https://doi.org/10.31674/book.2022macbs.010

Treatment for COVID-19: Current Therapy and Challenges

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ABSTRACT

The novel coronavirus disease, COVID-19, has been documented as the fifth pandemic since the flu pandemic of 1918, around a hundred years ago. It was first reported in Wuhan province in China. The coronavirus was officially named as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The cumulative death toll during this pandemic is 6,029,852, with an approximate death rate of 1.33%. This article focuses on the origin, and the virology of the virus. Then it focuses on various mutations occurring in the virus, with a special note on the mutation in spike protein. A mention of worldwide death statistics is then discussed. Several tests and how they are conducted in India are discussed thereafter. After that, various platforms for vaccine development alongside their manufacturing efficiency are discussed. It then focuses on remedies concerning vaccines both at the global and national level, with a special note on major manufacturers in India. The pros and cons of many new generation vaccines in the clinical or preclinical stage are also illustrated to some extent. Finally, the article focuses on several other challenges being faced or which can be faced in the future.

Keywords: *COVID-19; SARS-CoV-2; Origin; Death statistics; New generation vaccine; Challenges*

INTRODUCTION

The world is currently facing a pandemic of a deadly virus known as SARS-CoV-2 or nCoV-19, better known as COVID-19. This particular disease has led humankind to face a sociological, psychological, and economic crisis. Extensive measures like testing, social distancing, and isolation of the infected individuals are required to impede further spread and suffering. As of March 12th, 2022, the virus is responsible for more than a total of 6 million deaths. The coronavirus 2019 has caused an intimidating health emergency throughout the globe.

Origin of SARS-CoV-2

Tracing back to the emergence of SARS-CoV-2, this contagious disease was first observed as unexplained cases of pneumonia in Wuhan City, Hubei Province, China in December 2019. Later on, on February 11, 2020, the World Health Organization (WHO) declared those pneumonia cases as COVID-19 (CoronaVirus Disease 2019). As the epidemic in Wuhan was witnessed in the early weeks, an association was noted in the early cases, and the prime spot was the Wuhan Huanan Seafood Wholesale Market (also referred to as the Huanan Market), where cases were mainly reported among the operating dealers and vendors (Yang *et al.*, 2020). At the initial stage of transmission, 27 patients out of 41 patients infected were connected with the Wuhan wet food market. Huanan Market is known globally for its wide variety of wild animals, which are predominantly sold as aquatic products and seafood, as well as some farmed wild animals and live wild animals being slaughtered. The wet food markets are hubs for close contact between humans and animals taken as food, which results in the transmission of microbes from animals to humans (Cruz *et al.*, 2020). Therefore, this market was initially suspected as the epicentre of the epidemic. Due to the outbreak of COVID-19, the Chinese government took action to close many wet markets and temporarily ban wildlife trade. People around the world and several health organisations are urging the Chinese government to make this ban permanent. This kind of market can again lead to another pandemic. The wild farm animals should be vaccinated before being sold in the market. Monitoring of hygiene and sanitization of the wet market is mandatory. Steps have to be taken by the government to centralise slaughtering instead of many wet

markets. On January 30th, 2020, the International Health Regulations Emergency Committee of WHO deemed the virus as a "public health emergency of international concern". Within two months of the epidemic on March 11th, 2020, WHO declared COVID-19 as a "global pandemic" (Cruz *et al.*, 2020).

LITERATURE REVIEW

History of SARS-CoV-2

The world is now affected by the coronavirus disease 2019, i.e., COVID-19, which is recorded as the fifth pandemic after (i) the Spanish flu pandemic in 1918 (H1N1), (ii) 1957 Asian flu (H2N2), (iii) 1968 Hong Kong flu (H3N2), and (iv) the 2009 Pandemic flu (H1N1), which was the cause of an estimated death of 50 million, 1.5 million, 1 million, and 300,000 respectively.

The coronavirus is a member of the family of severe respiratory viruses, which was discovered first in the 1960s (Cruz *et al.*, 2020). Before SARS-CoV-2 emerged, there were two more viruses from the same family that had emerged, namely, SARS-CoV-1 in 2002 and MERS-CoV in 2013.

In 2002-2004, there was an outbreak of SARS (severe acute respiratory syndrome) whose causative agent was SARS-CoV-1 where masked pam civets were considered as intermediate hosts. And during the outbreak of MERS (Middle East Respiratory Syndrome) in 2013, the intermediate hosts were the dromedary camels.

Some studies and evidence suggest that SARS-CoV-2 shows zoonotic origins, i.e., it emerged from bats to pangolins and then infected humans. But the exact natural reservoir is unknown yet. Most of the viruses that are related to pandemics originate from animals, like some viruses that cause flu are from birds and pigs, while Ebola originated from bats (Cruz *et al.*, 2020).

All human coronaviruses are known to have animal origins, i.e., natural hosts. Bats have been identified as the main host of various zoonotic viruses (e.g. Nipah virus, SARS-CoV, MERS-CoV, and Hendra Virus), which also include coronaviruses with considerable genetic diversity (Latinne *et al.*, 2020).

Virology of SARS-Cov-2

Coronavirus is a member of the Coronaviridae family, whose subfamily is Coronavirinae. SARS-CoV-2 is a member of the same Coronaviridae family as SARS-CoV-1, which on further classification falls under the alpha, beta, gamma, and delta coronavirus genus and order is Nidovirales (Samudrala *et al*., 2020). The World Health Organization has said that these four versions are worrying (Duong, 2021).

