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# COVID-19 vaccines: Development, strategies, types and vaccine usage hesitancy

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Vaccine development using different platforms is one of the important strategies to address coronavirus disease pandemic. The global need for vaccines requires effective vaccine approaches and collaboration between pharmaceutical and biotechnological companies, governments and the industrial and academic sectors. About 72% of the vaccine candidates are being developed by the private sector, while 28% are carried out by the public sector and different non-profit organizations. COVID-19 vaccines are based on complete viruses (inactivated or attenuated), viral vectors (replicating or not), antigenic subunits (proteins or peptides), nucleic acids (RNA or DNA) or virus-like particles. Important aspects of vaccine development include manufacturing flexibility, speed, cost, safety, cellular and humoral immunogenicity, vaccine stability and cold chain maintenance. Vaccines can be prepared using different manufacturing platforms, computational biology, gene synthesis, structure-based antigen design and protein engineering. Individual confidence, convenience and complacency are factors that affect the attitude towards acceptance of COVID-19 vaccination. This could be complicated by socio-demographic, psychological, cognitive and cultural factors.

**Keywords:** COVID-19; SARS-CoV-2; vaccines; immunity.

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## Introduction

Around 2002 and 2012, two epidemic coronavirus infections (MERS-CoV and SARS-CoV) emerged and caused flu-like symptoms and lethal acute respiratory tract infections.<sup>(1)</sup> The newly emerged virus causing COVID-19 was named SARS-CoV-2 because it showed similarity to SARS-CoV during isolation and phylogenetic investigation of the strain.<sup>(2)</sup> The genetic sequence of the SARS-CoV-2, published on January 2020, triggered research and development activities worldwide for the development of a vaccine against the disease. The first COVID-19 vaccine candidate against SARS-CoV-2 entered human clinical trial on March 2020.

The entry of the virus into the host cells induces the immune response with the production of antibodies against the coronavirus surface spike protein. However, data on the type of immunity required to protect individuals from subsequent viral re-infection is not known. In experimental animal models, SARS-CoV immunization with nucleic acid, viral vector vaccines,

recombinant subunit proteins and passive immunization has been shown to be effective against the disease.<sup>(3)</sup>

However, in animal models or in human coronavirus disease, the role of T cell immunity in preventing disease is not clear.<sup>(4)</sup> Vaccine development using different platforms is one of the most important strategies to address the coronavirus disease pandemic.<sup>(4)</sup>

## Vaccine development worldwide

The development and distribution of effective and safe vaccines is crucial to the worldwide community for immunization and protection from morbidity and mortality related to SARS-CoV-2. The geographic distribution of COVID-19 and the global need for vaccines require effective vaccine approaches and collaboration between pharmaceutical and biotechnological companies, governments and the industrial and academic sectors, where each sector adds its individual strength.<sup>(5)</sup>

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development projects are carried out by the public sector and different non-profit organizations.<sup>(6)</sup> Along with large multinational companies (GSK, Pfizer, Sanofi and Janssen), different small companies are also involved in vaccine development. Hence, coordination of the COVID-19 vaccine manufacturing and supply capacity will be important to meet worldwide vaccine demand. The coronavirus vaccine development activity is 46% in North America, 18% in Europe, 18% in Asia (excluding China), 18% in China and 18% in Australia.<sup>(6)</sup> Although regulatory frameworks and vaccine manufacturing capacity exist in Latin America and Africa, no information regarding vaccine development is available in these globe regions.<sup>(6)</sup> However, clinical trials were authorized for Soberana 01 (Cuba's first vaccine candidate), by the Cuba's national regulatory agency, the Center for Quality Control of Medicines, Equipment and Medical Devices (CECMED) on August 13, 2020, which was the first from Caribbean and Latin America. On August 24, to evaluate vaccine immunogenicity and safety, parallel phase I and phase II randomized, controlled, double blind clinical trials were launched with phase III clinical trials in pipeline for early 2021.<sup>(7)</sup> In the battle against COVID-19, another milestone was achieved by Cuban scientists when clinical evaluations of a second candidate vaccine (Soberana 02) were conducted by approval granted by the CECMED.<sup>(8)</sup> On the basis of the results from this vaccine clinical trial, the Finlay Institute director general expects that vaccine to exhibit 80-95% efficacy. Therefore, for immunization of Cuba's citizens this summer, mass vaccination program was planned.<sup>(9)</sup> The epidemiology of the coronavirus can differ geographically, thus greater coordination of different regions will be required in research and development sector to control this pandemic situation.<sup>(6)</sup>

