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Humanity Struggles in an Agonizing Sprint to the Finish Line: Finding a Vaccine for Covid-19

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Abstract

The new situation has led mankind to face a more dramatic wave of expansion than in the previous months of the SARS-CoV-2 pandemic. The World Health Organization (WHO) has recently warned of the worsening outlook for the health crisis, and several countries have embarked on a biotechnology race to find an effective vaccine as soon as possible. Because of its relevance and the great geopolitical significance it carries, this dispute could be considered identical to an arms race or the race to conquer the moon. In the dispute to find the final vaccine that will bring humanity back to normal, countries such as China, Russia and the USA are at the forefront, but countries such as Mexico, Germany and the United Kingdom, among others, have also made a place for themselves in the dispute for different reasons. In this biotechnological race the pulse is not only on the consolidation of a vaccine with lasting and safe immunity so that the countries that develop it can benefit, but also on the benefits of the pharmaceutical companies that are expanding their profits due to the prolongation of the pandemic, the state of generalised fear of the virus, the economic state generated by the quarantines and also the leadership of the countries and their constructive position in the middle of the health crisis.

Keywords: vaccine, covid-19, pandemic, virus, immunity, drugs

1. Introduction

Almost at the same time that the coronavirus pandemic was beginning to cross borders as an unstoppable tsunami, laboratories around the world were racing against the clock to find a vaccine that could counteract the new pathogen. It is not the only scientific resource to stop the virus, but it is the most important. Research

always starts from the premise that vaccine development is characterized by a high level of failure, but there are 160 projects underway, 23 of which are at an advanced stage, and never before has the international scientific community acted in such a coordinated manner and with so many resources to solve a problem. Worldwide, some 22.5 million people are reported to have been infected, while deaths exceed 788,000, according to Johns Hopkins University. In total, 213 countries and territories have been hit by the disease, virtually all of them worldwide, making finding a vaccine against the new coronavirus a top priority.

Figure 1. Image obtained from Johns Hopkins University live (54). On the left appears the total number of infected and the most infected countries as of August 20, 2020. The map belongs to the most important nuclei of infection in Europe.

We are all aware that about four months ago everything worked differently than it does today. Some people have not yet reflected enough on what has happened, and why not venture to say, it will continue to happen; this is not yet over. The world has changed in many things, and these changes have been very noticeable, in such important structures of society as social and health. Healthcare workers have been heroes, fighting bravely against all odds, exposing themselves to infection without protective equipment and working tirelessly to bring infected people forward (50,53).

The world of information and news has allowed society to keep up with the evolution of the pandemic that is happening to us at the moment through the evolution of the coronavirus Covid-19. On the contrary, there has also been a lot of infotoxication, mainly due to the excessive use of social networks to which all users are exposed and use worldwide. The information has had to be filtered, and at times, it has been us who, at certain moments, almost out of desperation, have changed a certain piece of news according to our convenience, probably trying not to fall into discouragement in the face of the events of the new pandemic. Its rapid expansion due to the number of infections has led us to situations of overflow as has happened in many health centres and retirement homes, taking measures that we would never have thought of. We are talking about a virus that does not discriminate by gender,

sex, ideology, territory, cultural level, religion, etc., we are talking about a virus that has been able to take humanity almost against the ropes in some moments (13, 15,16,30).

The confinement of the population has achieved positive things, since by reducing the use of vehicles, the rates of environmental pollution in the cities have been reduced, even if only temporarily, and the ties within the family nucleus have also increased, however, there have also been situations of stress and loneliness in part of the population (38).

The pandemic has forced us to reorder our time, to slow down, perhaps this is also a good thing. We are responsible for the education of children who have also been forced to change their habits. The way of working has been changed and teleworking has been incorporated to a greater extent, perhaps with it human relations with friends and family, in the long term, being more impaired (2). But you learn to value more what you don't have.