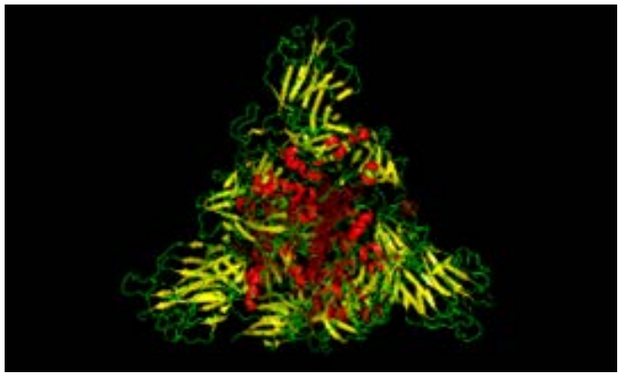
SARS-CoV-2 is spherically enveloped, contains a positive-sense, single-stranded RNA genome, and has a diameter of approximately 120 nm. The major known viral RNA genome has a length of 27 to 32 kb. The RNA genome present in SARS-CoV-2 contains a 5' methyl-guanosine cap, a poly (A)-tail, and 29,903 nucleotides according to WH-Human1 coronavirus (WHCV) (Chan *et al.*, 2020; Cruz *et al.*, 2020; Wu *et al.*, 2020a). Bats are considered to be the natural reservoir of all three of these viruses. And infections mainly occur through the intermediate host, like in the case of SARS-CoV-2, where pangolins are the primary suspects as an intermediate host (Andersen *et al.*, 2020). All coronaviruses are RNA viruses, which benefit them by mutation and homologous and non-homologous recombination, resulting in the expansion of their host range. Some club-like projections are present on the peripheral region of COVs, which are known as "spikes" (protein spikes). So, the name comes from the Latin word "corona," which means "crown," because the structure looks like a crown.The genome of SARS-CoV-2 is comprised of a 5' untranslated region including a 5′ leader sequence, an open reading frame (ORF) 1a/ab encoding nonstructural proteins (nsp) for replication, and four structural protein components including (i) spike (S) (ii) Envelope (E) (iii) Membrane(M) (iv) Nucleocapsid as well as several accessory proteins such as ORF 3a, 6, 7a/b, and 8; and a 3' untranslated region and transcribes nine subgenomic RNAs. The glycoprotein spike facilitates binding to the transmembrane angiotensin-converting enzyme (ACE) 2 in the host receptor and that is also dependent on S protein priming by the transmembrane serine protease TMPRSS2. The S protein is the primary determinant of transmissibility and pathogenicity. The S protein is also therefore considered as the primary target of vaccine design for its ability to neutralise antibodies (Chan *et al.*, 2020; Gao *et al.,* 2020; Salvatori *et al.*, 2020; Shang *et al.*,

2020; Walls *et al.*, 2020; Wang *et al.*, 2020; Wu *et al.*, 2020b). A similar panel of mammalian cell lines can also be infected with SARS-CoV-2. The host protease can cleave the S protein into two subunits, i.e., subunit-1 and subunit-2 (S1 and S2), which are responsible for recognition of receptors and membrane fusion, respectively. The S1 subunit can again be classified into N Terminal Domain, i.e., NTD, and C Terminal Domain, i.e., CTD. In SARS-CoV-2, the CTD of S1 shows strong affinity for human ACE2 (hACE2). The CTD is the key region of the receptor binding domain (RBD) within SARS-CoV-2 that interacts with the hACE2 receptor with higher affinity (Wang *et al.*, 2020; Wrapp *et al.*, 2020). In the host cell, the putative life cycle of SARS-CoV-2 begins with S protein and hACE2 receptor binding. A change in the structure of S protein, which is conformational in nature, facilitates viral envelope fusion with the cell membrane with the help of the endosomal pathway. The viral RNA genome is released, after the fusion, into the cytoplasm and it is translated into viral replicase polyproteins, i.e., pp1a and 1ab, which can be cleaved further into small products by virus encoded proteinases. A series of subgenomic mRNAs is transcribed by polymerase by discontinuous transcription. Viral subgenomic proteins are then formed by the translation of subgenomic mRNAs. The S, E, and M proteins enter the ER and the Golgi apparatus, where they form a nucleoprotein complex by combining the N terminal with a positive-stranded genomic RNA. at the golgi-Endoplasmic reticulum intermediate compartment, the viral envelope is assembled with structural proteins and the nucleoprotein complex. And then the newly assembled viral particles get released from the infected cell.

SARS-CoV-2 is genetically close to other coronavirus strains like SARS-CoV and MERS-CoV. The SARS-CoV-2 has a high homology (79.6%) with the SARS-COV from 2002-2004 (Zhu *et al.*, 2020). It shares 96.2% homology with a sequence of strains of coronavirus (RaTG13). This RaTG13 is the closest known sequence to SARS-CoV-2.

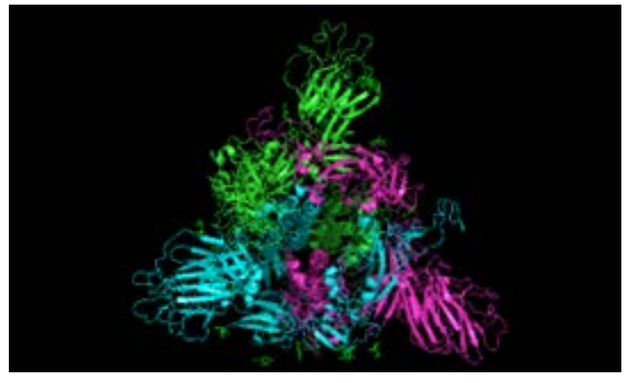
Spike Protein Mutations

As it is known, starting from the first wave, there were a lot of changes in the structure of the spike protein of SARS-CoV-2. The mutations in the spike protein led to the development of different variants like delta variant and omicron. The images and table below offer an insight.



