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RESEARCH ARTICLE

Development of first Generation COVID-19 Vaccines: State-of the-Art Technologies and future Implications!

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ABSTRACT

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) or Coronavirus was initially detected in Wuhan China in December 2019 and has subsequently resulted in the COVID-19 pandemic. The disease presents asymptomatically in some of individuals yet also causes symptoms ranging from those associated with influenza and pneumonia, acute respiratory distress syndrome (ARDS) and even death. The world is currently relying on physical (social) distancing, hygiene and repurposed medicines; however, it was predicted that an effective vaccine will be necessary to ensure comprehensive protection against COVID-19. There was a global effort to develop an effective vaccine against SARS-CoV-2 with approximately 300 vaccines in clinical trials, and over 200 more in different stages of development and anticipated that their success will change research clinical trials processes. Although every one of these vaccines comes with its own particular set of characteristics and difficulties, they were all developed as a direct result of research and development efforts that were carried out on a scale that had never been seen before. It is the first time in the history of vaccination that a worldwide immunization campaign has begun during a time of severe pandemic activity that is defined by high virus transmission. This achievement marks an important milestone in the history of vaccination. More than anything else, the most important aspect of the new game change in drug design is that the traditional drug discovery rules have been rewritten. This is especially significant for the development of vaccines, as it is possible for all clinical trials to be accelerated, which would bring a vaccine or drug molecule to market within a year rather than the traditional fifteen years for each phase of drug clinical trials. This review provides insight in respect to first generation COVID-19 vaccines, which were in clinical use as of December 2020 and focused on the Pfizer/ BioNTech/Fosun, Moderna mRNA-1273, Johnson and Johnson and AstraZeneca/Oxford AZD1222 vaccines.

Keywords: Coronavirus; Vaccines; AstraZeneca; Moderna (mRNA-1273); Pfizer, Johnson and Johnson, Gamaleya, Sinopharm, Viral Vector, Sputnik.

1.Introduction

In December 2019 a Coronavirus (COVID-19) outbreak was identified in Wuhan, China which subsequently spread across the globe. The COVID-19 pandemic has been attributed to the acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and exhibits a range of the clinical symptoms some of which are similar to influenza, include acute respiratory distress syndrome (ARDS) and pneumonia in addition to presenting with asymptomatic patients and all may ultimately result in mortality.[1] Initially the pandemic was perceived to be simple to manage with interventions such as physical (social) distancing, use of masks, adequate use of other personal protective approaches including hand sanitizer and face mask use however, at the same time and it was anticipated that the use of existing and new antiviral drugs, and effective vaccines would reduce mortality rates of COVID-19. Perhaps the initial naïve perception that the development of herd immunity through natural development of immunity through infection was the contributor to significant loss of life due to death[1]. By way of example, in Sweden, the authorities presumed that if 60% of the total population had been infected the resultant herd immunity would be adequate to protect the population.[1,2] However, this presumption failed, and a significant number of the Swedish population have since lost their lives due to COVID-19 infection.[2] Consequently, the development of an efficient vaccine was perceived as the only practical way to ultimately establish herd immunity on the globe. Researchers across the globe have been developing vaccines for COVID-19 resulting in many vaccine candidates in different stages of development of which some are in Phase 1 clinical trials.[3,42]

The development of a safe and effective vaccine requires pre-clinical and clinical trials be conducted to minimize the potential of severe adverse effects when used on a large scale. [3] This review will focus on the current vaccines in which a summary of the biological and immune responses observed from previous COVID-19 infections and SARSCoV-2 is provided. In addition, this review describes exploratory and pre-clinical stages of SARS-CoV-2 vaccine development and a discussion regarding the target platform for designing an effective and safe COVID-19 vaccine with relevant clinical trial data. Furthermore, the ethical concerns surrounding the development and production of these vaccines is considered.

2. Immunogenicity to SARS-CoV-2

Recovery following SARS-CoV-2 infection requires a strong immune response and individuals infected with COVID-19 exhibit a strong immune response to the virus which also facilitates their convalescence. [4,5, 43] Current evidence suggests that helper T cells in COVID-19 infected individuals recognise the spike proteins on the SARS-CoV-2 viral architecture. Consequently, T cells play a significant role in elimination of SARS-CoV-2 from the human body. [5] Moreover, the structure of SARS-CoV-2 includes a major trimeric glycoprotein envelope or S-protein located on the surface of the virus facilitating binding to host cells making it a primary target for the development of a successful vaccine.

