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REVIEW ARTICLE

Vaccines for COVID-19: perspectives and challenge

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The world watches speechless during these first months of 2020, the most serious health crisis in the last hundred years, caused by a new virus, SARSCoV-2. The lack of a specific treatment, validated with well-controlled studies, made vaccines the most promising and awaited hope[1]. An effective vaccine will be crucial to control the pandemic, which has already affected around six million individuals worldwide and killed at least 350,000 people[2,3]. The guarantee of immunity will enable us to be less concerned with social distancing and all of its implications.

The genetic sequence of the virus released on January 11 triggered an intense global research activity to develop a vaccine against the disease. The size of the human and economic impact of the COVID-19 pandemic stimulated the use of new vaccine technology platforms to accelerate research, and the first vaccine candidate started clinical trials in humans in mid-March with unprecedented agility[4].

Due to the speed of research, there is a possibility that vaccines may be available, on an emergency basis, by the beginning of 2021. If this really happens, it will be the fastest vaccine development program ever seen in history. It will represent a fundamental change in the traditional trajectory of vaccine release, which takes an average of more than 10 years for its implementation[5,6]. In addition, we will need new paradigms, involving adaptations in the development phases, regulatory processes and large-scale manufacturing capacity.

Reducing the entire vaccine production process to 12 to 18 months is really unprecedented. But is this all possible without impairing the effectiveness and adequate safety?

About 120 research teams around the world are studying the virus from various angles to develop vaccines. Vaccine development programs are continuously updated by the WHO, with projects coming from public and private sources[7].

There are several technologies available, including nucleic acid (DNA and RNA), VLP (virus-like particle - technology used in the HPV vaccine), use of viral vectors (replicating and non-replicating) and traditional technology vaccines, such as recombinant protein, inactivated viruses and live attenuated virus vaccines[8, 9]. Some of these techniques have never been used in currently licensed vaccines, but they have been applied in areas such as oncology and, this way, new vaccine production opportunities arise, with greater speed of manufacture[6]. However, this process, like everything that is new and untested, requires caution, so it does not offer unreal hope at such a difficult time for humanity.

The majority of all vaccines studied for COVID-19 aim to induce neutralizing antibodies against the virus's most conserved protein, Spike (S); thus, preventing the virus from being captured by the human ACE2 (angiotensin-converting enzyme 2) receptor[10]. It is not clear how the protein S variants used in different vaccine candidates relate to each other or to the genomic epidemiology of the disease[6]. Should we place our hope on this one protein?

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Viruses can challenge vaccine producers, changing so rapidly that the antibodies that work on one viral strain fail on another. Fortunately, the new coronavirus does not appear to undergo major changes, so a vaccine that proves to be effective should probably be successful in any country[11]. This does not mean, however, that this risk is ruled out; therefore, the necessary caution in this regard must also be maintained.

Scientists are increasingly optimistic that a vaccine can be developed in record time. But manufacturing and distributing it are other huge challenges. Another aspect, which should not be overlooked, are the possible barriers to achieving adequate vaccine coverage, such as the decrease in the number of cases when licensing a vaccine, the hesitation to receive a new product, in addition to the lack of trust in political and sanitary authorities of many countries.

The two vaccines in more developed stages are in the United States and Europe. The American Modern laboratory started the clinical trial of its messenger RNA-based vaccine (mRNA-1273) just two months after the virus sequence was identified and has already published encouraging phase 1 research results in human volunteers[12]. Vaccines based on viral vectors are under development at the University of Oxford, England, in partnership with the AstraZeneca laboratory, promising to induce strong immune responses. Oxford researchers initially declared that they could have a vaccine ready for emergency use as early as September 2020[13]. Both research centers have started phase 2 and 3 studies and claim to accelerate these results. Brazil will participate in the clinical trial of the vaccine including 2,000 adult volunteers in a controlled study. It is important to emphasize that the desired speed in these results does not occur at the expense of quality scientific research.

