Accademia Nazionale dei Lincei
Statement by the Lincei Committee on Covid-19

COVID-19 vaccines: Fall 2020 report

1. Introduction.

The hope and hype that the media and public at large are placing on having as soon as possible a vaccine that protects against COVID-19 is the result of the great triumphs that vaccines have had and are having in the control of infectious diseases. However, there is a long series of infectious diseases in which vaccines are only partially effective and we have a series of sensational vaccine defeats (Forni et al, 2018).

Indeed, each disease is an immunological problem in itself: even today, with all the data at one's disposal, it is difficult to predict what kind of vaccine can be truly effective. This difficulty is even greater for COVID-19, a young disease in which ongoing studies in laboratories worldwide are adding new data at tremendous pace. In addition, RNA viruses generally have a high mutation rate. This is one reason why it is difficult to develop effective vaccines to prevent diseases caused by RNA viruses.

In many cases, recovery from a viral disease rests on the combined action of antibodies in the biological fluids that neutralize the viral particles and the killer activity of lymphocytes that track down and kill virus infected cells. However, there are viral diseases whose healing depends mainly, if not exclusively, on the antibody response and others where the destructive action of the killer lymphocytes is fundamental. What is the case with COVID-19 is not yet clearly defined (Cox and Brokstad, 2020).

Often, healed patients display high titers of SARS-CoV-2 neutralizing antibodies. However, there are also healed patients with a low antibody titer. Data on the role of mucosal immunity and secretory IgA and IgM are scarce. Furthermore, we cannot yet know how long the protection acquired by recovered patients will last. This point is of interest since often, the duration of the protection after healing somewhat corresponds to the duration of the protection provided by the vaccine.

Despite the impressive amount of studies carried out since the virus was first characterized, there are still a large number of unknowns about this disease. And it is precisely these unknowns that fully justify the very different conceptual and technological strategies that are currently pursued in the preparation of vaccines against COVID-19. This diversification appeared essential precisely because, for many diseases, but particularly for a new disease as COVD-19, it is difficult to predict which type of immune response and therefore vaccine will be more effective.

Fig. 1, which was taken (with permission) by Lurie et al., 2020, shows the difference between traditional vaccine development and development under the pressure of a rampant epidemic. Because of the pressure created by the pandemic, multiple activities are carried at a financial risk to the developers, without knowing whether the candidate vaccine will be safe and effective, including very early manufacturing and scale-up to commercial scale before the establishment of clinical proof of concept (Callaway, 2020).

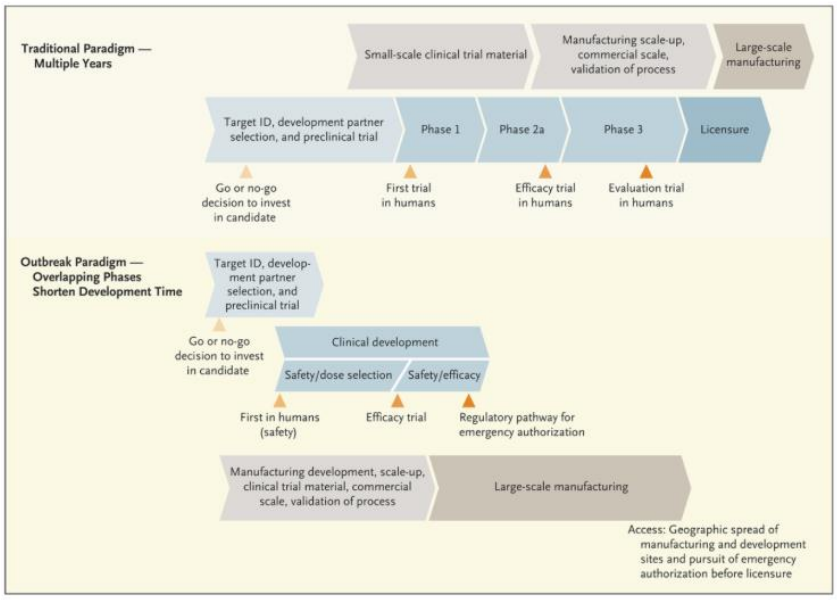

Fig. 1.