Society in general has had more time to think collectively, to respect confinement measures for a common good, to work together on the issue of opening borders between different countries, to be able to identify transit zones between their communities and to take care to keep the infected persons identified so that the effect on the population is as small as possible.

Each affected country has implemented the measures it has deemed most appropriate, there have been many countries affected in Europe, after the infection started in China (48,49), now those countries are recovering, and the infection has advanced to other continents in an alarming way such as Latin America and South Asia. The numbers of people infected and killed by the pandemic are soaring in these areas.

SARS, or severe acute respiratory syndrome, killed 774 people in 17 countries. These outbreaks had mortality rates of 9.5 and 34.5 per cent respectively (10,23,33). The coronavirus that started in Wuhan has so far caused a number of people infected with Covid-19 worldwide of about 7.5 million people, and a number of deaths of about 420,000 people. Currently, there are about 188 countries out of 194 infected, which means a level of infection of 96.9% of all countries in the world. The countries most affected by the pandemic so far are the United States, Spain, the United Kingdom, Italy, France, Germany, Russia, Turkey and Brazil, where the number of deaths has exceeded 100,000 (45).

It is time to reflect and join efforts in the same direction, to connect, to think logically, to feel, to reflect and to forget values in order to achieve a common goal, to get a vaccine as soon as possible and to put the virus against the ropes, before the virus puts us (40,41). It is a battle against time, a battle that we can and will win, but as a rule and according to the data of the last few decades, it seems that every

four or five years there are outbreaks of viruses that we may not be able to defeat in time, humanity is at stake, and time is golden now, let us make our way little by little but lay the foundations for a future that tends to be very dangerous. Perhaps we have realized that investing in science is investing in a safer future, a future from which a more promising and committed world can be glimpsed. Now it is time to find the saving vaccine that will make us return to the new normality of life, perhaps never again, but it is better than never returning to anything (4,6,18,31,32,51).

2. Methods and Materials

A study will be conducted on how the different developments of Covid-19 vaccines are going in the countries that are at the forefront of their development. It could be said that almost from the initial moment of detection of this pandemic, different laboratories around the world have been studying and looking for a vaccine to counteract the effects of this new type of coronavirus (26,27). Its symptomatology has been studied and it has been seen how it affects people who suffer from it. The most serious symptoms that have been diagnosed are a frragilization of the lung tissue into an inelastic tissue with a feeling of shortness of breath or air, chest pain or pressure, and an inability to speak or move. Other less common symptoms that have been detected include: dry cough, small tumors in the upper and lower extremities, fatigue, sore throat, diarrhea, conjunctivitis, loss of sense of smell or taste, headache, diabetes, skin rashes, or loss of color in the fingers and toes (5,7,8,12,19,42,46,47).

In the face of this pandemic, the scientific community is acting in a coordinated manner and with sufficient resources to find a vaccine as soon as possible. More than a hundred projects are currently being developed, some of which are already at an advanced stage.

2.1 The vaccine and its importance

For the moment, until a vaccine is found, SARS-CoV-2 coronavirus will be able to circulate freely among people, who will be fully exposed to the pathogen. This new virus has shown a higher capacity of contagion than originally estimated, which has allowed it to spread throughout the world very quickly, as indicated by the figures of contagion and deaths in scientific studies being conducted since its inception in Wuhan (China) (17,20,24,39,44).

Vaccines are biological preparations, which after being administered, are capable of producing an immune response, specific, effective and artificial against microorganisms, that is, a preparation whose function is to generate the body's immunity against a certain disease, stimulating it to produce antibodies that will then act to protect it against future infections, since the immune system will be able to recognize the infectious agent and destroy it. Vaccines are divided into monovalent (they have only one antigen), polyvalent (several anti-

gens of the same species, meningococcus) and combined (several antigens of different species, diphtheria, tetanus).

