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COVID-19 Vaccine: Is The Future Near Yet?

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ABSTRACT

Ever since the outbreak, the fight against COVID-19 has been never-ending. Countries around the globe are waiting with anticipation for a breakthrough in the vaccine against SARS-CoV-2.Strategies for development of COVID-19 vaccine has not only paved a way for new vaccine platforms but also various antigens of the virus that can be used. Before launch of any COVID-19 vaccine candidate, its reliability and effectivity must be assessed in the given population. However, there is a high risk of widespread use of this vaccine that is weakly effective due to the fast- track of the clinical trials conducted. Nonetheless, the combined efforts by various organisations around the globe in all aspects give a positive ray of hope to end the pandemic. Thus, this review article focuses on the current scenario of the COVID -19 vaccine.

Keywords: Coronavirus, pandemic, COVID-19, vaccine, SARS-CoV-2, COVAX

INTRODUCTION

On December 2019, an outbreak of pneumonia was noted in Wuhan city, China. The causative agent was later isolated as severe acute respiratory syndrome (SARS-CoV-2) also called as novel coronavirus.[1] This virus belongs to the family of coronaviridae and genus of beta coronavirus. Apart from its zoonotic transmission, the other routes include droplet and airborne transmission.[2] Considering its effects globally, World Health Organisation (WHO) declared it as a pandemic and named it as COVID -19.[3] The manifestation of the novel corona virus is seen more virulent in senile patients and those with underlying co-morbidities compared to healthy adults.[4] Taking children into account, the disease is usually mild however they are believed to have an increased viral load.[5] Even though a wide spectrum of symptoms exist among the people, currently loss of taste and smell is presumed as a classic sign of COVID-19.[6]

In view of the current pandemic, different strategies have been tried to reduce impact of the disease. [7] Despite making various effective management protocols to curb the novel virus millions of deaths are being recorded till date. Immunisation in the midst of this pandemic is speculated to play a major role in stopping the spread of this infectious disease. As the name suggests, the virus is novel, therefore humans have no natural immunity to it .Researchers must start from square one to develop a vaccine to educate the immune system to defend itself from the virus. The foregoing research for development of vaccine for SARS- CoV is used as a platform for rapid development of the COVID-19 vaccine. This race against time has not only pressurised the pharmaceuticals but also the scientific researchers for COVID-19 vaccine development. Consequently, various

countries like India, USA, Russia have come along for organisation of resources to make multiple vaccines on shortened timelines. This review article thus focuses on various aspects of COVID-19 vaccine and its current scenario.

1. Structural considerations of the novel coronavirus:

The family of coronaviruses (CoVs) belong to the category of enveloped viruses having a positive single stranded RNA genome that has a pathogenic trait.[8] SARS-CoV-2 currently causing the COVID-19 pandemic is considered more lethal in comparison to previously identified beta-coronaviruses.[9] The genome organisation of the novel coronavirus compromises of 5`-UTR (untranslated region), replicase complex (orf1ab),structural protiens, non-structural proteins (nsps), 3`-UTR (untranslated region) and various open reading frames (ORFs) that are yet to be researched.[10] The structural proteins include membrane (M) envelope (E), spike protein (S) and nucleocaspid (N) protein. These proteins play a role in membrane fusion, viral assembly, morphogenesis and release of viral particles [11].On the other hand, nsps are responsible for viral replication and transcription. [12] They are 16 in number. Among the structural proteins, the spike (S) protein acts as the important machinery that helps in entry of the virus in the host cell. [13] This class of glycoproteins are present on the cell surface that binds to the receptor on the host cell. The spike (S) protein has two subunits (S1 and S2) where S1 subunit helps in attachment to the receptor through the receptor binding domain (RBD) whereas S2 subunit provides the machinery for the fusion with the host cell. [13] The membrane (M) protein is located on the envelope and in the internal core of the virus.[14] Once it gets incorporated in the host cell, it lies in the Golgi apparatus and controls the viral assembly. The M and E protein on activation induce formation of virus like proteins (VLPs). Expression of the S protein along with the VLPs further infects the cells. Thus, these VLPs can be used as a target for the COVID-19 vaccine. [15] The last structural protein (N) protein interacts with the viral RNA. It forms a part of the viral core and nucleocaspid. [14]

2. Trained immunity as a strategy for COVID-19 vaccine:

The enhanced responsiveness of the activated innate immune system to successive triggers is termed as trained immunity. [16] Although, much research has been done on this aspect in the past decade, it is recently gaining popularity in developing the COVID -19 vaccine strategies. When live attenuated vaccines are used to confer immunity it not only provides protection against non- specific infections but also activates specific immune memory. [17] Extensive research on BCG vaccine (Bacillus Calmette–Guérin) that offers immunity against tuberculosis is believed to offer protection against COVID-19 as well. [18] However clinical trials are in progress to learn the effect of the BCG vaccine over COVID -19. Trained immunity when used as a vaccine strategy might boost the early virus control by enabling the activation of the adaptive immune system.[19] The significance of this early response is to avoid the overproduction of cytokines by macrophages at later stages of the disease.[19,20] Recent research in the field suggest that tissue distribution of cells in trained immunity is determined by the route of vaccination.[21] Thus, mucosal route of vaccination can be used as an effective strategy for early clearance of the novel coronavirus.