The AstraZeneca COVID-19 (AZD1222) coronavirus vaccine has been developed from a version of the common cold adenovirus. [6] The vaccine contains ChAdOx1, which includes the genetic sequence of the SARS-CoV-2 surface spike (S) protein.The S-protein located on the surface of SARS-CoV-2 is essential for the SARS-CoV-2 virus to infect host cells. [6] Most of the vaccines currently in clinical use have been developed using lipid nano particle-encapsulated mRNA, adenovirus 5 vector that expresses S protein DNA, nucleoside modified RNA (modRNA)uridine containing Mrna (saRNA), electroporation of DNA plasmid encoding S protein, inactivated virus following viral propagation in cells with a SARS-CoV-2 clinical strain, lentiviral vector dendritic cells modification (LV-DCs and antigen-specific cytotoxic T lymphocytes (CTL) approaches and are schematically represented in Figure 1, the SARS-CoV-2 spike protein binds to ACE2 receptors in order to enter and infect human cells. [44] The production of a vaccine using spike protein may prime the immune system to attack the coronavirus in subsequent infections. [45]

The spike protein is a major surface protein on the CoV virion and is the primary target for neutralising antibodies. [7] The S-protein undergoes dramatic structural re-arrangement when fusing the virus to the cell membrane of the host for viral genome delivery into the target cell. The 2 proline substitutions (2P) on the apex of the central helix stabilises the MERS-CoV, SARS-CoV and HCoV-HKU1 S protein. [7] The release of the SARS-CoV-2 sequence into the hose cell immediately triggers the manufacture of mRNA which expresses the prefusion-stabilised SARS-CoV-2 spike material (fig. 1). [8] The mRNA-1273 induces potent neutralising antibodies and CD8 T-cell responses and provides protection against SARS-coV-2. [9]

Therefore mRNA-1273 detects and encodes the SARS-CoV-2 prefusion-stabilised spike protein. BNT162b2 is lipid-nanoparticle formulation containing 5 nucleoside-modified RNA (modRNA) 6 which facilitates encoding of the full-length spike of SARS-CoV-2. [9,46] The encoding is modified by two proline mutations for locking into the prefusion confirmation. The doses of BNT162b2 used result in high SARS-CoV-2 neutralising antibody levels in addition to responses from antigen-specific CD8+ and Th1-type CD4+ T-cells as depicted in Figure 1.

