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Review Article

A REVIEW ON FIRST MEMBERS OF COVID-19 VACCINES IN PHASE 3 AROUND THE GLOBE

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ABSTRACT

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), a member of the coronaviridae family is the cause of the pandemic which started in 2019 and the world is still fighting against it. In spite of the usage of drugs like remedesivir, flavinavir and hydroxycholoquine along with different approaches to increase the immunity or to treat the respiratory infection in humans, even now this viral infection is uncontrollable. According to the stats, till November 10, 2020 over 10 million people have lost their lives around the world, touching the mark of 37 million plus patients around the world with epidemiology showing the most cases in USA followed by India, Russia, Brazil and Spain. After seeing the rapid spread and post disease effects of this air borne viral infection, an urgent need of the vaccine considered. This led to encourage researchers around the world to develop different types of vaccines, namely inactivated, live attenuated, nanoparticle based, viral vectored, recombinant type, DNA and RNA vaccines, among which few have already passed Phase 1 clinical trials and are under Phase 2 or 3 human trials. The vaccines which have the highest potential to be successful with minimal side effects proposed by different countries around the world with their type, mechanism of action and their effects along with the challenges and considerations regarded with these vaccines has been discussed in this paper.

Keywords: SARS-CoV-2, Remedesivir, Flavinavir, Hydroxycholoquine, Vaccines, Mechanism, Effects

1. INTRODUCTION

SARS-CoV-2, a novel coronavirus that emerged in China, caused a pandemic which lead to raise a serious concern about the public health. This virus is a member of family Coronaviridae, caused an infectious disease outbreak first reported in Wuhan, China during December 2019. Starting from the first patient traced in November, 2019 to 1 August, 2020, the total patients reported so far are more than 17.5 million worldwide across 188 countries with territories. The virus primarily transmits by coughing and sneezing among people in close contact due to the small droplets produced during these activities. The entry receptor for the virus was reported to be Angiotensin Converting Enzyme-2 (ACE2) and the beginning of symptoms, like cough, fever, shortness of breath along with no sense of taste or smell, visible after 5-14 days of the exposure to the virus. The genome of SARS-CoV-2 has been sequenced, but it is observed that it form new variants by mutation. The only primary treatment provided is symptomatic with supportive therapy. The diagnosis of the virus has been done so far by the serological testing (antibody testing), RT-PCR, CT scans and also have been proposed by the CRISPR-Cas13 protocol, isothermal amplification and microarray assays [1].

There were many treatments suggested by different laboratories and Universities studying the virus for the vaccination and drugs against it. The treatments proposed and executed had their own drawbacks like; short remdesivir treatment was not so specific in cure due to dependence on other factors, Type1 interferon treatment showed that it would only be efficient with other combination of corticosteroids in specific amount, and the corticosteroid treatment itself have shown adverse pulmonary function effect and worsening the hyper-glycemia cases, thus increasing the mortality [2]. In recent research, it was discovered that SARS-CoV-2 has 2 types of strain; L and S, where L is evolved from S and is more common with elevated replication rate inside humans, resulting in infection escalation in short period of time [3]. Therefore, making it a big challenged to make therapy available at this short time. Considering the health of the people worldwide critically and the high quality, effective and safe candidates for COVID19 vaccines, Solidarity Vaccine Trial protocol was developed by WHO which seeks the trial sites around the world to

participate in this protocol. The trial in the vaccine has to go through various phases until it reaches the commercialisation. The vaccines which have already entered or about to enter Phase 3 of the clinical trials worldwide are listed in Table 1.