Currently, there are combined vaccines, such as trivalent or hexavalent, which allow simultaneous immunization against several important diseases. And all this without appreciable risks, since the adverse effects of vaccines are very mild (mild redness and pain at the injection site, fever or muscle aches) and very rarely serious. The vaccines are administered intramuscularly and in some cases orally. Several time-spaced doses are usually necessary to achieve sustained immunity over time (37,43).

Any hygienic measures taken, such as the use of masks or physical distancing, will continue to be very effective and may slow the rate of infection to relatively safe levels, but a return to the pre-pandemic situation will depend on finding therapeutic solutions. Among these, the vaccine is the most important.

2.2 Is it just a vaccine or something else?

A fierce race has begun towards the development of that vaccine to end this pandemic, but there are many other things at stake at the level of scientific development and economic interests in selling the final product. However, there are different challenges that make this challenge, due to the different circumstances that surround it, one of the most important that science has faced in its history:

- Shorten manufacturing times, which in all vaccine developments are usually long because of the different phases it has to go through.

- The final vaccine, in addition to being effective, must be able to be manufactured on a large scale, in order to spread it globally.

- Ensure vaccination campaigns, which in this case, must be massive.

Some experts, the less optimistic ones, say that the efforts made by scientists in search of the vaccine could be in vain, but considering that most of the patients who have passed the virus have responded immunologically, there seems to be a glimmer of hope in the achievement of the Covid-19 vaccine.
For Russia and China, it is the treatment of the health crisis or the capacity to respond to the virus that has the characteristics of countermeasures formulated for a germ warfare scenario. This modality has several principles. The first of these is based on the fact that the response is the responsibility of the nation states. Secondly, that the virus is a matter of integral security and therefore it is one more front of the military management. Finally, the race to defeat the virus through a vaccine generated by the state apparatus will be a precise blow to the hegemony of Western pharmaceutical companies and their private/private

technologies, which can widen the gaps in access to vaccines from developed countries to Third World countries, a factor that would be an element of instability that could prolong the health crisis.

2.3 Time required

Scientists have projected a time frame of 12-18 months to find a viable and effective vaccine (3,27). In general, the processes have been accelerated to a maximum, however there are stages in the methodology that cannot be shortened and that need months to be tested. It is evident that for people, for humanity, time seems eternal, it seems that it will be played with the relativity of time and Einstein's theories. The doomsayers show that the times to find the solution could be years and even decades, I don't know if you could expect so much having such a fierce and threatening pandemic out there.

The development of effective vaccines generally shows a high error rate. Scientists use processes that are usually linear, and avoid making false steps, before moving on to the next phase. Nowadays, this has been changed, and it depends on the urgency, in this case a lot, the processes are carried out in parallel to go faster, and tending to abandon the previous linear scheme. The aim is to shorten the time to reach the solution sooner, even if this increases the risk of failure. One of the actions or measures taken is to start the clinical phase in humans before the end of the phase in animal models (21,28) . The vaccine is also beginning to be mass marketed, even before it is known whether it will be successful or not. As we can see, the behaviour of scientists has changed and everything has accelerated in order to achieve a solution as soon as possible, nothing more or less than the future of humanity is at stake (29).

2.4 Phases of a vaccine

The development of a vaccine can be done in the following phases:

- Phase 0: or also called pre-clinical, this phase includes in vitro and animal testing. The vaccine must be shown to be safe and to work in animal organisms. If you respond adequately, you move on to the clinical trial which is usually divided into three subphases plus an optional fourth.

- Subphase 1: The vaccine is tested on samples of a small human population, in groups of 20-100 healthy people. This is done to demonstrate that the vaccine can be safely applied in the human population and to be able to see and analyze possible side effects, if any. The right amount of vaccine doses is also studied.

- Sub-phase 2: In this phase the sample of the population to be studied is increased, and already applies to a population of several hundred people. The

most common possible short-term side effects and how people's immune systems react are reassessed.

- Sub-phase 3: The population of people to be educated continues to increase and extends to thousands of people. In this sub-phase, the evolution of vaccinated persons is compared with those who were not vaccinated. In addition, statistical data are collected on the effectiveness of the vaccine and its safety. Possible new side effects are checked in people who were not detected in the previous subphase.