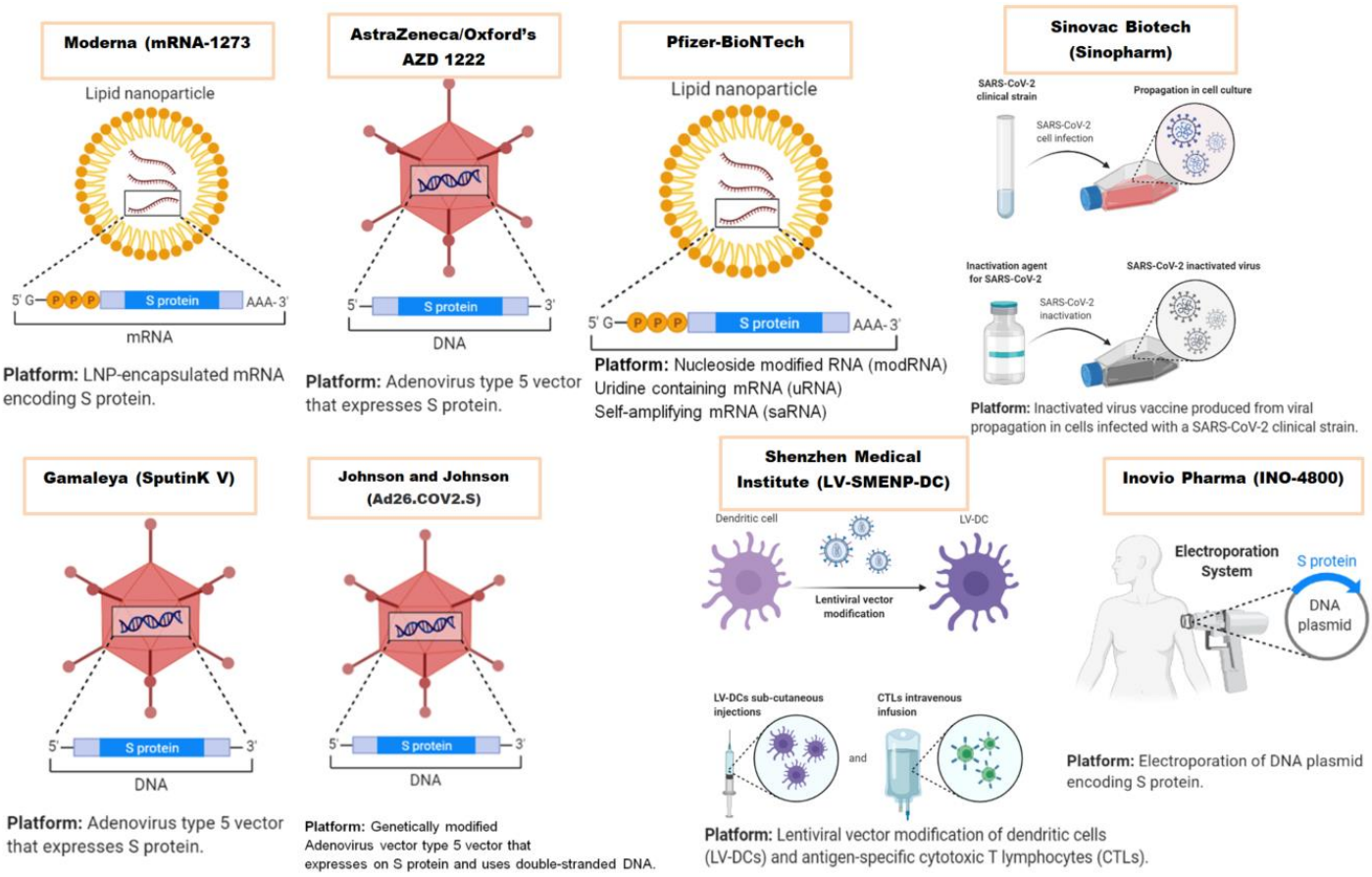

Figure 1: Immunogenicity to SARS-CoV-2 (Source: Author) [10]

3. Exploratory and Pre-Clinical Studies of SARS-CoV-2

Normally the development of new vaccines usually takes between 10 and 15 years, whereas the development of a vaccine for COVID-19 only took between 12-24 months and was astounding. The initial vaccine development phase or exploratory stage includes fundamental laboratory research augmented with computational modelling to facilitate identification of natural or synthetic antigens which can be used as vaccine candidates. [11] The second stage of the process includes pre-clinical studies in which cell or tissue culture and human model-based trials are used to establish the safety and immunogenicity of the test vaccine and/or an ability to provoke an immune response. [12] Initially safety, efficacy and immunogenicity are demonstrated in animal models after which clinical trials in small cohorts of human subjects are undertaken. [12, 38]

Due to the urgent need to develop prophylactic approaches against COVID-19, several vaccine candidates progressed to the clinical trial stage of development prior to demonstrating efficacy in animal models and provided the idea of pre-clinical research data were used to evaluate the Moderna mRNA vaccine candidate. [13] Vabret et al., the immunisation of mice with mRNA encoding alleviated perfusion and mediates $CD8^+$ T cell response, whilst exhibiting dose-dependent neutralisation SARS-CoV-2 spike trimers by antibodies. [14] Two doses of the mRNA provided in a prime-boost combination to the mice prevented nasal mucosa and lung infections, after challenging SARS-CoV-2 infected mice, however, the trial did

not show enhancement of immunopathology in animals receiving sub-protective doses. [14]

4. Technology for COVID-19 Vaccine Design

There are many technologies being considered for COVID-19 vaccine development, including DNA, RNA, non-replicating viral vectors and inactivated vaccines. [15] DNA and RNA based vaccines were not developed aggressively nor licenced for human use previously therefore DNA and RNA based vaccines may not be an advantage during a pandemic situation [15]. However, in the light of available evidence DNA and RNA platforms do not require bioreactor culture techniques for production of an inactivated vaccine, and are easily developed in a laboratory as they are based on the genetic sequence of the virus.[16] For this reason DNA and RNA based vaccines for Covid management are under investigation.[16] In contrast non-replicating viral vaccines have been proven safe and effective and can be manufactured on a large scale.[17] As there is an urgent need for more effective COVID-19 vaccines in the current pandemic situation several DNA, RNA and non-replicating vaccines have been investigated using DNA and RNA platforms.

4.1 RNA Based Vaccines

4.1.1 Moderna mRNA-1273

Moderna is a US-based company that has developed a mRNA-based vaccine referred to as mRNA-1273. [18,40] This vaccine codes for the production of spike proteins and administration of the vaccine results in immune cells present in the lymph nodes performing processing of mRNA, resulting in the marking of the protein in humans. The protein is subsequently recognised and marked for destruction. [19,41] The Moderna vaccine forms part of the Operation Warp Speed initiative for accelerating the production of a usable vaccine. The preliminary Phase I trial data released by Moderna revealed that the vaccine, tested on mice by immunising them with the doses of 0.01, 0.1 or 1 µg, demonstrated a high pseudovirus NAb response with the 1 µg dose. [13] Moreover, the pseudovirus NAb response was also observed in mice who expressed a mutated form of the spike protein viz., D614G. The 1 µg dose demonstrated a robust and cytotoxic response by T-cells, and balanced responses of Th1/Th2. [13] The mice did not exhibit increased pathology following administration of the 1 µg dose of vaccine. The Nab levels in mice in response to the 1 µg dose were comparable to that of a 100 µg dose in human subjects with the result that a 100 µg dose was considered necessary for carrying large scale efficacy trials.

