Cuban COVID-19 Vaccines for Children: Rinaldo Puga MD MS

Principal Investigator, Pediatric Clinical Trials for Soberana 02 and Soberana Plus

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Cuba's decision in September 2021 to launch a massive vaccination campaign against COVID-19 for children as young as two years old turned heads around the world—of clinicians, immunologists, public health experts, governments and regulatory authorities alike. Since then—and just as pediatric COVID-19 hospitalizations reached record numbers globally—some two million Cuban children and adolescents have received the Cuban Soberana vaccines (1.7 million, or 81.3% of that population through December 16, 2021).[1]

Why did Cuban health authorities decide to vaccinate children? What clinical trials provided the evidence for such a course of action, especially for the youngest? And what have been the results thus far?

To answer these and other questions, ***MEDICC Review*** spoke with Dr Rinaldo Puga, principal investigator for the completed phase 1/2 clinical trials of the Finlay Vaccine Institute's Soberana 02 and Soberana Plus vaccines in pediatric ages. Dr Puga's 30 years as a practicing pediatrician have been accompanied by teaching and research, the latter earning him awards from the Cuban Academy of Sciences, among others. He is currently chief of pediatrics and chair of the Scientific Council at the Cira García Clinic in Havana, which granted him leave to lead the pediatric vaccine trials.

MEDICC Review: **Cuba is the first country to vaccinate children as young as two years old for COVID-19. As a pediatrician, what circumstances led to this decision and does it make sense to you?**

Rinaldo Puga: At the start of the pandemic, we had relatively few pediatric cases: 1308 patients in 2020. But later, as happened in the rest of the world and particularly as new variants appeared, household transmission accelerated, accounting for a notable increase of COVID-19 in younger ages. Thus, over 2020–2021, pediatric cases totaled 176,708, with 11,692 of these in infants under one year old. We have had a total of 18 deaths among children and adolescents as a result of COVID-19, associated with other conditions that worsened their prognosis, representing a survival rate of 99.9% in the pediatric age group. So right now, we have over 176,000 convalescent youngsters, who can also be vaccinated.

Of course, the main goals of vaccinating youngsters are to prevent a greater proportion of severe forms of the disease and resulting deaths from COVID-19 by protecting them, and at the same time to achieve added protection for other vulnerable people in their social circles, such as family members. Thus, we can reduce incidence of infection in the community and decrease transmission. In turn, this permits reopening schools under much safer conditions for children and teens.

MEDICC Review**: You've been the principal investigator for the pediatric clinical trials of Soberana 02 and Soberana Plus, both vaccines approved for emergency use in children and adolescents by Cuba's regulatory authority. All Cuban COVID-19 vaccines and vaccine candidates have been described as relying on the same 'classic biotechnology platforms' already in use for other Cuban vaccines. Is this the case?**

Rinaldo Puga: Yes. The other Cuban vaccines and vaccine candidates that have shared the same platforms are those for *Haemophilus influenzae* type b (in the case of Soberana 02), for meningococcal disease serogroups B and C (Soberana 01) and hepatitis B (used in developing the Abdala COVID-19 vaccine).

Cuba's was the first synthetic conjugate polysaccharide vaccine for *Haemophilus influenzae* type b and was introduced in the National Immunization Program in 2004. More than 40 million doses have been administered since then. The Cuban meningitis vaccine has also been applied domestically and in other countries since the late 1980s, totaling over 30 million doses.

Soberana 01 is the recombinant SARS-CoV-2 receptor binding domain (RBD) dimer added to *Neisseria meningitidis,* external membrane vesicles, potentiating innate immunity. Soberana 02 antigen is the recombinant SARS-CoV-2 RBD covalently linked

to tetanus toxoid as carrier protein, potentiating T-cell response and immunological memory. Soberana Plus is also an RBD dimer. All have aluminum hydroxide as adjuvant. Soberana Plus has proved very effective as a booster in persons vaccinated with other Soberanas and in COVID-19 convalescents with a natural immunity against the virus. These vaccines and the other Cuban vaccine, Abdala, are based on protein subunits, the antigen being a recombinant copy of the viral protein; due to the absence of viral and genetic material, they are very safe. Each of them can be used as a booster for persons vaccinated with RNA- and viral-vector vaccines, among others. In short, these vaccines are highly safe and efficacious.

