard and stressful labor and chronic dehydration.

FUTURE DIRECTIONS: A CALL TO ACTION

The studies conducted have contributed to greater understanding of the epidemic afflicting rural El Salvador as described in this paper, and more are needed to identify and confirm causes and synergistic behaviors of risk factors. However, this alarming health situation requires swift action that cannot wait for the results of research that has not even begun.

The following actions, disaggregated by component, are considered necessary to address the health situation in El Salvador created by CKD and its variant, CKDnT.

Health promotion Strengthen social communication strategies and educational programs, as well as the legal and regulatory framework for environmental cleanup and preservation, to prevent and control CKD and CKDnT, protecting the health of farmers, their communities and the general population.

Prevention at the three levels of the health care system This implies upgrading and improving service quality:

- Swiftly adopt precautionary and preventive measures applied to agricultural and environmental practices, together with continued etiologic research.
- Strengthen health system capacity to implement a comprehensive approach to CKD and CKDnT, chiefly in the affected areas.
- Improve implementation, capacity building and compliance monitoring of existing programs or plans, as well as therapeutic guidelines for prevention, diagnosis, treatment and followup of CKD and CKDnT patients.
- Improve performance in primary care and provide laboratories with the diagnostic tools needed to actively screen at-risk groups and ensure early diagnosis of CKD and CKDnT; if possible, study the entire population in areas with high CKDnT prevalence.
- Strengthen capacity to provide inpatient and outpatient renal replacement therapy under the principle of bringing dialysis services closer to where patients live.
- Improve dialysis quality, develop kidney transplant capabilities, improve human resource capacity building and train more nephrologists.

Surveillance systems and health statistics

- Strengthen epidemiological, occupational and environmental surveillance systems.
- Improve CKD and CKDnT morbidity and mortality registries.
- Improve primary data quality.
- Implement the Kidney Dialysis and Transplantation Registry.

Research

- Increase advocacy for international cooperation among institutions and countries in research, and development of human and health care resources.
- Prioritize toxicology research on agrochemicals, both biotic and abiotic, including experimental studies.
- Improve quality of care and health service organization to create a favorable environment for research in all health facilities.
- Delve deeper into the causes of the increase in extreme obstetric morbidity.

CONCLUSIONS


Collaboration among PAHO and the health ministries of El Salvador and Cuba, facilitating joint work of Salvadoran and Cuban experts, contributed to better knowledge about the CKDnT epidemic in El Salvador, leading to the conclusion that it is widespread, selectively affects farming communities, results in high mortality (especially among people of productive age), and overwhelms the health system's capacity to provide care. Moreover, it is concentrated in farming communities with three basic factors that, taken together, set them apart: poverty as the predominant social determinant; an environment contaminated with agrochemicals; and working conditions marked by heat stress and dehydration, with no protection for workers. These factors coincide with those of other countries where the epidemic is found in farming communities.

The fact that CKDnT also affects residents of these communities who are not themselves farmers—for example, women who work at home, children and adolescents (not subject to the extreme heat stress of the work environment)—supports the hypothesis of toxic environmental exposure as a main causal agent, perhaps aggravated or associated with other factors. The presence of kidney dysfunction in children and adolescents and the high prevalence of obstetric

complications in women suggest that generations already may be doomed to suffer the effects of the disease, with catastrophic social and economic consequences for the country in the short and medium term.

The results of collaboration have laid the groundwork for the integrated intersectoral action urgently needed to combat the epidemic. Political and government commitment to take such action (involving not only health, but also sectors such as environment, social welfare, agriculture and business, as well as civil society represented by trade unions, community associations, farmers' groups, churches and others) is a prerequisite for any successful effort to improve health—including, of course, tackling the CKDnT epidemic. MINSAL, as the lead agency responsible for the health of the Salvadoran population, has the key role to play in coordinating these activities. The international community should also pay particular attention to this health crisis and must be ready to contribute to make national initiatives feasible.

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Cuban Strategy and Medical Cooperation to Combat Ebola, 2014–2016

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ABSTRACT

The Ebola virus is a pathogen that causes high morbidity and mortality in epidemic events during which health personnel are frequently infected. Such an epidemic occurred in West Africa, prompting WHO to issue a call in 2014 for health personnel to be dispatched to affected countries. Cuba responded and signed an assistance agreement under which 265 Cuban health professionals, members of the Henry Reeve Emergency Medical Contingent, volunteered their services in the Republic of Guinea, Sierra Leone and Liberia. This article presents Cuba's strategy of medical aid and organization of the three medical teams formed; refers to the teams' contribution to epidemic control in treatment centers where they worked alongside other personnel; and describes measures taken in Cuba to prevent the virus from entering the country through returning volunteers or other means. In the centers where Cuban medical teams worked with other health professionals in West Africa, case fatality decreased from 80%–90% to 24%, contributing to control of the epidemic; no Ebola outbreaks occurred in Cuba. During the epidemic, two Cuban health professionals died of malaria and one physician fell ill with Ebola. This paper includes an overview of the treatment and evolution of the latter case, a doctor who contracted the disease in Sierra Leone and was treated in Geneva and Havana.

KEYWORDS Ebola virus, treatment, strategy, followup, medical collaboration, Republic of Guinea, Sierra Leone, Liberia, Cuba

INTRODUCTION

Ebola virus disease (EBOV) was first identified in Africa in 1976, and was initially known as Ebola hemorrhagic fever.[1] Ebola virus affects both human and nonhuman primates, and EBOV can be serious, frequently fatal.[2]

In December 2013, a case of EBOV occurred in Guinea, in a border area near both Liberia and Sierra Leone. Given the absence of early detection and subsequent lack of measures to control virus transmission, the disease spread rapidly. The 2014–2016 epidemic in Liberia, Sierra Leone and Guinea was the largest to date, involving twice the number of cases reported over the four decades since the virus was first identified (1548 deaths from 2361 infected in 1976–2013; 11,310 deaths from 28,616 cases reported as probable, suspected or confirmed in 2014–2016, the latter reported by WHO in June 2016).[3] Recurrence is a continuing threat in the region since the virus

IMPORTANCE At a time when a new outbreak of Ebola threatens public health in Africa and in a globalized world, this article describes Cuba's contribution to combat the 2014–2016 Ebola epidemic in West Africa through collaboration with WHO, including training and organization of medical volunteers, infection control measures and preparedness to prevent an outbreak in Cuba upon the return of these health professionals.

remains in survivors' body fluids.[4,5] A small outbreak in the Democratic Republic of the Congo in April–July 2017 claimed four lives.[6] Another outbreak there resulted in 17 deaths in May 2018; it has continued through 2019, posing danger to other African countries.[7]

In 2014, faced with the rapid spread of EBOV in West Africa, WHO declared “a public health emergency of international importance.”[8] That September, the UN and WHO put out a call for international medical collaboration to respond to the crisis and the social disaster caused by the epidemic.[9] Cuba responded on October 9, 2014 and sent a delegation to Geneva, led by its Minister of Public Health, who offered the WHO Director Cuban medical collaboration to treat the affected population. Collaboration agreements between Cuba's Ministry of Public Health (MINSAP) and WHO were signed, under which Cuba would supply the medical and nursing personnel and WHO would finance the health professionals' expenses in the field (a stipend to cover costs of food, lodging, etc.), with no payment to Cuba for their services.

Before 2014, there were no specific vaccines or treatments for EBOV in humans. The principal treatment consisted of supportive measures to help maintain osmotic balance, anti-inflammatory medications for fever and pain, and specific treatment for any other concomitant infection, such as malaria, tuberculosis etc. [10,11] Clinical diagnosis and correct monitoring of patients during the disease course are crucial to avoid spread of infection and to control epidemics.

CUBA'S STRATEGY TO COMBAT EBOLA

Preparing the Cuban collaborative mission A recruitment appeal elicited responses from more than 10,000 health workers willing to volunteer in West Africa. The 465 professionals selected (all men) had the relevant specialties and experience in disasters and epidemics, primarily through their work as members of the Henry Reeve Emergency Medical Contingent created for such circumstances. They received initial intensive training from Pedro Kourí Tropical Medicine Institute (IPK) personnel in Havana and WHO, followed by two further training stages, described later.

A training site was built at IPK with tents for treatment and recovery (in conditions similar to those in existing Ebola treatment centers (ETC) in Africa (Figure 1), where medical personnel learned and practiced biosafety measures such as dressing and undressing using personal protection equipment (PPE); moving through areas where suspected, confirmed or convalescing cases might be located; and exiting these areas observing correct biosafety measures. These exercises established the foundation for health personnel performance in epidemic zones. The algorithm for the biosafety measures is outlined in Box 1.

Cuba also sent medical teams to other African countries (Angola, Democratic Republic of the Congo, Gabon, Burkina Faso and Guinea-Bissau) near those experiencing Ebola outbreaks, to

Box 1: Biosafety procedures established at IPK training and Ebola treatment centers (ETC) in Africa

Admittance into the red zone, where patients are treated, is always in groups of three professionals (a doctor and two nurses or two doctors and a nurse). All personnel must wear personal protection equipment (PPE) consisting of a one-piece gown of impermeable material covering the entire body, except face and hands. Special goggles and an N-95 respirator protect the face. Cuban professionals added an extra seal around the face with cloth tape, a procedure later adopted by workers in other African ETCs. Double sets of gloves protect the hands and a protective apron covers the front of the gown. Coworkers use a permanent marker to note on the gown the name and profession of the person entering the red zone, along with time of entrance.[12]

Undressing is one of the procedures with highest risk of contamination and must be undertaken in strict observance of established steps. In the area designated for undressing, an experienced hygiene worker soaks the entire PPE with 0.5% sodium hypochlorite solution before it is removed. An expert supervises each step of the undressing procedure in order to avoid violation of safety measures from fatigue, a major reason for noncompliance with protocol, and to avoid any increased risk of contagion to individual health professionals and the community of workers.[12]

Heavy perspiration can cause the temperature inside PPE to be 4 or 5 degrees above room temperature (38–40 °C). As this can cause the wearer to lose two or more liters of liquid from sweating, there are limits to the time they can stay at the ETC.

Three treatment areas for EBOV patients were established in both training and treatment settings: the Treatment Center, the Transit Center and the Community Center.

train Cuban and African doctors in procedures for handling Ebola patients. This training was also conducted in Jamaica and Venezuela.

The second stage of training for those headed to the affected countries was conducted at in-country ETCs and directed by WHO experts. The third preparatory phase consisted of training in the ETC treatment area (red zone) with patients confirmed to be infected by the virus.

A brigade of 165 professionals traveled to Sierra Leone for second-stage training including 5 coordinators. A total of 160 were sent to five ETCs: 40 to Maforki, Port Loko, staffed by Partners in Health (Harvard, USA); 52 to Kerry Town with Save the Children; 30 to Waterloo/Addra under the direction of the Sierra Leone government; 21 to the Ola During Children's Hospital; and 17 to Freetown.

Another team of 60 professionals went to Liberia (including 3 coordinators), where they underwent second-stage training in ETC MOD 1 in Congo Town, in collaboration with WHO and health authorities from Liberia and the USA. They continued to be based

there. A third team of 40 professionals (including 2 coordinators) traveled to Guinea for second-stage training, conducted by WHO experts in the Forécariah Transit Center. Once certified, they started working in the Coyah ETC, which the Cuban brigade helped to build. They were thus the last brigade to start their work and the last to leave the endemic zone.

Working sessions between high-ranking Cuban and WHO officials were held to establish agreements concerning organization and working conditions for volunteers. WHO officials recommended a four-week maximum of continuous presence in epidemic areas for volunteers, to avoid burnout. However, the Cuban delegation expressed preference that its medical teams stay at least six months in the affected countries, to better take advantage of their training and avoid constant redeployment and distribution of newly arrived medical personnel. Cooperants were consulted on this aspect and confirmed their willingness and commitment to the longer stay.

Organization of sanitary control, epidemiological surveillance, and diagnosis and treatment of possible Ebola carriers in Cuba To avoid spread of the infection in Cuba from possible contagious Ebola cases, international sanitary control was organized in Cuban airports. IPK built a special room for treating patients with EBOV (biosafety level 3) and purchased a high-security (also biosafety level 3) laboratory to process patient blood samples. A quarantine ward was prepared at IPK for travelers coming from areas with EBOV outbreaks, which functioned during the epidemic and through 2016. Blood samples from individuals placed in the quarantine ward and from patients with Ebola—should any present themselves—would be sent to the Canadian National Microbiology Laboratory in Winnipeg, designated by WHO to conduct diagnostic testing for any eventual Ebola cases in Cuba.

A total of 150 Cubans and 60 foreigners were admitted to the quarantine ward and kept in isolation for 21 days, monitored clinically and epidemiologically by three physicians and six nurses. The doctors, nurses and lab workers who cared for these possible Ebola cases in Cuba received training on the disease, its diagnosis, its treatment and protective measures against infection.

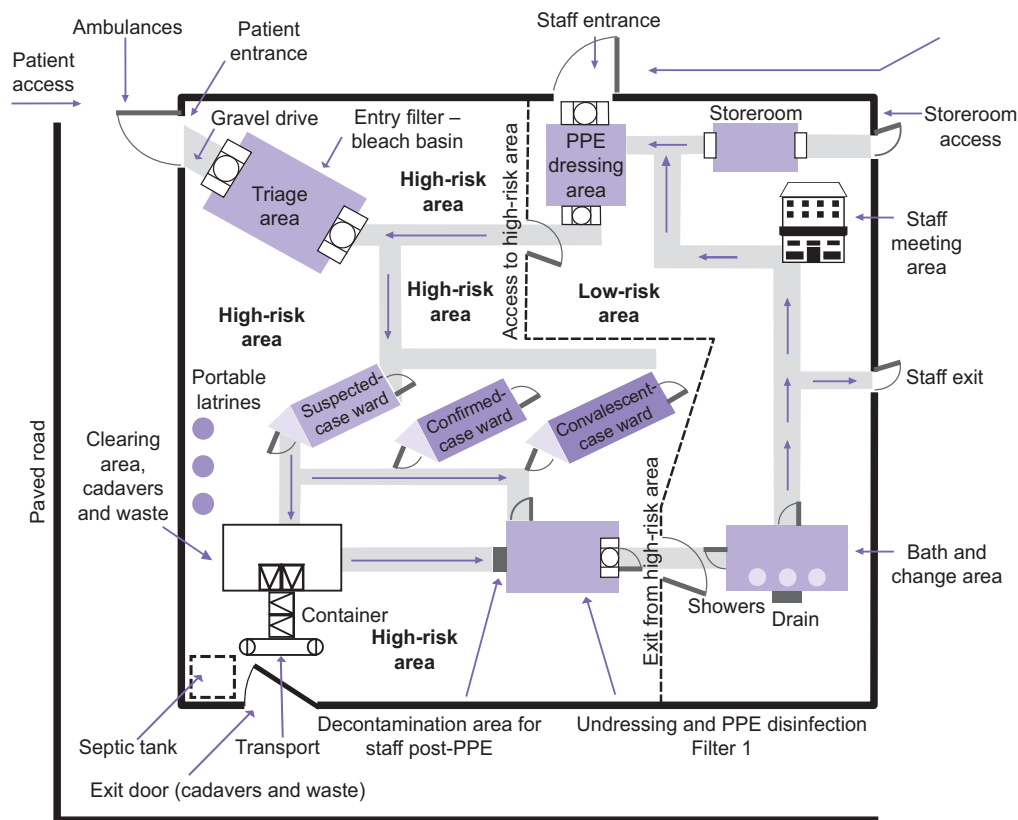
Cuban medical team activity in West Africa From Cuba, a technical commission led by MINSAP (composed of its officials, as well as Civil Defense, the Cuban Red Cross, IPK, and WHO/PAHO representation in Cuba) supervised the ongoing work of the Cuban medical missions in the countries affected by the epidemic.

To prevent Ebola virus infection, Cuban cooperants were instructed to avoid physical contact with local residents. Given that the main mode of contagion from Ebola is interpersonal contact via secretions, Cuban professionals also observed other prevention measures such as wearing long-sleeved shirts, using disinfectant gels, and wetting the soles of their shoes in trays of 0.5% sodium hypochlorite solution whenever they visited shopping centers or other public places.

To prevent malaria, which is endemic in Africa and the primary cause of death there, chemoprophylaxis was administered and use of repellents required. All cooperants had their temperature taken daily before breakfast, and were questioned about possible signs and symptoms of illness, receiving rapid medical attention if any responses were positive.

An indispensable requisite for the safety of Cuban personnel working in the ETCs was knowledge of Ebola's clinical and epidemiological characteristics, as well as biosafety and infection control measures. They put into practice knowledge and procedures learned in their first- and second-stage training, including appropriate conduct in ETCs, correct PPE dressing and undressing procedures, appropriate handwashing techniques and the importance of wearing gloves for every procedure, norms concerning personnel circulation (entering and exiting high-risk zones), and observance of safety barriers. ETC red zones have three wards: one for individuals suspected of carrying the virus; one for those probably infected; and one (separated into areas for men and women) with confirmed EBOV. The wards are separated from one another by three plastic barriers placed parallel to one another with a meter between them and the area of lower risk, according to norms established for these patients.

Figure 1: Map of IPK training units for Ebola treatment



PPE: personal protective equipment

Since the start of Ebola outbreaks, hundreds of health workers and NGO personnel have been infected for failing to comply with biosafety norms, with case fatality of greater than 50%. [13] Despite strict biosafety measures, frontline Cuban cooperants in the ETCs were not free of risk.

Shift assignment followed norms for rotation of medical and nursing personnel set by the technical commission in Cuba and international norms established by WHO. ETC work routines and biosafety measures followed a pattern similar to that employed in the IPK training unit (Box 1). Staff was on duty for shifts of six or twelve hours (8:00 AM to 2:00 PM; 2:00 PM to 8:00 PM, 8:00 PM to 8:00 AM). Shorter hours were later established due to loss of fluids and electrolytes through perspiration—resulting from PPE's hermetic enclosure—which produces fatigue and fainting, and can increase risk of infection. Based on experiences with prior Ebola outbreaks, professional staff were divided into three working groups: one to attend to patients; a second to prepare medications and hydration solutions; and a third to observe and alert the teams to any risks.

Analysis for Ebola virus RNA in blood samples of individuals suspected of Ebola infection and those supposedly cured was conducted in a WHO-certified laboratory. This allowed for rapid transfer of infected patients to the area for confirmed cases and facilitated ETC exit by virus-free patients.

