REVIEW ARTICLE

CORONAVIRUS DISEASE 2019 (COVID-19): PUBLIC HEALTH EMERGENCY

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ABSTRACT

An outbreak of a respiratory sickness started in Wuhan, China in December 2019 and the causative agent was found to be a novel betacoronavirus of the same subgenus as SARS-CoV and named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Coronavirus disease 2019 (COVID-19) quickly spread around the world, with clinical signs ranging from mild respiratory symptoms to severe pneumonia and a fatality rate estimated around 2%. Lower respiratory tract infections can occur in immunocompromised subjects and the elderly persons. Respiratory droplets are the causative agent for the person-to-person spread of the disease resembling the spread of influenza. Individual to individual spread turned into the primary mode of transmission. The transmission of the disease might be more likely in the earlier stage of infection as the viral RNA levels appear to be higher. Accurate diagnosis in the early stages of the epidemic helps control the spread of the disease.

Keywords: Betacoronovirus, Coronavirus disease 2019 (COVID-19), Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), Mode of Transmission, Preventive Measures

INTRODUCTION

As per the World Health Organization (WHO), viral diseases proceed to develop and represent a serious issue to general wellbeing. The severe acute respiratory syndrome coronavirus (SARS-CoV) and H1N1 influenza have been considered viral epidemics over the most recent twenty years. In 2012, the Middle East respiratory syndrome coronavirus (MERS-CoV) was first detected in Saudi Arabia1. In December 2019, an outbreak of respiratory sickness started in Wuhan, China, and a novel beta coronavirus was identified as the causative agent. In January 2020, it was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Coronavirus disease 2019 (COVID-19) has quickly spread worldwide with clinical signs of mild respiratory symptoms to severe pneumonia. The fatality rate was estimated at around 2% and increased gradually with the age. The death percentage in old age people above 80 years is around 14.8% and it is 0.2% in ages between 10 to 39. Individual to individual transmission is happening both in the community and healthcare settings. The WHO has recently declared the COVID-19 epidemic a public health emergency of universal concern2.

At present, cases of COVID-19 have been found in numerous nations around the globe. As per the report, up to the 1st of April 2020, the number of affirmed cases in China reached 81,590 of which 3,319 were dead, and 76,238 were cured. The number of confirmed cases in the world reached 879,675 of which 43,944 were dead, and 183,665 were cured3. On the 31st of January, 2020, the WHO announced that COVID-19 was recorded as the Public Health Emergency of International Concern (PHEIC), implying that it might pose risks to different nations and requires a coordinated international response4. Later, 20,000 cases were confirmed and almost 1000 deaths have been reported in the European Region by the morning of 12 March 2020. This made WHO’s Director-General, Dr. Tedros Adhanom Ghebreyesus announce COVID-19, as a pandemic5. Globally, as of 1st July 2022, there have been 545,226,550 confirmed cases including 6,334,728 deaths reported to WHO6.

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The most up-to-date source for the epidemiology of this emerging pandemic can be obtained from official sources such as the WHO Novel Coronavirus (COVID-19) Situation Board and the Johns Hopkins Center for Systems Science and Engineering site for Coronavirus Global Cases COVID-19 as depicted in Table I which uses openly public sources to track the spread of the epidemic. COVID-19 is a serious disease of international concern\textsuperscript{6,7}.