2. Technological platforms: The bright side of human creativity.

As of October 2020, just ten months after the definition of SARS-CoV-2 genome, there are over 150 official vaccine projects (WHO, 2020b; Akst, 2020). About fifty of them have already reached human experimentation and half a dozen of these are currently administered to some sectors of the general population. By exploiting different technologies, these antii-SARS-CoV-2 candidate vaccines are targeting the whole SARS-CoV-2, molecules or fragments of molecules expressed on this virus surface.

These different candidate vaccines can be grouped on the basis of the technological platform exploited to elicit a protective immune response. However, almost every vaccine project has its own peculiarities that make it unique and which could have significant consequences regarding the efficacy or duration of the induced protection or the safety of the vaccine.

Faced with this variety of projects and the determination and speed with which they are carried out, one cannot help but be amazed by the human scientific creativity. Even if these various projects compete with each other and have their technical secrets, their formulation comes from basic scientific research that is structured as an open cooperation between all laboratories in the world.

Vaccines based on attenuated SARS-CoV-2 viruses.

The history of vaccination begins with vaccines based on a living microbe that has been weakened so it can not cause disease. Since attenuated microbes retain the ability to replicate in vivo giving rise to a limited disease**, t**hey are very effective in stimulating the immune system and inducing a strong and persistent immune memory that is efficacious in preventing infection. Hundreds of millions of people have been protected from disabling and fatal diseases by using attenuated vaccines (Forni et al, 2018).

Strategy: This is the most traditional technology exploited in the construction of vaccines. Live attenuated vaccines can be obtained by growing the virus in unfavorable conditions or by generating a genetically weakened version of the virus. However, the attenuation of trillions of viruses is complex and delicate and can be associated with major biosafety risks (Cohen, 2020). Once produced, their storage and handling require carefully observed procedures.

The experience with attenuated virus vaccines show that rare but significant side effects could be expected since attenuated viruses cause a disease, even if this is a minor one. The oral route (as in the case of the Sabin polio vaccine) and the intranasal route could induce a mucosal immunity based on secretory IgA and IgM.

Frontrunners: Only three projects of attenuated SARS-CoV-2 vaccines are in active preclinical development at the following institutions:

- The Serum Inst of India, India, in collaboration with Codagenix, a New York private biotech;
- Indian Immunologicals Ltd, India, in collaboration with the Griffith University, Australia;
- Mehmet Ali Aydunar Univ, Turkey.

None of these vaccine projects have yet reached the stage of clinical trials.

Vaccines based on the inactivated SARS-CoV-2 viruses.

Vaccines based on killed microorganisms (inactivated vaccines) belong to a very traditional technological platform that has led to numerous vaccines. The vaccines produced using this method are more stable than live attenuated vaccines but their limit is mainly related to the short duration of immune memory which demands inoculation of higher amounts of vaccine or the association of the killed microorganisms with an adjuvant. The immune response elicited is directed not only against the Spike protein but also against many

other SARS-CoV-2 antigens. While the induced response is generally weaker with respect to that induced by attenuated viruses, the vaccine is more easily handled, less expensive and much safer.

Strategy: The SARS-CoV-2 is inactivated by exploiting different chemical techniques. All these candidate vaccines are injected intramuscularly.

