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Journal homepage: <https://www.ijmronline.org/>**Original Review Article****Two years of COVID-19: Challenges, opportunities and the way forward**Gopal Chauhan¹, Parul Sharma^{1,*}¹National Health Mission, Shimla, Himachal Pradesh, India**ARTICLE INFO***Article history:*

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ABSTRACT

Coronavirus has caused many outbreaks in the past. Two major outbreaks reported are SARS-CoV in China in the year 2003 and MERS-CoV in 2012 in the Middle East. The present outbreak of SARS-CoV-2 originated from a seafood market in Wuhan city of China in December 2019 with most common manifestation of atypical pneumonia. WHO declared it as a pandemic on 11th March 2020. Many newer strains of the virus have been identified so far and multiple diagnostic and therapeutic interventions have been tried to contain the spread. This virus is mutating very fast and causing huge loss of human lives and economy. Keeping in view the limited knowledge of the disease, it becomes necessary to take all protective measures to overcome the current pandemic and to prepare strategies to mitigate the future challenges.

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1. Introduction

Virus is an obligate intracellular organism which depends on the host for replication. Based on the type of nucleic acid, they can be classified into DNA or RNA virus. Coronavirus are large, enveloped positive-stranded RNA virus within the order Nidovirales. The family Coronaviridae includes members of the genera Torovirus and Coronavirus.¹ Coronavirus is so named because of the presence of club shaped peplomers that looks like solar corona.² Coronavirus was first isolated in 1930. The Severe Acute respiratory syndrome (SARS -2003) and Middle East respiratory syndrome (MERS -2012) outbreaks occurred due to a novel corona virus SARS-CoV.³ The family tree of Coronaviruses is closely related to the bat coronavirus. Bats act as natural reservoir of SARS CoV-2 and have a key role in its transmission. Much is still not clear about the spread of current pandemic which originated from the Wuhan city of China in December 2019.⁴ There are also reports that when cluster of pneumonia cases started in China most of

the bat species were hibernating and no bats were sold or found near the seafood market of Wuhan.⁵ During SARS-CoV and MERS-CoV outbreaks Himalayan palm civets Cats and dromedary Camels acted as an intermediate host whereas humans were the terminal hosts.⁶ So the presence of an unknown reservoir cannot be ignored for the spread of present SARS-CoV-2.⁷

2. History of Corona Virus

Corona virus outbreaks have been reported both in humans and animals in the past. The first major pandemic was reported in human in 1918. In 1930, it was identified in chickens as Infectious bronchitis virus. In 1960 the first Human corona virus was discovered and imaged in London.⁸ The SARS-CoV was transmitted from Himalayan palm civet Cats and Raccoon dogs and the MERS-CoV was transmitted from dromedary Camels. The present COVID-19 pandemic/SARS-CoV-2 is suspected to be transmitted by bats, following human to human transmission.⁹ However SARS-CoV-2 has a much lower fatality rate 6.6% as compared to SARS-CoV (9.6%) and

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MERS-CoV (34.3%).¹⁰ SARS-CoV-2 shares 79% genome identity with SARS-CoV and 50% with MERS-CoV.¹¹