**ORIGIN AND CLASSIFICATION**

CoVs are derived from the Latin word Coronam, which means crown. It is a positive-stranded RNA virus. Virus appears like a crown under the electron microscope and the spike glycoprotein on the envelope is responsible for the crown shape of the virus. CoV belongs to the subfamily Orthocoronavirinae of the family Coronaviridae and order Nidovirales. Alpha, beta, delta, and gamma CoVs are the four genera of the subfamily. Beta CoVs are again divided into five sub-genera or lineages (Fig. 1)\textsuperscript{8,9}. Alpha and beta CoVs are the two predictable gene sources for rodents and bats. Whereas delta and gamma CoVs are the probable gene sources for avian species. Seven human CoVs (HCoVs) have been identified so far. Some HCoVs were detected in the mid-1960s and the rest in the new millennium. 2% of the population are healthy carriers of a CoV. Acute respiratory infections occur in 5% to 10% of the population\textsuperscript{6}. HCoVs such as HCoV-229E, HCoV-NL63, and beta CoVs of the A lineage like HCoV-OC43, and HCoV-HKU1 are the source of common cold and self-limiting upper respiratory infections in immune-competent individuals. However, Immunocompromised and elderly persons suffer from lower respiratory tract infections. Other beta HCoVs of the B and C lineage such as SARS-CoV, SARS-CoV-2, and MERS-CoV spread epidemics which include various respiratory and extra-respiratory infections. The mortality rates are 10% and 35% in cases of SARS-CoV and MERS-CoV, respectively. The survivors with SARS-CoV-2 having clinically significant COVID-19 disease were not observed with long-term complications. The mortality rate was between 1% to 2% worldwide\textsuperscript{1}. COVID-19 shows clinical symptoms such as fever, nonproductive cough, fatigue, dyspnea, myalgia, normal or diminished leukocyte counts, and radiographic evidence of pneumonia\textsuperscript{10,11}. Adult males are more preferentially infected with SARS-CoV-2 than children\textsuperscript{12,13}. By some estimates, it has a higher reproductive number than SARS\textsuperscript{14}, and more people have been reported to have been infected or died from it than SARS\textsuperscript{15}.

**Genomics and gene sequencing**

CoV is an unsegmented, single-stranded, positive sense RNA genome of around 30 kb. It is 29,891 bp long, with a G+C content of 38%, and enclosed by a 5'-cap and 3'-poly(A) tail\textsuperscript{16,17}. An envelope containing viral nucleocapsid covers the virus. The positive sense RNA is attributed to the helical symmetry in the arrangement of the nucleocapsid\textsuperscript{16}. The electron micrographs of SARS-CoV-2 revealed a diverging spherical outline with some degree of pleomorphism. The diameters of virion are varying from 60 to 140 nm. The solar structure of CoV is due to the presence of distinct spikes of 9 to 12 nm\textsuperscript{18}. The CoV genome is arranged linearly as 5'-leader-UTR-replicate-structural genes (S-E-M-N)-3' UTR-poly(A)\textsuperscript{19}. It also contains accessory genes, such as 3a/b, 4a/b, and the hemagglutinin-esterase gene (HE)\textsuperscript{16}. SARS-CoV-2 is similar in genomics but lacks HE which is the characteristic of some beta CoVs\textsuperscript{17}. The positive-sense genome of CoVs serves as the mRNA. The polyprotein gene 1a/1ab (pp1a/1ab) formation may occur by translation through mRNA\textsuperscript{20}. The nonstructural proteins (nsp), encoded by the polyprotein gene form a replication-transcription complex (RTC) in double-membrane vesicles (DMVs)\textsuperscript{21}. Subsequently, a nested set of subgenomic RNAs (sgRNAs) is synthesized from RTC by a discontinuous transcription process\textsuperscript{22}. There are four important structural proteins such as spike (S), membrane (M), envelope (E), and nucleocapsid (N) which are encoded by CoVs (Fig. 2). The S protein is large and functional. The arrangement of the trimer on the virion surface gives a crown-like appearance. It is also considered a class I viral transmembrane protein. Interaction of this protein with the host cell receptor enables the infectious virion particles to enter the cell. The M protein is the most abundant viral protein. It gives a definite shape to the viral envelope. The E protein is the most enigmatic and smallest. The N protein is multipurpose. It plays a role in complex formation with the viral genome. It also enhances the transcription efficiency by facilitating the M protein interaction during virion assembly. SARS-CoV-2 genome also contains 15 nsp, nsp1 to nsp10 and nsp12 to nsp16, and 8 accessory proteins (3a, 3b, p6, 7a, 7b, 8b, 9b, and ORF14). All these proteins play a specific role in viral replication\textsuperscript{6,12,15,23-26}.