Table 1: The different vaccines developed by different countries in their last Phase 3 phases from vaccine tracker of Regulatory Affairs Professional Society (https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker)

COUNTRY	VACCINE	SPONSORS	PHASE
USA	mRNA-1273	Moderna	Phase 3
	AZD1222/ Covishield	The University of Oxford, AstraZeneca, IQVIA, SII	Phase 3
	NVX-CoV2373	Novavax	Phase 3
	JNJ-78436735	Johnson & Johnson	Phase 3
	BNT162	Pfizer BioNtech	Phase 2/3
INDIA	ZyCoV-D	Zydus Cadila	Phase 2
CHINA	Ad5-nCoV	CanSino Biologics	Phase 3
	Coronavac	Sinovac	Phase 3
AUSTRALIA	BCG live attenuated vaccine	University of Melbourne and Murdoch Children's Research Institute, Radboud University Medical Center, Faustman Lab at Massachusetts General Hospital	Phase 2/3

2. SARS-COV-2 VIRUS

An enveloped virus, known as SARS-CoV-2 of diameter 120 nm, caused a boundless global pandemic. The primary structure of virus include single stranded RNA along with the proteins necessary for the structure as well as the function of the virus, namely Spike protein (S), Envelope protein (E), Membrane Protein (M) and Shell Protein. The protein which is responsible for the recognition as well as receptor binding on the surface of the host cells is the trimeric Spike protein (S), which also plays a prominent role in the infection. The membrane protein (M) along with the envelope protein (E) has major roles in assembly of the virus while Nucleocapsid protein is required for synthesis of RNA [4]. The mechanism involved in the infection of the virus is when the S protein on the surface binds itself to the Angiotensin Converting enzyme 2 (ACE2) of the host cell, leading to the infection and viral multiplication. The S protein has 2 subunits: S1 and S2, where the receptor binding domain (RBD) of S1 subunit recognise and bind to the host receptor and S2 acts as a mediator between host cell membrane and viral envelope causing the fusion.

SARS-CoV-2 shows a wide range of symptoms ranging from the prime to rare and unique symptoms which makes the transmission of the virus through different ways:

A. Pre-Symptomatic- The incubation period between the vulnerability to the virus and the onset of symptom, ranging from 5 to 14days;
B. Asymptomatic- The way of spread from an individual to another with no signs and symptoms of the infection;
C. Symptomatic- In this case the patients develop the symptoms and transmitted through
   - Close proximity with contaminated objects
   - Respiratory droplets
   - Direct contact with the infected person
   - Surfaces
D. Environmental contamination-includes the transmission majorly affected by the fecal shedding and physical conditions like temperature and humidity

3. EPIDEMOLOGY

This pandemic has now hit over 200 countries and territories with more than 37 million cases till 10 November 2020 around the world with more than 10 million deaths. The top 5 countries which are the worst affected by the pandemic of the COVID-19 and it population affected is shown in the Figure 2.

