SARS CoV-2: Origin, Evolution,Treatment and Prevention

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) stands at the forefront of global attention as the catalyst for the ongoing pandemic, but it's not the first of its kind. Predecessors like SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East Respiratory Syndrome) also emerged from the same viral family, showcasing the recurring threat posed by these pathogens. The zoonotic origin of SARS-CoV-2 underscores the intricate relationship between humans and animals, serving as a stark reminder of the potential for future pandemics. Understanding the mechanisms of zoonotic transmission and identifying high-risk interfaces between humans and wildlife are critical for preempting future outbreaks.The rapid evolution and mutation rate of SARS-CoV-2 further complicate containment efforts. This viral adaptability underscores the importance of continuous surveillance and research to track and respond to emerging variants effectively. The development of vaccines has been paramount in curbing the spread of the virus, offering hope for ending the current crisis. However, vaccine distribution challenges, vaccine hesitancy, and the emergence of new variants necessitate ongoing vigilance and adaptation in public health strategies.Studying SARS-CoV-2 not only informs immediate pandemic response efforts but also provides invaluable insights into viral pathogenesis, host immune responses, and potential therapeutic targets. Collaborative research efforts worldwide have accelerated our understanding of the virus and its impacts on human health. Moreover, lessons learned from this pandemic will shape future preparedness strategies, emphasizing the importance of robust public health infrastructure, global cooperation, and investment in research and development.In essence, the study of SARS-CoV-2 transcends the urgency of the current pandemic, serving as a cornerstone for pandemic preparedness and reinforcing the interconnectedness of human, animal, and environmental health

Keywords:- *SARS-COV-2,Pandemic,zoonotic origin,evolution,mutation*

1.Introduction

SARS-CoV-2 causes an extremely infectious disease called the coronavirus disease [2]. SARS- CoV-2 stands for severe acute respiratory syndrome coronavirus 2[3]. Its first appearance was found to be in Wuhan, China and is believed to have spread from over there. It belongs to a bigger family of viruses called coronaviruses. This family of viruses were responsible for the SARS outbreak of 2002 and MERS outbreak of 2012. It makes SARS-CoV-2 the third member of the coronavirus family to cause a large-scale pandemic after the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) in 2003 and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in 2012[3]. As of 25th March 2023, the pandemic had caused around 761 million confirmed cases including 6.88 million deaths according to the World Health Organization [WHO]. The World Health Organization declared it a global pandemic on March 11, 2020. Before that on January 30, 2020, WHO had declared it a public health emergency. Thevirus causes fever, headache, cough, myalgia, fatigue, sputum production, and hemoptysis [2]. The concerning trait about this virus is its ability to spread quickly. Also, coronaviruses are known for their ability to mutate and recombine quickly [3]. The genomic sequence has altered a lot from what it was first reported. Many aspects of this pandemic indicate that this will not be the last outbreak of this sort which makes it necessary to study about this virus.

Furthermore, many viruses of the coronavirus family have the potential to harm the human population. The immediate source of SARS-CoV-2 and its related viruses is believed to be bats [1]. Hence, a future zoonotic transmission cannot be eliminated. Understanding the dynamics of forthcoming outbreaks and establishing well-informed strategies to stop further worldwide spread depend on elucidating the origin and evolution of coronaviruses

and other viruses [1]. The world health organization has mentioned that the current pandemic is by far the worst of its type in the global history. This article reviews the existing theories about the origin and evolution of the coronaviruses with a specific focus on the SARS-CoV-2 which has led to the current COVID-19 pandemic. Though no specific treatment has been found, we will also be looking at the possible treatment methods like different medications and combination of drugs that is being used world-wide. Furthermore, we will look at various preventative vaccines that are available in the market.

