Fight against SARS-CoV-2: prevention and vaccines

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Field: Science Output
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Abstract

The new outbreak of SARS-CoV-2 represents a new challenge for world health. Currently, it affects the world population, especially those with comorbidities and yet no treatment has proved successful; for these reasons, the development of an effective and safe vaccine becomes crucial for its prevention. The experience gained in the research of other coronavirus infections and the vaccine technology available today, serve as the basis for the rapid development of Covid-19 vaccine candidates, altogether with risk-based reduced clinical trials, which may represent an ethical conflict at the same time. However other challenges should be faced within this race, the market share and supply to satisfy the world population, or at least those in higher risk as soon as possible and the politicization played by some country leaders. For all these reasons, governments, pharmaceutical companies, and world organizations have joined as part of this unprecedented effort.

Introduction

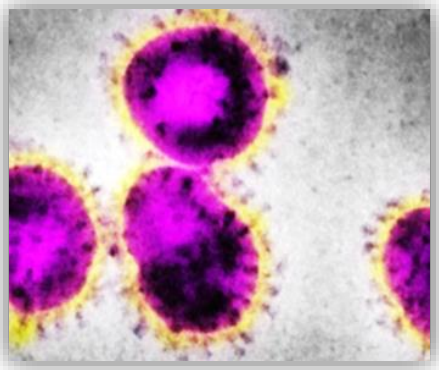


Figure 1. An electron micrograph of coronavirus, the cause of Severe Acute Respiratory Syndrome, or SARS. (Getty Images)

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the emerging virus causing coronavirus disease 2019 (Covid-19). Firstly identified in China, (December 2019), the outbreak was declared a pandemic by WHO in March 2020. The continuing spread of COVID-19 worldwide is driving the collective efforts of the scientific community towards the discovery of more effective therapies.

Although recently there was a significant development on various therapeutics, there is still no therapy elected as first-choice, due to the still lacking solid clinical evidence. For this reason, the vaccine against COVID-19, regarded as an effective prophylactic strategy for control and prevention, is being developed in about 90 institutions worldwide. Vaccination is the most effective way to reduce rates of morbidity and mortality caused by influenza viruses. Previous projects to develop vaccines for viruses in the family *Coronaviridae* that affect humans have been aimed at severe acute respiratory syndrome (SARS, 2002) and Middle East respiratory syndrome (MERS, 2012). Unfortunately, for both SARS and MERS, as of July 2020, there is no treatment or protective vaccine that is both safe and effective in humans [1][2]. The experiences and lessons encountered in the previous SARS and MERS vaccine research can be used for reference in the development of COVID-19 vaccine.

Vaccine technology platforms in place for COVID-19: short-circuiting" development process

Since COVID-19 pandemic proved to be very aggressive in terms of spreading, developers and governments are accepting a high risk of "short-circuiting" the vaccine development process [3]. It means that, to shorten the traditional vaccine development timelines, in particular **Phase II–III** clinical trials typically conducted over years, they have been compressed it to a few months. These challenging studies are ethically questionable because of the unknown risks for healthy volunteers to contract COVID-19 disease. For this reason, WHO has developed a guidance document with criteria for conducting COVID-19 challenge studies, including scientific and ethical evaluation, public consultation and coordination, selection and informed consent of the participants, and monitoring by independent experts.

Other ways, besides compressing the trial timeline, are being exploited, such as testing as many as possible different technologies at the same time

The CEPI (Coalition for Epidemic Preparedness Innovations [4], an organization founded in 2016 in Davos by the governments of Norway and India, the Bill & Melinda Gates Foundation, the Wellcome Trust, and the World Economic Forum) coordinates the development of future vaccines against targeted epidemic pathogens identified by the WHO. Since the genetic sequence of SARS-CoV-2 was published (January 2020) [5], the CEPI, already promoting financially independent research to develop vaccines against emerging infectious diseases, is working with global health authorities and vaccine developers to support the development of vaccines against COVID-19. According to CEPI scientists, there are ten different technology platforms under evaluation to find the best vaccine candidates [6]:

- Live attenuated virus
- Inactivated
- Non-replicating viral vector
- Replicating viral vector
- Recombinant protein
- Peptide-based
- Virus-like particle
- DNA
- RNA
- Other

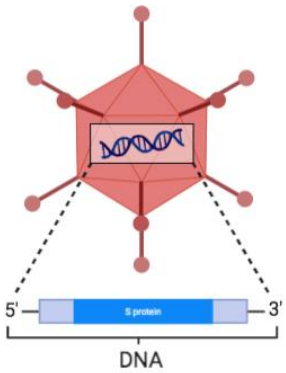
By applying these new technologies, it is possible not only to increase the speed of development of new vaccines but also to obtain very specific ones for the population subtypes (such as the elderly, pregnant women, or immunocompromised patients).

Vaccine candidates

A landscape database including vaccine development programs and a continually updated list of all the vaccine candidates is available in WHO website [7]. According to WHO, there are 23 vaccine candidates in clinical evaluation (see table 1) and 140 candidate vaccines in preclinical evaluation. It is an interesting strategy to evaluate as many vaccines as possible because we cannot predict how many will turn out to be viable. Industry analysis of past vaccine development shows failure rates of 84-90% [3][6], meaning that a company investment on a new vaccine has only 10-16% of the possibility to

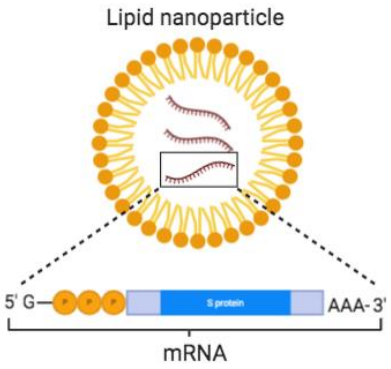
license it. Therefore, it is very important to explore as many roads as possible, to end up with a safe and efficient marketable vaccine.

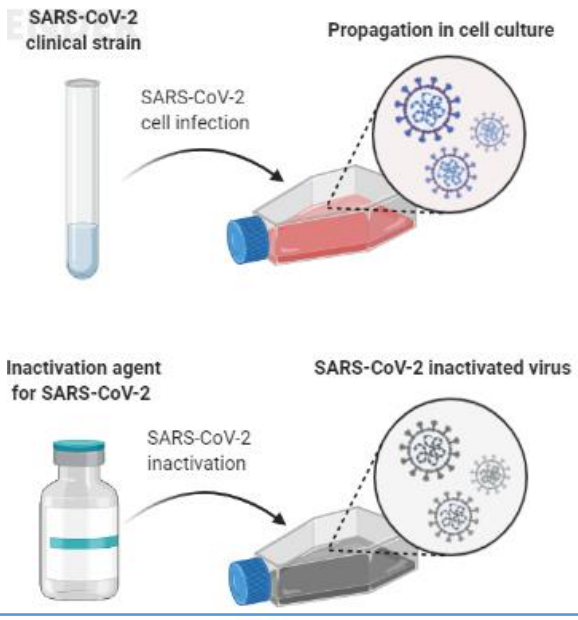
In the figures below, you can find some features of the more advanced vaccines in clinical trials.



ChAdOx1 nCoV-19 is an attenuated adenovirus that displays the SARS-CoV-2 spike protein on its surface. The **Ad5-nCov vaccine** is generated by incorporating a full-length SARS-CoV-2 spike protein gene into a replication defective Adenovirus Type 5 vector. These kind of vaccines will prompt the generation of antibodies against SARS-CoV-2 spike protein.

LNP encapsulated mRNA vaccine is comprised of a lipid nanoparticle (LNP) dispersion containing an mRNA that encodes for the prefusion stabilized spike protein of SARS-CoV-2. Upon vaccination, host cells uptake the mRNA, generate the protein, and display it to the immune system. The host can thus generate an immune response against the spike protein which will be protective against infection with SARS-CoV-2.