- Sub-phase 4: is a voluntary confirmation phase where the vaccine is further tested after being approved for manufacture and production. The main goal is to get more information about the vaccine so that it becomes more effective and safe.

2.5 Vaccine projects

On June 9, the World Health Organization (WHO) recognized 126 projects that have found a vaccine candidate and are in phase 0 or pre-clinical since the coronavirus outbreak was declared an epidemic. There are 10 other projects that have passed this phase and are already in the clinical phase with human testing.

The following are the most advanced projects in search of the definitive vaccine:

- CanSino Biological INc. / Beijing Institute of Biotechnology (China). This project is already in subphase 2, where a viral vector vaccine is being developed. It is a subunit vaccine (new generation formula that does not contain pathogens), and very safe. Tests have been conducted on people with satisfactory results. The population sample has now been expanded to test for efficacy, safety and posible side effects (http://www.cansinotech.com/homes/article/show/56/153.html).

- Modern / National Institute of Infectious Diseases NIAID (USA). This project is in subphase 2. A viral vector vaccine, combined with the genetic code of the virus, is performed. It is being developed at a productive level by means of a pharmaceutical, and the first tests on humans have given positive results. They will continue with the trials (https://www.niaid.nih.gov/).

- Sinophram / Wuhan Institute of Biological Products and Sinopharm / Beijing Institute of Products (China). This vaccine developed by the union of these two Institutes is in subphases 1 and 2. Two very promising independent projects have been developed, based on inactive viruses. Launched by Sinopharm, the state-owned pharmaceutical giant. (http://spanish.xinhuanet.com/2020-04/14/c_138974503.htm). The application of the vaccine in humans began in

April, and it seems to have been shown to be very safe, and the possibility is advanced that in May 2021, all the clinical trials could be completed to certify its efficacy and safety.

- Sinovac (China). It is found in subphases 1 and 2. It works with purified inactive virus, and has generated many expectations after scientifically demonstrating that this vaccine is capable of generating effective antibodies against coronavirus in macaques, rats and mice. Human testing is scheduled to begin later this year (http://www.sinovac.com/).

- Jenner Institute, Oxford University, UK. This vaccine is in subphases 1 and 2. (https://www.jenner.ac.uk/) It uses a modified version of chimpanzee adenovirus and human volunteer trials have begun. It is the great European gamble. AstraZeneca Pharmaceuticals is participating in the project. It is believed that by the end of 2020, this vaccine could be ready for limited use.

- BioNTech / Pfizer (Germany / USA). This vaccine is in subphases 1 and 2. BioNTech, allied with the American pharmaceutical company Pfizer in January of this year to obtain an effective and safe vaccine. It has been successfully tested in mice and is already being tested in humans with four variants of a synthetic messenger RNA-based candidate. The multiple approach of this project, allows a simultaneous assessment to be made to increase the chances of identifying the safest and most effective potential candidate. (https://investors.pfizer.com/investor-news/press-release-details/2020/BioNTech-and-Pfizer-announce-completion-of-dosing-for-first-cohort-of-Phase-1-2-trial-of-COVID-19-vaccine-candidates-in-Germany/default.aspx).

- Inovio Pharmaceutical (USA) . This project is in subphase 1. This vaccine candidate will be tested in humans in April based on the virus' RNA. (https://www.inovio.com/). Immune response data and possible side effects are expected by the end of the summer. Depending on these results, the project would enter sub-phase 2 with a larger sample of population

- Novavax (USA). This project is in subphase 1. He has just started human clinical trials with his protein subunit-based candidate, and expects to have the first results by July, where, depending on the results obtained, the second subphase would begin. (https://novavax.com/) Researchers say the vaccine will be highly immunogenic in humans, which will result in greater protection against Covid.19 and the spread of the virus.