Source: Wong et al., 2022

Figure 1: Spike Protein of delta variant



Source: Ye, Liu & Li, 2022

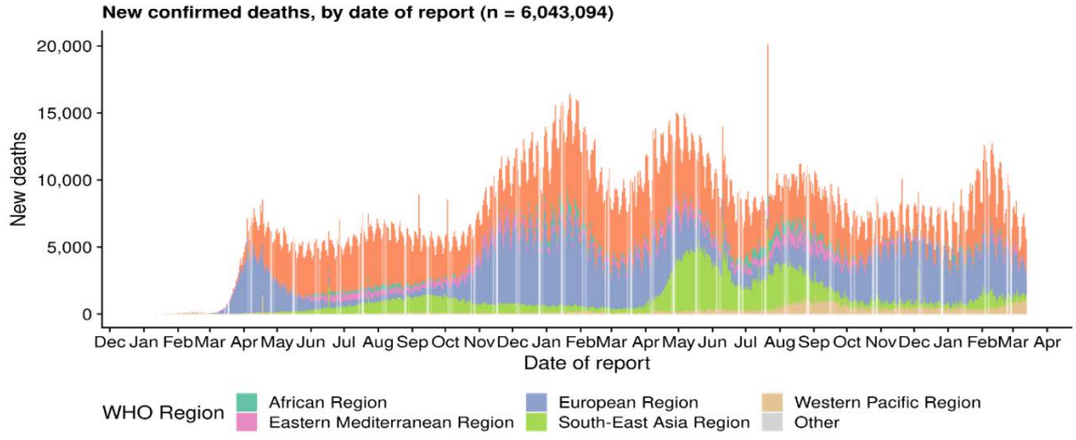
Figure 2: Spike Protein of omicron variant

Table 1: Mutation and its effects

Variant	Site of Mutation	Site of Infection	Infected Age Group
Wuhan-Hu-1		Lungs	Older
Delta	A67V, Δ69-70, T95I, G142D, Δ143-145, N211I, L212V, ins213-214RE, V215P, R216E, Δ213-214,L452R,T478K,D614G,P681R,D950N	Lungs (Majorly)	Children, younger and middle age
Omicron	K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F	Pharynx, Larynx, Sinus	Older

Statistics

WHO has made public the information about cases and death and other necessary information globally and nationally. Here some graphs are provided for an insight into the loss which people are facing due to COVID-19, both globally and nationally.



Source: https://worldhealthorg.shinyapps.io/covid/

Figure 3: New confirmed deaths worldwide

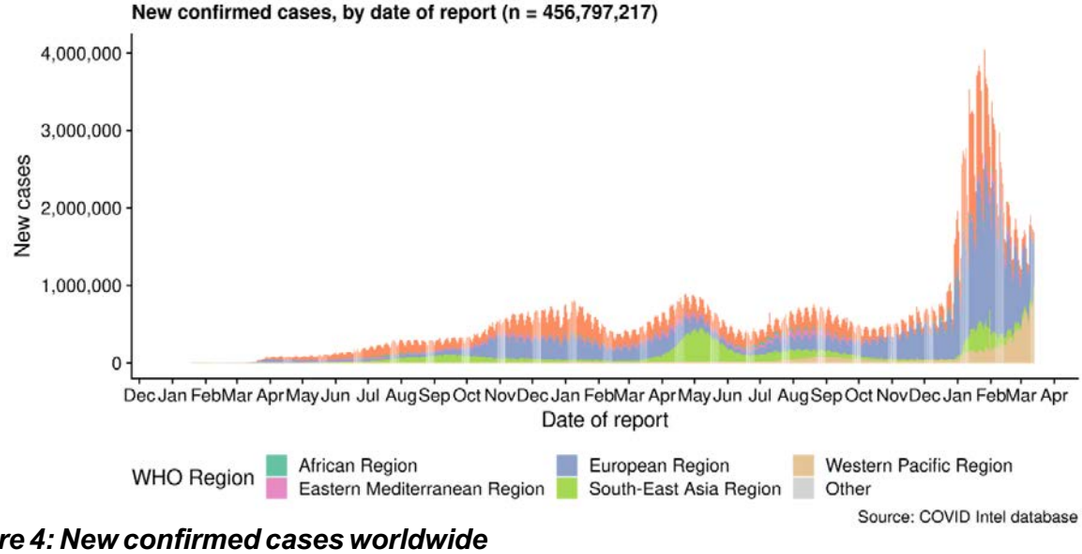
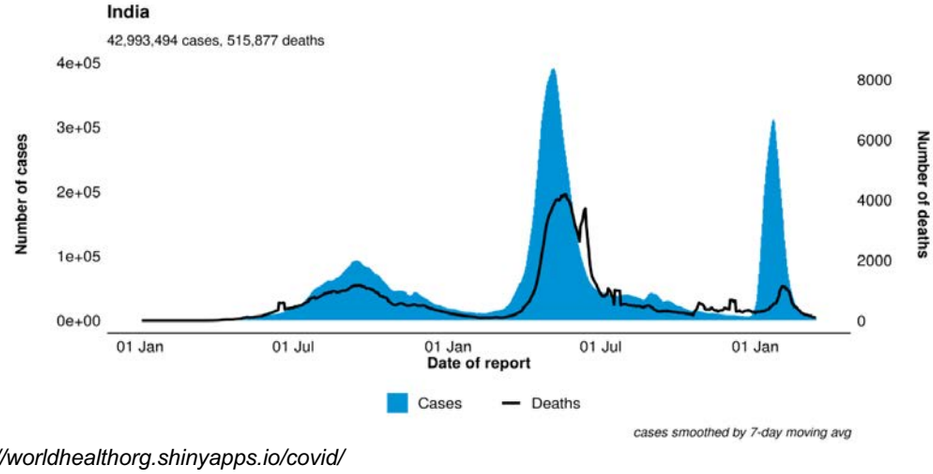


