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Review Article

The World under Lockdown: A Brief Sketch of Three Emerging Deadly Coronaviruses in Last Two Decades with Special Reference to Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-Cov-2; Coronavirus Disease-19)

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ABSTRACT

Pathogenic viruses are viruses that can infect and replicate within human/animal cells and cause several deadly diseases. The uninterrupted emergence and re-emergence of many deadly viruses have become a major threat to public health worldwide. A novel coronavirus named Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) was first isolated from a lower respiratory tract sample from Wuhan City of Hubei province in China in late 2019 December. The current outbreak of pandemic infections with SARS-CoV-2 is named Coronavirus Infectious Disease 2019 (COVID-19) by the World Health Organization (WHO). The Government of various nations already took necessary steps to stop the outbreak from rising into a global health emergency, but unfortunately now it became a serious problem for whole globe and end up in the complete lockdown of the world. We have also witnessed another 2 novel coronavirus outbreaks in the past 2 decades and they are Severe Acute Respiratory Syndrome (SARS) in 2002–2003 and Middle East Respiratory Syndrome (MERS) caused by MERS-CoV between 2012 and 2019 and these viruses leads to severe mortality among the people worldwide. This review aggregates and consolidates the pathology, genomic structure, pathogenesis, epidemiology, clinical manifestations, diagnosis, treatments, control and preventions of the coronaviruses with special reference to SARS-CoV-2. Many viruses infect humans and most are successfully controlled by our immune system with limited damage to the host. But certain viruses severely damage the host tissues beyond the control of the immune system. So, finally we can discuss on the immunity and immunopathology of our body against the SARS-CoV-2 attack. No therapies have been shown effective to date, but several potent candidates of antivirals and repurposed drugs are under urgent investigation. Hope a few potent antiviral drugs will come soon in market to fight against SARS-CoV-2. In conclusion, although various treatments have been proposed, self-quarantine is the only intervention that seems to be effective in reducing the SARS-CoV-2 contagion rate. Still, public health authorities should keep watching the situation closely, as the more we can learn about this novel virus and its associated outbreak, the better we can respond.

Keywords: SARS-CoV-2; COVID-19; Transmission; Prevention; Immunopathology

INTRODUCTION

The emergence of several infectious diseases has been a major threat to public health and global stability in terms of productivity. In history, emerging viral infections have caused the fatal catastrophic pandemics such as the influenza pandemic during 1918 (nearly 50 million lives) and the HIV/AIDS pandemic (nearly 35 million lives so far), etc. [1]. Emerging viral infectious disease incidences in humans have increased within the past two decades or will continue to threaten the coming years. This emergence of various deadly diseases especially viral origin can be caused by the spread of a novel pathogen, or by the re-emergence of an identified pathogen after a fall in infection [2]. Biological, social and environmental factors have been connected to the appearance of various infectious diseases. These include genetic changes of the microbes through rapid evolution, also the changes in the way human populations interact with each other, and with their environment. Furthermore, increased susceptibility to infection due to immunocompromised condition, the increased facility of international travel among people, weather and climate changes, have also been associated with novel diseases emergence especially caused by viruses. Pathogenic viruses that cause emerging diseases are called emerging deadly viruses. These emerging viruses are now playing a very important role in the various pandemic infections affecting worldwide recently especially causing respiratory infections [3].

Several viral species are identified to cause severe respiratory diseases in humans and this includes mainly rhinovirus, influenza virus, respiratory syncitial virus, SARS, varicella-zoster virus, adenovirus, cytomegalovirus, and viral hemorrhagic fever [4]. Out of above mentioned respiratory viruses, coronavirus especially SARS-CoV-2 causing COVID- 19 (Coronavirus infectious Disease 19) plays a significant role in the mortality of humans around the globe and this further led to the declaration of global health emergence by WHO (Figure 1).

SARS outbreaks during 2002–2003 [5,6] and MERS during 2012-current [7] in the last two decades are a significant threat to global public health among people. SARS and MERS signify a new class of public health concerns that may continue to emerge into human populations: respiratory disease syndromes caused by Coronavirus Species (CoVs) that are transmitted from person-to-person via close interaction, resulting in high morbidity and mortality in infected persons. Although SARS and MERS initially present as mild, influenza-like illnesses with fever, dyspnea, and cough, progression to more severe symptoms are characterized by atypical interstitial pneumonia and further leads to diffuse alveolar damage. Both SARS-CoV and MERS-CoV are capable of causing Acute Respiratory Distress Syndrome (ARDS), which is the utmost severe form of acute lung injury where alveolar inflammation, pneumonia, and hypoxic lung conditions that leads to respiratory failure, multiple organ disease/damage. Normally death will occur in 50% of ARDS patients if not treated properly [8].

Coronaviruses have been recognised in several avian hosts, as well as in many mammals, including camels, bats, masked palm civets, mice, pigs, dogs, pangolins and cats [9]. Novel mammalian coronaviruses are now regularly emerging from various animal sources are critically dangerous to humans [4,10]. These emerging viral diseases are frequent public health threats due to their capability to develop initially a small outbreak and which will further lead to major epidemics and pandemics in a short span of time. On 31st December 2019 Chinese health authorities announced a number of pneumonia infections in Wuhan city (Hubei province) without a known aetiology. The first reported patients in Wuhan with pneumonia had a back history of visiting or association with some local wet market where illegal wild animals are sold for meat [11].