Other protein subunit vaccines in development include:
- NVX CoV 2373 (Novavax, USA)
- SF-UZ Vac 2001 (Zifivax, Anhui Zhifei, China)
- Sanofi-GSK COVID 19 (France-UK)
- SCB 2019 (Clover Bioph, GSK Dynavax, China-UK-USA)
- COVAX 19 (Australia-Iran)

MEDICC Review: **What can you tell us about the clinical trials for Soberana 02 and Soberana Plus in pediatric age groups?**

Rinaldo Puga: We carried out trials in two pediatric groups: the first trials included children and adolescents who had never been infected with the virus, and a later group comprised those who were convalescent.

The first study involving healthy children and adolescents (phase 1/2) used a heterologous vaccine schedule (the same used in adults): two doses of Soberana 02, 28 days apart, combined with one dose of Soberana Plus on day 56. This was an open-label, adaptive, multicenter and sequential trial. After the safety results were confirmed for 12–18 year-olds, we proceeded with the 3–11 age group. It was an open trial, since we didn't use a placebo. The study included the Juan Manuel Márquez Pediatric University Hospital and the 5 de Septiembre and Carlos Juan Finlay community-based polyclinics in Havana's Playa and Marianao municipalities, respectively. We initiated the trial on June 14, 2021 (See table. —Eds.).

For the phase 1/2 clinical trial in convalescent youngsters, one dose of Soberana Plus was used. This was an open, adaptive study and began in Havana on October 5, 2021, with participants at least 8 weeks post-COVID. A total of 520 children and teens were involved, initially in Havana (at the Juan Manuel Márquez Pediatric University Hospital) and later also at the Paquito González Cueto Pediatric University Hospital in Cienfuegos province. Phase 1 included 40 participants: 20 aged 12 to 18 years, and 20 aged 2 to 11. Phase 2 included an additional 480 participants in the same age ranges.

A phase 3 trial was not organized, given the negative ethical implications of using a placebo for this age group. In order to grant emergency use authorization for children and adolescents, the regulatory authority considered the excellent results obtained in adults with the same heterologous schedule, as well as the phase 1/2 results in the pediatric population.

MEDICC Review: **Did the pediatric trials differ from those in adults?**

Rinaldo Puga: The rigor required for the clinical research, study ethics compliance and approval levels are virtually the same for trials in the adult and pediatric populations. And the formulations and vaccine schedules were also the same in this case (a heterologous schedule of two doses of Soberana 02 followed by one dose of Soberana Plus).

But there were differences regarding consent: parents gave written informed consent, but adolescents were also asked to approve their own enrollment in the study. There were also differences regarding the selection criteria, post-vaccination observation time (a full one hour) and active follow-up through periodic checkups.

MEDICC Review: **Did you have difficulties recruiting children and teens for the clinical trials? Were parents resistant or hesitant? We have seen that in other countries.**

Rinaldo Puga: Our experience in Cuba has been just the opposite: we really didn't experience resistance from parents and in fact, the list of volunteers seemed endless. This isn't surprising, since we're talking about a country with over 98% coverage for its vaccines, and of course this applies mainly to childhood vaccinations. So the response to our call for volunteers exceeded our expectations. The recruitment process took place several weeks before the studies began, mainly in the polyclinic health areas I mentioned. The trials were explained, and for children under 12 years old, parents provided consent; older participants recruited provided their own approval as well.

MEDICC Review**: What were the most important results?**

Rinaldo Puga: The results were quite favorable, since more than 90% of the youngsters showed seroconversion after two doses, and 100% after the third dose. Induction of neutralizing antibodies against circulating viral variants was also demonstrated (except omicron, still being studied). There were no serious adverse events related to vaccination.

The Soberana vaccines have proven to be very safe, with quite low reactogenicity, reflected in the fact that adverse events have been local, mild and mainly as expected, not serious or severe. As a result, there has been no need to suspend trials in any of their phases for any age group. These vaccines have also demonstrated very good immunogenicity, evaluated through anti-RBD IgG antibodies, as well as inhibition of RBD–ACE2 receptor interaction, and viral and molecular neutralization tests.