Inactive viral vaccines are created by propagating viruses in cell culture (such as in Vero cells) followed by inactivation using a chemical reagent (such as beta-propiolactone). Upon vaccination, this allows the body to generate a diverse immune response against numerous viral antigens while having no threat of actually being infected because the virus

Figure 2: Different kinds of vaccine candidates against COVID-19 attended the clinical phases [8]

Platform	Type of candidate vaccine	Developer	Current stage of clinical evaluation
Inactivated	Inactivated + alum	Sinovac	**Phase 3**
Non-Replicating Viral Vector	ChAdOx1-S	Oxford University /AstraZeneca	**Phase 3**
Non-Replicating Viral Vector	Adenovirus Type 5 Vector	CanSino Biological Inc./Beijing Institute of Biotechnology	**Phase 2**
RNA	LNP encapsulated mRNA	Moderna/NIAID	**Phase 2**
Protein Subunit	Adjuvanted Recombinant protein (RBDDimer)	Anhui Zhifei Longcom Biopharmaceutical/ Institute of Microbiology, Chinese Academy of Sciences	**Phase 2**
Inactivated	Inactivated	Wuhan Institute of Biological Products/Sinopharm	**Phase 1/2**
Inactivated	Inactivated	Beijing Institute of Biological Products/Sinopharm	**Phase 1/2**
Protein Subunit	Full length Recombinant SARS CoV-2 Glycoprotein nanoparticle vaccine adjuvanted with Matrix M	Novavax	**Phase 1/2**
RNA	3 LNP-mRNAs	BioNTech/Fosun Pharma/Pfizer	**Phase1/2**
DNA	DNA plasmid vaccine + Adjuvant	Osaka University/ AnGes/ Takara Bio	**Phase1/2**
DNA	DNA plasmid vaccine	Cadila Healthcare Limited	**Phase1/2**
Inactivated	Whole-Virion Inactivated	Bharat Biotech	**Phase1/2**
DNA	DNA plasmid vaccine with electroporation	Inovio Pharmaceuticals	**Phase 1/2**
Inactivated	Inactivated	Institute of Medical Biology, Chinese Academy of Medical Sciences	**Phase 1**
DNA	DNA vaccine (GX-19)	Genexine Consortium	**Phase 1**
Non-Replicating Viral Vector	Adeno-based	Gamaleya Research Institute	**Phase 1**
Protein Subunit	Native like Trimeric subunit Spike Protein vaccine	Clover Biopharmaceuticals Inc./GSK/Dynavax	**Phase 1**
Protein Subunit	Adjuvanted Recombinant protein (RBDDimer)	Anhui Zhifei Longcom Biopharmaceutical/ Institute of Microbiology, Chinese Academy of Sciences	**Phase 1**
Protein Subunit	Recombinant spike protein with Advax™ adjuvant	Vaxine Pty Ltd/Medytox	**Phase 1**
Protein Subunit	Molecular clamp stabilized Spike protein with MF59 adjuvant	University of Queensland/CSL/Seqirus	**Phase 1**
RNA	LNP-nCoVsaRNA	Imperial College London	**Phase 1**

RNA	mRNA	Curevac	**Phase 1**
RNA	mRNA	People's Liberation Army (PLA) Academy of Military Sciences/ Walvax Biotech.	**Phase 1**
VLP	Plant-derived VLP adjuvanted with GSK or Dynavax adjs.	Medicago Inc.	**Phase 1**

Table1: Draft landscape of COVID-19 candidate vaccines –17 July 2020. Complete list of 23 candidate vaccines in clinical evaluation [8]

Vaccine market: Global Vaccine Market Supply and COVID-19

Vaccine manufacturing technology is different from Drugs manufacturing one, they usually require a dedicated facility to be specifically manufactured due to their chemical and biological features.