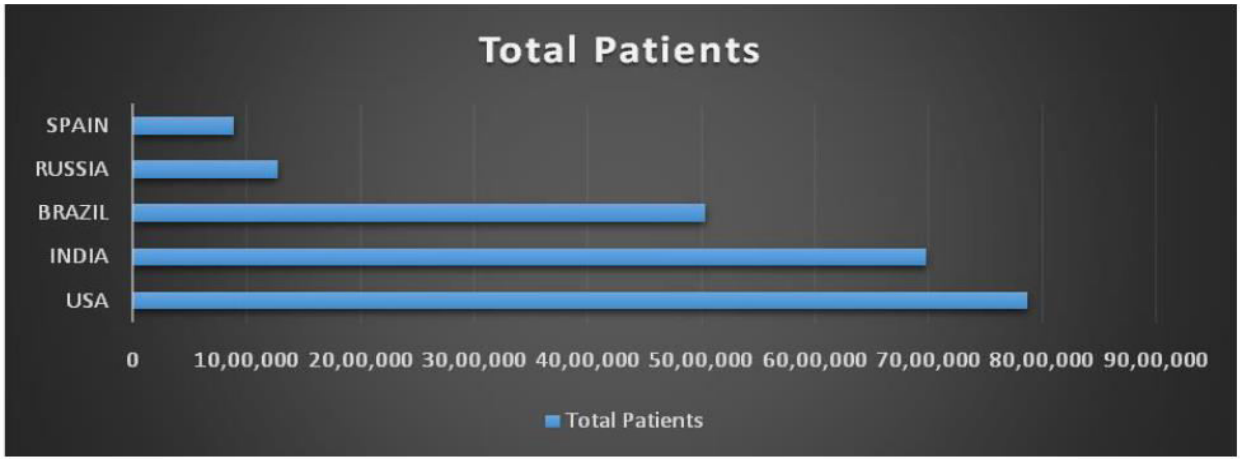

Fig. 1: The epidemology of SARS-CoV-2

4. AVAILABLE MEDICINES AND ITS DRAWBACKS

4.1. Chloroquine and hydroxychloroquine

Since there is absence of any specific therapy for the COVID-19 treatment, some combination of commonly used immunomodulatory and antiviral drugs were used. One of the drugs considered and tested for COVID-19 was Hydroxychloroquine (HCQ), which also got included in the guidelines of USA and India. In 2020, Elavarasi and group performed a review study to test the HCQ and CQ for SARS-CoV-2 infection along with meta-analysis [5]. The results observed were the reactions caused by the drugs in not so severe form caused vision impairment, nausea, digestive disorders and the severe forms like the cardiomyopathy and hemolysis, which are the types of cardiac toxicity in patients with deficiency of G6PD [6]. The high dose of CQ and the combination of HCQ along with azithromycin is against the recommendation due to high potential of toxicity. Overall this medication has low efficiency against the viral treatment [5].

4.2. Favilavir

Toyama Chemical developed the medicine, Favilavir to treat throat and nose infection [7]. China chose to rely on this anti-viral drug to treat the SARS-CoV-2 symptoms. The drug has shown efficiency in a clinical trial with lesser side effects but US has not approved its use for the treatment [8].

4.3. Remdesivir

Remdesivir, an antiviral medicine has shown efficiency against SARS-CoV as well as MERS-CoV (Middle East respiratory syndrome) in animals [9]. It is an antiviral broad spectrum drug, which was originally developed to target Ebolavirus by Gilead Sciences. The mechanism of its action is by inhibiting the replication of virus through the early termination of transcription of RNA, resulting in the disruption of virus reproduction [7]. China conducted the clinical trial to check its efficiency against the COVID-19 but the efficiency and the safety has to be further tested [10].

5. DIFFERENT APPROACHES FOR VACCINE

Utilizing the technique of bioinformatics and genome sequencing information methods, researchers were able to identify a series of B and T cell epitopes as vaccine candidate from proteome of the virus [11] [12].The vaccines are being designed by using different approaches that have cross-protection against the virus and also prevent it from continuous evolution and mutation.

SARS-CoV-2 could be cured if the binding of S protein or its Receptor Binding Protein (RBD) to the receptor of the host cell is blocked. The vaccines are made using the same mechanism, like in SARS vaccine it was observed that the S1 and S2 subunit as well as RBD of the virus have protective effect against the infection [13]. Thus making, S protein and RBD, a potential target for vaccine development.

The protein which is responsible for the binding of viral RNA and nucleocapsid formation is called N protein, resulting in the viral assembly and transcription. The DNA vaccines expressing the recombinant N protein (N1 and N3 not N2) specific antigen of SARS induce a specific cellular and humoral antibody responses [14]. Another potential approach is the intranasal inoculation of a carrier vaccine combined with the universal T cell

epitope of N protein, which induces the memory response of CD4+ T cell producing the protective response to both MERS-CoV and SARS-CoV [15].

6. TYPES OF COVID-19 VACCINES

According to the statistics of WHO, around 50 new crown vaccines under research and development projects have been introduced and in the coming time will be introduced. COVID-19 vaccines have been developed by many countries and are under different phases. All the recent forms of vaccine entered in Phase 3 will be discussed in Figure 3.

