OPEN ACCESS
Freely Available Online

JOURNAL OF CURRENT VIRUSES AND TREATMENT METHODOLOGIES

ISSN NO: 2691-8862

Review

DOI: 10.14302/issn.2691-8862.jvat-20-3513

COVID-19 Vaccine Development: Insights, Prospects and Challenges

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Abstract

This paper explores the trends, issues and challenges confronting the successful vaccine development for the novel Coronavirus disease (COVID-19). Right from the commencement of the COVID-19 pandemic, no drugs or vaccine has been developed nor approved for treating those down with COVID-19. This year, the scientific community and the vaccine industry have been asked to respond urgently to SARS-COVID-2 pandemic. Presently numerous vaccine development platforms are under process and DNA- and RNA-based platforms showing great potential followed by recombinant-subunit vaccines. Through explorative research, it was established that companies involved in COVID-19 vaccine development are facing big challenges in the scientific, economic and logistical perspectives. Amongst these challenges are distrust, misinformation, and about understanding the immune system interaction with the vaccine being developed, as well as with the pathogen itself. Adjudged as insurmountable may be too early a conclusion. The race is on and progresses are being made. Proper understanding of trends, metrics and dynamics revolving around COVID-19 vaccine development is crucial in expanding possibilities for positive results from ongoing vaccine research. In this review, we spotlight on the most recent developments in COVID-19 vaccine, including top 10 early candidates that may hit the market in next few months.

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Keywords: Coronavirus, COVID-19, Clinical trial, Infection, Vaccine

Received: Aug 12, 2020 **Accepted:** Aug 20, 2020 **Published:** Aug 25, 2020

Editor: William de Souza, University of Contestado - UnC. City Hall of Três Barras, Brazil.

Introduction

Since 2002, there has been a record of Coronavirus disease outbreak caused by SARS-CoV, MERS-CoV, as well as the novel SARS-CoV-2, the causal agent of the Coronavirus Disease 2019 that broke out in Wuhan, China in December the same year and has since become widespread across several countries and continents leading to thousands of deaths [1]. As at August 9, 2020, COVID-19 has spread to 213 countries and territories, with 19, 847,800 cases recorded globally and 730, 372 deaths. The global race for the development of vaccine for the novel Coronavirus disease became intensive upon the release of the genetic sequence of SARS-CoV-2 on the 11th of January 2020. Early efforts have been intensified into the clinical course of COVID-19, counting severe cases and treating those who are already infected [2]. Experience with pandemic influenza, Middle East Respiratory Syndrome (MERS), as well as other outbreaks has revealed that when there is an evolution of an epidemic and a pandemic, we are then faced with an urgent need to enlarge public health activities so as to influence the virus epidemiology and then characterize its possible impact [1,2]. Through scientific consultations, the expectation is that effective vaccine for the Coronavirus disease-2019 (COVID-19) may not come into the market this year. However, certain antiviral drugs are presently under investigation for possible cure of COVID-19. As the cases of infection continues to rise and mortality rate blossom, the recurring question had been; why has there been no vaccine developed yet for COVID-19? Researchers far and wide currently engaged in research for vaccine development for COVID-19 are facing big challenges in the scientific, economic and logistical perspectives. The fact remains that the entire human race is still currently naive to COVID-19, hence, bringing about repeated occurrences of unacceptably high mortality, significant changes to our way of life, and intense economic disruption. Therefore, the importance of having an effective vaccine developed cannot be overemphasized, and even greater if its deployment can happen in time in a bid to forestall sustained pandemic or continuous rise in COVID-19 infection.

The family Coronaviridae houses the Beta-Coronavirus genus for which the severe acute respiratory syndrome Coronavirus (SARS-CoV-2) belongs. SARS-CoV-2 is an enveloped single-stranded RNA virus with a 30 kb genome containing envelope (E), spike (s), nucleocapsid proteins (N), and membrane (M) as the four main viral structure proteins alongside 14 open reading frames [3-5]. Scientists have reported that there is a 93.1% nucleotide sequence similarity of SARS-CoV-2 S gene sequences with that of Rhinolophusaffinis bat Coronavirus RaTG13, of which only below 75% nucleotide sequence similarity with SARS-CoV-2 has been identified [6]. In comparing the viral S sequence of SARS-CoV and SARS-CoV-2, the latter possess three additional short insertions in the N-terminal group, with four out of five key residues changes in the receptor-binding motif of S protein receptor binding domain (RBD) [7]. Worthy to note is the fact that the human cellular receptor Angiotensin Converting Enzyme II (ACE II) are shared by both SARS-CoV and SARS-CoV-2, but findings have shown that SARS-CoV-2 appears to be more prone to human to human transmission than SARS-CoV [7, 8].

