Chapter

COVID-19: An Updated Insight of the Pandemic

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Abstract

Novel coronavirus (SARS-CoV-2) out-broke in the city of Wuhan in China and widely spread across the globe in a pandemic manner, causing societal and economic disruptions. Though the origin of the novel virus is still a debating topic, it is certain that SARS-CoV-2 acquired human to human transmission capacity. Regardless of aggressive containment and quarantine approaches, the number of confirmed cases continues to rise and being reported due to its highly infectious nature. As of the time, there is a little scope for the antiviral drugs or vaccines for the treatment of coronavirus infection; due to the vigorous mutation rate in the viral genome. However, existing anti-parasite drugs like ivermectin and chloroquine could effectively inhibit the virus has been reported. Few of the vaccines have come up with certain degree of efficacy and many are under the clinical trial phase. The research on novel coronavirus is still in the preliminary stage. In this chapter, we systematically summarize the origin, transmission route, molecular characterization, pathogenic mechanism, contagious nature, clinical symptoms, diagnosis, treatment, mutation and infection as well as prevention strategy of coronavirus disease based on the recently available literature. In addition to this, this chapter presents updated insights of the current state of knowledge pertaining to novel coronavirus and can be referred for potential future studies.

Keywords: Novel coronavirus (SARS-CoV-2), coronavirus disease, prevention strategy, transmission capacity, drug targets, treatment methods, virus structure, mutation

1. Introduction

In December 2019, Wuhan city in China became the center of origin of the novel coronavirus disease with the acronym COVID-19 outbreak that continues to spread quickly across the globe in a very short time. Due to its severe infection rate, on January 30, 2020, World Health Organization (WHO) declared COVID-19 as the public health emergency of international concern (PHEIC), followed by a worldwide pandemic declaration on March 11, 2020. As of May 5, 2020, it has spread to 220 countries with 3665403 confirmed covid-19 positive cases. The recent data (as of June 28, 2021) show that the number of countries affected by Covid-19 is 229, with a total of 181,741,361 confirmed cases of COVID-19 and 3,936,510 deaths. It is anticipated that the full extent of spreading and severity of this 2019 novel coronavirus is yet to be seen and global control of COVID-19 will be one of the toughest challenges humanity has ever faced [1, 2]. According to the international committee on taxonomy of viruses (ICTV) classifications,

coronaviruses belong to the order *Nidovirales*, family *Coronaviridae*, and sub-family *Coronavirinae,* as shown in **Figure 1**. These are the largest group of viruses belonging to the *Nidovirales* order. The sub-family *Coronavirinae* is further divided into four genera, such as *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*withfour different lineages (A (*embecovirus*), B (*sarbecovirus*), C (*merbecovirus*), and D (*nobecovirus*)) of the *Betacoronavirus*genus [3, 4]. COVID-19, officially named by the WHO on February 11, 2020, is caused by the severe acute respiratory syndrome coronavirus 2 (named by ICTV), otherwise known as SARS-CoV-2. The emerging SARS-CoV-2 is a beta coronavirus of lineage B and seems to be the seventh member of the coronaviruses that infect humans, primarily targeting the respiratory system [5]. The first human coronavirus (HCoV), named B814, was isolated in 1965 from patients with common cold [6]. The other six different HCoVs include severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), HCoV- 229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1. Among these HCoVs, HCoV-NL63 and HCoV-229E belong to *Alphacoronavirus*, HCoV-HKU1 and HCoV-OC43 belong to lineage A, SARS-CoV to lineage B, and MERS-CoV to lineage C of the *Betacoronavirus*as depicted in **Figure 1**.

HCoVs are zoonotic pathogens that originated in animals and all HCoVs are believed to have a bat origin, with the exception of *Betacoronavirus* lineage A that