### **Strategies and platforms for COVID-19 vaccine development**

The development of vaccines against COVID-19 has used several platforms, including: whole virus (inactivated or attenuated), viral vectors (non-replicating or replicating), nucleic acids (RNA or DNA) and subunits (recombinant proteins or synthetic peptides). Critical components for various inactivated and subunits vaccines are adjuvants (aluminum salts, emulsions) which induce specific, long lasting and robust immune responses. Evidence regarding the effects of the adjuvants used in coronavirus vaccines is needed.<sup>(4)</sup> There are certain advantages and limitations to each of these vaccine platforms. Important aspects in vaccine development include manufacturing flexibility,

speed, safety, cost, cellular and humoral immunogenicity, vaccines stability and maintenance of the cold chain. Multiple strategic approaches are critical to vaccine development, since a single platform is not sufficient to meet the global need. DNA and mRNA based vaccines can be developed based on the viral genomic sequence.<sup>(10)</sup>

Vaccines can be prepared with precision using different manufacturing platforms, computational biology, gene synthesis and structure-based antigen design. Examples are recombinant, nucleic acid and live-virus vaccines. The gene-based vaccines deliver genetic sequences encoding antigenic proteins which are produced by host cells. The protein-based vaccines include viral proteins particles or subdomains and inactivated virus manufactured in vitro. Precision for vaccine development is accomplished by knowledge of the structure of vaccine antigen and preservation of the vaccine targeted epitopes.<sup>(11)</sup>

Different companies have developed different vaccines. Strategies based on mRNA sequence have been used by BioNTech and Moderna, and based on DNA sequence, by Inovio.<sup>(10)</sup> Different adjuvants such as MF-59 by Novartis, CpG 1018 by Dynavax and AS03 (GSK) are accessible to the researchers involved in vaccine development to immunogenicity enhancement.<sup>(12)</sup>

### **Scale up for vaccines development**

In order to manufacture large quantities of vaccine doses, the vaccine-manufacturing capacity of the entire globe is needed. Hence, to achieve the target of SARS-CoV-2 vaccines development, global coordination of different health organizations in a dynamic and planned way is required.<sup>(13)</sup> Funding is necessary for the entire vaccine development process.

The cost of vaccines, the method of distribution and the maintenance of the cold chain are key elements for global vaccine coverage. The vaccine manufacturing capacity is about 2-4 billion doses annually and it will be sufficient by years 2023-2024.<sup>(14)</sup> The scale-up process for manufacturing of vaccines might be associated with problems in purification of viral vectors. Moreover, biosafety level-3 facilities must be mandatory for the manufacture of whole-inactivated vaccines.<sup>(15)</sup>

Different companies started large-scale production based on the prediction of the vaccine safety and efficacy testing in phase II or III clinical trials. Several companies have partnered with different manufacturers to scale-up vaccine manufacturing to an estimated level of hundreds of millions of vaccine doses. The company AstraZeneca for its SARS-CoV-2 vaccine has made partnership with

Serum Institute of India and SK Bioscience (Korea). The Chinese company Sinovac has partnered with Bio Farma (Indonesia) and Butantan (Brazil). Johnson and Johnson has partnered with Indian company Biological E.<sup>(16)</sup>

## Types of COVID-19 vaccines

### Protein subunit vaccines

They are based on recombinant antigenic proteins or synthetic peptides able to induce a prolonged immune response.<sup>(17)</sup> Due to its low immunogenicity, these type of vaccines require an adjuvant to enhance vaccine-induced immune responses, immunomodulatory cytokine responses or biological half-life. These types of vaccines use SARS-CoV-2 S protein or its receptor binding domain as an antigenic protein. The viral entry into host cells is via S- protein induced endocytosis, mediated by binding to hACE2 receptors.<sup>(17)</sup> Most used structural proteins of coronaviruses are S and N proteins. These vaccines use cost-efficient manufacturing and are comparatively safer than inactivated/killed and live attenuated vaccines.<sup>(18)</sup> There are already 30 vaccine candidates in the clinical phase.<sup>(19)</sup> The vaccine candidate in clinical trial phase, Novavax with the saponin-based Matrix-M adjuvant, showed 95.6% efficacy against the original variant of SARS-CoV-2. Moreover, clinical trial data showed that also provides protection against the newer variants B.1.1.7 with 85.6% efficacy and B.1.351 with 60% efficacy.<sup>(20)</sup>

