Citation: Shahnaz, G., Fatima, S. K., Rasool, A. T., & Sabir, A. (2020). An Overview on the Ongoing Clinical Trials of COVID-19 Vaccines. *Global Immunological & Infectious Diseases Review, V*(I), 39-47. https://doi.org/10.31703/giidr.2020(V-I).05

ISSN (Print): 2788-4961 | **ISSN (Online):** 2788-418X | **URL:** http://dx.doi.org/10.31703/giidr.2020(V-I).05

Pages: 39 – 47 | **DOI:** 10.31703/giidr.2020(V-I).05 | **Vol.** V, **No.** I (2020)

An Overview on the Ongoing Clinical Trials of COVID-19 Vaccines

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Abstract *COVID-19 has posed a great threat to mankind, there is a dire need to introduce a vaccine to combat this global pandemic. Several vaccines are underway to complete their phase 3 clinical trials. This article highlights events surrounding the ongoing clinical trials of vaccines effective against COVID-19, and different procedures and formalities the vaccine will have to endure to get EUA. Clinical trials are discussed stepwise along with the clinical endpoint desired at the end of these trials. In line with antimicrobial resistance, vaccine resistance has also emerged in this era and needs focused consideration, and the probability of development of resistance in these vaccines is discussed. This article specifically covers the latest research reporting clinical efficacy, safety profile, and adverse events following the administration of doses to patients and concerns regarding the rushed approval of vaccines. Four vaccines have been discussed in detail; BNT162b2, mRNA-1273, Sputnik V, ChAdOx1.*

Key Words: COVID-19, SARS-CoV-2, Vaccine, Clinical Trial, Vaccine Resistance, Clinical Endpoint

Introduction

COVID-19 emerged as a global pandemic and has taken millions of lives throughout the world. This pandemic was first discovered on 31st Dec 2019, when a group of cases relating pneumonia with unknown causes were identified inside the Wuhan town, Hubei China. In Jan 2020, WHO identified a new virus which was named after the year 2019, as COVID-19. Researchers in the fields of genetic science studied samples that showed the outbreak was due to this. In Feb 2020, the WHO named it as Coronavirus 2019; COVID-19 and later on as SARS-CoV-2 (Sheeren et. al., 2020).

Coronavirus

It is a family of the viruses which cause the respiratory or GI disorders. The range of respiratory diseases can be from the minor respiratory disorders to a lot of severe diseases including *MERS-CoV & SARS-CoV.* Recent evolution of this strain has been found in the form of SARS-CoV-2 (COVID-19).

Clinical Presentation

Characteristically, it causes metabolic process symptoms. Within people that got infected by virus, some will remain asymptomatic. People that are symptomatic could bear symptoms from light to moderate, however self-limiting unwellness have seasonal flu like symptoms. Following symptoms may be included; *Metabolic process symptoms, breath shortness, respiration difficulties.*

Transmission

Evidence remains emerging, however recent data is showing that the transmission is occurring from man to man. The transmission routes are not yet cleared, but proof from the metabolism unwellness and alternative coronaviruses shows that the disease could unfold by massive respiratory droplets and with infected secretions by direct or indirect contact.

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Diagnostic Procedures

Testing kit has been developed for the diagnosis of COVID-19 and is on the market in clinical testing labs. The gold standard for diagnostics is regarded to be the well-known reverse transcription polymerase chain reaction (Pang et. al., 2020).

Covid-19 Vaccines Clinical Trails

The genetic sequence of SARS-CoV-2 was revealed on Gregorian calendar month 11, 2020. A fast emergence of analysis and collaboration among scientists and biopharmaceutical makers followed. As of Nov 2020, the big apple Times Coronavirus vaccinium Tracker lists four to fifty vaccines in human trials and a minimum of eighty-seven diagnosing vaccines are under investigation in animals (Corum et. al., 2020).

