COVID-19: Who will produce the vaccine? *

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As the coronavirus pandemic (COVID-19) sweeps through many parts of world, many attempts are being made to develop methodologies to induce protective immunity against the virus infection. Different pathways are being employed: using vaccines to induce prophylactic antibodies and cellular reactivity, transferring plasma containing antibodies from convalescent patients, or administering monoclonal antibodies specifically induced against SARS-CoV-2. The development of a safe vaccine, effective in preventing infection and inexpensive, seem to be the only way to control the pandemic, thus allowing us to resume our normal daily activities and progressively mitigate the social and economic problems that we are struggling with (Cecconi et al, 2020).

In the 150 days that have elapsed since the molecular characterization of the SARS-CoV-2 in January 2020 by Chinese scientists, the international scientific community has worked with an unprecedented force to acquire as much information as possible on the biology of the virus and on the pathology of the infection, ensuring that the data obtained worldwide are made available to all. This, together with other findings obtained in the past regarding SARS and MERS outbreaks (both caused by members of the coronavirus family), has led to the design of "candidate vaccines" for prophylaxis and for "cocktails" of neutralizing monoclonal antibodies for therapy against COVID-19.

What is the probability of finding a remedy for COVID-19? Although much work still needs to be done before effective treatments become available, the results obtained so far appear to be encouraging. The virus that causes COVID-19 possesses a relatively large genetic information and produces many proteins, some of them effectively controlling its replication and structure, so that mutations are rare compared to other RNA viruses. Although several amino acid substitutions have been already observed, there is a need to carefully monitor them to avoid the evasion of the immune response driven by the vaccine or by the passive administration of monoclonal antibodies (Corum and Zimmer, 2020).

Based on official data, more than 50% of the infected patients have already recovered from the disease and the vast majority of these patients possess antibodies against the virus (Wajnberg et al, 2020). Several research teams - some of them in Italy (Andreano et al, 2020) - are obtaining monoclonal antibodies from the memory B cells obtained from the blood of the recovered patients. Alone or in combination, a few of these monoclonal antibodies targeting the Spike protein, a homotrimeric glycoprotein that is anchored in the viral membrane, are able to neutralize SARS-CoV-2 infectivity *in vitro* and in animal models.

*****This document is based on a paper entitled "Vaccino COVID-19: chi decide, chi rischia, e chi paga?" appeared on the Huffighton Post of May 19, 2020 https://www.huffingtonpost.it/entry/vaccino-covid-19-chi-decide-chi-rischia-chi-paga-di-g-forni-e-a-tagliabue_it_5ec39fb5c5b6d0826594147e?72&utm_hp_ref=it-homepage

We have learned from previous common cold infections that the development of vaccines for coronavirus family is not an easy task. How long the protection acquired by the recovered patients may last is a feature that cannot yet be clearly established, since the observation time since the arrival of SARS-CoV-2 is still very short. This missing information is important because a good vaccine must provide protection that lasts as long as the protection acquired by a patient after recovery. Some preliminary observations suggest that these antibodies may last only two to three months, but this issue requires further studies. Finally, in order to develop an effective and safe vaccine, we must be entirely sure that the antibodies induced by the "candidate vaccine" not only provide protection from infection, but also do not worsen the course of the infection as is the case with the Dengue vaccine, a disease where Antibody Dependent Enhancement (ADE) has been reported.

Despite the understandable haste and social pressure, the primary responsibility of scientists studying and producing vaccines is to ensure that the new vaccine is absolutely safe.

Lastly, a few studies have shown that SARS-CoV-2 stimulates a robust cellular immune response. However, how crucial the role of memory cellular immunity is in the protection from a subsequent SARS-CoV-2 re-infection has not yet been established (Leslie et al, 2020).

What type of vaccine? To address the new pandemic, researchers from over 170 laboratories around the world have started to design vaccines for COVID-19 based on rational assumptions and often bold hypotheses. These projects include a variety of experimental designs and differ greatly in their expected duration. For a detailed description of the various kinds of anti-SARS-CoV-2 vaccines see report in Accademia, 2020a.

Some laboratories have developed vaccines for COVID-19 following technologies successfully employed for vaccines against other microorganisms. Thus, some studies are assessing the efficacy of "candidate vaccines" based on attenuated SARS-CoV-2 or SARS-COV-2 completely inactivated. These "candidate vaccines" would induce an immune response against the entire virus, including those structures that do not play a role in infecting human cells.

