BRAZIL`S LAST CHANCE AGAINST COVID-19

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These are unique and particularly trying times as the World now collectively responds to what is now the second wave to the pandemic of the novel virus SARS-CoV-2 ("Severe Acute Respiratory Syndrome Coronavirus 2") and its resulting disease Coronavirus Disease 2019 (COVID-19).

First detected in December 2019 in Wuhan, China, its source is believed to be the downtown illegal "wet" market trade of live and dead wildlife animals for human consumption, including the bamboo bat. The SARS-CoV-2 is a beta-coronavirus, like SARS-CoV of the SARS epidemic of 2003 that had its origin in bats. According to the February 23, 2021 Weekly Epidemiological Update of the World Health Organization – that on January 30, 2020 declared the outbreak a "public health emergency of international concern" and a "pandemic" on March 11, 2020 – there are now over 110 million reported cases and over 2.4 million deaths globally to date.

As is now widely known, SARS-CoV-2 is highly contagious and, as there is no pre-existing immunity, it is spread person-to-person and follows the pandemic progression model of exponential acceleration that peaks and then decelerates depending on social distancing, and contact. And there are now more transmissible variants of SARS-CoV-2, such as VOC 202012/01, of which variant 94 countries (including Brazil as of December 31, 2020) now report imported cases or community transmission.

The general constant fear about Brazil, based on the pandemic progression model, is that widespread COVID-19 transmission, in addition to ever-increasing mortality numbers, will result in public and private healthcare system critical overload. This is now the present situation in Manaus (the capital of the State of Amazonas) for example, where the hospital situation has been totally overwhelmed. As reported in the international media, many people there are dying of COVID-19-related asphyxiation every day due to lack of commercially produced oxygen. In Rio de Janeiro, as reported on January 25, 2021, 90% of its intensive care unit beds are occupied with COVID-19 patients, as are 75% of its infirmaries. Also, as of January 30, 2021, the State of São Paulo registered (in every hour) 544 COVID-19 new cases and 9.6 new deaths, and 69.4% of its intensive care unit beds are now occupied.

Brazil – with 10,455,630 total Coronavirus cases and 252,835 total Coronavirus deaths (second to the United States in number) as of February 26, 2021[1] – had initially braced itself for the worst case scenario, taking action in similar fashion to other countries. On January 22, 2020, the Brazilian Ministry of Health COVID-19 Public Health Emergency Center of Operations was established, and published a National Contingency Plan. On February 3, 2020, Brazil declared a Public Health State of Emergency of National Importance relative to the disease, and on February 6, 2020 Law No. 13.979 was passed to implement the

[1] https://www.worldometers.info/coronavirus/#countries

same, directing that all Brazilian citizens cooperate with the public health authorities and avoid close contact with those who are infected and avoid circulation in so-called contamination regions. Furthermore, all federal, state, district, and municipal public health authorities were obligated to share essential information and identify those suspected of being infected and curtail COVID-19 propagation by their isolation and quarantine, which directive would also apply to the private sector when so instructed.

In spite of all this regulation, and the other emergency regulations that Brazil implemented since the onset of the pandemic, its supermarkets (including its high-crowd discount supermarkets) and much of its regular commerce, such as shopping malls and street-level retail stores, are fully open. The beaches and their food and drink-serving kiosks and restaurants are being frequented as normally and public transportation restriction directives are being only very loosely adhered to (take Rio de Janeiro`s dedicated bus rapid transit (BRT) buses continuing to be jam-packed as an example).

Also, according to 2019 Brazilian Institute of Geography and Statistics (IBGE) statistics, 13.5 million of Brazil`s total population live in extreme poverty (living on less that USD 1.90/day, the World Bank extreme poverty metric). And, as the United Nation's Millennium Development Goals database notes, 22% of Brazil's urban population lives in slums (favelas, as they are called in Brazil), which are overcrowded and unsanitary.

It is against this backdrop that Brazil`s attempts to mitigate the impact of the pandemic must necessarily be measured, and understood.