SARS-CoV-2 predominantly infects lower airways and binds to the alveolar epithelial cells on ACE2. Both SARS-CoV-2 and SARS-CoV are inflammatory cytokines potent inducers [9]. For organ damage, the postulated mechanism is that called "cytokine cascade" or "cytokine storm". SARS-CoV-2 causes the activation of the immune cells as well as the inducement of the secretion of inflammatory chemokines and cytokines into the pulmonary vascular endothelial cells [10]. SARS-CoV-2, the causative agent of COVID-19 infects people of all ages. Nevertheless, evidence currently available indicates that two groups of people are at a greater risk of acquiring a severe COVID-19. Those with underlying medical issues like cancer, cardiovascular disease, chronic respiratory disease and diabetes, and also the ones above 60 years of age are specifically at greater risk of infection. The risk of disease severity increase gradually with the 40 year age.

Findings have revealed that there is a close association between SARS-CoV and the novel SARS-CoV-2 [10, 11]. SARS-CoV-2 is known to be of zoonotic origin. Genetic analysis shows that the Coronavirus clusters genetically with the genus Beta Coronavirus; subgenus Sarbecovirus alongside two

strains derived from bat. It has 96% similarity at the whole genome level to other samples of bat Coronavirus (BatCov RaTG13). Chinese researchers discovered that only one difference in amino acid in diverse parts of the genome sequences between the viruses from pangolins and those from humans. When compared with the current virus (SARS-CoV-2), there are series of significant similarities and differences. Both SARS-CoV and MERS-CoV possess significantly higher case fatality rates of 10% and 40% respectively. The current SARS-CoV-2 has higher level of transmissibility, although it shares 79% of its genome with SARS-CoV. They both find their way into the cell through the ACE2 receptor [12].

Need for COVID-19 Vaccine

The whole world is concerned about the vaccine for COVID-19 due to fatality of this condition. On-time vaccination is highly imperative to contain the SARS-CoV -2 pandemic which has been identified to possess a high level of infectivity and high rate of human to human transmission. Traditional public health strategies are currently being employed towards mitigating the virus spread alongside the use of extensive lockdowns in communities and observance of physical distancing. Continuous enforcement of the preventive strategies has been challenging. Moreover, for how long shall the communities remain on lockdown? Experts have stated that the general public will have to live with the pandemic's social and economic disruption for quite a while. Obviously successful COVID-19 vaccine development is needed as soon as possible. However, vaccine trials are currently on course, yet development of vaccine can take many months to years [13]. A vaccine is targeted at boosting natural immune response to an invading virus by priming it to recognize antigens and distinct molecules located on the surface of pathogens. Basically, the response of the immune system is based on the availability of these antigens from the production of special immune cells to directly attack the pathogen, or by the production of proteins named antibodies. Antibodies become attached to an antigen, then become attracted by the immune cells that engulf and destroy the pathogen. Vaccine possesses the ability to usurp herd immunity in communities and territories in a bid to reduce disease incidence, prevent transmission, and lower economic and social burden of the disease. Increased immunization coverage is a potent approach in fighting the pandemic effectively, block secondary infection waves, and mitigate seasonal endemic infection outbursts. Along the way, there could be the eradication of the disease as seen in several past diseases (poliomyelitis, smallpox etc.) with higher potential than COVID-19 to result in pandemic [14,15].

Recent efforts by researchers is seen in the continuous monitoring of the genetic sequence of SARS-CoV-2 due to possible rapid mutations so as to acquire crucial data required to assist in providing adequate responses for this current outbreak and that to come in the future. This is very important for the vaccine development studies. Viruses originating from animal species and getting transferred to humans are specifically problematic. They have the capacity to undergo rapid mutations due to their animal origin, for which no preexisting immunity is essentially available in the human population. Interestingly, mutations do not practically affect the functioning of the virus regardless of the fact that mutations within the genome of the virus take place during outbreaks. Such mutations are also unlikely to present any significant resistance to a future vaccine [16].

