Vaccines and Public Trust: Containing COVID-19 in Cuba

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As 2021 drew to a close, Cuba struggled to contain the highly transmissible omicron variant of SARS-CoV-2, braced for a new wave of infections and kept a close eye on other variants of concern popping up around the world—a common experience to countries everywhere as we head into the second year of the pandemic. In Cuba, however, there is one marked difference making all the difference: by early January, 87% of the population was fully vaccinated using a three-dose schedule of vaccines developed and produced on the island. [1] This massive vaccination campaign is complemented by a rapid booster rollout—also using Cuban vaccines—that began in December 2021 and was ongoing as we finalized this issue.

The island nation was able to achieve the third highest COVID-19 vaccination rate in the world[2] after decades of scientific investment, research, discovery and innovation; regulatory oversight and compliance; professional training; and increased production capacity. But a vaccine is only as effective as the health system charged with administering it—in a safe and timely manner, to as many people as possible. Here too, Cuba has decades of experience, including a national pediatric immunization program where 98% of children under 5 are immunized against 13 diseases,[3] an annual polio vaccination campaign (both launched in 1962 and uninterrupted since) and campaigns to contain epidemics such as H1N1.

When the first COVID-19 cases were detected on the island in March 2020, Cuba harnessed this vaccine experience, making a hard tack towards developing its own vaccines. Two of the main protagonists in the country's biotechnology development, the Finlay Vaccine Institute (IFV) and the Genetic Engineering and Biotechnology Center (CIGB), both with several groundbreaking preventive and therapeutic vaccines in their portfolios, led the search for a vaccine. Today, Cuba has three vaccines authorized for emergency use—Soberana 02 and Soberana Plus developed by IFV, and Abdala, developed by CIGB. Schedules with these vaccines have demonstrated more than 90% efficacy in clinical trials,[4] and after regulatory approval for emergency use, became the backbone of Cuban COVID-19 vaccination efforts. A fourth vaccine, Mambisa (CIGB), administered nasally, and a fifth, Soberana 01 (IFV) are still in clinical trials.

For this installment in ***MEDICC Review's*** series spotlighting leading women of Cuban science, we sat down with Dr Verena Muzio, Director of Clinical Research at CIGB. A pioneer of Cuba's biotechnology sector, she is an immunologist with a doctorate in biological sciences. Her professional trajectory began researching the genetically engineered hepatitis B surface antigen that led to the development of Cuba's recombinant hepatitis B vaccine in 1989. The same technological platform used in this vaccine was used to develop CIGB's Abdala vaccine against SARS-CoV-2—part of the reason Cuba was able to secure a vaccine so quickly. A phase 3 clinical trial determined a 92.28% efficacy rate for Abdala, with results to appear in forthcoming publications.

MEDICC Review: **The recombinant hepatitis B vaccine, Heberbiovac-HB, developed over 30 years ago by CIGB, foreshadowed the potential of Cuba's biotechnology sector. Can you tell us about that experience?**

Verena Muzio: Developing the hepatitis B vaccine was a huge challenge, involving a lengthy clinical development and production process which began in 1986 under the direction of Dr Luis Herrera, founder and former research director of CIGB [interviewed by *MEDICC Review*, April 2020, Vol 22, No 2, Eds]. This was our first foray into developing a recombinant vaccine—using genetic engineering technology to obtain the surface antigen used in the final product. It turned out to be a watershed event.

With any vaccine, you first need a safe, effective product. Just as important, however, is having an appropriate vaccine strategy for administering it to the population. Our strategy with Heberbiovac-HB was to vaccinate our entire population under the age of 20 against hepatitis B by the year 2000. After phase 1−3 trials demonstrated its safety and immunogenicity and following approval from our national

regulatory authority, Heberbiovac-HB was incorporated into our national pediatric immunization program in 1992; every child born since has been vaccinated against hepatitis B within 24 hours of birth using our vaccine. And since 2000, no Cuban child under 5 has contracted acute hepatitis B. I've always said we can develop the vaccines, but it's our health professionals who implement the strategy, who make it possible to protect our population. And this is true in any health system, not just ours.

MEDICC Review: **Heberbiovac-HB was not only the first recombinant vaccine developed wholly in Cuba, it was also the first to receive WHO prequalification, correct?**

Verena Muzio: That's right. In 2001, Heberbiovac-HB was the first Cuban vaccine and the first from Latin America to receive WHO prequalification. It's a rigorous evaluation process and every prequalified vaccine is submitted to periodic review—it's not a designation that's authorized once and then retains this status. In 2009, another CIGB product, Quimi-Hib, our *Haemophilus influenzae* type B (Hib) vaccines, also received WHO pre-qualification.