Worldwide, countries and pharmaceutical companies have been applying full efforts toward developing and producing safe and effective COVID-19 vaccination for some time.[2] With respect to Brazil, its first edition National Plan for the Vaccination against COVID-19 was elaborated in formal manner on December 16, 2020, in accordance with Brazilian Health Regulatory Agency (Anvisa) Collegiate Directorship Resolution (RDC) vaccination registration, licensing orientation, and technical regulations.[3] Most recently RDC 444/2020, of December 10, 2020, established the temporary authorization for emergency use, on an experimental basis, of COVID-19 vaccines. In accordance with the National Plan, negotiations are now presently underway as a result of which close to 350 million doses are expected to become available within the course of this year.

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[22] As of January 19, 2021, according to the World Health Organization`s Draft landscape and tracker of COVID-19 candidate vaccines, there are more than 64 COVID-19 candidate vaccines in clinical development and 173 in pre-clinical development towards safe and effective deployment. Phase III clinical trial candidate vaccines now in rollout have most noticeably included that of Pfizer-BioNTech, of Germany and the United States of America (LNP-mRNA), Moderna, of the United States of America (LNP-encapsulated mRNA), AstraZeneca/University of Oxford, United Kingdom of Great Britain and Northern Ireland (ChAdOx1noV-19, Non-Replicating Viral Vector) and CoronaVac (Sinovac Life Sciences), of Beijing, China (Inactivated SARS-CoV-2 Vaccine with Aluminum Hydroxide).

[3] Anvisa Collegiate Directorship Resolutions (RDCs) 55/2010 (Biological Product Registration), 348/2020 (Extraordinary and Temporary Criteria for COVID-19-related Medication, Biologic Product and Diagnostic Product Registration Petitions) and 415/2020 (New Extraordinary Criteria for COVID-19-related Medication and Biologic Product Registration Petitions).

The co-invented AstraZeneca/University of Oxford COVID-19 vaccine ChAdOx1noV-19 (formerly AZD1222) is the main vaccine being held forth under this first edition of Brazil`s National Plan.

The AstraZeneca/University of Oxford COVID-19 vaccine is a replication-deficient chimpanzee viral vector based on a weakened common cold virus (adenovirus) containing the SARS-CoV-2 virus spike protein, which, following vaccination, is produced, priming the immune system against SARS-CoV-2 attack. Its Phase III trials were conducted both in Brazil and the UK and, as published on December 8, 2020 in The Lancet, the pooled results were 70.4% efficacy (54.8% to 80.6% confidence interval), with zero vaccine group cases of severe infections and hospitalizations. Its storage and transport are at the normal refrigeration temperatures of 2-8 degrees Celsius (36-46 degrees Fahrenheit).

On June 26, 2020, via its Official Letter 743/2020/DATDOF/CGGM/MS, the Brazilian Ministry of Health appointed its affiliated Oswaldo Cruz Foundation (Fiocruz) – which controls the Ministry`s vaccine-developing, manufacturing, distributing and selling Bio-Manguinhos laboratory – for absorption of the AstraZeneca/University of Oxford COVID-19 vaccine technology and local production. As result of the September 8, 2020 Technological Order Agreement 01/2020 between Fiocruz, Bio-Manguinhos and AstraZeneca, an estimated 100.4 million doses of the AstraZeneca/University of Oxford vaccine are anticipated by July 2021 and 110 million doses of finished national product between August and December 2021.

In follow up and in anticipation of the National Plan and its implementation, a number of non-binding Memoranda of Understanding were also signed by the Brazilian Federal Government, including with Pfizer-BioNTech (70 million doses total, 8.5 million by June 2021) and Janssen Pharmaceutical Companies/Beth Israel Deaconess Medical Center/Emergent BioSolutions/Catalent (Ad26.COV2.S adenoviral vaccine; 38 million doses total, 3 million by the second quarter of 2021).

On September 25, 2020, Brazil executed a Commitment Agreement with Covax, the Gavi Vaccine Alliance, The Coalition for Epidemic Preparedness Innovations (CEPI) and World Health Organization co-led vaccine-focused area of the Access to COVID-19 Tools (ACT) Accelerator [4] as a Self-Financing Participant in its Facility purchasing pool,[5] opting for the Optional Purchase Arrangement (as opposed to Committed Purchase Arrangement) under which it chose to make an upfront payment covering its full pro rata share of required investment and secured doses (at USD 3.10/dose) from the manufacturer candidates it would decide to purchase from.

