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What you should know about the four Cuban vaccine candidates against COVID-19

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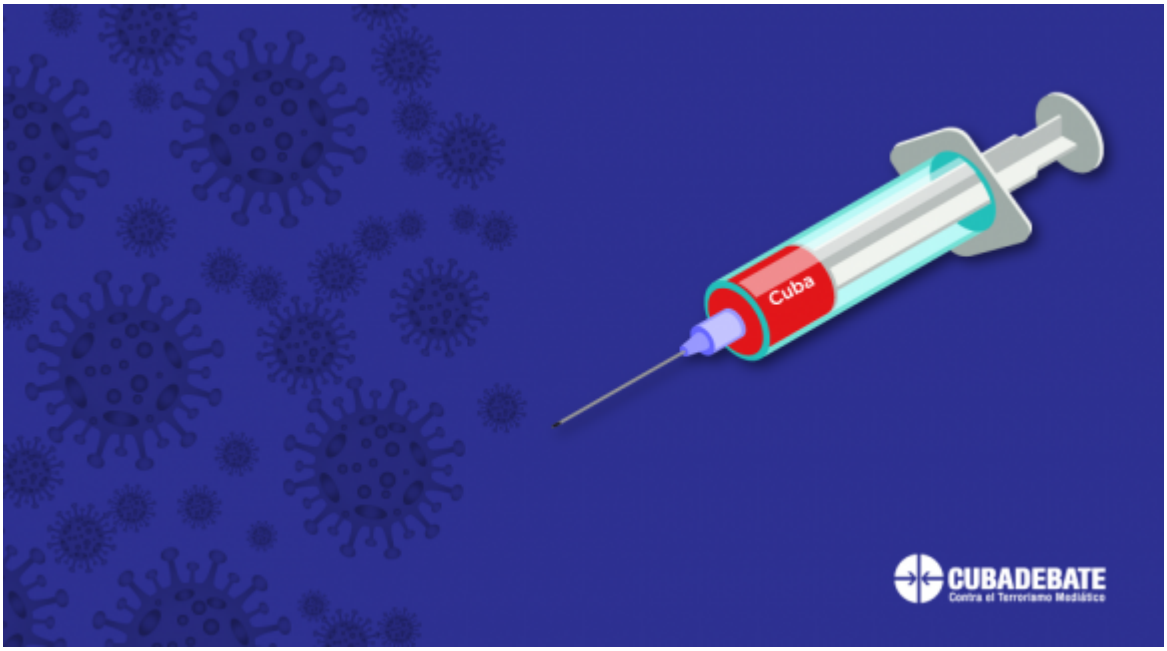

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Cuba currently has four vaccine candidates in clinical trials. What are the characteristics of each one? What results have they produced so far? What steps is the country taking to confront the new strains of the SARS-CoV2 virus? To learn about these issues, the president of BioCubaFarma, the general director of the Center for Genetic Engineering and Biotechnology, the general director of the Finlay Vaccine Institute and the general director of the Center for Molecular Immunology appeared on the Cuban public affairs show, The Round Table, on Thursday, February 4th.

Why is Cuba working on four vaccine candidates?

Why is Cuba working on four vaccine candidates and not concentrating efforts on one, some ask? Dr. Eduardo Martínez Díaz, president of BioCubaFarma, the umbrella group for Cuba's biopharmaceutical research, production and marketing institutions and enterprises, explained that ever since the epidemic emerged in China, they had thought about developing a vaccine. Once it became a pandemic, they accelerated the whole process."

"We made a design that included many more proposals than we are working on today. Based on new information and experiences, initial efforts were discarded and we concentrated on the four vaccine candidates that are in clinical trials in humans now".

The four candidates, Dr. Martínez Díaz specified, use the same type of antigen. "This virus has a protein on its surface, called the spike, and if we look at it in more detail we see the domain that binds to the cell's receptor where the virus is later incorporated."