Current Status of COVID-19 Vaccine

Vaccine development is a long, tedious and costly process with multiple clinical trials to ensure safety. WHO reports that as at July 2020, they are tracking over 140 vaccine candidates out of which 24 are in the clinical development phase [17]. By July 31, testing on 27 potential COVID-19 vaccines are ongoing across the globe, while over 139 vaccines are currently in the pre-trial development phase. Highest performing vaccine candidates have transcended into clinical development, inclusive of INO-4800 from Inovio, mRNA-1273 from Moderna, pathogen-specific aAPC and LV-SMENP-DC from Shenzhen Geno-Immune Medical Institute, and Ad5-nCoV from CanSino Biologicals (Table 1). Diverse other vaccine developers have declared their plans to kick start human testing subsequently in 2020. One significant COVID-19 vaccine development landscape feature is the series of technology platforms on evaluation, some of which are featuring viral vector (non-replicating and replicating), nucleic acid (DNA and RNA), peptide, virus-like particle, inactivated virus approaches, recombinant protein, and live attenuated

virus [18,19]. Although quite a number of these platforms are currently not the yardstick for licensed vaccines, yet the fields experience in oncology (among others) is propelling the vaccine developers to explore opportunities in next-generation approaches to fast track development and manufacturing speed. It is possible that some vaccine platforms may be better applicable to particular population subtypes (like the children, elderly, pregnant women or immunocompromised patients) [20].

Table 1. Top 10 Vaccine Candidates in different stages of vaccine development for COVID-19

Vaccine Candidate	Clinical Trial	Description
Inactivated Vaccine	Phase 3	Inactivated COVID-19 vaccine initiated through ChiCTR2000031809; a double-blind randomized, Placebo-parallel regulated phase 1/2 clinical trial using Healthy individuals of 5 years old and above.
mRNA 1273	Phase 3	Being developed by Moderna on the premise of past studies on the other Coronaviruses (MERS and SARS). Successful phase 1 completed using 105 healthy individuals with results showing successful antibodies neutralization. Both in mouse model and in healthy individuals subjected with the phase 1 and 2 trials. Phase 3 features 30,000 Participants with high risk of SARS-CoV-2 infection.
CoronaVac	Phase 3	Previously called PiCoVacc, an alum-adjuvanted and formalin-inactivated vaccine candidate with results from animal studies showing partial or complete protection in macaques. A record of positive immune response with more than 90% neutralizing antibody seroconversion rate after phase 1/2 trials.
Bacillus Calmette-Guerin (BCG) live-attenuated vaccine	Phase 2/3 clinical trials	Being a vaccine previously developed for tuberculosis. Currently studied in the randomized and controlled phase 3 trials.
AZD1222	Phase 2/3 clinical trials	A Chimpanzee adenovirus vaccine vector scaled through phases 1/2 trials featuring a single-blinded multi-centre study. Vaccine proves to have acceptable safety profile with the majority of Patients showing antibody response.
BNT162	Phase 2/3 clinical trials	A modRNA candidate with report of robust immunogenicity after Clinical trials phase 2. Received FDA fast track designation for two of its kind – BNT162b1 and BNT162b2.
Ad5-nCoV	Phase 2	Recombinant COVID-19 vaccine incorporating the adenovirus type 5 vector. Phase 1 trial result indicates a humoral and immunogenic Response with series of adverse reactions recorded. Phase 2 shows Specific interferon γ enzyme-linked immunospot assay and Neutralizing antibody responses.
Adjuvant recombinant vaccine candidate	Phase 2	Results from phase 1 trial yet to be released, phase 2 trials Underway.
ZyCoV-D	Phase 2	A plasmid DNA vaccine candidate targeting the virus' membrane Protein during viral entry.
Covaxin	Phase 2	Inactivated vaccine candidate with encouraging prospects, already Progressed into phase 2 clinical trial.

Vaccine Development Stages

Six stages of the development of vaccine have been outlined by the CDC: Exploratory stage, preclinical stage, clinical development, regulatory review and approval, manufacturing, and quality control. The entire vaccine development process often takes several years, sometimes up to decades [17]. Currently, numerous vaccine candidates are transcending from the exploratory stage which is the first stage of vaccine development, into the preclinical and clinical stages. Worthy to note is the fact that 2 months away from the release of the full genome map of SARS-CoV-2, first in-human clinical trials commenced. Of the six stages, the clinical stage remains the longest. Due to the fact that no biologics (vaccines inclusive) or drugs are always with one or two risks, it is imperative to engage safety assessments in human clinical trials. The clinical phase has three divisions namely phase I, phase II and phase III. Two regulatory permissions are required; the Clinical Trial Authorization prior to the clinical stage in order to permit "first in-human" testing, and the Biologic License Application/Approval for vaccine marketing after successful clinical trials. Following clinical studies, there is enrolment and treatment of patients suffering from COVID-19 with aim of achieving sufficient safety and effectiveness of potential vaccines. There is a possibility that thousands of COVID-19 patients may have to take part in the clinical studies prior to approval of therapy or vaccine for use by the general public [19, 20].