Frontrunners: Seven vaccine candidates based on variously inactivated SARS-CoV-2 virions are in clinical trials or are already approved for limited use. When available, reports from Phase II trials suggest that the vaccine is safe and induces a high titer of antibodies. The seven clinical trials are run by:

- Sinovac Biotech, China, this vaccine called CoronaVac is in late stage Phase III trial and interim results are expected in late November. Meanwhile, CoronaVac has already been approved for limited use among the general population and it is offered to essential workers and other high risk groups for about 30 €/dose (Reuters Staff, 2020). Two injections are recommended.
- Sinopharm, China, two of its distinct projects are approved for limited use in the general population;
- Wuhan Inst Biol Products, China, this vaccine has been approved for limited use in the general population;
- Chinese Acad Med Sci, China;
- Bharat Biotech, India;
- RIBSP, Kazakhstan.

Vaccines based on SARS-CoV-2 proteins.

There are a number of human vaccines based on protein present on the surface of microbes (Accad Naz Lincei, 2018). Initially, these proteins were purified from the microbes while today, in most of the cases, they are produced in vitro exploiting the recombinant DNA technology.

Strategy: The large trimeric aggregates of the Spike protein that protrude outside the virion play an essential role in the docking of the SARS-CoV-2 to human cells. Therefore, the Spike protein or its fragments are the target of all these vaccines even if in a few cases other SARS-CoV-2 proteins -mostly the nucleoprotein (N)- are also targeted. To activate a robust immune response, often these vaccines exploit adjuvants, either of bacterial or synthetic origin.

Frontrunners: There are very numerous vaccine projects based on SARS-CoV-2 proteins, their fragments or their fragments combination. At least 16 candidate vaccines are already in human trials:

a) Spike protein or its fragments plus adjuvant	Adimmune, Taiwan; Bektop, Russia; Biotechnology Vector, Russia; Clover Biopharmarm plus GSK adjuvant, China - Italy; COVAXX, US**;** Inst Finlay de Vacuna Vaccine, Cuba plus adjuvant; Medigen, Taiwan-US, plus CpG adjuvant; Sanofi plus GSK adjuvant, France - Italy; The Univ of Queensland, Australia; Univ Tübingen, Germany; Vaxine, Australia, plus adjuvant; West China Hosp Sichuan Univ., China; ZFSW Anhui Zhifei Longcom, China, plus adjuvant.

b) Proteins carried by nanoparticles	Novavax, US, Australia and South Africa, plus adjuvant.
c) Oral tablet containing Spike protein fragments	Vaxart, US.
d) Microneedle skin patch delivering Spike proteins	Unv Queesland, Australia
e) Spike protein or its fragments inserted in virus like particles (VLP)	SpyBiotech/Serum Institute of India, India.
f) Tobacco plant produced proteins	Kentucky Bio Processing, US.
g) Tobacco plant produced proteins in virus like particles (VLP)	Medicago plus GSK adjuvant, US-Italy.

Naked DNA-based vaccines.

The DNA and mRNA based platforms offer great flexibility in terms of manipulation of the coded antigen and great potential for speed. Currently, there are no DNA vaccines registered for human use; however, DNA vaccines are commonly used in veterinary medicine. These vaccines are stable and can easily be produced in large amounts in bacteria.

Strategy: Once injected into the muscle or skin, DNA plasmids enter human cells, and their ability to enter ma be enhanced by a very short local electrical pulse (electroporation). Once entered, plasmid DNA induces the cell to produce temporarily the target protein. In this way DNA vaccination stimulates the production of antibodies and the activation of killer T cells.

Frontrunners: Six DNA vaccines are entering in human trials. All code the Spike protein or its fragments.

a) Naked DNA plasmids	Zydus Cadila, India; AnGes, Japan; Takis, Italy.
b) Naked DNA plasmids plus electroporation	Inovio, US; Genexine, Korea; Karolinska Inst, Sweden + Inovio, Italy.

mRNA-based vaccines.

While messenger RNA (mRNA) has not yet produced any registered vaccine, several vaccine projects exploit this technology for the creation of SARS-CoV-2 vaccines. Unlike DNA, RNA must be transported in various ways to enter the human cell. Once entered, the mRNA vaccine temporarily induces the cell to produce the antigen protein coded by the mRNA.