4.1.2 BioNTech BNT162

The collaboration between the German company BioNTech and American company Pfizer resulted in the development of an mRNA-based vaccine for encoding the RBD domain of the SARS-CoV-2. The BNT162 product incorporates modified mRNA and includes a trimerisation domain derived from T4 fibritin.[19] For the phase I trial 45 healthy volunteers who were separated into groups to receive 10 µg, 30 µg, and 100 µg doses, were recruited and 9 participants received a placebo dose [19]. On the basis of the interim data, the participants demonstrated an increased level of IgG, which increased and remained elevated for 14 days following the second dose. [20] Individuals who received the 100 µg dose did not exhibit an increase for one day after vaccination, and exhibited peak IgG levels at 21 days following the initial dose. [19] The individuals who received the 100 µg dose did not receive the second booster dose and based on this information no difference between the health outcomes of individuals who received doses of 30 µg and 100 µg were observed. [19]

4.2 Non-Replicating Viral Vectors Vaccines

The University of Oxford in partnership with AstraZeneca, a British pharmaceutical company, developed a viral vaccine, previously referred to as ChAdOx1. The pre-clinical trials for this vaccine were undertaken in a porcine model with a large antibody response observed.[20] A randomised controlled trial with 1077 healthy individuals was performed in the UK with participants receiving either 5×10^{10} vaccine particles or the meningococcal vaccine MenACWY[21]. The participants were further subdivided and categorised on the basis of paracetamol prophylaxis as this was used as a to reduce adverse events. The production of a recombinant adenovirus for ChAdOx1 nCoV-19 was undertaken and administered at a dose of 5×10^{10} viral particles dose by intramuscular injection.[21] Local and systematic events were fewer in individuals in the paracetamol group when compared to those individuals who received no prophylaxis. [21] However, liver enzyme upregulation through paracetamol use was not considered in this evaluation.

4.3 DNA-Based Vaccines

The American company Inovio developed the DNA-based INO-4800 vaccine. which is injected into the dermis after which electroporation is applied to ensure uptake into cells. The participants were

divided into two groups who were administered a high (2mg) or low (1mg) dose. [22] The analysis of adverse events revealed that 28% of the individuals experienced Grade I adverse events after two months. [22]