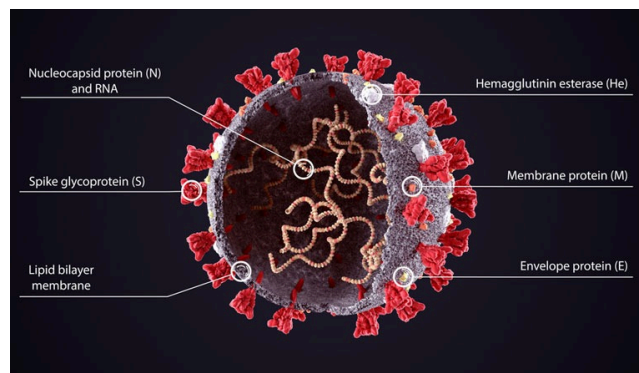


Fig. 1: Structure of SARS-CoV-2:¹²

Coronavirus has a round structure 100 to 160 nm in diameter with long, petal shaped spikes on its surface. Coronavirus is largest amongst the RNA viruses. They have a lipoprotein envelope with large multifunctional S (spike) protein.¹³ Antibodies produced against S protein can neutralize viral antigen. During its evolution the virus has crossed the species barrier from bats to palm civet and humans. The S protein during their evolution adapted to inter species host cell receptors the angiotensin-converting enzyme 2 (ACE 2) receptors.¹⁴ During the 2003 epidemics the S protein gradually adapted to the human proteins. S protein has a key role in the pathogenesis of the virus and fusion of the viral envelop with host cell membranes. The envelope also contains the M (transmembrane) glycoprotein and E (envelope) protein.¹⁵

3. Classification of SARS-CoV-2

Serologically coronavirus group I and II were isolated from mammals and group III from birds.¹⁶ SARS-CoV can infect a wide range of mammals including humans, primates, Himalayan palm civets, raccoon Dogs, Cats, Dogs and Rodents. The α , β viruses cause infection in humans and γ , δ viruses cause infection in animals and birds.^{17,18}

4. Transmission of SARS-CoV-2

The transmission of SARS-CoV occurs as droplet, airborne, close personal contact, fomites and feco-oral routs.¹⁹ Respiratory droplets are $> 5\text{-}10\ \mu\text{m}$ in diameter which are generated during coughing, sneezing, talking and singing etc. Droplets $\leq 5\ \mu\text{m}$ are also known as droplet nuclei or aerosols. Fomite transmission or indirect contact transmission involves contact of a susceptible person with a contaminated object or surface. Droplet nuclei remain suspended in air and can travel long distances and time. Transmission can also occur by close personal contact and the virus can reach the mouth, nose or eyes of a

susceptible person.²⁰

5. Pathogenesis of SARS-CoV-2

The three known pathological steps of COVID-19 infection are: Viral replication, immune-pathogenesis and cytokine storm.²¹ S protein binds to the angiotensin converting enzyme-2 (ACE2) receptor for SARS-CoV.²² ACE2 receptors are present on other body sites as well such as type II alveolar epithelial cells in the lungs, heart, gastrointestinal tract and kidneys. They are associated with increased transmissibility.²³ S protein has a cleavage site and is divided into two sub-domains S1 and S2. S1 helps in binding to the ACE2 receptors and S2 mediates the fusion of the virus membrane to the cell. The expression of another co-mediator is also necessary for viral entry TMPRSS2.²⁴ In serious infection with SARS-CoV-2 impairment of the immune system with low T cells, NK cells, CD4, CD8 levels are seen leading to exaggerated immune response due to massive release of inflammatory cytokines such as IL 1 β , IL 6, IL7, IL8 etc known as “cytokine storm”. Following infections there is an increase in the thrombotic tendency and multi organ failure leading to death.²⁵

6. Chronology of Events of Current COVID Pandemic

1. On 31st December 2019, WHO China country office was alerted to several cases of pneumonia of unknown aetiology detected in Wuhan city in Hubei Province of China.
2. On 7th January 2020, Chinese authorities confirmed identification of a new strain of novel coronavirus “2019-nCoV”.
3. On 11th January 2020, WHO received the detailed information from NHC China about outbreak and its association with exposure to the seafood market in Wuhan city.
4. 12th January 2020, China shared the genome sequencing
5. 13th January 2020, Ministry of Public Health, Thailand reported the first imported case of lab confirmed 2019-nCoV from Wuhan City China.
6. 30th January 2020, WHO declared it as a “Public Health Emergency of International Concern (PHEIC)”.
7. 11th February 2020, WHO renamed the disease as coronavirus disease-2019 COVID-19. On the same day it was designated as severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) based on the phylogenetic analysis of related corona viruses.
8. 11th March 2020, WHO declared COVID-19 as a Pandemic.