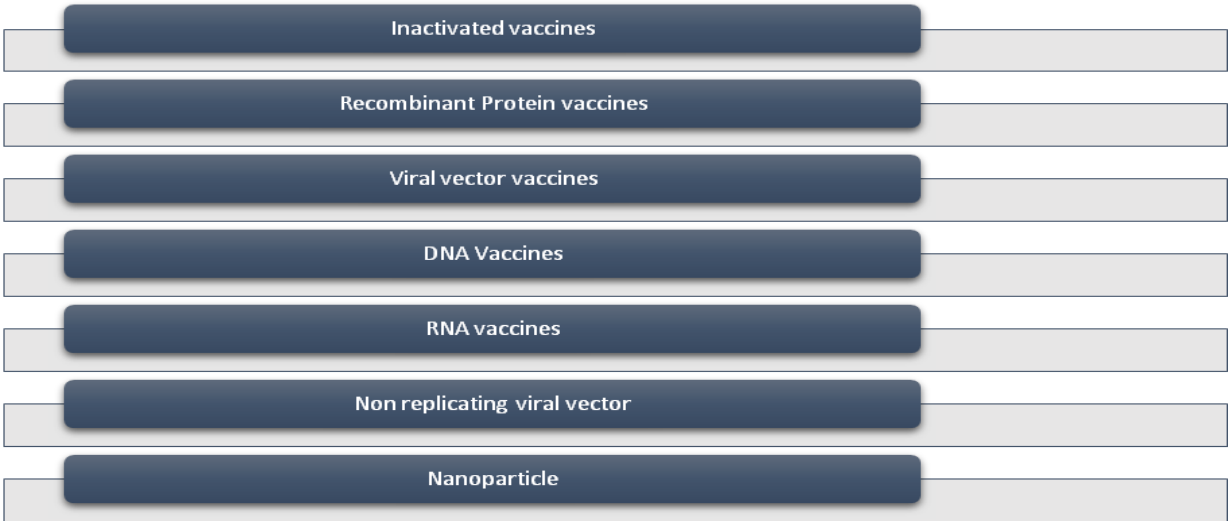

Fig. 2: Types of vaccines developed against SARS-CoV-2

7. VACCINES UNDER PHASE 3 TRIAL

The major mechanism which is responsible for the respiratory failure is 'cytokine storm' [16]. A therapeutic drug is needed for the blockage of cytokine production along with TNF α-signalling, but a vaccine is preferred and expected to have an immediate and more effective action against it. The vaccines acting on SARS-CoV-2 by different mechanisms under the Phase 2 or 3 trials by different countries are explained below:

7.1. USA

7.1.1. mRNA-1273

A promising approach towards the vaccination of COVID-19 by combining the manufacturing along with modification of immunogen with accelerated development is considered to be the messenger RNA approach. Since, the RNA vaccines which encode the viral antigens have always shown to be safe in clinical trials, this vaccine which is a potential candidate for SARS-CoV-2 [17, 18], also passed the phase 1 trial successfully [19]. The mechanism by which this vaccine works is by inducing the higher binding inhibition of ACE2, along with the increase in the neutralising activity, it also showed more potential to the RBD, receptor binding domain as well as antibody responses by N terminal domain in comparison to the specimen of convalescent-phase serum. According to a study, the vaccine was observed to induce the S protein specific CD4 T cells which produce interleukin-21 and the mRNA-1273 activity of neutralising activity is primarily based on 2 factors:

- S protein stabilisation: improved immunogenicity by stabilisation of the class I conformation fusion protein [20]
- RNA formulation, purification and delivery: the RNAs are modified by translational facilitation along with the prolong production of protein, in vivo to elevate the CD4 T cells frequency to promote the antibody response [21]