[4] The Access to COVID-19 Tools (ACT) Accelerator was launched in April 2020 by the World Health Organization and the European Commission to provide "innovative and equitable" access to COVID-19 diagnostics, treatments and vaccines globally.

[5] Covax consists of the "Facility" purchasing pool for higher income countries and "Advance Market Commitment (AMC)" fundraising effort for poorer countries, intending to provide 2 billion doses of vaccines worldwide by the end of 2021 towards priority population protection (that of healthcare workers and risk groups) and full return to economic activities.

On October 9, 2020, USD 148 million was made in upfront payment and 42.5 million doses are expected to be received, the exact manufacturers and delivery calendar to be determined.

Following National Plan publication, on January 7, 2021, the Brazilian Federal Government executed Contract 5/2021 with the Butantan Institute, the immunobiological and biopharmacological product-producing Brazilian scientific institute linked to the State of São Paulo Secretary of Health, for 46 million doses of the Chinese Coronavac COVID-19 vaccine, with an option for an additional 54 million, the first 8.7 million to be delivered by January 31, 2021 (6 million imported and 2.7 million national product), the final 9.93 million doses (in national product) to be received by April 30, 2021.

The CoronaVac COVID-19 vaccine is based on an inactivated pathogen (the virus in grown in the lab and then inactivated. Its vaccination stimulates the body to induce immunity.). Its Phase III human clinical trials were/are being conducted in China, Turkey, Brazil, Indonesia, and Chile. As was formally divulged by the State of São Paulo Government/Butantan Institute on January 12, 2021, its overall Brazil study efficacy is 50.38% (with 77.96% light case efficacy and 100% severe case/hospitalization efficacy). Priced at USD 10.30/dose, its storage and transport temperatures are that of normal refrigeration temperature 2-8 degrees Celsius (36-46 degrees Fahrenheit).

On January 17, 2021, Anvisa`s Collegiate Directorship unanimously approved temporary authorization for the emergency use of Coronavac and the AstraZeneca/University of Oxford COVID-19 vaccine Covishield, manufactured by the Indian biotechnology and pharmaceuticals company (and World's largest vaccine manufacturer) Serum Institute of India, both authorizations conditioned on the signing of Terms of Commitment and their respective publication in the Official Gazette of the Union (DOU).

On January 19, 2021, the Brazilian Federal Government formally initiated its vaccination rollout program with 6 million doses of the Sinovac Biotech Ltd.-produced Coronavac vaccine, the same to be initially dedicated, it was announced, towards an estimated vaccination of first 410 thousand native Indians and 20 thousand healthcare professionals attending to the indigenous population on a priority population basis. And, on January 22, 2021, two million doses of the AstraZeneca Covishield vaccine, manufactured by Serum Institute of India, were shipped to Brazil.[6]

All this being told, it truly remains to be seen how well Brazil`s attempts at containing COVID-19 transmission, morbidity and mortality will actually be effective through its vaccination campaign.

[6] Serum has partnered with Covax under AMC worldwide supply agreement for the supply of 200 million doses of AstraZeneca/University of Oxford, with the option of up to additional 900 million of either the AstraZeneca/University of Oxford or Novavax candidates, as well as a statement of intent for 200 million recombinant protein-based Sanofi/GlaxoSmithKline COVID-19 vaccine doses. AstraZeneca's COVID-19 vaccine had been granted emergency use authorization in India on January 7, 2020 and apparently India is not restricting COVID-19 vaccine supply to other countries.

According to the Brazil`s Ministry of Health, Brazil`s National Immunization Program is the largest public immunization program in the World. It distributes hundreds of millions of doses of 19 different types of vaccines yearly through a network of 37 thousand public health system (Sistema Único de Saúde - SUS) vaccination posts throughout 5,570 Brazilian municipalities. The Brazilian Federal Government is responsible for their transport through Anvisa,[7] which oversees The National Center for the Storage and Distribution of Immunobiologicals (CENADI) in Rio de Janeiro, and is responsible for inventory control and distribution nationwide by plane, train (albeit limited), refrigerated truck and boat transport. Each Brazilian state has its own regional likewise laboratory-determined CENADI refrigeration units. Transport out is typically prioritized on an EEFO (Earliest-Expiry-First-Out) basis.