3. Herd immunity to overcome COVID -19?

Herd immunity is considered when majority of population is immune to an infectious disease. Once achieved provides `herd protection` to those who are not immune to the infection. [22]This immunity can be achieved naturally or by use of vaccines. [22] Taking into account the current

scenario acquiring herd immunity through widespread exposure cannot be considered. This is attributed to high death rates due to the disease and absence of immunity in children. Thus, an effective vaccine is the safest way to reach herd immunity. [23]

4. COVID-19 Vaccine Design:

The development of vaccine for the novel coronavirus relies on selection of antigen, vaccine platform, route and regimen for the vaccine. [24]

- **Selection of antigen:** The antibodies against the novel coronavirus can be neutralising and non – neutralising type. [25] Research suggests that antibodies directed only to S protein of the virus can prevent the infection. [26] Accordingly, major part of the vaccine strategy involves S protein. However, it is only limited to S1 domain or the RBD. [26]A combination of both the types of antibodies have also been suggested against the structural proteins. The rationale of this combination is to create a balanced response between the humoural and T cell mediated immunity.[27]

- **Vaccine platforms:** In order to develop a vaccine two major components are taken into consideration. Firstly, antigen from the target pathogen that are generated by the vaccine recipients.[28] Secondly, infection signal to alert the host immune response.[28] Vaccine platforms can be broadly classified into 6 categories:[29]

1. Live attenuated virus
2. Recombinant viral vectored vaccines
3. Inactivated/ killed virus
4. Protein subunit vaccines
5. Virus like proteins
6. Nucleic acid based proteins

Of these, live attenuated vaccines provide both of these components. On the other hand, non -viral vaccine platforms can only provide antigens but may require an artificial endowment to signal the host immune system known as adjuvants.[30] Characteristically, non- viral vaccine platforms require multiple vaccination to induce the immune protection in comparison to the live virus based vaccine that can provide `one –shot` immunity.[31]

- **Regimen and route:** Besides, the importance of antigen and platform selection, route of vaccination also forms a major consideration for development of vaccine strategies. For a virus like SARS-CoV-2 this step is crucial since the host requires a triad of neutralising antibodies, innate immunity and adaptive immunity to ward of its infection.[32] The regime for the COVID-19 vaccine should always be considered in the asymptomatic period which is around 2-12 days.[33] The advantage of getting vaccinated in this period not only allows control on the virus particles but also allows the immune cells to be present in the tissue before the viral entry.[32] Frequently, those with less immunogenic potential like protein subunit vaccines require repeated doses to produce its effect.[32] Regardless of the type, same or different route can be used for its delivery.

5. Safety aspects of COVID-19 vaccines:

Since there is a spectrum of severity of disease among people, vaccine safety is of prime importance. The safety of a vaccine depends on the nature of vaccine platform, adjuvant selection and mode of vaccine administration. Any kind of latitude in this aspect can lead to deleterious effects. Additional Safety considerations for a vaccine of COVID -19 are related to possibility of antibody- dependent enhancement (ADE) of the disease and risk of cytokine storm. [32]

6. Antibody dependent enhancement:

ADE is a condition which subneutralizing or nonneutralizing antibodies are produced followed by

primary infection or vaccination. [33] These antibodies increase the infectivity of subsequent infect Research has shown that when a host gets infected by one serotype of virus (primary infection), they produce its antibodies. However, if the host gets re-infected with another serotype of virus (secondary infection), the pre-existing antibodies cannot fully neutralise the virus .As an alternative, the antibodies bind to the target virus and the associated immune cells to facilitate its entry into the host cells.[34] Although, the presence of ADE with COVID -19 is unclear. Taking into account the crucial role played by the host immunity, ADE causes a serious concern in developing a vaccine design. [35]

6. COVID-19 Cytokine storm:

The immune response to the SARS-CoV-2 virus in some patients is hyperactive resulting in an excessive inflammatory reaction. [36] This aggressive inflammatory response in severe stage of the disease leads to release of a large amount of pro-inflammatory cytokines is known as "cytokine storm."[36] Cytokine storm appears to be one of the major causes of deaths due to COVID-19. [37]