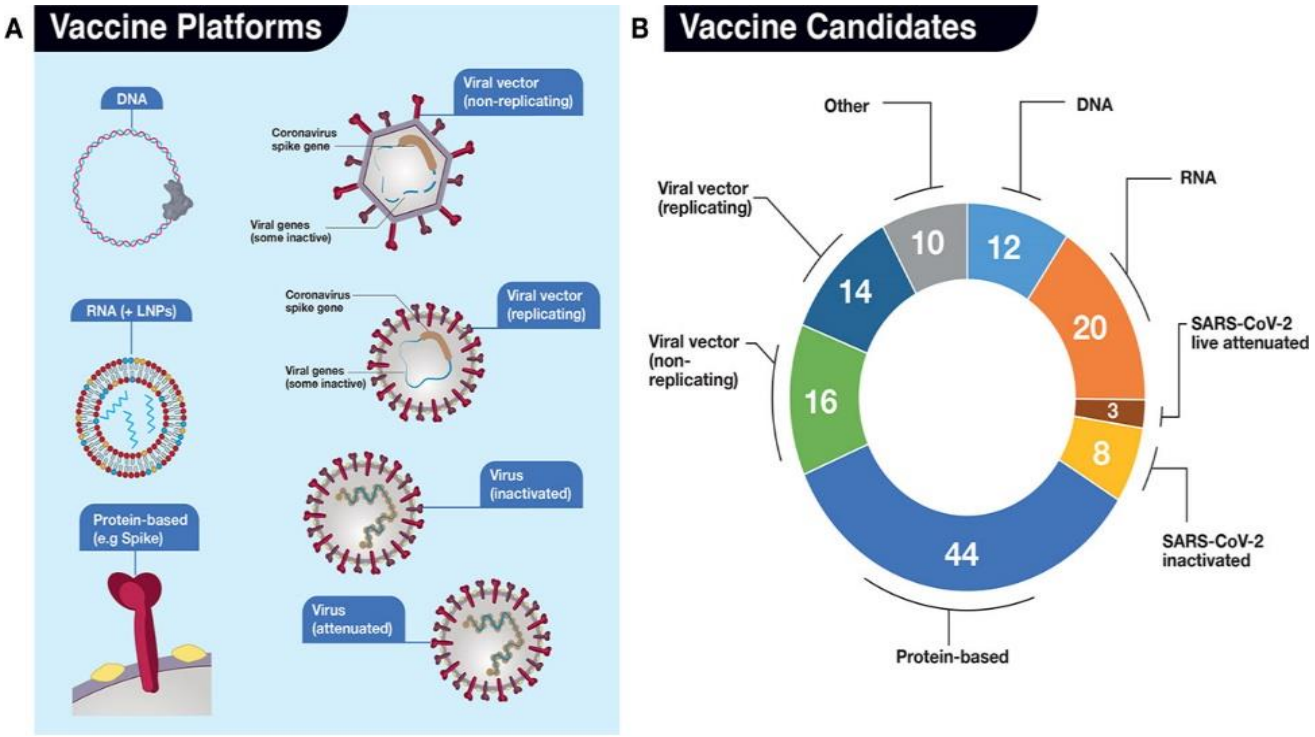

Figure 2: Vaccine platforms and candidates for SARS-CoV-2 and the COVID-19 (Adapted from Funk et al. 2020) [23]

5. Essential clinical trials data for first generation SARS-CoV-2 vaccines

5.1 mRNA-1273

The primary endpoint for establishing the efficacy of the mRNA-1273 vaccine is the prevention of COVID-19 symptoms within at least 14-days following a second injection. [24] The efficacy levels of the mRNA-1273 were analysed and the consistency of the vaccine at the primary endpoint evaluated in subgroups for age, e health-related risk for severe disease, gender, race, and ethnic groups in addition to risk for COVID-19. [24] A secondary endpoint was defined in terms of mRNA-1273 efficacy in preventing severe COVID-19, with reference to pre-defined criteria which included a respiration rate of > 30 breathes per minute, heart rate of > 125 beats per minute, oxygen saturation of 93% or lower less (the oxygen partial pressure to the oxygen reaction inspired ratio of < 300 mm Hg), acute respiratory distress syndrome and respiratory failure .[24] The criteria used included clinically significant neurologic, hepatic, renal dysfunction in addition to admission history to the intensive care unit. Some additional secondary endpoints included the efficacy of the vaccine to prevent COVID-19. Of interest solicited adverse events at the injection site were more frequent in the mRNA-1273 group compared to the placebo group. [24] Following the first dose, solicited adverse events totalled 84.2% in the mRNA-1273 and 19.8% in the control groups whereas, following the second dose the solicited adverse events were 88.6% in the mRNA-1273, and 18.8% in the control groups. The severity of injection site events in the mRNA-1273 group were reported as grade 1 and grade2 and observed more frequently in individuals who were SARS-CoV-2 positive at baseline when compared to subjects who were negative at the baseline.[24]

The efficacy of mRNA-1273 vaccine was calculated by determining the difference in ratio of infected individuals in the control and vaccinated groups, respectively.

The number of individuals in the vaccine group was n1= 15000 and in the control group n2= 15000. In the vaccinated group, x1=11 individuals were infected by the virus, whereas in the control group x2=185 individuals were infected by the virus during the stud. [24] The ratios of the infected individual within the vaccine group, 'r1' was 0.000733, whereas the ratios of the infected

individual within the control group, 'r2' was 0.012333. The analysis of ratio of infection in the mRNA-1273, and placebo group revealed that a greater number of individuals were infected in the control group. Efficacy was determined by considering the difference in the ratios 'r1'and 'r2', which revealed that mRNA-1273, vaccine was 94% effective and facilitates removal of 94% of cases which would otherwise occur.

$$r1 = \frac{x1}{n1}$$
$$r1 = \frac{11}{15000}$$
$$r1 = 0.000733$$
$$r2 = \frac{x2}{n2}$$
$$r2 = \frac{185}{15000}$$
$$r2 = 0.012333$$
$$E = \frac{r2 - r1}{r2}$$
$$E = \frac{0.012333 - 0.000733}{0.012333}$$
$$E = 0.94$$
$$E = 94\%$$

Where,

n1= Number of individuals in control group

n2= Number of individuals in vaccinated group

x1= Number of individuals in control group infected by virus

x2= Number of individuals in vaccinated group infected by virus

r1= Ratio of individuals in control group infected by virus to the total number of individuals in the control group

r2= Ratio of individuals in vaccinated group infected by virus to the total number of individuals in the vaccinated group

E= Difference in the ratios of infected individuals in the control and vaccinated groups.

