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An Overview on Evolution of Novel Corona Virus and its Challenges

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Abstract: ***This article aims to give a detailed outline on the wide-spreading, infectious coronavirus disease and also describes about its morphology, modes of transmission, diseases caused, symptoms, treatment, and various preventive measures. COVID-19 has become a global issue, which has caused a drastic change in the environment. The impact that it has caused on the day-to-day lives of common people is beyond what one has expected. It is estimated that it would take several years for everything just to go back to the old normal.***

Keywords: COVID- 19, morphology, transmission, symptoms, treatment, preventive measures, global issue, pandemic

1. Introduction

During late December 2019, a mysterious outbreak occurred in the Huanan Wholesale seafood market in Wuhan, China. Which then expanded throughout the globe, including Thailand, Japan, Korea, United States, Europe, Russia, Germany etc [1]. Since the disease was characterized by fever, cold, fatigue, and occasionally gastrointestinal syndromes, it was considered a strain of pneumonia [1,2]. Hence, the disease was first named as severe pneumonia on 15th of January 2019 by the Taiwan CDC, the Ministry of Health [1]. The World Health Organization on 11th February 2020 termed the as Corona Virus Disease (COVID-19).

In 2003, a novel virus, which also had the same features such as pneumonia, originated from China, specifically from Guangdong province, and was termed severe acute respiratory syndrome coronavirus [SARS-CoV]. Its death rate was around 10%-15% [2]. Still no proper treatment and vaccine are available for the disease. Another outbreak which occurred in 2012 share similar features to this virus and was coined Middle East respiratory syndrome coronavirus [MERS-CoV] [7,4]. Both SARS and MERS share similar clinal manifestations. Clinically, patients presented with fever, cold, cough, and other respiratory symptoms [1,9,10]. Reports suggests that SARS-CoV mutated itself during the 2002-2004 period and is even more adaptable to optimize its replication in human cells because these viruses have error-prone RNA-dependent RNA polymerases, which makes the mutation and recombination easier, whereas MERS-CoV is not [6,8]. It can be noted from previous studies that SARS-CoV was transmitted from exotic animals to human beings, as the spread of infection started from the wet markets of China, whereas the MERS-CoV is said to be transmitted from camels to human beings [7,3,5].

Since the emergence of SARS-CoV-2, its infection has been spreading like a wild fire, affecting more than 213 countries, with an estimated number of cases over 3,218,800 and estimated deaths up to 1 Million to date, as reported by the WHO [5,11,13,29,19]. The study by Chan et al. reported the first case of transmission from human to human was reported in a family that visited Wuhan during December 2019 and January 2020. An additional member, who did not visit Wuhan, was also tested positive, when came into contact with the rest of the family members[12,15]. PCR and Sangers sequencing results showed it to be SARS-CoV-2. They presented with fever, diarrhoea, and other respiratory symptoms[14,17,18]. Various modes of transmission of the disease have been reported[16]. The modes of transmission can be broadly classified into the following two different types: direct transmission and indirect transmission. The direct mode of transmission occurs via oral–fecal contaminations, aerosol droplets, tears, saliva, semen, etc. The indirect mode of transmission occurs via the fomites. Although most articles state that SARS-CoV-2 is air borne and is transmitted through close contact with an infectious person or contagious environment and poor personal hygiene, contradictory evidence exists that there are also other modes of transmission, such as from the mother to the child and through stools, for the vast spread of this virus[18,29,27]. Studies have shown that the disease spreads the fastest in confined spaces with densely crowded population. Confined spaces are especially at risk for the maximum spread of the disease[9,21,23]. However, the WHO suggested various hygienic practices, such as maintaining a good personal hygiene, maintaining a minimal distance of at least 2 feet from people, wearing personal protective suits such as masks and gloves, and disinfecting hands and other regularly used objects, to minimize the spread of the disease[8,9,22,28,26,25]. Social distancing plays a major role in minimizing the spread of the disease[10,24,30,39,35].