MEDICC Review: **Can you talk about how these early experiences informed the development of CIGB's COVID-19 vaccines, specifically Abdala, used to vaccinate the majority of the Cuban adult population?**

Verena Muzio: Our work on the COVID-19 vaccines benefited directly from the evidence and experience accrued developing, producing and administering the hepatitis B vaccine through all stages: research, development, pre-clinical, and clinical, as well as production and management processes and quality control. It also served as a fundamental learning experience for many of those working at CIGB today. In fact, many of us who developed Heberbiovac-HB are also working in one way or another on the COVID-19 vaccines—there's a continuum and link between the work we did then and the work we're doing now.

One link is related to the science: there were several strategies and projects under consideration simultaneously when we started looking for a COVID-19 vaccine in early 2020. In the end, what showed the most promise was a recombinant antigen vaccine—in this case the optimal antigen was the SARS-CoV-2 receptor-binding domain, RBD, protein—produced in the yeast *Pichia pastoris*. This is the same technology and production platform used in Heberbiovac-HB, providing an important advantage.

Since we decided to pursue a recombinant vaccine using the same surface antigen component used in our hepatitis B vaccine, we knew from the start that our clinical strategy would be based on administering three doses. At that time, other vaccine developers around the world using different technology platforms were emphasizing one-dose strategies, that a 'one and done' approach would be sufficient. But our experience with recombinant proteins told us that a three-dose strategy would be best. The immunization schedule could vary, but we knew it would take three doses.

Obviously, evidence accumulated during the laboratory, pre-clinical and clinical stages isn't sufficient to make a definitive determination about immunization schedules. Nevertheless, 30 years of clinical evidence applying our hepatitis B vaccine provided a road map. Within seven months of administering the first dose of Abdala in December 2020, we amassed the clinical efficacy data and met the other requirements needed to request emergency use authorization (EUA) from our national regulatory authority, the Center for Quality Control of Medicines, Equipment and Medical Devices (CECMED). This was granted in July 2021 and the vaccination of our adult population began.

MEDICC Review: **Given the urgency and severity of this global pandemic, some have questioned Cuba's decision to develop its own vaccines for COVID-19. Can you speak to this?**

Verena Muzio: We knew it would be very difficult for us to procure a vaccine from abroad—the prices would be out of reach, the demand would be enormous and we are Cuba, which is an issue for some—plus we knew we had the technological and scientific capabilities to make our own. And we did. Today we have five COVID-19 vaccines developed and produced in Cuba. Three of them have received EUA.

At the beginning some people asked: why so many vaccines? But our experience has shown that it's beneficial to have options. This increases production capabilities and provides alternatives for our immunization strategy—by combining vaccines, for example. I think this is another important element and we're exploring it further: we helped develop the vaccination strategy for our pediatric population together with IFV and CECMED, and are evaluating the feasibility of administering IFV's Soberana 02 with Abdala in a heterologous schedule for Cuban children, and making it available to other countries.

MEDICC Review: **Cuban and other vaccines helping control the pandemic were developed very quickly—in a year, as opposed to the typical five-to-ten years. In Cuba's case, what made this possible?**

Verena Muzio: First, our government and health authorities took early, coordinated action. In January 2020, Cuba convened an Innovation Committee of all research institutes, CECMED, manufacturers and other institutions to prioritize products and design strategies to control the pandemic. This Committee issued the first version of our National COVID-19 Prevention & Control Plan and we set out to forge solutions—developing a Cuban vaccine against COVID-19 paramount among them.

The urgency and severity of this health problem, with so many cases and deaths, not only in Cuba but around the world, presented a new challenge to develop a safe, effective vaccine in record time while adhering to rigorous scientific practices. Given these conditions, our regulatory authority, like others around the world, established mechanisms to shorten the vaccine timeline—faster revision times, seamless trials and more—to be able to address COVID-19 quickly.

Another factor is the close and fluid working relationship CIGB has maintained with CECMED—from pre-clinical to post-clinical processes—for all CIGB products introduced into our health system [see *MEDICC Review* interview with CECMED's Director Olga Lidia Jacobo-Casanueva, July-October 2021, Vol 23, No 3−4, —Eds.] This spans decades and predates the current pandemic of course, but has been advantageous given the urgency of the current health problem.

Last, both CIGB and IFV, developers of our COVID-19 vaccines, have manufactured vaccines for decades using the same technology platforms. There is public trust in our vaccines and immunization programs. Once a vaccine is approved for use and released to immunize our population, people know they are not being used as guinea pigs, they trust the vaccines and the science. This makes for a smooth vaccine rollout.