7. Clinical Features of COVID

SARS-CoV-2 primarily causes pneumonia. In majority of individuals it causes a mild upper respiratory tract infection

with influenza like illness such as fever, sore throat, running nose, cough, chest pain, breathlessness, headache, body aches etc. No special treatment or hospitalization is required for mild infections. The incubation period for coronavirus is 14 days and symptoms usually start from 4 to 5 days after infection. Only few become seriously ill and need special care especially people living with chronic disease such as diabetes, hypertension, immune-suppression, chronic kidney disease etc.²⁶ During the first wave of COVID-19 majority of individuals who got infected were those who were elderly and had any underlying chronic illness. The second wave was more devastating and affected people in the younger age group.²⁷ Invasive fungal infections such as Mucormycosis (black fungus), Aspergillosis (yellow fungus), and Candida (white fungus) were also reported in comorbid individuals adding to the mortality rates.²⁸

8. Sampling of SARS-CoV-2

For the purpose of diagnosis upper respiratory tract samples including per-nasal, oropharyngeal swabs, saliva, broncho-alveolar lavage are collected. Combination of per nasal and oropharyngeal swab improves the sensitivity of the test. A single negative test in individuals having symptoms suggestive of SARS-CoV-2 is not sufficient to rule out infection. Lower respiratory specimens have higher diagnostic value compared to upper respiratory tract specimen as the virus travels to the lower respiratory tract during its course of replication.²⁹ Newer diagnostic methods using Saliva and breath of an individual to diagnose infection on airports for the purpose of travelling are still under development.³⁰

9. Diagnosis of COVID-19

SARS-CoV-2 pandemic has caused more than 5 million deaths and more than 250 million infected till March 2022. This situation has exposed healthcare infrastructure across the World.³¹ On 13th of January 2020, WHO published its first protocol for the use of RT-PCR assays to diagnose the novel coronavirus.³² RT-PCR is the gold standard test using E gene for screening. If E gene is elevated, confirmation of COVID-19 positive is done using RdRp gene. Due to the increase in sample load and infectivity scientists around the world are searching for newer diagnostic options to test the large number of infected individuals within a shorter time span.³³ The use of serological tests for Rapid antigen testing (RAT) was introduced on 22nd September 2020, for SARS-CoV-2. The sensitivity and specificity of RAT are in range of 50.6%-84% and 99.3%-100% respectively. Results for RAT are available within 15-20 minutes. Other diagnostic modalities available for testing COVID-19 patients are CRISPER/Cas system which is a biotechnology based nucleic acid detection system. Imaging modalities such as X-ray, Ultrasound, CT scan and MRI are also useful in

diagnosis.³⁴

10. Treatment of COVID

SARS-CoV-2 in majority remains asymptomatic or causes minor flu like symptoms. Treatment protocol for mild cases is purely based on symptoms and can be managed at home. Management of fever, antiviral drugs improves recovery time of patients with moderate to severe illness. Anti-inflammatory drugs help in reducing inflammation, severity and hospital stay. Immunomodulators interferon- β -1a and interleukin IL-6 are cytokines that help to fight against SARS-CoV-2. Interleukin IL-1 and tocilizumab are also contributing in reducing the mortality. Monoclonal antibodies and antibody cocktails can act on the receptor binding domain (RBD) of the spike S protein thereby inhibiting viral replication and decreasing the viral load. Anti SARS neutralizing antibodies, convalescent plasma, anticoagulants heparin, antiretroviral drugs, anti malarial drugs were used initially but proved to be ineffective hence its use was stopped. In severe patients, the conventional oxygen therapy was also indicated.^{35,36}

11. Vaccination

On 11th of April, 2020 WHO published a draft on COVID-19 vaccine. A global collaboration facility was created for epidemic preparedness and innovations (CEPI). The committee was formed to accelerate development and manufacturing of COVID-19 vaccines. It also ensures that every country in the world has free access to COVID-19 vaccines.³² Vaccines provide protection against different existing variants of SARS-CoV-2. COVID-19 vaccines available globally are: mRNA based vaccines, inactivated whole virus vaccine, Recombinant viral vaccine and various other using different mechanisms to fight SARS-CoV-2.³⁷