Human coronaviruses

Coronaviruses belong to the family of *Cornoviridae*, subfamily of *Coronavirinae*, and order *Nirolovirales* [77,73,75,40]. They are single-stranded, positive-sense, RNA viruses that can be listed into four different genera: *Aphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*[43,44,47,48]. These are also known as the pathogens of the birds and mammals. Alphacoronavirus and betacoronavirus are primarily identified in mammals, whereas gammacoronavirus and deltacoronavirus are known to cause infection in birds[11,42,45,47]. These viruses are

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transmitted into the human hosts through the cell surface receptors, and they enter the host cells after cytoplasm or by fusion, occurring at the plasma membrane. They replicate in the cytoplasm [12,43,46,49,50]. Bats are usually called the reservoirs of the coronaviruses[55,57,59]. More than 60 strains of CoVs have been identified from bats, most of which belong to the betacoronavirus genra[56,51,53,59]. CoVs are not only cause threat to the humans but also to the animals. A Pig Cov in 2014 caused countless death of Piglets in United States[13,52,58,54].

Disease caused by Corona Virus

To date, infectious bronchitis virus (IBV) remains a worldwide problem, especially in densely populated areas [60,62] . Until 2020, Human CoVs were known to cause only mild respiratory tract diseases, with estimates ranging upto 15%-25% of all common colds. However, in 2002, a HCoV was identified as the cause of a new disease called SARS [61].

The outbreak of SARS was controlled, but in 2014 another novel CoV was isolated from patients in Saudi Arabia who were hospitalized for respiratory diseases, which causes a disease called MERS [63,65,64] . Since most infected patients were from Middle East countries, the new diseases were named MERS, and the coronavirus responsible for this disease is called HCoV- MERS. Transmission of most of these CoVs occurs via the oral- fecal route, and their replication occurs in the epithelial cells, resulting in mild respiratory diseases and diarrhea. At times, CoVs, causes severe to fatal diseases [84,83,66] .

Origin of infection

An outbreak of such kind has happened for the third time as far as the previous literature is concerned. This virus was later found to be a new strain of coronavirus species that is known to cause severe respiratory infection in human beings. This virus was first identified in people who were exposed to the seafood markets or the wet sea markets, a place where the sea meat is sold, in the Wuhan city, Hubeic province, China. From there, China, the infection has spread to nearly 213 countries throughout the globe [20,19]. Theories exist saying that the infection spreads through animals, birds, and various other means. Recent studies have found that human-to-human transmission is also possible. As a measure to control the spread of the disease the WHO suggested worldwide quarantine, which was brought into action from March, 2020. However, the damage has already begun, and despite the lockdown for several months the spread of the disease still continues [17,16].

Transmission:

However, at the beginning, it was assumed that the CoVs got transmitted from the bats to the humans via an intermediate. Various studies have proved that bats are the reservoiers of CoVs. Human-to-human transmission has been recorded as the fastest means of the transmission by the WHO. There still remains a lack of understanding regarding the modes of transmission of the virus. To control its spread, people should be well aware of the transmission modes of this virus[125] .

Stages of COVID-19 transmission

It primarily includes four stages:

Stage 1: When a person gets infected by travelling to a virus-hit country or has a travel history to the virus-hit country.

Stage 2: When a person gets infected by getting into contact with a person who has a travel history.

Stage 3: When a person gets infected, although having no travel history or without even coming into contact with an infected person.

Stage 4: When the disease grabs an endemic space with no end point throughout the country [66,67].

Modes of transmission

Recently published studies suggest various possible modes of transmission for the virus so far. However, the most predominant modes of transmission are classified into the following two categories: direct transmission—via human contact, unhygienic cleaning practices, oral–fecal contaminations, aerosol droplets, tears, saliva, semen, and contact with infected objects or person—and indirect transmission—via fomites [[8,9].

Direct transmission

Research exists stating that the transmission of virus from an infected person to a healthy person could take place within a distance of 2 cm, when a healthy individual person comes into contact with an infected person[123]. Therefore, maintaining inter-personal distance between people was suggested the WHO and the governments of all countries. This is suggested to reduce the spread of the disease that usually occurs via droplets disseminating through the infected person's nose or mouth. However, this could possibly be reduced by maintaining a safe inter-personal distance among people, wearing protective equipment such as face mask, gloves, and coveralls. Airborne transmission is said to be the fastest route of transmission among other[121,122] .

