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Anti-Covid vaccines: a look from the Collective Health

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Abstract *The paper discusses the complex nature of the pandemic by highlighting the various intrinsic and extrinsic dimensions in the development of SARS-CoV-2 vaccines, with an emphasis on the two most advanced products in clinical testing, namely, the vaccine developed by the University of Oxford associated with the British pharmaceutical company AstraZeneca, and the one developed by Chinese company Sinovac. This choice also stems from the fact that both have testing activities, which, if successful, will lead to future production in Brazil, by Bio-Manguinhos/Fiocruz, Rio de Janeiro, and the Butantã Institute, in São Paulo, respectively. From a conceptual viewpoint, this paper builds on the reflection from the field of Collective Health that addresses the boundaries between the biological and the social spheres. It also seeks to show that, if successful and while important tools for coping with the pandemic, vaccines will not dispense with the continuity of other non-pharmacological measures already used.*

Key words *COVID-19, Collective health, Vaccines*

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The object of Collective Health is constituted within the limits of the biological and the social and comprises the investigation of the determinants of the social production of diseases and the organization of health services
[Jairnilson Paim, 1982][1]

The approach to complex themes

Mass diseases are often intricate. In the case of the SARS-CoV-2 pandemic, the complexity was exacerbated in the beginning by the almost complete lack of knowledge about the characteristics of the pathogen that caused it and the consequences thereof. In its biological dimension, the existing clues referred to the knowledge of other Coronaviruses already identified that, after all, hardly assisted in the management of the new organism. In its pathophysiology, what was thought to be a respiratory disease turned out to be a systemic condition. Concerning the clinical approach, more surprises with a heterodox trend where prodromal symptoms quickly turned into a severe disease, without the good general condition of the patients being consistent with the severity of their real respiratory function measured by the oximeter. In the epidemiological field, the monitoring of the population's immune status was also surprising due to the low presence of antibody carriers compared to the experience of other viral epidemics, which currently raises an intense debate about the immunological mechanisms involved in the disease. At the level of health services, because the speed of illness and the severity of part of the patients proved to be higher and more intense than their ordinary organization was prepared to support. Finally, in the social environment, the pandemic reached the patterns of work, affection, and leisure that were also unexpectedly disorganized, as were the national economies, which were already very fragile even before the pandemic. While intense, as we will see below, the results of the search for effective drugs have been frustrating so far. Now, we are witnessing a race for one or more good vaccines.

A lesson should be drawn from the description mentioned above. No one measure or even offensive on one of the dimensions described above can solve, *per se*, the problem as a whole. Its confrontation must be organized from actions articulated in the multiple dimensions mentioned. The corollary of this assertion is that one or more good vaccines will be critical to contribute to coping with COVID-19, but it is improbable that they can solve the problem alone in its entirety. On the other hand, several steps involving vaccines intrinsic and extrinsic characteristics must be established before fulfilling their mission and essential role. This text aims to discuss the intricate field of vaccines.

Efficiency and Safety

As of July 15, 23 vaccines in the world were being tested in humans, with only two in the last stage of this testing (phase III), There were also 140 candidates in earlier stages of development[2]. Currently, Brazil is involved in the clinical development of both. The Butantã Institute is associated with the Chinese company Sinovac and Fiocruz/Biomanguinhos with the British firm AstraZeneca.

At the end of this phase of human testing, a vaccine against SARS-Cov-2 must show efficacy with few side effects to be sold and applied. However, in the current world emergency, as we will see, some of them are already being sold before their safety and efficacy are established. Usually, it must be approved by the World Health Organization (WHO) and the national health regulatory agency of the country that will use it (Anvisa in Brazil). The World Health Organization and the United States health regulatory agency (FDA) have decided to approve only vaccines that can prevent or forestall severe cases in more than 50% of those vaccinated[3].

All clinical testing incorporates some probability of failure, which varies according to the three-staged phases (Phase I to II, Phase II to III, and Phase III to approval). Lo and Siah[4] who analyzed 881 clinical trials with candidate vaccines against infectious agents between 2000 and 2015, argue that the aggregate probability of success for the three-staged phases was 33.4%. In the stage of interest to this text (Phase III to approval), which included the analysis of 269 clinical trials, the probability of success was 85.1% (± 2.2%). This is, therefore, the current scenario of the two vaccines now involved in Phase III trials. If the next two criteria to be discussed (effectiveness and efficiency) are not satisfactory, they do not prevent, a priori, the sale of the vaccine. However, they are crucial for use in public mass vaccination programs.