There is, however, considerable operational and other challenge to be taken into account in addition to that of the necessary large-scale vaccine production (the National Plan only provides for 350 million doses of imported and local vaccine in 2021; Brazil has a present total population of over 213 million; there is marked vaccine shortage under the Plan at double dosage) in order to effectively contain transmission of COVID-19 across the scattered regions of Brazil.

According to FGV Transport-cited statistics, Brazil has 1.72 million kilometers of roadway, of which only 214 thousand kilometers are paved. The majority of highway is under public oversight, 66% of which are to be considered to be of reasonable, bad or terrible condition based on a recent National Transport Confederation - CNT study.

Hundreds of millions of COVID-19 vaccine vials will need to be transported in Brazil during the course of 2021 and, depending on the temperature requirements of the particular vaccine, may require in addition to very many thousands of refrigerated storage units and trucks, portable batteries, generators, and refrigerators.

As noted in the first edition of Brazil`s National Plan, at the time of its publication the co-developed Moderna/US National Institutes of Health's National Institute of Allergy and Infectious Diseases (NIAID) mRNA-1273 COVID-19 vaccine (a messenger RNA (mRNA) vaccine, which works by encoding form of the SARS-CoV-2 spike protein) and the Pfizer-BioNTech mRNA-based vaccine candidate, BNT162b2 (in the negotiation phase of negotiation with Brazil's Ministry of Health), both double dose vaccines with an efficacy rate of approximately 95%, were both in Phase III clinical testing but from the transport and storage perspective presented considerable operational obstacle for reason of their Ultra Low Temperature (ULT) requirement (-20 Celsius or -4 Fahrenheit for Moderna and -70 Celsius or -94 Fahrenheit for Pfizer). Pfizer, if and when delivered, would thus only be distributed to certain capital cities and metropolitan regions, to be determined, and the prioritization would be directed to only COVID-19 exposure highest risk health professionals.

[7] Regulated by Laws 6.360/1976 and 9.782/1999, Interministerial Ordinance 802/1998 and Anvisa Collegiate Directorship Resolutions (RDCs) 234/2005 and 38/2010.

The Janssen (a Johnson & Johnson company) non-replicating viral vector Ad26.COV2.S vaccine candidate works the same way as the AstraZeneca/University of Oxford COVID-19 vaccine in adenovirus antigen genetic code vector (carrier) prompting of the immune system. It is 85% effective in preventing severe disease and its single dose characteristic is certainly very important for rapid large-country mass vaccination deployment purposes. It is compatible with standard vaccine transport and storage as it remains stable for two years at -20°C (-4°F) and can be transported and stored for at least three months at temperatures of 2-8°C (36°F-46°F). But as stated in the first edition of Brazil`s National Plan, it is in the phase of negotiation with Brazil's Ministry of Health and the strategy regarding use of this vaccine is only to be presented in the second edition.

Both the to-date emergency use-only Brazil-approved double-dose AstraZeneca/University of Oxford COVID-19 and CoronaVac COVID-19 vaccines now being exclusively applied in Brazil rely on a cold chain transport and storage infrastructure that is of typical refrigerator temperature. But even the standard vaccine cold chain storage environments and minimized time-out-of-refrigeration (TOR) risks to these two vaccines are not guaranteed to be 100% percent constant due to the irregular electricity supply, and the electricity outages, that occasionally seriously affect the North and Northeast of the Country. Take for example the electric energy blackout that affected 90% of the state of Amapá in the North of Brazil for most of the month of November 2020 when a substation energy generator caught fire and transmission lines and hydroelectric plants shut down automatically and substation supply and backup power transformers were "unavailable."

Vial, syringe and needle supply and supply of other COVID-19-vaccine-related resources is also a major concern, subject to local plant production as well as international capacity. At present there are only four syringe manufactures in Brazil and one needle manufacturer. Current syringe production capacity in Brazil is 10 million/month. On December 16, 2020, Brazil`s Ministry of Health sought to purchase 331 million syringes (via public Electronic Bid n. 00159/2020) but its reference prices (RPs) were too low and only 7.9 million were obtained. On January 14, 2021, the Brazilian Ministry of Health formally stated to the Brazilian Federal Supreme Court (STF) that the Brazilian states of Acre, Bahia, Espírito Santo, Mato Grosso do Sul, Paraíba, Pernambuco and Santa Catarina do not have sufficient syringe stock to meet initial demand going into this year. There needs to be a Brazilian pharmaceutical industry wartime-like organized footing to produce these basic needs (as likewise such organization is needed to produce the necessary precursors and chemicals for local, quality, standard process vaccine manufacture and production).