Indirect transmission

These kinds of transmissions also occur when a healthy individual comes into contact with infected objects, such as the stethoscope, handles, glasses, etc, used by an infected person. Such transmissions usually occur via the fomites. Fomites are inanimate objects that are used by an infected person. These objects are known to a source of transmission of the disease. Hence, transmitting diseases from one person to another. Spread of such diseases could be avoided by properly sanitizing the fomites and keeping them clean and free of germs.

Transmission by environmental factors:

Research has also proved that environmental factors also play an important role in the transmission of the viruses. Such transmission occurs because of the longer half-life times of the coronaviruses. These transmissions also usually occur through the waste water, waste bag, and containers and also through aerosols and contaminated waste surfaces[22]. Essential practices such as waste water treatment and proper waste collection could help reduce the spread of the transmission. A report from the WHO states that SARS-CoVs-2 transmission occurs via droplets and close contact between the infected person and a healthy person. The increasing rates of COVID-19 cases among the

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aircraft passengers, cruise workers, and healthcare works help us come to a conclusion that this transmission is faster in densely-populated and confined places[55]. These transmissions occur via the fomites. Data suggest that the viruses remain viable in air for a longer duration of time and hence increasing the risk of contamination. Studies also show that the survival times of the CoVs are longer and can be viable in the environment ranges from several hours to several days. Hence, proper disposal of the waste, that is, the objects used by the infected person, wastes generated, and quarantined and household wastes, is really very important to so as to reduce the transmission the infection and virus. The importance of practices, such as waste handling and hygiene, should be emphasized among the people especially during the pandemic time. Because the strains of viruses were extracted from the stools of the infected patients in the hospitals, following these safe self-hygienic methods are a necessity. However, the impact of environmental factors on the transmission of the virus still needs to be explored and studied[122,124].

Transmission from animals to humans:

Literature search of the Google Scholar, NCBI, and various other web sites has shown that bats are the primary ancestry reservoirs of the CoVs. SARS was transferred from wet seafood markets to humans, whereas MERS has a known history of transmission from camels to the human[3,4]. In both cases, it is believed that the ancestry begun from the bats. Understanding whether SARS-CoVs-2 transmission has occurred directly via the bats or via through means of any intermediate host is of utmost importance to determine its pathogenicity and to understand the zootonic transmission patterns[6,9,10].

Symptoms of infection

The symptoms of COVID-19 range from mild to severe upper respiratory infections such as cold, cough with or without sputum, dyspnea, myalgia, muscle fatigue, headaches, sore throat, wheezing, and fever. These are most commonly reported symptoms among the infected people[111]. However, SARS-CoV-2 is also known to cause gastrointestinal symptoms, such as diarrhea[47,46]. Reports suggest that the effect of SARS-CoV-2 is usually mild in children and severe in adults who are older than the age of 40 years—children and these adults are more prone to the disease. Other rarely reported symptoms include rashes, conjunctivitis, mucous membrane involvement, neurocognitive impairment, swollen hands and feet, and lymphadenopathy[117]. Most patients reported fever persisting two to five days, although fewer durations are also reported. Neurocognitive symptoms are also common, such as lethargy, confusion, and irritability. Very few numbers of patients reported severe neurocognitive symptoms such as encephalopathy, seizures, coma, meningoencephalitis, muscle weakness, and brainstem and/or cerebellar signs[22,23,25].

Mechanism of replication

Replication and transcription:

The transmission, replication, and infection of the CoVs depend on both the human hosts and the viral genomes. The spike proteins of the CoVs on their surfaces are the key determinants for entering into the human hosts (9). It consists of two major subunits—the S1 subunit is responsible for the attachment of the virus onto the host and the S2 subunit is responsible for the transmission of the viral genome into the host cells. Viral RNA synthesis occurs via the translation and assembly of the viral replicase complexes (12). Both genomic and subgenomic RNAs are produced by the viral RNA synthesis. Research states that subgenomic RNAs works as mRNAs for the structural and accessory genes that reside downstream of the replicase polyproteins. CoVs replication mainly depends on how the leader and the body segments fuse during the production of the subgenomic RNAs. Initially, although this was believed to occur during the positive-strand synthesis, studies have proved now that that the replications occur during the discontinuous extension of negative-strand RNA synthesis (111,12,13). Finally, CoVs are known for their ability to recombine using both homologous and nonhomologous recombinations, which plays a key role in viral evolution and is the basis for the targeted RNQ recombination—a reverse genetic tool used to engineer viral recombinants.