COVID-19 Vaccine Development Challenges

The vaccination decision making calculus spans equilibrium of risk and benefit alongside uncertainty. The SARS and Zika epidemics were ended before the development of the vaccine funding agencies reallocated funds that had been committed for it, leaving manufacturers with great financial losses and slowing down other vaccine-development programs. Since the overall impact of vaccines demands extensive public acceptance in achieving population-level immunity, right from the onset, policies on vaccination have been subjected to ideological and political debate, featuring individual rights against public health. Several of the vaccine candidates have passed through intensive clinical testing protocols in a bid to prove their efficaciousness and safety [22]. However, there is an unrealistically high expectation for COVID-19 vaccine. Paraded as the only "way-out" of the present situation, COVID-19 vaccines are seen by many to be 100% safe and effective even when they are yet to scale through the several rigorous approval protocols and conditions. If there is no "repentance" from the extremely high expectations on COVID-19 vaccine, they might end up catalyzing the narrative that challenges the quality and reliability of vaccines in a bigger way [22, 23].

Something more is the distrust, wildfires, rumors encompassing the vaccines and even the virus itself. These elements are described by WHO as "infodemic"; in reference to fake news spreading spontaneously and readily than the novel Coronavirus [2]. Another striking problem is on the side of vaccine and drug makers. This time, it is not about which vaccine or therapeutic platform should they operate with, it is rather about the paths of conventional clinical development which has proven to be cumbersome, demanding longer time in addressing the present public health threat. With this challenge, quite a number of groups and researchers are now retooling the development process and protocols in a bid to seek for solutions [23].

In giving response to a pandemic arising from a novel viral pathogen with very high infectivity (like wildfire), discovery of commercial biopharmaceuticals may not be solely palatable as response. Vaccine and drug manufacturers are naturally used to charting the course of clinical and regulatory development protocol spanning several years (sometimes up to decades). In the same vein, there is little experience on the side of drug development regulators in pandemic context. There is yet to be an accelerated pathway for COVID-19vaccine development or even for any other emerging infectious disease.

Considerations for COVID-19 Vaccine Development

The efforts in progress towards developing a vaccine should be monitored using three prompts: speed, production and deployment in terms of scalability and accessibility globally. Funding is highly needed to achieve a successful vaccine development. The estimate given by the CEPI indicates that at least US$2 billion investment will be needed to develop three vaccines over the nest 12-18 months excluding manufacture or

delivery costs.

As obtained in times past, vaccines still serve as a kind of diplomacy aimed at maintaining the basic level of global cooperation. Trust remains the fundamental standpoint that underpins vaccine acceptance. Trust in the steps, processes, practices, licensure, policies, manufacturing and even the deployment of developed vaccines. Having trust in the policy makers, the healthcare professionals – nurses, doctors, community health practitioners and others. If the issue of trust remains unaddressed and understood, efforts at improving the confidence of vaccines to be developed may fail, particularly when the new vaccine technologies currently used as well as the speed through which the vaccines are being developed are involved.

Conclusion

The journey into COVID-19 vaccine development only began several months ago. The state of development is obviously taking new turns overtime. More can be said about the role of stakeholders in ensuring eventual success in the long run. However, there are signals calling for deeper understanding of practical and real-time issues bordering on successful development of vaccines. Particularly, there is need to address the complex challenges related to vaccine hesitancy. To prevent stagnancy along the way, concerted efforts on the part of all stakeholders – healthcare professionals, government, civil society, the general public cannot be overemphasized. Particularly in the area of making explanations on what is not known and what needs to be known regarding vaccines, alongside their risks and benefits as well as their values to communities and individuals is highly imperative. As the COVID-19 pandemic continues to ravage the world featuring stigma, suspicion, fear and the worst of it all, death, the development of COVID-19 is still on the field of play.

Recommendation

Control of intentional and purposeful scare strategies alongside rumours management should be strengthened around COVID-19 vaccine development efforts, while essential hints, updates and suggestions requiring further investigation should be encouraged and strengthened. In case if the pandemic appears to unexpectedly end before effective vaccines are prepared, we should keep building up the most encouraging contender to a point where they can be stored and prepared for preliminaries and emergency authorization should a outbreak recur.

Declaration of Competing Interest

The authors assert that there is no conflict of interests concerning the publication of this review.

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