From the beginning, he continued, it was seen in experiments that when this region is blocked with antibodies, the entry of the virus into the cell is inhibited. Hence, arousing an immune response against that region could then be effective in neutralizing the virus and preventing it from entering the cell.

“Therefore, the focus on working became working with this antigen,” said Dr. Martínez Díaz.

Dr. Martínez Díaz explained that they began by inserting all the genetic information into bacteria, yeast and cells of higher organisms (mammals). “We discarded the bacteria in the tests because the levels of immunity were not adequate. But the versions in yeast and in mammalian cells did awaken a suitable immunological response”.

“As we have the capacity to produce this mammalian protein at the Molecular Immunology Center and that of yeast at the CIGB, we decided to carry on two projects in parallel to obtain this antigen,” he said.

The vaccines differ in formulation. “Those of the Finlay Institute (the Molecular Immunology Center) use this antigen from mammalian cells in several formulations and those of the CIGB in two others.”

He noted that the formulations are part of platforms that had already been used in other vaccines, “with proven effectiveness and safety.”

Dr. Martínez Díaz reported that “the vaccines are working well”, but as we still cannot say that they are effective, “we must continue the studies…. We cannot bet on a single variant and then afterwards the studies do not give the expected results. If that happened, we would have to start over. “

Another reason behind the decision to advance simultaneously in the four projects is that if one of the Finlay vaccines and also the CIGB vaccine were to be effective, “we

would have the capacity to produce a large number of vaccines at the same time."

Dr. Martínez Díaz confirmed that between Finlay and CIGB, there already is a program in place so as to be able to increase vaccine production per month, through to December. Once we have the final results, we will be able to move immediately into production and be able to immunize our entire population, perhaps the first in the world to do so, he affirmed.

In addition, he said, it is possible for one of these variants to be directed, for example, to the phenomenon of patients who have low levels of response. "We also are evaluating the vaccines in terms of different doses. For example, perhaps that of children is 25 mg. For the hepatitis-B vaccine, children take 10 mg and adults 20. And so that we can position them according to age group."

Why does the country not acquire the vaccines already produced by other countries?

Given the current outbreak of the disease in Cuba, many wonder why the country does not acquire any of the vaccines already produced by other countries, at least until the island's projects are completed. Dr. Martínez Díaz stressed that there simple is not enough vaccine. "To date, only 108 million doses have been applied, which means that only slightly more than one percent of the population have been vaccinated. The countries that have vaccinated the most are the United States and China. Only 13 countries have applied more than a million doses of vaccine".

"We see in the news that there are even pre-established contracts that were made previously that are not being fulfilled," added Martínez Díaz. "Of course that rate is going to increase as more doses of vaccines become available," he added, but in the meantime estimates suggest that at the current rate of vaccination it will require 21 years to vaccinate the entire world population.

Martínez Díaz also spoke of the prices at which the vaccines are currently being marketed. “In data that we have read, in public purchases of large quantities the doses vary between 10 and 35 dollars. In other words, to immunize a million people who need two million doses, it takes (multiplied by 10) 20 million dollars. Let’s hope that prices will drop so that the poorest countries have access ”.

Another advantage of the Cuban candidates, Martínez Díaz added, is that they do not require large refrigeration facilities, as does the Pfizer-BioNTech, but temperatures of two to eight degrees that can be found more typically in this industry.

“Another advantage of our vaccines, with respect to others that are currently being produced, is that with the appearance of new variants of the virus, they are already talking about implementing a third dose and there are some of those approved vaccines where it is not possible to apply a third dose. In the case of ours, it is possible to apply successive booster doses.”

Levels of antibodies with sufficently equivalent capacity to those of convalescents

Dr. C. Vicente Vérez Bencomo, general director of the Finlay Vaccine Institute, also appeared on the program. He emphasized first of all the hundreds of Cuban science and health workers who have worked without rest in the face of the challenge of achieving a vaccine against COVID -19, and that they deserve all the recognition.

“In simple terms, so that the population understands, what we are trying to do with our vaccine candidates is to prevent the key that the virus has from opening the ‘lock’ of the cell, that is, prevent it from penetrating”.