Several vaccines for SARS-CoV-2 are in, or have completed, phase three clinical trials within the United States. Some methods are utilized in previous vaccines, whereas others are additional fresh developed. More than 50 vaccines are under Clinical trials *(Center for Disease Control, 2020)*. They include Viral vector vaccine which is 62-90% effective and made by Oxford Uni-AstraZeneca. RNA type that is 95% effective by Moderna and Pfizer-BioNtech company. Shifa International is doing Global Landmark vaccination trials and Pakistan is amongst 7 countries worldwide who are in Phase 2 clinical trials for Covid-19 Vaccines (Shafi, Liu & Ren, 2020). Sputnik V vaccine is 91.4% effective and made by Russia.

Covid-19 Pandemic and Pakistan

The COVID-19 affected over 209 countries as well as Pakistan. in keeping with the WHO (World Health Organization), total number of confirmed cases 1,093,349 with mortalities of 58,620. Until now, the amount of most positive cases encountered in USA following Italy and Kingdom of Spain. The Health Ministry of Pakistan Government confirmed the first positive case in Karachi on 26th February 2020. Pakistan Federal Ministry of Health in Islamabad confirmed another case on a similar day. Up till now, more than 4 lakh Pakistanis have been reported and thousands have died. According to a recent report by *Dawn,* more than 8,000 cases are being reported per week, and no. of deaths per day has risen to >70. On 19th November 2020, 313 Pakistanis died of this dreadful disease.

Overall, there are total of 465,070 confirmed positive cases in the country, 9668 deaths, 417,134 recovered, 6,428,240 Total Tests and 2,361 critical cases until 24 December,2020. *(Ministry of Health)*

Types of Vaccine

Protein Subunit Vaccine

Subunit vaccines are those which are required for a long-term protection or therapeutic immune response based upon recombinant antigenic proteins they show very less Immunogenicity. To provide a vaccine induced response it needs support of an adjuvant.

NVX-CoV2373 Vaccine

An immunogenic based vaccine which is in list to increase the immune system response against spike proteins of SARS-Cov2 using Matrix M adjuvant by inducing neutralizing antibodies in animal models.

PittCoVacc (University of Pittsburgh)

It includes the administration of recombinant immunogens. The preclinical stages in mice used as models a great significance increase in antigen specified antibodies has been noticed, which is beneficial and provides a support for vaccine.

Triple Antigen IPV

It has great charm to go into pre-clinical trials because of its advantages of cost effective, easy to handle and safe
to use.

Viral Vectored Vaccine

These types of vaccines based on vectors are very specific to induce the efficient immune response. They have great opportunity to be used as prophylactic.

Coro flu (university of Wisconsin-Madison)

It is influenza virus vaccine which is currently got modification by adding SARS-Cov2 genetic sequence of spike proteins to combat this disease.

ChAOdx1

It functions by encoding the amino acid sequence of SARS-CoV2 inserted in shuttle plasmids. By nature, it is a recombinant adenovirus.

mRNA Vaccine

It is composed of lipid nanoparticles that used to code the spike proteins of SARS-CoV2. It has got approval to proceed in phase2 trials.

BNT162b1

A codon -optimized mRNA vaccine which has been made for encoding the Trimerized SARS-CoV2 that is very critical target of neutralizing antibodies.

INO4800

A vaccine has been found to use for SARS-CoV2 got enter clinical trials phase one. It is a prophylactic vaccine .in upcoming it's trials its efficacy, safety tolerability will be evaluated.

Live Attenuated Vaccine

It is an influenza vaccine which is now being reorganizing to show the domains if SARS-Cov2 spike of proteins.

To develop vaccines for COVID-19 has increased the potential immunogenicity and some adverse events too.

Trial Designs and Target Population

It is an important consideration for clinical development of COVID-19 vaccine. Trials are designed to get approximate estimate accuracy of incidence rates of COVID-19 end points in placebo arm, so that simple robust size samples are obtained for calculations on conventional trials.