7. Challenges faced in development of COVID -19 vaccine:

In spite of various available novel vaccine platforms, the development of this vaccine poses challenges. Firstly, developing an antigen design that ensures adequate immune response is critical. Secondly, raised concerns about exacerbating lung disease due to antibody enhancement disease. Third, the duration of the immunity it confers is unknown. There are still many unknown facts related to coronavirus immunity and that is the reason why procurement of a vaccine for COVID -19 is difficult. [38]

8. COVID -19 vaccine candidates:

The speed with which these COVID -19 vaccines are being developed by countries is remarkable. This rapid pace in development of vaccine against COVID-19 can be attributed to several factors. Firstly, prior knowledge about the role of spike (S) protein and the confirmation that antibodies against this protein confers immunity. Secondly, the evolution of nucleic acid vaccine platform. [38] Since 31st July 2020 there were 27 vaccine candidates in clinical evaluation and 139 vaccines in preclinical development. [39] Among these three major vaccine candidates that have entered clinical trials are viral vectored and m RNA based. o date, just one coronavirus vaccine has been approved.[40] Sputnik V – formerly known as Gam-COVID-Vac and developed by the Gamaleya Research Institute in Moscow.[40] Ideally it takes atleast 15–20 years for a vaccine to pass through the phases of assessment. Firstly, the target that has potential to be a vaccine candidate is identified. Once the target is selected, it is checked on animal models for its immune response and safety. When these levels have been cleared by the vaccine, only then only then it is considered for clinical trials in humans. The selected vaccine is checked for safety in Phase I and efficacy to protect against the disease in Phases II and III in humans. [41] (Figure 1 and 2)

9. Outline of the COVID -19 vaccine developers:

Of the confirmed active vaccine candidates, 56 (72%) are being developed by private firms with the remaining 22 (28%) of projects being led by public sector and other non-profit organizations. Although a number of large multinational vaccine developers (such as Janssen, Sanofi, Pfizer and GlaxoSmithKline) have engaged in COVID-19 vaccine development, many of these lead developers are inexperienced in large-scale vaccine manufacture. These lead developers of active COVID-19 vaccine candidates are distributed across 19 countries. This accounts for three-quarters of the world population. [41]