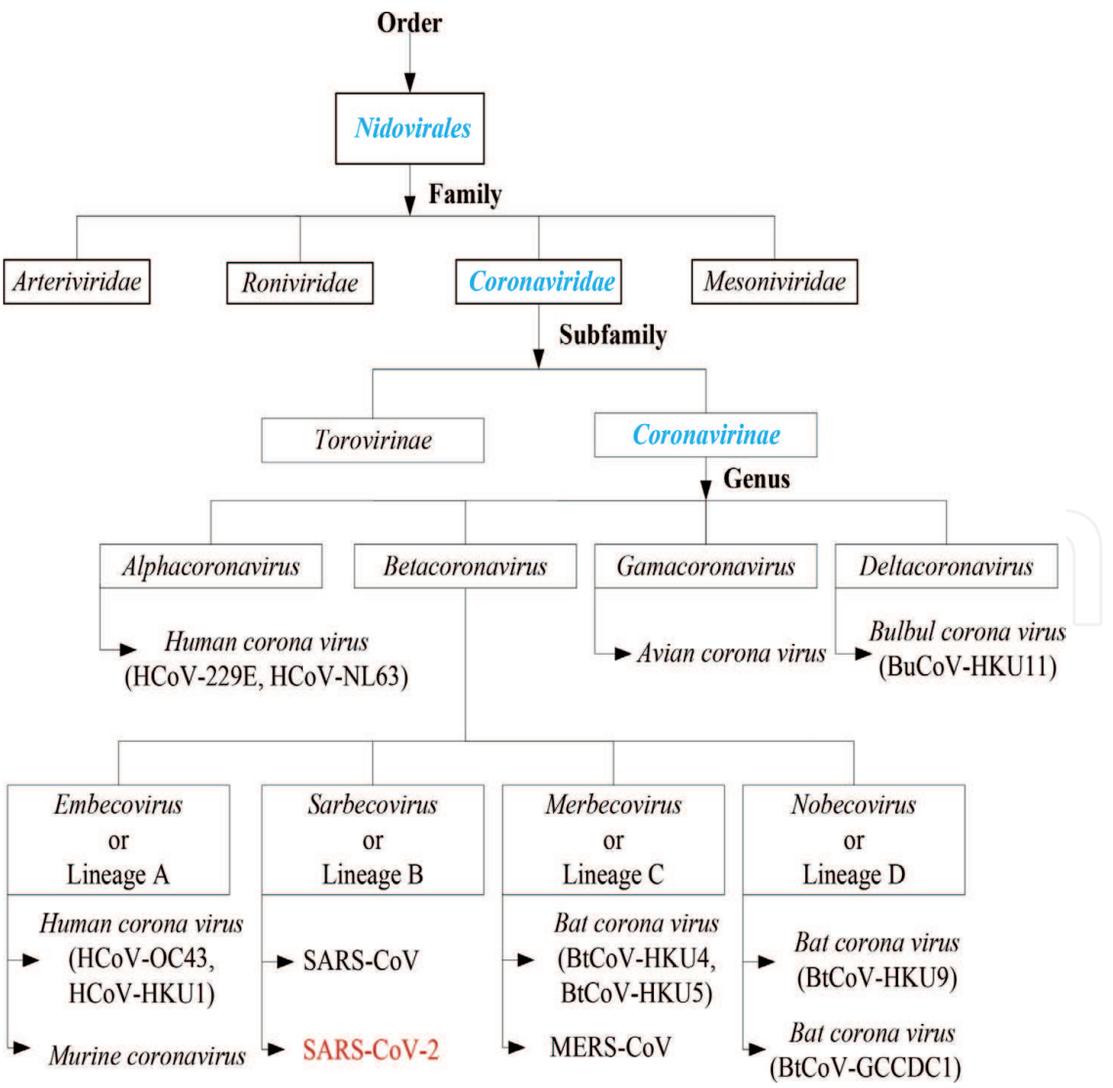

Figure 1.
Classification of novel corona virus.

may have rodent origin [7, 8]. Similar to the case of other SARS-CoVs, the bat might be the probable origin for SARS-CoV-2 as SARS-CoV-2 shares about 96% whole-genome sequence similarity with the bat coronavirus (BatCoV). The confirmed and suspected origins of HCoVs are summarized in **Figure 2**.

Zhou et al. (2020), through complete genome analysis of samples collected from COVID-19 patients, found that SARS-CoV-2 is a *Betacoronavirus* with a sequence identity of 96% with a bat coronavirus [9]. Studies of Pasteur Institute, Shanghai also highlighted that the natural hosts of SARS-CoV-2 might be the bats [10]. However, few studies also highlighted that the pangolin is expected as an intermediate host of the SARS-CoV-2 [11, 12]. Zhang et al. (2019) reported that coronavirus from the pangolin might be the origin of the SARS-CoV-2 on the basis of genome sequence identity [11]. However, the claim was rejected by Cyranoski (2020), based on the fact that the origin is not by the genomic sequence similarity but by the receptor-binding domain (RBD) of the virus that enables the virus to enter the host cell [13]. Although, the potential natural and intermediate host of the virus is not fully established, regardless of its initial transmission source, it is certain that SARS-CoV-2 acquired the capacity for human to human transmission [14]. SARS-CoV-2 is highly infectious; the entire population is generally highly susceptible to infection, and respiratory droplets through coughing and sneezing of COVID-19 patients and coming into contact with them are the primary infectious source in the population. It is even claimed by some experts that transmission during conversations through micro-droplet may possibly be the third infection route. The digestive tract can also be a potential route of infection as SARS-CoV-2 is detected in the stool and gastro-intestinal tract of COVID-19 patients, in addition to its detection in saliva, tear, urine, etc. [15, 16]. There was no evidence of transmission from mother to child during pregnancy [17]. Though based on the currently available evidence, bats are considered to be the natural hosts and pangolins are the intermediate hosts, the origin of SARS-CoV-2 necessitates further in-depth investigations.