5.2 BioNTech BNT162

The efficacy of the BNT162b2 vaccine by considering primary and secondary endpoints was reported by Polack et al. [9]. The primary endpoint was efficacy of BNT162b2 against confirmed cases of COVID-19 within at least 7 days onset following administration of the second dose and secondary endpoints included the efficacy of BNT162b2 against severe COVID-19 infection [9]. The effectiveness of the vaccine was estimated using,

$$Effectieveness = 100x(1 - IRR)$$

Where,

IRR is the ratio of confirmed cases of COVID-19 illness per 1000 individuals.

Analysis of reactogenicity revealed that recipients of the BNT162b2 vaccines exhibited more local reactions and mild to moderate pain at the site of injection within seven days of treatment when compared to the placebo group. [9] Analysis of systemic reactogenicity revealed that events including headache and fatigue were experienced by 59% and 52% of the younger participant in the BNT162b2 group, whereas the event rate in the placebo group was comparatively lower after the first and second doses.[9]

The number of individuals in the vaccine group was n1= 21720 and the control group n2= 21728. In the treatment group x1=8 individuals were infected by the virus, whereas, in the control group x2=162 individuals were infected by the virus. [9] The ratios of the infected individual within the vaccine group, 'r1' was 0.000368, whereas, the ratios of the infected individual within the control group, 'r2' was 0.007456. Analysis of the ratio of infection in the BNT162b2, and placebo groups revealed that a greater number of individuals were infected in the control group. In the analysis of data if the control group provides the rate of infection in the absence of using a vaccine, the number of infections eliminated by use of the vaccine in the other group is established by comparing the difference between r2 and r1 and in this case, it was found that the BNT162b2 vaccine was 95% effective and facilitates removal of 95% of cases which would otherwise occur.

$$r1 = \frac{x1}{n1}$$
$$r1 = \frac{8}{21720}$$
$$r1 = 0.00036$$
$$r2 = \frac{x2}{n2}$$
$$r2 = \frac{162}{21728}$$
$$r2 = 0.007456$$
$$E = \frac{r2 - r1}{r2}$$
$$r2 = \frac{0.007456 - 0.000368}{0.007456}$$
$$E = 0.95$$
$$E = 95\%$$

Where,

n1= Number of individuals in control group

n2= Number of individuals in vaccinated group

x1= Number of individuals in control group infected by virus

x2= Number of individuals in vaccinated group infected by virus
r1= Ratio of individuals in control group infected by virus to the total number of individuals in the control group
r2= Ratio of individuals in vaccinated group infected by virus to the total number of individuals in the vaccinated group
E= Difference in the ratios of infected individuals in the control and vaccinated groups.

5.3 AstraZeneca

According to the MHRA Information for Healthcare Professionals, [9] the levels of protection following a single dose of the AstraZeneca vaccine were evaluated by exploratory data analysis by including participants who had received one dose of the vaccine. [25] Participant data were removed from the analysis performed as soon as possible following administration of the second dose, 12 weeks after the first dose. [25] Vaccine efficacy analysis revealed that 22 days post-dose, efficacy of the vaccine was 73% with 95% CI limits of 48.79 and 85.76. [25] It was also observed that hospitalisation was reduced from 21 days after the first dose up to two weeks after the second dose. Consequently, it is likely that a single dose of the AstraZeneca vaccine will provide short-term protection against COVID-19 infection. [25] Protective immunity from the first dose was reported to last for up to 12 weeks. Exploratory analyses suggest that increased immunogenicity was highly correlated to a longer dose interval. In this exploratory trial the number of individuals in the vaccine group was n1= 7998 and the control, group n2= 7982. [25] In the vaccinated group x1=12 individuals were infected by the virus following treatment whereas, in the control group, x2=44 individuals were infected by the virus. The ratio of infected individual within the vaccine group, 'r1' was 0.001500, whereas the ratio of the infected individual within the control group, 'r2' was 0.005512. Analysis of the ratio of infection with the AstraZeneca vaccine and placebo groups revealed that a greater number of individuals were infected in the control group. The comparison of number of infections eliminated by use of the vaccine in the other group was carried out by analysing the difference between r2 and r1 and in this case, it was established that the AstraZeneca vaccine was 73% effective and facilitates removal of 73% of cases which would otherwise occur.