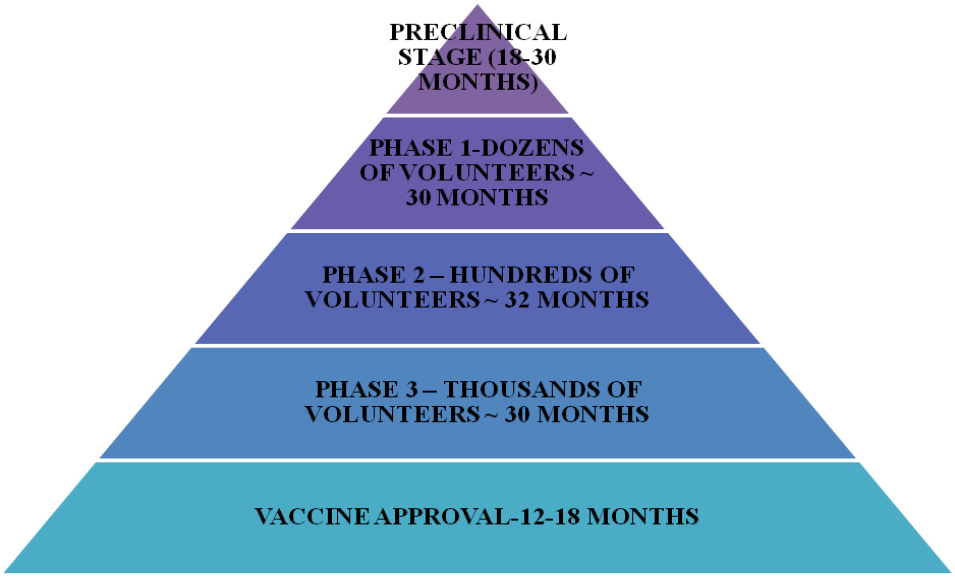

Figure 1: Ideal paradigm of phases for clinical trials for a vaccine

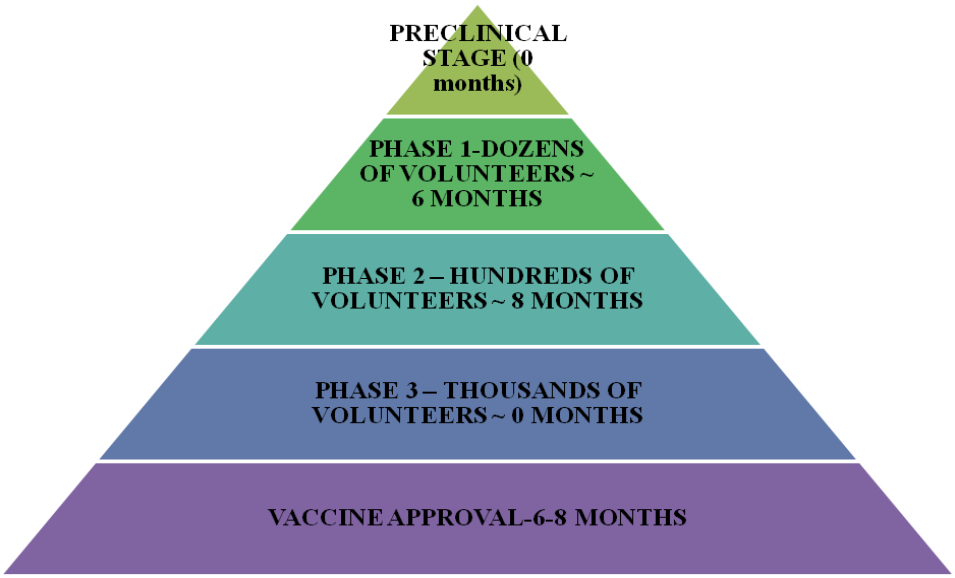

Figure 2: Modified paradigm of phases for clinical trials for a COVID -19 vaccine

9. Vaxart`s oral COVID-19 vaccine:

Vaxart,Inc. is a clinical stage biotechnology company that develops oral recombinant vaccines. These are administered in the form of tablets. Research on COVID-19 oral vaccine has shown its efficiency in inducing immune response at three levels. Firstly, it induces potent serum antibodies. Secondly, it can induce a mucosal immune response. Third, it can induce a T cell response. However, these findings were made from the studies on a mouse model. Further human trials are required for its application as a vaccine strategy against COVID -19. [43]

10. Animal models for COVID-19 vaccine:

In order to determine the antigen as a vaccine candidate, animal models are of utmost importance in deciding various aspects of vaccine design.[53] It is considered to play a crucial role before proceeding with the clinical trials in humans. For an animal to be used as a model for a vaccine development, the pathogen should be able to infect the animal using the same receptor on host cells.[54] A number of animals have been tested and have varied susceptibility to SARS-CoV-2.Currently, ACE 2 rhesus macaques has shown greater affinity for SARS-CoV-2.[55] Various COVID -19

specific models are also being developed like ACE 2 transgenic mice, hamsters, ferrets for better assessment of the COVID -19 vaccine.[56]

11. Role of COVID-19 Tools (ACT) Accelerator:

It is a global collaboration to accelerate development, production and equitable access to COVID-19 tests, treatments and vaccines.[57] Various global health organisations that have joined forces to accelerate and put an end to the current COVID-19 pandemic include[58]:

1. Bill and Melinda Gates foundation
2. World health organisation (WHO)
3. The Coalition for Epidemic Preparedness Innovations (CEPI)
4. The World Bank
5. The Global Fund
6. FIND
7. GAVI –the vaccine alliance

12. Role of COVID-19 vaccines global access (COVAX):

It is an association launched by CEPI, GAVI and WHO to ensure adequate access to COVID-19 vaccines.[59] Its objective is to accelerate the development and manufacture of the COVID-19 vaccines. It further aims to ensure a fair and equal access for every country in the world. It acts as a platform that supports research, development and manufacturing of a wide range of COVID-19 vaccine candidates.[60] Regardless of the income levels, all countries will have access to these vaccines. Currently, an estimate of 2 billion doses is speculated to be available by the end of 2021. These doses will be given to protect the high risk and frontline healthcare workers.[61]

13. Future perspectives of COVID-19 vaccine:

The development of an effective vaccine against COVID-19 is need of the hour. The increased mortality rates and absence of effective treatment have further increased the pace to vaccine development. Many companies have claimed that the COVID-19 vaccine will be available by early 2021 for use. Although the phases of clinical trials have been compressed to a shorter time frame, the quality and longevity of immunity the vaccine confers is still questionable.[62] This cycle of vaccine development shall continue until more clinical trials are carried out and host defence against the novel coronavirus is better understood. Therefore even if a vaccine against COVID -19 is made various clinical and serological tests will be required to determine which populations are at high risk. Furthermore, implementation of these vaccination programs would be uneven due to different vaccine strategies used around the globe.[63]

14. Factors to be considered during COVID -19 vaccination program:

Once global immunisation becomes a reality there a certain set of factors that will require further research. Firstly, the response of the immune system to vaccine in every individual. Secondly, the requirement of booster dose of the vaccine in individuals already immunised. Third, response to the vaccine in individuals who have already caught the infection.

CONCLUSION

COVID-19 has become one of the major health concerns having an increased mortality over the globe. The norms ‘social distancing’ and ‘lockdown’ have further increased the economic burden on the world. In the midst of this crisis, vaccine development has been the only solution to overcome the pandemic. Although, the availability of vaccine is still a long way to go in terms of clinical reality, increased efforts by all sectors provide a hope for success.

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