MEDICC Review: **What kinds of adverse events presented?**

Rinaldo Puga: Almost all were those you would expect, and fundamentally local. The most frequent was pain at the injection site, and others expected included local swelling or heat, induration, itching in the injection area and so on. Systemic events with low frequency included general discomfort, fever and headache.

MEDICC Review: **Are heterologous vaccination schedules beneficial then? That is, applying two different vaccines instead of one?**

Rinaldo Puga: Yes, that's been the experience. In our case, the two initial Soberana 02 doses are equivalent, in the best sense of the term, to training a person's immune system to act as if they had already had the disease, and then reinforcing that training

with one dose of Soberana Plus. So, while the two-dose results in children are excellent, since we are facing a mutating virus we opted for a third heterologous dose. This sort of approach is being used a lot now worldwide in booster strategies, and it's an approach we have consolidated with the Soberana vaccines.

MEDICC Review: **You were also principal investigator for studies completed recently of Soberana Plus in COVID-19 convalescent youngsters.**

Rinaldo Puga: Yes, the results after one dose of Soberana Plus have been very good, even better than expected, since at first, we thought convalescent children and adolescents who had been asymptomatic or had mild symptoms might need more than one dose, that is, a full three-dose schedule. But results showed that the anti-RBD IgG titers, percent inhibition of RBD–ACE2 interaction, and the molecular and viral neutralization titers increased significantly compared with the levels after natural infection. Even children who were asymptomatic throughout their illness responded quite favorably to a single dose of Soberana Plus (See table. —Eds.).

MEDICC Review: **The Soberanas aren't the only Cuban COVID-19 vaccines. Abdala has also received emergency use authorization. Are these vaccines similar? Why did vaccinations among children and adolescents begin first with the Soberanas?**

Rinaldo Puga: The Soberanas and Abdala are all protein subunit vaccines, built on different tried-and-true biotech platforms used extensively in Cuba and elsewhere for decades, as I mentioned.

We already had conditions in place for a heterologous pediatric study involving the Soberanas based on earlier results in adults, which meant we could begin the clinical trials with those vaccines first and thus these were the first to obtain emergency use authorization for children and adolescents. So, in September 2021, when Cuba decided to vaccinate this age group, we used the Soberanas, while at the same time Abdala was being used to continue vaccinating the country's adult population.

Later, pediatric trials for Abdala were carried out in Camagüey province, duly registered and approved by the regulatory authority. So now, both the Soberanas and Abdala have received emergency use authorization for the pediatric population.

MEDICC Review: **As principal investigator for the Soberana pediatric clinical trials, how was the rigor of these studies ensured? What processes were in place?**

Rinaldo Puga: From the early stages, a research ethics committee delved deeply into the trial design to review and suggest modifications. Cuba's regulatory authority, the Center for State Control of Medicines, Equipment and Medical Devices (CECMED) received an exhaustive presentation, and periodically supervised the clinical trial. Of course, the studies were listed in the Cuban Registry of Clinical Trials (https://rpcec.sld.cu), and accompanied, reviewed and corrected throughout the process by specialists at the National Clinical Trials Coordinating Center (CENCEC). An external committee on data management carried out their analysis, in our case composed of specialists from the Pedro Kourí Tropical Medicine Institute and the Molecular Immunology Center, among others.

Also participating in the supervision of the entire process were the national Maternal–Child Health Program, the National Pediatrics Expert Group, the Cuban Pediatrics Society, and both the National and Provincial Immunization Groups.

The trials also received extraordinary assistance from the San Miguel del Padrón Pediatric Teaching Hospital in Havana, and the San Alejandro isolation center that acted as an extension of the Juan Manuel Márquez Pediatric University Hospital…and from others such as the CIMEQ Hospital, the Immunoassay Center and the Civil Defense laboratories in San José de las Lajas municipality.

Mobilization of resources was key to ensure the trials' quality: vaccine refrigeration and transportation, ambulances at all the community vaccination sites in case of a serious adverse event, guaranteeing safe, non-toxic meals for all participants (provided by Cuba Catering) …a whole range of services.