- Institute of Medical Biology (China). The project is in subphase 1. It's another of the Chinese vaccine candidate projects. He just started his human trials. It is a project based on the inactive virus:

(https://www.rtve.es/noticias/20200617/se-sabe-vacuna-contra-coronavirus/2013431.shtml).

In Spain, research is also being carried out on a vaccine that can tackle the coronavirus. To date, there are 10 projects that make a difference, but for now they are in the preclinical or phase 0 phase. The most outstanding projects are:

The National Centre for Biotechnology (CNB), which belongs to the Spanish National Research Council (CSIC) (https://www.cnb.csic.es/index.php/es/), will soon begin animal testing of a vaccine candidate based on a modification of the vaccine used to combat smallpox disease, using a highly attenuated strain of the Vaccinia virus (MVA), of the smallpox family, as a viral vector to insert genes of the new coronavirus that can provoke an adequate immune response to SARS-CoV-2.

There is another team at the same Centre that is working on creating a vaccine from a genetic reconstruction of the coronavirus itself, attenuating and eliminating the most virulent genes, with the possibility of soon having a viable vaccine candidate.

And there is a third group of CSIC researchers who are looking for a vaccine using a coronavirus antigen to stimulate immunity. The method consists of placing the antigen gene in the synthetic 'vehicle' of genetic material that can be introduced into the patient's body and induce protection against infection. It is believed that in two months it will be tested on mice.

2.6 Other solutions

In addition to vaccines, there is another line of research to combat the coronavirus, and that line is drugs (1,9). According to estimates, some 200 new investigational drugs, mostly antiviral, have been identified that could combat the new coronavirus.

The use of existing drugs to combat the new coronavirus has multiplied in the last weeks of the pandemic. Around 1700 clinical trials have been registered, of which approximately 80 are being carried out in Spain.

These existing or developing drugs, administered individually or in combination, are mainly divided into three groups (11,14,37,51):

- Those intended to prevent the virus from progressing within the human body.

- Those designed to calm the immune system's response (in the most severe cases of the disease, an exaggerated and potentially fatal immune reaction is triggered, called a 'cytokine storm').

- Those based on antibodies, either obtained in laboratories or from the blood plasma of patients who have overcome the disease.

Since the beginning of the pandemic, the treatments used have been oriented towards three objectives: antiviral, anti-inflammatory and antibiotic (viral infections are often associated with bacterial infections). However, clinical evidence has led to the addition of other drugs such as antithrombotics or anticoagulants over the weeks (22,25,34,35,36,52).

Conclusion

As can be deduced from the above study, the leading research centres in Virology, Pathogens and the study of rare diseases, are fighting to find as soon as possible a vaccine that can, for the time being, bring humanity to safety. At the moment, hopes are pinned on five Chinese research centres, four American, one British and one German, as the leading or most advanced centres in terms of clinical sub-phases applied to arrive at an effective and safe vaccine definitively.

From what has been analyzed so far, the most advanced centers are in subphase two, and are a Chinese center (Institute of Biotechnology) and an American one (Modern / National Institute of Infectious Diseases (NIAID)). There are five other centres between subphases 1 and 2, and the remaining centres (three) at the forefront of research to achieve the final vaccine are in subphase 1. They have been shown to be safe and capable of inducing immune responses in most patients, as revealed in a phase 2 human study. The researchers found that the Ad5-nCOV vaccine, which was given to 508 healthy adults not exposed to Covid-19, induces immune responses from antibodies and T cells that attack the virus, while causing no serious side effects. China has also coordinated from the ruling Communist Party and the high command of its People's Army the dedication of its scientists in the development of treatments for the virus, as well as the first prototypes of vaccines. This is a clear sign that for the Chinese this is also a matter of strategic security.

