1. Introduction

Coronaviruses (CoVs) are a group of viruses named after their crown-shaped spike proteins. Coronaviruses are known for infecting a broad range of classes in the Animalia kingdom, including humans, mice, snakes, and other vertebrates [37]. Till the mid-1960s only six human coronaviruses were known HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1s, severe acute respiratory syndrome coronavirus (SARS-CoV), and Middle East respiratory syndrome coronavirus (MERS-CoV) [29, 30]. These six HCoVs can be divided into two groups based on the severity of the infection they cause. Group A includes HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1 usually causes a less virulent disease, in one study HCoV-229E and HCoV-OC43 accounted for 15–29% of the respiratory pathogen with low virulence for humans [29, 30].

Group B includes SARS-CoV and MERS-CoV. These two have different pathogenicity but have a high fatality rate when compared to other members of coronaviruses. MERS-CoV caused renal failure and acute pneumonia in its first patient from Saudi Arabia in 2012. That virus infected 2494 people with 858 deaths reported from 27 countries with a case fatality rate (CFR) of 34.4%. SARS-CoV caused respiratory failure in patients firstly recognized and reported from China and infected 8422 people with 919 deaths from 32 countries between November 2012 and August 2013 with CFR of 11% [41]. Emerging at the end of 2019 in Wuhan, China, SARS-CoV-2 was initially recognized as a pneumonia-causing unknown agent related to coronavirus, after which it was declared as a Public Health Emergency by WHO on 30 January 2020. On 11 February 2020 WHO officially declared the name “COVID-19” for this novel coronavirus disease [13]. It has become an international calamity affecting over 32.1 million people worldwide with over 980,000 deaths overall and these numbers are still increasing day by day [38]. The countries severely affected by COVID-19 included the USA, India, Brazil, Russia, France, Italy, China, Spain, Germany, and in short the rest of the world, however, the highest deaths...
are being reported from the USA, India, Italy, France, Spain, and UK [39]. The new variant SARS-CoV-2 causes severe acute respiratory syndrome and leads to death [26]. On 22 April, CFR worldwide of COVID-19 is calculated to be 6.89% [39] compared to on March 3 was 3.4% [38]. However, if we take account of mortality rate between different countries for example, in Italy the virus has a mortality rate of 7.2% vs 2.1% in China. According to current information, the suggested source of SARS-CoV-2 is likely bats (it is normally host to many CoVs), but there is no absolute evidence on its origin [2].

Coronaviruses have been known for years since the 1960s but how long they had existed is not known. Commonly they cause mild disease, but some highly pathogenic strains do occur that are noted by being given a distinct name after causing an outbreak. COVID-19 is the current pandemic the whole world is fighting. The pathogenesis of this novel virus is still unclear. In this article, we aim to discuss the transmission, pandemic, genetic diversity, and antiviral treatments, and precautionary measures against COVID-19.

2. Pathogenesis of coronaviruses

CoVs enters a human body when coming in contact with a source animal, or infected human body fluids via sneezing droplets, coughing, sharing food, touching virus soiled inanimate objects, etc. In the case of SARS-CoV2, the virus will bind to Angiotensin converting enzyme 2 (ACE2) in the lower respiratory tract of an infected individual using its spike (S) proteins [9, 10]. For SARS-CoV, only single stranded (ss) positive sense RNA genome is released inside the cytoplasm of a cell through fusion between a host cell’s membrane and the virus [28]. But the same entry mechanism used by SARS-CoV-2 still needs to be confirmed. Once inside the cell ss+RNA act as mRNA and the host ribosome initiates translation of viral proteins: two polyproteins and structural protein (NS and S) which help in viral genomic replication and capsid formation [23]. Newly formed envelope glycoprotein migrate to the Golgi apparatus or Endoplasmic reticulum (not shown in figure 2), after which packaging of viral RNA inside a capsid occurs [9]. Once the virion particles are mature they are released through lysis or exocytosis from the cell. Due to lack of knowledge about this new virus and lack of detailed insight about which proteins are involved in causing host cell disruption and overcoming the host immune system, no particular treatment is present for it.

3. Genetic diversity

SARS-CoV-2 was previously shown to be a close relative of SARS-CoV and their Receptor binding domain of S-proteins also resemble each other [15]. The known differences in proteins encoded by both viruses are presented in table I. The phylogenetic trees’ comparison has shown that SARS-CoV-2 is most closely related to the SARS-like bat viruses than human SARS-CoV [19]. Whole genome sequences of SARS-CoV-2 and coronavirus of bats has shown 96% similarities [40].