During the training sessions, WHO experts advised against any direct contact with patients, handling of intravenous catheters or of contaminated biological fluids. Cuban medical personnel, who are not accustomed to keeping their patients at a distance, and

understand the importance of such interventions in healing and recovery, did insert catheters, assisted patients with drinking and eating, and bathed and dressed patients in order to promote hygiene and increase their chances of survival. The advantage of this form of handling infected patients has been demonstrated in developed countries with P4 (biosafety level 4) units where many survived and were discharged in good health. The Cuban teams obtained a higher survival rate with patients by carrying out these actions without violating safety procedures. [12]

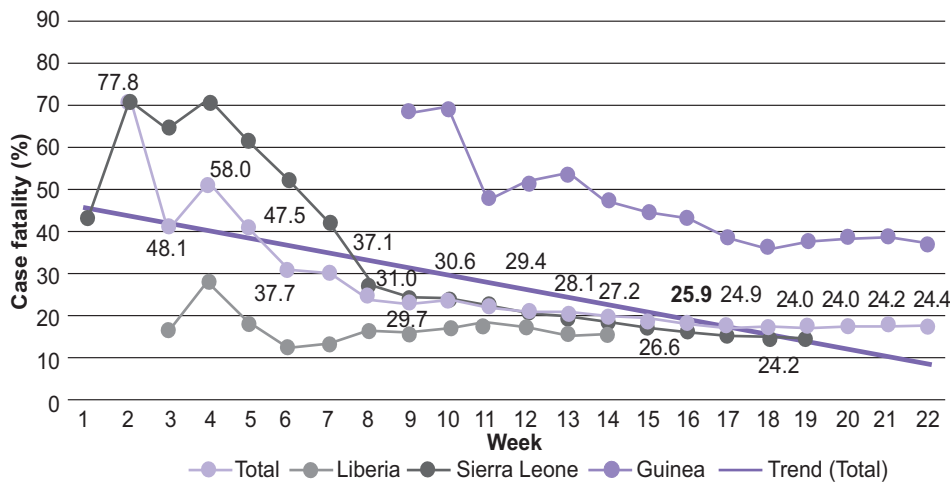
The results of the work of the Cuban medical teams are presented in Figure 2 and Table 1. Initially, the fatality rate in ETCs was 80%–90%. This was reduced to 24% through comprehensive treatment of clinical manifestations (vomiting, diarrhea, fever) and administration of parenteral electrolytic solutions to patients to restore and maintain electrolyte balance.

In 2017, WHO rewarded the Henry Reeve Emergency Medical Contingent's work with the Dr Lee Jong-Wook Memorial Prize for Public Health. [14] The volunteers were also featured in video documentaries and testimonies in a book by Enrique Ubieta Gómez, *Red Zone: The Cuban Experience with Ebola*. [15]

A CUBAN HEALTH PROFESSIONAL WITH EBOLA: OVERVIEW OF TREATMENT AND CLINICAL COURSE

Despite strict biosafety measures, a 43-years-old Cuban doctor who worked in Sierra Leone was infected with Ebola virus. After admission to an isolation ward in Sierra Leone, he was transferred to the Geneva University Hospitals (Switzerland) where he was treated with a cocktail of humanized monoclonal antibodies (ZMab, Mapp Biopharmaceutical, USA), considered a promising candidate for

Figure 2: Cumulative case fatality among patients treated by the Cuban teams in Liberia, Sierra Leone and Guinea. November 2014–April 2015



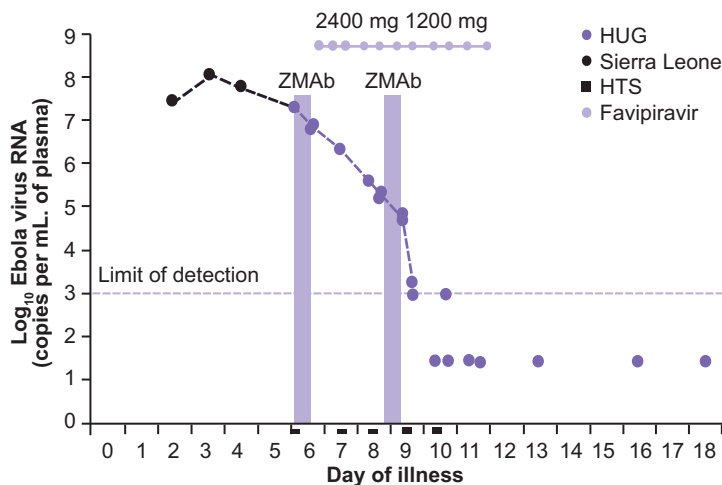
Source: Internal program data

Table 1: Results of the Cuban medical team’s work in West Africa*

Category	Location			
	Liberia 11/19/2014– 2/9/2015	Sierra Leone 11/5/2014– 3/19/2015	Guinea 12/31/2014– 5/7/2015	Total 11/5/2014– 7/5/2015
Outpatients				
Non-Ebola symptoms	201	—	334	535
Suspected Ebola	189	1628	350	2167
Ebola Inpatients	203	1640	342	2185
Deaths				
All	45	346	143	534
Ebola-confirmed	20	275	129	424
Case fatality (%)	22.2	21.1	40.6	24.4
Lives saved	23	300	111	434

*Liberia, Sierra Leone, Guinea Source: Internal program data

Figure 3: Kinetics of plasma viral load* for Cuban Ebola patient during 18 days of infection



*Schibler modification[18]
 EBOV: Ebola virus HUG: Geneva University Hospitals (Switzerland)
 HTS: high-throughput sequencing. ZMab: cocktail of humanized monoclonal antibodies
 Source: Reference 18

Ebola treatment,[16] as well as favipiravir, an antiviral that inhibits RNA polymerase (released for use during the 2014 Ebola epidemic, with good results).[17,18] Treatment with the two medications reduced viral load in a few days and made RNA virus undetectable (Figure 3). In December 2014, when the patient was declared cured and not contagious, he returned to Cuba and was admitted to the IPK Hospital during periods in 2014–2015, where he began additional treatment with Vimang, a Cuban antioxidant product extracted from mango tree bark and known for its beneficial effect on infection.[19] He continued to be monitored for various biomarkers, as noted in Table 2. To date, he has shown none of the sequelae observed in other survivors, such as vision and central nervous system problems, among others.[20,21]

LESSONS LEARNED

At the time of writing, there are still no specific treatments for EBOV. Some triple monoclonal antibodies have shown promising results[16] and antiviral medications and injections are being developed.[16,17] Conventional treatment in epidemics is intravenous water and electrolytes to recoup the loss of liquids from diarrhea and vomiting, and reestablish electrolyte balance; oxygen therapy to maintain high saturation levels; medication to lower fever, reduce pain and maintain blood pressure within normal ranges to reduce vomiting and diarrhea; and blood transfusions.[22] Cuban cooperants enhanced treatment with attention to personal hygiene, feeding and oral rehydration of their patients as part of medical and paramedical care, while still observing biosafety measures and obtaining good survival results.[12] This provided an important lesson, that this type of patient care should be included in the treatment regime, breaking the barriers of prejudice and fear of contagion associated with Ebola.

As mentioned above, administration of ZMab and favipiravir to the infected Cuban cooperant quickly reduced viral load to undetectable levels (Figure 3). The efficacy of triple humanized monoclonal treatment is still debated because clinical trials have been few[17], and the single clinical trial of favipiravir found it ineffective in patients with a high viral load, observing adverse renal reactions.[23] So perhaps biological conditions, specific virus variant, and initial viral load contributed to the favorable outcome in the Cuban patient and could be useful prognostic factors for treatment in future epidemics.

While use of antioxidants to modify the redox environment in patients with acute and chronic disease has been the subject of multiple studies, antioxidants are considered nutritional supplements, not drugs. One reason is that oxidative stress is not classified as a disease but is associated with a broad spectrum of diseases and is unrelated to any specific syndrome. [18] According to the Napralert Natural Products Data Base (University of Illinois, USA), extract of mango tree bark is an antioxidant widely used in natural medicine in many countries to treat infections.[24] The Cuban extract, known by its commercial name Vimang, showed good clinical and laboratory results when administered to the Cuban patient (Table 2) and could be

Table 2: Clinical course and findings in case of Cuban physician infected by Ebola in Sierra Leone

Date	Event	Clinical signs	Exams and results
Nov. 16, 2014	Entered isolation ward in Sierra Leone	High fever	Positive for Ebola virus
Nov. 19, 2014	Transferred to HUG	Conscious state, asthenia, hypoxia	Oxygen saturation 85%–88%
Nov. 20, 2014	Entered HUG ICU	Headache, tachycardia, asthenia, intermittent cough, crackling rales in lungs, maculopapular rash in thorax and abdomen spreading to rest of body, encephalitis. 38.5° C fever.	
Dec 1, 2014–Dec. 3, 2014	In HUG ICU		Negative viral RNA serology Semen collected to look for viral RNA
Dec. 6, 2014	Returns to Cuba, admitted to IPK	Muscular pain in legs	Biochemical and blood exams and indicators of redox state Increase in AOPP and concentration of HPO, increase in hepatic enzymes, ALAT, ASAT and ALP
Followup during 2015	Cuba	Gradual resolution of muscular pain and other symptoms	Return to normal values for oxidative stress indicators and hepatic proteins

ALAT: alanine aminotransferase ALP: alkaline phosphatase AOPP: advanced oxidation protein products ASAT: aspartate transaminase HPO: hydroperoxides
 HUG: Geneva University Hospitals (Switzerland) ICU: intensive care unit
 Source: Patient's medical records

considered for inclusion in treatment regimens for Ebola patients after the acute phase of illness.

This was the only Cuban medical volunteer to fall ill with Ebola. After recovery, he returned to Sierra Leone to complete his mission, and is now back in Cuba. Two others became ill with malaria and died, one in Guinea and the other in Sierra Leone.

One lesson the world learned from the 2014–2016 Ebola epidemic was that global health authorities did not recognize the international emergency nature of this epidemic in time. Another observation is that many governments did not become involved in providing care for sick people in Africa whose numbers were increasing daily—until the first case of Ebola was reported outside the continent in July 2014. [25] Others did send both human and material resources; and in any case, the greatest burden was borne by local public health authorities and professionals, as well as nongovernmental organizations (including Médecins Sans Frontières), which established services to diagnose, treat and prevent Ebola's spread.[26]

Cuba was an example of a country with limited resources responding quickly and effectively to WHO's call, by sending teams of health professionals trained in patient management and establishing a strategy to limit or prevent outbreaks of the disease within its own borders after volunteers returned.


CONCLUSIONS

Given the slow and inadequate international response initially to the Ebola epidemic, the Cuban health system played a prominent role, in number of professionals mobilized, technical quality of their intervention, and their disciplined sense of responsibility.

Training experienced health workers before leaving for the ETCs in the affected countries ensured the quality of their work and protection against infection by the virus. Without neglecting the necessary sanitary controls designed to minimize risk to professionals and the possibility of introducing the pathogen into Cuba, these Cubans cared for patients in close collaboration with international, national and local health authorities, with high levels of commitment to their work.

Nevertheless, the epidemic tested Cuba's capacity to mobilize in the face of health emergencies far from its national borders, as well as to effect measures to stop EBOV infection from becoming a health problem in the country itself. The experience proved that, even with limited resources, proper international and domestic health control measures can avoid outbreaks and epidemics of the disease. Finally, the Cuban health professionals who volunteered, successfully addressing the disease, also brought back lessons in clinical care and human solidarity in emergency situations, highly useful for future missions of the Henry Reeve Emergency Medical Contingent and other Cuban global health cooperation efforts.

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The Challenge of Eliminating Childhood Tuberculosis in Cuba

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ABSTRACT

WHO's 2015 End Tuberculosis Strategy can succeed only through universal health coverage, social protection, poverty alleviation and effective multisector actions to tackle social determinants in general. The pediatric age group is particularly vulnerable to tuberculosis and historically neglected worldwide. However, this group is a priority within Cuba's National Tuberculosis Control Program that has functioned since 1970, and Cuba is considered a low-incidence country with rates <7 per 100,000 population since 2011. Tuberculosis incidence in children aged <15 years is <1 per 100,000, similar to that reported in high-income countries and representing less than 2% of total cases in Cuba. Since 1999, no deaths from tuberculosis, coinfection with HIV or resistance to the two first-line TB drugs have been reported in affected children,

and most diagnosed cases correspond to early, primary forms of the disease. These results place Cuba among the countries on track to eliminate TB by 2050. This article reviews the pillars and components of the 2015 End TB Strategy and the strategies developed by the National Tuberculosis Control Program that enabled Cuba to bring incidence below the 2035 targets of WHO's End TB strategy. The article also proposes other actions Cuba can take, despite limited resources, to eliminate TB, particularly in the pediatric age group.

KEYWORDS Tuberculosis, communicable disease control, disease control programs, preventive health services, child health, World Health Organization, Cuba

INTRODUCTION

The numbers of people with tuberculosis (TB) and deaths from the disease worldwide are alarming: in 2017, 10 million people developed TB, and the disease caused 1.3 million deaths. Of the total number of people with TB, 1 million were youngsters aged <15 years.[1]

The objectives of a post-2015 strategy for ending the TB epidemic were proposed at the World Health Assembly in 2014. WHO's End TB Strategy 2015–2035 set as targets a 95% reduction in TB deaths by 2035 (compared to 2015) and incidence rates of <10 cases per 100,000 population, without catastrophic costs for families. The 2050 target is <1 case per million population per year.[2,3]

According to WHO, this ambitious objective can be achieved with existing resources only with universal health coverage, social protection, poverty alleviation and effective multisector actions on social determinants in general.[1]

In Cuba, the National Tuberculosis Control Program (PNCT) has functioned since 1970 and Cuba is considered a low-incidence country (<10 cases per 100,000 population), on track to eliminate TB by 2050, despite its status as a middle-income, resource-constrained country.[4–6]

Worldwide, the pediatric age group is particularly vulnerable to TB,[6] yet historically has been neglected.[7–10] Thus, children constitute a growing reservoir of TB infection with a high risk of primary TB progression that can, however, be avoided with preventive treatment.[8,10]

IMPORTANCE This article describes Cuba's approach to controlling tuberculosis and proposes further actions to eliminate it, particularly in the pediatric age group.

According to WHO, the burden of TB in children is largely due to the difficulty of making a diagnosis, given the clinical overlap of TB symptoms with other common childhood diseases, and because bacteriologic confirmation is rarely obtained.[8,10,11] This problem is compounded by lack of access to health care and poor quality health services in many countries. It is not strange, therefore, that case definitions between and within countries are inconsistent, with deficient disease recording and reporting practices.[8] Estimates of the burden of childhood TB are usually calculated based on the percentage of children who are ill with the disease compared to the adult population, which is obviously inexact.[3,10]

Child health is a priority in Cuba. The National Maternal Child Health Program has achieved impressive, internationally recognized results, including an infant mortality rate of 4 per 1000 live births and an under-5 mortality rate of 5.3 per 1000 live births in 2018.[12] TB incidence in children aged <15 years represents under 2% of TB cases (Figure 1), similar to proportions reported in high-income countries. In the USA, TB in children and adolescents accounted for 7% of cases reported annually between 2008 and 2010;[13] whereas in European Union countries, an average of 4.4% of TB patients in 2011 were children aged <15 years, with a range of 0–11.1%.[9,14,15]

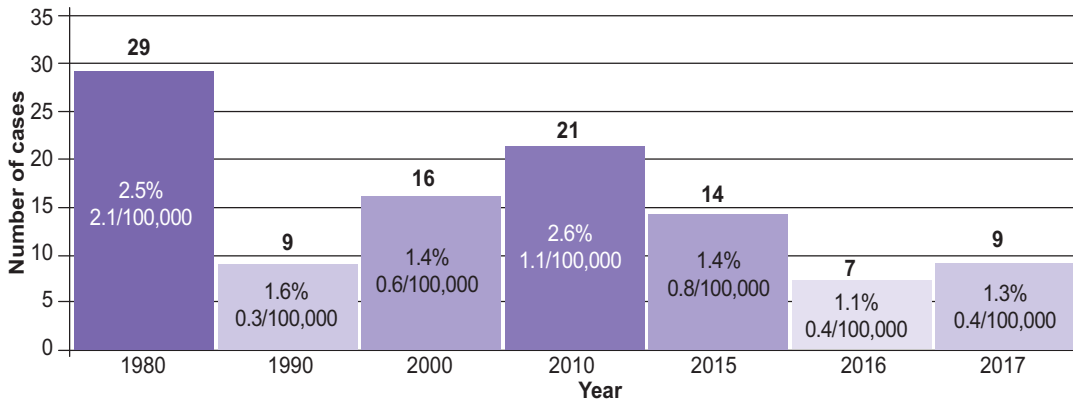
Since 1999, no child with TB in Cuba has died, suffered coinfection with human immunodeficiency virus (HIV), or experienced multidrug resistance (MDR, resistance to the two first-line TB drugs).[6,12,16]

This article reviews the main components of the WHO's End TB Strategy and analyzes the strategies developed by the PNCT in this context. Thanks to their implementation, Cuba has already brought incidence below WHO's 2035 target. This paper also examines other actions Cuba can take to eliminate TB, particularly in the pediatric age group.