Assembly and release

After replication, the viral structural proteins are transferred into the endoplasmic reticulum of the host(19,11). These then move into the endoplasmic reticulum and Golgi pathway and then form the mature virions. These proteins react with the nucleoplasids, hence completing the formation of their assembly. However, the exact mechanism through which the interaction takes place remains unclear (88, 87).After assembly, these virions are transferred into the host cell surfaces through the vesicles and are said to be released by exocytosis. It is not known whether the virus is transported through the Golgi pathway or whether it has a pathway of its own(55,53). The cell fusion takes place between the infected and the uninfected cells, which leads to the formation of giant, multinucleated cells that allows the spread of the virus from one cell to another.

Laboratory testing

Real-time polymerase chain reaction is the standard diagnosis for the CoVs. However, the sensitivity of the testing varies based on the duration of diagnosis of the symptoms[33,65]. The predominant factors that contribute to the negative test results are the adequacy of specimen collection technique, time from exposure, and specimen source. Studies demonstrate that lower respiratory samples are more sensitive than upper respiratory samples. CoVs can be detected in the fecus samples, but not in the urine samples. A systematic review indicated that the typical laboratory abnormalities seen are elevated levels of serum protein, lactate dehydrogenase, aspartate aminotransferase, etc. However, these characteristics are common in pneumonia[96,95]. The more severe the abnormalities, the more sever the disease. The mechanism of action involves isolation and purification of RNAs extracted from upper and lower respiratory regions, which are then reverse transcribed to cDNA and then subjected to a real-time PCR instrument with SDS for its subsequent amplification[99]. This process is said to provide appropriate conditions for the binding of probes between forward and reverse primers; however, during the extension phase of the PCR cycle, these probes are degraded by the 5′ nuclease activity of Taq polymerase,

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separating the reporter and quencher dyes. This separation generates a fluorescent signal, and with each cycle, more and more cleaving of reporter dye occurs, thereby increasing the fluorescence intensity. The intensity of each cycle is measured using a PCR detection software system[115]. The results of the RT-PCR must always be interpreted by professional experts to avoid any bias.

Serological testing

Initially, when the CoVs were identified, there were no proper diagnostic methods to identify these viruses[9]; hence, these serological tests emerged as a supplementary diagnostic tool. Serological testing is also used when other tools and kits provide unsatisfactory results. The main basis of this testing is the detection of antibodies, Antibodies are specific proteins that are generated within the host cells in charge to any infection[11]. An antibody test deals with the identification of antibodies present in the specimen, in case to identify whether the specimen has been exposed to any viral pathogens. However, the following four different serological tests have been used primarily for the identification of the CoVs in laboratories: neutralizing test—it helps in the identification of antibodies in the patients' serum based on the ability to inhibit the replication of the virus; enzyme linked immunosorbent assay—the identification is done based on the presence of the antibodies through the formation of pigmented products that are formed after the binding of secondary antibodies to the antibody–antigen complex; chemiluminescent immunoassay— the presence of the antibodies is identified through the formation luminescence that occurs when a secondary antibody binds to an antibody–antigen complex; and rapid diagnostic test—it works by the identifications of the presence or absence of the antibodies in the patients' blood serum specimens. It basically works on the lateral flow assay where the antigen–antibody complex is moved by the capillary action across a membrane and gets immobilized by capture antibodies producing a chromatic change[14,15].

Serological testing using ELISA

Here, the microtiter plates is coated with specific viral antigens, and each well is then loaded with serum samples of the patients[101]. If the patients previously have been exposed to the virus, then the antibodies from the serum samples of the patients will bind with the antigen in the well. Such binding produces a color change. The presence of the antibody depends on the intensity of the color—that is more the presence of the antibody in the serum sample, more the intensity of the color.