$$r1 = \frac{x1}{n1}$$
$$r1 = \frac{12}{7998}$$
$$r1 = 0.001500$$
$$r2 = \frac{x2}{n2}$$
$$r2 = \frac{44}{7982}$$
$$r2 = 0.005512$$
$$E = \frac{r2 - r1}{r2}$$
$$E = \frac{0.005512 - 0.001500}{0.005512}$$
$$E = 0.72786$$
$$E = 73\%$$

Where,
n1= Number of individuals in control group
n2= Number of individuals in vaccinated group
x1= Number of individuals in control group infected by virus
x2= Number of individuals in vaccinated group infected by virus
r1= Ratio of individuals in control group infected by virus to the total number of individuals in the control group
r2= Ratio of individuals in vaccinated group infected by virus to the total number of individuals in the vaccinated group
E= Difference in the ratios of infected individuals in the control and vaccinated groups.

6. Clinical trials data of interest for first generation COVID-19 Vaccines

6.1 Johnson and Johnson

The efficacy and safety of the Janssen COVID-19 candidate vaccine for protection against moderate to severe COVID-19 was evaluated in a phase 3 clinical trial by considering co-primary endpoints of 14 and 28 days after vaccination.[25] It was found that the Janssen candidate was 66% effective for the prevention of moderate to severe COVID-19 at 28 days after vaccination. [26, 27] A single dose of the Johnson & Johnson vaccine showed a 66% percent effectiveness at preventing moderate to severe disease from COVID-19 and 85% at preventing severe disease. However, there were variations in efficacy in regional clinical trials when evaluated for moderate to severe COVID-19 with a 72% effectiveness in the United States, 57% in South Africa and 66% in Latin America reported. The vaccine also exhibited good results when multiple

variants of COVID-19, such as B.1.351 variant found in South Africa were tested.

Johnson and Johnson reported that the onset of protection was also observed as early as the 14th day of infection. The Janssen COVID-19 vaccine provided complete protection against COVID-related hospitalisation and death 28 days after vaccination. The vaccine was reported to have a clear effect on the number of COVID-19 cases requiring extracorporeal membrane oxygenation (ECMO), mechanical ventilation, or other medical interventions.

6.2 Gamaleya

The Sputnik V vaccine developed by Gamaleya is based on a human adenoviral vector platform and makes use of adenovirus 26 (Ad26) and 5 (Ad5) as vectors to express the genetic sequence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein. [28] Logunov et al (2020) reported the interim results from a phase 3 clinical trial of the Sputnik V COVID-19 vaccine and the results revealed that the vaccine provided strong protection in all age groups that participated. [28,29] The efficacy of the vaccine established by monitoring confirmed cases of COVID-19 from 21 days after vaccine administration revealed 91.6% efficacy (95% CI 85·6–95·2) [29] and was equally effective in individuals in all age groups.

6.3 Sinopharm

Sinopharm, a pharmaceutical company based in the Republic of China, have developed an inactivated SARS CoV-2 vaccine, which has been administered to approximately 1 million individuals. [30] Additional phase 3 trials of the vaccine are currently being undertaken in Indonesia and Turkey.[30]In Brazil, the vaccine has been administered intramuscularly to participants in two different doses provided at an interval of 14 days. [30] The Sinopharm vaccine has been reported to be 79% effective however, efficacy trials on the same product have produced efficacy data of 50%, 65%, 78% and 91%.[30, 31,32]

7. Ethical Considerations Surrounding Vaccine Development and Production

A concerted application of science and technology is required to ensure that the research undertaken in respect of the COVID-19 outbreak includes risk assessment, management, vaccine development, and production whilst always promoting human rights. The development and production of an effective vaccine for dealing with the pandemic is y dependent on the outcomes of appropriately designed clinical and non-clinical trial outcomes performed in vitro, in animal and human subjects. [33] For this reason, there is a bioethical debate surrounding the trials conducted in respect of these vaccines developed during the pandemic. In respect of the COVID-19 situation, no vaccine has been proven to be effective for treatment of the disease and therefore an ethical dilemma when including healthy subjects for testing the efficacy of the vaccine exists. [33] The development and production of vaccines during pandemics is always likely to raise ethical concerns.