Figure 4: New confirmed cases worldwide

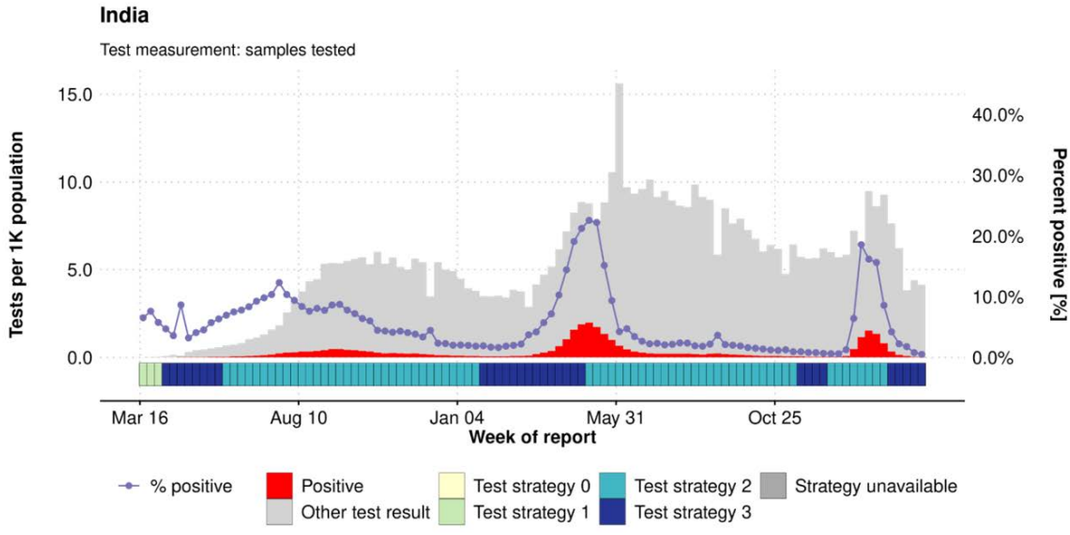


Source: https://worldhealthorg.shinyapps.io/covid/

Figure 5: Cases and deaths in India

Test Related to Covid-19

Seeing the mortality rate and morbidity rate, test and treatment has really become an important issue to combat COVID-19. There are certain kinds of tests like 'swab test' where samples of saliva and mucus are taken from the mouth and nose to diagnose COVID-19. Some other tests like RT-PCR, antibody testing was also performed. Even certain drugs like Lopinavir, Ribavirin were also tested but they didn't turn out to be so effective to fight against SARS-CoV-2. Below is a chart showing various test strategies in INDIA



Source: https://worldhealthorg.shinyapps.io/covid/

Figure 6: Testing strategies in India. Test strategy 0 depicts no strategy. Test strategy 1 depicts only those who both (a) have symptoms AND (b) meet specific criteria. Test strategy 2 depicts anyone showing symptoms. Test strategy 3 depicts open public testing (i.e. available to asymptomatic people)

The only strategy to combat this deadly virus is by vaccinating the people. Discussion of some of the handful of vaccines manufactured by some of the countries are in the following section.

Platforms of Vaccines

Various novel approaches are now being taken for the development of new-gen vaccines. Gavi, the vaccine alliance, has taken an active part in informing how these novel approaches work on a public level. Below, four basic approaches and their manufacturing efficiency are discussed. The number of candidates can be found in the COVID-19 Vaccine Tracker and Landscape (WHO, 2022).

Protein Subunit

Protein subunit vaccines contain protein fragments and/or polysaccharide chains. The fragments and other molecules are studied carefully to produce the desired immune response. By restricting the access of the immune system to the whole pathogen, side effects are minimised. These are generally produced using living organisms. The organisms also require a certain substrate and culture medium, alongside strict hygiene to avoid contamination. The manufacturing process is also precise and depends on the subunits to be used. So generally, these are expensive. As of March 11th, 2022, 48 vaccine candidates enlisted in the WHO candidate list are protein subunit based.

Viral Vector

Viruses invade the host cells and replicate themselves in order to survive. This makes the infection in the host cell. They make new viruses by hijacking ribosomes. The virus particles contain antigens which cause the immune response. This is the underlying principle for viral vector-based vaccines. In this case, the host cells only receive the codes to produce antigens. Thus, the immune response is invoked

by the host cell. The carrier which carries the code is known as the vector. Viral vectors are generally attached to substrates. But this is also a major drawback for large scale manufacturing. Suspension cell lines are now being made for producing vectors in bioreactors. Additionally, assembling vectors is a complex process that requires testing before each step and has a high chance of contamination. Thus, it obviously increases the cost. As of March 11th, 2022, 21 non-replicating and four replicating vaccine candidates enlisted in the WHO candidate list are viral vectors.