The Russian Federation has announced that it already has its first vaccine against Covid-19. This was reported by the country's Ministry of Defence, which developed the long-awaited drug in conjunction with the Centre for Epidemiology and Gamaleya Microbiology. The institutional and military revelation of this news is not a fortuitous matter. For the Russians, the biotechnological solution implied by the vaccine is a matter of the highest strategic interest inherent to their national security and global stability. Previously, the Russian Ministry of Health announced that four types of Covid-19 vaccines could be produced industrially, so that by the end of 2020, 200 million doses would be available, both for domestic use and for the international market. For the Russian population, vaccination will be free.

The U.S. government has taken a step forward in the fight against the virus according to capitalist methods, this time by ordering from the Pfizer Corporation some 100 million vaccines against Covid-19 that are developed by this pharmaceutical company. According to the supply agreement, the U.S. government will also be able to acquire up to 500 million additional doses. The Administration will benefit from these first 100 million doses after Pfizer successfully manufactures the vaccine and obtains approval or authorization for its use from the U.S. Food and Drug Administration (FDA).

During the pandemic, the U.S. government had pursued a very aggressive policy of ventilator recruitment and also by purchasing the entire three-month production of the drug Remdesivir, manufactured by the pharmaceutical corporation Gilead. This leaves a clear tendency for Americans to favor the proprietary scheme of which corporations are the beneficiaries.

However, in geopolitical terms, the questioned US "leadership" in the face of the crisis, including its erratic management on US soil, has placed the Americans in a race oriented only to their own benefit and to the detriment of allied or "friendly" countries, which have been made to lose their place on the world stage.

Preliminary results have recently been published from a phase 1/2 trial of a Covid-19 vaccine developed by Oxford University in the United Kingdom. They suggest that this developing vaccine is safe and induces an immune response. The vaccine elicited an antibody response within 28 days and a T-cell response within 14 days. The trial included several thousand people aged 18 to 55 with no history of Covid-19 and took place in five UK hospitals from late April to late May. Participants received either the Covid-19 vaccine, or the meningococcal conjugate vaccine, as a control group.
However, Mexico, the Latin American country second most affected by the pandemic after Brazil, has entered the race for a vaccine, but at the political-diplomatic level, through a proposal by Andrés Manuel López Obrador before the United Nations (UN) to seek a global (joint) response to the creation of a vaccine. Last April, and at the request of Mexico, Resolution 74/247 was unanimously approved at the UN General Assembly with the aim of ensuring global access to vaccines and avoiding their monopolization. This resolution, says the Russian media Sputnik, opened the way for the creation of the COVAX Platform, which so far consists of 77 countries that are building a consolidated purchasing mechanism for the future Covid-19 vaccine jointly and in advance, regardless of the payment capacity of the platform's members. This resolution is presented as incongruent with the actions of the Americans during the pandemic.

In line with breaking the potential for vaccine deprivation in poor countries, China has offered a large credit to Latin American countries for access to

vaccines. This announcement came from the Ministry of Foreign Affairs of the People's Republic of Asia, and assumes that this line of credit would give countries access to the vaccine at really low prices. China is the developed country that is projecting its lines of support more towards Africa, a continent where the pandemic continues to gain ground, and which is also a region of the world that could be excluded from the vaccines manufactured in Western countries.

The multilateral character in the fight against the pandemic has specific denominators and China and Russia are in the vanguard, together with other countries such as Cuba, which is already preparing to manufacture the Russian treatment against Covid-19 Avifavir and has been recognized worldwide for sending its medical personnel to care for patients affected by the pandemic in other countries.

The related factors and interests of the emerging world point to an arms and biotechnology race for world stability as the only viable alternative to the policy of dismemberment, deprivation and chaos that has been heralded by the old Western powers. All this endangers the balance of Humanity and makes the sprint agonizing in a world that is increasingly unbalanced in terms of health, economic and political factors. Humanity plays with fire, and as the saying goes, in the end it could end up burning.