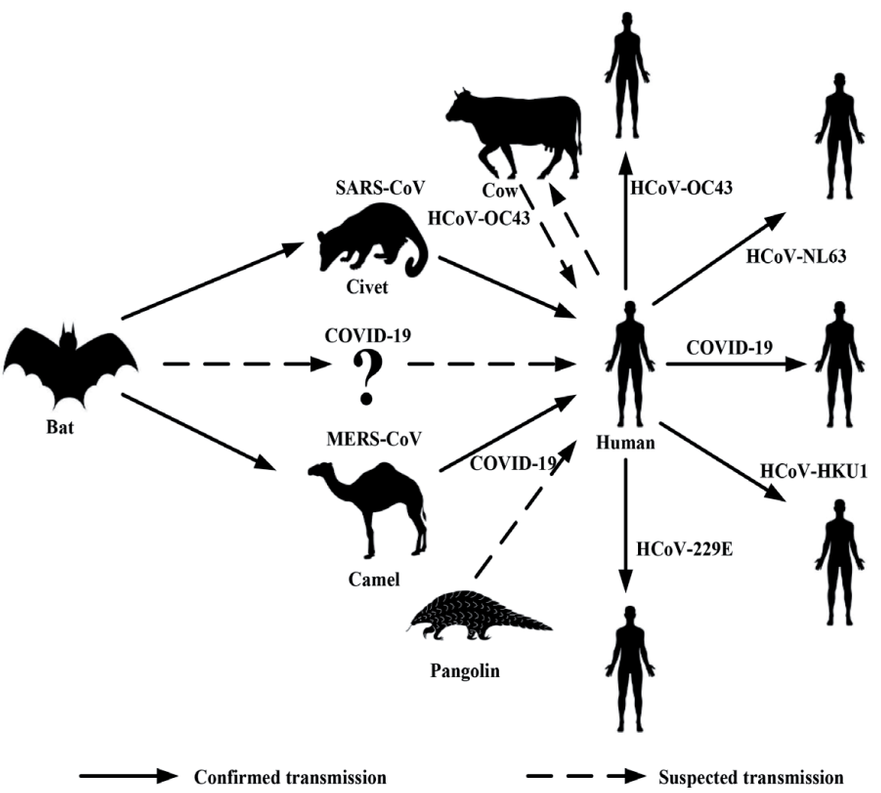

Figure 2.
Probable origin and intermediate host during interspecies transmission of the corona virus.

2. Molecular characterization and pathogenic mechanism

Coronaviruses are enveloped, spherical, or exhibit size and shape variation (pleomorphic) with a diameter in the range of 60–140 nm containing a positive sense, single-stranded RNA genome of approximately 26–32 kilobase size, the largest genome among RNA viruses [8, 18]. The genomic RNA contains multiple open reading frames (ORFs) for encoding 16 non-structural proteins (nsps) and four structural proteins like spike (S), envelope (E), membrane (M), and nucleocapsid (N). About two-thirds of genomic RNA is located in the first ORF (ORF1a/b) that helps in the translation of two polyproteins viz. pp1a and pp1ab at the 5′ end. Further, the subsequent proteolytic cleavages of polyproteins generate 16 non-structural proteins (NSP). The remaining part of the virus genome encodes the four important structural proteins, E, S, N, and M, including other accessory proteins that interfere with the host's innate immune response [19, 20]. The invariant gene order is 5'-ORF1a-ORF1b-S-E-M-N-3′, with additional small ORFs in between the structural genes for encoding accessory proteins. The term 'corona' in Latin means 'crown' under the electron microscope observation; the spike protein projections of the virus appear as a crown, hence termed as 'coronavirus' (**Figure 3a**).

3. Infection strategy

2019-nCoV is extremely contagious and with very high transmission capacity, the virus is transmitted from person to person with ease. The transmission capacity is represented based on the reproduction number symbolized as R_0 that signifies the average number of secondary cases (infectee) caused by the primary case (infector) in a population highly susceptible to infection [21]. The value $R_0 > 1$ indicates the rapid spreading of the infection whereas $R_0 < 1$ signifies the low extension capacity of the infectious disease. The R_0 value of COVID-19 is in the range of 1.4–2.5, whereas severe acute respiratory syndrome coronavirus (SARS-CoV) is 0.67–1.23 and Middle East respiratory syndrome coronavirus (MERS-CoV) is 0.29–0.8; therefore, COVID-19 could be more easily transmitted [22, 23]. However, there are cases when an infected individual will not transmit the disease to anyone or can infect far more people than the standard transmission rate and the individuals are termed as "super-spreaders" [22]. In COVID-19, for the first time in early 2020, two patients were reported to be super-spreaders. One was a British national who had infected a dozen others whereas another suspect, a South Korean woman, had infected several dozens of others. The rate of initial spread is also dependent on the serial interval, which means the time gap between the onset of illness in an infector and in an infectee. The serial interval can be estimated by linking dates of onset of illness for infector-infectee pairs. The serial interval for COVID-19 is 4.4–7.5 days, whereas the mean value for SARS-CoV was 8.4 days, indicating the rapid transmission nature of COVID-19 [24].