On average, it takes between 12-36 months to manufacture a vaccine before it is ready for distribution, depending on its complexity. Successful manufacturing of high-quality vaccines requires international standardization of starting materials, production and quality control testing, and the setting of high expectations for regulatory oversight of the entire manufacturing process from start to finish [9].

They have to comply with the standards defined for Good Manufacturing Practices (GMP). These strong quality requirements involve several quality controls at each stage and adequate infrastructure and separation of activities to guarantee vaccine identity, purity, sterility, efficacy, and safety.

According to WHO, nowadays about 80% of global vaccine sales come from five large Multi-National Corporations (MNC), resulting from mergers and acquisitions of pharmaceutical companies over the past decades. To compete in these markets, MNCs will often outsource and participate in joint-development activities and technological transfers.

Other challenges in Covid-19 vaccine development and manufacturing

Ethical, economic, and political challenges can be foreseen within COVID-19 vaccine development completion.

Researchers have often found a connection between political beliefs and attitudes to vaccines. They highlight a crucial issue for public health interventions: “how can we assure the public that recommendations reflect the state of scientific knowledge rather than political interests?” This problem is exacerbated in times of crisis, during which there is considerable scientific uncertainty, available measures have a limited effect, and politicians—rather than experts—are the public face of crisis management [11]. This was observed during H1N1 influenza pandemic of 2009 in France as an example and nowadays we have heard of promises of a vaccine supply “very soon” in the case of the US, with no basic facts to support the statement.

As a result of the Global Vaccine Summit, world leaders, together with the Bill & Melinda Gates Foundation, pledged $750 million to AstraZeneca for 300 million doses of AZD1222 on a no-profit basis as part of the Gavi [12] Covax Advance Market Commitment and the Serum Institute of India was also committed to producing up to 1 billion doses for low-income and middle-income countries.

Still many big questions remain. Have the funders agreed to equitable access? How will the vaccines be priced? Will governments commit to sharing vaccines according to fair allocation rules being developed by WHO? Can technology be transferred royalty-free to multiple manufacturers? There is an urgent need for new arrangements at the global level to facilitate the development, finance, production, and equitable distribution of COVID-19 vaccines.

Conclusions

Since no specific treatments for COVID-19 exist right now, the availability of a vaccine against COVID-19 is an effective strategy for control and prevention of this disease, locally and globally. A huge effort is being made by the entire scientific community to shorten the traditional clinical trials and vaccine manufacturing timelines, pouring enormous amounts of public money and resources into vaccine research and development. This effort has resulted in more than 150 COVID-19 vaccine candidates so far. Needless to say, that global solidarity is needed and resources must be pooled and shared to reach a solution for all humankind.

In order to ensure a globally-fair allocation system for eventual vaccines, CEPI published in June guidelines for equitable distribution of COVID-19 vaccines. Particular attention was paid to the prices that should be set as low as possible: for example AstraZeneca, detaining the most advanced vaccine candidate in clinical trials, stated that initial pricing of its vaccine would not include a profit margin for the company.

In an "optimistic" scenario, most of the experts think a vaccine is likely to become available by mid-2021. Even if there are already very promising vaccine candidates, considering the huge amount of failure possibility, there is still no guarantees that these hypothetical timelines will be achieved.

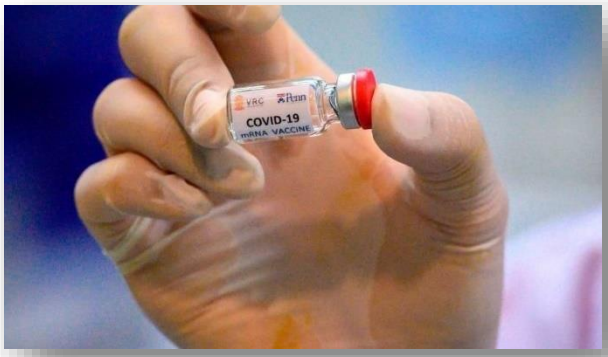


Figure 3 Sample of Penn mRNA vaccine against SARS-CoV-2
(images via AP)

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