MEDICC Review: **Cuba's vaccines were developed quickly, but still have not received WHO emergency use listing or prequalification—a process CIGB knows intimately. Is this on the horizon?**

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Verena Muzio: The steps required of all vaccine manufacturers to obtain WHO prequalification are well established and begin with a formal request, which we submitted at the end of 2021. This request is for WHO emergency use listing (EUL), a designation used during global health emergencies; once we receive that, we can proceed to prequalification. Both EUL and prequalification typically take a long time. But just like national regulatory authorities have established mechanisms for shortening the timeline from research and development to EUA, WHO has also made their process more efficient, instituting rolling reviews that evaluate processes in stages, for example.

People say: since you have the clinical data and the vaccine demonstrates efficacy, what's holding things up? But WHO doesn't only evaluate vaccine clinical studies; they also inspect and evaluate production facilities, each step of lot production, quality control, warehousing, cold chain, adverse events, everything. And not only within the manufacturing institution but also the regulatory authority in their six basic functions—medicine registration, lot-by-lot vaccine release, inspections, clinical trial authorizations, laboratory access and post-marketing surveillance [CECMED is a WHO Level 4 National Regulatory Authority of Reference, —Eds.] It is very comprehensive and complex.

Throughout the pandemic, we also have maintained a close working relationship with PAHO about our progress, data and milestones concerning our COVID vaccines. In short, our formal request is with WHO now and we are preparing all the other materials required for the evaluation including the vaccine prequalification dossier, production and clinical data, etc.

MEDICC Review: **Is WHO prequalification necessary for Cuba to sell and/or donate your vaccines to other countries?**

Verena Muzio: WHO prequalification is not required for a country to authorize use of an imported vaccine—that is the role of each country's national regulatory authority. They conduct the established evaluations and analysis required to approve use of a vaccine for their population. We recognize the importance of WHO prequalification, it's always good to have and we are pursuing that, as well as exporting to other countries.

MEDICC Review: **Is Cuba exporting its vaccines now? What is the strategy for sales abroad?**

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Verena Muzio: As you know, Cuba has a long history of global medical solidarity, not only in terms of health professionals but also regarding its pharmaceutical products, which have been authorized for use in dozens of countries. This is why we have a combination approach of vaccine donation and sales; between donations and sales, 17 million Abdala doses are now available overseas. This is in addition to the 40 million doses delivered to Cuba's Ministry of Public Health (MINSAP)—including the booster shots now being administered across the country.

Abdala has received EUA in various countries of the region including Venezuela, Nicaragua and Mexico, and elsewhere like Vietnam. This involves a rigorous evaluation process by each country's regulatory authority, reviewing the data, production facilities and more before the vaccines can be purchased or administered.

We are pursuing this process in various countries. Our approach is based on helping address health problems in these nations and what they need to do that, not to profit from illness.

MEDICC Review: **CIGB has had to scale up capacity during the pandemic. What role does the new CIGB Mariel Biotechnology Industrial Complex play?**

Verena Muzio: This mega-project within the Mariel Special Development Zone was inaugurated in November, 2021, but predates COVID-19, obviously. It was conceived several years ago with the attendant design, investment, construction, and equipment and technology acquisition, plus the training of professionals such a complex project implies. Given that CIGB produces pharmaceutical inputs for its own products and other scientific institutions and the number of products in our pipeline and portfolios is growing, especially oncological treatments, it became necessary to have another manufacturing facility to scale up capacity.

What's notable about the CIGB-Mariel project is that it brings together decades of biotech experience and knowledge under one roof, while integrating the latest and most advanced technology and equipment. It's a gold standard installation designed to produce what we need first in our health system and then, for export. It's fully financed by Cuba and will include everything: production, quality control, clinical trial design and analysis, etc.

It's important to note that this project is fully in line with our public health and biotechnology approach in that it is designed first and foremost to address health problems facing our population. No Cuban institution produces pharmaceuticals strictly for export—our commitment is to improve population health in Cuba, using our products in our health system. And the same applies to the facility at Mariel.

MEDICC Review: **CIGB has another vaccine candidate, Mambisa, administered intranasally. How is this research progressing?**

Verena Muzio: One of our early strategies was to develop an intranasal COVID-19 vaccine; CIGB already has a therapeutic hepatitis B vaccine in its portfolio, HeberNasvac, administered nasally [see *MEDICC Review*, January 2021, Vol 23, No 1, —Eds.] Mambisa is a new formulation combining the RBD protein used in Abdala with the recombinant antigen used in HeberNasvac—the latter contains properties that serve as an adjuvant in the nasal mucous membranes. Considering the properties of this vaccine, we knew it was not going to be our candidate for a massive vaccination campaign (for this we had Abdala), but we decided it could be developed as a next-generation vaccine and for different uses.

One of the challenges of a nasal vaccine is evaluating what delivery mechanism is most effective: drops or aerosol, if aerosol, which one. We also have to consider how practical and financially feasible it would be to scale up production. Nevertheless, a booster administered using a simple spray in the nose is a very attractive alternative—some people are afraid of needles and may avoid injections as a result. Offering Mambisa boosters to visitors to Cuba who request them could be another possibility with this easy-to-administer vaccine.