Nucleic Acid

These can be of mainly two types, depending on the type of nucleic acid used. The nucleic acid is injected into the bacterial plasmid. This gene is stored in the bacteria as it may be helpful in the survival of the organism. In the case of DNA, the antigen is injected into muscle cells. But one challenge is bypassing the cell membrane, as the ribosome, which translates the gene, is situated inside the cell. On the other hand, in the case of RNA, the antigen is encoded in mRNA or self-amplifying RNA (saRNA). It can be injected by itself or encapsulated in nanoparticles. Once inside the cell, antigens are produced and surfaced. This causes the immune response, including killer T cells. Once the pathogen's genomes are sequenced, it is relatively fast to build one nucleic acid-based vaccine. Moreover, both kinds of vaccines can be produced in the same facility, reducing the costs even more. As of March 14th, 2022, 16 DNA-based and 26 RNA-based vaccine candidates enlisted in the WHO candidate list are nucleic acid-based.

Whole virus

Live attenuated vaccines use the lab-weakened version of the original pathogen. Once inside the cell, they cause the natural immune response and may cause slight symptoms of the original disease. In the case of inactivated virus vaccines, the pathogen or part of it is injected. But their genetic material is destroyed prior to injection. As inactivated viruses contain destroyed genetic material, they are considered safe compared to live attenuated vaccines. Different vaccines will contain different substrates and culture media to grow the virus. Additionally, there will be a high chance of contamination. Eliminating this will certainly increase the cost of manufacturing. As of March 14th, 2022, 21 inactivated virus and 2 live attenuated virus vaccine candidates are enlisted in the WHO candidate list.

An Insight to Vaccines

Covishield

The Oxford-AstraZeneca vaccine was first prepared in the United Kingdom (UK), which is also known by its local name 'Covishield'. It is also called AZD1222. In India, the covishield vaccine was prepared by the "Serum Institute of India (Pune)'. This vaccine is actually based on viral vector based technology. The covishield vaccine mainly constitutes disabled adenovirus having certain segments of coronavirus, L-histidine hydrochloride monohydrate, polysorbate 80, ethanol, aluminium hydroxide gel, L-histidine, magnesium chloride hexahydrate, sodium chloride, EDTA (also called disodium edetate) (Phiddian, 2022). The method of administration of the vaccine is intramuscular injection. Here, ChAdOx1 (also known as modified chimpanzee adenovirus) is used as a vector. The covishield vaccine is actually a replication-lagging simian adenovirus vector which constitutes a full length codon-optimised coding sequence of the S protein of SARS-CoV-2 having a tPA (a.k.a. plasminogen activator) leader sequence. Since in adenovirus, many vital genes are eliminated and restored by the gene with no contribution from the S protein of SARS-CoV-2 virus, that is why the adenovirus does not undergo replication. This vaccine contains the incapacitated genre of an adenovirus which contains the genetic material of the S protein of SARS-CoV-2. After the vaccine is given, the S protein that is formed primes the immune system to attack the SARS-CoV-2 virus if it later attacks the body. Covishield vaccine is stored in refrigerated conditions at 2°C to 8°C.

The Covishield vaccine is given in 2 doses, and the time gap between the 2 doses is stretched from 4-6 weeks to 4-8 weeks. After the vaccination, the adenovirus vector enters the cells. Then it releases its genetic material, which is transferred to the nucleus of the cell. After that, the cell undergoes transcription into mRNA and proteins (by translation). Since it is known that S protein is the protein of

interest, an exterior protein which sets up the SARS-CoV-2 virus enters the cell machinery through the ACE2 (angiotensin-converting enzyme 2) enzymatic domain. By preparing this, the vaccine provokes the immune system to attack the SARS-CoV-2 virus through T-lymphocyte cells (or T cells) and antibodies if this virus attacks the body in the future.

Covaxin

The Covaxin vaccine is manufactured by Bharat Biotech. Covaxin contains the whole virion of inactivated SARS-CoV-2, which makes it quite different from Covishield. It is not capable of replication and constitutes some crucial ingredients like aluminium hydroxide gel, TLR 7/8 agonist, 2-Phenoxyethanol, phosphate buffer saline as mentioned (Firdous, 2021). Like COVISHILD, it is also stored at the same temperature. After the covaxin is given inside the body, certain antigen-presenting cells shred the inactivated virus apart and then it splits into certain pieces flaunted on its surface. Now certain helper T cells get exposed to those fragments. Then the T cells get activated if they fit properly on the fragments, and it also assists other immune cells to respond to the vaccine. When these helper T cells get activated against the coronavirus, it can attach to the fragments and, due to this, B cells also get activated. It basically multiplies and oozes out the antibodies that have similar shapes as their surface protein. The immune system responds when any live SARS-CoV-2 virus infects the body once the covaxin is injected. These antibody-producing B-lymphocyte cells get attached to those invaders. So, these antibodies prevent the virus by targeting the S protein. On March 3rd, 2021, it was found that the covaxin had an efficiency of around 80.6%.

Sputnik V

Sputnik V is also a viral vector vaccine that was prepared by the Gamaleya Research Institute of Epidemiology and Microbiology'. This vaccine was also prepared from adenovirus and then the gene of S protein was added to two types of adenoviruses, Ad26 and Ad5. These were made in such a way so that they could invade the cells. When the Sputnik V is injected, the adenovirus gets attached to the peripheral region of the proteins. Then the adenovirus goes into the nucleus of the cell; after that, it pushes its genetic material into the nucleus. The adenovirus is engineered in such a way so that it doesn't replicate, but a gene of S protein could be copied into mRNA molecules. After reading its sequences, the mRNA leaves the nucleus of the cell, and then it starts to accumulate the S protein. Some of these proteins made by cells form spikes which get transferred to the surface. Now these proteins are split up into small pieces by the vaccinated cells present on the surface. After that, the immune system recognises the extended S protein and fragments of S protein. By switching the alarm system of the cell, the adenovirus exasperates the immune system.