Vérez Bencomo used slides to show how the antibodies are expected to be generated, and how these basically act as a “key” that does not allow the “lock” of

the cell to be opened. “The vaccines are best to the extent that they induce more antibodies, and that these are functional,” he said.

Referring to the broad spectrum of convalescentsin the country, ranging from asymptomatic to severe, each with a different immune response, the expert pointed out that people who end the disease may be left with very low antibody titers, while others develop elevated levels of antibody titers.

“What is asked of vaccines is that we at least reach sufficiently capable antibody levels like those of convalescents. That is the challenge, to be as good as the disease by inducing an immune response, at least to the average of the people who have responded best,” he explained.

Where are we with Soberana 01 regarding the challenge of inducing an immune response at adequate levels?

Dr. Vérez Bencomo said that in the case of this vaccine candidate, Soberana 1, five formulations were studied, so as to be able to adjust the amounts of each of the components to see which was able to maximize the immune response.

“The Phase I trial, which included 100 people in total, showed that the vaccine candidate is very safe”

According to the director of the Finlay Vaccine Institute,Vérez Bencomo, they are now concluding a Soberana 01 trial of 60 subjects divided into three groups each inducing antibodies at different levels.

He added that they needed to see how good the vaccine was at producing an immune response in order to select which of the formulations should be advanced. Between 80-90% of people have had production of antibodies against the virus, which is considered a positive result, he explained.

Of the above mentioned three groups, it was decided to administer a third dose to those who had received the lowest dose, affter which virtually all of the people who participated in the trial moved to better levels of immune response. “About 95% of the participants responded with antibodies,” summarized the Vérez Bencomo.

He clarified that it is not only about responding with antibodies, but that these have to have the ability to block the “key” with which the virus infects the cell, a fundamental first element. Hence, he argued, first objective is achieved.

With that third dose, and from the appearance of mutant strains that decrease the neutralizing capacity of the serum, the need to explore further before moving to phase II arose, that is, what happened with the ability to block the “key”, for which a trial was developed.

This showed, he said, that “after the second dose there is a significant percent of people who inhibit this key well, but after the third this number is higher.”

Such criteria allow us to move to Phase II-III, said the expert. “Once we completed the study, it was decided to give all the participants a third dose, to see in each group which one responded better after this third dose, and from there we would be in a better position to move on to phase II-III clinical trials with that candidate.”

The director general of the Finlay Vaccine Institute reported that this phase II-III should begin in the month of March. “Based on the incidence of the virus that we are having of the virus in the country, it should move to include between 40,000 and 50,000 people,” he commented.

In summary Vérez Bencomo said that Soberana 01 has advanced satisfactorily and is concluding Phase I of clinical trials with very positive results. “We have more than one formula that works very well and therefore we have to make the decision of whether to move with one or more formulas to the next phase in March.”

Why is Sovereign 02 going faster?

Regarding Soberana 02, although it started Phase I of clinical trials later than Soberana 01, it advanced faster, said the director general of the Finlay Vaccine Institute.

“Its Phase I trial showed that it is a very safe vaccine, which allowed us to move to phase II.”

“The second important criterion that allowed us to advance to a second phase is that it was found that after a first dose there are already a significant number of people who respond with antibody titers. This is a criterion of success, because while these levels of antibodies are not enough to protect, that there is a response to the first dose is very positive and allows us to move on to a second phase without fully completing the first, “ he explained.

He added that occurring mainly with Soberana 02, more than 70% of the people in the Phase I trial showed a strong specific cellular vaccination response against the virus.

According to Vérez Bencomo, the antibody response, when accompanied by the response of the cells, is much more effective, and it also generates memory.

He commented that Phase II A has already begun with 100 participants in two groups of 50 people, including the population up to 80 years of age whose response was shown to be similar to that of the subjects between 19 and 59 years of age.