**Mutation in coronavirus**

Coronavirus (Fig. 2) just like other viruses holds a simple structure and has long RNA polymerase tightly packed into the core surrounded by a protective protein layer known as capsid or nucleocapsid. There is protein structure projecting out of envelope are known as spikes or peplomers. The spikes help the virus adhere to the host cells and get into the host. While multiplying or replication there can be slight changes during the replication or reading codons due to alterations or missing codons,
Table I: Name of the official sources for COVID-19

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Name of official source</th>
<th>Weblink</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>The Johns Hopkins Center for Systems Science and Engineering site for Coronavirus Global Cases COVID-19</td>
<td><a href="https://coronavirus.jhu.edu">https://coronavirus.jhu.edu</a> › map</td>
<td>7</td>
</tr>
</tbody>
</table>

Table II: Vaccines offered in India

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Brand name</th>
<th>Mfg. by</th>
<th>Vaccine type</th>
<th>Age range</th>
<th>Efficacy (Highest)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Covishield</td>
<td>Astrazeneca (Oxford)</td>
<td>Non-Replicating viral vector</td>
<td>18+</td>
<td>91%</td>
<td>109</td>
</tr>
<tr>
<td>2</td>
<td>Covaxin</td>
<td>Bharat Biotech</td>
<td>Inactivated</td>
<td>14&lt;</td>
<td>77.8% (In adults &gt;60) 93% overall</td>
<td>110</td>
</tr>
<tr>
<td>3</td>
<td>Moderna</td>
<td>NIAID</td>
<td>RNA</td>
<td>18+</td>
<td>90%</td>
<td>111</td>
</tr>
<tr>
<td>4</td>
<td>Sputnik V</td>
<td>Gamaleya Research Institute</td>
<td>Non-Replicating Viral vector</td>
<td>12&lt;</td>
<td>91.6%</td>
<td>112</td>
</tr>
<tr>
<td>5</td>
<td>Johnson &amp; Johnson</td>
<td>Janssen Pharmaceuticals</td>
<td>Non-Replicating Viral vector</td>
<td>18+</td>
<td>82%</td>
<td>113</td>
</tr>
<tr>
<td>6</td>
<td>Novavax</td>
<td>Novavax</td>
<td>Protein Subunit</td>
<td>18+</td>
<td>90.4%</td>
<td>114</td>
</tr>
<tr>
<td>7</td>
<td>ZyCov D</td>
<td>Cadila Healthcare Ltd.</td>
<td>DNA based vaccine</td>
<td>12-18 yrs</td>
<td>90% or higher</td>
<td>115</td>
</tr>
</tbody>
</table>

and deletion of amino sugars leading to the formation of an altered protein structure. There can be misreading of amino groups during the transcription or translation process. As the virus replication and multiplication is a repetitive process, the chances of variation or mutation also increase. This mistake leads to changed information, making slightly changed viruses with variations known as variants. Mutation does not change the mechanism much but may alter transmissibility adherence to a host that may or may not be more lethal than the previous one. Even though the mutation may appear in the entire genome of the virus’s RNA when the subset is observed a small potion can be easily noticed in the spike proteins. The spike proteins act as an antigen for the preparation of vaccination and thus play a crucial role in the study of viruses and vaccine preparations. Virus keeps multiplying themselves inside the human host but they are not competent enough to carry out the multiplication so they use the host cells. They depend on host cell metabolism, proteins introduce their RNA or viral DNA to replicate and form proteins into a cell. Any change in the protein structure will need different vaccine preparations, studies, and measures27, 28.

COVID variants

The variant is slightly different from the same entity. In the case of the SARS-CoV 2 virus, it is a mutation in viruses that they adapt to survive in the changing environment; every time a virus is transferred from one person to another, there is a change in the strains. Few variants are as follows29:

1. α Variants (Alpha variants) from the UK, aka B.1.1.7.
2. β Variants (Beta variants) from South Africa aka B.1.351. Found in parts of Nigeria. It is more easily transmissible but less than the original variants.
3. γ Variants (Gamma variants) from Brazil aka P.1. These are first detected in Brazilian people traveling to Japan in Jan 2021. These are observed to be more contagious than their preceding variants.
4. Δ Variants: From India aka B.1.617.2. It is about 50% more contagious/transmissible and more lethal variants than the actual virus.
5. Ω (Omicron): From South Africa aka B.1.1.529 was reported to WHO on November 2021 to be less lethal than its previous variants.
Fig. 1: The phylogenetic tree of Coronavirus (representative CoVs, with the new coronavirus 2019-nCoV)\textsuperscript{8,9}

Fig. 2: Structure of Coronavirus\textsuperscript{9,12,15,23-26}
Fig. 3: Predicted infection from COVID-19 in INDIA. Total infections (asymptomatic+ hospital+ symptomatic)\(^{106}\)