Apart from vaccines, which will still take some time, drugs are another possible short-term solution. There are some drugs where their safety has already been proven, among them are Remdesivir (Ebola), the only one already in clinical phase 3, prior to commercialization; Lopinavir and Ritonavir (HIV), Hydroxychloroquine and Chloroquine (malaria). However, according to clinical data, the latter two drugs do not appear to provide any benefit over patients treated with Covid-19. In view of the doubts generated, the World Health Organization (WHO) has decided to suspend all its hydroxychloroquine trials while the risks are reviewed.

There are other drugs whose development is based on antibodies and where several researches worldwide focus their efforts on identifying proteins that prevent the SARS-CoV-2 virus from parasitizing human cells and using them to replicate its genetic material. Two independent laboratories, one in the Netherlands and one in Israel, have already obtained antibodies capable of neutralizing it, following the example of other diseases already treated with this same technique.

One of the measures to see the number of people infected by the virus, has been the vaccination of a part of the population to which are added the people who are immune because they have developed antibodies after a previous infection, this is called 'herd or collective immunity', which provides indirect protection

to the non-vaccinated individuals. Epidemiologists estimate that 60 to 70% of the population needs to be immune to the virus to achieve this kind of collective immunity.

Until the vaccine arrives, there are very conflicting positions on taking action. There are advocates that contagion should occur freely without putting in place any measures to combat it, with the intention of increasing herd immunity in the population. This allows an increase in the number of positive cases and in the number of people circulating to increase the generation of antibodies and the creation of an immune barrier. But this strategy does not seem to be a good solution, as it could lead the health system to a situation of collapse, and consequently, to the death of a large number of patients.

In Spain, the first data from the seroprevalence study carried out by the Ministry of Health are quite discouraging in this regard. Only 5% of the Spanish population would have generated antibodies, so this 'herd immunity' without a vaccine seems an extremely difficult horizon to reach, especially considering the high human, health and economic costs that such a low percentage has implied.

Who will reach the goal first, is a dilemma that we hope will soon have a solution, the important thing is to reach that goal that for now seems a little distant.

Discussion

The fact that only 5% of Spaniards have been in contact with the most destructive pathogen of this century, leaves citizens at the mercy of the discovery of a vaccine: the only thing that could guarantee the famous herd immunity, and that most people could return to normal life without risk of infection. In this race against the clock in which there is no limit to the number of participants, there are several major obstacles. Overcoming them will be necessary so that the desired immunization can be given to healthy people.

Now vaccines cannot or should not be developed that would be counterproductive for the population, as was the case in 1996 in the United States, where the first vaccine against respiratory syncytial virus was tested, because controls are very demanding. This is something that slows down the process, but it is necessary. A vaccine is not given to repair damage, but to prevent it. This means that the sample sizes for testing have to be much larger than those used in the drugs.

There are four main vaccine routes to combat the new coronavirus, one using attenuated virus, one using recombinant DNA, one using RNA and one based on recombinant purified antigens. The new vaccines are never easy to obtain, it is a very complex biological product, and the research capacity is what it is.

Although the results could be encouraging, there are groups of scientists who have reached subphase 2, many more experiments have to be performed, to analyze how

the immune system is stimulated, to see the correlation between the different parameters of protection against the virus (protective correlates). Antibodies and cellular immunity have to be studied. Currently, there is very interesting work regarding the cellular immunity that induces SARS-COv-2 infection and that is very relevant when designing vaccine candidates.

We also have the problem of the circulation of the virus, it could be that it circulates little or not at all when it comes to demonstrating its effectiveness on a large scale. One possible solution, this has been suggested before, would be to purposefully infect volunteers in a controlled way, this is a very controversial open debate especially for a disease for which there is no treatment, with very serious complications even with death of the patients, and there are many ethical aspects to consider.

A bet could be made to start vaccination in high-prevalence areas, and see if vaccinated individuals do not get infected or get infected only very mildly. This type of procedure is usually followed to test vaccines such as tuberculosis. It is initially studied in volunteers to assess toxicity, but the successive clinical phases are done in countries with high incidence. Groups that are vaccinated are then compared with groups that are not, and the percentage of people infected in each group is analyzed.