He explained that this trial made it possible to confirm safety and decide to go on to Phase II B with 810 participants, of which about 100 are a placebo group. Of the total number of participants, there are already 700 who received the first dose of the vaccine. These studies are being carried out in Havana, at the “19 de abril” polyclinic in Plaza de la Revolución municipality, and at Clinic 1, in La Lisa

municipality.

Soberana 02 demonstrated the ability to induce antibodies, but how much they could inhibit the virus from infecting the cell? "With Soberana 02 the results were positive. However, we decided that in a small group of those who had first been vaccinated with Soberana 02, we would give a third dose of Soberana 01, which is just the antigen. As a result these people moved to the higher levels of the inhibition curve of the key, one of the best responses we have seen."

Having two candidates at the same time made possible the decision to apply the third dose to all the people who participated in the Phase I trial. "We are waiting for the results, and if we confirm those we already had with the first group, then we will request authorization to apply a third dose to all the people who are participating in a Phase II, and we would be in a position to evaluate in a Phase III what happens with a scheme of two or two doses of Soberana 02 plus one of Soberana 01 ".

Vérez Bencomo pointed out that the hope is to start the Phase III study in the month of March in several municipalities of Havana, with a design of 42,600 participants and with a placebo group.

By the month of April, the first million doses of vaccinesadministered should be reached

He reported that production of the Soberana 02 vaccine is already underway. "Today we are making the first batch of more than 100,000 doses of the vaccine, from the antigen obtained from the Center for Molecular Immunology. The scaling of Soberana 01 was also started, in order to first have the doses for the Phase III trial, but obviously the capacity to produce the vaccine must be reflected in its impact on the population."

He spoke of four pillars: the first is the need to have sufficient evidence that the

vaccine works and for this “there is still a group of results that are yet to come in and that can confirm that the levels of functioning of the vaccine are sufficient to go to a phase III.”

The second pillar, he said, is the regulatory authority, which in all countries is in charge of protecting the population. For this, he said, there are guidelines that have been modified in the face of the COVID-19 emergency but that imply certain requirements to which scientists must adhere to in the production of the vaccine.

A third element is that we cannot lose sight of the context in which we find ourselves, where there is a great need to apply the vaccine, and that application should ultimately help us build that efficacy. It cannot be an application that does not show that efficiency.

[Translator’s note: The fourth pillar is not discussed at this point in the article.]

Vérez Bencomo said that by the month of April the first million doses of vaccines must be reached, and that it would be part of a Phase III but also of a controlled application that allows compliance with the aforementioned four pillars.

Vérez Bencomo said that the possibility of extending Phase III trials to other countries was considered and discussed, at this time, unfortunately, the increase in the incidence of cases on the Island has led to conditions favoring a conventional Phase III so as to determine the effectiveness.

How is the trial with Soberana 01 in convalescent patients going?

Vérez Bencomo referred to a Phase I trial led by the Institute of Hematology and Immunology that has been developed with Soberana 01 in convalescent patients, 30 patients with low antibody titers after being infected and at risk of reinfection.

When a first dose of the vaccine was applied, 23 of those 30 convalescent patients

were over 90% inhibited in the interaction of the virus with neutralizing titers. “This becomes a very important instrument, since in Cuba we already have more than 20,000 convalescent patients, and there are millions in the world, who are exposed to reinfection, even with new strains, if their neutralizing capacity decreases,” he said.

Mambisa, the Cuban candidate exploring intranasal application

Dr. C. Marta Ayala Ávila as general director of the Center for Genetic Engineering and Biotechnology (CIGB), spoke to the Mambisa vaccine candidate and to development of the Abdala candidate.

Dr. Ayala Ávila said that the institution put all its products and molecules in function of the creation of vaccines. The team, she stressed, “has not stopped for a minute in the work to transfer the results as quickly as possible ino assuring the health of the people” and that while ordinarily a vaccine could take 12 years to get into the health system, “in times of pandemic people work differently.”