It is reported in the literature that SARS-CoV-2 uses angiotensin converting enzyme 2 (ACE2) as its cell surface receptor and the binding of the S protein to the ACE2 receptor is the first step of viral infection followed by fusion with the cell membrane and subsequent viral entry to the respiratory mucosa [3, 18, 25]. As demonstrated in **Figure 3b**, after entry and un-coating, the translation of ORFs from the viral genomic RNA occurs for encoding non-structural proteins. Subsequently, the nsps assemble into the replicase-transcriptase complex (RTC) to facilitate RNA replication and transcription. First of all, full-length negative-sense anti-genome is synthesized using the genomic RNA as a template, and subsequently, the negative-sense strand serves as a template for the synthesis of new genomic and sub-genomic

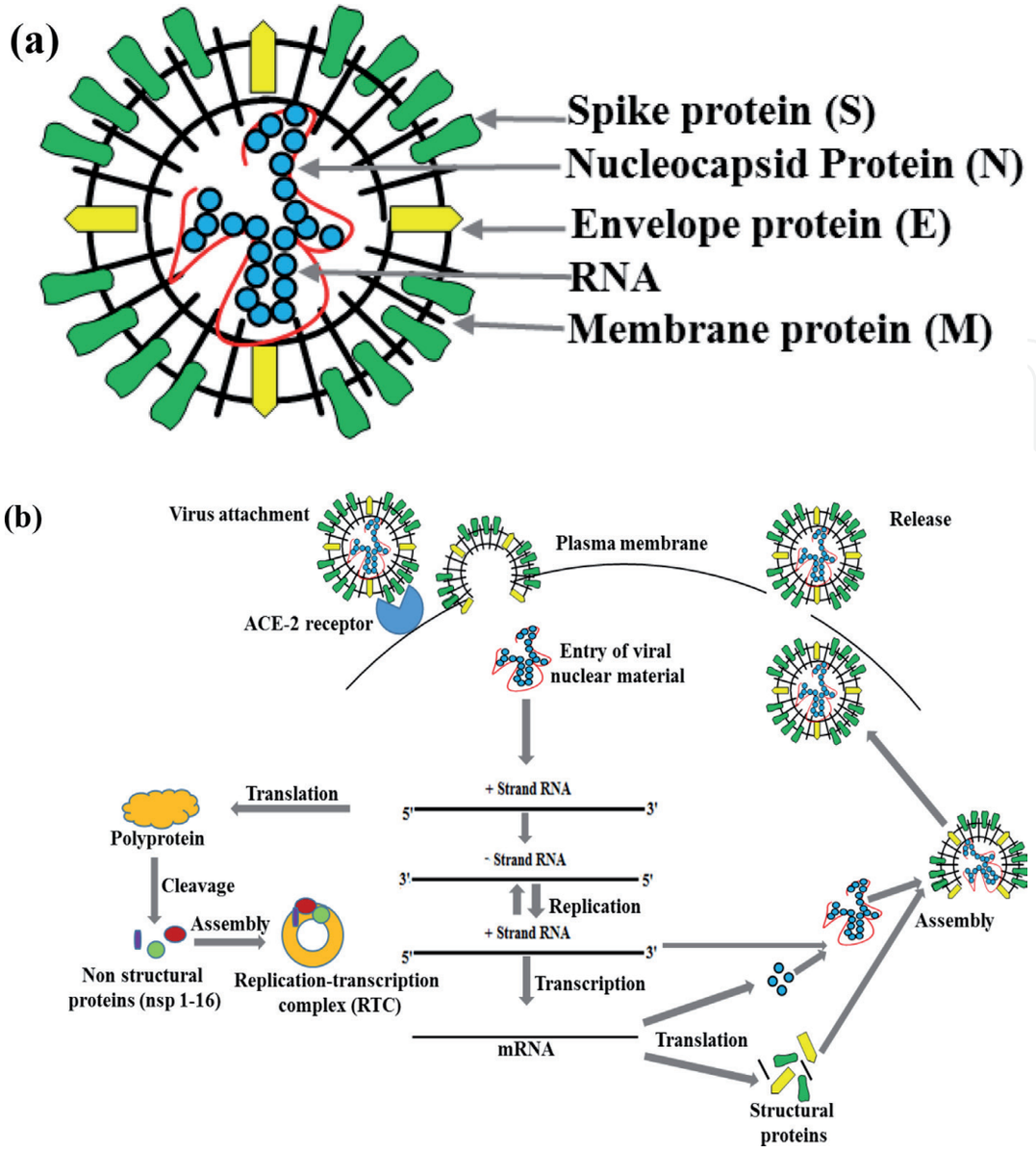

Figure 3.
(a) Basic structure of Covid-19, (b) life cycle in the host.