Considering a mouse model, observations recorded the neutralising antibody induction along with the high level protection in a low dose of vaccine. Thus, the vaccine clearly showed the potential to prevent along with limit the infection. The studies showed no proof of decrease in the replication of the virus in the nasal tissue which raised question on the potential of the vaccine against

transmission. A study showed the results defying the previous results in which showed the early prevention of the replication of the virus in lower and upper airways after giving a high dose challenge with SARS-CoV-2.The vaccine favoured prevention of the disease and transmission both depends on the vaccine's ability to limit the viral replication. With the results of various serologic assays, the study showed mRNA-1273 induced the neutralising activity as well as strong S-specific antibody [22]. The lower airway protection provided by the mRNA-1273 vaccine were observed with the increase in neutralising activity along with the antibody binding activity as compared to the previous reports of whole inactivated DNA [23] [24] or other vaccines like adenovirus vector vaccines [25] [26].

7.1.2. AZD1222/Covishield

The vaccine is also notified as ChAdOx1 due to the presence of simian adenovirus ChAdOx1 in it, along with the SARS-CoV-2, Spike (S) protein with tissue plasminogen activator leader sequence. A coding sequence which is codon optimised for the S protein is expressed by ChAdOx1 nCoV-19. The trial of vaccine included the testing on Rhesus macaques, which showed the development of persuaded humoral along with cellular immune response in a single vaccination and it was safe and easily tolerated by the candidate. A high dose of vaccination when given to the non-human primate showed the protection against infection of lower respiratory tract as well. The observations included no adverse events occurred while giving single dose but moderate severity was observed while increasing the dose [27-30]. The unfavourable events reported were similar to that of different ChAdOx1-vectored vaccines developed for other virus, which expressed different antigens.

After the analysis and different tests run on the dosage of vaccines along with the previous experience with ChAdOx1 MERS, a dose of 5×10^{10}vp was chosen. Even with the increase in the reactogenicity, a relationship between dose and neutralising antibodies were also observed [30].The rise in spike-specific antibodies by the 28th day after a single dose and neutralising antibody which target the specific glycoprotein of the virus, in all the candidates after the booster dose [31].

The data obtained by various researches, suggested that in mitigation of COVID-19, T cell responses play a major role. In the case of asymptomatic individuals, it was observed that a robust memory T cell was developed in them [32-34]. The response of T cell after vaccination was observed as early as on 7th day and peaking at 14th day which maintained up to 56th day, following the same pattern as Adenoviral vectored vaccine but no boost in the cellular responses were observed after the second dose. When further studies were conducted, anti-vector antibodies potential effect on homologous boosting were reported to show that the individuals who were vaccinated twice in 28 days duration showed the boost in the antibody response against spike protein of SARS-CoV-2. Overall, ChAdOx1 nCoV-19 is reported to be safe, tolerable as well as immunogenic and the reactogenicity easily reduced by paracetamol. The phase 3 trials of the vaccine are now underway in South Africa, Brazil and United Kingdom to evaluate the efficacy of vaccine in diverse population [35].

7.1.3. JNJ-78436735

A potential vaccine, previously called Ad26.CoV2, against SARS-CoV-2 was developed by Johnson and Johnson company based on the non-replicating viral vector mechanism and controlled clinical trials were performed to test the safety, immunogenicity and the reactogenecity of the vaccine. After giving positive results from phase 1 and 2, it has now successfully entered in Phase 3. This vaccine consists of a non-replicating adenovirus 26 which expresses the pre fusion spike protein (S) of SARS-CoV-2 in a stabilized form. Two dose levels were decided at a level of 5×10^{10}or 1×10^{11} per vaccination in the interval of 56days in adults. The post vaccine effects showed adverse reactions in participants which occurred most frequently was pain at the injection area and most frequent was headache, myalgia, fatigueness as well as fever but was mostly moderate and resolved after 1 or 2 days. Overall the dose of 5×10^{10} viral particle was observed to pass the safety profile and immunogenicity stage with single dose in clinical development [36].