The vaccine's effectiveness

Efficacy and safety are established based on the observation between the candidate product

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and a human in a controlled environment. However, efficacious and safe vaccines must embrace criteria transcending the product's intrinsic characteristics. Criteria that mediate between the technologies inherent to them and their arrival at the organisms of people who belong to the target populations for which they are intended. These are criteria related to their effectiveness.

A good vaccine should provide a long immune memory. If possible, it should protect over a lifetime, and if not, for one or more decades of life. It must not show signs of enhancement, which means to cause (or aggravate) the disease that should prevent or alleviate specific subsets of vaccinated people. Recently, a vaccine against Dengue (Dengvaxia) approved by WHO and duly registered at ANVISA with poor efficacy,also proved to be dangerous because it increases the likelihood of severe forms of the disease in people who had never come into contact with the virus, which is why the Brazilian public health system (SUS) did not incorporate it. Another example are the vaccines available against polio. The Sabin vaccine, made from live attenuated viruses, increased the effectiveness of combating the disease through oral administration and allowing this attenuated virus to immunize other people when dispersed by the already vaccinated. However, rare cases of polio caused by the vaccine virus have been identified, and this has become an huge problem in situations where the incidence of the disease becomes very low. In That case, the risk of falling ill in vaccinated comes close to the risk of falling ill with the "wild" virus. Hence, some health systems have replaced the Sabin vaccine with the previous one, the Salk vaccine, developed using inactivated viruses. In Brazil, the current scheme prescribes the Salk vaccine in three doses below one year of age and Sabin in subsequent boosters[5]. To date, there is no evidence of enhancement in testing for SARS-CoV-2 vaccine candidates in humans. However, in preclinical tests, this has been observed in the development of vaccines against another SARS-CoV. The topic is commented on by Hotez et al.[6].

As a challenge to effectiveness, a vaccine must reach comprehensive coverage in the target populations through an adequate vaccination campaign (logistics, cold chain, among others). In this respect, Brazil has a substantial advantage due to the National Immunization Program of the SUS (PNI/SUS), with extensive experience (46 years) in the dispensation of a robust basket of vaccines in the country. Despite the logistical challenges arising from our geographic dimension, the approximately 30 thousand vaccination rooms usually used in national campaigns reduce problems of this nature.

It will also be necessary to overcome the multinational anti-vaccine ideological movements. Born in the late 1990s in Europe, the current wave of this movement has been growing worldwide, particularly in the northern hemisphere. Johnson et al.[7] show data and discuss the current situation of these movements. More specifically, concerning a vaccine against SARS-CoV-2, opinion polls in the U.S. show a worrying situation. Only half of the North American population is convinced of having a vaccine against COVID-19, and 25% are undecided[8].

In Brazil, due to the good services provided by the PNI/SUS, anti-vaccine movements did not prosper as they did in North America and Europe. However, they are alive. Since 2019, there has been a sustained outbreak of measles cases among us, with about 15,000 cases that year and whose epicenter was the city of São Paulo and its surroundings. Several factors seem to be contributing to the exacerbation of a disease whose transmission was interrupted in the country in 2000, after introducing a vaccination two years earlier[9].

Among the various reasons put forward for this outbreak, there is a consensus that the lower vaccination coverage was decisive for its occurrence and the reasons for this were, alongside the SUS de-financing after the 2016 Constitutional Amendment N° 95, possibly the implicit or explicit absorption of ideas from the worldwide anti-vaccine movement. The enormous impact of the COVID-19 pandemic on the population's mind should attenuate adherence to this ideology. However, it is essential to mention this potential obstacle to vaccine effectiveness and be prepared to fight it if it manifests.