RNA. Sub-genomic RNAs serve as mRNAs for the translation of structural proteins. The structural proteins and viral genomic RNA assemble in the endoplasmic reticulum (ER) - Golgi intermediate compartment (ERGIC) mediated by M protein to form the mature virions. Ultimately, the virions are transported to the cell surface through smooth-wall vesicles and released by exocytosis for subsequent rounds of infection [3, 25].

4. Clinical symptoms

SARS-CoV-2 attacks the lower airway as the primary target of infection, causing a respiratory and systemic illness that subsequently progresses to a severe form of pneumonia in 10–15% of patients [26, 27]. Clinical symptoms of COVID-19 vary from asymptomatic state to critical illness, with acute respiratory distress (ARDS), acute cardiac injury, multi-organ failure (MOF) and at the end, development of small blood clots throughout the bloodstream (intravascular coagulopathy) [17, 28]. The symptoms of COVID-19 illness are cough, fever, fatigue, headache, muscle pain (myalgia),

difficulty in breathing (dyspnoea), decreased lymphocytes in blood (lymphocytopenia), lower platelet count (thrombocytopenia), etc., which are indifferent from other respiratory infections [29]. However, the unique clinical symptoms of COVID-19 are runny nose (rhinorrhea), sneezing, sore throat, presence of infiltrate in the upper lobe of the lung that causes shortness of breath and subsequent decreased level of oxygen in the blood (hypoxemia), detection of viral RNA in samples of plasma, serum, whole blood, etc., (RNAemia) and sometimes gastrointestinal symptoms like diarrhea [29]. The incubation period of the virus is usually between 3 to 7 days on average, however with 1 day as the shortest and 14 days longest is observed in some circumstances. The symptoms of infection appear after the average incubation period of 5 days approximately however, the average time from onset of symptom to dyspnoea is five days, ARDS is eight days, and death is 6 to 41 days with a median of 14 days [18, 29, 30]. These periods are variable and dependent on several parameters like age and immunity of the patient, typically shorter periods are observed for patients above 70 years old [30].

5. Diagnosis and treatment

As discussed in the previous section, based on the preliminary clinical features such as fever, sore throat, and dry cough of a suspected COVID-19 infectee can be investigated to confirm the exposure history of the person. In some of the cases, this may be asymptotic, i.e., showing none of the above mentioned clinical symptoms, hence, in those cases, the detection of viral genomic material is considered as the only reliable source of COVID-19 diagnosis. The method includes taking the samples from the (suspected) infectee in the form of nasopharyngeal swab, sputum, bronchoalveolar washing, endotracheal aspirates, followed by RNA extraction and subsequent analysis by reverse transcription polymerase chain reaction (RT-PCR) for synthesis, amplification, and identification of viral nucleic acid [18, 25]. Since RT-PCR based techniques take a relatively longer time, therefore, the development of rapid diagnosis kits is on works. Clustered regularly interspaced short palindromic repeats (CRISPR) based diagnostics are such techniques believed in delivering the results within an hour without the need for sophisticated laboratory equipment. Based on this technology, SHERLOCK and DETECTR are two test methods developed by Sherlock Biosciences, and Mammoth Biosciences, respectively and waiting for clinical verifications and approvals [31]. Another sophisticated approach would be a serological assay in which the antibodies from the blood sample of the patients are analyzed to detect viral infections. Computed tomography (CT) imaging is also a highly specific and sensitive method and a chest CT scan of the patients generally shows ground-glass opacities and infiltrates [17, 18].

As of the time, there are no specific, effective and proven antiviral drugs (and/or) vaccines for the treatment of COVID-19 infection, so treatments are limited to support and palliative care only. The first-line treatment emphasizes maintaining hydration and controlling fever and cough through routine dosages of antipyretics and expectorants [32]. Patients with severe respiratory distress should be administered with supplemental oxygen. The alternative treatment is based on the use of broad-spectrum antiviral drugs like neurominidase inhibitor (oseltamivir), nucleotide analogues (remdesivir), nucleoside analogues (ganciclovir), HIV-protease inhibitors (lopinavir, ritonavir) that can reduce the virus infection [33, 34]. As per a recent report by Chen et al. (2020), the effective dosage for the treatment of COVID-19 patients includes oral administration of 75 mg oseltamivir, 500 mg lopinavir, 500 mg ritonavir twice a day and the intravenous administration of 0·25 g ganciclovir for 3–14 days [35]. Also, it is reported by many researchers that

the antimalarial-drug chloroquine could effectively inhibit the virus by virtue of its immune-modulating activity [36, 37]. Deng et al. (2020) confirmed the antiviral activity of Arbidol (small indole derivative molecule) on COVID-19 patients and the antiviral activity against SARS-CoV and also it blocks the viral fusion against the influenza A and B viruses and hepatitis C viruses [10, 38]. A clinical candidate, EIDD-2801, with high therapeutic potential against the influenza virus, is in development, which can be a promising drug to be considered for the COVID-19 [39].