Right now, we're conducting phase 2 clinical trials in convalescent adults, and have just concluded a randomized multicenter phase 2 trial that evaluates Mambisa as a booster dose for the general population. We have preliminary data from this trial on how a Mambisa booster affects viral transmission. The main goal of COVID-19 vaccines is to protect people from developing severe forms of the disease. Nevertheless, cutting the transmission chain would be incredibly important—particularly with more transmissible variants like omicron—and we are looking at both possible effects in the case of Mambisa.

MEDICC Review: **Returning to Abdala, there are other studies being conducted with vulnerable populations including pregnant women. Can you elaborate?**

Verena Muzio: Pregnant women and other vulnerable populations are typically not included in the study universe of clinical trials for a new vaccine or therapeutic treatment due to their higher risk status. However, once you proceed to phase 3 trials, involving thousands of volunteers—48,000 people in the case of Abdala—some of them will become pregnant after being inoculated. Given this reality, we designed an evaluation strategy incorporating long-term follow-up of those volunteers who became pregnant after being vaccinated during clinical trials to analyze the safety data in this population.

Given the unfortunate reality that a number of pregnant women infected with COVID-19 have died in Cuba, the strategy to begin vaccinating this high-risk group was evaluated by MINSAP authorities, a panel of OBGYNs and directors of the National Maternal-Child Health Program (PAMI), CECMED and others. Once we had the pre-clinical and clinical data plus other information including adverse events from phase 3 trials, we applied for EUA from CECMED to being vaccinating pregnant women, which we received. On July 29, 2021, we began vaccinating this vulnerable population with Abdala. This helped reduce infections in this vulnerable group and we launched a post-authorization observational study in late 2021 to assess safety data in those pregnant women vaccinated during different trimesters of their pregnancies and the immunological status of their newborns.

This wasn't the first time we implemented a strategy to vaccinate pregnant women during a pandemic: in 2011, Cuba vaccinated pregnant women against H1N1 using an imported vaccine. The approval for use in our health system of this vaccine—like any imported pharmaceutical product—was issued by CECMED. Pregnant women were hit hard by this virus and the vaccine campaign yielded positive results.

MEDICC Review: **How about infants and children? Cuba is vaccinating its pediatric population, as well.**

Verena Muzio: Yes. We are vaccinating children as young as two, primarily with IFV's Soberana vaccines—results from the pediatric vaccination campaign are being prepared for publication. Additionally, we are getting ready to launch a series of clinical evaluations of children under two. Right now, this segment of the population is not vaccinated. Although we are studying the immunological protection passed from vaccinated mothers to their newborns, what happens to those babies when they approach their first birthday? It's possible that the vertical protection from the mother has diminished and these babies can be susceptible to infection—not necessarily severe forms, but they may become infected nonetheless. This study will begin by March 2022 and is based, again, on years of experience immunizing children under 2 with Heberbiovac HB, Quimi-Vio (a heptavalent pneumococcal conjugate vaccine against bacterial pneumonia and meningitis) and other pediatric vaccines produced in Cuba. This accumulated experience has informed clinical trial design and implementation for the current study.

MEDICC Review: **Developing these vaccines, under such stressful circumstances, is hard to grasp. What was the most difficult moment for you during this pandemic?**

Verena Muzio: The worst, I think, was when the virus spread across the country in the summer of 2021: we had this wave of infections and deaths and it was very hard. I personally didn't lose any family members but my brother and nephew were infected, in isolation centers and we were worried about their health. Some co-workers and their families were also infected, and I was concerned for them. The country was facing a shortage of medicines and at one point there was virtually no oxygen—it created a lot of pressure points at once. This, together with the urgency of our work, the intense pace and circumstances under which we were working to produce results—it was a lot.

MEDICC Review: **And the happiest moment for you?**

Verena Muzio: Definitely one of the happiest moments was in June 2021, when the team responsible for analyzing efficacy results for Abdala crunched the data from the first cutoff date. We couldn't believe how high the efficacy was! 'This can't be. Re-analyze the data, it's not possible' we said. We ran the data again, followed by data analysis from the second cutoff date, and then again when the phase 3 trial concluded and there it was: 92.28% efficacy. When we were sure and delivered these final results, there were tears of joy, it was very emotional.

In a broader sense, one of the most hopeful and positive results of working on these vaccines for me personally, was traveling across the country and working side-by-side with colleagues in Santiago de Cuba, Guantánamo and elsewhere during the clinical trials. I met so many good people. This country is full of hard working, professional people—statistical analysts, database entry clerks, regular folks, young people, it's not just us scientists—who have sacrificed and thrown themselves into the task of helping Cuba emerge from the pandemic. The potential feels limitless.

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