CUBA AND THE END TB STRATEGY

WHO's End TB Strategy is composed of four key principles and three pillars with their respective components. The principles are:

Figure 1: Childhood TB cases, percentage of total cases and incidence rate per 100,000 children aged <15 years, Cuba 1980–2017 (selected years)



Source: National Medical Records and Health Statistics Bureau, Ministry of Public Health (CU), Annual Statistical Yearbooks, 1980–2017

- government stewardship and accountability, with monitoring and evaluation;
- strong collaboration with civil society and communities;
- protection and promotion of human rights, ethics and equity; and
- adaptation of the strategy and targets in each country, with global collaboration.[2]

Cuba’s approach adheres to these principles, although the multi-sector comprehensive intervention strategy still needs reinforcement.[17,18] Limitations associated with an antiquated housing stock deteriorated by extreme weather events; population growth and aging; internal migration to urban areas; and other local problems still need to be addressed.[16,17]

Pillar 1 The first pillar of the End TB Strategy is patient-centered prevention and care with these key components: early diagnosis; treatment of all people with TB; treatment of people at risk and vaccination against TB; and collaboration between TB and HIV programs, aimed at simultaneously addressing the risks of both diseases.[2]

Early diagnosis[2] As indicated, childhood TB is difficult to diagnose, due in part to low proportion of bacteriologic confirmation (<50%).[8,19] The PNCT has achieved 100% for the process indicator of sample adequacy for diagnostic testing of ill children. Another PNCT process indicator is testing 100% of contacts of people with TB, regardless of age, which ideally leads to early diagnosis of 90% of exposed children who develop active TB.[16]

Several requirements of early and efficient identification of patient contacts have not been fully resolved, such as including all frequent contacts within and outside the home, coordinating—with multisector support—prompt initiation of contact monitoring, and systematic compliance with the four doctor visits indicated for monitoring identified contacts.[6,20] Although the goal of diagnosing at least 85% of cases has not been met,[16] PNCT actions make possible not only diagnosis of new active TB cases, but also latent TB infection (LTBI). There is a high risk of developing the disease within 2–3 years after becoming infected, especially in children aged <5 years.[7,11,16,21]

Treating LTBI is a cost-effective strategy that is systematically applied and supervised in children aged <15 years, as recommended

by WHO.[4,21] In 2003, the Stop TB Initiative created a global working group on childhood TB[8] that recommended creating childhood TB groups in each country. This strategy had been implemented in Cuba eight years earlier.[16]

In Cuba, childhood TB diagnosis and prevention activities are carried out at neighborhood family doctor-and-nurse offices (CMFs). These are supervised by a pediatrician at the polyclinic to which the CMF reports

(Cuba’s primary care system includes two levels, CMFs and polyclinics, which are community-based multispecialty clinics).[22] the municipal epidemiologist and the Provincial Childhood TB Commission (CPTB), the latter comprised of pediatricians from hospital respiratory disease services in each province. Suspected cases are discussed with the National TB Reference Center (CNTB). This approach was implemented in 1995 to strengthen PNCT activities and address the reemergence of TB.[6,16] A systematic effort is made to include each child contact of a TB patient in a CPTB clinical–epidemiologic record, once the child has been assessed in their respective health area, in order to avoid errors detected in operations research, for example: not keeping a record of primary preventive therapy, delayed initiation of contact identification, or failure to conduct all necessary exams (Mantoux test and chest x-ray) in a timely fashion.[20]

The CNTB holds annual workshops with all CPTB heads to review the country’s childhood TB situation and incorporate the PNCT’s new knowledge and practices. The workshop lays the groundwork for further systematic training of pediatricians and family doctors. Given the country’s low incidence rates, medical students have few opportunities to learn firsthand how to evaluate and manage childhood TB cases.[12,23] Instructional activities about TB using CNTB-created materials are offered as student electives, providing additional training, and in 2008, a childhood TB demonstration clinic was added to the 4th year medical school pediatrics rotation. When possible, cases diagnosed in a community health area are used as learning opportunities for doctors and nurses,[24] both as scientific activities and published case reports, respecting confidentiality of personal data.[25]

With the introduction of molecular testing using the Xpert MTB/RIF assay, priority has been given to rapid positive diagnosis of childhood cases and rapid antibiotic sensitivity tests.[6,24]

Through efforts of the CNTB and its provincial counterparts, in 2013–2017, 48 of 55 diagnosed cases (87.7%) were early forms of the disease, none of them serious: 36 primary complexes, 9 cases of adenitis and 3 pleurisies. (Data from the National Medical Records and Health Statistics Bureau, Ministry of Public Health). No deaths in children aged <15 years have been reported since 1999.[12,16]

Treatment of people at risk and vaccination[2] Since 1960, prevention has also involved BCG vaccination of all newborns before discharge from a maternity hospital (99% of births in Cuba occur in hospitals). In 2018, BCG vaccination coverage was 99.7%. [12]

Treatment of all people with TB[2] In 1984, Cuba adopted the DOTS strategy (directly observed treatment, short course, a short-term treatment strictly supervised by health personnel). Since 1994, all diagnosed cases are reported and treated, even without microbiological confirmation (the case with most children). In 2014, Cuba updated national PNCT protocols and expanded its norms and procedures pertaining to childhood TB, including diagnostic criteria and treatment monitoring.[4] A single, universal public health system fosters use of standardized intervention protocols.

Drug-resistant cases are few and treated according to their resistance pattern, especially those with MDR (not found in children since 1999). Drug resistance is rare: 20 of 1529 cases in an analysis of the 2009–2010 cohort, mostly isolated isoniazid resistance, with only 6 (0.3%) MDR, contributing to successful treatment.[6,26]

Medications are free for all TB patients, who also receive government-subsidized healthy foods, supplementing basic food rations and other foods purchased. Since 1970, adult patients in the workforce receive their full salary during treatment. Costs to families are minimal, since medical care is government funded and free of charge.[5]

Collaborative TB/HIV activities[2] Cuba's Strategic Plan for the Prevention and Control of STIs and HIV/AIDS includes community-based health promotion activities, testing and free antiretroviral treatment,[27] operating in close collaboration with the PNCT. Coinfected patients are assessed by teams of experts and complete their treatment at home under supervision.[4,27] Elimination of vertical transmission of HIV in Cuba was WHO-certified in 2015.[18] In 1986–2016, fewer than 200 childhood cases were reported[28] with 8 children aged <15 years of a total of 692 cases nationwide (1.2%). No cases of coinfection in children aged <15 years have been reported since 1999.[29] However, TB/HIV coinfection has increased in the general population, especially in young adults, despite educational efforts. This is a challenge to be overcome, since coinfection threatens the goal of eliminating TB.[6,27]

Pillar 2 The second pillar involves multisector actions, resources and strategic components to implement Pillar 1. A broad social determinants approach to early diagnosis and treatment of all people with TB, including TB/HIV coinfection, demands participation not only of the health sector, but also of other government agencies and civil society organizations.[2]

Pillar 2's components are political commitment guaranteeing adequate resources; universal health coverage; regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control; engagement of communities, civil society organizations, and all public and private care providers; social protection, poverty alleviation, and actions on other TB determinants.[2]

Political commitment, universal health coverage and adequate resources Health care has been a fundamental part of the social

transformation begun in Cuba in 1959: a national public health system was established in the early 1960s, providing free, universal, accessible and equitable coverage, later enshrined in the constitution and law.[5,30] This commitment responds to the first principle of the End TB strategy: a national government-led and government-financed program, integrated into all levels of health care, with periodic monitoring and evaluation.[2]

According to 2014–2015 data, Cuba's health budget represents 8.9% of its national budget (equivalent to 10.4% of GDP) and covers 94.7% of health spending.[31] Out-of-pocket health spending is about 5.3%, the lowest in Latin America.[32] Human resources are guaranteed with training of doctors, nurses, technologists and other allied health workers graduated from Cuban universities, which are also public and tuition free. Cuba has 13 medical sciences universities with 25 medical faculties.[12] In 2017, there were 84.8 doctors per 10,000 population, working in 450 polyclinics, 150 hospitals (22 of them children's hospitals) and 10,869 family doctor-and-nurse offices distributed throughout the country, including the most remote mountainous regions.[12] There is a decentralized laboratory network for microbiological TB diagnosis throughout the country with municipal laboratories (only bacilloscopy), provincial laboratories (bacilloscopy and cultures), and a national reference laboratory that is a WHO Collaborating Center.[6] In 2018, the diagnostic component was strengthened with the opening of three regional molecular biology laboratories (western, central and eastern) for rapid TB diagnosis,[12] but this activity needs reinforcement at the primary care level.

Eliminating TB is a national priority. The National Action Plan of Cuba's 2016 End TB Strategy proposes, among other goals, speeding up implementation of new diagnostic technology and guaranteeing financial investments to meet the heavy demands of the TB elimination stage.[6] Although Cuba has sought funding support and signed cooperative agreements with other countries, access to costly new technologies needed to bolster the national laboratory network (Xpert, liquid culture media, LED microscopy, etc.) is hampered by the US trade and commercial blockade on Cuba's economy.[6]

Regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control TB case notification has been mandatory since 1962,[5] and all information is received and processed by the Ministry of Public Health's National Medical Records and Health Statistics Bureau. Health statistics have been certified as reliable.[33] Case notification follows 2014 WHO recommendations.[3]

Each birth is registered before the baby is discharged from a maternity hospital.[34] Imported medicines, tuberculin reagents and vaccines are analyzed by Cuba's regulatory agency (the Center for State Control of Medicines and Medical Devices) upon entering the country.[35] When a person with latent or active infection is identified, the health team determines and prescribes full treatment, adjusting the dose to that person's needs, and the family doctor takes charge of administering and monitoring the prescribed treatment.[4]

Engagement of communities, civil society organizations During the 2009–2013 PNCT enhancement project, financed by the Global Fund to Fight AIDS, Tuberculosis and Malaria,[6,18] special attention was given to training facilitators and engaging the public in activities aimed at TB prevention and early detection. Student

groups in all Cuban universities were trained as facilitators to work at all educational levels and in communities with the highest rates of TB.[36,37] Educational posters and brochures were also distributed, and television spots and documentaries were created and used in community forums. Nevertheless, greater mobilization of social actors is needed, including participation by members of religious groups that provide support to patients' families. Contact tracing also needs to be strengthened to maximize the benefits of prevention and early diagnosis.[11,16]

Social protection Social services provide care and subsidies to patients with a variety of social problems that may put them at risk of TB.[32] TB elimination requires improved living conditions, a priority for Cuba's government even in the context of limited resources.[38]


Pillar 3 The third pillar calls for development and rapid uptake of new tools, interventions and strategies, along with research to optimize their impact.[2]

Development and rapid uptake of new tools, interventions and strategies Cuba participates in surveillance of TB drug resistance in the Latin American region[26] and applies internationally established strategies, despite economic obstacles to rapid uptake of new technologies.[4,6] At the November 2017 Congress of the International Union Against Tuberculosis and Lung Disease,

Cuba joined the Ibero-American Network for Infantile TB, formed to highlight the historical neglect of TB in children, describe the problem in country members, and strengthen multicenter collaboration.[39] Cuba is currently part of a comparative study among participating countries to characterize TB in youngsters who were aged <15 years in 2013–2017.

Research to optimize implementation and impact, and promote innovation Operations research is conducted at primary, secondary and tertiary care levels on fundamental problems identified in the PNCT, such as efficacy in case detection and guaranteed adherence to treatment, risk factors in the population, associations between TB and other health problems (diabetes, alcoholism, etc.), and use of synthetic indicators to evaluate process quality, among others.[6,35] Recommendations are applied in PNCT updates.[6]

CONCLUSIONS

PNCT's results, especially in the pediatric age group, show that political will in a context of universal access to health care services at the primary care level can have a major impact on health indicators. These results are the fruit of actions aimed at social protection of populations most vulnerable to TB, with children as top priority, and designed in the framework of the PCNT, which functions despite economic difficulties and makes TB elimination possible in line with the WHO End TB Strategy 2015–2035. 

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A Cuban Perspective on the Antivaccination Movement

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ABSTRACT

Vaccination is one of the most cost-effective interventions for control of communicable diseases. This health achievement could flounder if measures are not taken by health systems to prioritize immunization, increase vaccination rates and educate health professionals to address public concerns about vaccine safety and efficacy. Parents' refusal to vaccinate their children directly affects public health, because it puts both individual and group immunity in danger; immunization coverage is effective only when high population coverage is attained. The growing number of antivaccination (antivaxxer) groups around the world is alarming, contributing to falling vaccination rates. Troubling consequences include disease outbreaks in several countries globally and in our hemisphere. This article looks at the history and features of antivaxxer movements around the world and proposes ways the Cuban health system, through its National Immunization Program, can address dangers for the population associated with potentially negative influences of social-network antivaxxer campaigns. The paper underscores the role of mass and social media, health professional training and sustained competence, and the importance of a vaccine-related adverse events surveillance system.

KEYWORDS Vaccination, immunization, antivaccination movement, antivaccine groups, primary health care, society, communications media, social media, Cuba

INTRODUCTION

Vaccination is one of the most cost-effective actions to prevent infectious diseases. Every year vaccinations prevent an estimated 2.5 million deaths of children aged <5 years.[1–4]

Despite this indisputable health achievement, vaccination refusal by citizens (parents in particular) and even some health professionals is on the rise. In general terms, vaccine refusal is defined as the temporary or permanent refusal of parents to allow administration of one, several, or all vaccines for their children.[5]

Such refusal imperils immunization as a fundamental pillar of global public health policy and practice. Refusals are based on reservations about vaccination safety not founded on scientific evidence, but rather on lack of information or distorted information from unreliable sources, distrust resulting from false rumors about possible adverse reactions, and occasionally on high costs of vaccines not covered by health systems.[6]

The hesitancy tends to be based on isolated episodes rarely related to problems with the vaccines themselves. Increasingly, hesitancy

IMPORTANCE This article explores antivaccination movements' Internet presence and their activities' impact on global public health contrasted with broad public understanding and acceptance of vaccination in Cuba, proposing ways to maintain public trust in vaccine safety to sustain the country's high immunization coverage.

has led to outright refusal, stoked by a growing antivaccination movement, dubbed "antivaxxers." This movement's influence through social and other media is hindering immunization programs, with serious consequences for the public's health. This is due to the fact that both individual and group immunity are endangered when individuals refuse to be vaccinated or parents refuse vaccination for their children: herd immunity is only effective when a population's vaccination rates are high.

Certain infectious diseases can only be eradicated with vaccination, and antivaccination movements today constitute a major obstacle to reaching that objective.[6,7] At risk are millions of lives due to the reappearance of once- or near-eliminated diseases and indefinite postponement of eradication deadlines for diseases thought to be close to eradication.[8]

This threat makes it ever more important for immunization programs to a) increase vigilance to ensure that vaccines used are of high quality, thoroughly tested for safety and efficacy; b) invest in robust surveillance of vaccine-related adverse events; and c) prepare health workers to address public concerns about vaccine safety and practices by providing them the most current information from both national and international sources, and establishing specific venues for its dissemination.[9] Given the ubiquitous nature of social networks, health personnel should be encouraged to use them, in addition to other media and opportunities, to confront the spread of misinformation about vaccination, contributing their experience and knowledge to the debate.

TO VACCINATE OR NOT TO VACCINATE

Society and antivaccination movements The role of society is fundamental to sustain vaccination programs. Often, however, incomplete or distorted information circulates about vaccine benefits and safety. Moreover, vaccination programs can be "the victim of their own success" for at least two reasons. First, reduced incidence of a particular disease may make people think it is no longer a risk (reduced risk perception). Second, substantial drops in morbidity and mortality following the introduction of vaccines has paradoxically made adverse events more visible, exaggerating perceived vaccine risks, and contributing to weakened adherence to immunization programs.[10] Antivaxxer movements have mainly sprouted in developed countries, but as a result of globalization, they are spreading into low- and middle-income countries as well.

Vaccine refusal is not a new phenomenon; it appeared with the earliest immunization efforts in the world. One 20th-century situation that involved several continents was the 1970 controversy about the safety of the diphtheria, tetanus and pertussis (DTP) vaccine. In the UK, doubts arose following media reports about a London pediatric hospital, claiming that children immunized with the vaccine developed neurological disorders. Many physicians opposed vaccination and reported cases linking DTP with neurological disorders. As a result, vaccination rates fell and three outbreaks of whooping

cough followed. Immunization rates rose only after the Joint Committee on Vaccination and Immunization organized a study showing that vaccination-related risk for neurological diseases was extremely low.[11] In the USA, a similar controversy erupted in 1982 when a television documentary reported supposed adverse reactions to DTP. Parent groups began opposing vaccination of their children, but energetic responses from Centers for Disease Control and medical associations kept immunization rates from falling as drastically as they had in the UK.[11]

The biggest controversy in recent years was touched off in 1998, with Dr Andrew Wakefield’s article in *The Lancet*, questioning the safety of the triple vaccine against measles, mumps and rubella (MMR). Although he did not directly blame MMR for the occurrence of ileocolonic lymphoid nodular hyperplasia and neurological disorders (both commonly associated with autism spectrum disorder) in 12 previously normal children, he affirmed that the parents of 8 of the children associated the date of symptom onset with vaccination, and stated that the disease was the result of an “external trigger.”[12]

This assumption unleashed a media campaign that spread fear among parents, with many in the UK refusing to vaccinate their children. In 2004, Dr Richard Horton, editor of *The Lancet*, stated that the article should not have been published because it was based on a clear conflict of interest. An investigation by the UK’s General Medical Council revealed that a law firm representing the interests of parents of children supposedly harmed by the vaccine had paid Wakefield to explore evidence of this association. The Council ruled against Wakefield and he lost his medical license.[11] *The Lancet* retracted the article in 2010[13] and in 2011 the *British Medical Journal* reported that Wakefield’s arguments were based on weak evidence. Some of the most egregious inaccuracies found were:

- not all the children were correctly diagnosed with autism (only 3 of 9);
- of the 12 children classified as neurologically normal before vaccination, 5 had developmental disorders; and
- onset of symptoms claimed to be within days of vaccination actually had appeared months later.[14]

It has been shown that neurological and autoimmune and degenerative diseases that provoke such controversies are not the result of vaccination,[15] and that benefits (both individual and collective) of vaccination programs far outweigh possible adverse events;[16,17] the scientific evidence on vaccine safety is overwhelming.[16,18]

The effects of mass vaccination on incidence of measles have been well documented throughout the world, and countless studies in the field confirm the efficacy of the MMR vaccine. In fact, research has demonstrated that the various measles vaccines are safe, effective and can be used interchangeably in immunization programs. Natural strains of the virus have never been shown to be transmitted from a vaccinated individual to another. Thanks to an inexpensive and effective vaccine, vaccination with the MMR vaccine constitutes one of the most cost-effective public health interventions in low- and middle-income countries, as elsewhere.[18,19]

Nevertheless, erroneous associations between vaccine administration and occurrence of different types of diseases now extend to almost all vaccines (Table 1), creating confusion and doubt, and resulting in parental refusal of vaccination for their children. Parents also hesitate to vaccinate their children due to fear of manipulation by the pharmaceutical industry in its eagerness to increase profits, growing interest in natural products for health care and belief in return to a more natural life. They underestimate the true risk of diseases and their consequences, preferring the risk of disease over the “uncertainty” they associate with possible adverse vaccine reactions. [16] Many tout the appeal of freedom of choice as a guiding principle for their actions.[17]