Moderna mRNA-1273

The Moderna mRNA-1273 vaccine is based on mRNA and helps to fight against COVID-19. Here the mRNA gives all the information to those host cells which helps in the formation of the protein S antigen, which is very much outlandish to SARS-CoV-2. So, in order to keep that information in the memory immune cells, the protein of S-antigen allows the body to generate an immune response. After certain clinical trials, it was found that the efficiency of the Moderna mRNA-1273 vaccine was around 94% for those patients who received two doses of vaccines (that is, a full series of vaccines) and with a negative baseline SARS-CoV-2 status. This vaccine is stored in a freezer at -25°C to -15°C.

Pfizer-Biontech

Pfizer and Biontech collaborated with each other and are now working on their COVID-19 vaccine candidate. The Pfizer vaccine mainly consists of modRNA (or nucleoside modified mRNA), which encodes a mutated form of the S protein of SARS-CoV-2 encapsulated in lipid nanoparticles. Along with the mRNA molecule, the vaccine comprises of many ingredients like sucrose, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), ALC-0315, ALC-0159, cholesterol, dibasic sodium phosphate dihydrate, monobasic potassium phosphate, potassium chloride, sodium chloride, sucrose etc. This vaccine is also given by intramuscular injection. This vaccination is given in 2 doses, with 3 weeks' aside. After certain clinical trials, it was found that the Pfizer vaccine has an efficiency rate of around 91.3% to fight the SARS-CoV-2 virus. Some researchers found that the modRNA had a sequence of

around 4,284 nucleotides. It is mostly made up of a 5' cap, a 5' UTR (untranslated region) made from the sequence of human-alpha globin, a signal peptide, and two proline substitutions.

Booster Doses

It was found that when 2 doses of the Moderna mRNA-1273 or BNT162b2 were given, they were unable to provide sufficient protection against the omicron variant, but after giving the booster dose, there was a hike in the rate of protection against omicron. This dose basically accelerates the neutralizing antibody. A single booster was also given by Pfizer-BioNTech to the 18-year-old and older age groups who had already taken the primary doses. So, it was found that these booster doses showed quite encouraging results for preventing the infection caused by Omicron. Booster doses showed protection of around 90%.

Problems with Traditional Vaccines

There are many kinds of vaccines available on the market. The vaccine can treat, or at the very least try to protect by increasing the immunity. But SARS-CoV-2 is a new virus. The vaccines available now are not able to treat it. The development of a conventional vaccine is time-consuming. Normally, the average period for vaccine production is 12–15 years. Classical vaccines use the antigen itself. For this reason, a huge amount of antigen, the key element, as well as human subjects with consent are needed. Traditional vaccines have fought well against highly contagious diseases, viz., measles. But in the case of COVID-19, no cure is still available. So, people are not willing to volunteer as test subjects. Again, time is short, and thus, conventional vaccines are not an alternative in this case.

Advantages and Disadvantages of New Generation Vaccines

Many new generation vaccines have emerged that can be used, though further research is required.This part will explore those kinds along with their advantages and disadvantages, respectively.

Recombinant Protein Vaccines

In this case, a part of a whole protein or fragment of proteins, such as the RBD or fusion of RBD with carrier or other elements, can be used. It has been shown that animals can be immunized with the help of recombinant protein vaccines. The main disadvantage with these kinds of vaccines is that they can only provide partial immunity and thus need auxiliary elements, termed adjuvants, to boost immunity. The vaccine candidate 'NVX-CoV2373', for COVID-19, uses Matrix-M as an adjuvant.

Viral Vector-Based Vaccines

In this case, the antigen is cloned in a virus unit unable to reproduce itself in the host body. The viral vectors stimulate the same kind of reaction in the body that would otherwise be produced only while encountering the toxic virus. By this means, the vaccine actually "trains" the body on what to do while encountering the virus and thus delivers protection against the virus and an immunity boost. Adenovirus is being used in the case of COVID-19.

Bacterial Vector-Based Vaccines

As the name suggests, the vector used in this case is bacteria. LAB (Lactic acid bacteria) is very promising in this case. Symvivo's vaccine candidate for COVID-19, bacTRL-Spike, uses LAB along with the S protein, and is currently in the clinical trial phase.

Plasmid DNA Vaccines

Plasmid DNA vaccines do provide a higher safety profile because the use of live viruses is eliminated. Again, double-stranded DNA is much more stable than RNA, protein, or even the virus itself, and can be frozen or put into a cryo period for a long time. But the main drawbacks of this kind are low transfection efficacy. INO-4800, Inovio's COVID-19 vaccine candidate, uses a hand-held electroporation device, known as CELLECTRA. The vaccine is injected intradermally with electrodes. The electric pulses open up the cell membrane for the plasmid to enter without any defect. But adequate infrastructure and cost will be vital points for this on a bigger scale.