Fig. 4: Predicted hospitalizations from COVID-19 in INDIA (hospitalized cases)\(^{106}\)
CLINICAL MANIFESTATIONS

Much like the manifestations of SARS-CoV and MERS-CoV infections, patients with positive COVID-19 show clinical symptoms such as fever, nonproductive cough, fatigue, dyspnea, myalgia, normal or diminished leukocyte counts, and radiographic evidence of pneumonia\textsuperscript{12,14,30,31}. Less common symptoms include headache, dizziness, abdominal pain, diarrhea, nausea, and vomiting\textsuperscript{12,30}. Pregnant and non-pregnant women have similar characteristics\textsuperscript{32}. Common laboratory abnormalities found in COVID-19 patients are lymphopenia \textsuperscript{25,26,33} prolonged prothrombin time, and elevated lactate dehydrogenase\textsuperscript{30}. ICU-admitted patients had more laboratory abnormalities\textsuperscript{12,30}. Some patients had elevated aspartate aminotransferase, creatine kinase, creatinine, and C-reactive protein\textsuperscript{12,33,34}. Most patients showed normal serum procalcitonin levels\textsuperscript{12, 30,33}.

PATHOGENESIS

Even though the pathogenesis of COVID-19 is ineffectively comprehended, the similar mechanisms of SARS-CoV and MERS-CoV still can give us a great deal of data on the pathogenesis of SARS-CoV-2 contamination to encourage our recognition of COVID-19\textsuperscript{35}, although the analysis of the risk associated with the transmission rate is incomplete. Epidemiologic investigation in Wuhan towards the start of the outbreak recognized an underlying relationship with a seafood market that sold live animals. Subsequently, the market was closed for disinfection since most patients had worked or visited\textsuperscript{36}. The progression of COVID-19 was due to the primary mode of transmission which is attributed to individual-to-individual spread. It is estimated that the respiratory droplets are the causative agent for the person-to-person spread of SARS-CoV-2 resembling the spread of influenza. The virus gets discharged in the respiratory secretions because of droplet transmission. A person can be infected when he or she comes into direct contact with the mucous membrane of the infected person while talking, sneezing, and coughing. When a person touches his or her eyes, nose, or mouth after touching the infected surface can cause infection. Droplets generally do not linger in the air and travel not exceeding two meters (about six feet)\textsuperscript{37}. The size of the droplets also determines the severity of the respiratory infection. Respiratory droplets are \( > 5-10 \mu m \) in diameter whereas droplet nuclei are \( \leq 5 \mu m \) in diameter\textsuperscript{38}. As per the literature the mode of primary transmission was through respiratory droplets and contact routes\textsuperscript{39,40,41,42,12,34}. Droplet transmission refers to the presence of microbes within droplet nuclei. Droplets travel over distances greater than 1m and remain for a longer period in the air. Hence airborne transmission is different from droplet transmission. As the mechanism of transmission is uncertain, airborne precautions are recommended routinely in some countries. Infected droplets can spread 1–2 m and deposit on surfaces. In favorable atmospheric conditions, the virus can remain viable on surfaces for days. However, common disinfectants like sodium hypochlorite, hydrogen per-oxide, etc. can destroy the virus in less than a minute\textsuperscript{43}. The virus is also present in the stool. Water contamination with subsequent transmission of the infection through aerosolization/feco oral route is also assumed\textsuperscript{44}. Transplacental transmission from pregnant women to their fetus is not clear till now but the post-natal transmission is described\textsuperscript{45}. The incubation period varies from 2 to 14 d [median 5 d]. The virus enters the respiratory mucosa via angiotensin receptor 2 (ACE)\textsuperscript{46}. It mainly affects the respiratory system of our body such as the nasopharyngeal tract and lungs because the ACE2 receptor is highly present in those areas to which spikes of SARS-CoV-2 bound. The life cycle of the virus with the host consists of 5 steps; attachments(A), penetration(P), biosynthesis(B), mutation(M), and release(R). Once viruses bind to host receptor(A), they enter into host cells through endocytosis or membrane fusion(P). Viral content is released inside the host cells and the viral RNA enters the nucleus for replication. The viral mRNA converts itself into viral proteins through translation. The new viral proteins are made and get mutated(M) inside the host cell, replicate, and released(R) outside for the new host\textsuperscript{47}.