### Viral vector vaccines

These vaccines are made from a carrier such as poxvirus or adenovirus which after modification contains a gene from the virus of interest.<sup>(21)</sup> The commonly used viral vectors include adenovirus, parainfluenza, rabies, Newcastle, Sendai and influenza viruses. For synthesis of these vaccines, the viral vector genomic sequence is grafted with a part of the viral DNA which encodes for immunogenic components, whose expression leads to cellular and humoral immune response activation.<sup>(22)</sup> These vaccines are characterized by the targeted delivery of genes with high efficiency to evoke gene transduction and immune response.<sup>(23)</sup> Viral vector vaccines offer prolonged antigenic protein expression, thus can be used prophylactically. Cytotoxic T cells produced in response to these vaccines leads to the elimination of virus-infected cells.<sup>(6)</sup> Moreover, data from viral vector-based vaccine development strategies for SARS-CoV and MERS have been shown to be beneficial for the speedy development of the COVID-19 vaccine.<sup>(24)</sup> A total of 17 viral vector-based COVID-19 vaccines are

already in clinical trials, among which, 3 are replicating and 14 are non-replicating viral vectors.<sup>(19)</sup>

Adenoviruses are commonly used for the development of SARS-CoV-2 vaccines; clinical studies have proved vaccines based on these vectors reduce the incidence of viral pneumonia. A vaccine candidate, based on adenovirus as viral vector which express full-length S protein (Ad5-nCoV), was studied in a phase I clinical trial by CanSino Biologics.<sup>(25)</sup> Healthy volunteers subject to a randomized, double-blind, placebo-controlled phase II trial, that received two doses of Ad5-SARS-CoV-2 S vaccine, developed strong neutralizing antibodies; the vaccine candidate showed good safety and tolerability profiles with induction of T cell and humoral responses.<sup>(26)</sup> Other vectors like vaccinia virus MVA strain has been engineered for SARS-CoV-2 S protein expression;<sup>(27)</sup> healthy volunteers have been recruited for a phase I clinical trial.<sup>(28)</sup> Four adenovirus-based vaccine candidates entered phase III clinical trials: rAd26 + rAd5-S (Gamaleya Research Institute), adenovirus type 5 vector (Cansino Biological Inc.), ChAdOx1-S (AstraZeneca), and Ad26CoV-S1 (Janssen Pharmaceutical).<sup>(19)</sup> The rAd26-S/rAd5-S vaccine exhibited good tolerability with 91.6% efficacy against COVID-19 in phase III clinical trials.<sup>(29)</sup> A potential option for COVID-19 vaccine delivery comprises intranasal administration taking into account SARS-CoV-2 infections occur intranasally.<sup>(30)</sup> Regarding this aspect, an influenza virus vector expressing the SARS-CoV-2 S RBD (DeINS1-2019-nCoV-RBD-OPT1) has been administered as an intranasal spray; phase I and phase II clinical trials has been registered in China.<sup>(31)</sup> The safety of viral vectored vaccines (Ad5 and Ad26) was determined in phase III clinical trials and the results showed acceptable protection by vaccine against COVID-19 after one dose.<sup>(32)</sup>

### mRNA vaccines

These vaccines are gaining more attention due to their efficacy, safety and ease in gross scale manufacturing. They can be administered by various methods such as injection needles into muscle tissues, spleen, skin and mucous membranes. These vaccines are non-infectious with almost no risk of mutagenesis.<sup>(33)</sup> The mRNA vaccines are prepared in the form of lipid nanoparticles. Although they protect and deliver mRNA, the stability and scalability of mRNA lipid nanoparticles are issues that need to be addressed. There are 16 RNA-based vaccines in the clinical phase.<sup>(19)</sup>