Other "candidate vaccines" are based on portions (sub-units) of the virus. To enter the human cells, the SARS-CoV-2 exploits the homotrimers of the Spike protein protruding from the viral envelope. Instead of a vaccine against the entire virus, some research teams aim to develop a vaccine against the Spike protein, therefore neutralizing virus infectivity. Other researchers are attempting to create "candidate vaccines" that induce an immune response only to the small portion of the Spike protein that plays a critical role in establishing a contact with the human cells, rather than against the whole protein. These studies aim to induce an immune response only against a clearly defined molecular target, responsible for the infection.

But how can we induce the immune response against a specific target of the virus? With recombinant RNA or DNA technology we can obtain fragments of the Spike protein that are then inoculated in the vaccination procedure, mixed with a special oil/water blend called adjuvant: the adjuvants facilitate the induction of a strong immune response. This is particularly important in the elderly, who are the most in need but who often do not respond well to vaccines. Effective adjuvants have been developed in Siena by Glaxo Smith Kline (GSK).

Instead of directly using fragments of the Spike protein, other researchers are using the corresponding coding DNA or RNA segments to instruct human cells to synthetize the fragments of the Spike protein that will induce an immune response. Other "candidate vaccines" for COVID-19 are based on viruses where a nucleic acid segment, coding for the immunogenic portion the Spike protein, has been inserted. Some of these viruses are able to replicate to some extent and give rise to a very small-scale infection; other viruses no longer replicate and can act only as vectors of nucleic acids. Nucleic acids carrying the information to produce the Spike protein or its fragments, can also be delivered in microscopic lipid vesicles. Alternatively, microscopic rings of DNA can be injected directly into the skeletal muscle of the person to be vaccinated; the association with a small local electric shock that lasts only a few microseconds may facilitate the penetration of the DNA into the muscle. In addition to these innovative techniques, which have been used previously, several others are being tested.

In many countries around the world, during the 150 days since the first molecular identification of the SARS-CoV-2 virus, the creative impetus of human intelligence has prompted academic research laboratories, small biotechnology companies, or even laboratories of huge pharmaceutical companies to design these new "candidate vaccines" as briefly sketched above. This widespread involvement and ample spectrum of experimental designs is very opportune and needed to fight a largely unknown new disease. The 170 attempts to develop "candidate vaccines" will increase the probability of developing one that proves to be really effective, among the many that will prove to be partially or not effective at all (Accademia, 2020a).

In any case, the path to obtain a new vaccine is complex, long and proceeds through different stages. In brief, research leads to a hypothesis on the composition of the vaccine. Its safety and efficacy are subsequently verified in animal models. However, since reliable animal models are not always available, there has been a tendency to move quickly to experimentation in humans. In several recent cases, the effectiveness of the "candidate vaccine" was assessed for its ability to induce an immune response in vaccinated volunteers. Although the ability to induce an antibody response and a specific T lymphocyte reactivity are important indicators, the end proof of the effectiveness of a "candidate vaccine" is achieved by field studies. Groups of hundreds, thousands and sometimes tens of thousands of volunteers in areas of high prevalence of infection are vaccinated while similar groups are not. The number of people that have fallen ill in the two groups is evaluated at progressive time intervals. These studies, which are costly and very long, are also influenced by the spread of the infection during the study period, which may sometimes vary unexpectedly.

In a pandemic situation, such as the current one, the question arises as to whether it is ethically acceptable to evaluate whether the immune response induced by the new "candidate vaccine" can also protect against an experimental inoculum of SARS-CoV-2 in volunteers. The risks associated with this type of human trial, which greatly shortens the time needed to verify the effectiveness of the "candidate vaccine", would be outweighed by the human lives that could be saved from the early development of a vaccine (Eyal et al, 2020).

Who decides? Who takes the risk? Who pays? Experimental design and lab research are activities that can be carried out by a few researchers, some technicians or students. Expenditure is relatively small and may be covered by funds not specifically targeting the "candidate vaccine" project.