TRANSMISSION

The transmission of the disease is faster at the initial stage due to higher viral RNA levels soon after the onset of symptoms in comparison to the later stage of infection\textsuperscript{48}. Additional data are yet to produce for confirmation of this hypothesis. The transmission rate might be influenced by infection control interventions and locations in the case of an individual with symptomatic infection. The secondary transmission rate is documented to be from 1 to 5 percent among tens of thousands of close contacts of confirmed patients in China as indicated by a joint WHO-China report\textsuperscript{49}. The symptomatic secondary attack rate was found to be 0.45 percent in the U.S.\textsuperscript{50}. Transmission of SARS-CoV-2 has also been reported from asymptomatic individuals or individuals within the incubation period but the degree to which it occurs stays obscure\textsuperscript{51,52,53,54,33}. A few serological tests are under development. Serologic screening may provide information on the epidemiologic analysis and asymptomatic infection\textsuperscript{55}. RNA sample has been detected in blood and stool specimens in the case of SARS-CoV-2 infection\textsuperscript{56,57}. In some cases, the live virus has been cultured from stool\textsuperscript{58}. At room temperature, the
virus is stable in faeces and urine for at least 1-2 days. In stool of diarrhea patients who have higher pH than normal stool, the virus is stable for up to 4 days. Further infection can be prevented by the use of disinfectants and fixatives. The minimal reduction in virus concentration is observed after 21 days at 4°C and -80 °C. For quick reduction in virus concentration, it should be heated at 56 °C at around 10000 units per 15 mins. SARS-CoV-2 is more stable than HCoVs as one log reduction in virus concentration was observed at stable room temperature\(^6\). The spread of infection was not due to fecal or oral transmission as reported jointly by WHO-China\(^4\).

**DIAGNOSIS**

COVID-19 is diagnosed by auxiliary examinations such as nucleic acid detection, immune identification technology Point-of-care Testing (POCT) of IgM/IgG, enzyme-linked immunosorbent assay (ELISA), CT scan, and blood culture. Clinical manifestations of the infection are based on epidemiological history. However, the patients are showing atypical clinical symptoms such as respiratory symptoms, cough, fever, dyspnea, viral pneumonia, etc. Hence, auxiliary examinations are necessary along with the epidemiological history for diagnosis\(^4\). The availability of testing will vary based on which country a person lives in and the increasing number of cases on daily basis also affects the availability of the testing. A normal or decreased total white blood cell count can be observed in the early stage. Total lymphocyte count also decreases at the initial stage.

The ARDS (Acute Respiratory Stress Syndrome) in COVID-19 is due to the occurrence of cytokine storms that results in exaggerated immune response, immune regulatory network imbalance, and, finally, multiple-organ failure\(^6\). It is reported that the liver enzymes, LDH, muscle enzymes, and C-reactive protein level are increased, whereas lymphopenia appears to be a negative prognostic factor. Patients in critical condition show increased D-dimer value but the procalcitonin level is normal. Decreased blood lymphocytes count and multiorgan imbalance such as high amylase and coagulation disorders were also found in critical conditions. Some epidemiologic and clinical information is required to determine who should have testing performed. Certain criteria are fixed in the U.S. to put the persons under investigation (PUI). Patients with positive COVID-19 have developed symptoms of acute respiratory illness such as cough, and difficulty breathing with fever as reported by the U.S. CDC. PUI are put in place of infection control and prevention measures immediately after a recommendation and tested for other sources of respiratory infection. In addition to the exaggerated inflammatory response, hepatic tissue injury is also seen in patients with COVID-19 due to compensatory proliferation of hepatocytes and upregulation of ACE2 expression\(^6\). Epidemiologic factors were used for the confirmation of COVID-19. Within 14 days of symptom onset, the person who was in close contact with a laboratory-confirmed COVID-19 patient or has a history of travel from affected geographic areas like China, Italy, Iran, Japan, South Korea, etc. are included under epidemiologic factors\(^1\).