Antivaccination movements on the Internet Antivaxxer ideas have gained followers and spawned an expanded movement now present in many countries. Social media networks have provided its main thoroughfare. Two centuries ago, antivaccination articles in European newspapers and magazines reached an extremely limited readership, but today millions of people visit health pages on the Web.[20]

While provaccination voices grow stronger,[21,22] as does the role of WHO and other global agencies in defense of vaccines,[23] intervention strategies have yet to be effectively implemented at most national levels to stem such a widespread campaign; hence, more vaccination refusals.[24] This movement continues to grow as a consequence of easy access to non-evidence-based claims, spread particularly through the Internet’s social media and other networks, constituting a setback for science and public health progress.[25]

Antivaccine discourse is based on doubts or supposed certainties, arguing that vaccines are ineffective or unsafe, or both. Antivaxxers allege that it is not the vaccines that protect against diseases but rather diseases stop spreading because of improvements in the economy and health. They claim a vaccine can provoke disease because it is made with microbes or “toxic” substances. They dispute the results of vaccine safety studies, hiding or distorting information provided by health authorities. Their arguments allude to parental responsibility to protect children’s health and play on parents’ desire to avoid risks, fomenting distrust in the skills and ethics of professionals who administer vaccines.[6,26]

Table 1: Recent controversies on vaccination safety

Diseases attributed to vaccine	Vaccine blamed
Autism, neurodevelopmental disorders	MMR, vaccines with thiomersal
Demyelinating and autoimmune diseases	HB
Guillain–Barré syndrome	T, MMR, HB
Spongiform encephalopathy	DTaP, Hib, HA
Permanent encephalopathy	DTwP
Sudden infant death syndrome	DTwP
Diabetes mellitus type I	Hib, HB
Bronchial asthma, atopy	DTwP, MMR, OPV, Hib, flu
Inflammatory bowel disease	M, MMR
Chronic arthritis	Lyme disease
Immune depression	Combined vaccines
Retroviral infections	MMR, OPV, yellow fever

DTaP: diphtheria, tetanus, acellular pertussis vaccine
 DTwP: diphtheria, tetanus, whole-cell pertussis vaccine
 HB: hepatitis B vaccine HA: hepatitis A vaccine
 Hib: *Haemophilus influenzae* type b vaccine M: measles vaccine
 MMR: measles, mumps, rubella vaccine OPV: oral polio vaccine T: tetanus vaccine
 Source: Corretjer[19]

Public health authorities and health workers are increasingly concerned about such campaigns' reliance on digital technology to negatively influence perceptions of vaccines and readiness to accept vaccination. There is no doubt that the threat is growing, as search engines make it easy for people to access antivaccination sites. One study reported that a search for the keyword "vaccination" in seven major search engines (including Google, Yahoo, Netscape, and Lycos) contained antivaccination messages on 43% of sites found.[26]

Social media such as Twitter, Facebook and personal blogs enable contact among people and groups with similar ideas through links or suggestions of related content. Many antivaccination groups sponsor their own websites (which both provide "information" and solicit donations) that generate pamphlets and documents that can be downloaded for free or for purchase by their members. Among these are Spain's "Freedom from Vaccination League," "Affected by Vaccines," "Discovery Dsalud," and "There's No Pandemic: Stop the Vaccine!" and others. On this side of the Atlantic, there is the Facebook group, "Freedom from Vaccination for a Democratic Chile." [26] Beyond the Internet, there are groups like "The Refusers," a musical group that sings antivaccine protest songs (although they deny they are antivaxxer activists, arguing that their songs just promote safe vaccines and freedom of choice).[27]

WHO views antivaccination movements as a growing threat to vaccination programs. In 2019, WHO included a section on vaccine hesitancy in its new five-year strategic plan (WHO 13th General Programme of Work). The WHO Strategic Advisory Group of Experts (SAGE) identified complacency, inconvenience in accessing vaccines, and lack of confidence as main underlying reasons people refuse vaccination for themselves or their children. The group affirmed that health workers (especially in communities) continue to be the most trusted influences on vaccination decisions.[28] WHO's Global Vaccine Action Plan and SAGE have provided guidance, monitoring indicators and targets for addressing vaccination hesitancy; [23,29] and the Global Vaccine Safety Initiative aims to strengthen national capacities to address the public's concerns about vaccine safety in a clear, objective, timely manner.[30]

Undoubtedly, today's public health communication strategies must focus on generating, maintaining or restoring public trust in vaccines and immunization, trust that has been badly damaged by antivaxxer disinformation campaigns on the Internet and beyond. Access to reliable, precise, objective information is essential, for both the public and health professionals,[31] lest public health gains be reversed.

Consequences of reduced global vaccination coverage

An emerging health problem in some countries and regions is the occurrence of outbreaks of vaccine-preventable diseases previously considered controlled or eradicated (measles and diphtheria, for example). In 2017, significant measles outbreaks occurred in Europe; most affected were Romania (5560 cases), Italy (5004), Greece (967) and Germany (929).[32] In 2018, the WHO Regional Office for Europe reported 82,596 cases of measles (4 times more than in 2017 and 15 times more than in 2016) and 72 deaths (children and adults). The reasons for this increase vary from country to country. Eastern European health systems did not have the capacity to control the outbreaks or maintain high immunization coverage, while in Western Europe,

immunization coverage fell due to distrust in vaccination spread by antivaccination movements.[33,34]

The Americas Region has also experienced outbreaks of vaccine-preventable diseases in recent years. In 2017, PAHO reported that suspected and/or confirmed diphtheria cases appeared in 5 countries: Brazil (39), Colombia (14), Haiti (120), Venezuela (511) and the Dominican Republic (3).[35] In 2018, Colombia, Haiti and Venezuela confirmed cases of diphtheria.[36] In the affected countries, children were unvaccinated.

In the USA in 2019, measles cases reached a 25-year high. From January 1 to April 19, 2019, 626 cases of measles were confirmed in 22 states. This increase is associated with incorrect and scientifically baseless information spread by antivaxxer networks, particularly in states where vaccination is not mandatory. Most children with measles are unvaccinated. Such unvaccinated individuals are the initial locus of an outbreak that can lead to an epidemic.[37,38] Adding inadequate immunization coverage or failure to complete the immunization schedule (due to health system organizational problems) to the effects of antivaxxer movements, the Americas Region can expect a worsening epidemiological profile for vaccine-preventable diseases.

Around the world, parents' refusal to vaccinate their children is addressed in different ways. In Spain, the Spanish Pediatrics Association's Advisory Committee on Vaccines, together with its Bioethics Committee, determined it was not advisable to obligate parents to vaccinate their children, but parents should be required to sign a vaccine refusal document, in which they acknowledge having received information about vaccination, its importance and benefits, and risks to unvaccinated children.[39,40] Others hold that courts should oblige parents to vaccinate their children, based on WHO guidelines.[41]

New York City's mayor declared a public health emergency in April 2019, obligating vaccination in selected neighborhoods where measles outbreaks had occurred.[42] and new legislation in the state has removed school vaccination exemptions for philosophical reasons (permitting only medical exemptions). US medical authorities have asked social networks and popular search engines to censor false information circulating about vaccines, given the threat that antivaccination groups represent in a country where 15 out of 50 states allow philosophical exemptions from school vaccinations.[43]

Antivaccination movements' challenges for Cuba

Since creation of the National Immunization Program (PNI) in 1962, vaccinations are included in primary health care (PHC): against diphtheria, tetanus and pertussis (DTP vaccine), polio (oral polio vaccine, OPV), and the severe forms of tuberculosis (BCG vaccine); and later against other diseases such as hepatitis B, viral meningitis, and Hib.[44,45] Explaining the balance and scale of risk in the risk-benefit equation allows the public to weigh the importance of immunization for individual and community health. Since its beginnings, PNI's vaccination activities rely on four basic principles: the entire population is targeted; activities are integrated into PHC; they depend on active community participation; and all vaccinations are free of charge.[45]

Since 1999, all Cubans are protected against 13 diseases, previously potentially fatal or disabling. Thanks to biotech development, 8 of the vaccines are manufactured in Cuba; imported vaccines are BCG, MMR and OPV.[45]

Cuba is one of the countries that does not have a recognized antivaccination movement and, in general, PAHO and other expert evaluations have found that parents are both aware of and anxious to vaccinate their children.[45] In 2015, a study in a primary care unit exploring health culture and vaccination in families of children aged <2 years found that vaccination was highly valued. Participants considered vaccinations important, had confidence in PNI, and were satisfied with health service organization and their care from healthcare providers. Mothers considered vaccinating their children a responsibility, part of protecting their children's health. In addition, they observed coherence in messages from PNI, traditional mass media and social networks, describing information from these media as science based.[46]

Cuba's vaccine-related adverse events surveillance system

One of the main arguments in antivaxer discourse is lack of vaccine safety, so an important complement to information on the benefits of PNI, which ensures safety and reliability, is the vaccine-related adverse events surveillance system instituted in Cuba in 1999.

Surveillance of vaccine-preventable diseases was adapted to the Cuban context from WHO guidelines for effective management of its Expanded Program on Immunization (EPI). Surveillance performs the basic functions of gathering, analyzing and evaluating information on vaccine quality, efficacy and safety.[47]

Surveillance of vaccine-related adverse events is conducted at the primary care level, family physicians mainly responsible. Ongoing training of health personnel at all levels in the health system in surveillance of possible adverse effects enables decision-making in case management, event management, notification and timely investigation of severe events, all of which contribute to PNI's credibility and success.[47] In addition, health professionals who are knowledgeable about the realities of adverse events help to prevent rumors that could provoke vaccination refusal in their communities.

Cubans' increasing access to social media and the Internet in general as a result of expansion of services[48] places the public in contact with information posted on antivaccination groups' websites, blogs and profiles. Although Cuban citizens are well educated, trust health professionals and are satisfied with PNI, [44] the risk of unscientific influences remains. At this writing, there is no specific strategy to respond to the threat, but we believe it is possible to keep Cuba's high immunization coverage from falling and avoid outbreaks of vaccine-preventable diseases if there is continuing effective communication on vaccination, particularly in PHC, where physicians and nurses mingle with families and neighborhoods.

Cuba's public health system, based as it is in PHC, is ideally suited for health professionals to organize educational programs in their communities, enabling residents to critically assess information disseminated by antivaccination sites, building on knowledge of scientific results about the benefits of vaccination in Cuba and the world, where diseases have been controlled, eradicated or kept from becoming public health problems. Important messages to convey include how systematic vaccination with high coverage prevents death and disability of millions of children annually, and that data from the vaccine-related adverse events surveillance system supports that there is low risk associated with vaccination.


Communication should be a continuous process that enables professionals to properly explain vaccine benefits and risks, address the public's concerns, tackle incipient or persistent rumors about vaccine safety, and prepare responses to any crises regarding vaccine safety that might occur. Such efforts would help prevent dissemination of messages questioning vaccination safety with no scientific basis.

In addition, Cuban health professionals and medical institutions should take advantage of the presence of the 6.47 million Cubans on Internet (56% of the population) to post messages related to results of vaccination drives and the immunity achieved throughout the country. The rates of connectivity continue to climb, with Facebook the most frequently used social media (59.3% of Internet users) in 2018.[49]

CONCLUSIONS

Vaccination is the most effective preventive health intervention, after clean water, in terms of cost-benefit balance in control of communicable diseases. But the growing refusal of parents to vaccinate their children as a result of misinformation spread on the Internet by antivaccination groups puts global public health in danger of outbreaks of diseases such as measles and diphtheria.

High immunization coverage (≥99%) has been achieved in Cuba with the 11 vaccines (against 13 diseases) administered in the national vaccination program, and there are no reports of vaccination refusal.[50] There is public trust in the program and satisfaction with its implementation: Cuban parents consider child vaccination to be a personal and social responsibility.

While this is the situation now, we cannot ignore the danger posed by antivaxer messages. Cubans have steadily growing access to the Internet, both to scientific information and to misinformation, so effective education and communications strategies are needed for health professionals and the public they serve, to maintain gains in control of infectious diseases. 

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Cuban Experience Using Growth and Development as a Positive Indicator of Child Health

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ABSTRACT

Growth and development is considered the best positive indicator of children's quality of life and well-being. Studies have been carried out in Cuba since the early 20th century and large scale, periodic anthropometric surveys have been regularly conducted by its National Health System to chart modifications in growth patterns of children and adolescents. These surveys have produced national references for the anthropometric indicators most commonly applied in individual assessment of the health and nutritional status of children and adolescents in health care settings. These have also provided data for estimating the magnitude and characteristics of secular growth trends, and for comparing growth of Cuban children with that of children in other countries and with WHO's proposed growth standards. The data

have also served as evidence of persisting social gradients. The most important results include, as positive data, the positive secular trend in school-aged children's growth of 9.7 cm between 1919 and 2005, with an average increase of 1.1 cm per decade, and, in preschool children, 1.9 and 1.8 cm in boys and girls, respectively, between 1972 and 2015. More recent studies have detected unfavorable changes associated with a marked increase in adiposity and, therefore, in the prevalence of excess weight and obesity. Another interesting result is the gradual movement toward WHO height-for-age standards in preschool children in Havana, verified in surveys conducted in 2005 and 2015.

KEYWORDS Growth and development, growth, child development, children, adolescents, nutrition, obesity, pediatrics, Cuba

INTRODUCTION

Increasing interest in anthropometric surveys in the coming decades will alert us to problems such as obesity and its unfavorable consequences for health. We have reached the stage in which we should not only "measure disease" but must also, at the same time, dedicate ourselves to "measuring health." (J. Jordán, 1979. [1])

One of the most interesting biological attributes of human beings is the change in their size, shape and functions from childhood to adulthood. This explains scientists' interest in children's growth throughout the 300-year history studying growth and development.[2] Developmental plasticity in response to environmental or ecological stressors has also aroused researchers' interest. It has long been known that a child may stop growing during situations of extreme deprivation followed by varying degrees of compensatory growth once deprivation is reversed.[3]

More recently, Barker's hypothesis about the developmental origins of health and disease introduced the concept of fetal programming in response to environmental insults and consequences in the cyto-architecture, structure and functioning of different organs and systems.[4] There is substantial evidence that these effects may cause a broad range of dysfunctions that can generate multiple chronic non-communicable diseases affecting health, starting in the earliest stages of life. Growth monitoring starting in the antenatal period fulfills an important role in prevention of such illnesses.[2-5]

In recent decades, various academic groups and international organizations have insisted on the need to use positive health

indicators, which presupposes a trend towards evidence to guide health-promoting behaviors and build healthier societies. Growth is the most important positive indicator of child health, since it combines three key factors: nutrition, health status and overall well-being. Psychomotor development of children at the population level has recently been included, based on evidence of measurement feasibility and the association of this with other development indicators.[6,7]

Changes in Cuban health policy derived from the consolidation of the National Health System (SNS) and creation in 1970 of the Infant Mortality Reduction Program—with the primary objective of a 50% reduction in mortality in children aged <1 year by 1980—established the need to complement morbidity and mortality indicators with positive health indicators based on in-depth knowledge of the full growth and development process from birth through adolescence.[8]

That idea, which was quite advanced for its time, was promoted by Dr José A. Gutiérrez Muñiz, a prestigious figure in Cuban pediatrics and public health. To put it into practice, the Human Growth and Development Group was created in 1971 as part of the Research Division of the Childhood Institute, the institution then in charge of policy for comprehensive care of preschool children (and whose functions were later absorbed into the Institute of Health Development and then the Department of Human Growth and Development in the Julio Trigo López Medical Faculty at the Medical University of Havana).[9] Its mission was monitoring the growth of Cuban children using anthropometric population surveys, initially under the leadership of Cuban pediatrician José Jordán Rodríguez and later Gutiérrez Muñiz until his death in 2014. Together they initiated training of researchers in various disciplines who have sustained the Group's work to this day.[9]

Principal growth and development studies in Cuba The first recorded growth and development study was carried out by

IMPORTANCE This paper presents convincing evidence that child growth and development surveys provide important, direct positive indicators contributing to health and well-being assessments of children in Cuba and can be important tools for other low- and middle-income countries.

Georges Rouma, a Belgian anthropologist who gathered information about growth of school-aged children in Havana in 1919.[10] A few studies were carried out in the 1950s, but important information about child growth in Cuba was not obtained again until the 1960s, from studies addressed by anthropologists of the European socialist bloc countries in collaboration with Cuban anthropologists. The most important of these was conducted in 1963 by Polish anthropologist Laska-Mierzejewska, who researched not only the physical development of school-aged children and adolescents in Havana, but also, for the first time in Cuba, their pubertal development.[11]

In 1972, Jordán led the Growth and Development Survey of the Cuban Population, carried out in consultation with James Tanner and Harvey Goldstein, prestigious researchers of the Institute of Child Health of University College London (Tanner is reported to have described it as “one of the most complete carried out in any country”).[9] At the time, only a few nationwide studies based on representative population samples had been conducted: Holland in 1955, 1965 and 1980; and Czechoslovakia in 1951, 1961, 1971 and 1981. Whole-country studies were done in Hungary in 1981 and 1985; and the USA since the 1960s.[1,2]

In 1982, the Second National Survey on Growth and Development of the Cuban Population was carried out as part of an international consensus recommending periodic child growth surveys at approximate ten-year intervals to assess changes in child health. The Survey’s results also provided references for new nutritional assessment indicators.[12]

During the 1990s, national surveys could not be continued due to the economic crisis in Cuba after the collapse of the socialist bloc. Provincial surveys were conducted instead, such as the 1993 growth and development survey in City of Havana Province (hereinafter Havana), which was the most feasible and appropriate place to obtain information concerning child growth at the time, because the study population was accessible to researchers, the province included approximately one fifth of the Cuban population, and Havana was also the main destination for internal migration. That survey included only basic anthropometric indicators, age at menarche and some socioeconomic variables. Based on its results, a similar study was repeated in Havana five years later, in 1998, followed by a new study in 2005.[13]

In 2002, as part of the provincial-study strategy, a growth and development survey was carried out in Guantánamo, one of the least socioeconomically developed provinces in Cuba. The sample design, data gathering, processing and analysis techniques were similar to those applied in previous surveys, so results could be compared with those previously obtained for Guantánamo Province in the national surveys and with results of the Havana surveys.[13]

In 2015, as part of a project between the National Hygiene, Epidemiology and Microbiology Institute and the Growth and Development Group, a survey was conducted to determine the ages at which a set of psychomotor development milestones were met in a representative sample of children aged <6 years in Havana. Weight and height values obtained from that study were used to determine secular growth trends in preschool children.[14]

In addition to the studies described—all of them cross-sectional—several longitudinal studies have been conducted, such as the

17-year, Perinatal Research Cohort Study that gathered valuable information about the Cuban population (still not fully utilized) related with Barker’s hypothesis.[15] Longitudinal studies in children aged <2 years with low birth weight,[16] have also contributed valuable knowledge on the growth of these Cuban children.