There is also the challenge of equitable distribution to be faced. In the geographic locations of proven community transmission in Brazil only patients presenting severe symptoms have been tested due to test kit shortage and unreliability and most favela communities have needed to self-organize – including via resident drug lord intervention – so as to attempt social isolation and related food, hygiene and information dissemination and to prevent the spread of COVID-19 amongst themselves. Vulnerability also clearly relates to vaccine application in the many unprotected favela populations.

Rapid mass vaccination is clearly vital but the vaccine rollout in Brazil has been chaotic so far, as observed by Bloomberg`s Brazil Country Chief:

> Almost two weeks after national vaccinations began, Brazil is still not reporting consolidated figures. Officials say there are technical issues preventing the Health Ministry from publishing data it receives from local governments. So for now, it's up to Brazil's 26 states (and the Federal District) to publish their own numbers. Several have set up websites that are updated daily or even in real time, like São Paulo and Rio Grande do Norte. Some are still sending tallies by email – Rio de Janeiro, for example. Others aren't publishing information at all. Some Brazilians have taken data collection into their own hands, including a popular website that reports vaccination totals. So far, regions aren't providing breakdowns of which vaccines are being given.[8]

Most significantly impacting on the immunization effort has been the widely-known politicization preceding it. To quote from the Brazil - Events of 2020 publication of Human Rights Watch World Report 2021:

> [In 2020,] President Bolsonaro downplayed Covid-19, which he called "a little flu;" refused to take measures to protect himself and the people around him; disseminated misleading information; and tried to block states from imposing social distancing rules. His administration attempted to withhold Covid-19 data from the public. He fired his health minister for defending World Health Organization recommendations, and the replacement health minister quit in opposition to the president's advocacy of an unproven drug to treat Covid-19.[9]

Brazilian public sentiment has, resultantly, been mixed regarding the seriousness of the disease. Without public health expert-led open and transparent communication, and cross-governmental collaboration, Brazil's management of the pandemic to date is considered the World's worst, as ranked by the Australian think tank Lowy Institute, which assessed 98 countries on the metrics of total confirmed cases, total deaths, confirmed cases per million, death rate per million, tests performed and confirmed cases per tests.[10]

[8] Julia Leite, Where's Brazil's Data?, Bloomberg (blog), January 28, 2021, https://www.bloomberg.com/news/live-blog/2021-01-21/methodology-and-analysis-for-the-covid-19-vaccine-tracker#6012F60FB2240001

[9] https://www.hrw.org/world-report/2021/country-chapters/brazil

[10] https://interactives.lowyinstitute.org/features/covid-performance/

At the present time, only the two vaccines approved on an emergency use basis in Brazil are being administered, and supply is limited.[11] The natural expectation is that as time goes by further vaccines will be approved and product capacity and supply expanded, with gradual wind down after general public open access to vaccines. To turn this expectation into reality there must be full operational capacity and rigid coherence and alignment to the vaccine program. Mass testing and contact tracing is not viable and has not been implemented in Brazil, nor have full-hearted lockdowns been implemented. With high vaccination coverage the chance obviously exists for reduction of disease transmission and achieving the much needed widespread immunity.

With immunity to the virus of around 75% of the population (the so-called herd effect) there are less people available to become infected and the infection rate eventually stops increasing and dies down. The new mutations of COVID-19 however are increasingly contagious, so transmission is increasing rapidly, and mutations increase with virus spread. The urgent World problem is now to get ahead of the virus spread by a massive increase in the World population immunity, through vaccination.

For Brazil, the real success of its immunization vaccine program is crucial. The recovery of the Nation depends on it.

[11] On February 23, 2021, the Pfizer-BioNTech COVID-19 vaccine was granted definitive registration in Brazil by Anvisa (emergency use only registration had not been sought for the vaccine but rather definitive registration), however there are no contracts signed with Pfizer-BioNTech and the vaccine is not available in the Country.