Strategy: In most of these vaccine projects, the mRNA is carried by lipid micro vesicles (liposomes). Also in the case of anti-SARS-CoV-2 mRNA vaccines, the target antigen coded by the mRNA is mostly, if not only, represented by the Spike protein, its variants or its fragments. These vaccine preparations have to be kept at minus 80 degrees centigrade.

Frontrunners: There are many vaccine projects based on mRNA coding for the Spike protein, its variants or its fragments that are already in clinical trials. The vaccine mRNA may be carried by:

a) Lipid vesicles (Liposomes)	Abogn, China; CureVac, Germany; Moderna, US;

Pfizer, US, candidate vaccines tested in parallel;
Univ Oxford, UK that will also test an inhaled form.

b) Nanoparticles — Arcturus Ther, Singapore.

Vaccines based on viral vectors.

The selected DNA can be conveyed into human cells by viral vectors. By inserting the DNA in a virus, it is possible to exploit the virus great ability to infect cells to efficiently deliver the DNA into the human cells.

Strategy: In most of the cases, the virus vector inside which the DNA is inserted is a virus made unable to replicate. Since a preexisting immunity against the virus vector may affect vaccine efficacy, primate viruses (from chimpanzee, gorilla….) are often exploited as vectors.
In other cases, the DNA is inserted into replication active virus vectors: as these viruses are able to propagate to some extent, they may induce a more robust immune response (Krammer, 2020).
Also in these vaccine projects, the target antigen coded by the inserted DNA is mostly, if not only, the Spike protein, its variants or its fragments. Commonly, these virus-based vaccines are injected intramuscularly. However, there are numerous and interesting projects aiming at administering the vaccine into the nose by inhalation. If effective, the candidate vaccine could induce a mucosal immunity capable of neutralizing the virus, thus inhibiting its ability to enter the human body.

Frontrunners: There are very numerous vaccine projects based on viral vectors that are already in advanced clinical trials. The vaccine DNA is inserted inside:

a) Engineered non-replicating virus vectors

1) Chimpanzee adenovirus:
AstraZeneca, Sweden-UK
that is also testing a vaccine inhaled form;

2) Gorilla adenovirus:
ReiThera, Italy.

3) Human adenoviruses:
- CanSino, China;
- Johnson&Jonhson, US;
- Acad Mil Med Sci, China
- Gamaleya Res Inst, Russia: this vaccine based on two human adenoviruses has been approved for limited use among general population.

4) Adenoviruses specifically modified for nasal spray:
- Beijing Wantai Biol Pharm Enterprise, China;
- Acad Mil Sci, China, two projects;

Bharat Biotech-Washington Univ, India-US;
- AstraZeneca, Sweden-UK;
- Altimmune, US.

5) Other viruses

b) Engineered replicating virus vectors

1) Injected i.m.:
- Measles virus, Merck, US;
- Vesicular Stomatitis Virus.

2) Influenza virus administered by nasal spray:
- Influenza virus:
  Univ Hong Kong;
  Valavax-Abogn, China;
  Beijin Vantal Biol Pharm, China.

Other technological platforms for SARS-CoV-2 vaccine.

1) Symvivo, Canada: A Phase I human trial is underway with orally administered *Bifidobacterium* probiotic engineered to carry the DNA encoding the Spike protein.
2) Immunomonitor, Canada: A Phase I/II human trial is underway with heat inactivated plasma from donors with COVID-19.
3) Aivita Biomedical, US: A Phase I/II human trial is underway with patient's own dendritic cells modified to express SARS-CoV-2 antigens.
4) Shenzhen Geno-Immune Medical, China: A Phase I human trial is underway with dendritic cells engineered to express SARS-CoV-2 proteins.