Contribution of growth and development studies to assessment of Cuban child health and well-being These studies have provided national references for monitoring growth and nutrition, used since 1984 at all levels of the SNS. Thus, each new indicator assessed in the different studies included diagnostic and monitoring references. One example is waist circumference for age, which since 2016 has been included as standard practice throughout Cuba as an indicator of visceral adiposity, a diagnostic criterion for metabolic syndrome in children.[16,17]

Secular trends Height The most visible expression of secular growth trends in children is intergenerational height variation resulting from changes in living conditions.[18,19] Cuban studies have always shown a positive secular trend for this variable. Height values from the 1982 national survey exceeded 1972 values by 0.6 cm, on average, in both sexes. These differences did not occur at all ages; the greatest differences occurred in the pre-pubertal age group and were greater in children from lower socioeconomic strata living in rural areas, who benefited the most from changes in living conditions and nutrition during that decade.[12]

Comparison of Havana studies reveals a similar phenomenon. The 1963 Havana survey found a positive secular trend in childhood growth compared to Rouma’s study,[10] with an average height increase of 1.4 cm/decade. In 2005, children of comparable age to those studied by Rouma were 9.7 cm taller, representing an average increase of 1.1 cm per decade. This trend has been seen in all studies carried out in Havana: in 2005, children and adolescents in Havana were, on average, 2.0 cm (boys) and 2.1 cm (girls) taller than in 1972; 1.4 cm taller (both sexes) than in 1993; and 0.6 and 0.9 cm taller (boys and girls, respectively) than in 1998. In the 2015 study, a positive secular trend was also observed in preschool children compared to 1972, with a height increase of 1.9 and 1.8 cm (0.4 cm per decade) in boys and girls, respectively.[13]

The trend’s magnitude varies with age and is greatest in early adolescence, possibly due to the accelerated rhythm of maturation at that stage. It is also influenced by economic conditions: In 1993, during a period of drastic economic decline, increases in height were small compared to the 1972 value (0.2 and 0.3 cm/decade in boys and girls, respectively), whereas in 1993–2005, coinciding with the period of economic recovery, a 1.2 cm/decade increase was found in both sexes. These results highlight the value of Tanner’s often-quoted designation of growth as a mirror that reflects a society’s health and changing living conditions.[20]

Weight This indicator has shown positive secular trends, similar to those for height, except when comparing 1993 values with those of 1972: weight declined, fundamentally in school-aged children and adolescents, as a result of the economic crisis of the early 1990s, which also had a negative impact on body mass index and skinfold thickness. Subsequently, in 1993–2005 the weight again increased with the economic recovery of the country and reached gradients of 1.2 and 0.8 kg/decade in boys and girls respectively. Marked increases in prevalence of overweight and obesity in chil-

dren and adolescents were seen, increasing the risk of chronic non-communicable disease beginning in the earliest stages of life. Preschool children also showed weight gains in 2015 compared to 1972 with average values of 0.9 and 0.7 kg in boys and girls, respectively, equivalent to 0.2 kg per decade.[13]


Age of menarche Median age of menarche in adolescent girls in Havana (with their respective standard deviation, SD) were: 12.6 (0.06) in 1972, 12.4 (0.14) in 1993, 12.9 (0.09) in 1998, and 12.5 (0.09) in 2005. This temporal pattern of change, showing delayed sexual maturation of girls during the economic crisis of the 1990s and subsequent recovery, demonstrates the association between pubertal development and living conditions.[13]

Social gradients In growth and development studies, social gradients are the differences in body size and maturation among children from different socioeconomic groups within the same country. In the Cuban population, differences in growth were found between boys and girls living in the eastern province of Guantánamo, characterized by lower socioeconomic development, and their counterparts in Havana. Average height of boys and girls in Guantánamo was 98.5% and 98.7%, respectively, of height of children in Havana, and average weight of children in Guantánamo was 93.6% and 94% of weight of boys and girls in Havana. [13] These results are very useful for setting policies aimed at the most vulnerable populations; however, particular attributions of causality can only be determined with further studies.

Population differences Variations in growth are expressed as a result of the interaction—mediated by epigenetic factors—between genetic factors and the environment in which children develop. One example of these differences is seen in Cuban height and

weight references, whose values are lower than WHO's proposed standards in the lowest weight percentiles and in the height-for-age indicator, which leads to differences in results of nutritional assessment in children.[21,22] The 2005 and 2015 surveys carried out in Havana offer an interesting result associated with those standards: initially negative height-for-age z-scores gradually approach positive values as age increases.[14,22] This differs from results reported in more than 50 low- and middle-income countries in which z-scores in this dimension moved quickly and progressively down from WHO standards up to age 2 years, and then rose, but always maintaining z-scores under -0.25 . [23] Median z-scores for children aged 0–5 years, (with their respective SD) were -0.07 (1.08) in the 2005 survey and 0.02 (1.17) in the 2015 survey.[14]

CONCLUSIONS

Cuba is one of the few countries in the western hemisphere with reliable population-wide growth references, despite many years of economic hardship. Study results demonstrate positive changes in Cuban children's and adolescents' physical development, such as the positive secular trend in height. They also show other less favorable changes, such as increased adiposity, which raises the risk of chronic non-communicable diseases starting early in life. Finally, they reveal regional differences between sociodemographic groups that have to be confirmed with more comprehensive studies including a broad set of health, economic and social variables, and that should be addressed through strategies to benefit the most vulnerable. The research presents convincing evidence that child growth and development surveys provide important, direct positive indicators contributing to health and well-being assessments of children in Cuba and can be important tools for other low- and middle-income countries. 

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Universal Health in Cuba: Healthy Public Policy in All Sectors

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ABSTRACT

Health is a universal human right, which should be safeguarded by government responsibility and included in all social policies. Only as such it is possible to ensure effective responses to the health needs of an entire population. The Cuban Constitution recognizes the right to health, and the country's single, free, universal public health system and high-level political commitment promote intersectorality as a strategy to address health problems. Intersectorality is reflected in national regulations that encourage participation by all social sectors in health promotion/disease prevention/treatment/rehabilitation policies and programs. The strategy has increased the response capacity of Cuba's health system to face challenges in the national and international socioeconomic context and has helped improve the country's main health indicators. New challenges (sociocultural, economic and environmental), due to their effects on the population's health, well-being and quality of life, now require improved intersectoral coordination in the primary health care framework to sustain achievements made thus far.

KEYWORDS Universal coverage, public health, health policy, social planning, intersectoral collaboration, Cuba

INTRODUCTION

Universal health coverage and universal access to health care require participatory policies including all sectors of society that in one way or another are associated with social, economic and environmental conditions—key aspects for sustainable human development.[1]

Public and social policies should be at the center of national responsibility for the State and the various sectors of public administration, to ensure human health and safety and exercise of civil rights, as well as to generate capacities and avenues for active, creative, committed popular participation, the basis of sustainable development.[2]

In 2000, the UN established the Millennium Development Goals (MDGs), with specific targets to be met by 2015. At the global level many of these targets were not met, or progress was irregular, with wide differences among countries and population groups within

IMPORTANCE This paper underscores health as an essential component in policies for all Cuban sectors and society in general. As other countries debate ways to overcome segmentation and fragmentation in their health systems, Cuba can point to the successes of a unified system that recognizes health as a universal right. The system now is challenged to increase efficiency while maintaining quality services, as well as to strengthen scientific research and continuing professional education.

countries.[3,4] These have been superseded by the 17 social, economic and environmental goals known as the Sustainable Development Goals (SDGs). The SDGs have 169 associated targets, to be met through partnerships and concerted actions that prioritize the most vulnerable groups. The agenda also proposes guidelines to reach these targets.[5] The third SDG ("Ensure healthy lives and promote well-being for all at all ages") is subject to the success of the rest, indicating the integral and indivisible nature of these goals.[6]

The expanded conceptual framework called new public health or one health recognizes health as a social product, the result of the interrelationships among nature, society and social reproduction. [6] This perspective implies that all social sectors should be actors in the construction of health.[7] Furthermore, health plays a dual role as component and condition of development. *Component*, because it is essential to the concept of development, one of the basic dimensions of the human development index, represented by life expectancy at birth.[8] *Condition*, because poor health (at both individual and population levels) limits the possibilities for society's sustainable development. Cuba's recognition of health as a right and a priority—both conceptually and in development strategies, considered a broad social responsibility rather than a single sector's exclusive mission—has contributed to the outcomes achieved despite the country's scant resources. The purpose of this paper is to outline the results and challenges of public health in Cuba as an expression of health in social policies.

Cuba's universal focus on public health Article 1 of the country's Public Health Law (Law No. 41), in accordance with the 1976 Constitution, "establishes basic principles for regulation of social relations in the field of public health in order to contribute to ensuring health promotion, disease prevention, health recovery, patients' social rehabilitation, and social welfare." [9]

In the recently approved 2019 Constitution, Article 46 of Chapter II establishes that "all person have the right to life, physical and moral integrity, freedom, justice, security, peace, health, education, culture, recreation, sports and comprehensive development." Article 72 states "public health is a right of all persons and it is the State's responsibility to guarantee access to free, quality medical care, health protection and rehabilitation.[10] The State, to make this right effective, institutes a health system accessible to the population at all levels and develops preventive and educational programs, to which society and families contribute." [11]

Cuban law recognizes health as a component and condition of development and as an instrument of social cohesion that includes all people and depends on the interrelation and conscious, active, committed participation by all actors and sectors of society. It also recognizes the need for organizational systems, as well as biomedical and public health technologies.

In this context, primary health care (PHC) becomes the crosscutting strategy for care at all levels. Professional and technical personnel are prepared for work in PHC through undergraduate and graduate educational programs across the

country. Currently there are 81.9 physicians and 77.9 nurses per 10,000 population,[12–14] staffing some 10,000 neighborhood family doctor-and-nurse office, nearly 450 community polyclinics, 150 hospitals and various research institutes, as well as serving abroad. Newly graduated physicians do much of their training in PHC settings and are required to do a residency in family medicine before applying for any other specialty.

The health sector has evolved with the updating of Cuba's economic and social model.[15] A process of transformation beginning in 2011 redefined the functions and structure of human resources needed and reclassified the various units of the health system's three care levels, an important organizational initiative. Proposals to reorganize, regionalize and consolidate services (once institutions were reaccredited) were applied throughout the country. In the process, health indicators in Cuba have continued improving, relying on expansion of health care activities—from those based on health promotion and disease prevention, to curative and rehabilitative services. This transformation has involved the whole country and has reduced costs.[15]

These legal, strategic and operational frameworks sustain the universality of Cuban health care, which is not limited to providing easily accessible, quality services for all. The system also adheres to rational decision-making rooted in strategic planning, the concept of social determinants of health, and participation by broad societal sectors involving citizens at the community level.[15]

INTERSECTORALITY AS A STRATEGIC COMPONENT IN FORMULATING CUBAN PUBLIC HEALTH POLICY

Intersectorality is defined as coordinated intervention of representative institutions from various social sectors in actions partially or entirely aimed at addressing issues associated with health, well-being and quality of life.[11] It is a vital strategic component for formulating public health policy and the single consistent route to confronting health problems based on their causes and determinants, through integration and coordination of sectoral objectives and strategies.

Both conceptually as well as operationally, intersectorality rests on four pillars:

- Information, to construct a common language that facilitates understanding the aims and priorities of stakeholders in the health-building process;
- Cooperation, which can be strategic/systematic or ad hoc, manifested through implementation of policies, programs and interventions and not through their mere design or formulation;
- Coordination, which involves linking each sector's policies and programs to seek greater effectiveness and efficiency, within a repertory of planned actions with concrete goals and defined responsibilities; and
- Integration, which represents a higher level from the policy- and program-formulating stages forward, reflected both in proposals and implementation strategies.

Intersectorality's political foundation in Cuba—which includes health in the missions of all sectors and therefore as a component in all policies—is the recognition, first, of health as a right, and second, of public health and all its functions (promotion, prevention, curative care and rehabilitation) as organized efforts by the State and society as a whole. In this responsibility, the health sector plays a leading role in consolidating the four pillars described above.

For an intersectoral strategy to be successful, in addition to a clear conceptual definition and concrete goals, it must have a scientific approach based on sound health management practices and competent leadership with participation by leaders and managers in the intersectoral actions required to address each problem.[16]

Although intersectorality is a universal component in Cuba's national health system, the natural setting to materialize it is the community and its local spaces, attuned to their particular contexts; geographic, sociodemographic and cultural characteristics; health needs and coordinated participation of related sectors and the community itself.[16]

The intersectoral approach has increased the national health system's capacity in key areas, including childhood immunization; improved nutrition for pregnant women, children, and older adults; injury prevention; production and use of natural and traditional medicines; and addressing emerging and reemerging diseases. It has supported development of improved adolescent sexual and reproductive health, and contributed to healthier population aging. It has helped reduce the impact of environmental/climate-related disasters[17] and enabled access to improved water sources, as well as to sanitation in urban and rural areas.[13–15] All these advances have been possible through the coordinated actions of multiple sectors: education, agriculture, road infrastructure, waterworks, communications, culture, sports and recreation, science, technology, environment, housing, transportation, political organizations, civil society organizations, citizens in general and the health sector.

Table 1 presents recent achievements in Cuban health as well as the main challenges, several of which are common to the Americas Region and the world, while others have their own nuances due to Cuba's particular geographic, economic and sociodemographic conditions.

UNIVERSAL HEALTH IN CUBA: CHALLENGES THROUGH 2030

In the Americas Region and globally, strategies are debated concerning how to place universal health at the center of all policies, not simply as a goal but as a continual process of construction. In Cuba, with its single, public health system offering full coverage and access, the problem consists of ensuring system sustainability, including continual improvements in efficiency, while maintaining quality of care.

During the Cuban health system's transformation (which began in 2011 as the health sector's response to the updating of the country's economic and social model), several difficulties were identified and a set of actions proposed to resolve them.[15] Along with factors related to managerial competence and the system's structure, organization and efficiency, inherent problems were identified in the geodemographic context, such as low fertility and birth rates, rapid population aging and effects of climate change.

Especially regarding these last factors, it is clear that the only way to address them is through concerted actions with other sectors and institutions. After a period characterized by increased efficiency from more rational administration/use of resources, without affecting quality, Cuba faces a special situation with the current US administration's hostile actions, including a campaign to discredit Cuba's health professionals and measures affecting important revenue sources associated with medical services provided overseas.[20]


Table 1: Main health outcomes in Cuba (2001 and 2018) and challenges through 2030

Main health outcomes		Challenges	
Increased life expectancy (years)		Lower birth rate (live births per 1000 population)	
2001	77.0[18]	2001	12.4[18]
2018	78.5[19]	2018	10.4[19]
Reduced infant mortality (deaths per 1000 live births)		Ageing population (% of population aged ≥60 years)	
2001	6.2[18]	2001	13.9[18]
2018	4.0[19]	2018	20.4[19]
Reduced under-5 mortality (per 1000 live births)		High mortality from chronic non-communicable diseases (2018)[19]	
2001	8.0[18]	<ul style="list-style-type: none"> • 769.8 deaths per 100,000 population • Heart disease and cancer 47.6% of all deaths • Injuries 5th leading cause of death (51.6 per 100,000 population) • Falls 45.3% of injury deaths, motor vehicle collisions 14% 	
2018	5.3[19]		
Reduced index of low birth weight (%)		Emerging and reemerging communicable disease	
2001	5.9[18]	Outbreaks of dengue, Zika, and chikungunya	
2018	5.1[19]		
Lower maternal mortality (per 100,000 live births)		Increased frequency of natural disasters[17]	
2001	47.6[18]	<ul style="list-style-type: none"> • From 2001 to 2017, Cuba was hit by 11 hurricanes: one Category 5 (Saffir-Simpson scale), eight Category 4, and two Category 3 • >11.7 million people evacuated, 54 deaths • Infrastructure damage (housing, industry, agriculture) >US\$30 million 	
2018	43.8[19]		
Reduced mortality from infectious and parasitic diseases 2018:[19]		Health system adaptation to changes in population's epidemiologic/demographic profile	
rate per 100,000 population	9.8		
% of total deaths	1.0		
Broad immunization coverage of population aged <1 year. 2018 (%) [19]		Restrictions imposed by tightened US financial/trade/economic blockade	
OPV	99.9		
DTP	99.9		
MMR	100.0		
Meningococcal disease	100.0		
Hepatitis B	99.7		
Hib meningococcal disease	99.9		
Tuberculosis (BCG)	99.7		
		Health system development and sustainability in new global socioeconomic context	

BCG: Bacillus Calmette-Guérin DTP: diphtheria, tetanus and pertussis
 Hib: *Haemophilus influenzae* type b MMR: measles, mumps and rubella
 OPV: oral polio vaccine

Transforming the health system is a work in progress. Ongoing tasks include: reduction of costs, improved use of technology, training and ongoing renewal of human capital, as well as the system's capacity to gather and analyze relevant, reliable information and to conduct monitoring and evaluation. Other actions include reengineering the system to align with the new life course perspective,[21] which has shifted understanding of the causal paths of health–disease processes, the skill set of traditional medical specialties, and the role of health services

(particularly in older adult care), along with recognition of the growing importance of self care and the complementarity of individual and social responsibility for health.

Finally, it is critically important to strengthen and adapt education and training processes to generate sustainable skills in all sectors of Cuban society, in order to empower local leaders and managers, conduct scientific research projects responsive to local needs, and disseminate lessons learned. 

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Cuba's Role in International Atomic Energy Agency Regional Cooperation in Cardiology

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ABSTRACT

Cardiovascular diseases are the leading cause of death worldwide, and a health problem in low- and middle-income as well as high-income countries. They also constitute the main cause of death in Latin America, with ischemic heart disease as the principal cause in most countries of the region. In Cuba, heart disease is the first cause of death, followed by cancer and stroke. In its 2030 Agenda for Sustainable Development, the UN recognizes the importance of chronic non-communicable diseases, including cardiovascular diseases.