12. Infection Prevention Strategies

In addition to vaccination the most important tool to combat COVID-19 pandemic is to wash hands with soap and water frequently and maintaining a safe distance. Wearing mask is very important to contain the spread as the virus is transmitted through respiratory route by coughing, sneezing and even talking to an infected individual.³⁸

12.1. Mutations

Mutations arise naturally during the course of evolution of the virus and in turn provides fitness to the virus. Due to the low precision in the RNA polymerase enzyme, mutations are more commonly seen in the RNA viruses as compared to DNA viruses.³⁹ Mutations in coronavirus are estimated to be approximately 10^{-4} nucleotide substitutions per site per year during every replication cycle. It is seen that the rate of mutations are quite high in coronaviruses in SARS-CoV-2

and 1-2 mutations are seen per month.⁴⁰ Mutation in SARS-CoV-2 can be defined as a genetic change in the virus. The newer strains can differ from the original strain in being more transmissible, difficult to diagnose and thereby giving false negative results. The new strain can be resistant to the available treatment options and vaccines.

13. Strains/Variants of Concern of SARS-CoV-2

Alpha /B.1.1.7 lineage was initially detected in UK in September 2020. It was considered as a variant of concern with mutations in the receptor binding domain (RBD) of the spike protein at position 501, the amino acid asparagine (N) was replaced by tyrosine (Y) it is also known as N501Y. There were also other mutations associated with this variant the 69/70 deletion causing conformational change in the spike protein, P681H at the S1/S2 furin cleavage site.

Beta / B.1.351 lineage was initially detected in South Africa in October 2020, it is associated with multiple mutations in the spike protein, includes K417N, E484K, N501Y, E484K, known to neutralize some polyclonal and monoclonal antibodies formed.

Gamma/ P.1 lineage initially identified in a traveller from Brazil who was screened on the Japan airport. It contains three mutations in the spike protein receptor binding domain K417T, E484K, and N501Y are associated with increased transmissibility and antigenic profile, these may also affect the ability of antibodies generated from previous natural infection or vaccination to recognize and neutralize the virus.

Delta/ B.1.617.2 lineage, initially identified in India in December 2020.

Omicron/B.1.1.529 Variant of concern, initially identified in South Africa in December 2021.

XE a recombinant strain of Omicron BA.1 and BA.2 has been identified in January 2022 in UK.

14. Conclusion

After more than two years of the COVID -19 outbreak, the situation of pandemic is uncertain. The pandemic has exposed the health systems around the world. The virus is mutating fast and changing its course. Much is still to be known about the virus and its behaviour. Multiple strategies have been tried to contain the spread but the effectiveness of all such interventions is still questionable. This pandemic has divided the public health fraternity and different schools of thoughts have emerged about the origin, spread and preventive strategies including vaccination. There are possibilities of a lab created virus as a part of the biological warfare strategy also. However the ongoing vaccination strategy has shown reduction in severity of disease but it still needs further validations. The virus may remain as an endemic strain causing minor flu like symptoms and sporadic cases in future also. There are possibilities that the newer strains of SARS-CoV-2, Variants

of concern (VOC) can have increased transmissibility, longer incubation period, and increased pathogenicity not detectable by routine screening or diagnostic methods and decreased susceptibility for existing treatment options. They can escape recognition by the immune system and cannot be neutralized by available vaccines. COVID-19 has caused huge loss of life and economy in the world so far. People have faced number of lock downs and public at large especially children have resorted mainly to excessive online and social media platforms. The cases of depression and domestic violence have increased during lockdown. This study provides information about the origin, evolution, transmission, clinical features, diagnosis, treatment options, mutations in coronavirus and anticipated future pandemics. A lot is still to be known about COVID -19. Till then the common preventive strategies like good hygiene, social distancing, vaccination and COVID appropriate behaviour has to be continued. However, there is a need to develop evidence based strategies at global and local levels to mitigate such pandemics in the future also.

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None.

16. Conflict of Interest

None.

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