In addition to this, the synthetic recombinant interferons could be used for the treatment of COVID-19 based on their effectiveness against SARS-CoVs and MERS-CoVs [10]. It is also discussed that a small recommended amount of vitamin C supplementation could effectively prevent COVID-19. Convalescent plasma therapy in which plasma of patients recovered from COVID-19 enriched with virus neutralizing antibodies is administered in a prophylactic manner to prevent infection in high-risk cases could also be an effective approach to alleviate COVID-19 infection. On 31st March 2020, the first US patient received convalescent plasma therapy for the COVID-19 treatment [40]. In the latest development, Caly et al. (2020) reported that Ivermectin existing anti-parasite inhibited SARS-CoV-2 and a single treatment, reduced approximately 5000 fold viral RNA in 48 h in in-vitro [41]. However, the anti-parasitic drug is not approved by U.S Food and Drug Administration (FDA) due to lack of well-designed clinical trials. It is also recommended that the existing related vaccines for RNA virus including encephalitis B and influenza, etc., could be explored as possible alternatives until the development of an effective COVID-19 vaccine. There is an urgent need to establish a nonhuman animal model for a better understanding of the virus-host interactions and subsequent testing of potential drug/vaccines for COVID-19 infections [17].

6. Preventive measures to control the spread of the infection

Since there is limited availability of effective treatment for COVID-19, therefore, currently, *prevention* is used as a vital step in controlling the (community) spread of the infection. However, some unique features of the disease like a transmission from asymptomatic people, long incubation period, and infectivity in the incubation period even before the onset of symptoms, prolonged illness, and transmission after recovery, etc., make the preventive measures really more challenging [18]. First of all, extensive measures should be taken to limit human to human transmission with an emphasis on susceptible populations like healthcare providers and older people to prevent further transmission amplification and spread [42]. The second essential step must be the facilitation of advanced health surveillance systems along with rapid diagnostic facilities for the identification of cases. It should be followed by quarantine or isolation when necessary, with intensive care for patients and contact tracing for preventing further transmission by contacts who are infected [43]. Patients should be isolated in well ventilated room with regular decontamination, and they should follow cough and sneeze hygiene, practice hand hygiene and should be asked to wear surgical masks to prevent infection spreading. The healthcare workers attending the patients should be advised to use personal protective equipment (PPE) like gloves, N95 masks, goggles, protective suits, etc. The use of masks by healthy people though not recommended by WHO, owing to the recent finding by Japanese scientists that simple conversations in close proximity without coughs and sneeze could spread the virus through micro-droplets, it is advisable to wear masks, particularly in crowded public places [44]. Owing to the community spread nature of the virus, the government's action to ban mass gatherings is an important preventive step and locking down cities, states, provinces as part of

the action plan of many governments, including India, the US, European Union, etc., will definitely be beneficial in flattening the pandemic. Physical contact with inanimate objects should be avoided since coronaviruses can remain infectious on these surfaces for up to 9 days, however, surface decontamination with ethanol (> 70%) or 0.1% sodium hypochlorite can significantly reduce the virus infectivity even within 1 min exposure time [45]. The public should avoid non-essential travel to places with ongoing transmission and the countries should strictly implement preventive measures like travel screenings and quarantining of the travelers to control further spread of the infection. In countries with resource limitations, to triage a large number of cases, the proposed simple screening algorithm by Ayebare et al. (2020), as shown in **Figure 4** can be followed for effective infection prevention and control [46].

International collaborations and co-operations are highly essential to minimize social as well as economic disruptions [43]. The government's strategy for timely education and training of hospital staff and health care providers along with awareness and counseling to the general public about the risks of COVID-19 are absolutely necessary for minimizing the spread of the infection and managing an economic downturn. However, during this crisis, personal rather than government