3. Efficacy assessment.

Even if incomplete, the list of ongoing clinical trials shown above gives an idea of the grandiose scientific, technical and organizational effort that is currently underway. The administration of the new vaccine makes it possible to understand whether the vaccine induces a significant immune response and whether its administration causes clear adverse events. The candidate vaccines which are considered worthy of study in complex Phase III human trials are the ones that on a limited number of volunteers in Phase I and II clinical trials, caused minor short-term side effects while inducing a good production of antibodies capable of neutralizing the infectivity of SARS-CoV-2 (neutralizing antibodies), and, in some cases, a significant T cell activation. Even if the assays to evaluate the immune response vary vastly, protein-based vaccines appear to elicit the strongest antibody response (Krammer, 2020).

The real evaluation of the effectiveness of a new vaccines is based on Phase III randomized controlled trials that compare the incidence of COVID-19 in large groups of vaccinated and non-vaccinated people. This evaluation will determine whether one, several or none of the new COVID-19 vaccines protects effectively or only marginally and if its administration is associated with important collateral events.

There is no doubt that, by the end of the year, major results will be announced when several large Phase III studies, performed with a large number of people in different countries where COVID-19 epidemic is spreading rampantly, will be closed. The situation may arise where the scientific efforts and the huge funding investments will result in the development of fifteen or more frontrunners that will be registered for general use and compete head-to-head.

Comparative evaluations.

-Mirror, mirror on the wall, who's the fairest of them all? Data from Phase III studies will provide an excellent indication of the efficacy, limits and safety of the candidate vaccines. However, only a few of the long list of vaccines will be directly compared. The WHO has put forward Solidarity efficacy trials open to vaccines from every country and has made public detailed criteria on how to prioritize vaccine efficacy (WHO 2020a). The vaccines included in the Operation Warp Speed, the US government's private–public partnership to support COVID-19 vaccines, have a harmonized efficacy protocol in order to streamline oversight and run immunological analyses in central labs for achieving a direct data comparison (HHS.gov, 2020). But, what about all the other projects? Although any vaccine that will be registered in Europe and USA will be assessed on a long series of data for its efficacy and safety, it is likely that it will be a long time before industrial policies and national political issues could allow a solid comparative assessment of the efficacy of the various vaccines. Quantitative comparisons of the efficacy of different vaccines in inducing immune responses is hampered by the lack of international standards. For instance, there is no international standard at the moment for titering IgG anti-spike serum antibodies, let alone for neutralization assays or T cell responses. This current technological limitation makes it difficult to compare immune responses elicited by vaccines in different trials.

It is also conceivable that "the best" COVID-19 vaccine could not exist at all, as vaccines developed on distinct technological platforms could induce different forms of immunity, each of them appropriate in different environmental and human contexts. The polio vaccine provides an interesting example. The injectable killed Salk vaccine is turning 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. Thus, evolution of the pandemic could make some vaccines more appropriate in different geographic context or for different clusters (infants, elderly…) of human population (Tagliabue and Forni, 2020). It is quite possible that the sequential arrival of subsequent wages of vaccines could increase and make more appropriate the protection initially induced by the first vaccines.

Selected vaccines in clinical evaluation.

As this report was being drafted, about eleven candidate vaccines have entered the most advanced phase (Phase III) of clinical assessment. For five of these, results obtained in Phase II have been made available in peer reviewed journals (Xia et al, JAMA 2020; Folegatti et al, Lancet 2020; Poland et al, Lancet 2020; Jackson et al, NEJM 2020; Zhu et al, Lancet 2020). Here we will briefly comment on available information based on these publications. The number of subjects enrolled ranged from 100 to 1,077 and the study design was usually single arm. The AstraZeneca Phase II trial included 1,077 patients randomized to an irrelevant meningococcus vaccine or to the adenovirus-based SARS-CoV2 vaccine (Folegatti et al 2020). Selected common findings include: activation of innate immunity, as revealed by local and systemic inflammation; induction of antibodies, including neutralizing antibodies; induction of type 1 T cell responses with Interferon gamma production. Type I immune responses are considered a cornerstone of antiviral immunity. At least in the most extensive study, the AstraZeneca vaccine trial, induction of type 2 potentially deleterious T cell responses was not observed. Collectively, these results are encouraging but suffer from limitations, extensively discussed in some of the reports (e.g. Folegatti et al, 2020). Follow up was limited (<60 days) and duration of persistence of immunological memory remains to be determined. The actual significance of immunological parameters for protection remains to be defined. Aging is associated with loss of immunological memory, reduced repertoire of responses and increased inflammatory tone, (e.g. Bottazzi et al., 2018). As a consequence, for instance, vaccines designed for the elderly have been introduced for influenza. At the time of writing this report, no information is available in peer reviewed or open access publications on responses elicited by COVID-19 vaccines in elderly people. Finally, and most importantly, protection against incidence or severity of disease remains to be demonstrated and there is a consensus that it should last at least 6 months.

