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COVID-19 Vaccine Race: An Overview and Update

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Abstract

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A sudden health crisis has shut down the entire world for almost a year due to a new virus called Covid-19 and thus the WHO has declared the COVID-19 as a pandemic disease. As vaccines stimulate the immune system to fight against future infections, thereby conferring immunity, so far, vaccine development in a race throughout the world. Therefore, disseminating the overview of the vaccine development at present with their critical situation for COVID-19 is the aim of this review. The world is looking eagerly for a potential vaccine candidate that can save every life. Here, we reported the overview of the possible types of vaccines against Covid-19 as well as a glimpse of vaccine race with different phases of clinical trial data, comparison of the rate of success of phase-III clinical trials and their safety, and drawbacks with the present status. We have studied literature from clinical trial data of respective vaccine candidates published in the journals and collected data from databases dedicated to corona vaccine and the vaccine company's website to enrich our review and aiming to focus on clinical trial data stages, how consequences it faces, and how to position it belongs towards a successful vaccine candidate.

Keywords: COVID-19, SARS-CoV-2, COVID-19 vaccine, Clinical trial.

Introduction

In late November of 2019, a highly contagious respiratory virus was noticed in Wuhan, China and later, it has spread all over the world[1]. Along with the other zoonotic viruses (SARS and MERS) of the beta corona viridae family, the bat is thought to be the source of SARS-CoV-2. [2, 3]. Although the mortality rate of Covid-19 (1.4%) is comparatively low compared with other coronaviruses, the contagion rate of Covid-19 (R0 = 2-3) is higher than that of the Spanish flu (0.9-2.0), which made the virus even more deadly [4-6]. Generally, people of all ages may be attacked by the virus but older, and patients with acute respiratory distress syndrome are more prone to death [7, 8]. Current reports indicate that as of January 04, 2021, approximately 85,599,504 Covid-19 positive cases had been identified and 1,853,005 people had lost their lives due to this Covid-19 attack.

(https://www.worldometers.info/coronavirus/?utm_campaign=homeAdvegas1?).

Like SARS virus, ACE2 (angiotensin converting enzyme 2) is also the receptor for SARS-CoV-2 through which the virus enter the human body and destroy our immune system, and multiply [9]. The whole genome sequence of covid-19 is available in gene bank since early March (Gene Bank ID: MN908947.3)[10]. With 30kb genome, four major structural proteins (spike protein, membrane protein, envelope protein and nucleocapside) and non-structural proteins, SARS-Covid-2 is a single stranded RNA virus [11-13]. Various sites of Covid-19 have been selected as drug and vaccine targets to inactivate the virus, including S proteins[11], N protein[14], mpro

[15], RNA dependent RNA polymerase[16], etc. With the onset of the second wave of Covid-19, infections in the last week of November increased about 2% over the previous weeks. Scientists are speculating that the second wave may be worse than the first [17]. Several countries are planning to re-impose lockdown to combat the spread of virus[18]. Now nothing but an effective and safe vaccine will allow the world to return to its normal state. Although various researches are underway to identify and control the virus, so far no positive vaccine has been found against it [19]. However, vaccine development is a long term process with several phases, an unpredictable race is in full swing with more than 160 vaccine candidates in several countries. All updated information regarding the COVID-19 vaccine is being published by the WHO and the necessary information regarding the COVID-19 vaccine is regularly published in the scientific literature[20,21]. Although vaccine trials against Covid-19 began in China on February 15, 2020 [22], it could not stay forward at the race. So far, BNT162b2 is the most likely by the UK. All eyes are on the race of the Covid-19 vaccine[23]. This review is intended to provide an overview of dedicated efforts to provide effective vaccines against COVID-19 that is crimpling the world.

Why vaccine is important for Covid-19 patients

According to WHO, vaccination is a safe and effective way to protect people from harmful diseases before they come into contact with them. Protection from viral infections is developed by induction of immune response through virus-

neutral antibodies against the diseased particle, which is generally achieved through vaccination.

Vaccines have saved millions of people's lives in the past, so for overcoming this pandemic we are eagerly waiting for an effective vaccine. Natural plant compounds are getting priority in this vaccine development. As plants phytochemicals are considered safe for human bodies so from the ancient time plant compounds are being used for this pharmaceutical purpose [24]. Although the development of a vaccine is a long-term process with several steps and issues, scientists around the world are working hard to reduce the time duration to develop an effective vaccine against Covid-19 [24]. Each potential vaccine candidate need to be evaluated for safety, immunity and protective efficacy in humans before being licensed [25].