<table>
<thead>
<tr>
<th>Protein</th>
<th>SARS-CoV</th>
<th>SARS-CoV-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>8a</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>8b</td>
<td>84 amino acids</td>
<td>121 amino acids</td>
</tr>
<tr>
<td>3b</td>
<td>154 amino acids</td>
<td>22 amino acids</td>
</tr>
</tbody>
</table>

The coronaviruses are the largest RNA viruses, with a genome size range of 26–32 kb [8]. A variable number of ORF (open reading frames), in the range of 6 to 11, exists in the genome of the coronavirus, ORF’s are shown in figure 3. The 1st ORF, which is 67% of the whole genome, encodes 16 non-structural proteins. Genes for eight accessory proteins and four structural proteins are encoded at the 3’ terminus of RNA, while genes encoding orf1a and orf1b proteins (comprise non-structural proteins) are located at the 5’ terminus [15, 40]. There are five structural genes E, N, M, SM, and S, which encode envelope, nucleocapsid, membrane glycoprotein, small membrane protein, and spike protein, respectively [32]. N-proteins of SARS-CoV and SARS-CoV-2 have a 90% similarity in sequences.
Fig. 2. General mode of replication of SARS-CoV. Starting with the attachment of viral S protein, present on the envelope, with ACE-2 receptor on lung cells the viral RNA is released inside the cytoplasm through membrane fusion. Once inside the cell +ssRNA act as mRNA and the host ribosome will start making viral proteins (2 polyproteins and structural protein) which help viral genomic replication and capsid formation, after which packaging of viral RNA inside a capsid occurs. Once the virion particles are mature they are released through lysis or exocytosis.

Fig. 3. ORF’s of the genome of HB01 strain of SARS-CoV-2 (previously called 2019-nCoV) are shown. Structural proteins are encoded at the 3’ terminus and non-structural at the 5’ terminus (Modified from [40]).
The N-protein of SARS-CoV acts as a viral suppressor protein of RNAi, to overcome the host immunity. The N-protein of SARS-CoV-2 can also have the same effect [15, 34]. The functions of non-structural proteins (Nsp) of coronaviruses are mentioned in table 2, except Nsp 2 and 11, whose functions are currently unknown.

### 4. Transmission

The natural host reservoir for SARS-like coronaviruses are reported to be bats, the intermediate host for the viruses are reported to be civets or camels and then they are transmitted to humans hence these viruses are capable of a host-species jump [16]. One of the major transmission routes of SARS-CoV-2 is human-to-human transmission within close contact and has caused an exponential increase in the number of cases. Aerosol transmission happens when an infected person coughs or sneezes shedding the virus in the air and touching inanimate objects infected with the virus are possible transmission routes [14, 17].

The current epidemic started when the earliest patients who went to Huanan seafood market in Wuhan city, Hubei province, China got infected with SARS-CoV-2 after coming in contact with some animals; the intermediate animal source is yet to be confirmed. These infected patients became a source of infection for other healthy people [20]. Reportedly a large number of infected people did not have exposure to the seafood market so it is likely they got infected from the earliest patients hence person-to-person contact became a major reason for the spread of this epidemic [5]. The reason why coronavirus caused havoc throughout the world and became a cause of lockdown in multiple countries is its high transmission rate [3].

One recently published study indicated a whole family of 6 was infected with this novel coronavirus although none of the family members visited the Wuhan seafood market, only 2 persons of the family visited Wuhan hospital where they might have caught the virus from infected patients. From the two infected family members the whole family got infected. Real time RT-PCR was used to test the RNA extracted from patient samples with new coronavirus virus specific primers and probes [17]. The patients had symptoms such as fever, upper or lower respiratory tract infections however, older patients (> 60 years) showed more systemic symptoms [5].

A recent report suggested that the virus can also take an ocular route of transmission [18].

### Table III

<table>
<thead>
<tr>
<th>Vaccine strategy</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRNA vaccines</td>
<td>Easy preparation,</td>
<td>High unstable under physiological conditions</td>
<td>[24]</td>
</tr>
<tr>
<td></td>
<td>High Adaptability,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Can induce strong immune responses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DNA vaccines</td>
<td>Easy preparation</td>
<td>Low immune responses</td>
<td>[24]</td>
</tr>
<tr>
<td></td>
<td>Neutralizing antibodies with high titer</td>
<td>May induce toxicity with repeated doses</td>
<td></td>
</tr>
<tr>
<td>Viral vector vaccines</td>
<td>Induces high humoral and cellular immune responses</td>
<td>Pre-existing immunity will be a problem</td>
<td>[11]</td>
</tr>
<tr>
<td>Subunit vaccines</td>
<td>Neutralizing antibodies with high titer,</td>
<td>High cost</td>
<td>[11]</td>
</tr>
<tr>
<td></td>
<td>Induces high humoral and cellular immune responses</td>
<td>Low immunity, Repeated doses may require</td>
<td></td>
</tr>
<tr>
<td>Attenuated virus vaccines</td>
<td>Quick development,</td>
<td>Genotypic &amp; phenotypic reversion possible</td>
<td>[25]</td>
</tr>
<tr>
<td></td>
<td>High immune responses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactivated virus vaccines</td>
<td>Easy preparation,</td>
<td>Not applicable for immunosuppressed individuals</td>
<td>[25]</td>
</tr>
<tr>
<td></td>
<td>Neutralizing antibodies with high titer</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
transmission is not found to be a route for this virus, as pregnant women with COVID-19 had virus negative newborns [6]. The best way suggested by the World Health Organization to limit the epidemic is by social distancing along with practicing good hygiene such as washing your hands regularly and wear protective masks.