The unknowns.

It is expected that the first vaccines that will be made available will significantly contribute to the normalization of social life, even if their arrival will be accompanied by a long list of unknowns. Most of these unknowns are inherently associated with the dramatic pressure brought on by the pandemic and the reactive speed at which these vaccines are being developed. The passage of time along with the luxury of being able to develop more detailed studies will lead to the clarification of many questions left open by the first Phase III studies.

Only time will tell how long the vaccine-elicited protection will last and how frequent the booster injections should be administered to keep the protection fully active. Over time, population data will better clarify what kind of protection the various vaccines are able to induce. Will the vaccine protect people only from the mildest form of COVID-19, or will it be one that prevents serious complications and reduces mortality? Often

Phase III trials are designed to test whether the vaccines reduce cases of symptomatic COVID-19, not cases of severe disease, such as those that require hospitalization and can end in death (Mallapaty and Ledford, 2020). Who will be protected is another crucial question that only more detailed studies can answer. Phase III trials currently underway are mainly focused on a healthy population aged 18 to 55 (or 65) years. A vaccine judged to be effective on this population may not work equally well in elderly individuals, frail and other at-risk persons. There will be no data for children, adolescents and pregnant women since they have been excluded (Doshi and Topoi, 2020). Even if children are not a high-risk group, as the schools reopen, the transmission of the virus could take place among students, their parents and school staff (Boehmer et al, 2020). Vaccinating children could help reopen society, ensuring that schools do not become hot spots (Zimmer, 2020). Pregnant women are another high-risk group since they have a higher risk of being admitted to an intensive care unit and of requiring mechanical ventilation (Delahoy et al, 2020). Will the vaccines also be able to prevent the spread of the disease? In effect, while protecting from the clinical disease vaccines might not reduce virus transmission (Peiris and Leung, 2020). Among many other unknowns that can be solved over time, there is the question of whether the arrival of vaccines will be able to create the herd immunity capable of controlling the spread of SARS-CoV-2 (Saad-Roy et al, 2020). Complex social policy issues and the acceptance or rejection of vaccination by the population will significantly affect the possibility of achieving this crucial goal (See also 6).

Risks associated to fast track vaccine evaluation.

The administration of a new vaccine must always be carefully associated with a rigorous study of its safety. This is particularly important because a vaccine is not a drug for sick people at risk of dying, but rather a treatment that is given to those who are well so as to prevent the risk of falling ill (Forni et al, 2018).

The race to develop a COVID-19 vaccine is not only justified but absolutely necessary. However, the time required to evaluate the dangers and risks that may arise from a new vaccine must be included in its development. In some cases, vaccines prepared against other coronaviruses or other viruses have worsened the disease (Jiang, 2020) and have induced T helper 2-type immunopathology (Tseng et al, 2020). These issues must be carefully evaluated and excluded before a new COVID-19 vaccine is distributed to combat the pandemic or its subsequent outbreaks. These basic considerations take on a special importance when inappropriate political pressures may lead to accelerate the evaluation of vaccine safety. Claiming to have won the race to develop a COVID-19 vaccine or the distribution of a candidate vaccine to clusters of the population before all data from clinical trials are obtained and carefully analyzed can be dangerous and erode trust in both the vaccine and regulatory bodies (Gold and McKinley, 2020). In this weird contest, the pledges put forward both by pharmaceutical companies (Thomas et al, 2020) and the director of the US Objective Warp Speed (Cohen, 2020) to keep rigorous efficacy and safety standards as an absolute central issue in COVID-19 vaccine development are reassuring.