Since the outbreak of coronavirus, several biopharmaceutical companies have announced the establishment of mRNA vaccine projects for SARS-CoV-2. To fight the ongoing SARS-CoV-2 pandemic, these vaccines have become an increasingly attractive platform for various reasons. Firstly, to produce a vaccine candidate, the requirement for only a DNA template of the desired antigen results in fast manufacturing time.<sup>(34)</sup> Secondly, potent immune response was evoked by these vaccines in different animal studies and human clinical trials followed by a significant protection from COVID-19 in phase II and III clinical trials.<sup>(35)</sup> The two mRNA vaccine candidates, mRNA-1273 (Moderna) and BNT162 (BioNTech/Pfizer) entered phase III clinical trials after showing convincing efficacy and safety against SARS-CoV-2 in phase I and II. Although a minimum of 50% efficacy is required by SARS-CoV-2 vaccines to qualify for approval by FDA,<sup>(36)</sup> the aforementioned mRNA vaccines approved for emergency use, reported more than 94% efficacy without any safety concerns except transient and mild local and systemic reactions.<sup>(35)</sup>

Modification of these mRNA vaccines can be made if needed. The target immunogenic epitopes can be easily switched in and out of the vaccine candidates, with the antigen DNA sequence as a template. Hence, to target a newly emerged coronavirus strain, a SARS-CoV-2 vaccine can be quickly modified.<sup>(37)</sup> To enhance the stability of these vaccines, modifications that allow their repeated administration can be made, thus the immunogenicity of the mRNA could be minimized.<sup>(38)</sup>

One of the major concerns for mRNA vaccine is the need for ultra-cold storage. However, studies have showed the stability of these vaccines at 4°C for one week duration.<sup>(39)</sup> To preserve potency, the storage recommendations of mRNA vaccine (BNT162b2) are -80°C to -60°C for 6 months or 2°C to 8°C for 5 days.<sup>(40)</sup> For Moderna vaccine (mRNA-1273), the FDA storage recommendations are 2°C to 8°C for 30 days and at -25°C to -15°C for long-term storage.<sup>(41)</sup>

### DNA-based vaccines

Introduction of DNA vaccine is the most comprehensive approach in vaccination which utilizes adjuvant to evoke immune response. For DNA-based vaccines, an injection delivery device or electroporation is required to facilitate entry of DNA into cells. Transfection of myocytes or keratinocytes results in expression of transgene (DNA segment containing a gene sequence) and release of

derived protein/peptide via exosomes. Moreover, cell mediated and humoral immune responses are enhanced by endocytosis of antigenic material by immature dendritic cells, which in association with MHC2 and MHC1 antigens, ultimately present these cells to the CD8<sup>+</sup> and CD4<sup>+</sup> T cells.<sup>(42)</sup>

On January 11, 2020, after the public release of the genomic sequence of SARS-CoV-2, the design and synthesis of synthetic DNA-based vaccine was initiated immediately. A synthetic DNA vaccine candidate (INO-4800), by competitive inhibition of SARS-CoV-2 spike protein expression, evoked humoral and T cell immunity in different animal models. In lung washes of INO-4800-immunized guinea pigs and mice, anti-SARS-CoV-2 binding antibodies were detected; these antibodies had the potential to protect against severe infections of lung tissues by SARS-CoV-2. T cell response against SARS-CoV-2 was induced after 7 days of vaccine administration, with lower viral load and could potentially reduce the spread of SARS-CoV-2.<sup>(43)</sup>

### Vaccine usage hesitancy

Vaccine hesitancy is the term described as refusal of vaccination or delay in the acceptance of vaccines.<sup>(44)</sup> Individual confidence, convenience and complacency are factors that affect the individual attitude towards acceptance of vaccination.<sup>(44,45)</sup> Confidence refers to trust in safe vaccination and effectiveness, along with healthcare competence. Convenience refers to affordability, easy availability and delivery of vaccines in a comfortable service. Complacency refers to the lack of understanding of the disease risk; hence, vaccination is perceived inessential by this group of people. The governments may first consider building public trust before imposing vaccination. Fairness, competence, consistency, sincerity, objectivity and faith are six determinants of trust identified by WHO that must be transformed to the general public, which makes people to develop more confidence in vaccination and government.<sup>(46)</sup> WHO has encouraged all people to promote the vaccination process.<sup>(47)</sup>