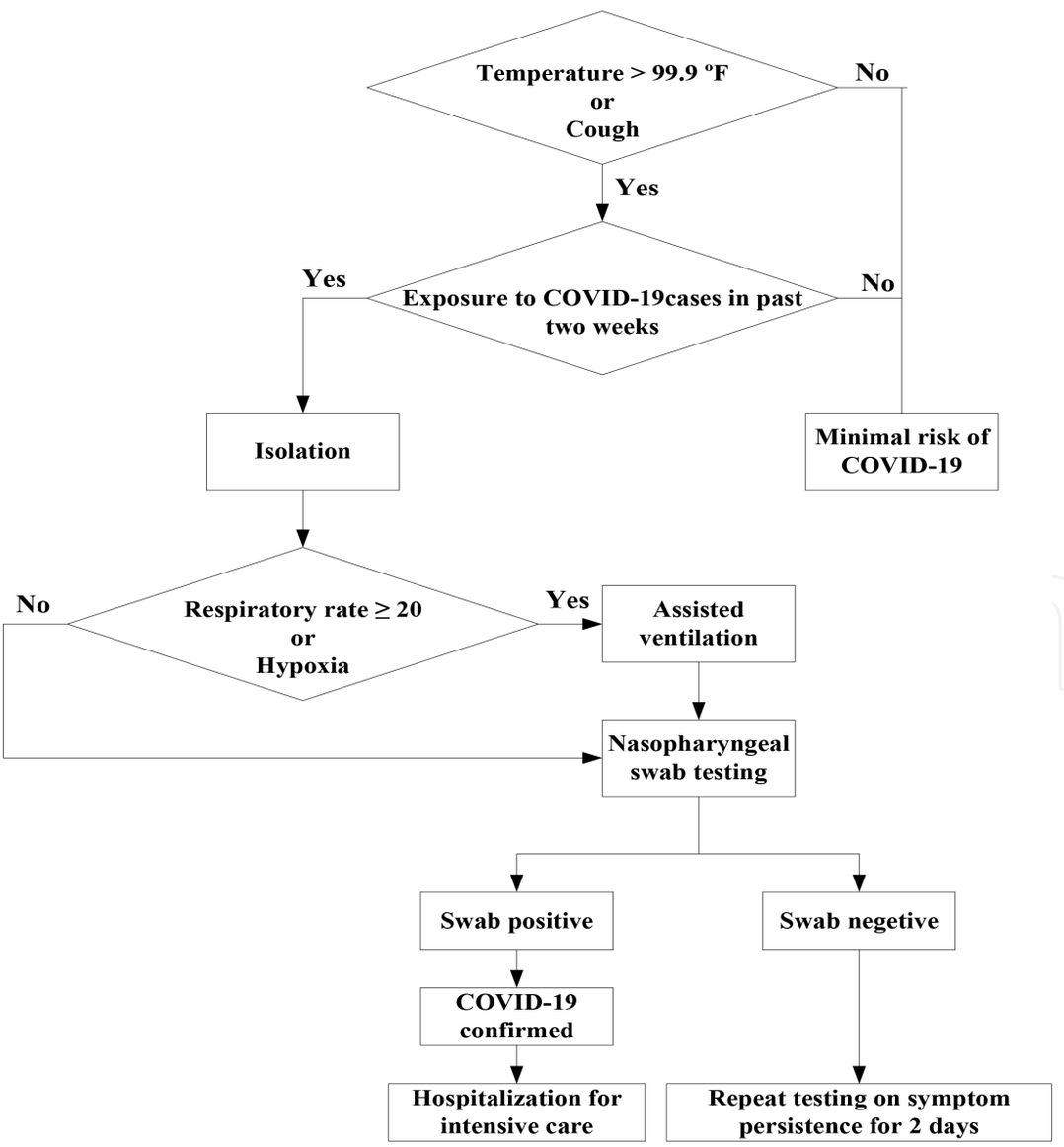

Figure 4.
Outline of infection prevention and control (IPC) strategies.

S.No	Trade name of the vaccine	Company and country	Remark
1	Comirnaty	German company BioNTech, American company Pfizer	RNA vaccine
2	Covishield	Oxford–AstraZeneca COVID-19 vaccine	viral vector vaccine
3	Sputnik V COVID-19 vaccine	Russian Gamaleya Research Institute of Epidemiology and Microbiology.	viral vector vaccine
4	BBIBP-CorV	China National Pharmaceutical Group (Sinopharm)	inactivated virus vaccine
5	Johnson & Johnson COVID-19 vaccine	Janssen Pharmaceutica and Beth Israel Deaconess Medical Center.	viral vector vaccine
6	Moderna COVID-19 vaccine	American company Moderna	RNA vaccine
7	CoronaVac	Chinese company Sinovac Biotech.	inactivated virus vaccine
8	Covaxin	Bharat Biotech, India	inactivated virus vaccine
9	Convidecia	Chinese company CanSino Biologics and the Beijing Institute of Biotechnology of the Academy of Military Medical Sciences.	viral vector vaccine
10	EpiVacCorona	Russian State Research Center of Virology and Biotechnology VECTOR	peptide vaccine
11	RBD-Dimer	Chinese company Anhui	subunit vaccine
12	WIBP-CorV	China National Pharmaceutical Group (Sinopharm)	inactivated virus vaccine
13	CoviVac	Chumakov Centre at the Russian Academy of Sciences.	inactivated virus vaccine

Table 1.
Showing developed vaccine details for Covid-19 infection.

action might be most important and individual behavior will definitely play a crucial role in infection prevention and control the spread of COVID-19. To date some of the countries have approved many anti-viral drugs as pharmacological treatment strategies for COVID-19. However, some approved COVID-19-specific vaccines are available (**Table 1**). Several companies have developed various vaccine candidates for human CoV infections which are in the clinical trial stage [47].