The WHO recommends collecting specimens from both the lower respiratory tract such as expectorated sputum, endotracheal aspirate, or bronchoalveolar lavage (BAL) and the upper respiratory tract (nasal- and oropharyngeal samples). Mechanically ventilated patients were subjected to the collection of BAL samples as lower respiratory tract samples seem to remain positive for a longer period. Collected samples were stored at a temperature of 4 °C. Reverse polymerase chain reaction (RT-PCR) technology is used for the amplification of the genetic materials extracted from the collected samples. Subsequently, a double-stranded DNA molecule from an RNA mold is developed through this process. The genetic code particularly for CoV is conserved after sufficient development of genetic material. The probes used are based on the initial gene sequence released by the Shanghai Public Health Clinical Center & School of Public Health, Fudan University, Shanghai, China on Virological.org. It was subsequently followed by confirmatory evaluation by additional labs. In case of a positive result, the test is repeated for verification. Viral clearance is required before release from observation. It is evaluated by repeating the laboratory tests in case of positive COVID-19 diagnosed patients\(^1\).

Clinically proven specific antiviral agents are not available for SARS-CoV-2 infection\(^62,63\). The important supportive treatment like the use of broad-spectrum antibiotics to cover secondary bacterial infection, oxygen therapy, and conservation fluid management is coming under the COVID-19 management strategy\(^64\), whereas hemodynamic support is essential for managing septic shock. Several potential therapeutic agents have been recommended to reuse the existing antiviral agents or develop effective interventions against this novel coronavirus based on the research on molecular mechanisms of coronavirus infection\(^65\) and the genomic organization of SARS-CoV-2\(^66\).

**TREATMENT**

A novel nucleotide analog, remdesivir show strong activity against SARS-CoV-2 under in vitro condition.
Randomized trials are under process to evaluate the efficacy of remdesivir which is a potential target for moderate or severe COVID-19. Remdesivir also shows strong activity in both in vitro and in vivo conditions against related coronavirus including SARS and MERS-CoV. Remdesivir is used compassionately in the case of one of the first patients with COVID-19 in the U.S. which is described through an investigational new drug application case report. Any clinical effect of remdesivir against COVID-19 remains unknown. Both chloroquine and hydroxychloroquine inhibit SARS-CoV-2 in vitro, although hydroxychloroquine is reported to be a more potent antiviral agent. Several clinical trials are under process in China to evaluate the efficacy of chloroquine and hydroxychloroquine against COVID-19. Chloroquine shows strong antiviral impacts on SARS-CoV infection of primate cells. The inhibitory effects on the cells are examined before or after exposure of the drug to a virus that was therapeutically advantageous. It also indicates the prophylactic use of infected persons. Chloroquine interferes with terminal glycosylation of the ACE2 receptor. Additionally, it elevates endosomal pH. The combined protease inhibitors lopinavir and ritonavir have primarily been used for HIV infection. The combination also shows the in vitro activity against the SARS-CoV and in vivo activity against MERS-CoV respectively. Many case studies depicting the use of this combination against COVID-19 are available but its efficacy is unclear. Enormous randomized trials are being conducted for the evaluation. Another IL-6 inhibitor, tocilizumab, is used in severe conditions as reported in the guidelines from China’s National Health Commission. Still, the drug is under clinical trial for evaluation.