It is very difficult to predict the incident rates of COVID-19 due to change in its epidemiology on regular basis. Trials have also been complexed, as public is not practicing proper social distancing and other interventions on health of people to control the fast spreading of virus.

As a required minimum incident reached, recruitment is stopped to get better and rapidly growing trial designs. One of the key factors in advanced clinical trial phases is to implement the simple eligible criteria as it broadens the target population. Basically, studies performed on population must be broader and wider.

Every process or procedure to be taken must be strategically evaluated, only then will it result in to obtain the effectiveness and safety of vaccine quickly.

At the high risks of COVID-19 infection and its brutal effects to older people (Zhang et. al., 2020), front liner health workers, to get an opportunity to represent a population is worth encouraging, because population might get benefits from an effective treatment of vaccine. (Le et. al., 2020)

Clinical and Immunological End Points

To select a clinical end point is very important because it shows the desired benefit of vaccine and it requires lots of discussion. It could be discussed in two most important points.

1. Safety from infection defined by seroconversion
2. Prevention of symptomatic ailment

There is a great variety of epidemiology and other medical conditions between young and older patients of COVID-19, so vaccine treatment effects need to get evaluated very closely. Primarily end points which overcome the rate of disease gets enrollment in trials in large numbers. Endpoint and serology pose an immense challenge that may cause huge complexity if there is a deficiency of basic precise information and knowledge about incident rates. It is also important to establish independent laboratories for multi-trial approach to get a linking bridge among multiple vaccine trials and products. Apart from the benefits trials must be evaluated for harms too. The chances of SARS-Cov2 are much greater in second exposure than to first exposure, so it must be evaluated on long term basis. It has been suggested to continue human clinical trials on small number of people who are volunteers treated with vaccine (Mehrotra et. al., 2020). This approach might have some utility, but it has some disadvantages also regarding efficacy and pathophysiology of disease. As death rate from COVID-19 in young and healthy people is very low, we lack the proper effective therapy for virus to save the people from complications, who are volunteer to vaccine (Wang et. al., 2020). It is likelihood that mild ailment will be caused by SARS -Cov2 strain in most of the volunteer people. Furthermore, it would not predict same effective rate in adults (Zhu et. al., 2020). These approaches need to be carefully evaluated from a panel of independent ethicists and trialists. (Corey, 2020)

Vaccine Platforms

Work on development of vaccines for corona virus has begun and it's worth appreciating. Now a number of platforms regarding vaccine development are forwarding for clinical evaluation. These platforms include DNA and mRNA approach, non- replicating and replicating virus vectors and recombinant proteins. Every one of the above-mentioned platforms has some disadvantages along with advantages. Meaningful characteristics of these approaches are following; flexibility and speed of preparation, cost of preparation, stability of vaccine, immunity durability, cellular immunogenicity, safety and the requirements of cold chains.

As a single vaccine platform can't fulfil the global needs so multiples companies are working on

different approaches like some are involved with Nucleic acid-based vaccine including *Pfizer, Moderna, Gamaleya, AstraZenca, and Inovio*. Nucleic acid-based vaccines produced very rapidly because of viral sequence that permits a fast way to clinic. While optimization of Immunogenicity of DNA affords electroplating an injecting device to accommodate the delivery of DNA cells into host cells. The mRNA vaccines are using nanoparticles for protecting and delivering the mRNA.

No nucleic acid-based vaccine has got license to be used widely, although route going to develop vaccines and their clinical trials are optimized still some uncertainty remains. Another approach is traditional recombinant proteins that are used to describe the spikes of proteins. Though time required for the establishment of cell lines is long as compared to nucleic acid-based vaccine, here in this traditional recombinant technique there is a commercial experience with proteins vaccines like licensed vaccines for influenza, Varicella Zoster, Papilloma virus. Encoding the viral gene of desired interest into characterized vectors like adenovirus or vesicular stomatitis virus is the technique of viral vector vaccine. (Corey,2020)