7. Future challenges in controlling the global pandemic

From the end of July 2020, an increase in new cases of SARS-CoV-2 infections was appeared in the different geographical territories of the European Union, confirmed about the origin of the second wave of outbreaks of these infectious diseases. On September 20, a new variant type of SARS-CoV-2, called B117, was first time identified in the United Kingdom (UK). Also, In December 2020, an unexpected rise in reported COVID-19 cases was observed due to the emergence of a new variant of SARS-CoV-2 (B.1.351) in South Africa. However, it was observed that that B117 is far more transmissible with comparatively less fatality rate [48–51]. Hence, it is important to correlate the mutation of the virus as well as the degree of pathogenicity. The existence of

genetic diversity and specific mutations in the genome of SARS-CoV-2 and the virulence property has been investigated by Abdullahi, et al. In this work, they focused on the mutations of the non-structural proteins (NSPs) such as nsp 2 and nsp 3, Spike protein and RNA-dependent RNA polymerase (RdRp). The spike protein is the key determining factor for the evolution, virulence and transmission [52]. Similarly, the enhanced infection property and pathogenicity in case of SARS-CoV-2 is related to mutation at S-protein receptor-binding domain, has been studied by Padhi and Tripathi [53]. To address the significance of mutation to infection, Yao et al. conducted an experimental work by considering eleven numbers of SARS-CoV-2 viral isolates and observed that the mutations are directly related to the increase in viral load as well as a cytopathic effect [54]. Bakhshandeh et al., emphasized that the gradual accumulation of the genomic mutation in SARS-CoV-2 are having a crucial role in genetic variability of the virus. This helps the virus to escape from the host cell immunity and converts the strain in to a drug resistance virus with more deadly behavior [55]. Another recent study has uncovered that the rate of infection of novel corona virus is not only due to the mutation of the viral genome but also associated with host genetics, the genetic and epigenetic variations of the human population. For example, the ACE2 gene variation might be the key genetic factor for SARS-CoV-2 infection that facilitates the virus entry into human cells [56].

Currently, several strategies are being followed, such as contact tracing of infected people, enforcing the social distancing, maintaining the quarantine, and restricted mobility of people and use of disinfectant for self-protection purpose. However, none of these methods have proved to be effective in controlling the global pandemic caused by COVID-19. Usually, there are three basic areas that is to be emphasized more for the best control of the global pandemic [57–64].

1. Mass vaccination of the people:

2. The government of each country should take the initiative for the mass vaccination for all the people that may be the most effective way of control. However, it may be challenging as the country should cross the financial burden and human resources to develop the technology as well as the material for mass production of the vaccine. Also, international collaboration for the same may be fruitful. In addition to this, the possible long term efficacy and the side effects of the vaccine should be well-studied.Herd immunity

3. Several studies have proved that the COVID-19 infection leads to the production of antibodies in the patient against the SARS-CoV-2. So, if a large group of the population will induce resistance for the virus in their immunosystem, then it is expected that the entire population may be protected gradually, called herd immunity. However, the establishment of herd immunity in the population is determined by a large number of molecular and immunological factors. Also, frequent change in the viral genome may be another hurdle for acquiring herd immunity.Implementation of new technologies

In order to protect the human population and in the limited effective treatment strategy for COVID-19 infection, the implementation of new and effective online technologies in different sectors is desirable. These technologies will help the people in the timely response and control of epidemics in the areas of public training, education, medication, including digital surveillance systems, telemedicine, rapid identification and diagnosis devices, and prediction about the future infection.

8. Conclusion

The global impact of coronavirus disease is one of the heightening concerns of the present time. Though at this stage, it is not possible to determine the precise source of the coronavirus, however, the bats are considered as their natural hosts based on the available sequence based phylogenetic study. Genomic analysis revealed the arrangement of gene order and ORF positions. The largest genome RNA of coronavirus might be the reason behind the *intraspecies variability* and *interspecies transmission* via mutations and recombination mediated flexible genome modifications. Therefore, future outbreaks of zoonotic viruses cannot be overlooked. So, to avoid the future threat of zoonotic viral outbreaks, comprehensive measures should be planned alongside curbing this corona pandemic. In addition to this, the mutation acquired by the virus from time to time changes its pathogenicity is a concern. So a thorough study is essential to establish the relationship between the mutated forms of the virus with respect to the different geographical areas to predict the future genotypic pattern change of the virus. Further, in-depth investigations at individual protein levels of the virus are necessary to precisely predict the origin, to predict mutation mediated evolutionary selection pressure, and for a better understanding and development of the potential drug molecule binding efficacy.

Author contributions

All authors contributed equally to the conception of the study, data analysis and interpretation and drafting the article and final approval of the version to be submitted.

Conflict of interest

The authors declare that they have no known conflict of interests.

Ethical approval

Not required.

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