1.1 Origin:

The SARS-CoV-2 is a species of virus that belongs to the Coronaviruses. They are positive stranded viruses [1]. They belong to the subfamily Coronavirinae in the family Coronaviridae and the order Nidovirales [International Committee on Taxonomy of Viruses]. On the basis of their phylogenetic relationships and genomic structures, this subfamily consists of four genera: Alphacoronavirus, Betacoronavirus, Gammacoronavirus and Deltacoronavirus [5]. The alphacoronaviruses and betacoronaviruses infect only mammals. The gammacoronaviruses and deltacoronaviruses infect birds, but some of them can also infect mammals [6]. Domestic animals can act as an intermediate source for the transmission of these viruses to humans [5]. They are believed to have zoonotic origin. Furthermore, these animals may themselves suffer bat-borne or closely related coronaviruses. 7 of 11 and 4 of 9 species of alphacoronaviruses andbetacoronaviruses respectively have been identified only in bats. This makes bats the most possible natural reservoir for both these genera of coronaviruses [6].The three coronaviruses that has caused the recent epidemics belong to the betacoronaviruses[1]. These are SARS-CoV, MERS and SARS-CoV-2. These viruses undergo frequent recombination [7]. This means that if many strains of these viruses are in close contact, they recombine to form a more deadly and easily transmissible variant.Coronaviruses are zoonotic pathogens. All coronaviruses that caused epidemics are considered to have began from bats. But, there transmission to humans occurred through various intermediate sources. For SARS-CoV the intermediate hosts were market civet cats. MERS coronavirus spread with direct contact from dromedary camels. In case of COVID-19, the spreadof SARS-CoV-2 is believed to have begun from the Wuhan seafood market. Most of the current studies believe that this virus originated in bats and were transmitted to humans through an intermediate host in the seafood market. The intermediate host in this case is quite disputed [3]. There are various other theories that are suggested for the origin of the SARS-Cov-2. Another theory states that there was a lab leak from the nearby Wuhan Institute of Virology[BBC]. But this theory has been long disputed.

2. Evidences to support the zoonotic origin of SARS-CoV-2

SARS-CoVss-2 is the ninth coronavirus that is known to infect humans [9]. All of the previous human coronaviruses have zoonotic origins. SARS-CoV which has a lot of similarities to SARS- CoV-2 spilled over to humans in Guangdong province, China in November 2002 and again in 2003 [8]. Both of these emergences were associated with the selling and buying of live animals,like civets and racoon dogs, that were also sold in Wuhan market in 2019 from where the current virus is believed to have emerged [10]. Various serological studies has shown approximately 3% positivity rate to SARS related coronaviruses among the residents of Yunnan

province, close to bat caves, indicating regular exposure in rural locations [8].

The closest relative for both SARS and SARS-CoV-2 are the viruses sampled from the bats of Yunnan province. There is a considerable distance between Yunnan and the location of first human appearance of both these viruses making it impossible to identify the exact pathway of spillover. SARS-CoV-2 have been identified to show similarities to four different strains of coronaviruses that were found to be endemic among humans. They are human coronavirus-OC43 (HCoV-OC43), human coronavirus-HKU1 (HCoV-HKU1), human coronavirus-229E(HCoV- 229E), and human coronavirus-NL63 (HCoV-NL63) [8]. The circumstances of the origin of theseviruses are unknown although they have zoonotic origin. There is a direct analogue between SARS-CoV-2 and HCoV-HKU1 which was identifies in 2004 in Guangdong. It contains a furin cleavage site in its spike protein and was identified in a case of human pneumonia [11]. On thebasis of epidemiological data, two of the first three documented cases of coronavirus and 28% of all cases reported until December 2019 were directly liked to the Hunan or Wuhan markets [WHO].Post the closure of Wuhan and Hunan markets in 2019, environmental samples of SARS-CoV-2were detected, fundamentally in the sides that traded wildlife and domestic products [WHO]. Although animal remains repeatedly tested negative for the

virus, they are not representativeof the live animal stock that were being sold in the markets.Viruses closely related to SARS-Cov-2 has been found in bats and pangolins in different parts of China, Thailand, Cambodia and Japan. It has been found that there is a large evolutionary gap between SARS-CoV-2 and bat virus RaTG13 collected by the Wuhan Institute of Virology [8]. Thegenetic distance of approximately 4% indicates decades of evolutionary divergence [12]. SARS- CoV-2 has more genetic similarity to three bat viruses- RmYN02, RpYN06 and PrC31. But none of these viruses were collected by WIV and were sequenced only after the onset of pandemic.Therefore, beyond doubt we can conclude that SARS-CoV-2 has a zoonotic origin and RaTG13 isnot it's progenitor [8]. No bat reservoir or animal intermediate is yet identified. This may be because of the fact the right animal species is yet not sampled.