5. Vaccination strategies against COVID-19

A study found a correlation between the universal BCG vaccine policy and reduced mortality and morbidity ranges for COVID-19. They found that countries without a universal BCG vaccine policy were more adversely affected by the pandemic compared to

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Vaccine candidate</th>
<th>Phase trials [31]</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderna</td>
<td>DNA-based vaccines which code or a stabilized form of SARS-CoV-2 spike protein</td>
<td>Phase 3 starts in the 1st week of July. It will include the study of 30,000 patients</td>
<td>[4]</td>
</tr>
<tr>
<td>Curevac</td>
<td>Lab-made RNA to spur the production of corona proteins</td>
<td>Begins the human trials</td>
<td><a href="https://www.curevac.com/en/covid-19/">https://www.curevac.com/en/covid-19/</a></td>
</tr>
<tr>
<td>Inovio</td>
<td>DNA-based vaccines</td>
<td>Human trials to start in later June</td>
<td><a href="https://www.inovio.com/our-focus-serving-patients/covid-19/">https://www.inovio.com/our-focus-serving-patients/covid-19/</a></td>
</tr>
<tr>
<td>Takis Biotech</td>
<td>DNA-based vaccines</td>
<td>Results of dose-response trials to be published in June</td>
<td>[27]</td>
</tr>
<tr>
<td>Zydus Cadila</td>
<td>DNA-based vaccines</td>
<td>Project is in pre-clinical trials</td>
<td><a href="https://zyduscadila.com/">https://zyduscadila.com/</a></td>
</tr>
<tr>
<td>Stemirna Therapeutics</td>
<td>mRNA-based vaccines</td>
<td>Clinical trials expected to start in Mid-April</td>
<td><a href="http://www.stemirna.com/en/index.aspx">http://www.stemirna.com/en/index.aspx</a></td>
</tr>
<tr>
<td>Imperial College London</td>
<td>DNA-based vaccines</td>
<td>Human trial started</td>
<td><a href="https://www.imperial.ac.uk/covid-19-vaccine-trial/">https://www.imperial.ac.uk/covid-19-vaccine-trial/</a></td>
</tr>
<tr>
<td>Vaxart</td>
<td>Oral vaccine half of 2020</td>
<td>Phase I begins in the second</td>
<td><a href="https://vaxart.com/">https://vaxart.com/</a></td>
</tr>
<tr>
<td>University of Saskatchewan</td>
<td>A protein-based candidate</td>
<td>Animal trials</td>
<td><a href="https://www.vido.org/covid19/covid-19-news/">https://www.vido.org/covid19/covid-19-news/</a></td>
</tr>
<tr>
<td>Sanofi</td>
<td>Recombinant DNA platform swapping the part of corona-virus with genetic material from a harmless virus</td>
<td>Phase 1 to be started in the last quarter of 2020</td>
<td><a href="https://www.sanofi.com/en/about-us/our-stories/sanofi-s-response-in-the-fight-against-covid-19">https://www.sanofi.com/en/about-us/our-stories/sanofi-s-response-in-the-fight-against-covid-19</a></td>
</tr>
<tr>
<td>Geovax Labs/ Bravovax</td>
<td>Develop a live horsepox virus which will be modified to express protein fragments from SARS-CoV-2</td>
<td>Pre-clinical stage</td>
<td><a href="https://www.geovax.com/news/geovax-progresses-in-coronavirus-covid-19-vaccine-development-program">https://www.geovax.com/news/geovax-progresses-in-coronavirus-covid-19-vaccine-development-program</a></td>
</tr>
<tr>
<td>Cansino Biologics</td>
<td>Viral vector-based vaccine</td>
<td>Phase II – All volunteers developed neutralizing antibodies</td>
<td>[42]</td>
</tr>
<tr>
<td>Greffex</td>
<td>DNA-based vaccines: Adenovirus based vector vaccines that involve a harmless virus that will express foreign genes like SARS-CoV-2 spike protein</td>
<td>Pre-clinical stage</td>
<td><a href="https://www.greffex.com">https://www.greffex.com</a></td>
</tr>
<tr>
<td>Generex Biotechnology</td>
<td>The firm uses insect cells from fruit flies to produce viral antigens</td>
<td>Ex-Vivo Human Immune System screening of 33 li-Key-SARS-CoV-2 peptides</td>
<td><a href="https://www.generex.com/covid-19">https://www.generex.com/covid-19</a></td>
</tr>
</tbody>
</table>
countries having a universal BCG vaccine policy. They also found that BCG vaccination reduced the number of cases in a country [21].