Safety Considerations

Vaccines having safety and efficacy to treat this pandemic are needed urgently. The FDA has granted and checking the safety and efficacy of vaccines from their large clinical trials and determining the data from manufacturers of vaccines. Clinical trials are done to evaluate the safety of Covid-19 vaccines on a large number of participants. Scientific data will be generated from these trials and FDA will use this information to find the safety and effectiveness of the vaccines. Emergency Use Authorization (EUA) will approve the vaccines to be used in US if vaccine fulfills its safety and efficacy standards by FDA. After determination of vaccine candidate to be effective and safe by FDA, a committee consisting of public and medical health specialists which is Advisory Committee on Immunization Practice (ACIP), reviews and investigates the overall information data before making the vaccine approval to CDC.

Vaccine Safety Monitoring

Vaccines are watched for their adverse or probable side effects after being legal or recommended for use for safety monitoring of respective vaccine. If vaccine is showing several adverse effects and risk to health, then it will be withdrawn and cancelled for further investigation. Vaccines fulfilling the complete safety and efficacy criteria will further process to be used in the future for Covid-19.

Vaccine Resistance Reported in Clinical Trials

Drug resistance is the biggest drawback of any vaccine, just like antimicrobial drug resistance, resistance to vaccine does and can evolve (Kennedy & Read, 2020). When vaccine resistance is developed, it may occur by mechanism exhibiting antigen change and increase in severity of disease. Resistance has not developed for many vaccines like for measles. Vaccine resistance against Covid-19 can also be evaluated after getting licensure. The possibility of vaccine resistance should be small as it will have a major negative impact to public health. Mostly, a large count of the Covid-19 vaccine candidates targets the spike protein of the coronavirus and resistance to one vaccine will cause vaccine resistance against others; commonly referred as a cross resistance.

Vaccine Resistance Testing

Various standard samples are taken to check the vaccine resistance of Covid-19. First one taken is the blood sample; it is collected throughout all the clinical trials for Covid-19. The blood sample is taken and tested to quantify the individual response of the immune protection produced by candidate vaccines. Resistance against monoclonal neutralizing antibodies has been quickly developed already for SARS-CoV-2.

Secondly, many of the Covid-19 clinical trials for vaccine are nasal swab and fecal samples. It is taken from the vaccinated and control group in order to quantify the protection of vaccine against infection.

Third is nasopharyngeal swab samples for Covid-19 clinical trials. It is taken from symptomatic vaccinated and control persons for the confirmation of SARS-CoV-2 as a causative agent of disease. We can do better revolutionary changes by learning from past pandemics and their management to create a vaccine attributed to a good safety profile and clinical efficacy.

Role of Nanotechnology in Covid-19 Vaccines In Clinical Trails

Viruses are tiniest and nanoscale objects and they can be called naturally taking place nanomaterials. The same length scale operation is required for viruses and nanoparticles and this makes possible the approaches for vaccine development. Novel technologies are being used and employed to design a vaccine for Covid-19.

Nanotechnology formulation has already been achieved through clinical trial. They have received a boost despite their lack of clinical trials. Due to availability of their technology vaccine candidates can be repurposed using previously nanostructures.

Major role has been played by nanotechnology in development of Covid-19 Vaccine. The viral vaccines are so

small that they can also be called as nanoparticles themselves. LAVs, IVs and viral vectors are nanotechnologies that play a role in covid-19 vaccine design.

Covid-19 phase 3 clinical trials have been announced by BioNtech and Pfizer on 18th of November,2020. Moderna also claimed their phase 3 outcomes of the study to be 95% or 94.5% effective by using nanotechnology. Synthetic nanoparticles platform is being used for the manufacturing of nanoparticles-based vaccines.