7.1.4. NVX-CoV2373

A vaccine for SARS-CoV-2 developed by Novavax company, consist of a SARS-CoV-2 recombinant version (rSARS-CoV-2) and matrix M1 adjuvant that is made into a nanoparticle vaccine, NVX-CoV2373 [37]. The anti-body magnitude, functional antibody induction as well as Tcell responses clearly increased due to Matrix M1 adjuvant present in the vaccine. This vaccine is constructed from a full length spike glycoprotein which chooses human angiotensin converting enzyme-2 as a target for the development of the antibodies. The

vaccine works by production of high level of antibodies which works against the anti-spike protein which blocks the binding of hACE2 receptor, achieving the neutralization of wild type of virus and providing the protection against it [38, 39].The responses of CD4+ and CD8+ cells were induced along with T helper 1 dominant phenotype [40, 41]. Two doses were selected to study, 5 µg and 25 µg. There were no adverse events reported in the overall study in double doses patients but patients with a single dose suffered from mild cellulitis which was associated with infection. The mild adverse events were mainly fatigue, headache, tenderness and malaise but few severe effects were joint pain or fatigue but not after the 7 days of second vaccination it was observed to be mild or absent. The laboratory grade 2 abnormalities were also observed like the decrease in haemoglobin level but were later recovered in the patients [42]. Overall this vaccine showed potential to treat COVID-19 with great efficiency and all passed the safety parameters.

7.1.5. BNT162

The RNA based vaccines and RNA therapeutics against the infectious disease have given the results to be endurable and safe by the clinical trials. The RNA vaccine can be altered by the incorporation of 1-methyl-pseudouridine which increases the mRNA translation and decreases the innate immunity sensing [43]. When clinically studied, the BNT162b1 vaccine showed the incorporation of modified RNA which encoded the RBD of spike protein of SARS-CoV-2, targeting the neutralising antibodies [44]. But the RBD present in the vaccine is a modified RBD with the addition of T4 fibritin- derived "foldon" trimerization domain which eventually increases its immunogenicity by showing multivalency [45]. For the efficient delivery of the vaccine, it is constructed in lipid nanoparticles [46]. In the laboratory findings, the reactogenicity of the virus was observed to be higher in the second dose with the decrease in lymphocyte count. After 21 days of the first dose, the RBD binding IgG were detected followed by further increase in coming 7 days after the second dose, which were marked to be more with 8 fold to 50 fold of the convalescent serum panel (Geometric Mean Concentration, GMC) unlikely of the first dose which showed similar to those of panel of convalescent obtained after 14days of the PCR confirmed tests of asymptomatic patients. A dose between 10-30 µg has considered to be an ideal dose which produces enough neutralization titers to be more than that of the naturally induced ones after the infection of host from COVID-19 [17].

7.2. India

7.2.1. ZyCoV-D

The vaccine developed by the Zydus cadila company of India is the plasmid DNA vaccine to prevent the infection of SARS-CoV-2 was found to be tolerated and safe in the Phase 1 and phase 2 trial. The vaccine increased the level of neutralising antibodies after the administration. The plasmid DNA used in the vaccine is a non-integrating and non-replicating plasmid which carries the gene of interest. The mechanism of action of the vaccine containing the plasmid DNA undergoes translation in the host cell and a viral protein is formed which triggers a strong immune response against it mediated by the humoral and cellular immunity. The additional advantage in this vaccine is that the platform for the modification of the virus could easily be done according to the mutation of the virus to ensure the potential effectiveness and the safety of the vaccine (https://www.expresspharma.in / covid19-updates/ zydus-starts-human-trials-of-zycov-d-its-covid-19-vaccine/)