6. In process vaccination strategies against COVID-19

Vaccines help the body enhance the immune response by triggering the generation of antibodies in addition to the development of T and B cells. Vaccines induce active immunity and provide immunological memory which enables the immune system to remember and respond rapidly in case of exposure. Vaccines often provide long-lasting immunity, but sometimes they don't. Scientists at research institutes are working on the development of vaccines all over the world. Vaccine development can take a minimum of 18 months.

7. Lack of antiviral treatment and antiviral treatment studies

In current times, there is no specific antiviral therapy to control this virus only supportive treatment for the coronavirus. Recombinant interferon only has a limited response with ribavirin against a coronavirus infection. The two viral protein inhibitors as an available option of treatment are Baricitinib (Janus and AAK1 kinases inhibitor) and Remdesivir (adenosine analog) [12].

The other antiviral drugs like chloroquine and hydroxychloroquine show an effective response against this virus. The drug chloroquine was first identified in 1934 which is used against SARS-CoV infection, also used to treat other human diseases such as malaria, amoebiosis, HIV, and autoimmune diseases without any side effects.

Leronlimab (CCR5 antagonist) and Galidesivir (nucleoside RNA-polymerase inhibitor) are other possible treatment options [34]. According to guidelines, Interferon-alpha (IFN-alpha) and lopinavir-ritonavir (combined therapy) are recommended antivirals. Chinese medicines, tested to treat influenza H1N1, such as Lianhua Qingwen and ShuFeng Jiedu capsules are also tested against SARS-CoV-2 [7, 18].

The compounds tryptanthrin and indigodole B extracted from the plant Strobilanthes cusia, can reduce the cytopathic effects of human coronavirus NL63. *S. cusia* has also been used to treat SARS-CoV. The spikes of NL63 and SARS-CoV-2 are genetically identical. Hence, *S. cusia* can also be a treatment option for SARS-CoV-2 [33].

Recovering patients' plasma and antibodies are proposed for treatment. Some vaccine strategies are assessed in animals, including recombinant proteins, DNA vaccines, live and killed attenuated vaccines, and subunit vaccines [6].

8. Precautions

As the virus spread increases with each passing day we have to minimize the transmission cycle by following the different precautionary measures as suggested by the World Health Organization:

- Avoid contact with suspected people.
- Ensure social and physical distancing to prevent the transmission of disease.
- Use of protective surgical masks in public.
- Proper hand washing with sanitizer after every ten minutes.
- Use a mask at all times within an airport facility and outside while traveling.
- Avoid crowded places.
- Avoid contact with unwell people (having flu or cough like symptoms).
- Avoid traveling overseas.
- Ensure good hygiene (wash hand frequently with soap).
- Avoid eating raw or undercooked meat of any type.
- Avoid contact with animals.

9. Conclusion

Coronaviruses are +ssRNA viruses with 7 human coronaviruses, they mainly affect the respiratory system. Group B coronaviruses are the main concern for researchers as it includes the causative virus of the SARS-CoV-2 epidemic. This virus has a high pathogenicity and high virulence rate [41]. SARS-CoV-2 has now spread all around the Globe and is declared a public health emergency by WHO. Its sequence was found to be 96% similar to coronaviruses found in bats [43].

The high transmission rate of the virus is the main concern. Research has been conducted to find effective measures in controlling the speed of the disease with one study reported to minimize person-to-person contact rate to 30% [35]. Real Time Polymerase chain reaction (PCR) with new coronavirus virus-specific primers and probes is the main diagnostic test used to test RNA extracted from a patient [17].

The most commonly reported clinical manifestations are fever, cough, fatigue, and pneumonia. Patients with mild cases recover early, mostly after one week, while serious cases lead to alveolar damage which causes progressive respiratory failure and ultimately leads to death [1]. The genomic nature of this virus is single-stranded RNA which makes it harder to develop vaccines and yet no approved vaccine exists.

Many research groups around the world are working to make vaccines and antivirals as explained in the vaccination and antiviral section above. Some antivirals
that have shown in-vitro results against novel coronavirus include chloroquine and remdesivir [36] but the virus has error-prone RNA dependent RNA polymerases that are responsible for mutations and recombination events which are of major concern.

References