2.1 Is there a chance for lab leak of SARS-CoV-2?

There have been previous cases of laboratory escape of viruses that has led to isolated infections [8]. The only case of laboratory escape that has led to epidemic is of H1N1 influenza. It is believed to have escaped during large scale vaccination trials [13]. There is no evidence thatproves that Wuhan Institute of Virology or any other laboratories were working with SARS-CoV-2 or any closely related variants. In case of laboratory outbreaks, the initial spread of virus will be among those working in the laboratory and there relatives. Even after extensive contact tracing, it was found that neither the workers nor their close contacts reported the virus. As perthe catalogue of WIV, the three successfully cultured bat viruses were: WIV1, WIV16, and Rs4874 [14]. All three of them are more genetically close to SARS-CoV than they are to SARS- CoV-2. Mutations like N501Y that helps in replication would have been presentif SARS-CoV was being modified [8]. But no such things are identified. All these points us in the directionthat a lab leak is less likely to have occurred.

3.Evolution

Coronavirus was first isolated from chickens [2]. But there were not considered to be infectiousin humans until 2003, when a type of coronavirus caused the SARS outbreak. Many believe SARS-CoV-2 to have evolved from SARS-CoV. The share a similarity of about 90% [27]. It has only less that 90% similarity with MERS virus. RaTG13 is identified an immediate relative of SARS-CoV-2 [1]. Itis a strain of coronavirus that was isolated from bats in 2003 in the Yunnan province of China [1]. It shares a 98% similarity to the current virus [28]. Like other coronaviruses, the genome of SARS-CoV-2 is made entirely of genes that codes for protein. Thismakes it important to study the difference between nucleotide substitution that can bring fortha change in the amino acid and that which do not affect it. This brings about two different kindsof substitutions. Nonsynonymous substitutions are those which can change the amino acid thereby changing the protein. The chances of these reactions are very less. Synonymous substitution does not change the amino acid. It occurs more readily as it keeps the protein stable even after mutation [1]. Those sequences that underwent nonsynonymous substitution will undergo the process of natural selection [26]. These substitutions can be used to understand the time to its most recent ancestor. Synonymous substitutions are generally used for this purpose because only it will be indicating of the exact mutation rate of a virus. When only Synonymous substitutions are taken into account the similarity between the currant virus and RaTG13 is only 83%. The virus is estimated to have a mutation rate of $1.5–3.3 \times 10{-}3$/site/year [1].

The genome of SARS-CoV-2 has numerous recombination blocks that are joined together. A study was conducted on 68 Sarbecovirus strains and it was found that they contain several breakpoints with highest percentage of them in ORF1a [29]. Any recombination involving spikeprotein is important as it is the spike protein that binds to ACE2 receptor of cell and facilitates the entry of the virus into the human host [1].The next closest relative of SARS-CoV-2 is the GD Pangolin SARSr-CoV [2]. All six necessary amino acids were same for GD pangolin CoV and SARS-CoV-2. Various studies has shown thatthis similarity between the current virus and GD pangolin CoV may not be due to recombination, but is rather a result of natural selection [30].S and L lineages are the two main lineages of the SARS-CoV-2 [1]. 72 strains show CT haplotypeand is called L lineage due to the presence of Leucine. 29 strains show TC haplotype and is called S lineage due to the presence of Serine in its codon. It was shown that L lineage is more identical to SARS-CoV-2, although animal coronaviruses have more phylogenetic similarity withS lineage [25].

A variant of interest is a viral strain that is of public importance as it may pose risk due to it highlevel of pathogenicity, high rates of transmission or due to severity of illness developed [31]. Asof March 2023, there are five variants of interest. These are alpha, beta, gamma, delta and omicron [WHO].For the alpha strain, 50% of the new mutations happen at the spike protein. p.N501Y is an important mutation that has occurred to the spike protein. Another mutation of importance isd p.P681H. Both these mutations affect the critical protein epitopes [31].p.N501Y mutation of the spike

protein remains in the alpha, beta and gamma variants of SARS- CoV-2. This mutation is often associated with increased rate in transmission. This may be due tothe increased strength in the interaction between cellular receptor and spike protein [32].p.L452R mutation is seen in delta variant. Studies has shown that it is associated with a resistance to some monoclonal antibodies [31]. p.69-70delHV in alpha strain is associated withan increased infection rate [31].