Long Term Monitoring of Covid-19 Vaccine

Due to the immediate rush and lack of time dedicated to the clinical trials of COVID-19 vaccines marked by their sheer need at the moment, there has been a deficiency reported in clinical evidence testing the long-term effects of COVID-19 vaccines. Although few studies have been summarized here regarding the proposed long-term monitoring of these vaccines. In a vaccination campaign led by doctors, vaccine was found to be safe. Moving onwards to the clinical trials, some side effects reported include; fatigue, fever, headache, pain on injection side, weakened muscles. Nevertheless, when vaccine trial given to older adults it showed some allergic reactions after getting vaccine (reactogenic). Most reactions after receiving vaccine are apparent and some might be of long term or appear late. Scientists believe the vaccine is safe and effective, but the question is that is it work or effective for older adults.

Vaccine trials and research is done again and again with their adverse events monitoring. Vaccines are needed to be stored in a low temperature and their safety and efficacy is noted during this period. Safety follow up is done to check and manage the vaccine safety and efficacy. CDC and FDA are playing major role in long term monitoring of vaccines to be approved for Covid-19. Vaccines are tested and checked whether they can treat symptomatic and asymptomatic infections caused by coronavirus. Positive clinical trials have been done according to AstraZeneca managed by Oxford University and FDA advisors are discussing this.

Global Phase III Clinical Trials

There is an appalling need for the discovery of a vaccine to fight the dreadful virus taking the lives of millions around the globe (Caddy, 2020; Lythgoe & Middleton, 2020), although the spontaneous rush for a vaccine has also left certain loopholes in the process that may be responsible for any following unwanted events (Thorp, 2020; Chakraborty & Parvez, 2020; Lurie et. al., 2020; Cyranoski et. al., 2020). It seems almost impossible a target to manufacture and distribute the vaccine to safely immunize the global population (Corey et. al., 2020). Several renown pharmaceutical companies have proposed certain solutions to this disease in the form of drugs and vaccines. Some of which have been given Emergency Use Authorization (EUA) by FDA to be used on hospitalized patients struggling between life and death (Singh et al., 2020). More than 50 are undergoing clinical trials to fight their way to meet FDA's minimal requirements for authorization (Cohen, 2020). Three vaccines will be discussed in this article along with the present status of their clinical trials, their safety profile, efficacy, and reported adverse events.

Pfizer's Vaccine-BNT162b2

Clinical Trials

Marking the dire need of a vaccine to combat the deadly virus killing millions, Pfizer finally stepped in and in collaboration with Biotech, introduced their vaccine BNT162b2 with triumph from their phase 1 (Mulligan et. a., 2020). This article focuses on the phase 3 clinical trials were held by Pfizer, sponsored by Biotech to examine the clinical efficacy, safety profile, and adverse events following the use of Biotech's vaccine. The subjects deployed were adults older than 16, and a group of people> 55 years. Two doses of both the vaccine and placebo were injected, and the results were compared. Patients participated from 4 countries with a total of 43,548.

Safety Profile

Two patients died in the vaccine group, and 4 died from the placebo group, but none of these deaths were linked to the vaccine, or to COVID-19. These deaths may have a link with the history of the patient, as it was excluded in this research. Overall, the vaccine was found to have a safety profile and fulfilled the minimum requirement to procure FDA's emergency use authorization.

Efficacy

Vaccine was found to be 95.0 % effective against COVID-19. Result indicates only 8 patients in the vaccine group contracted COVID-19 while 162 contracted it from the placebo group.

Adverse Events

Reactogenicity events as well as adverse events were reported in the recipients of the vaccine by a greater percentage as compared to the placebo group; 15% more reactogenicity events, and 0.2% more adverse events reported in vaccine recipients. Number of deaths occurred in both the groups as a result of heart

diseases; 2 in vaccine recipients, and 4 in placebo group. This may be attributed to the fact that the medical history of these patients was excluded. (Polack et. al., 2020)

Authorization for Use

FDA authorized the emergency use of BNT162b2 on 11th December 2020.

Countries Participating in Trials

UK, Bahrain, Canada, US, Mexico, Kuwait, Singapore, Jordan, Oman, Costa Rica, Ecuador, Israel, Panama, Chile, Qatar, UAE, Argentina, Iraq.