8. Challenges of Acquisition and Distribution of SARS-CoV-2 Vaccine in Middle- and Low-Income Developing Nations.

The rapid spread of the contagion crosses the globe and within less developed countries in Asia and Africa has resulted in a significant global health emergency. Countries require context-specific responses dependent on the prevailing situation such as number of COVID-19 cases ranging from none to a limited number or increased number of cases [32]. Decisive actions are required and effective physical (social) distancing, use of quarantine and/or lockdowns, implementation of widespread testing, contact tracing in a systematic manner are necessary to reduce the risk of further spread of the disease. [32] In combination with extensive testing the distribution of vaccines in low income developing counties is a significant challenge due to conflict, over population in rural and urban areas, and lack of accessibility to basic health services. [30] In developing countries, the most significant challenge includes the need for systematic decontamination measures and massive testing to reduce the risk of a devastating outbreak. The acquisition of COVID-19 vaccines requires an in-depth analysis of the changing epidemiology of the disease including the period of incubation between appearance and duration of symptoms. [35]

The distribution of a vaccine is currently determined by considering an ability to develop and initiate testing and purchase vaccines. [35] A small number of multinational companies produce most of the vaccines globally and are also involved in negotiating with the private and public sectors to sell their vaccines. [34] In this respect developed countries of the world attempt to purchase access to vaccine candidates well in advance whereas due to a lack of resources, developing countries are unlikely to have early access the vaccines.[35, 47] Consequently there is likely to be inequitable access and an unethical allocation of vaccines, depending on the ability of countries to pay for vaccines and distributive justice is one of the fundamental

considerations necessary when distributing vaccines during such a pandemic so as to ensure that the principles of distributive justice are met and the allocation of scarce resources are applied equally to all viz., local, national and global communities. [35] However, the limited supply of vaccines and the mass demand during pandemic situations is a challenge when aspiring to equal distribution of resources.

The lack of accessibility to vaccines and storage conditions required may result in failure to achieve desired clinical outcomes even if bulk distribution of vaccines to developing countries was successful. [35] The inadequate refrigerated cold chain network in many developing countries therefore poses a significant challenge. Consequently, vaccine candidates for COVID-19 requires that require long term storage at -20 °C to -70°C are likely to result in the loss of vaccine particularly if inadequate refrigerated cold chain networks exist. [35,37] Therefore, the acquisition, distribution, and successful clinical application of SARS-CoV-2 vaccine in low- and middle-income developing nations may be extremely challenging.

9. Future implications

Knowledge of host–pathogen interactions, clinical science, population-level epidemiology, and biomechanical production requirements are all necessary for vaccine development. Traditional vaccine development can take between 10 and 15 years. So, what are the likely long-term effects of expediting the development of COVID-19 vaccines?[45] This question is difficulty to answer as only time will tell for scientist to truly comprehend with the long-term effects of the COVID-19 Vaccines.[47]

The frantic search conducted all over the world for a vaccine that can protect against Covid-19 has had both beneficial and harmful repercussions. "The accelerated process included obtaining regulatory approvals, funding, performing data analysis, and submitting it to the FDA" (Food and Drug Administration). The assurance is that regulatory agencies conducted due diligence on the process and yet many questions still arise how we managed to move from 15 years duration to under a year in completing all clinical trials phases, new state of the art technology expedited the process. As a result of the increased pace of development, professionals in public health are concerned that vaccinations may be licensed despite having insufficient data and analysis. Some vaccine candidates may not have undergone extensive animal clinical trials phase. The possibility that a vaccine developed using accelerated methods will have adverse consequences that were not planned is one of the primary sources of concern. How much time would be needed to ascertain whether or not a vaccine may impart immunological memory for a period of one year or more? On a positive stance, fast tracked COVID-19 vaccine clinical trials have opened a new window of how future vaccines will be studied for efficacy and safety by benchmarking from SARS-CoV-2 vaccines.

10. Conclusions

In light of the analysis and review of the vaccines that have been developed and approved for emergency use in many countries, it is evident that grey areas exist, and scientists are yet to establish conclusive solutions to ensure successful treatment strategies. Similar concerns are shared by the World Health Organization (WHO) in that assurance of long-term immunity or estimated time of immunity protection with the current vaccines are not yet known. In addition, there is no certainty of immune response or durability thereof. Evidence from the clinical trial data has revealed that the current vaccines have a capability to protect some individuals against disease but are not conclusive in respect of an ability to prevent transmission and subsequent infection following exposure to the COVID-19 virus.

Furthermore, there is a dearth of evidence regarding the age-related use of these vaccines as, by way of example, the use of the vaccine in paediatric subjects has not yet been undertaken and efficacy established and as such these populations remain at risk to transmission and infection by the virus.

An additional concern relates to the availability of the sufficient vaccine doses to cater for entire communities and/or populations so as to ensure protection to a significant number and wide range of individuals, which may reduce confidence in the current intervention strategy and fight against COVID-19.

Consequently, it is recommended that adherence to COVID-19 protocols such as hand sanitization, physical distancing and wearing of masks is maintained despite the state of vaccination of an individual or population as the COVID-19 pandemic is essentially a live performance and anything can go wrong.

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