The vaccine's efficiency

The concept of efficiency usually revolves around economic and financial aspects. Vaccines must achieve a positive balance in the cost/benefit equation to be effective. In the last 20 years, substantial changes have been observed in the world vaccine market. Their main drivers are: (1) a market growth rate well above the corresponding rate for medicines, despite representing only 2% to 3% of this market; (2) an increasingly more significant business (and "cultural") merger with major pharmaceutical companies; (3) an acceleration in the development of more complex

and more expensive vaccines; (4) an increased epidemiological relevance of communicable diseases, leading to increased demand; (5) biotechnological advances in vaccine development and production; (6) more profitable vaccines, with the appearance of blockbuster vaccines (e.g., influenza); (7) more significant concern by WHO, UNICEF and PAHO on this issue and the emergence of nonprofit organizations and public and private coalitions geared to vaccines; (8) organization of new company marketing (pharma-like marketing) strategies.

Part of these market changes is related to what I understand as a "capture" of vaccine-manufacturing companies by big pharmaceutical companies. Between 2005 and 2012, the 13 most significant purchases and mergers between vaccine and pharmaceutical producers moved around US$ 220 billion and, at the end of that period, transformed the pharmaceutical companies GSK, Sanofi, Pfizer, Merck, and Novartis into the most significant global producers, who were then responsible for about 75% of the global vaccine market[10]. Currently, the ranking may be modified, but the outlook remains the same. The mergers and acquisitions process, among other consequences, caused certain ethical and commercial "Big Pharma" practices, widely known and often condemned, to migrate to the vaccine industry, once much more committed to public health. Vaccines have become Big Business.

The pandemic's impact, measured by the number of cases and, mainly, of deaths, has meant that most of the international community of researchers turned their efforts to face COVID-19 since the onset. On 14/07, 76,645 papers and preprints on COVID-19 were available. On 10/07, 4,271 registered clinical trials were ongoing[11]. However, the pandemic mobilized three other political and financial spheres, besides efforts of the world scientific community: governments, multilateral organizations, and large philanthropic organizations. The fact that the pandemic has had a substantial impact on China, the European Union and the United States has caused global political centers to put the problem at the center of their concerns. Humanitarianism and the search for prestige and new business seem to have been the drivers of this remarkable mobilization.

The interest of the global scientific community seems to derive, in the first place, from a humanitarian feeling towards the pandemic, and its side component is the search for prestige among peers, financing agencies, and society. This mobilization, particularly in the Northern Hemisphere, was supported by the allocation of extraordinary financial resources in a rarely seen dimension. As usual, the leadership stayed with the United States, where this contribution reached the mark of US$ 3.6 billion, allocated in the National Institutes of Health[12] and the Biomedical Advanced Research and Development Authority (BARDA) created in 2006. Extraordinary contributions were also observed in other countries, such as China, and the European Union. However, it is worth noting that, despite these contributions, R&D budgets in central countries are expected to suffer after the pandemic because of the global economic crisis[13].

In the industrial health complex, the pandemic impact generated an immediate increase in the demand for some segments (respirators and personal protective equipment) and the prospect of new products in the pharmaceutical and vaccine segments. In the latter, this motivation is confirmed by the already mentioned numbers of vaccine candidates and clinical trials that have emerged. Considering the commercial practices of the pharmaceutical industry (recently called Biopharmaceutical), everything indicates that the humanitarian feeling was incidental. Besides the traditional and well-known participation of public resources in the development of vaccines in their proof-of-concept (preclinical) phases, the pandemic's impact generated an unusual extension of this participation. In China, the European Union and the U.S., public resources were released to support more advanced (clinical) stages of development, and the urgency in vaccine development has even led governments to finance the construction of manufacturing facilities in companies and anticipate purchases of products that do not yet exist in their marketable form. Furthermore, it generated changes in regulatory standards in several countries to adjust the rules to the urgency in the development and production of vaccines. An attempt at harmonization inspired by the North American and European agencies was carried out by the International Coalition of Medicines Regulatory Authorities (ICMRA), which, however, presented very generic results[14] whose application are not mandated by national regulatory agencies.

Besides the pandemic's political impact, the humanitarian component of business interest in vaccine development was probably due to the role that the WHO took on the issue. Despite the political and financial difficulties that it has been experiencing for several years, the WHO embraced the task, and the most important result

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of this action was the construction of the mechanism that extended the contribution of public resources to the search for vaccines. However, to achieve this, it had to give up the executive leadership of this mechanism, assigning it to a nonprofit organization called Global Alliance for Vaccine and Immunization (GAVI), launched in 2000 to expand access to vaccines in Low Income Countries (LICs). GAVI is supported by multilateral (UNICEF, World Bank, WHO) and private bodies (Gates Foundation, biopharmaceutical industry, and others).