4. SARS-CoV-2 genetic instability and implications for vaccine development.

At the time of writing there are over 5,000 complete sequencing data of viral isolates reported and at least three peer reviewed papers available (Young et al, 2020; Grubaugh et al, 2020; Li et al, 2020). SARS-CoV-2 is relatively stable and no evidence has been obtained that an attenuated virus has spread globally. For instance, sequencing of 346 virus isolates in the Lombardy region has shown that the spike protein does not undergo mutations including at glycosylation sites. The relative stability of SARS-CoV-2, unlike HIV, provides a strong rational for vaccine development. However, following introduction of effective vaccine(s), mutant virus may appear and have selective advantage, thus posing the issue of adapting the vaccine strategy.

5. Pathogen agnostic protection conferred by COVID-19 unrelated vaccines.

There is strong evidence that selected vaccines confer what has been referred to as pathogen-agnostic protection against infectious agents unrelated to the one specifically targeted (Sala and Miyakawa, 2020; Shet et al, 2020; Mantovani and Netea, 2020; Giamarellos-Bourboulis et al, 2020).

For instance, the measles and BCG vaccines are strongly associated with a reduced incidence of unrelated respiratory tract infections. The mechanisms of pathogen agnostic protection are complex and include avoidance of virus–induced immunosuppression and increased effectiveness ("training") of innate immunity. The evidence for pathogen-agnostic protection and training of innate immunity is strong for BCG (Mantovani and Netea, 2020). Moreover, it has been speculated that the intense vaccination calendar for children contributes to their as yet unexplained resistance to COVID-19. Based on these considerations a number of prospective clinical trials are ongoing aimed to assess the value of BCG for instance for protection of health care workers (de Vrieze, 2020). At this stage, usage of BCG as a preventive measure against COVID-19 cannot be recommended outside of clinical trials (Mantovani and Netea, 2020). However, available information suggests that vaccines such as influenza, pneumococcus and herpes in the elderly represent a general training strategy for innate and adaptive immunity.

6. Production and ethical issues.

Once the new vaccine has been validated, subsequent problems will be related to its production and distribution. Technological, organizational, regulatory and economic problems will have to be overcome. The industrial technology needed to scale up the production to a billion doses will depend on which kind of vaccine will work best. Initially, it might not be physically possible to make enough vaccines for the world's population, although, various vaccines are already in production without being sure that they will be registered and distributed. In addition, political and economic constrains may limit vaccine access to the country that produces it or to the countries that can afford to pay for it. To make the new vaccines available to the global population will be challenging (Khamsi, 2020). The problem of a fair distribution of the vaccine in all the nations of the world is much discussed and various initiatives are about to be implemented by several nations and international organization (Kupferschmidt, 2020; Krammer, 2020; Gates,2020). To ensure equitable access to future COVID-19 vaccines the Coalition for Epidemic Preparedness Innovations (CEPI), The Global Alliance for Vaccines and Immunization (GAVI), and WHO have launched the COVID-19 Vaccines Global Access (COVAX) Facility, a global risk-sharing mechanism for pooled procurement and equitable distribution of eventual COVID-19 vaccines (GAVI, 2020).

For a technical discussion on the possible role the Italian Government could play during its 2021 G20 Presidency to promote equitable distribution of the first COVID-19 vaccine, see Accad Naz Lincei, 2020.