Covid-19 and its vaccine target

Within short period of outbreak on 10 January'2020 the genome sequence of Covid-19 become available on the web side of the Virology department and later after several sources submitted almost whole genome sequence of Covid-19 on GISAID database[26]. Like other known corona virus SARS-CoV-2 uses host's ACE receptor to seize the target cell through its unique N-glycosylated spike proteins (S2 subunit)[27]. As the head of the virus appears to be less shielded, indicating that the protein could be an easier target to defeat the virus[28]. In addition to the S protein, the other proteins such as N proteins, M proteins, non-structural

proteins (NSPS) and ancillary proteins may have the potentiality to serve as antigens. The viral main proteinase, 3CLpro, is thought to be an effective target for drug development.

In contrast to COVID-19, there are a variety of vaccine candidates, ranging from conventional whole pathogen vaccines (live-attenuated vaccines, inactivated vaccines etc.) to various new generation vaccines (recombinant protein vaccines, viral vector-based vaccines, plasmid DNA vaccine etc.)[29]. Currently, the most clinically advanced COVID-19 vaccines are non- replicating viral vector vaccine (28%) [30] or protein sub-unit vaccine(26.5%) [31], other types of vaccine candidates include inactivated vaccine (19.5%), RNA-based vaccine (13%), DNA based vaccine (6%) and replicating viral vector vaccine (5%) etc.

Vaccine strategies and the race of COVID-19 Vaccine

To develop a successful vaccine candidate is a long term process. In addition, several strategies are followed and different targets are identified to develop different types of vaccines including Live attenuated, Inactivated vaccine, RNA vaccine, DNA vaccine, Replicating Viral Vector, Non replicating viral vector, Protein subunits, Virus Like Particles (VLP), etc. Here, advantages, limitations, and previous success of above-mentioned type of vaccines are outlined, and finally, it has paved the way towards the race of COVID-19 vaccine development (Table 1 and Fig. 1).
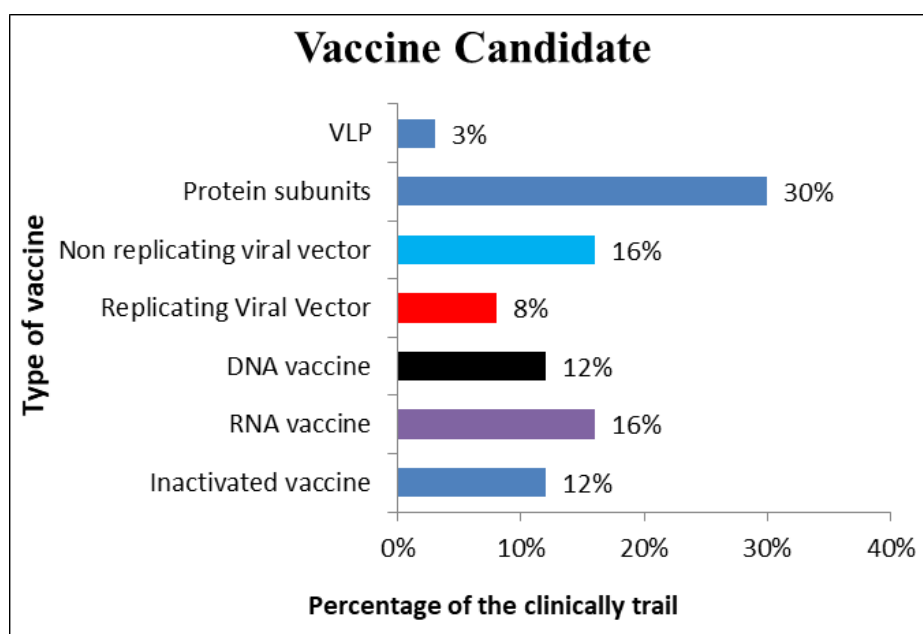

Figure 1: Outline of different vaccine candidates and its position in clinical trial

Source: https://covid-nma.com/vaccines/mapping/#void

Table 1: Outline of vaccine strategies and platform for COVID-19 vaccine development