Cuba has participated actively as lead partner in design and implementation of the two regional technical cooperation projects conducted over the last six years by the International Atomic Energy Agency to address cardiovascular diseases in Latin American and Caribbean member states. These projects have generated greater interest among participating countries in the use of myocardial

perfusion for dilated cardiomyopathy and coronary artery disease compared to other imaging techniques; disseminated knowledge about nuclear cardiology techniques and clinical applications in heart failure and coronary artery disease; and made important contributions to implementing harmonized, appropriate and safe clinical protocols. Cuba's contribution to the International Atomic Energy Agency's regional cardiology projects has fostered development of human resources and harmonized protocols both nationally and regionally, and demonstrated the importance of region-based scientific cooperation that ensures greater opportunities and more equitable access to resources. This participation has also accrued important benefits to Cuba's own nuclear cardiology program.

KEYWORDS Cardiovascular disease, myocardial perfusion imaging, nuclear cardiology, scientific cooperation, low-income populations, Latin America, Caribbean region, Cuba

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death worldwide[1] and is a health problem not only for high-income countries. Due to the epidemiological transition; increased life expectancy, and increases in atherosclerotic risk factors such as diabetes mellitus, obesity, high blood pressure and smoking, CVD has also become a major health problem for low- and middle-income countries. These include those of Latin America and the Caribbean, a region with a 2016 population of over 640 million.[2–4] CVDs constitute the main cause of death in Latin America, with ischemic heart disease as the principal cause in most countries of the region.[3]

In Cuba, CVD is the first cause of death, followed by cancer and stroke; in 2017, it was responsible for 27,176 deaths (241.6 deaths per 100,000 population).[5] In men, the cancer mortality rate is slightly higher than that for CVDs (260.2 and 256.6 deaths per 100,000 population, respectively), while in women, it is the reverse, with respective rates of 188.1 and 226.8 deaths per 100,000 population.[5] The 2017 male:female ratio for cardiovascular mortality was 1.1.[5]

Primary prevention is essential for effective control of atherosclerotic risk factors and for reducing the burden of ischemic heart disease and other chronic diseases of atherosclerotic origin, such as

cerebrovascular disease and peripheral arterial disease. Cuba's Ministry of Public Health aims work in this direction, advised by national expert groups in the relevant specialties and supported by international organizations such as PAHO and WHO.

The UN has included chronic non-communicable diseases (NCDs), including CVDs, among targets in its 2030 Agenda for Sustainable Development. The UN Development Program has established 17 global Sustainable Development Goals (SDG).[6] SDG 3 ("Ensure healthy lives and promote well-being for all at all ages"), includes among its targets a 30% reduction of premature mortality from NCDs by 2030. To this end, WHO's Global Action Plan for Prevention and Control of Noncommunicable Diseases 2013–2020 includes a series of objectives aimed at NCD reduction, specifically at control of risk factors such as smoking, sedentary lifestyles and hypertension.[7]

At the same time, it is important for countries to have access to cutting-edge technologies for treating NCD patients in specialties such as cardiology, where nuclear medicine is fundamental. Application of nuclear medicine in Latin America and the Caribbean (LAC) varies markedly by country with regard to technological infrastructure, trained human resources, availability of radiopharmaceuticals and regulatory frameworks.

CUBA'S ROLE IN INTERNATIONAL ATOMIC ENERGY AGENCY (IAEA) REGIONAL CARDIOLOGY PROJECTS

As part of joint efforts by UN agencies, IAEA works systematically with member states to train medical personnel, physicists, radiochemists and technologists involved in nuclear medicine (considering training key to care quality); facilitates procurement of key medical equipment; and promotes communication among participants.

Cuba has been the lead partner in design and implementation of the two regional technical cooperation projects that IAEA has

IMPORTANCE Cuba's contribution to the International Atomic Energy Agency's regional cardiology projects has fostered development of human resources and harmonized protocols both nationally and regionally, and demonstrated the importance of region-based cooperation for greater opportunities and more equitable access to resources also with important benefits to Cuba's own nuclear cardiology program.

conducted in the last six years to address the problem of CVDs in Latin American and Caribbean member states. Cuba participated in the proposal of the main topics, project design, and organization and hosting of both first coordination meetings, and was the coordinator of the projects with the IAEA technical officer and project management officer. These projects were: Harmonization of Nuclear Cardiology Techniques in Patients with Congestive Heart Failure, with Emphasis on Chagas Cardiomyopathy (2012–2013) and Facing the High Incidence of Cardiovascular Diseases in Latin America and the Caribbean through Nuclear Cardiology (2016–2018).

Harmonization of Nuclear Cardiology Techniques in Patients with Congestive Heart Failure, with Emphasis on Chagas Cardiomyopathy Heart failure is a growing global epidemic affecting more than 15 million people worldwide—costly in terms of health, disability and mortality, as well as economically.[8,9] Coronary heart disease, diabetes mellitus and high blood pressure are the main risk factors. Dilated cardiomyopathy refers to a heterogeneous spectrum of myocardial diseases characterized by ventricular dilation and reduced myocardial contractility. Once patients become symptomatic, prognosis is relatively poor, with 25% 1-year mortality and 50% 5-year mortality.[10]

Among the causes of acquired dilated cardiomyopathy in Latin America, Chagas cardiomyopathy is one of the most frequent and is the leading cause of systolic heart failure in areas where Chagas disease is endemic.[11]

Given the morbidity and mortality from heart failure, as well as the considerable resources required to diagnosis and treat it, appropriate diagnosis and adequate prognostic evaluation are vital. The main objective of this regional project was to improve diagnosis in patients with heart failure, with special emphasis on Chagas cardiomyopathy, through the use of nuclear cardiology techniques, considering two fundamental aspects:

- Harmonization, which consists of the standardization of protocols for diagnosis, prognosis and risk assessment in patients with heart failure; and
- Training on and establishment of a methodology for evaluating intraventricular synchronism.

This was achieved through regional courses, visits from experts, training fellowships, a meeting of experts and standardization of nuclear cardiology protocols for managing patients with heart failure. An example of cooperation in the region was the active participation of local experts in regional courses, at no cost to the project. The first course on imaging, diagnosis and prognosis techniques in evaluation of heart failure took place in Cuba (Havana, July 2012), with participation by ten Cuban professors as well as international experts.

As a result of the project, 177 of the LAC region’s professionals in the field of nuclear medicine and referring physicians in cardiology were trained through four regional courses and one conference on integrated cardiology imaging, the latter held in Vienna (September 2013).

Among nuclear techniques used in cardiology, gated myocardial perfusion scintigraphy with single photon emission computed tomography (gated SPECT) or with positron emission tomography

is the only imaging technique capable of offering information about overall and regional ventricular function, presence of intraventricular synchronism and myocardial perfusion (including information on myocardial viability in the case of patients with previous myocardial infarction and poor ventricular function) in a single, reproducible test.[12–14]

Cuba participated in a meeting of 13 experts from the region in Rio de Janeiro, Brazil (September 2012), which resulted in publication of consensus-based guidelines on the important role for nuclear medicine in evaluating management of patients with heart failure.[12] Cuba also participated in the proposal preparation for a coordinated research project (Value of Intraventricular Dyssynchrony Assessment by Gated-SPECT Myocardial Perfusion Imaging in the Management of Heart Failure Patients Undergoing Cardiac Resynchronization Therapy).[15] developed with participation of 10 centers from 8 countries (2013–2018).

Facing the High Incidence of Cardiovascular Diseases in Latin America and the Caribbean through Nuclear Cardiology Techniques The second research project was aimed at building capacity for early diagnosis and risk stratification of coronary artery disease (CAD), and providing guidance for evaluating patients before proceeding with interventional treatments.

Visits and meetings of experts, regional courses, training grants and two publications all served to meet objectives regarding use of nuclear cardiology techniques in evaluating CAD patients. [16,17] Several project country representatives participated in educational activities including: 7th Ibero-American Congress on Nuclear Cardiology (Havana, April 2016); International Conference on Integrated Medical Imaging in Cardiovascular Diseases (Vienna, October 2016); regional course on using nuclear cardiology techniques for diagnosis and risk stratification (Madrid, February 2017); regional quality assurance course and 26th Congress of the Latin American Biology and Nuclear Medicine Societies Santiago de Chile, November 2017); and a regional course on diagnostic imaging in cardiology and 8th Ibero-American Congress on Nuclear Cardiology (Bogotá, June 2018).

Country experts actively participated in the regional courses at no cost to the project and 42 specialists from the region (including 4 Cubans) attended the 2016 International Conference on Integrated Medical Imaging in Cardiovascular Diseases in Vienna. The American Society of Nuclear Cardiology collaborated with experts who participated in regional congresses and courses. In total, training was given to 487 nuclear medicine professionals and referring physicians in cardiology, 152 of them funded by IAEA. Ten percent of attendees participated in more than one event.

In Cuba, the first regional course was held in April 2016, in conjunction with the 7th Ibero-American Congress on Nuclear Cardiology and Cardiac Imaging, attended by 133 Cuban specialists as well as international participants. During 2017, for the purpose of disseminating the information and knowledge acquired by Cuban participants in the project’s other regional courses, two workshops were held for national and international experts: Multimodal Imaging in Cardiology (160 participants, April 2017) and Imaging in Cardiology, from Diagnosis to Management (180 participants, December 2017). This knowledge also contributed to raising the level of the nuclear cardiology classes

in the third iteration of the Nuclear Medicine Certificate Program taught in 2017 in Cuba.

Communication of the project's outcomes was another important aspect for both individual participating countries and the region as a whole. In Cuba, a video on CAD in women and the role of nuclear techniques in its diagnosis and management was created and disseminated through the IAEA website, major social networks and various specialized websites. Cuba also participated in an expert meeting (Costa Rica, September 2017) to prepare a consensus document, later published, on use of nuclear techniques in diagnosis, stratification and therapeutic practice.[18]

The regional projects were successful, generating awareness and interest among participating countries on the use of myocardial perfusion in evaluating patients with dilated cardiomyopathy and in CAD, compared to other imaging modalities and in particular in assessment of cardiac synchronism; disseminating knowledge about nuclear cardiology techniques and clinical applications in heart failure and in CAD; and contributing to advances in implementation of standardized, appropriate and safe clinical protocols.

A consensus document on the assessment of CAD patients with nuclear techniques, including the value of ischemia-guided therapeutic strategies was elaborated and published. All national health authorities of the participant countries were informed of the project's results as was the majority of their cardiology and nuclear medicine societies.

Due to the multidisciplinary nature of nuclear cardiology, various groups of professionals involved in its practice were included in the activities (not only nuclear medicine physicians and cardiologists, but also medical physicists, radiopharmacists and technologists). Training was expanded to include professionals from cities other than national capitals. One of the features with the greatest impact was the presence of experts sent by IAEA to national and regional conferences on both nuclear medicine and the medical specialties of referral practitioners.

The project revitalized the Ibero-American Conference on Nuclear Cardiology and Cardiac Imaging, an important regional framework for presentation of experiences in the region, held twice (Havana 2016 and Bogotá 2018).

What does participation in regional projects mean for Cuba?

For our country, which has universal coverage and access to health services, participation in regional projects has provided its specialists and residents in cardiology, internal medicine and imaging, as well as medical physicists, radiopharmacists and technologists, with the opportunity to acquire knowledge that results in better care for heart patients.

The work of Cuban experts has contributed to better harmonization and increased use of nuclear techniques in cardiology, both in Cuba and regionally, as an example of collaboration among countries in Latin America and the Caribbean under the auspices of IAEA and national health authorities.


In low- and middle-income countries, careful selection of the appropriate diagnostic technique for each patient is especially important to achieve personalized, cost-effective medicine,

as is evaluation of the impact of introducing new protocols or technologies. Almost two decades ago, the Economics of Noninvasive Diagnosis Study[19] of symptomatic women with suspected stable CAD showed that myocardial perfusion scintigraphy could be used as a tool to identify patients who should not have invasive coronary angiography, leading to cost reduction. Therefore, identifying a patient with CAD using nuclear techniques (or another imaging technique to detect ischemia, such as stress echocardiography or stress cardiac magnetic resonance, depending on availability and experience at a particular facility), enables an aggressive secondary prevention strategy to be initiated through optimal medical treatment according to clinical guidelines, as well as invasive treatment indicated by presence of ischemia in cases where necessary. Participation in these IAEA regional projects helps build capacities in this regard.

Issues persist requiring joint work by health authorities, scientific societies in the specialties involved and the Agency for Nuclear Energy and Advanced Technologies, with the advice of national groups. Among them:

- Implement an appropriate approach to use of nuclear techniques in multimodality imaging, with adequate cost-benefit analysis. Training specialists in different imaging techniques will enable an interdisciplinary approach to patient care and better integration of appropriate indications for each technique.
- Continue implementation of quality control systems in nuclear medicine services to sustain improved care and increase patient satisfaction levels.
- Continue work to obtain approval of a medical specialty in nuclear medicine, although the country already has a nuclear medicine certificate program.
- Disseminate throughout Latin America and the Caribbean the importance of presenting and conducting projects related to regional health needs, specifically to reduce CVD morbidity and mortality. In this regard, cooperation among national health authorities, national and regional scientific societies and UN agencies such as IAEA, PAHO and WHO contribute to strengthening human and technological capacities in the region.
- More deeply study differences between men and women in relation to physiopathology of coronary heart disease and gender influence, a little-examined question nationally and regionally that leads to disparities in CAD treatment.[20,21] Along these lines, national and regional support is needed, including from UN agencies, with an approach that does not overlook the clinical and pathophysiological specificities of female patients.

CONCLUSION

Cuba's involvement in regional IAEA projects in cardiology has contributed to development of human resources and standardized protocols both nationally and in the Latin American and Caribbean region and demonstrated the importance of regional scientific cooperation that ensures greater opportunities and more equitable access to resources. 

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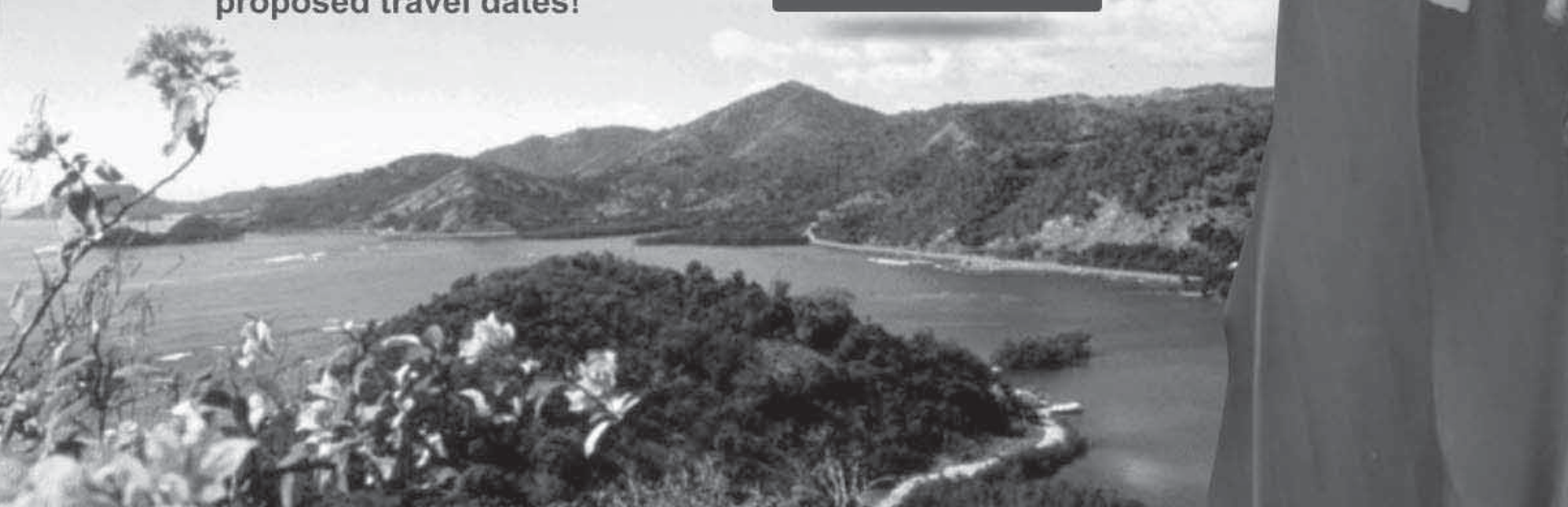
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Six Decades of Cuban Global Health Cooperation

Conner Gorry MA

In 1978, the world was put on notice: health inequalities exacerbated by lack of access to essential services was a ticking time bomb threatening social and economic development everywhere. That year, over 100 countries signed on to the Declaration of Alma-Ata, which affirmed that “health . . . a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity, is a fundamental human right.” To guarantee this right, governments were urged to prioritize the provision of quality, continuous, comprehensive and affordable primary care for their entire populations by the year 2000.[1]

Forty years after Alma-Ata, many countries have failed unequivocally to attain that goal. In 2017, the World Bank and WHO released sobering data that nearly half the world’s population was still without essential health services. Meanwhile, the cost of those services—when accessible—had already pushed nearly 100 million people into extreme poverty.[2]

This dire state of affairs is not limited to developing countries. According to the Association of American Medical Colleges, the USA will be short 21,000–55,000 primary care physicians by 2032[3] and recent data are not encouraging: the percentage of fourth-year medical students filling primary care positions in the 2019 US National Residency Matching program was the lowest on record.[4] Furthermore, access to a primary care physician for US patients has remained flat—76.4% in 2015 compared to 76.8% in 1996—despite evidence that “access to primary care improves health outcomes and lowers health-care costs.”[5]

From astronomical medical school tuition to inconsistent political will, numerous factors contribute to this global human rights crisis. To forge a plan towards ‘building a healthier world,’ experts and governments were invited to share data, analysis and experiences at the 2019 UN General Assembly’s first High-Level Meeting on Universal Health Coverage (UHC). Among the countries presenting findings is Cuba, a small, developing nation whose health system aimed for universal care and coverage as early as 1960, when the rights to health and education were recognized. Through that decade’s Rural Medical Service, doctors fanned out nationwide to extend health services to all Cubans, reaching universal coverage well before the Alma-Ata Declaration was adopted.