She said given the extensive experience of the Finlay Institute and the CIGB, the industry was in a good position to take assimilated knowledge and convert it into the development of vaccines, especially. At the same time, she emphasized, work has continued on vaccine products that are also of interest to public health, such as those for dengue, Zika, HIV and active immunotherapies against cancer.

Ayala Ávila also explained that due to that extensive experience in genetic engineering management, it was possible to design these molecules or proteins, while the extensive development in computer design platforms allowed the creation of different formulations. As well, the fact that almost every living organism except humans has already been used to express these proteins has also made it possible for development of the Cuban vaccine candidates.

The CIGB, explained the Ayala Ávila proposed the development of two subunit vaccine candidates, which were developed from the work and study of a group of experts.

In addition to these projects, the CIGB continues research with other molecules based on the ability to synthesize peptides and also joined the study of the phenomena of mutations that have appeared.

“We have had the ability to design a gene that contains these mutations and that will be put into the same system to produce this protein and evaluate how the responses of our vaccines might be able to combat these mutations,” she added.

Ayala Ávila explained that the candidate Mambisa (CIGB 669) explores the intranasal route, which also participates in the body’s immune response to the presence of the virus. “In that case, we created the formulation in the form of a spray and we sought not only to stimulate the antibody response, but also T cells, another interesting way to fight the virus.”

The specialist commented that from the beginning an immunization scheme with three doses was proposed, although two guidelines were established: a short immunization at intervals of six, 14 and 21 days, and a long one in which the vaccine candidate would be applied on day zero, again day 28 and then day 56. “In the case of the short path, it allows us to know more quickly what happens in the individuals who receive the vaccine”

This study is in Phase I at the National Poison Control Center and has 88 volunteers divided into four groups. Its start date was December 7, 2020 and it is already possible to talk about some results. The Director of the CIGB said that the study is already on its 56th day and all the volunteers have received the three immunizations.

“So far it has been shown that the doses are safe and well tolerated, and we have only had mild reactions associated with the routes of administration and that resolve spontaneously. Now we are in an intense analytical activity to determine the induced immunity and lead us to the advance to Phase II, always without violating the established protocols,” she commented.

Abdala: Antibody values up to 4 times higher than those they had before vaccination

For its part, the vaccine candidate CIGB 666 Abdala does use the intramuscular route. In it, the research institute took advantage of extensive research on Hepatitis B to create a formulation that induces a systemic and T-cell response. This trial also assesses the safety and immunogenicity of the vaccine.

As was the case with Mambisa, the study with this candidate also began on December 7, 2020, in this case with 132 volunteers divided into six groups. So far, all participants have received all three doses of vaccination.

“When we evaluated the immune response, we found that all individuals had the ability to respond to RBD antibodies. Likewise, the vaccine candidate was able to inhibit the binding of RBD to its receptor. We also found that 86 percent of those who received the highest dose developed antibody levels up to four times higher than those they had before vaccination,” she said.

According to these results, there is already progress in Phase II with this immunization scheme, a stage that is taking place in Santiago de Cuba and should conclude in March 202. In fact, between Monday and Tuesday of the present week they had already vaccinated 330 of the 660 volunteers, who are between 18 and 80 years old.

Despite these results with the short schemes, Dr. Ayala Ávila said that he he long

scheme studies for both candidates have been maintained. Phase III of the studies are scheduled to be carried out between March and May 2021, while the Center prepares to produce higher doses of vaccines, especially through alliances with Laboratorios AICA.

We have sufficient capacity installed to be able to handle clinical development

Dr. Eduardo Ojito Magaz, general director of the Center for Molecular Immunology (CIM), said that the procurement strategy was conceived from the beginning by BioCubaFarma.

The organization, he affirmed, had conceived three fundamental pillars. First, an organizational dimension of sufficient productive capacity; second, a scientist dedicated to the discovery of all necessary technologies; and third, the technological capacity, that is the levels of production required to meet the vaccine needs for Cuba and for supplying abroad.

A strategic alliance was created at the Finlay Institute for the production of Soberana 01 and 02, as well as for the Center for Genetic and Biotechnological Engineering and the AICA llaboratories.