Vaccine type	Attenuation	Advantages on the field of Covid-19	Limitations	Previous success history	On the race of Covid-19	Ref
a) Live attenuated	Live attenuated virus vaccine is produced by mutating or deleting the virulence genes of a live virus.	Deletion of non-structural genes and deoptimization of codon are being used to develop vaccine against Covid-19. Adjuvant is not necessary.	Genetic reversion is the most prominent barrier against the vaccine development. Storage issues	BCG vaccine, MMR vaccine; Rotavirus vaccine and Poliovirus vaccine.	1 vaccine is on the race of clinical trial.	31
b) Inactivated vaccine	Through chemical and physical treatment the whole virus particle is inactivated.	Generally, destroy the viral RNA; adjuvant is necessary to boost up the immunity.	Adjuvants may show side effects.	IPV vaccine, whooping cough vaccine, rabies vaccine, hepatitis A virus vaccine	7 vaccines are on the race of clinical trial.	32-34
c) RNA vaccine	RNA vaccines are prepared using an mRNA sequence that codifies for a specific antigen and when induced in the body, the antigen could be recognized by the immune system of the body to fight.	Lipid nano particles are being used to deliver the viral mRNA sequence. The RNA could work as self adjuvant.	There is a big storage issue. In vivo vaccine delivery and uptake is a challenging task.	Cancer therapy	10 vaccines are on the race of clinical trial	35,36
d) DNA vaccine	Genetically engineered DNA particle is used to code viral protein.	Circular DNA plasmid is used which later transcribed into mRNA. Solely genetic material is used.	Weaker induction of immunity. Insertional mutation may occur.	Partially effective against Swine flu	7 vaccines are on the race of clinical trial	32, 37
e) Replicating Viral Vector	The vaccine mimics what happens during natural infection with certain pathogens - especially viruses.	No antigenic particle is used instead of the vaccine influence the body to produce antigen. So, strong immune response is produced in body.	It may be harmful for immune compromised patients.	Ebola	5 vaccines are on the race of clinical trial	33, 38
f) Non replicating viral vector	Non-replicating vector vaccines generally enter cells and produce the vaccine antigen, but no new virus particles are formed.	The viral vector vaccines result in endogenous antigen production, both humoral and cellular immune responses are stimulated.	Booster doses are needed.	No	10 vaccines are on the race of clinical trial	33, 39
g) Protein subunits	Potential protein particle is injected which have the ability to defeat the disease causing virus.	It is relatively safe. Viral or bacterial protein is used. It can trigger the immune response.	Needed of booster dose. May be weaker over time	BCG vaccine	18 vaccines are on the race of clinical trial	40
h) VLP	It is one kind of protein vaccine that use viral protein.	The vaccine has self adjuvental properties and it is comparatively safe than other vaccines as it does not induce infection.	There is several challenges to produce the vaccine by maintaining quality.	Vaccine candidate for Chikungunya, Japanese Encephalitis, Yellow Fever and Zika Virus.	2 vaccines are on the race of clinical trial	41, 42

Different stages of Clinical trial of leading COVID-19 Vaccines

In vaccine development pipeline, basic 3 phases are strictly maintained in clinical trials to assess the quality of a vaccine candidate. In phase 1, a small number of healthy volunteers are tested, who have not been exposed to the pathogen to test the safety of the vaccine[45]. According to the latest data, Figure 2 indicates different phases of Covid-19 vaccine stages. For COVID-19 vaccine development process, 39% of vaccines are in this stage. In phase 2, after meeting the criteria for the first round, a vaccine candidate goes through the second round of testing. At this stage, it is recommended to keep focus on immunity and expansion of the vaccine across a wide population, allowing resilience to analyze considering age, gender, ethnicity, and other variables[46]. Presently, 11% of COVID-19 vaccines are in the phase 2. The success rate of this stage is often determined by whether the vaccine could decrease the number of cases or severity of the disease[25]. At present, 30% of COVID vaccines are on this phase. Till date, 15 different COVID-19 vaccines are being conducted phase 3 clinical trial hosted by several countries of different corners of the world (Table 2).

As on November 19, 2020, 117 vaccines are on trial in several stages. Figure 2 denoting the steps of Covid-19 vaccine. A total of 21 vaccines have completed stage 3, and we are hoping to get effective candidate from those.