It is now widely recognized that UHC contributes to overall social and economic development. Where health care services are not universal, the most vulnerable and poorest patients are either without care altogether, or often shunted to public facilities—making public health care essentially poor people’s health care. Cuba’s global cooperation policy has been to help staff and strengthen public health institutions and systems in coordination with host governments, primarily in developing countries, rather than “setting up shop” on their own. However, early experiences revealed a daunting challenge: many of these countries’ public systems were dysfunctional, poorly run and sometimes in danger of complete collapse, aggravated in cases of natural disasters or war. Often, the health systems where Cubans served were characterized by crumbling infrastructure, health worker shortages and spatial inequality, financial and material resource scarcity, ineffective or insufficient health surveillance mechanisms,

and inconsistent national health protocols. This reality begged the question: could long-term improvements in patient outcomes be achieved in such contexts and might Cuba play a larger role?

The island nation had shown that even poor countries can make significant gains in population health. Today, Cuba’s main health indicators rank alongside those of many high-income countries—despite the challenges of providing universal access at all three levels of health care for 11 million people amidst serious resource scarcities—results that support the island nation’s people-centered strategy emphasizing community-based preventive and primary care.

Since the 1980s, that primary-care foundation was bolstered by vastly increasing the numbers of physicians (from 15,247 in 1980 to 95,487 by 2018). As a result, today some 10,000 family doctors live and practice in the neighborhoods that geographically define their patient load, working with family nurses to provide preventive, curative and rehabilitative care guided by the community polyclinic to which they report and refer.[6] Thirteen health universities dot the country, offering medical, nursing and allied health professional training; some 150 hospitals provide secondary and tertiary care, bolstered by research institutes in 12 specialties and a world-class biotech sector. The country also moved early to strengthen health data collection and analysis, institute national protocols, dedicate more of its GDP to the national health budget (over 11% by 2014); and implement whole-health strategies that prioritize a biopsychosocial approach.[7]

Critical reflection by Cuban health authorities on their own public health practice and its evolution, the knowledge accumulated, and innovative technologies introduced, made the country a natural laboratory for applying and assessing Alma-Ata’s proposals. Furthermore, Cuban training is founded on the principle that health is a right and primary health care a cornerstone of practice—concepts advanced by Alma-Ata that have gained global traction and are now recognized as key to social and economic development. With UHC as a tangible goal for other developing nations, aiming at more effective, sustainable and inclusive health systems that reach the most vulnerable first, Cuba’s experience can offer valuable lessons.

During the past six decades, Cuban doctors, nurses and allied health professionals have worked in public health systems in over 150 countries through bilateral and international cooperation accords; by the end of 2018, more than 400,000 Cuban medical professionals had served abroad.[8] Over time, these programs evolved beyond staffing to include training, technical and epidemiological components, as well as incorporation of pharmaceuticals and targeted specialty-care initiatives.

CUBA GOES GLOBAL: SEEDS OF INTERNATIONAL COOPERATION

The new revolutionary government of Cuba was still finding its footing when the strongest earthquake on record struck Chile in May 1960. Although the two countries had no diplomatic ties at the time, a Cuban team was dispatched to provide medical services to the thousands injured and two million left homeless—marking the country’s first foray into disaster medical relief. Three years later,

Feature

at the request of newly-independent Algeria, Cuba sent doctors, dentists and nurses to help staff the gutted public health system, with Cuba's first bilateral accord in medical cooperation.

These seminal experiences established a framework for structuring effective, sustainable medical cooperation, and also offered important lessons for the future. In Chile, Cuba pioneered solidarity-based medical assistance, providing aid regardless of negligible—or even hostile—government relations with the country in need. Continuity of this approach was revealed following Hurricane Katrina in 2005, when Cuba offered 1500 doctors to the Gulf States (refused by former President G.W. Bush). That same year, Cuban postearthquake disaster teams were welcomed by Pakistan's government, even though Cuba had no diplomatic representation in the country at the time. Algeria solidified a bilateral (and later, multilateral) cooperation strategy whereby the modality and duration of cooperation, type and number of specialists and remuneration, are tailored to the needs of, and in negotiation with, the host country. Often, this includes nonmedical professionals such as engineers, teachers and technicians—a needs-based, mix-and-match model.

TARGETED & TAILORED MEDICAL COOPERATION

As Cuba gained more UHC experience at home—instituting national programs and protocols for maternal–child health, epidemiological surveillance and control, chronic and communicable diseases, older adult health and integrative medicine—it broadened and refined its international commitments. Meanwhile, expanded medical education increased the numbers of health professionals in Cuba itself (after nearly half its physicians emigrated to the USA in the early 1960s), and the island extended staffing assistance to over two dozen countries in Central America, the Caribbean, Africa and the Middle East throughout the 1970s.[9] In the 1980s, it began training more doctors with the express purpose of making their services available abroad as well as at home.

Over time, the principles and practices of Cuba's international cooperation programs were formalized. These include:

- All overseas postings are voluntary;
- In addition to scientific qualifications, professionals serving overseas are expected to conduct themselves according to high standards of ethics and humanistic values;
- Postings are primarily in underserved, including remote, areas for at least two years;
- Cuban personnel staff public facilities offering no- or low-cost services;
- Health professionals are selected for overseas postings from services, locales and institutions with available staff, to avoid causing shortages in the domestic system;
- Composition of international teams depends on needs of host country;
- Participants must successfully complete predeparture training and coursework, including foreign language instruction, emerging and endemic diseases, and history and culture of the country in which they will be serving;
- Local customs and culture will be respected (e.g. women patients are seen only by women physicians in countries where this is customary, collaboration with traditional healers, etc.);
- Professionals working overseas have regular contact with their families in Cuba. In the event of an emergency, all efforts are made to swiftly reunite families;
- Professionals working internationally receive their regular Cuban salary throughout their posting, plus remuneration agreed upon



Cuban doctors in Asia, the Amazon and Africa: rough, rural, remote.

with the host country taking into consideration modality of cooperation, host-country salary levels and in-kind contributions supplied by each party;

- Each volunteer has guaranteed vacations during their posting (timing and frequency depends on length and type of posting); and
- Those who successfully complete international service will be prioritized for future international work depending on their availability and domestic Cuban staffing needs.[8,10]

Which bilateral/multilateral commitments are evaluated for inclusion and enrollment of Cuban volunteers is based on a strategy balancing the needs of Cuba's health system with the type and amount of help requested. Factors taken into consideration include the kind and number of specialists requested, language capabilities, and possible effects on Cuban health services. In some cases, host-country health authorities participate in choosing from the pool of applicants. Volunteers are solicited throughout Cuba from those health facilities with available staff. "I submitted my name for an international posting after talking to a colleague at one of our weekly polyclinic meetings," says Dr Eduardo Ojeda, who first served in Indonesia following the 2005 tsunami. "People were suffering and I wanted to make a contribution. I was also interested in learning what international health and medical aid is all about." Solidarity, broader professional experience plus extra salary mean "there is no shortage of medical personnel volunteering for two-year stints abroad." [11]

In 1984, the Central Medical Cooperation Unit (UCCM, *Unidad Central de Cooperación Médica*) was founded to coordinate Cuba's overseas health commitments. At that time there were 1717 Cuban health professionals serving abroad; today there are more than 39,000 health professionals working in 68 countries in various cooperation modalities (Table 1), plus a small working group in Mexico coordinating application of Heberprot-P, Cuban biotech's innovative treatment for diabetic foot ulcers. Countries often request several types of medical cooperation, depending on their staffing, technical and training needs.[8]

COOPERATION MODALITIES

Just as the 1960 Chilean earthquake marked Cuba's entry into international medical cooperation, a duo of natural disasters in 1998 led to a profound evolution of that cooperation. Within weeks of each other that year, Hurricanes Georges and Mitch struck Central America and the Caribbean, killing more than 30,000 and leaving nearly 3 million people homeless. The response to these storms—2 of the deadliest on record—was swift, with Cuba and other countries sending medical teams to the hardest-hit areas in Honduras, Haiti, Nicaragua and Guatemala.

Three realities snapped into focus for Cuban teams providing health services in the wake of Georges and Mitch: 1) vulnerable populations, including the poor, infirm, elderly and children, bear the brunt of natural disasters and are slower to recover mentally, physically and materially; 2) inaccessible or ineffective public health systems collapse during major adverse events (weather-related or otherwise), increasing fatalities and the probability of disease outbreaks; and 3) in many areas, Cuban doctors were the only health professionals people had ever seen, and they would be without medical care once these physicians returned home. These realizations led to innovations designed to increase access, reduce vulnerability and strengthen the affected health systems in a cost-effective manner.



Cuban medical education in South Africa and the Latin American School of Medicine.

The **Comprehensive Health Program (PIS, Programa Integral de Salud)** was launched in 1998 to implement this strategy. PIS is long-term, South–South medical cooperation whereby teams of primary care doctors, specialists and other health professionals serve for two years in some of the world’s poorest and most underserved contexts. PIS teams are currently helping staff public health systems in 30 countries, including Haiti, Honduras, Bolivia, Niger, Lesotho, Congo, Chad and Kiribati. Key components include continuing education for participants during their posting, such as degree-conferring courses and annual scientific congresses to present research; epidemiological surveillance to assess main health problems; and Continuous Assessment and Risk Evaluation (CARE) for patients in the areas where Cubans serve. Bilateral agreements are tailored for each situation, but in general, Cuba finances the lion’s share of PIS cooperation, and its health professionals receive (in addition to their regular salary at home) a stipend to cover basic necessities, while the host country provides housing and logistics.

“I came back a better doctor and stronger clinician,” says two-time volunteer Dr Sara Teresa Aldecoa. “I was seeing diseases I had never seen before, ones that don’t occur or were eradicated in Cuba long ago. I saw the benefits of being a family doctor and how comprehensive care mitigates health care silos. I’m extraordinarily proud of this work,” she adds, noting that she is currently preparing for a posting in Algeria.

Vision Program The majority of PIS countries also participate in Cuba’s sight restoration and improvement initiative, *Operación Milagro*, a program providing free examinations and surgery for reversible vision problems. Fifteen years on, the program has restored or improved the vision of more than three million people, most of them poor, who otherwise would not have had access to such life-changing interventions (Table 1).

The Latin American School of Medicine (ELAM, Escuela Latinoamericana de Medicina), a six-year medical school offering scholarships to students from underserved areas, initially was designed to provide sustainability to those health systems supported by PIS teams. Founded on the precept that Cuban doctors cannot staff foreign health systems indefinitely and that the ideal provider is a well-trained, homegrown health professional, ELAM was a bold, expensive gamble in socially accountable medical education. This approach is based on providing hands-on learning about social determinants’ effects on health; sharing responsibility for addressing spatial inequalities and delivering equitable, accessible services; going beyond pedagogical innovations to include integration of graduates into local health systems; and anticipating the type, mix and number of health professionals needed, making adjustments as required.[12]

Inaugurated in 1999 with 1900 students, the majority from the countries hardest hit by Hurricanes Mitch and Georges, ELAM enrollment was up to 10,000 students from around the world in 2005, including the USA. In exchange for these scholarships, students make a nonbinding pledge to practice in areas where they are most needed. Upon its 20th anniversary in 2019, ELAM had graduated nearly 30,000 doctors (in addition to those foreign MDs already trained over the years in Cuban medical universities).

From the USA to Ghana, Niger to Nicaragua, international doctors trained in Cuba are making an impact. In remote La Mosquitia, home

to the Garífuna (a Honduran ethnic and racial minority subjected to structural barriers to health, education and economic development), ELAM graduates, led by Dr Luther Castillo, built and staff the First Popular Garífuna Hospital. This coastal region was previously without permanent health care services. In Chile, Dr Juan Carlos Reinao, descendent of indigenous Mapuche, returned home after graduating from ELAM to work in a rural health clinic in Renaico, a town of 12,000. Here he plans to launch several programs adapted from Cuban approaches, including establishing an integrated day facility for elders, increasing staffing in his health area, guaranteeing access to essential medicines and launching prevention initiatives to improve community health. Sound ambitious? It is, but not impossible: Dr Reinao was elected mayor of Renaico in 2012.

In Haiti, Dr Patrick Dely had to leave his hometown of St. Michel L’Attalaye after primary school to continue his education in the capital—there was no other option closer to home. Since graduating from ELAM, Dr Dely has built a school in St. Michel which educates, feeds and provides primary health care for over 100 students; was the Haitian Director for the CDC’s Field Epidemiology Training Program 2011–2017; and was the only Haitian doctor to work in West Africa fighting Ebola. In 2017, Dr Dely was appointed Director of Hygiene and Epidemiology by Haiti’s Ministry of Public Health.

Perhaps the most visible example of ELAM graduates in leading roles are two women who have been appointed ministers of health, in Costa Rica and Bolivia.

Table 1: Cuban international medical cooperation, 2018

Indicator	Value
Countries with Cuban health cooperation	68
• Sub-Saharan Africa	28
• The Americas	26
• Middle East and North Africa	3
• East Asia, Pacific	9
• Europe	1
• Oceania	1
Cuban professionals serving abroad	39,532
Physicians serving abroad	19,160 (48.5%)
Women serving abroad	24,861 (62.9%)
Surgical interventions	900,968
Births attended	331,033
Countries with PIS services	30
Countries with vision restoration and improvement services	12 (Angola, Argentina, Bolivia, El Salvador, Guatemala, Guyana, Haiti, Honduras, Jamaica, St. Lucia, Uruguay, Venezuela)
Vision restoration/improvement surgeries	103,522
Countries with students at ELAM	24
Students currently enrolled at ELAM	>7,000
Students in home-country medical schools studying under Cuban professors, with Cuban curriculum	47,852 (38,045 in Venezuela)

PIS: Comprehensive Health Program ELAM: Latin American School of Medicine
Source: Delgado Bustillo F, editor. *Anuario 2018 de la Colaboración Médica. Vol 8 No 1. Havana: Central Medical Cooperation Unit (CU); 2019. Spanish.*



Cuba's Henry Reeve Medical Contingent in Pakistan (2005) and joined by this ELAM graduate in postquake Haiti (2010).

Judging from the available data, US ELAM graduates are also living up to their commitment: as of 2019, of the 182 US doctors trained in Cuba, 92 were in residency or practicing after passing their licensing exams, over 90% of them in primary care specialties. Additionally, 75% serve in Health Professional Shortage and/or Medically Underserved Areas, and nearly all work in the public sector with vulnerable communities.[13]

The Henry Reeve Emergency Medical Contingent Almost 700 ELAM students and graduates volunteered to join hundreds of Cuban health professionals as part of the Henry Reeve Emergency Medical Contingent in Haiti after the 2010 earthquake. Founded in 2005 in response to the increasing threat of natural disasters, this specialized team is trained and equipped to provide emergency medical services in postdisaster scenarios and epidemics. Although Cuba's offer to send the team to areas in the USA affected by Hurricane Katrina was rejected, these professionals provided emergency medical aid and services that year to Guatemala in the wake of Hurricane Stan and in postquake Pakistan. Since then, the Contingent has provided free postdisaster health services in over 20 countries following earthquakes, mudslides, hurricanes and tsunamis, and during cholera and Ebola outbreaks.

The principles and practices of Cuba's Henry Reeve Contingent incorporate those outlined above for PIS, plus other strategies designed to strengthen public health systems and primary care access throughout the recovery stage and even after the Contingent leaves. These elements include:

- Team stays long-term, depending on type/volume of services needed and epidemiological situation (in some cases, like Pakistan and Haiti, this can be six months or more);
- Primary care teams do field visits to remote/underserved areas (including those outside the disaster zone) to provide frontline health services (often the first doctors these populations have seen);
- People needing urgent or specialist care unavailable in these remote areas are remitted to Cuban field hospitals and/or the closest appropriate health facility;
- Field hospitals and surplus supplies are donated to the stricken country when the Cuban team withdraws;
- Team works in coordination with local authorities and other relief agencies for more efficient, effective service delivery;
- Multilateral efforts combine Cuban staffing and expertise with material resources from third countries; and
- Teams seek opportunities for collaboration in other areas of population health (e.g. identifying eligible students for ELAM scholarships, forging cooperation in technology transfer, joint pharmaceutical manufacture, etc.).

In Haiti, Mozambique, Guinea, Guatemala and elsewhere that the Henry Reeve Contingent has served, Cuban PIS teams have been among the first responders when disaster strikes. This is because they were already on the ground, serving long term in communities, with valuable working knowledge of local customs and languages. This predisaster presence and the trust built facilitate logistics and communications with health/emergency authorities before the Henry Reeve Contingent arrives. The region affected by the disaster or outbreak may also have ELAM students or graduates, receive technical assistance, or have other health system support from Cuba. These overlapping elements and long-term South–South cooperation contribute to continuous and expanded access to care. (Table 2)

THE STRATEGY EVOLVES: SOLIDARITY PLUS SUSTAINABILITY

Successful, sustainable cooperation is mutually beneficial. In addition to PIS, Cuban professionals help staff public health systems in those nations with the ability to pay for services rendered. This modality, known as remunerated assistance, can take the form of technical, staffing or biotech manufacturing assistance financed by the host country. Part of the funds remunerates the health professionals and technicians working in-country, while half (or more) is retained by Cuba to enhance sustainability of its own universal health system by supplying sorely-needed revenue. In 2018, over 27% of Cuba's national budget was spent on health and social welfare,[14] which included \$6.4 billion pesos/dollars in funds from such remunerated assistance.[15] This revenue has been used to upgrade equipment, repair and build health and social welfare facilities such as nursing homes and senior day care centers, and extend new services nationally.[14] In 2019, Cuban health professionals also received across-the-board salary increases—financed in part by these international agreements. Currently, dozens of countries participate in this cooperation model, including Qatar (Cuban-staffed hospital), East Timor (family doctors in every health center; specialists in six hospitals), Angola (broad staffing of primary care facilities, advisors in public health) and South Africa (professors, family physicians and other specialists throughout the country, concentrated in the eight provinces with greatest spatial inequality).

Evidence suggests that solidarity and sustainability are both strong components of Cuban global health cooperation going forward (Table 3). One example is the response of Cuban doctors and the health system to the 2014 Ebola epidemic that ripped through West Africa, killing thousands and infecting many more, including most local health providers who were exposed. When WHO issued a global call for help, Cuba's Henry Reeve Contingent answered. After specialized training at Havana's Pedro Kourí Tropical Medicine Institute (IPK), 256 Cuban health professionals, all volunteers with previous Contingent experience, headed to Sierra Leone, Liberia and Guinea. There, they received another four weeks of in-country training in prevention, protection and treatment protocols, cultural norms and team integration.