However, as soon as the “candidate vaccine” appears to be promising, funding becomes crucial. Who pays? Who takes the risk of investing a huge amount of resources to pursue the project and address the clinical studies? At the moment, about 70 of the initial projects have managed to collect the necessary resources to continue. Of these, around a dozen have reached or are approaching the first testing in monkeys or humans, i.e. the Phase I-2 trials (WHO, 2020a). The cost of getting a “candidate vaccine” to Phase I is very high. But what scenario will open if the new candidate vaccine will be shown to protect monkeys from COVID-19 and induce a strong immune response in human volunteers?

Once this data has been acquired, the scientific and medical aspects fade away to some extent, as technical problems and economic factors regarding the vaccine production become imposing. Who has the funds and technology to move forward? The game, by its very nature, becomes hard at this point. To reach the marketing stage, a vaccine costs approximately one to two billion euros, and the chances of success are low. Under normal conditions only 6 % of the “candidate vaccines” is put on the market. However, a pandemic does not fall under a normal situation, in view of the social and economic costs as well as the undeniable political reward in finding an effective vaccine (Accademia, 2020b).

Who can risk investing all the necessary resources on a vaccine that may arrive too late or may perhaps prove to be only partially effective? Or a vaccine that in the long run may show to have serious side effects? In the process, vaccines may also end up being too complicated to be produced and too expensive or too difficult to store. There is always a high risk of failure with “vaccine candidates” development projects.

In January 2017, during the World Economic Forum in Davos, at the request of some governments, the Coalition for Epidemic Preparedness and Innovation (CEPI) was established. CEPI is an international organization based in Oslo, which aims to promote the development and storage of vaccines against microbes that are expected to cause new and alarming epidemics. It was precisely CEPI that, together with many other public and private initiatives, at the very early stages of the epidemic activated, financed and coordinated numerous projects for the preparation of vaccines against the SARS-CoV-2 virus. Other major philanthropic organizations, such as the Bill and Melinda Gates Foundation, both individually and through CEPI, have collaborated to support the initial development of the new “candidate vaccines” for COVID-19. However, when it is comes to clinical trials, the commitment and resources required become too great to be supported by these supranational bodies (Lurie et al, 2020).

The undertaking of a global vaccine becomes too great and too risky to be taken on by a single research team a or even a single company. Large pools of resources are forcibly created. An interesting example is the three companies that are focusing on the emerging RNA vaccine technology. One of the three companies is Moderna in the USA, the company which first injected its “candidate vaccine” against COVID-19, mRNA-1273, into a human being (Moderna, 2020). Moderna collaborates closely with NIAID, the U.S. governmental institute directed by immunologist Tony Fauci; with BARDA, the US military research organization, and with Lonza, the company that has the technology to produce the required doses of the “candidate vaccine”. In Europe, Biontech

operates on the same technological platform in Germany and collaborates with the multinational Pfizer, while CureVac (the company that President Trump wanted to buy a few months ago) cooperates with the UK multinational AstraZeneca. Hence, this is the pattern: a medium-sized company with new technologies joins a multinational company. A large number of other alliances are emerging. For example, the French company Sanofi, which is studying a protein vaccine to be developed with traditional technologies, collaborates with GSK for the adjuvants.

The development of a vaccine against COVID-19 has also become a political issue. Only a few hours ago President Trump announced the establishment of a US project called Operation Warp Speed. The expression 'Warp-speed' was used in a science-fiction film (Star Trek) to indicate an extremely high speed. At a warp-speed, with unlimited funding and the collaboration of the National Institutes of Health, the Food and Drug Administration, the private pharmaceutical sector and the necessary resources from the US army, this efficient cooperation hopes to develop and make available several million doses of a COVID-19 vaccine by the end of this year. The operation is under the direction of Dr. Moncef Slaoui, a former director of GSK who developed numerous vaccines and, more recently, a member of Moderna's board of directors and one of its important stockholders. Slaoui stated that the first results of Phase I on the human volunteers have been achieved and is confident that the Operation Warp Speed will reach its objectives by the end of the year (HHS.gov, 2020).

Initially, fourteen promising candidates have been chosen from the over 170 vaccine candidates currently in development—some of them already in clinical trials with U.S. government support.