Messenger RNA Vaccines

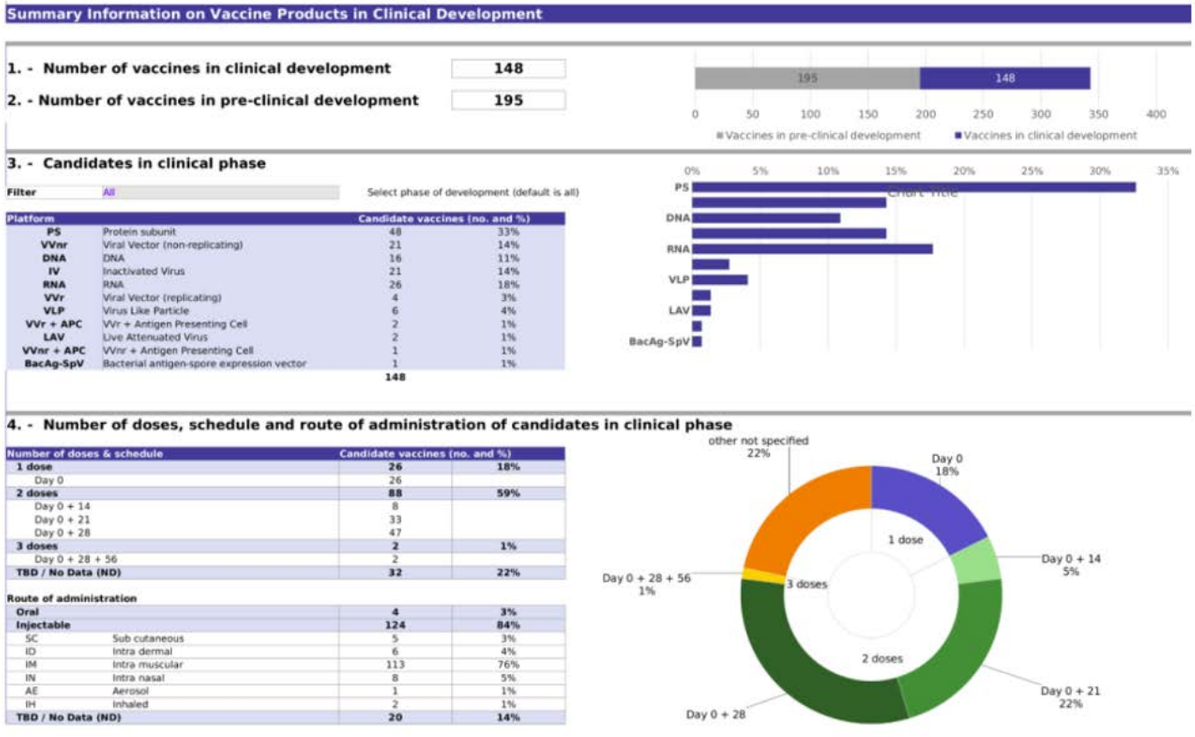
These are the newest generation of vaccines. All the components of an m-RNA vaccine can be

"chemically synthesised". The elimination of any living agent from the virus or antigen makes it the safest of all. Again, the manual synthesis gives a large number of quality checks for large productions. And it prevents any chance of transmission from the production facility, by human or non-human means, especially for high-risk pathogens like ebola. Generally, mRNA molecules have low apparent transfection efficacy. Lipid nanoparticles (LNP) are added to incorporate the mRNA for transfection. The mRNA-1273 vaccine candidate for COVID-19 from Moderna is an LNP-encased mRNA vaccine (Baden *et al.*, 2021).

Trained Immunity-Based Vaccines

Traditional and conventional vaccines provide a safe guard only against the toxic virus. But trained immunity-based vaccines (TIV) provide protection against unwanted pathogens from entering the bodies, thus keeping one healthy. Currently, BCG, a vaccine against tuberculosis, is under clinical evaluation (Jirjees, Bashi, & Al-Obaidi, 2021) for its power to suppress SARS-CoV-2. Still, the exact cause is unknown. And that's preventing it from being used on a larger scale, as the long-term side effects, if any, are still unknown.

For the lack of space, all kinds of vaccines and their detailed discussion can't be done here. One can find a detailed table and discussion on the website of WHO about various vaccines (WHO, 2022). Some relevant charts are provided below (data taken from WHO draft-landscape as of March 11th, 2022).



Source: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

Figure 7: A glimpse of vaccines in clinical and pre-clinical development and their platforms and doses

Challenges

In the following part, it will be discussed in detail the challenges being faced or likely to be faced in the future. These will mostly contain challenges imposed by various limiting entities or on social or economic grounds. The challenges being faced, or which can be faced in the future, are

Data collection and management

The very first challenge to preventing COVID-19 is accessing data. If any person comes into the

COVID cluster, chances are high that she/he will get infected. But without adequate data, the spread of disease or insight into the actual situation or the trend of infection is impossible. GIS (Geographic Information System) was used by India, as well as many other countries. Under immense pressure, the Govt. of India launched the AarogyaSetu app. It is developed under the Ministry of Electronics & IT. The app uses Bluetooth and GPS capabilities. It keeps records by analysing nearby users of the app. Thus, it forms the cluster, and by analysis of data, it can be used to determine the spatial propagation pattern, spatial and temporal transfer of the COVID-19 hotspots. It was noted through the information maps that, almost in all cases at the city level, the concentration of infected people occurred in clusters. In the age of artificial intelligence and social media, the government of India, along with the state governments, provided the Aarogyasetu app and WhatsApp and FB chat bots.

Market competition

Sooner or later, a cure for COVID-19 will be found. But right now, who holds the vaccine (possibly) holds either the greatest cure of recent times or the most money-making agent in recent history. One should not treat the vaccine as an agent of profit. On November 9th, 2020, Pfizer and BioNTech shared their primary findings about the efficacy of their candidate. Nine days later, they announced 95% efficacy. On November 16th, Moderna announced their candidate's efficacy to be 95%. Two days later, Oxford and AstraZeneca reported their safety and immunogenicity in a larger context (Mills & Salisbury, 2021). It should be taken into account that there should be more openness about the test and how the vaccine is distributed and used.