Sputnik V

Clinical Trials

Sputnik V has emerged victorious from the clinical trials phase 1 and 2. Currently phase 3 is underway to further
test the efficacy, safety profile, and the adverse events that may follow this vaccine (Voysey et. al., 2020). Russia has successfully used this vaccine on over 200,000 patients, it is produced at a rate of 20$ and is determined to export it to the world at a price of 10$ per vaccine (Burki, 2020).

Safety Profile

The ongoing clinical trials indicate the promising safety profile of this vaccine with no severe adverse events in any of the patients, however some scientists believe the rush in the evaluation and shortage of time may lead to loopholes in the future (Soto, 2020).

Efficacy

A study was conducted on 19,000 patients that concluded with 91.4-95% efficacy of the vaccine.

Adverse Events

Patients complained of headache, fever, and fatigue with overall no severe adverse event reported.

Authorization for use

It was authorized for use in Russia on 11th August 2020 by the Russian Ministry of Health.

Countries Participating in Trials

Russia, Belarus, and Argentina.

Oxford- AstraZeneca's Vaccine (ChAdOx1)

Clinical Trials

The clinical trials of this vaccine trace back to April 2020 when the phase 1 was initiated, and immediately thereafter, the success of this phase led to phase 2 and 3 (Knoll & Wonodi, 2020). Phase 3 is underway in UK and has emerged with positive outcome, yet the immediate rush to authorize this vaccine pose a threat to the prediction of its long-term effects.

Safety Profile

Clinical trials concentrated in Brazil and UK predict no such concerns compromising the safety profile of this vaccine, however some researchers are of the view that the emergency approval and shortage of evaluation time may create loopholes in the process which may pose a dilemma in the long term effects of the vaccine (Folegatti et. al., 2020).

Efficacy

Oxford's vaccine shows an unusual trend in its efficacy, showing a 60% efficacy at high dose, and upon decreasing dose, it shows 90% efficacy (Callaway, 2020).

Adverse Events

A total of 175 adverse events were reported; 84 in the vaccine recipients & 91 in the control group, but none of these adverse events were associated to the treatment, or the vaccine, they were rather linked to the medical history of the patients which was excluded in the research.

Authorization for use

It has been approved for use in UK on 30th December 2020.

Countries Participating in Trials

It is approved for use in UK, India, Mexico and Canada.

Moderna's Vaccine (mRNA-1273)

Clinical Trials

Moderna's vaccine is one of the first ones to gain FDA's approval for EUA, their phase 1 traces to back to the start of February 2020. After the successful triumph of this vaccine in the initial Phase 1 and 2, Moderna started the third phase in collaboration with FDA and NIH. October 22nd, 2020 marks the completion of the enrollment of phase 3.

Safety Profile

Clinical trials have predicted a stable safety profile

Efficacy

Moderna's vaccine is reported to have an efficacy of 94.5%.

Adverse Events

The adverse events reported were short lived, they include; redness & pain (grade 3) at injection site, myalgia, arthralgia, & headache.

Authorization for use

FDA has authorized an EUA to Moderna for their vaccine on 18th December 2020.

Approval

Approved for use in US and Canada. (Moderna Press Release, 2020)

Conclusion

COVID-19 is a global threat that has taken more than a million lives globally. Current situation elucidates the dire need of a vaccine to combat the virus. Even in Pakistan it has affected more than 4 lakh individuals and the infected cases are on the rise.

So far, the ultimate solution to this problem has been presented forward in the form different types of vaccines introduced by renown pharmaceutical companies including *Pfizer, Moderna, AstraZenca, Gamaleya,* and many more; their vaccines have shown acceptable clinical efficacy and a good safety profile and are on their way to be distributed globally. However, the swift approach adopted in the approval of these vaccines and lack of evidence to prove their safe long-term effects may leave a loophole in the process and pose a threatening concern in the future.

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