Serological testing using chemiluminescent assay

This is also called as the modified ELISA technique where the luminesce is determined for the detection for the antibodies. This is an analysis test that can quantify the presence of IgG, IgM, and IgA antibodies. It is then detected by the formation of complex that bindsto another antibody that undergoes a chemical reaction that gives rise to luminosity.By measuring the number of antibodies present in the sample the amount of light emitted is calculated[92,93].

Serological testing using rapid diagnostic tests

These are compact, transportable diagnostic kits. The principle behind this test is lateral flow assay where samples are collected from the nasal swabs, saliva, and blood shows colored lines, which demonstrates the positive and negative results[98,96,95]. Here, gold coated nanoparticle labelled antibodies are present in a membrane and in two different lines the captured antibodies are present. As the patient's sample is filledin the membrane, it starts to moves across the membrane by the capillary action. At first, this sample comes across the gold nanoparticle labeled antibodies and the viral antigens present in the sample binds to form a complex[90]. This so-formed complex then travels further into the membrane where it encounters the capture antibodies in the second line. Thus, their interaction results in the formation of colored lines, confirming the test[104,103].

Serological testing using neutralizing tests

The basic working principle of this assay is to identify the antibody that inhibits the viral replication in vitro. Here, serum samples from the suspected infectious people are collected. The collected samples are then cultured. As soon as the replication of the virus takes place, the serum samples containing the antibodies are added into the culture, respectively[107,105]. If the specific antibody exists, then it binds with the virus and then inhibits the replication of the virus thus confirming the presence of CoVs in the infected patient’s sample.

Nucleic acid amplification test

The laboratory diagnoses of the CoVs are usually performed by the nucleic acid amplification tests, such as the real-time polymerase chain reaction tests. Furthermore, the nucleic acid amplification tests (NAATs) are used to identify the mutation in the genomes of the CoVs. The targeted viral genes of COVIS-19 include N, E, F, ORF, and RdRp genes according to the WHO[109,108]One of the following criteria should be met for the nucleic acid amplification test: At least one of the two unlike targets of the viral genome should result positive, with one target testing positive by a confirmational assay. One positive resultconfirms the presence of beta coronaviruses; hence, further confirmation is done by the whole genome sequencing. In case, if ambiguity is suspected in the results, then the sample should be collected once again from the respective patients and tested again with the NAAT assay, different from the one that was previously used, to obtain reliable results[115,116]. However, there are a number of factors that lead to negative results of the NAAT test. Few of the factors include poor quality of the specimen, the sample collected was either late or too early after the person was infected, the sample was not handled properly or sealed perfectly, and technical errors of the test[119,120]. If a patient is tested negative though suspected with CoVs despite the sample being collected from the upper respiratory tract, samples from the lower airways should be tested.

Treatments for coronavirus

Until date, the COVID-19 pandemic is still posing a major threat to the health of human beings. Several trails have been conducted across the world to find a potential treatment and preventive options[111,113]. However, vaccines have proven to be most effective in preventing and controlling the spread of the disease. Vaccines are considered to be economical by the common people. The fragments of SARS-CoV-2 used in the development of vaccines are S protein, the cell antigens, the

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N terminals, and the RBD domain. Furthermore, it is estimated that the development of vaccines for the disease will take up at least 10 to 20 years[111,112]. In addition, it is also noted that there are no treatments available for severe and critically ill patients with COVID-19. Only supportive measures such as treatments with corticosteroid, antiviral drugs, and mechanical ventilation exist. Although studies show that antiviral drugs are effective, there are no data to support this statement [107,10,108,110]. However, basic treatments of CoVs include treatment with anticoagulants and antithrombotic agents, monoclonal antibodies, mesenchymal stem cells, and artificial intelligence and bioinformatics.