Assuming that the first part of development is overcome and a prototype of the Covid-19 vaccine will soon be available, we are now entering the production part. You'd have the brake on mass production. Despite advances in pharmaceutical R&D, the technology has been around for many years and has not evolved much. The time it takes to develop the product, once you have it, and to manufacture it remains the same. It is estimated, objectively, that the time to achieve a large-scale vaccine with millions of doses will be between 14 and 18 months from the start of the research. This 'long time' could be solved with alliances and business clusters that could use multi-dose vials among other solutions. The antigen should be produced in GMP (good manufacturing practice) companies, but this in turn could trigger a 'bottleneck'.

Recently, outbreaks of the new coronavirus have begun to be detected, suggesting that the factor of speed in the manufacture of the vaccine is becoming increasingly important. You can choose to start making it before you know if it is effective as researchers at Oxford University have done in human clinical trials.

The Pharmaceutical industry seems to have committed itself to producing it on a large scale while it is in subphases 1 and 2 of development. However, a pharmaceutical product can only be legally manufactured when it reaches subphase 3, which includes a clinical trial in humans. Ideally, the technology should generate a faster product development, which is scalable and cost efficient. The future points to recombinant proteins, which are the drugs of the future, however, the technologies applied to produce them are always based on bioreactors, which are very complex and expensive facilities.

We enter a phase where we have to weigh up the speed in order to get the required information as soon as possible to first select from the vaccines that are being developed which one of them can be more or less effective, without ignoring the

safety of the vaccine. In a rush, there is always a possible decrease in vaccine safety. In this case, the risk/benefit of protection must be assessed. At this moment the processes are being speeded up in a very important way, especially skipping the study in animal models and going directly to test in humans.

Even if the steps in the development and production of the antigen are shortened, there are other difficulties to be taken into account. There might be a logical temptation for the country that finds the vaccine first to want to vaccinate its population first, but to avoid this are the institutions. One could consider giving priority to the administration of the vaccine, in the country where the virus is circulating at that time. It is estimated that about 7 billion doses would be needed immediately, assuming that one dose would be sufficient and that other types of vaccines would be discontinued. WHO is expected to be the agency that provides order and sanity in the delivery and distribution of vaccines.

To provide the vaccine at the same time and to everyone seems an impossible task, so priority should be given to the most vulnerable population, to the health workers and the elderly, perhaps also to the state security forces. But it would depend on the characteristics of the vaccine, because it might work, for example, better in the young population.

The economic issue also plays an important role, some politicians are betting on a shared risk, that is, that the governments contribute economically to the development and production of the vaccines, risking to be betting on a product that finally does not work. It must be taken into account that the development of a vaccine from its initial phases is very costly in terms of time for experimentation, and in its implementation, passing through the different clinical phases required for final approval by the regulatory agencies, in addition to the added cost of producing the vaccine.

The cost of the vaccine will depend on the type of vaccine you have. If the pathogen is attenuated, for example, it has to be grown under GMP conditions, it may not grow well, it may have to be repeated. You have to look for cells that can be infected by the particular virus, and not many companies can manufacture this type of vaccine. It must be taken into account that the safety and regulation conditions are very extreme to work with pathogens. It can also happen that the successful vaccine is developed with protein, DNA, and RNA components. In that case, the type of production is different, of course also under GMP conditions, but in a different way, and it is usually other types of biotechnology companies that could develop them. It is also necessary to see what kind of adjuvants are used, and what kind of combination is finally used. These are certain conditions that must be taken into account," he specifies.

All these reflections lead to the conclusion that the important thing in the end will be to reach the goal and get the right vaccine so that humanity, this time, will be safe. What will happen next? We don't know, but what seems to be true is that this time the work has been done side by side, that the work has been done differently and that the efforts of many scientists from all over the world have been united, sharing more than other times, to achieve the common goal, to find the Covid-19 vaccine.

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