“From the beginning, two parallel lanes were created so that no candidate would compete with others and at the same time, we would have the necessary productive levels in view for the need to produce for Cuba and the world.”

The two lanes have capacities for the production of complex biomolecules at CIM and CIGB, while Finlay has capacities for protein formulation, plus there are two companies that are productive outlets, at BIOCEN and AICA laboratories.

“During the development of vaccine candidates there was negative press saying that we are producing vaccines of other producers in the world. But the reality is that

that our installed capacities are sufficient to be able to meet clinical development," he said.

The other organizational dimension has to do with material supply chains. He recalled that 2020 was a complex year, affected by the aggressiveness of the United States blockade and by the pandemic, where all raw material suppliers were affected.

He stressed that BioCubaFarma has to fight very hard to provide itself with the necessary raw materials, as many suppliers demand that nothing provided to the company has a component that comes from the US market. "This has led us to seek internal solutions in the country to strengthen our position as producers."

The other element is related to production costs. "The big vaccine manufacturers today are the only big manufacturers in the world. No sub-American country can afford to have great formulation and filling capabilities. This ability that we have gives us independence when facing a pandemic like this."

He also referred to the scientific dimension associated with these projects and commented that the CIM has developed monoclonal antibodies, cancer vaccines, knowledge that was available to and provided the basis for the antigen of the Sovereign 01 and 02 candidates.

A second scientific dimension is related to the scaling of the productive platform of the candidates. "From the first moment we proposed a development capacity to meet Phase III and the vaccine deployment in the population."

The last element is technological. "All four candidates have the same protein antigen, RBD. The production scales in the CIM are 50/500/2000 liters. In the CIGB these reach 300/1000 liters of fermentation."

Ojito Magaz explained that both AICA and BIOCEN have capacities for more than

100,000 vaccine bulbs to be filled daily in each of the laboratories. “They are reason enough to tell our people to be calm and have confidence. The technologies are available and ready for when the regulatory authority approves Phase III to begin mass production and distribution.”

What is Cuba doing in the face of coronavirus mutations?

In the last section of the Round Table, Eduardo Martínez Díaz, president of BioCubaFarma, updated the audience on the mutations of the coronavirus and assured that it is normal for this to happen.

Since SARS-Cov-2 emerged, he explained, mutations have appeared, such as the one in the UK virus at the end of the year. “The mutation opens the lock more easily and enters the cell easier, which has caused it to spread faster.”

Next, he continued, the South African variant emerged, “another worrying mutation because it changes the structure of the RBD. The American company Moderna, for example, has studied and found that its vaccine reduces its capacity against this variant. Hence, they are talking about using a third dose of vaccine.”

Towards this end, Martínez Díaz reported that Cuba has created working groups to study these variants and how to deal with them: using the antigens that these mutations have, studying what mutations can occur, in order to incorporate other antigens that we would have prepared at the laboratory level and, if necessary necessary, incorporating them.

On the subject of medicines, the president of BioCubaFarma pointed out that there are difficulties in manufacturing them due to lack of resources. However, he assured that those of the protocol for COVID-19 have priority because “they save lives and prevent patients from progressing to gravity.”

“Today in the world more than 10% of patients who become infected go to

gravity, but in our country, as a result of the protocol and the action of doctors, it is less than 3%.”

Likewise, in the world the lethality is over two percent and in Cuba it is 0.74. “We very much regret the death of 220 Cubans and that is why we insist that regardless of whether we work hard and we are going to have the vaccines, more individual and collective responsibility is necessary to try to get out of the situation we currently are in.”

Even when we are in the vaccination stage of any illness, he recalls, that first dose does not solve the problem. “Vaccines so far do not protect 100 percent. Until the circulation of the virus is cut off, it is necessary to maintain the measures and protect oneself ”.

“March and April will be decisive months for Cuban vaccines and we are confident that the results will be what we expect and we will be able to enjoy the Sovereigns”, he concluded.