4.Treatment

From the onset of the pandemic to date, there is no specific treatment that has been proved. Several antiviral drugs and a combination of them is being used. Most of there mode of actionare still under research [15]. Various drugs that are most commonly used are described in thisarticle.

4.1 Remdesivir

It is an RNA polymerase inhibitor [15]. It works by stopping the replication process of the virus.It is an adenosine nucleoside analogue drug [3]. It acts against RNA viruses. In the 53 documented cases in which the drug was used, 68% showed improvement, 47% were cured and 13% died [16]. There were various side effects like infusion site reactions and gastrointestinal tract dysfunction were reported.

4.2 Favipiravar

It is a RNA polymerase inhibitor. It is a purine nucleotide that will inhibit the replication of viralgenome [15]. Adverse effects include teratogenicity, hyperuricemia and QTc prolongation.

4.3 Lopinavir/Ritonavir

Lopinavir is a protease inhibitor enzyme in Human immunodeficiency virus by forming enzymeinhibitor complex [3]. Ritonavir will increase the concentration of Lopinavir. Thus, these drugs are used in combination with one another. The effect of these drugs on the virus is not yet confirmed. But based on a study conducted in Wuhan, it was shown that administrating a combination of these drugs helped to reduce the mortality rate [15].

4.4 Ribavirin and Interferon

Ribavirin is a guanosine analogue. It interferes in the process of RNA capping and also inhibits polymerase [15]. It is efficient against the WIV04 strain of SARS-CoV-2. A research based in Hong-Kong has shown that a combination of Ribavirin and Interferon β-1b will improve the symptoms among patients [17]. Interferons are cytokines that will eliminate virus-infected cells.Its adverse effects include anemia, bradycardia, and hypomagnesemia.

4.5 Chloroquine and Hydroxychloroquine

They are anti-malarial drugs. Chloroquine can prevent the expression of phosphatidylinositol- binding clathrin assembly protein and thus prevent it's endocytosis. Lysosomal acidification alsocan be prevented [15]. Hydroxychloroquine has also the same method of action as Chloroquinebut has less adverse effect making it more preferred in the treatment of Malaria [3]. In vitro studies has proved their efficiency against SARS-CoV-2 [18]. The recurrent use of these drugs may lead hepatitis and fatal arrhythmia. The FDA has also warned about the usage of these drugs outside of a clinical scenario.

4.6 Losartan, Telmisartan, Baricitinib

Losartan, Telmisartan block the substances that causes narrowing of blood vessel [3]. They canblock the ACE2 receptor thus interfering with the entry of SARS-CoV-2. Baricitinib also interferes with the entry of virus by the inhibition of Janus kinase pathway [3].

4.7 SARS-CoV-Specific Human Monoclonal Antibody (CR3022)

Passive immunization can give short time protection against a virus by producing their antibodies in our body. CR3022 is a monoclonal antibody isolated from a SARS recovered patient [3]. It has a highly conserved epitope that can bind with SARS-Cov-2. This principle alsohas it's application in the avoidance of SARS-CoV-2.

4.8 Cepharanthie, Selamectin, and Mefloquine Hydrochloride

They decrease the yield of viral RNA in the target cell. They are shown to be effective in thetreatment of the virus [3].

5.Preventative Vaccines

In order to stop the COVID-19 pandemic it was necessary to make preventative vaccines and administer it to most of the general public. There are no commercially available vaccines for theprevious SARS and MERS viruses, though a lot of effort was made towards it. The chief reason for this was the lack of availability of suitable animal models and the fact that the virus was localized to a small region [19]. But with SARS-CoV-2 making a vaccine was the need of the hour with increasing death toll and also due to the global spread of the virus. Therefore, it was necessary to move away from the traditional aspects of vaccine preparation [20]. Usually, thedevelopment of a vaccine takes several years, but for COVID vaccines it was accelerated to an unimaginable speed. From the beginning, it just took 6 months for the clinical trial to begin andwithin 10 months vaccines received conditional approval. This was never seen in the history of vaccine making [21]. There were further challenges like the quickly happening mutations in thespike protein of the virus giving rise to different strains that had capabilities to question the efficacy of the vaccines.Among the 138 vaccine candidates worldwide 21 of them are approved for emergency use [19].The spike protein (S protein) found on the surface of SARS-CoV-2 is the primary method by which they cause infections. All these 138 vaccine candidates can be grouped into five categories [19]. The number of vaccines in clinical trial in various categories is summarized in Table 1.