OPERATION WARP SPEED: Selected vaccine candidates					
COMPANY	PLATFORM	EXISTING VACCINES	DOSES	FINANCE	PHASE 1-2 CLINICAL TRIALS
MODERNA	mRNA	No	Multiple	483 M$	Phase 2
Univ Oxford AstraZeneca	Adenovirus	No	Multiple	1.2 B$	Phase 2
Johnson & Johnson	Adenovirus	No	Multiple	500 M$	
MERCK	VSV Measle	Ebola No	Single Multiple	38 M$	
PFIZER	mRNA	No	Multiple	Faster alone	Phase I-2
SANOFI	Protein	Yes	Multiple	30 M$	

Table I. Operation Warp Speed: selected "candidate vaccines"

The fourteen vaccine candidates are being winnowed down to about eight candidates, and then to five and four (the top four, Table I) (Cohen, 2020). The Pfizer company, which was initially selected, has decided to continue independently of the support of Operation Warp Speed. The French company Sanofi, which received a great deal of funding from the US Government has denied its involvement in providing its "candidate vaccine" in a privileged or exclusive way to the US Government.

It is interesting to compare the technological platforms of the candidate vaccines selected for the Operation Warp Speed with those currently in Phase 1-2 clinical trials in China (Table II). While Operation Warp Speed favors innovative technologies that lead quickly to a "candidate vaccine", the vaccine that have reached clinical test in China have been developed using mostly the traditional platform.

Vaccine candidates in China				
COMPANY	PLATFORM	EXISTING VACCINES	DOSES	PHASE 1-3 CLINICAL TRIALS
Can Sino Biol	Adenovirus	No	Multiple	Phase 2-3
Wuhan Inst & Sinopharm	Inactivated SARS-CoV-2	Yes	Multiple	Phase 1-2
Beijing Inst & Sinopharm	Inactivated SARS-CoV-2	Yes	Multiple	Phase 1-2
Sinovac	Inactivated SARS-CoV-2 plus adjuvant	Yes	Multiple	Phase 1-2
Inst Med Biol & Cinese Acad Med	Inactivated SARS-CoV-2	Yes	Multiple	Phase 1-2

Table II. Candidate vaccines that are currently clinically tested in China

Various other "candidate vaccines" are currently in Phase 1-2 clinical trial (Table III). Of the two major European companies, CureVac has obtained financial support from the European Commission and the Oxford candidate vaccine has started to be injected in healthcare workers in Brazil, even if many other candidate vaccines will soon enter in clinical trials. It is indeed very probable that what is reported in the Tables will soon change.

Other vaccine candidates in clinical trial				
COMPANY	PLATFORM	EXISTING VACCINES	DOSES	PHASE 1-2 CLINICAL TRIALS
Novavax, USA	Spike protein	Yes	Multiple	Phase 1-2
Inovio, USA	DNA	No	Multiple	Phase 1
Univ Oxford & AstraZeneca, UK	Adenovirus	No	Multiple	Phase 2-3

Table III. Other "candidate vaccines" that are currently clinically tested

Following the data from the human volunteers, we will be faced with a completely new scenario on the various potential candidate vaccines.

Mirror, mirror on the wall, who's the fairest of them all? There is no doubt that Operation Warp Speed can quickly achieve great and interesting results. There is no doubt that by the end of the year, major results will be announced also from China, USA and Europe. The enormous scientific effort and huge funding investments will lead to the development of fifteen or twenty vaccines that will compete head-to-head. While comparative efficacy will have to be planned, it is easy to predict that the various companies may not be very enthusiastic about comparisons. Very large economic interests are involved.

In order to plan comparative studies, it is necessary to establish what could be considered a successful COVID-19 vaccine: Must the vaccine prevent infection? And in what percentage of the volunteers? Or can the vaccine be considered successful if it moderates the severity of the disease? The various end-points will have to be better calibrated as the first protection data are available. It is probable that different vaccines will provide different forms of protection.

Currently, many companies are organizing their own clinical trials with a significant number of people in different countries where COVID-19 epidemic is spreading rampantly. The data obtained will provide an excellent indication of the efficacy, limits and safety of the vaccine, while an alignment of clinical and immunological data obtained with the different vaccines will be difficult. By contrast, Operation Warp Speed plans to harmonize the protocols of the efficacy trials in order to streamline oversight and run immunological analyses in central labs so data will be easily compared.