Several attempts are being made to design and develop vaccines for CoV infection, mostly by targeting the spike glycoprotein. We are dependent solely on implementing effective infection control measures to lessen the risk of possible nosocomial transmission due to the lack of effective antiviral therapy and vaccines. The majority of the treatment options and strategies that are being evaluated for COVID-19 have been taken from previous experiences in treating SARS-CoV, MERS-CoV, and other emerging viral diseases. Several therapeutic and preventive strategies, including vaccines, immunotherapeutics, and antiviral drugs, have been exploited against the previous SARS-CoV and MERS-CoV outbreaks. The S protein plays a significant role in the induction of protective immunity against SARS-CoV. The development of an effective vaccine depends upon the identification of the immunodominant region. The C-terminal domain of the S1 subunit is identified as the immunodominant region. Hence, knowledge and understanding of S protein will help to develop the potential vaccine candidates based on the whole S protein, S protein subunits, or specific potential epitopes of S protein against SARS-CoV-2. Scientists from all over the world are trying hard to develop working vaccines with robust protective immunity against COVID-19. Vaccine candidates, like mRNA-1273 SARS-CoV-2 vaccine, INO-4800 DNA coronavirus vaccine, and adenovirus type 5 vector vaccine candidate (Ad5-nCoV), are a few examples under phase I clinical trials, while self-amplifying DNA vaccine, oral recombinant COVID-19 vaccine, BNT162, plant-based COVID-19 vaccine, and li-Key peptide COVID-19 vaccine are under preclinical trials. Similarly, the WHO, on its official website, has mentioned a detailed list of COVID-19 vaccine agents that are under consideration. Vaccines that are under different phases of trials are live attenuated virus vaccines, formaldehyde alum inactivated vaccine, adenovirus type 5 vector vaccine, LNP-encapsulated mRNA vaccine, DNA plasmid vaccine, and S protein, S-trimer, and li-Key peptide as a subunit protein vaccine, etc. Effective vaccines and viral shedding are essential to reduce the severity of the disease which will help to control coronavirus outbreaks. In addition to recombinant DNA, and protein vaccines other vaccination strategies such as live-attenuated virus, viral vectors, inactivated virus, and subunit vaccines are tested against SARS-CoV. The very first experimental coronavirus vaccine was injected into volunteers in the US on 16th March 2020. The initial trial included 45 people aged 18 to 55 and doses of mRNA-1273 into the arms of healthy participants at Kaiser Permanente Washington Research Institute (KPWHRI). It was considered the first-stage study of a potential COVID-19 immunization. The study included the tech company operations manager Jennifer Haller. He was the first participant in this study. The biotech company Moderna prepared an investigational vaccine that is free of any part of the actual coronavirus and cannot cause infection. It rather incorporates a short segment of lab-grown messenger RNA and the various doses are being tested to check the safety, immune response, and any side effects after collecting the blood samples. According to Anthony Fauci of the U.S. National Institute of Health, a vaccine will not be available for widespread use for another 12 to 18 months even if all goes well.

The effectiveness of a vaccine can be evaluated by giving deliberately it to the people who are infected with the bug in question. Vaccines for the flu, common cold, and other respiratory illness have been developed through these challenging studies. The signs of illness after infection were observed by tracking the record of the
participants. A study conducted by hVIVO – a subsidiary of pharmaceutical-services company Open Orphan PLC in London, has attracted more than 20,000 volunteers in exchange for a fee of £3,500 ($4,480) which provided detailed insights into the course of COVID-19 infection with potentially positive health implications. Such investigation played important role in the development of the vaccines for the treatment of coronavirus infection. These trials don’t replace the larger field studies, but they help give direction on whether a vaccine is worth pursuing.

CONTROL AND PREVENTION

The basic reproductive number (R0) is an indication of an increase or decrease in the endemic. The R0 value has been estimated with varying results and interpretations. An average number of infections resulting from one infected individual in a fully susceptible population can be measured by the R0 value. Studies from previous outbreaks were found to be 2.7 for SARS and 2.4 for 2009 pandemic H1N1 influenza. The epidemic will increase if R0 is greater than 1 whereas R0 is 2.2 for COVID-19. Further analysis of 12 available studies found that R0 was 3.28. R0 is also considered a super spreader as it is an average value. It may hugely be responsible for outbreaks within large clusters but not influence the R0 value. During the acute phase or pre-pandemic, R0 may be unstable. Hence it is required to focus on reducing the value to less than 1 to control the infection. Preventive measures are the only strategy to limit the spread of cases. Preventive measures included the isolation of the patients with careful infection control. Simultaneously appropriate measures have to be taken during the diagnosis and clinical care of the infected patient. Sputum induction and droplet contact should be avoided during sample collection. Airborne precautions should be taken while collecting the sample. The effective way to stop the spread of the disease is by disrupting the chain of transmission. Further spreading of the infection in clinics and hospitals can be limited by applying triage, following correct infection control measures, isolating the cases, and contact tracing. Middle-aged and elderly patients with primary chronic diseases, especially high blood pressure and diabetes, were found to be more susceptible to respiratory failure and, therefore, had poorer prognoses. Providing respiratory support at early stages improved the disease prognosis and facilitated recovery.

The WHO and other organizations have issued the following general recommendations:

- Wash your hands frequently, especially after contact with infected people or their environment.
- Avoid unprotected contact with farm or wild animals.
- People with symptoms of acute airway infection should keep their distance, cover coughs or sneezes with disposable tissues or clothes and wash their hands.
- Application of strict hygiene measures for the prevention and control of infections particularly in emergency medicine departments.
- Individuals that are immunocompromised should avoid public gatherings.