Teamwork is essential during such crises, since agencies and providers with little to no experience working together are beholden to strict protocols requiring coordinated action. Dr Jorge Delgado, who headed the Henry Reeve Contingent in Sierra Leone for their seven months there, says his team worked with other volunteers daily, including those from the USA: "we worked shoulder-to-shoulder with US doctors for months

fighting Ebola even though our countries still hadn't normalized relations." In this and other disaster/epidemic situations, Cuban health professionals have joined those from the country affected, as well as international aid workers from Partners in Health, the International Red Cross, Doctors Without Borders, CARE and even US military personnel.

While the Henry Reeve Contingent is dispatched primarily at the request of governments in postdisaster situations, the Ebola crisis was only the second time teams were contracted through an international agency, and the first where they were directly paid by WHO. Training modules at IPK and in Africa were coordinated, assessed and certified by WHO specialists. Additionally, the organization assumed all responsibility for providers contracted by them who fell ill, said Dr Félix Báez, a Henry Reeve Contingent veteran who was infected with the deadly virus and airlifted to Geneva for treatment. Once healthy, he chose to donate his blood for research and return to Sierra Leone to serve out his posting: "I decided to go back

Table 2: Types of Cuban international medical cooperation

Modality	Characteristics
Comprehensive Health Program (<i>PIS, Programa Integral de Salud</i>)	Staffing support for public health facilities including hospitals and clinics, prioritizing poor, remote, and underserved areas. Oftentimes, a Cuban doctor is the first health care provider to attend these populations.
Remunerated Technical Assistance*	Paid postings to provide staffing support to health institutions in the Caribbean, Latin America, Africa and Asia. These are a mix of family physicians and specialists including pediatricians, neonatologists, maxillofacial surgeons, oncologists, neurosurgeons, psychiatrists and more. First launched in the late 1980s.
Vision Restoration and Improvement Program (<i>Operación Milagro</i>)	Since 2004, this vision restoration program has offered free surgical interventions for reversible conditions including cataracts, diabetic retinopathy, and pterigium. Over 3 million people in Latin America, the Caribbean and Africa have had sight restored or improved under this program.
Medical Education & Training	Includes the Latin American School of Medicine (ELAM; founded in 1999) providing full medical school scholarships; tuition-based medical degrees; and medical schools established by Cuban professors in other countries.
Henry Reeve Emergency Medical Contingent	Founded in 2005, this specialized team is trained and equipped to provide medical services in post disaster scenarios and during epidemiological outbreaks. In most cases, costs are assumed by Cuba; commitment can be up to 6 months. 28 disaster relief missions to date.

*Does not include specific contracts signed with Servicios Médicos Cubanos (Cuban Medical Services, SA), which offer specialized services and contracts to entities in 18 countries, some nations already included in modalities above. Source: Delgado Bustillo F, editor. *Anuario 2018 de la Colaboración Médica*. Havana: Central Unit for International Medical Cooperation (CU); 2019 Jul 9. Spanish.

Table 3: Milestones in Cuban international medical cooperation, 1960–2019

Event	Year	Notes
First disaster relief aid	1960	Chile, after strongest earthquake on record
First public health staffing cooperation	1963	In newly independent Algeria
Disaster relief accompanied by donations	1970	Peru earthquake, 6 field hospitals and 106,000 blood donations
Medical schools opened/staffed overseas	1975–2003	11 (Southern Yemen, Guyana, Ethiopia, Guinea Bissau, Uganda, Ghana, Angola, The Gambia, Guinea, Haiti, Eritrea)
Central Medical Cooperation Unit (UCCM) founded	1984	All international medical cooperation (except ELAM) now coordinated by this entity
Treatment for children from Chernobyl disaster	1990–2011	>25,000 children treated in Cuba (in 2019, Cuba announced it would restart the program to treat the next generation who are showing signs of ailments similar to their parents)
Comprehensive Health Program (PIS) founded	1998	Staffing and technical assistance provided by Cuban health professionals in underserved areas of developing countries
Latin American School of Medicine (ELAM) opened	1999	Six-year Cuban medical school scholarships to thousands of students from underserved areas, the “world’s largest medical school program” and largest experiment in socially accountable medical education
<i>Barrio Adentro</i> program launched	2003	Bilateral Venezuela-Cuba accord to guarantee universal access to essential health services for all Venezuelans
Henry Reeve Emergency Medical Contingent founded	2005	1586 Cuban medical professionals volunteer for specialized team; goes on first missions to Guatemala and Pakistan
Cuban Medical Services (<i>Servicios Médicos Cubanos</i>) founded	2005	Remunerated cooperation agreements managed by this entity, coordinated through UCCM
Psychosocial, Pedagogical, & Genetic Disabilities Study	2010	Total population, multicountry disabilities studies (Venezuela, Bolivia, Ecuador, Nicaragua, St. Vincent and the Grenadines)
More Doctors for Brazil (PMMB, <i>Projeto Mais Médicos para o Brasil</i>)	2013–2018	Multilateral program to provide essential services to highly vulnerable municipalities throughout Brazil. Cuba sends >11,000 health professionals
WHO lauds Henry Reeve Emergency Medical Contingent	2017	Team awarded WHO’s Dr Lee Jong-wook Memorial Prize for Public Health
Heberprot-P approved for use in Mexico	2018	Cuba’s novel treatment for diabetic foot ulcers, approved for use in nearly 30 countries, made available to Mexican patients; three Cuban specialists work in-country as application rolls out
ELAM celebrates 20th anniversary	2019	Class of 2018–2019 graduates 466 doctors from 84 countries (>29,000 to date from over 100 countries)

Sources: Delgado Bustillo F, editor. *Anuario 2018 de la Colaboración Médica. Vol 8 No 1. Havana: Central Medical Cooperation Unit (CU); 2019. Spanish; Cole C, Di Fabio JL, Squires N, Chalkidou K, Ebrahim S. Cuban Medical Education: 1959 to 2017. J Med Educ Training. 2018 May 14;2(1):1033; Gorry C. Your primary care doctor may have an MD from Cuba: Experiences from the Latin American Medical School. MEDICC Rev. 2018 Apr(2):11–6.*

because people need us. Besides, my dad always told me not to be a quitter.”[16] In 2017, WHO awarded the Henry Reeve Contingent its Dr Lee Jong-wook Memorial Prize for Public Health in recognition of its contribution to global health, including their work fighting Ebola in West Africa.

Increasingly, Cuban health professionals have answered the call *en masse*, not only for disaster relief, but also to help relieve physician shortages and implement proactive strategies extending UHC to underserved areas. Such was the case with the More Doctors for Brazil program (PMMB, *Projeto Mais Médicos para o Brasil*), launched in 2013 by Brazil’s national Unified Health System (SUS, *Sistema Único de Saúde*). The program was designed to provide essential health services to 40% of Brazilians without access to primary care, alleviating the country’s shortfall of 40,000 health professionals, particularly in remote, vulnerable and indigenous regions.[17]

PMMB was not “an end [but] a means to extend universal access and coverage to all Brazilians...a strategy to develop and strengthen primary care services, including training of doctors from those [underserved] communities,” according to WHO/PAHO consultant in Brazil, Dr Carlos Rosales. Although the call for participants was extended to local health professionals first,

few responded; then countries with “better health indicators than Brazil,” were invited to join, including Cuba.[17] In year one, a total of 1846 Brazilian physicians and 12,616 foreign physicians from 49 countries participated, including 11,429 Cubans—the latter through a PAHO/SUS/Cuban Ministry of Public Health partnership.[18]

In addition to staffing, *Mais Médicos* incorporated elements for strengthening infrastructure, increasing medical school enrollment, and requiring new Brazilian medical graduates to pursue primary care specialties. Global public health experts, regional and municipal authorities, and most importantly, the millions of Brazilians accessing these services applauded the program: research reveals 95% of them approved of the responsiveness of the PMMB health professionals. [17–19] Dr Rafael Urquiza went from urban Havana to live and serve in the mountainous village of Espírito Santo, population 3000, providing integrated care for three years. “I did a health assessment for each individual, resulting in a health snapshot of the whole population. I documented, evaluated and treated chronic disease, pediatric cases, pregnant women, everybody. I did a lot of home visits—it surprised families to have a doctor sitting on their dirt floors having coffee with them, asking them about salt intake, how well they were sleeping. They’d never been cared for like that; I wasn’t on a pedestal; I was like another neighbor.”

Feature

Studies analyzing the impact of PMMB found that “service provision by Cuban physicians shows an equal or higher level of quality than that of high-performance professional teams in the country, improvements in the connection and humanization of service provision and reduction in regional inequities. And the ratio of physicians per inhabitant increased.”[19,20] PAHO’s Dr Rosales noted: “The world associates Cuban international health providers with high quality; the Cuban doctors participating in *Mais Médicos* have provided essential support to Brazil’s most excluded populations.”[17] In fact, in some regions of the Brazilian Amazon, a Cuban doctor was the first health provider residents had seen and in 10% of municipalities, the only physicians were Cuban.[19,20]

Despite these results, the Brazilian Medical Association vilified the presence of foreign doctors, particularly the Cubans. In 2018, far-right presidential candidate Jair Bolsonaro described the Cuban physicians as unqualified and imposters, objected to the part of their salaries remitted to Cuba, and threatened to stop honoring the agreement if elected. When he won, the agreement came crashing down. After more than four years of providing primary care to millions, the Cuban doctors (numbering 8471 at the time) were recalled by Cuba’s health ministry. In an about-face on his own rhetoric, the Brazilian president then offered to contract directly any Cuban physicians who decided to stay; international press reports indicate the overwhelming majority returned home. One who did write a scathing “open letter to Jair Bolsonaro,” indicating that although he might not always agree with his own government, his grievances with Bolsonaro were far greater: “I accepted the terms of this contract by my own free will. I am aware that with this money, my mother, siblings, nephews, cousins, uncles, neighbors, my whole family is guaranteed health care without paying anything...I ask for respect for my colleagues. I ask respect for my people’s free choice. I ask respect for those who are poor, uneducated. I ask respect for public health. I also ask the gentleman to study what it means to love thy neighbor, and also to study what homeland means, what dignity means, what diplomacy means, what family medicine means, what equality means, what respect for ideas means, what it means to be the president of poor Brazilians and not just the rich and powerful.”[21]

The collapse of *Mais Médicos* has left an estimated 28 million without access to primary health care services; data shows that six months after the Cuban doctors departed, 3847 public health positions remained vacant in some 3000 municipalities across the country unfilled by a Bolsonaro initiative.[22] This is tragic for the communities without access to primary care, and problematic for the Brazilian government, since universal health care is a right guaranteed by law.

The most comprehensive example of integrating South–South solidarity with sustainability is the regional Bolivarian Alliance for the Peoples of Our America (ALBA, *Alianza Bolivariana para los Pueblos de Nuestra América*), an agreement among Venezuela, Cuba and eight other Caribbean and Latin American countries. Initiated in 2003 between Cuba and Venezuela, these accords are designed to strengthen economic, health, education and cultural cooperation as well as regional integration. The financing of the agreements over the years has been heavily dependent on Venezuelan oil shipments to several of the member states, including Cuba.[23]

Inside the Neighborhood (*Barrio Adentro*), the first program launched under this collaboration, was designed to “guarantee universal access to essential, comprehensive medical services to all Venezuelans.”



Primary care: cornerstone of Mais Médicos, PIS and Barrio Adentro.

Based on the PIS model and incorporating similar curative, preventive and academic components, including the vision restoration program, it is the largest international medical commitment in Cuba's portfolio. By December 2018, there were 22,793 Cuban health professionals serving in Venezuela—of these, 6154 were physicians.[8] Since its inception, the scope of *Barrio Adentro* has broadened to include centers for ophthalmologic services, high-tech diagnostics and laboratory analyses, comprehensive rehabilitation services, and a hospital staffing and modernization program. All *Barrio Adentro* services are free of charge.

In order to build sustainability into the *Barrio Adentro* program, the two countries launched an aggressive bilateral medical education program. Using Cuban curriculum taught by Cuban and local medical professors, Venezuela's National Community Medicine Training Program graduated 2130 new physicians and 4251 family medicine specialists in 2018. An additional 38,045 Venezuelan students are currently studying medicine in their home country, with Cuban professors and curricula (2160 are in postgraduate degree-conferring programs).[8]

CHALLENGES & ROADBLOCKS

In the increasingly complex and often volatile political and economic context of Latin America, the Venezuela–Cuba portion of the ALBA accords has become a target of the US administration. This is just one example of the fact that Cuba's global health collaboration is neither seamless nor problem-free.

The different modalities require significant logistical and human resources, which can stress Cuba's own universal health system—particularly at the primary care level during certain years. Over time, addressing these challenges has required reorganizing domestic health services. In 2008, when more than 20,000 neighborhood family doctors were serving abroad, primary care was reorganized to strengthen the role of family nurses and polyclinics in service delivery; some neighborhood family doctors' offices were closed as a result. [24] While this relieved pressure on family doctors, it contributed to patient dissatisfaction related to wait times and accessibility to physicians. Public health authorities responded to this challenge by increasing medical school enrollment. The result has been to ratchet up the number of physicians, now numbering >94,000, with family doctor-and-nurse offices back to their full complement of staff.[6]

Still challenging, however, is figuring out the mix of family physicians and those in various specialties, and sorting out who can actually be spared for volunteer postings. It is also a tough balancing act to ensure that 150 hospitals, 450 community polyclinics, 13 medical schools and 12 research institutes are fully staffed, while at the same time, guaranteeing resources for the necessary tools, equipment and medicines to provide quality care. The complex formula is possible in part, based on the hard currency brought in by colleagues serving abroad that, as noted above, both helps guarantee the sustainability of Cuba's universal health system and at the same time helps health professionals individually, increasing their families' standard of living. (Due to depressed peso purchasing power since the 1990s, a physician posted abroad can earn some 25 times his or her guaranteed salary back home.)

Low salaries are related to another challenge going forward: like every other developing country, Cuba faces outward migration of its professionals, including health professionals, with an increasingly

unstable global economy and tightened US sanctions complicating resource scarcities at home. This, coupled with the fact that many high-income countries do not respect the WHO Global Code of Practice on the International Recruitment of Health Personnel, puts Cuba in a particularly vulnerable spot, given the sheer numbers of physicians traveling. In response, while family physicians have no restraints on trips abroad for any reason, specialists in other fields are required to seek health ministry permission for travel. Although permissions may be generally granted, this regulation may be a source of irritation for health professionals.

Cuban programs for training foreign doctors have required adjustments as problems were identified. This includes better preparation for reinsertion to home health systems, certification of Cuban medical degrees and addressing language challenges. Many countries with students at ELAM were not prepared financially or logistically to incorporate these new MDs into their public health systems. Haiti lagged in its commitment to place more than 1000 ELAM graduates in understaffed and underserved areas, for example, until the ELAM chapter of the International Medical Society (headed by Haitian graduate Dr Patrick Dely) and locally elected officials—some of whom also graduated from ELAM—exerted pressure on national authorities to honor that commitment.[25]

In South Africa, multiple adjustments were made to reintegrate graduates and strengthen the efficacy of the program, including three years of supplemental training back home on conditions not found in Cuba (e.g. malaria and mother-to-child HIV transmission), and involving South African deans and universities in selecting students for Cuban scholarships. There, stigma experienced by ELAM graduates upon returning home is another difficulty worth noting, including racial and ethnic barriers compounded by having studied in Cuba.[26]

Reinsertion to home health systems also presented challenges in the USA, where the first graduates struggled to pass the US Medical Licensing Examination (USMLE), the multipart exam all medical graduates are required to pass—a problem largely overcome by later graduating classes. ELAM graduates have reported difficulties adjusting to medical care in the USA, due to its reliance on high-tech diagnostics; restrictions on patient care related to insurance coverage and costs; the plethora of electronic recordkeeping systems; other administrative duties; and differences in prescription drug options. In short, the Cuban medical curriculum, combined with transitioning from a UHC system to a mixed- or for-profit system, and cultural and language differences can all affect reinsertion into the usually more fragmented systems back home.[27,28]


In many developing countries, returning ELAM graduates also encounter resistance from medical societies that perceive competition from these doctors committed to no- or low-cost health models. This has been a problem in Honduras, Venezuela and elsewhere, and was at the heart of objections to *Mais Médicos* in Brazil. Nevertheless, these countries have largely failed to entice doctors from their medical societies (many of whom come from the middle upper class) to work in the poor, remote, rural areas where Cuban-trained doctors are committed to serve. In too many cases, instead of forging solutions for integrating the newly graduated ELAM physicians, vulnerable communities are left without health services.

Critics' old argument of “substandard medical education” in Cuba has not stood the test of time. The evidence base—on the quality

of Cuban family doctors and specialists, emergency responders, researchers and professors, as well as ELAM graduates—speaks to the contrary. So does the depth and breadth of international cooperation with, and oversight by, scores of governments and health authorities where Cuban-trained doctors serve. This includes WHO/PAHO, UNICEF, and other UN agencies with which Cuban health professionals work, and medical school deans and professors where Cubans teach. Moreover, improved health indicators from Cape Verde to the USA, Brazil to Haiti,^[9,29] and increased patient satisfaction—in communities spared disease outbreaks, among mothers getting prenatal checkups, and in rural villages with primary care services for the first time—perhaps provide the most important litmus test of how and how well these health professionals contribute to extending quality health care for all.

CONCLUSIONS

Cuba's extensive international experience supporting public health systems around the globe, combined with multistakeholder

collaborations, has shown that addressing the human rights health crisis requires joint work by different actors, with differing strengths and knowledge, including the people and communities most in need. Identifying problems, innovating solutions and evolving strategies to bolster effectiveness and sustainability is part of the equation. But governments and international aid agencies must demonstrate an unwavering commitment to primary care access and UHC—including apportioning sufficient funds for the effort and putting public health before politics. Reinforcing health systems using a mix of qualified, experienced foreign health service providers and local health professionals, combined with capacity-building of the latter to support sustainability, has been shown to be effective in increasing access to health services, ameliorating spatial inequalities and segmentation, and improving health outcomes. Cuba's experience over six decades of international cooperation argues for such a multilateral, multidisciplinary evidence-based approach, keeping people—the most vulnerable especially—at the heart of the matter. 

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Editors' note: Senior Editor Conner Gorry is the only foreign correspondent to report from inside the Henry Reeve Emergency Medical Contingent, traveling and living with the teams in Pakistan and Haiti.

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