Table 2: Overall vaccine race up to date

Vaccine Candidate Names	Actual Starting Date of Study	Estimated Completion Date of Study	Sponsor/Company name	Vaccine type	Developer Country	Success rate
BNT162b3 (NCT04368728)	September 9, 2020	December 2021	Pfizer and BioNTech	Nucleoside modified mRNA (modRNA)	USA	90 %
ChAdOx1 nCoV-19 (NCT04400838) ISRCTN89951424	May 28, 2020	September 2021	University of Oxford	Viral vector-based vaccines	UK	70%
mRNA-1273 (NCT04405076)	May 29, 2020	August 20,2021	ModernaTX, Inc.	mRNA-based vaccine	USA	94.5%
Sputnik V vaccine (NCT04526990)			Gamaleya National Research Centre for Epidemiology and Microbiology of the Russian Healthcare Ministry.	Non-replicating viral vector	Russia	92%
Ad5-nCoV (NCT04283461)	July 31, 2021	September 11, 2020	NPO Petrovax	Recombinant novel coronavirus vaccine	Canada	40-70%
AZD1222 (NCT04516746)	August 28, 2020	October 25, 2022	The University of Oxford; AstraZeneca IQVIA Serum Institute of India	Replication-deficient viral vector vaccine (adenovirus from chimpanzees)	UK	62-90%
CoronaVac (NCT04456595)	July 21, 2020	October 2021	Sinovac	Inactivated vaccine (formalin with alum adjuvant)	China	90%
Gam COVID-Vac NCT04564716	September 28, 2020	April 10, 2021	Gamaleya Research Institute of Epidemiology and Microbiology, Health Ministry of the Russian Federation	Non replicating viral vector	Russia	92%
JNJ-78436735 (formerly Ad26.COV2.S) (NCT04614948)	November 6, 2020	May 11, 2023	Johnson & Johnson	Non-replicating viral vector	USA	-
NVX-CoV2373(NCT04611802)	November 2020	December 30, 2022	Novavax	Nanoparticle vaccine	USA	-

https://covid-nma.com/vaccines/mapping/
(https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker)
(https://tbsnews.net/world/who-are-frontrunners-race-covid-vaccine-146320)
https://www.bbc.com/news/health-51665497
(https://clinicaltrials.gov/ct2/search)
https://www.biopharmadive.com/news/coronavirus-vaccine-pipeline-types/579122/
Fobs statistics.
https://www.forbes.com/sites/niallmccarthy/2020/11/23/how-effective-are-the-covid-19-vaccine-candidates-infographic/?sh=5b15f914205d
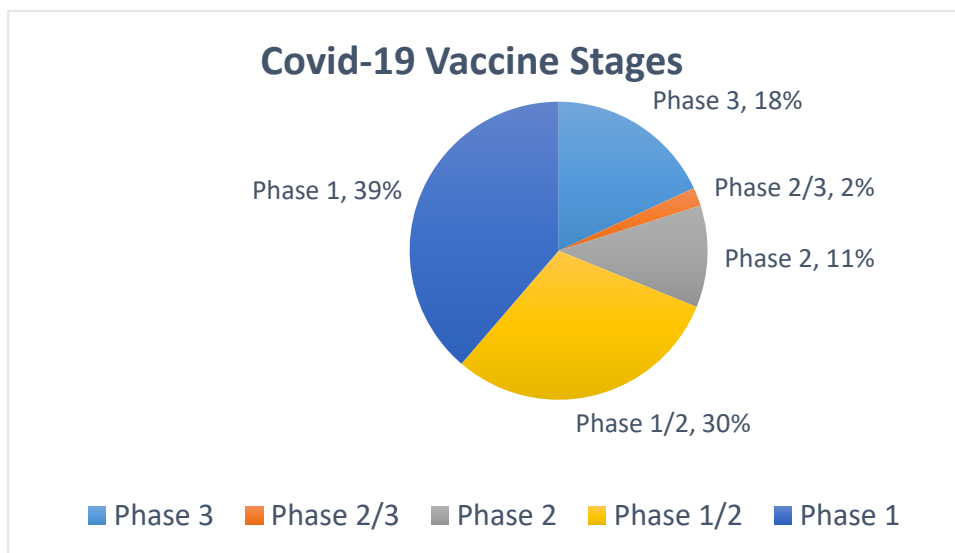
Figure 2: Different phases of COVID-19 vaccine and its required time duration.

Top leading countries towards the vaccine race

In COVID-19 vaccine race, several countries including but not limited to the United Kingdom, the United States, the people's republic of China, Russia, and India are most probably on the front line. Among them, Oxford/ AstraZeneca: AZD1222 from England, BioNTech/Pfizer: BNT162b2 and Moderna: mRNA-1273 from USA, Sinovac: CoronaVac from China, Sputnik V from Russia and, Bharat BioTech's Covaxin from India have shown promising outcomes in phase 3 clinical trial. So, the people from over the world are optimistic to get a successful vaccine candidate from the above mentioned vaccines.

BioNTech is a German company made partnership with Pfizer to develop a vaccine which is very much effective against COVID known as BNT162b2, the generic name of this vaccine tozinameran or the brand name Comirnaty

In vaccine race, BNT162b3 (NCT04368728), ChAdOx1 nCoV-19, mRNA- 1273, Sputnik V vaccine, Ad5-nCoV shows promising result in phase 3 clinical trial. Till date, top leading vaccine candidates namely, BioNTech/Pfizer: BNT162b2, Moderna: mRNA-1273, Gamaleya: Sputnik V, Sinopharm: BBIBP-CorV have gotten acceptance on several countries (Table 3).