7.3. China

7.3.1. Ad5-nCoV

This vaccine when injected showed induced specific immune responses on the 28th day to the spike glycoprotein. The factors affecting the humoral immune responses after the vaccination is the increasing age along with the pre-existing immunity to Ad5 vector causing fever [47]. In few cases with participants of 55years or older, showed that only one injection is not enough for the humoral immunity response as they have high pre-existing anti Ad5 immunity, making them more tolerant towards higher doses. A potential solution for the enhancement of the immune response is the additional flexible dose in between 3 to 6 months [48]. The post vaccination reaction were observed to be moderate which turned out to be adverse within 28 days were all resolved in a shorter period of time. Grade 3 adverse reactions were reported in the patients given high dose (1.5×10^{11}) of vaccine as compared to low (5×10^{10}) or moderate (1×10^{11}) dose and the lower dose of vaccine showed better safety profile than moderate or high. The T cell responses along with the neutralising antibody played major role in the elimination of virus as well as in the control of the disease development, in the patients who were naturally affected by the SARS-CoV-

2. The effectiveness of the vaccine solely in prevention of infection is yet to be tested in the further clinical trials as the specific T cell responses are mandatory for the direct attack and killing of the virus [49]. Overall, it was concluded to have a good safety profile and tolerable in adults [50].

7.3.2. Coronavac

A potential candidate of vaccine (earlier known by the name, PiCoVacc) which was developed by Sinovac, a Chinese biopharmaceutical company is currently under the Phase 3 trial which uses the inactivated corona virus to produce antibodies against the virus. In the phase 2 trial which completed in 2020, at low dose of 3 μg, the vaccine showed immunogenicity which in adults (18-59 years) provided 92.4% seroconversion under 14 days of injection [51] and 97.4% under 28 days of injection. The neutralising antibodies level increased after 2 dose vaccinations under 28days. The phase 1 and 2 trials of the Coronavac was done in 2 stages with separate category involving adults and children. It was observed that the N specific IgG which is observed to be high in the serum of the patients were drastically decreased by 30 folds than the antibodies targeting S or RBD in mice showing the potential of inducing high antibody response. To evaluate the safety and efficiency of the vaccine on 9,000 health professional volunteers across 6 states of Brazil. The preliminary results of the vaccine showed potential to cure the infection. After the positive results of the vaccine in the states of Brazil, for the phase 3 trials it has been transported to different countries including Bangladesh, Indonesia, Turkey and Philippines. It has been decided that once the vaccine is proved to be successful and safe, Sinovac would produce 300 million doses a year in Beijing where the stability of vaccine is up to 3 years for storage. The vaccine with the ideal dose of 3μg to 6μg, was well tolerated but the adverse reactions were in the mild severity category and most reported problem was the pain at the site of injection but no grade 3 vaccine related adverse reactions were reported [52].

7.4. Australia

7.4.1. BCG live attenuated vaccine

In 1993, Tuberculosis was declared as a Health emergency by WHO and a BCG vaccine was introduced to combat this disease and showed results against the spread of *Mycobacterium tuberculosis*. Similarly, in the current scenario of the SARS-CoV-2 pandemic, it is believed that this BCG vaccine could provide protection against the virus. In the study conducted by the Tameris et al (2020) [53], it was observed that the protective effect is dose dependent which means that protection was maximum at minimum pathogen exposure along with decrease in effectiveness of it with age. The vaccine works on the non-specific immune response generated during the time of the second infection, independent of the initial antigen [54, 55].

The kind of immunity generated by the vaccine is known as 'trained immunity' which works in the monocyte derived macrophages (MDM) on the principle of epigenetic reprogramming, stimulating the production of various cytokines (like IFN- γ, TNF- α, IL). Among all the interleukins stimulated, the one that brings out the long effectiveness in the bone marrow progenitors by reprogramming is IL-1β. This results in the prevention of the systemic infection affecting the survival of *Mycobacterium tuberculosis* intracellularly [56]. This feature of the vaccine make it able to protect the host against a non-related viral infection [57]. The BCG vaccine has earlier been used against various viral diseases and so is believed to work against the SARS-CoV-2 infection as well because it increases the phagocytosis of the airborne pathogens along with T cell population (mainly, CD4+ cells which are associated with increase in CD4+ and CD8+memory cells) in lungs [58, 59]. In studies, it has also been observed that it also increases the IgG along with memory B cells. An observation drawn from the random experiment gave a result of 3 times more immunity to a girl injected with BCG to acute lower respiratory tract infection of virus [60]. Overall this vaccine has created a scope for the treatment of virus in the existing vaccine for tuberculosis [61].