Funding

It has already encountered one outbreak in early 2000. The National Institute of Allergy and Infectious Diseases of the United States contributed approximately $100 million (Prudêncio & Costa, 2020). But it dissolved in 4 years. No further funds were organized, and thus the SARS-CoV-1 research was finished. Unfortunately, the low priority for long-term medical research is not new. As one researcher points out, in the post-COVID-19 era, without any hesitation or political controversy, research funds should be provided for adequate, fair, and sustainable research. Only by that means, will it ensure healthy lives for humanity. The global economy is now at a pivot point, as it was after the last SARS encounter. An unstable economy points towards chaos in every level of society and government. To get the economy back to where it was, scientific models should be used, and funding for long-term research on these kinds of high-risk pathogens should be given in a sustainable way.

Quality control

With many new technologies at the disposal, the challenge is not to make a vaccine but to provide it to people. As time is the key factor here, testing for standardizing the vaccine isn't a possible approach. There is a need to test the vaccines on human subjects only by deliberately infecting them with the pathogen. But no cure for this has been found till now, and thus inhibits the way. The Goldilocks approach (Billings & Bernacki, 2014) may be used for this purpose.

Route of administration

The route of administration for a vaccine is important. SARS-CoV-2 is an airborne virus. It attacks through the air that is breathed. The vaccines currently in progress are injected into the blood. But it would be better if they could be intranasal or inhalation or oral (Wu, 2020). Again, many people are trypanophobic in nature. They will be encouraged if the vaccine is intranasal, etc. in nature.

Thermostability

Thermostability is now the most problem causing aspect. Current vaccines are stable within 2°C to 8°C. But, for a vaccine drive of this magnitude, this can cost up to 80% of the cost of a vaccine. And also, maintaining a cold chain is still very costly and immobile for both developed and developing countries. A lack of adequate knowledge about the cold chain may result in serious consequences while transporting the vaccines.

Priority of being vaccinated

Due to the scarcity of supplies and the urgency of the situation, a decision on who to vaccinate first must be made. A clear distinction on the basis of age has been shown. Many countries have relied upon various strategies. In India, as published by the Ministry of Health and Family Welfare (MoHFW), the government of India has worked on priority groups. The government decided that the first group would include healthcare and front-line workers. The second group will include people over 60 years of age and people aged between 45 and 59 years of age with comorbid conditions. At last, as of March 1st, 2021, all eligible candidates over 18 have been vaccinated. Vaccination for candidates under 18 has started from January 3rd, 2022.

Fast track vaccination

COVID-19 vaccines are and will be introduced to the market in a very short time. There can be negligence in manufacturing them or transporting them. Even, for several vaccines, the dosage provided is different. It is very difficult to make people aware of the remaining dosage after day 0. In India, this is being done by the Aarogyasetu app. Distributing vaccines in clusters in such a short time is also equally risky, as studies on them are still going on.

Supply chain logistics

Thermostability is already discussed above. Asian countries will find it very hard to cope with this problem with poor and inadequate infrastructure (Haque & Pant, 2020). Production of not only vaccines but also glass vials, etc., will be subjected to a sudden boost. The world economy is now facing a challenge. Boosts of this kind will only make the situation worse. WHO has arranged the logistics on a global level. WHO is working with CEPI and GAVI to manufacture a vaccine, alongside UNICEF as the delivery partner. Approximately 80 rich nations have signed on for COVAX, the global vaccine (Haque & Pant, 2020). Money will be invested for fair manufacturing and distribution purposes.

SARS-CoV-2 genetic instability

SARS-CoV-2 undergoes certain mutations in a small amount of time. Five prominent signatures have been reported as of 2020. They are all reported from various geographic locations. They differ from the viruses in Wuhan in genetic aspects. Many vaccines use the viral S protein, which has, till now, been found to be resistant to mutation. Certainly, this helps to some extent. But, after the introduction of effective vaccines, mutant viruses may appear with selective advantage, posing a threat (Forni & Mantovani, 2021).

The unknowns

There can be various other problems. People don't know them yet. They don't know the effects of vaccines in the long term. Besides, there can be political arguments over the possession and distribution of vaccines. The impact on the climate due to the waste generated by manufacturing vaccines is still unknown. The fate of used equipment during vaccination is also unclear. Lastly, we should be extremely cautious as this pathogen can be used as a bioweapon, like ebola (Gunaratne, 2015).

CONCLUSION

Viruses that have evolved from the conventional to the modern age of science pose a significant threat to humanity. History shows that in every century, one or more viruses have evolved and caused a significant effect on the fate of humanity. On one hand, people face a significant loss of human lives and resources; on the other hand, unrestful socio-economic conditions. They began to question the own knowledge and morality in various aspects. But on the other hand, science and technology are greatly beneficial as there is much more activity going on in this kind of time. The coronavirus pandemic is a similar kind of situation. Many lives have been lost, and the whole world is in mourning over it. But in contrast, science and technology related to microbiology and medical professions have

experienced a certain boom. Many new generation vaccines are on their way, which would otherwise require a lot of time and ethical controversy. The vaccine drive for coronavirus over the globe is a mammoth task. Politics and private interests should not hamper the vaccine drive, which is manufacturing them and providing them to the people at a nominal cost. This mammoth task must be achieved through altruistic partnerships between industry, governments, and international organizations for the universal benefit of human health. It may take some more time and could cost more lives, but it is certain that people will find a cure for COVID-19.

ACKNOWLEDGEMENT

The authors acknowledge the department of Biotechnology at Haldia Institute of Technology for the support received during the writing of the article. Also, the authors declare no conflict of interest.

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