PRACTICE POINTS FROM AN INDIAN PERSPECTIVE

A total of 1,397 COVID-19 cases including 49 Foreign Nationals had been reported from 27 states/union territories across India as on 31 March 2020 at 08.30 PM according to the Ministry of Health & Family Welfare. All states had issued appropriate instructions for all children below 10 years of age and all citizens above 65 years (except for public representatives/government servants/medical professionals) to remain at home and avoid mass gatherings unless there is a medical reason and essential services requirement. A high-level Group of Ministers is constantly reviewing the status of cases in India. Necessary steps are being implemented by the Government of India across states. Social distancing measures have been issued by the government advisory board to slow down the rate and extent of disease transmission. Non-urgent hospitalization and elective surgeries are avoided by the instruction of the health advisory board in consultation with professional associations. This was to maintain a strategic distance from hospital-related infections to the vulnerable and prepare hospitals effectively for meeting current and future challenges presented by COVID-19. Ministry of Health and Family Welfare was regularly evaluating quarantine facilities. In addition to that preparedness of the hospital in terms of adequate isolation wards, OPD blocks, availability of testing kits, medicines, and personal protective equipment (PPEs), etc. are evaluated. All public hospitals have been directed to ensure sufficient accessibility of protective gear for all healthcare workers. A confirmed covid-19 case must be hospitalized and placed in a single patient room with negative pressure – a minimum of 6 charges per hour. Exhausted air has to be filtered through High-Efficiency Particulate Air (HEPA) and medical personnel entering the room need to wear PPE particularly facemask, gown, and eye protection. The greatest risk of COVID-19
is transmission to healthcare workers. In the SARS outbreak of 2002, 21% of those affected were healthcare workers\textsuperscript{106}.

COVID-19 modeling with India SIM predicted that the community transmission of COVID-19 in INDIA most likely started in early March 2020. To stop the transmission, state or local containment was the best option rather than National containment. Approximately 300 and 400 million Indians were likely to be infected by July 2020, without interventions. Most of these cases would be mild. Somewhere between April and May 2020, around 100 million individuals would be infected. Amongst them, approximately 10 million would be severely and about 2-4 million will require hospitalization (Fig. 3 & Fig. 4). As per the report, this may be the most dangerous period. This peak load would be reduced by 75% by generalized social distancing. It would be a major issue of hospital outbreaks of COVID-19 induced by the admission of infected patients into hospitals. Thus there is a need for large temporary hospitals to handle this patient load over the next three months period. Hospital-based secondary transmission may fuel the epidemic\textsuperscript{107}.

On 11\textsuperscript{th} July 2020, India started Phase-I clinical trials, 16 candidates were opted and examined at AIIMS, Delhi. Usually, it takes 8-10 years for vaccines to reach the market from labs, but in the case of COVID vaccines due to emergencies, this period is shortened to a few months. The shortening of the time duration was done by limiting the time of regulatory approvals (licensing registration applications and submissions authorized by CDSCO) and not the specific approvals and thus not comprising with applications and submissions authorized by CDSCO. DCGI permitted 2 vaccines- Bharat Biotech’s Covaxin and ZyCoV-D by Zydus Cadila\textsuperscript{116,117}.

CONCLUSION

Since the first outbreak of coronavirus (COVID-19) in Wuhan, China, the disease spread worldwide. The current COVID-19 pandemic is an international public health problem. This new virus outbreak has challenged the economic, medical, and public health infrastructure of the whole world. Individuals at extreme ages are at higher risk. Risk is more significant in the case of immunocompromised patients. Complete elimination of risk is not possible but prudent adjustments may be warranted. All health care workers should understand the presentation of the disease and workup. Supportive care by the health care workers also plays an important aspect in the response. Health professionals should be aware of the precautions necessary to avoid the transmission and spread of the disease. Accurate diagnosis in the early stages of the epidemic helps control the spread of the disease. More so future outbreaks of viruses are likely to continue. So, comprehensive measures should be devised to prevent future outbreaks. However, the development of suitable therapeutic agents such as designing antiviral drugs and vaccines against COVID-19 will help to control the infection.

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