MEDICC Review: **What were the main challenges during preparation, the trials themselves and data analysis?**

Rinaldo Puga: The main challenge was to create the necessary infrastructure and optimal conditions to ensure the correct sequence of activities for everyone involved: workshops for healthcare staff on good clinical practices, certification of vaccination sites and of the nursing staff applying the vaccines, seminars and instruction workshops for parents, and so forth. Plus, the detailed attention to ensure correct data processing, including sampling, digitalization and statistical analysis of results.

MEDICC Review: **You also serve as chief of pediatrics at the Cira García Clinic, where international patients are seen. Have children from other countries received the Cuban COVID-19 vaccines?**

Rinaldo Puga: Yes, children of permanent residents, or whose parents are here in Cuba with various foreign companies or international agencies, children of diplomats and some who have traveled from their home countries through Cuban Medical Services expressly for the vaccines. In the case of such visitors, Abdala is used since its schedule is shorter. For those living in Cuba and for convalescent children, we are using the Soberanas. As you know, all three vaccines have emergency use authorization for the pediatric population from CECMED.

MEDICC Review: **Globally, a growing consensus is emerging about the need to vaccinate the pediatric population against COVID-19. Will Cuba be sharing its results in this age group with WHO to apply for emergency use listing for use of these vaccines in children and adolescents?**

Rinaldo Puga: Yes, results of the pediatric Soberana clinical trials will be included in the dossier provided to WHO for emergency use listing. Not all COVID-19 vaccines have such a formidable safety record in pediatrics as these protein subunit vaccines, and thus our clinical trial results are quite important, coupled with those evaluating the impact of vaccination in Cuba's pediatric population.

We are not the first country to apply COVID-19 vaccines in children, but we are the first to carry out a massive, nationwide vaccination campaign for our children and teens. And we are the first and still

COMPLETED CLINICAL TRIALS FOR SOBERANA COVID-19 VACCINES IN THE PEDIATRIC POPULATION (as of January, 2022)

	CLINICAL STUDY DESCRIPTION	SELECTION CRITERIA, CLINICAL SITES	VACCINATION SCHEDULE & DOSES	GENERAL CONCLUSIONS	EMERGENCY USE AUTHORIZATION
SOBERANA PEDIATRIA VACCINES: FINLAY-FR- 2 (SOBERANA 02) and FINLAY-FR-1A (SOBERANA PLUS) REGISTRATION IN PRIMARY REGISTRY: June 10, 2021 ISSUING AUTHORITY-SPONSOR: Finlay Vaccine Institute (IFV) PRINCIPAL INVESTIGATOR: Rinaldo Puga MD MS	**Study type:** Interventional **Purpose:** Prevention **Study design:** Single group **Phase:** 1/2 **Target sample size:** 350 Phase 1/2 study, sequential during phase 1, open-label, adaptive and multicenter to evaluate the safety, reactogenicity and immunogenicity of a heterologous two-dose schedule of SARS-CoV-2 prophylactic vaccine FINLAY-FR- 2 and one dose of FINLAY-FR-1A, in Cuban children and adolescents.	**Population type:** Children/Adolescents **Sex:** M/F **Minimum age:** 3 years **Maximum age:** 18 years **Participant type:** Healthy volunteers **Clinical sites:** Juan Manuel Marquez Márquez Pediatric University Hospital, Havana 5 de Septiembre Polyclinic, Playa Municipality, Havana Carlos J. Finlay Polyclinic, Marianao Municipality, Havana	FINLAY-FR-2: 25 µg of RBD-TT, by intramuscular route, 0.5 mL, in scheme 0–28 days. FINLAY-FR-1A: 50 µg of d-RBD + Aluminum hydroxide gel, by intramuscular route, 0.5 mL as dose booster 56 days	The FINLAY-FR-2 vaccine is well tolerated following 2-dose schedule in children and adolescents (3–18 years). There were no serious or severe adverse events following immunization. The safety profile is similar to that for young adult subgroup (19–29 years) in phase 1/2 study. Immune response is >50% from day 14 post-second dose in phase 1/2 for 3–18 year-olds, and >90% of anti-RBD IgG seroconversion post-second dose. All immunological variables had similar results as those in young adults (19–29 yrs) in phase 2 trial, and superior to those in the 19–80 years population, and significantly superior to those in the Cuban convalescent pediatric COVID-19 panel. As of September 6, 2021, results for the third dose (FINLAY-FR-1A) became available for the adolescent subgroup (12–18 years). After this dose, seroconversion was 100%, with a significant increase in IgG titers, and molecular virus neutralization.	September 3, 2021 Note: Children 2–3 years of age were included in the authorization based on results of the study and the clinical-epidemiological arguments endorsed by the National Pediatrics Expert Group.
SOBERANA PLUS PEDIATRIA VACCINE: FINLAY-FR-1A (SOBERANA PLUS) REGISTRATION IN PRIMARY REGISTRY: September 28, 2021 ISSUING AUTHORITY-SPONSOR: Finlay Vaccine Institute (IFV) PRINCIPAL INVESTIGATOR: Rinaldo Puga MD MS	**Study type:** Interventional **Purpose:** Prevention **Study design:** Single group **Phase**: 1/2 **Target sample size:** 520 Phase 1/2, open-label, adaptive study to evaluate the safety, reactogenicity and immunogenicity of the prophylactic vaccine candidate FINLAY-FR-1A against SARS-CoV-2 in COVID-19 pediatric-age convalescents.	**Population type:** Children/Adolescents **Sex:** M/F **Minimum age:** 2 years **Maximum age:** 18 years **Participant type:** Healthy volunteers (recovered from COVID-19) **Clinical sites:** Juan Manuel Márquez Pediatric University, Havana Paquito González Cueto Pediatric University Hospital, Cienfuegos	One dose of the prophylactic vaccine candidate FINLAY-FR-1A a minimum of two months after medical discharge. **Dosage:** 50 µg of RBD + adjuvant, 0.5 mL by intramuscular route.	The study demonstrated that a single dose of the vaccine is safe, and provided indications of immunological benefits against possible risk of reinfection by SARS-CoV-2.	December 7, 2021 Emergency use authorization for COVID-19 convalescent pediatric patients (from 2 years and 1 day through 18 years), after at least 2 months of hospital or home-hospital release.