7. Diverse vaccine platforms, biohackers and vaccine mistrust.

- The pandemic drama has prompted many scientists around the world to design possible alternative COVID-19 vaccines. Thus, in addition to the large number of official projects enlisted by WHO (WHO, 2020b), numerous university laboratories and small biotech firms are studying fresh vaccines. This clever intellectual and technological effort provides myriads of diverse projects, some of which could become important if front runner projects will confer only partial protection or work poorly in certain clusters of the population. High costs and other barriers might make some of the front runner vaccines unsuitable for wide-scale deployment in lower-income countries (Calleway, 2020). For example, bacteriophage-based vaccines that infect nose and throat microbes and make them to produce the Spike protein, or other vaccines that could be administered by nasal insufflation or by mouth appear to be stimulating alternatives. It would really be a great achievement

to develop a vaccine that is able to induce an effective immunity on the mucosal surfaces: it could impede the viral infection and the virus spread through respiratory droplets.

- The enthusiasm to design different COVID-19 vaccines is also plaguing the biohacking community. Biohacking is a "do-it-yourself biology", a somewhat romantic biotechnological social movement in which individuals and small organizations are involved in transforming both life sciences and information systems using low cost, open source alternatives and open access tools, claiming independence from both academic and corporate institutions (Biohacking, 2020). In recent weeks, several biohackers have taken part in online biology forums to help investigate potential vaccines and innovative methods of testing them, often on the vaccine inventors themselves. The hunt for a free, open science Coronavirus vaccine is on (Brown, 2020; Heidt, 2020).

- Along with the progressive development of modern vaccines, opinion movements against vaccination have flourished in the Western world. Currently, the news on anti-COVID-19 vaccines have further ignited opposition protests (Cornwall, 2020; Wadman, 2020). In addition to the movements openly opposed to vaccination, several polls show that a significant percentage of people in the Western countries would be hesitant or contrary to take a COVID-19 vaccine once it is approved. The chief concern among those surveyed was that the vaccine approval process would move too quickly without taking time to properly establish safety and effectiveness (Gold and McKinley, 2020). Certainly, the intrusion of political issues into the pace of vaccine evaluation process does not help to build confidence in new vaccines (Gold and McKinley, 2020). However, by the time vaccines are registered and made available, data on their efficacy and safety will have been carefully reviewed by several national and international agencies. On the other hand, these vaccines will have had a short documentation history and might elicit hypothetical side effects after a long time, that could not have been previously appreciated.

This is, however, a conjectural situation. Instead, it is likely that, once the efficacy of a COVID-19 vaccine will be demonstrated, much of the hesitation about this vaccination will quickly vanish. It will be commonly apparent that a marked reduction in the risk of dying from COVID-19 largely compensates the risk of hypothetical late side effects.

8. Conclusions.

As we are completing this briefing, the COVID-19 vaccines are on the way. Shortly, fresh data from Phase III trials will permit vaccine registration. Soon after, few vaccines based on different technologies will be mandatory or made available for selected clusters of the population of China, Russia, United States and Europe.

Thus, the landscape of the pandemic will take on completely different features. We will know if vaccines to efficaciously control the SARS-CoV-2 virus spreading remain a far goal or if they are already here. In the latter case, the next burning issue will be the vaccine availability and its equitable distribution in all areas of the world. Predatory national politics aimed at ensuring that the first vaccine doses are made available to the population of their nation will clash with attempts of many international organization to set up a more fair distribution in all countries of the world. This noble effort is severely contrasted by the political significance that the COVID-19 vaccine is assuming. The political leader or the country that produces a first salvific vaccine can exploit it to affirm its ability to protect its citizens as well as the inhabitants of friendly countries. The vaccine, thus, may become an inappropriate measure of power (Accad Naz Lincei, 2020). How many seeds of disease, despair and death will a difficult access to the vaccine sow among the people of the earth? Cynically, it could just be the relentless predatory rush to grab the first doses of the vaccine that could produce a fair distribution of surplus vaccines to the less rich nations in a relatively short time (Bollyky, 2020).

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