8. PROTECTION INDICATORS OF IMMUNITY

Currently, the efficiency of effector molecules and cells types against viral infection is still unclear. The predicted mechanism of the vaccine is induction of B cell response to produce antibodies, especially neutralising antibodies that prevents the binding of virus to cell receptors and prevent from entering the cell. If different immune route taken, the mucosal vaccination can activate IgA, a mucosal secretory antibody to directly fight against infection on the site. The stimulation of specific and effective T cell immune response, where the specific memory CD4 and CD8 cells are activated by it and swiftly activated when

exposed to virus in order to produce cytotoxic T cells. In a study, it has been confirmed that T cell immunity plays an important role in the recovery of SARS-CoV infection [62] along with the experiments showing vaccine - specific memory CD4 T cells against the infection [15].

9. CHALLENGES AND CONSIDERATIONS FOR VACCINE DEVELOPMENT

The challenges faced by the mRNA-1273 vaccine are Vaccine Associated Enhanced Respiratory Disease (VAERD), which is directly related to the induction of non-neutralising antibodies leading to formation of immune complex along with immunopathological complications. Another challenge faced by the vaccines is their effect on the antigenicity as well as on mutation, which is required to be observed for the evaluation of the potency it. One of the major thing to be kept in mind while developing medicine is their effect of on the patients of old age as well as the patients suffering from chronic diseases i.e., the ones with weakened immunity, along with their different medicines reactions has to be closely monitored. After the development of vaccine, the delivery system of vaccine is designed depending on the immune route it follows for the optimised results. The vaccines mainly cause increase in the B cell, CD4+ and CD8+ cells as well as the T cells but their dynamical changes has to be monitored as it give rise to the aggrevation in the severity of the HIV conditions of the patients. The major phenomenon to be considered in the terms of post vaccine responses, is the Antibody dependent enhancement (ADE), if is active then the replication as well the entry of virus could enhance in the host even after the vaccination.

10. CONCLUSION

The different approaches for the development of the vaccine by various countries used to combat the pandemic causing air borne viral infection of COVID-19 caused by the SARS-CoV-2 vaccine, ranges from DNA, RNA, inactivated and live attenuated along with different ingestions like intramuscular or oral have been studied and evaluated by different organisation. Since the medications available only are the combinations of broad spectrum drugs used to combat the respiratory damage caused by virus and combining it with vitamins to improve the immunity but in return the patients are suffering from nominal side effects to high like cardiac diseases. The total amount of vaccines developed around the world (more than 150 countries) is more than 100 in count but only 8-9 vaccines have entered phase 3 or on the edge of phase 2, which is the human trials. The vaccines of different types uses different approaches like Ad5-nCoV use recombinant vaccine mechanism, Corona Vac use inactivated virus mechanism, mRNA use RNA approach and BCG use live attenuated vaccine approach. These vaccines along with different mechanisms also show different effects on the vaccine and the challenges mainly faced in the vaccine is the efficiency of the vaccine in old age group as few vaccines did not show the optimum result in that category of population, chronic disease suffering patients, coping up with the fast mutation of the virus as the rate of mutation in virus is high. The side effects of the vaccine is important consideration as in vaccines dependent on the doses the adverse reactions observed ranged from high to mild to low like adverse in ADZ1222 when dose is high and in CoronaVac as pain at site of injection , the design and optimisation as well as the delivery system and antibody dependent enhancement (ADE). These challenges and considerations are very important before the commercialization of the virus which is the reason phase 3 of the trial takes time.

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