Treatment with antivirals and antithrombotic drugs

It is known that SARS-CoV-2 predisposes to arterial and venous thromboembolisms. Research has indicated high rates of thrombotic events in patients infected with COVID-19, hence anticoagulation therapies and thromboembolism imaging checks have gained much importance and attention. Furthermore, low molecular weight heparin acts as a powerful inhibitor of antiviral and anti-inflammatory activities and also is known to prevent thromboembolic complications [105,106]. However, it can be concluded that further studies are needed to validate the effects of anticoagulants in this disease.

Treatment with monoclonal antibodies

Monoclonal antibodies are laboratory-made proteins, produced by the immune systems when they encounter any virus or pathogen. These antibodies, either monoclonal or natural ones, bind to the surfaces of the virus, hence preventing the virus to start the infection cycle. Hence, these have gained much attention in the field of prevention of infectious diseases, such as COVID-19[101]. Therefore, studies have shown that these antibodies have provided short-term prevention of the disease. These can be sued until proper vaccinations have been developed, thus reducing the rate of mortality. However, more clinical trials are required to further study its safety and efficacy to treat patients with SARS-CoV-2[111].

Treatment with mesenchymal stem cells

The anti-inflammatory functions of mesenchymal stem cells have the potential to reduce the occurrence of COVID-19. On the other hand, mesenchymal stem cells secrete various cytokines that interact with immune cells, such as T cells, B cells, macrophages, etc[102]. However, currently, there are no approved treatments based on mesenchymal stem cells, but there are increasing number of clinical investigations on this treatment process. This treatment was usually suggested because SARS-CoV-2 share similar features to the avian influenza virus, causing pneumonia, lung failure, etc [103,104]. Therefore, mesenchymal stem cell therapy can be used as an alternative to treat the disease[100]. Further studies are still required to come to a conclusion.

Treatment with artificial intelligence and bioinformatics

It is well known that the mechanisms if the virus requires to be studied in much detail, and the design of antivirals and vaccines are time consuming and require years to develop[110,102]. Hence, bioinformatics is of great help to various scientists in predicting the drug, its targets, and side effects. As such, bioinformatics in widely used in drug development for SARS-CoV-2. Studies have used bioinformatics in the development of a 3-D model, which was used to detect the structure of the protein and was further used for drug designing. Twenty-six herbal medicines were identified in the study of Zhang et al. by using molecular docking. Thus, may research scholars have stated that bioinformatics and artificial intelligence play a huge role in the development of antivirals[114,115,117].

Upcoming challenges

The coronavirus disease has been affecting lives throughout the globe since December 2019. Measures such as isolation, social distancing, shutdown of the entire country since March 2019 have not only mentally affected children but also adults are in prone to anxiety, high levels of stress, etc[124]. External support seems to have fallen away. Besides worries and anxiety, the economic situation has gone down, and high levels of unemployment are noted in every country. This has eventually put both parents and students under pressure. The major challenge after this pandemic will be returning back to normal life scenarios. While some have lost their jobs and businesses, other have a load of work to be completed. For children and adolescents, the pressure to catch up for the time lost may increase. However, a lot needs to be done. The real need is to build the capacity to handle all these economic issues[117,115]. Despite the economic and health-related issues, the major issues are to develop a proper treatment and vaccine to control the disease, which is difficult to bring to practicality. This is not only time consuming but also involves a huge sum of money. In such situations where the economy has been really down, investing large sums of money into research might result in additional tax burdens to the common people[120,119].

2. Conclusion

COVID-19 has brought a tremendous impact on the lives of each and every individual. In this study, we reviewed the origin, infection, transmission, detection, and also treatments of SARS-CoV-2, as well as the economic impact of this virus[90]. We would like to conclude that SARS-CoV-2 is a very infectious virus and the best way to reduce the spread of the disease is to maintain interpersonal distance and by using protective personal equipment to save guard and also to prevent the transmission from one person to another. However, by following these measures, we will only able to prevent the spread of the disease to some extent. Since, there are no proper treatment sources available, these are at least what a person could do to keep the transmission under control. Other means would be by increasing one's immune system[125]. This is one of the alternatives available. Although enhancing ones' immunity might protect them, however, in the end, they may become carriers of the virus and transmit to other persons. Caution should be exercised during these critical times of the pandemic.

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