The mechanism developed by GAVI is called COVAX (Global Vaccine Access Facility – Covax Facility) and proposes the establishment of a pool of financial resources to escalate the development of vaccines against SARS-CoV-2 for the whole world. It works with the possibility of subsidies and vaccine donations for LICs and Low Middle Income Countries (LMICS). For Upper Middle Income countries (UMICs) and High Income Countries (HICs), it proposes a public financing mechanism (Gavi Advance Market Commitment for COVID-19 Vaccines – GaviCovax AMC) to accelerate the development and production of vaccines against the commitment to ensure preference in providing doses purchased or donated to LMICs and LICs. As of July 15, 75 HICs and UMICs and 90 LMICs and LICs had joined the mechanism[15]. The association between the WHO and GAVI also has the virtue of seeking to make vaccine prices affordable during the pandemic. What will happen after its end remains to be seen. While there is generally a positive appreciation of the agreement between the WHO and GAVI, some voices ask questions that they feel are not yet adequately answered. These questions concern the lack of transparency in GAVI-Covax decisions, its lack of experience in negotiating with rich countries, the extrapolation of its mandate – limited initially to LICs– and the question about why the WHO is not the plan's formulator and implementer. An overview of these questions can be found in a recent document by the organization Doctors Without Borders[16].

Brazil is among the 75 countries adhering to the Covax Facility through an agreement established between the Ministry of Health/Fiocruz/Bio-Manguinhos and AstraZeneca/University of Oxford, of US$ 127 million, for the acquisition of 30.4 million doses of the vaccine developed by them (designed by the platform of a viral vector), including the transfer of their technology to Bio-Manguinhos and the possible opening of the Latin American market for the vaccine produced here. This bold decision aims to ensure some level of priority in supplying it to the Brazilian population in the event of a happy ending for the product. Equally relevant is the inclusion of a technological compensation clause in the purchase of the vaccine, implying the transfer of technology, which is only possible because of the technological and productive capacities already existing in Bio-Manguinhos. However, the decision of the MS/Fiocruz is not without risks, given the level of uncertainty about the success of the product at the end of clinical trials.

Another critical, equally correct, domestic initiative for the production of a vaccine against SARS-CoV-2 was sponsored by the government of São Paulo/Instituto Butantã, which, on June 11, announced an agreement with the Chinese company Sinovac to participate in phase III of the clinical trial, already started in Brazil, and future production of its vaccine. It uses an inactivated virus platform, on which Butantã has extensive development and production experience. According to the Institute's report, the signed agreement refers to participation in the trial and includes a technological compensation clause with technology transfer.

The North American government and the European Union have committed to the advance purchase of 400 million doses of the AstraZeneca vaccine at the cost of US$ 1.2 billion each[17,18]. Likely, other countries have joined the Covax Facility mechanism or other agreements such as that of Butantã with Sinovac. Both the initiatives of the Ministry of Health/Fiocruz and the State of São Paulo/Butantã, if the respective vaccines are to be registered with ANVISA, may experience difficulties in supplying them. It will be necessary to observe each vaccine's production capacity in the United Kingdom and China, given that the first batches will be supplied by producers and will have to compete with other national or local supply agreements. Most likely, both agreements provide clauses that refer to delivery dates, but the experiences already lived during the pandemic suggest that contracted deadlines have not always been observed.

Conclusion

This text aimed to address the pandemic's intricate nature, dissecting only one of the dimensions of its coping– the existence of one or more vaccines against SARS-CoV-2 approved and made available to the Brazilian population,

which could put the coping of the pandemic in another landing. As has been reported so far, this single dimension is also not without complexity and risks and is far apart from being considered a "silver bullet", as the press, authorities, and even researchers have reported. Our approach also emphasizes this place of observation and analysis, which, as Jairnilson Paim reminds us in the text's epigraph, is at the "border of the biological and the social". Hence, in the discussion of the vaccine impact on COVID-19 pandemic it would be quite useful to take into account the conceptual framework of Collective Health, whose primary *raison d'être* is precisely to act on those interfaces.

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