Religious prohibitions, questioning of dosing recommendations, poor quality of vaccines, myths and rumors related to the presence of active virus in vaccines are some of the misleading claims causing hindrance in vaccination.<sup>(48)</sup> One of the major factors which lead to non-compliance to vaccination includes distrust of vaccine safety, vaccine novelty concerns about side effects and the long term effects on health. Moreover, inappropriate risk messages from public health experts may also

reduce vaccine usage.<sup>(49)</sup> Various socio-demographic, psychologic, cognitive and cultural factors also contribute to vaccine hesitancy.<sup>(44,50,51)</sup> Analysis of these factors is required to address the hesitancy of COVID-19 vaccine usage, followed by the evaluation of the magnitude and scope of the pandemic.<sup>(52)</sup> Consequently, this may help in planning interventional measures aimed to tackle this global pandemic.<sup>(53)</sup>

The acceptance rates of COVID-19 vaccine were found to be highest in Malaysia (94.3%),<sup>(54)</sup> Ecuador (97.0%),<sup>(55)</sup> China (91.3%)<sup>(56)</sup> and Indonesia (93.3%),<sup>(57)</sup> while the acceptance of these vaccines was low in France (58.9%),<sup>(58)</sup> Poland (56.3%),<sup>(55)</sup> Russia (54.9%),<sup>(55)</sup> Jordan (28.4%),<sup>(45)</sup> Italy (53.7%),<sup>(55)</sup> US (56.9%)<sup>(55)</sup> and Kuwait (23.6%).<sup>(45)</sup> In a survey conducted among the general public, there is an acceptance rate of more than 70% of the use of coronavirus vaccine with low acceptance rates in Africa, Russia, the Middle East and different European countries. However, how speedily the majority of the population gets vaccinated will have a major impact on the death toll. The coming few months are important to overcome vaccine hesitancy.<sup>(59)</sup>

As warned by the World Health Organization, the world is facing another type of epidemic called ‘infodemics’ that spreads wrong information and misleading scientific claims.<sup>(60)</sup> With the advent of vaccine against COVID-19, there is a high hope of ending the pandemic that has disturbed the lives of people around the globe. It is recommended to address the scope and issue of COVID-19 vaccine hesitancy in various nations as an initial step for building trust among the community.<sup>(45)</sup>

## Conclusion

Since the need for vaccine development is a worldwide challenge, it requires collaboration between pharmaceutical and biotechnological companies, governments and the industrial and academic sectors. Significant aspects in vaccine development include flexibility and speed of manufacture, safety, cellular and humoral immunogenicity, scale of manufacture and cost and stability. Along with them, individual confidence, convenience and complacency are factors which need to be addressed.

## Conflict of interest

The authors declare that there is no conflict of interest.

## Author’s contributions

Ayisha Shaukat designed the title, did the literature survey, wrote the content of the manuscript and revised it during the peer-review process.

Khalid Hussain assisted in the literature survey, writing the manuscript content and revision during the peer-review process.

Naureen Shehzadi assisted in the literature survey and writing the manuscript content.

All authors reviewed and approved the final version of this manuscript for publication.

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## **Vacunas contra la COVID-19: desarrollo, estrategias, tipos y reticencia al uso de la vacunación**

### **Resumen**

El desarrollo de vacunas utilizando diferentes plataformas es una de las estrategias importantes para abordar la pandemia de COVID-19. La necesidad mundial de vacunas requiere enfoques de vacunas eficaces y la colaboración entre las empresas farmacéuticas y biotecnológicas, los gobiernos y los sectores industrial y académico. Alrededor del 72% de los candidatos vacunales están siendo desarrolladas por el sector privado, mientras que el 28%, por el sector público y diferentes organizaciones sin fines de lucro. Las vacunas contra la COVID-19 se basan en virus completos (inactivados o atenuados), vectores virales (replicantes o no), subunidades antigénicas (proteínas o péptidos), ácidos nucleicos (ARN o ADN) o partículas similares a virus. Aspectos importantes del desarrollo de vacunas incluyen la flexibilidad de fabricación, la velocidad, el costo, la seguridad, la inmunogenicidad celular y humoral, la estabilidad de la vacuna y el mantenimiento de la cadena de frío. Las vacunas se pueden preparar con precisión utilizando diferentes plataformas de fabricación, biología computacional, síntesis de genes, diseño de antígenos basado en estructuras e ingeniería de proteínas. La confianza individual, la conveniencia y la complacencia son factores que afectan la actitud hacia la aceptación de la vacunación contra la COVID-19. Esto podría complicarse por factores sociodemográficos, psicológicos, cognitivos y culturales.

**Palabras clave:** COVID-19; SARS-CoV-2; vacunas; inmunidad.

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