Table-1: Summary of COVID-19 vaccines as of March 10 2023 [WHO]

Type	Platform	Candidate vaccines
Inactivated Virus	IV	22
Live Attenuated Virus	LIV	2
Replicating Viral Vector	VVr	4
Non-replicating Viral Vector	VVnr	25
Protein subunit	PS	59
DNA	DNA	17
RNA	RNA	43
Virus like particle	VLP	7

5.1 Whole virus vaccines

They are weakened or inactivated virus that can trigger the host to produce antibodies against the virus thus giving immunity without causing infection. It is generally of two types: inactivated vaccines and live attenuated vaccines.Inactivated viral vaccines are prepared by inactivating them with heat or chemicals or radiations post their culturing [20]. They contain shells but is killed and hence they cannot prompt host cell interference but will evoke strong humoral immune response leading to theproduction of antibodies.In live attenuated vaccines the pathogenicity is reduced by treatment, but they are not killed [20]. It therefore can induce both cell-mediated and humoral immunity [19]. There effect is longtime compared to inactivated viruses. But there safety is questionable in people with weak immune system. COVI-VAC is an example of live attenuated vaccine [19]. The vaccine is in phase3 of its trial and is not yet approved [22].

5.2 Viral vector vaccines

Viral vector vaccines use non-toxic viruses to deliver pathogen coding genes to the host. It will then use the host cells translation to produce antigens rather than its own. Incase of SARS-CoV-2 the spike protein genes are the pathogen coding genes that are delivered either using a non- replicating or replicating viral vector (modified virus). Replicating viral vector will produce whole viruses whereas non replicating viral vectors will give rise only to the viral antigen.

5.3 Recombinant Protein vaccines

It is genetically engineered virus or protein that can trigger immune response in host cell that can help in the treatment or prevention of illness [20]. It can have viral or bacterial vector. Thefirst step is to identifies the specific antigen coding gene, in this case the S protein [23]. Then itis fused with adenoviruses and is introduced to the human body. Post entry it will produce thecorresponding antigens that will evoke humoral and cellular immunity. These vaccines are not easy to produce. The main advantage of recombinant protein vaccines is that there is no needto use live viruses [20]. But S protein is difficult to express, thus the yield of these vaccines is questionable.

5.4 Nucleic Acid Vaccines

It uses the viral genetic material to give immunity against a virus by encoding its antigen [19]. Itcan be of two types: RNA and DNA-based vaccines. In RNA-based vaccines an mRNA encoding the antigenic protein is introduced into the host cell instead of injecting pathogenic proteins. Itwill induce cell-mediated and humoral immune response. This method can reduce the adverse effect on the human body [20]. Self-amplifying mRNA vaccine has an alpha viral genome with an undamaged replication mechanism. As they replicate inside the body, they produce massivequantities of antigen from a small quantity of vaccine [24]. Non-replicating vaccines include whole mRNA that is artificially transcribed. The fact that they can be produced completely in- vitro is their greatest advantage.

In DNA-based vaccines the DNA that encodes the antigen is introduced into the body. Post that,the DNA on transcription will form mRNA that is translated to form the antigen. This antigen will then trigger a strong immune response [20]. It has an advantage over RNA-based vaccines as it can be stored for a longer time.

5.5 Virus-like particle Vaccines (VLPs)

They are proteins that imitate virus but has no viral genetic material and is not pathogenic butare capable of eliciting B and T cell mediated immunity.