Sources: CENCEC, CECMED, Finlay Vaccine Institute blog (https://www.finlay.edu.cu/blog/resumen-de-los-resultados-de-ensayo-clinico-soberana-pediatria/)

today only country to have vaccinated the pediatric population as young as 2 years old, and through age 18. We have also vaccinated convalescent children and adolescents in the same age range.

MEDICC Review: **In 2021, COVID-19 took its toll in every aspect of Cuban life, and in particular in the Maternal–Child Health Program and infant mortality rates. How many deaths have occurred in pediatric ages from this disease? What are your hopes for the future, and in particular for under-five mortality?**

Rinaldo Puga: Certainly the pandemic has created a more complex situation in the country, for the population as a whole and for the health system itself. Since the first pediatric case was diagnosed on March 21, 2020, as I mentioned, 18 children and adolescents have died from COVID-19 in Cuba, not all of them infants, of course, for an overall survival rate of 99.9%.

Nonetheless, the increase in infant mortality from 4.9 per 1000 live births in 2019 to 7.6 in 2021 has multiple causes, only some of which may be directly or indirectly related to COVID-19. Low birth weight and prematurity have heavily influenced this change, according to initial assessments by National Maternal–Child Health Program experts.

With respect to under-five mortality, our hope is the same as for all Cuban children and adolescents: that the introduction of our vaccines will continue to improve the indicators by reducing progression to severe forms of the disease or death.

We can't be 100% optimistic, since we know that vaccines alone cannot solve the problem. On the contrary: if we don't comply with classic public health measures such as physical distancing, handwashing and sanitizers, as well as masking, then the situation could become very tense.

MEDICC Review: **Other reflections on your experience? Future studies?**

Rinaldo Puga: I'm very grateful for the generous support I've received throughout from my director at the Cira García Clinic and my colleagues, in order to dedicate myself full-time to the Soberana pediatric studies, and am grateful to the Finlay Vaccine Institute for the confidence they placed in me.

We're generating further research to evaluate the effectiveness of the vaccines in the pediatric population, measuring the B- and T-cell responses, duration of the immune response over time, the overall impact of the vaccination campaign, the need (or not) to modify vaccine schedules, given the appearance of more highly transmissible variants of concern such as omicron, to prevent severe forms of the disease and deaths. In fact, we're obtaining quite interesting results concerning omicron's behavior related to our vaccines that we look forward to sharing publicly.

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