Table 3: Approved Vaccines

Name of the vaccine	Developer	Approved Countries
BioNTech/Pfizer: BNT162b2	BioNTech, Pfizer	Bahrain, Canada, Saudi Arabia ,United Kingdom, United States, Chile ,Costa Rica, Ecuador, Kuwait, Mexico, Panama, Singapore, Switzerland Israel.
Moderna: mRNA-1273	Moderna, NIAID	United States and Canada
Gamaleya: Sputnik V	Gamaleya Research Institute, Health Ministry of the Russian Federation	Russia and Belarus
Sinopharm: BBIBP-CorV	China National Biotec Group Company Limited, G42 Healthcare company, Abu Dhabi Health Services Company, Wuhan Institute of Biological Products Co. Ltd, Beijing Institute of Biological Products Co. Ltd	United Arab Emirates, China, Bahrain

Source: https://covid19.trackvaccines.org/vaccines/

BNT162b3 (NCT04368728) a Promising Hope

So far BNT 162B3 is the most likely vaccine candidate. At first Canada and USA allowed it for only temporal use. However, detailed data and regulatory review is required for its final approval[47].

The BNT 1622B3 vaccine is now the world's most promising vaccine, sponsored by BioNtech RNA Pharmaceuticals GmbH, based on preliminary data that has been shown to be

more than 90% effective in preventing Covid-19 (https://www.npr.org/sections/health-shots/2020/11/24/938591815/pfizers-coronavirus-vaccine-supply-contract-excludes-many-taxpayer-protections). The 43,538 participants were considered in Phase 3, which will go through a definitive final analysis in 164 cases. Germany, Argentina, Brazil, South Africa, Turkey, United States of America, and Japan were chosen for its

phase 3 trail. About 76 million doses reserved by Canada for the BioNtech potential vaccine candidate.

A clinical trial was completed by this company and confirmed that the vaccine has a power of preventing 95 percent Covid-19 pathogens (https://www.nytimes.com/.). An Emergency Use Authorization (EUA) for the Pfizer-BioNTech COVID-19 (BNT162b2) vaccine (Pfizer, Inc; Philadelphia, Pennsylvania) was released on December 11, 2020 by the Food and Drug Administration (FDA), a lipid nanoparticle-formulated, nucleoside-modified mRNA vaccine encoding the SARS-CoV-2 perfusion spike glycoprotein, the virus that causes coronavirus disease 2019 (COVID-19). The Pfizer-BioNTech vaccine COVID-19 consists of 2 doses, each intramuscularly administered (30 µg, 0.3 mL, 3 weeks apart). On December 12, 2020, the Advisory Committee on Immunization Practices (ACIP) issued an interim recommendation for use of the Pfizer-BioNTech COVID-19 vaccine in persons aged ≥16.

Drawbacks of the vaccines of Covid-19 vaccines

Most of the vaccines against COVID-19 have shortcomings. Most of them are based on a common cold virus that many people have been exposed to, potentially limiting their effectiveness. As well as most of them are made using adenovirus vector this has many drawbacks even it could enhance the chance of HIV[48]. Another main obstacle which we have to face is preservation problem of the vaccine at much less temperature like −80°C[49] and it is assuming that the patients having allergic problem could not take this vaccine.

Concluding remarks and future prospects

Although novel coronavirus disease 2019 (COVID-19) was first reported in late 2019 at Wuhan, a city of central China, it travelled rest of the world in 2020 as a deadly one that created a pandemic situation. Therefore, it can be said that 2020 was the year of COVID-19. Till date, it is reported that 81.7 million people got infected worldwide and 1.78 million died. To avoid further loss of life, a successful vaccine candidate is an emergency issue. An effective COVID-19 vaccine is the need of the hour which can awaken a suitable immunity to stop this epidemic. There are currently a number of potential vaccine candidates that shows promising result in clinical trials. Recently, top leading vaccine candidates namely, BioNTech/Pfizer; BNT162b2, Moderna; mRNA-1273, Gamaleya; Sputnik V, Sinopharm; BBIBP-CorV got approval in different parts of the world that are expected to hit the market as early as 2021 for saving every single loss of life.

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Competing Interest

Authors have no conflicts of interest.

Ethics Approval

Not required

Consent to participate

Not applicable

Consent for Publication

Not applicable

Availability of Data and Material

All the relevant data are within the manuscript

Authors Contributions

MRC, SI, MNM developed the concept, involved in literature study and wrote the draft manuscript. MNM revised the manuscript and assisted with literature search. MNM supervised the work and approved the manuscript for submission. All the authors carefully read the manuscript.

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