At least ten other manufacturing companies are also in advanced stages of research. The CanSinoBiologics laboratory (China) recently released its phase 1 studies, showing promising results after 28 days of testing with 108 healthy volunteers[2]. In Germany and the USA, the Pfizer laboratory in association with the German company BioNTechestá is conducting phase 1 and 2 studies on the same messenger RNA platform and believes that vaccines will be produced later this year[14]. The American laboratory Johnson & Johnson promises vaccines for next year[15] and, finally, in an unprecedented collaboration, two of the largest vaccine producers in the world, the Sanofi Pasteur laboratories (France) and GlaxoSmithKline (GSK-United Kingdom), joinede forces to produce an adjuvant protein unit vaccine, which will soon begin phase 2 and 3 studies[16]. The remaining companies not mentioned are four Chinese (researching inactivated vaccines) and two American (protein and DNA units) [7].

The World Health Organization (WHO) made a proposal to the European Union recommending a voluntary patent pool, which would pressure companies to give up their monopolies on the vaccines they developed[17].

Oxfam, an international charity institution, has published an open letter to 140 world leaders and experts asking for a "people's vaccine" that is "available for free to everyone, in all countries." Helen Clark, former Prime Minister of New Zealand, who also signed the letter, commented that "vaccines against COVID-19 need to be a public asset and we are not safe until everyone is safe" [18].

Experienced vaccine researchers are concerned that, surrounded by a massive desire to end the COVID-19 pandemic, vaccine producers have become over-enthusiastic about the chances of their products working.

Several other vaccine companies have released statements with a more realistic look, establishing possible timelines for the conclusion of studies in 2021. Recently, the University of Oxford has retreated somewhat from its initial "optimism", since there is no solid evidence that the vaccine will actually be available before year-end.

Another important aspect is the profile of vaccine developers. While 72% of confirmed vaccine candidates are being developed by private companies, only 28% of projects are led by universities, the public sector and other non-profit organizations. In addition, although several developers are multinationals with extensive experience in vaccines, many of the main groups of the COVID-19 vaccine developers are small and/or inexperienced in the manufacturing of large-scale immunobiologicals[6]. So, would we have a production that enables access to the entire population?

The main active vaccine research for COVID-19 is distributed in 19 countries, which collectively represent more than three quarters of the global population. North America is responsible for 46% of the surveys, followed by China, Asia (excluding China), Australia and Europe, with an 18% each[6]. However, currently, there is little involvement and resources allocated to vaccine research in Africa and Latin America.

There is no doubt that strong international coordination and cooperation between researchers, regulators, policy makers, funders, public health agencies and governments will be needed to ensure that promising vaccines can be manufactured in sufficient quantities and provided equitably to all affected areas, particularly in poor countries.

Ensuring that vaccines are safe and effective requires extensive testing, careful planning and execution. We are all vulnerable to the new coronavirus, with the exception (probably) of those who have already contracted the disease. Each person may need more than one dose of a vaccine to receive protective immunity, so it may take more than 15 billion doses for the world to be protected from COVID-19[19].

Some knowledge gaps, especially in relation to the immune response to the virus, can represent obstacles to the development of a safe and effective vaccine. We do not know the correlates of protection against the disease, the exact role that cellular immunity plays in the immune response, the duration of neutralizing antibodies induced by a vaccine, the

immune response in different age groups and the possibility of developing ADE - antibody dependent enhancement- secondary to the application of the vaccine[19, 20].

We must also consider ethical aspects related to clinical research in a pandemic scenario. Would it be possible to shorten the observation and follow-up time in a study? Is flexible licensing criteria acceptable? Is voluntary exposure to the virus after administering a candidate vaccine ethically acceptable?[21]

Confidence in vaccines needs to be maintained at all costs, otherwise we will put at risk all the achievements obtained in the control and elimination of diseases worldwide.

Therefore, there are many challenges, yet to be overcome for the effective development of the vaccine.

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