6.Globally Approved Vaccines for COVID-19

A vaccine must go through three phases of trial before it gets approved [19]. Phase 3 of the trialwill have more individual under study compered to phase 1 and phase 2. Some of the globally approved vaccines for emergency use are listed below.BBV152 developed in India by Bharath Biotech, National Institute of Virology and Indian Councilof Medical Research has inactivated SARS-CoV-2 [20]. The Vaccine is reportedly 93.3 % effectivein individuals with severe symptoms and 78 % among asymptomatic individuals [19]. Further it was proved that administering a booster shot can make it effective against variants like delta and omega [20]. It targets the spike protein and is administrated as a single dose. It is available under the brand name Covaxin [WHO].

BNT162b2 is a vaccine developed by Pfizer-BioNTech. It is an mRNA vaccine that targets the spike protein. It has a reported 93% efficacy against the alpha variant and an overall efficacy of95% [19]. Two doses are administrated with a duration three weeks between them. Its trade name is Comirnaty.mRNA-1273 is a vaccine developed by National Institutes of Health and Moderna. It is an mRNA-based vaccine that is available under the brand name SpikeVax [WHO]. It encapsulatesSARS-CoV-2 in a lipid nanoparticle. It is 100% effective against the alpha variant and has an overall efficacy of 94.1%. Two doses are given with a gap of four weeks between them [19]. Ittriggers both humoral and cell mediated immune response.ChAdOx1 nCoV-19 is a vaccine developed by the Oxford University and AstraZeneca [20]. It is aviral vector vaccine that is non-replicating in nature [22]. It is available under the brand name Covishield in India. In the European Union it is manufactured under the name Vaxzevria. It induces IgG mediated response against the SARS-CoV-2 [19]. It showed 79% efficacy in phase 3trials. Two doses are given in twelve-week gap.Ad26.COV2.S is a vaccine developed by Johnson and Johnson [19]. It is a non-replicating virus vector vaccine that targets the spike protein of the SARS-CoV-2. It is manufactured under the trade name Jcovden [22]. It can trigger cellular and humoral immunity [20]. It is proven to have67% efficacy in phase 3 trial based at US. A single is administrated.Gam-COVID-Vac is a non-replicating viral vector type vaccine developed by Gamaleya Research Institute. It is marketed under the name Sputnik V [22]. It can evoke both humoral and cell- mediated immune response. The phase 3 trials showed a 91.6% efficacy [19]. With a time gap of three weeks, two doses are administrated. Studies has shown that there is no adverse effectafter vaccination.BBIBP-CorV is vaccine developed by The Beijing Institute of Biological Products. It is an inactivated virus vaccine which has shown 79% efficiency in phase 3 trials [19]. Two doses aregiven with a gap of 3 weeks in between the shots. There were rashes and swelling seen at thesite of injection. It can only trigger humoral immune response.Ad5-nCoV is a vaccine developed by The CanSino Biologics and the Institute of Biology. It is available under the brand name Convidecia [22]. It is a non-replicating virus vector vaccine. It activates CD4+ and CD8+ t cells [19]. It was reported to have side effects like headache, fatigue,and fever. It is a single dose vaccine with 65.28% efficiency.

CoronaVac is developed by Sinovac life sciences [19]. It has inactivated SARS-CoV-2 in it. It induces humoral immune response in most cases. Two doses are administrated in a gap of 2weeks. An overall efficiency of 50% was reported.Other than these there are a lot of vaccines that are available in clinical trials worldwide. Itincludes ZyCoV-D, AG0302-COVID-19, INO-4800, and so many other [19].

7.Conclusion

SARS-CoV-2 is a member of the coronavirus family that has caused the current COVID-19 pandemic. The virus is believed to have originated from Wuhan, China. Bats are considered to be the natural reservoirs of SARS-CoV-2. But so far, the intermediate host through which they reached humans are to be identifies. RaTG13 is a bat coronavirus that is believed to be the closest relative of the current virus. It is fast evolving virus and has undergone numerous mutation from when it was first identified. Among the identified variants some are considered as variants of interest and variants of concern. There are no approved drugs that are yet available for the treatment of the virus, though a combination of many antiviral drugs are used.The only way to stop the current pandemic is to immunize majority of the world population against this virus. There are about 50 vaccines that are approved globally. More than 5.6 billion people worldwide have received the vaccine.

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