By contrasting the individual initiative of the companies and increasing the efficacy of a comparative assessments, WHO proposes Solidarity efficacy trials in which the vaccine efficacy is compared against a shared placebo group. This approach reduces the number of volunteers the researchers need to recruit and follow. The Solidarity trials are open to vaccines from every country and have public detailed criteria for how to prioritize vaccine efficacy (WHO 2020b).

A COVID-19 vaccine, for whom? Next, the process of obtaining authorization for the vaccine production from the regulatory authorities will begin. But what will be the ultimate winning technology? How many vaccine doses can be produced with that technology, taking into account the technological structures currently available worldwide? And what if additional doses of vaccine per person are needed to induce effective immunity? The current world population is 7,5 billion and therefore adjustments on our calculations must be made.

It therefore seems inevitable that the new vaccines, once developed and tested, will not be available for some time to all those who wish to be vaccinated. Part of the world's population will not be interested in these vaccines, either because COVID-19 does not significantly affect certain countries or because some countries are facing much more serious health problems. But, almost certainly, for a period of time whose duration is difficult to predict, the vaccines for COVD-19 will be available only in some countries. In a recent article published in the Journal of American Medical Association (JAMA) Thomas Bollyky et al. report that during the 2009 influenza A (H1N1) pandemic, rich nations purchased nearly all the supplies of vaccines (Bollyky et al, 2020). Even following the World Health Organization's (WHO) appeal for donations, the supplies of vaccines to low- and middle-income countries remained very limited. In the case of COVID-19, the White House has already indicated,

first with Germany and more recently with Sanofi in France, that it intends to have exclusive or priority access to a possible vaccine. With a similar predatory attitude, European and Asian countries have recently imposed limits and controls on the exports of facemasks and other sanitary protection items, and it would not be surprising if such controls and export limitations are extended also to future COVID-19 vaccines. Regarding the facemasks, which are produced with a much simpler technology with respect to the vaccines, we have recently witnessed political blocking of the masks and confiscation by some countries, with the result that some people in Italy have been exposed to greater risk of infection. The spread of sovereign attitudes, with the closing of borders and the limited transportation ordained by the lockdowns, favor or almost impose on nations predatory attitudes and hoarding. The recent announcement that the US Government, the European Union UK and Italy have "bought" several million doses of a "candidate vaccine" studied at the Jenner Institute in England in collaboration with ADVENT-IRBM in Pomezia (Italy) and AstraZeneca is part of the race for a vaccine. Why order 30 million doses of a vaccine that does not exist yet? What is the cost of 30 million doses of a vaccine which is still in the study phase? To stop these predatory attitudes, the WHO is proposing to various countries an equity agreement for the distribution of the new vaccine. An agreement which may be quite difficult to establish and risks being generic and ineffective, and which has not received a favorable response from United States, which for political reasons is challenging the WHO by discontinuing (or threating to discontinue) funding. But isn't it possible, or may be likely, that the fast-global race for COVID-19 vaccines will lead to the creation of new astronomical injustices? (Accademia, 2020a, and 200b).

How many seeds of disease, despair and death will the impossible access to the vaccine sow among the people of the earth? However, this may be the case only if there will be a rampant return of the pandemic. More likely, the different vaccines that will be made available more or less simultaneously, and the various distribution policies, will mitigate this tension, even if, inexorably, there will still be a period in which some people or some groups of people will have easy access to the vaccine, while for others access will be more difficult.

The unpredictable course of the pandemic could also make the vaccine unsought and used only for the protection against a hypothetical return of the epidemic, for reinforcing protection while time goes by or it could almost become superfluous. Perhaps, the virus will stay with us forever, so someone has suggested that there will always be a need for a vaccine against SARS-CoV-2 for the newborn babies. In this regard, the example of polio vaccines is quite interesting. The injectable killed Salk vaccine turns out to be appropriate for the industrialized world: it is safe and effective in areas of the world where polio no longer exists. By contrast, the attenuated Sabin vaccine, more effective and easier to be administered orally, is appropriate for the developing world were the wild virus is still circulating. In a similar way, COVID-19 vaccines developed on distinct technological platforms could induce different forms of immunity, each of which could be appropriate in different environmental and human contexts.

Acknowledgements: We wish to thank Prof. Giuseppina Barsacchi for her support.

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