On 7th January 2020, the Chinese Center for Disease Control and Prevention (Chinese CDC) identified a novel strain of coronavirus from the samples of the lower respiratory tract of the patients with pneumonia and revealed its genomic sequence on January 11th 2020 [12]. This novel coronavirus was later named Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). The WHO named the infection caused by SARS-CoV-2 as Coronavirus Disease 2019 (COVID-19) [13]. On March 11th 2020, the WHO declared COVID-19 outbreak as a pandemic infection [13]. In spite of the several efforts to stop the transmission of COVID-19, the infection spread throughout the mainland of China, and in mid-January 2020, several new cases were reported in Thailand, Japan, and South Korea [14]. Within less than 11 months since the discovery of the SARS-CoV-2, the infection spread to at least 188 countries with 85,141,293

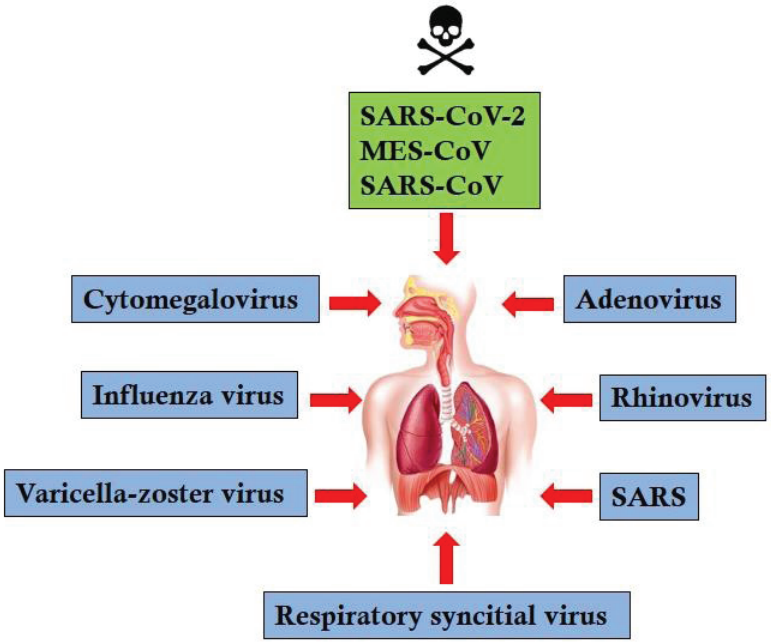

Figure 1: Major viruses infecting the respiratory tract of humans. In the current scenario, SARS-CoV-2 causing COVID- 19 is highly dangerous due to its fast spreading among persons resulted in a global health emergency.

positive cases and caused more than 1,843,479 deaths (As on 4th January 2021) worldwide.

Since the first epidemic of SARS, thousands of people worldwide were harmed by the pathogenic coronaviruses. Considering the severe adverse outcomes of the current COVID-19 epidemic, developing effective novel therapeutic strategies is necessary to cope with the lack of effective drugs, high mortality rate, and the potential of the virus to cause further epidemics. In this review, we initially focus on the origin, evolution, and pathogenicity of SARS-CoV, MERS-CoV, and SARS-CoV-2. The review will further focus on the basic epidemiology, virology, treatment, prevention, control measures, host immune response and immunopathology of SARS-CoV-2. Through this review we will shed light on the basic foundation, clinical care, prevention, public health, medical therapeutics, immunity, immunopathology and various clinical trial practices of the above-mentioned viruses with special reference to SARS-CoV-2. This will enhance the research and developments to take appropriate countermeasures such as prevention and mitigation from the bench to the bedside especially to SARS-CoV-2. This review will be really useful in the preparation against future viral outbreaks and continuing pathogenic contagions by this class of novel coronaviruses virulent to humans.

THE THREE EMERGING MOST DANGEROUS CORONAVIRUS DISEASES THAT AFFECT OUR RESPIRATORY SYSTEM-THE STORY BEHIND SARS, MERS, AND NOW COVID-19: SIMILARITIES AND DIFFERENCES AMONG THEM

SARS-CoV

In the past 20 years, the world has witnessed the emergence and the outbreak of three main deadly coronaviruses that have caused significant global health concern. The SARS-CoV outbreak in 2002 started first in Guangdong provinces of China, and from there it further spread to several countries in Southeast Asia, North America, Europe, and finally South Africa. The origin of this virus is bats. Transmission of SARS-CoV was mainly person to person through droplets that comes out during coughing or sneezing, through personal contact (which include shaking hands), or by touching SARS-CoV contaminated surfaces and objects [6]. Unfortunately, health care professionals were predominantly at high risk of getting this disease, as transmission of this disease also occurred if isolation precautions were not followed strictly according to the health care protocols. The last case of SARS-CoV was reported in September 2003, after having infected more than 8,000 persons and resulting 774 deaths with a case fatality rate calculated at 9.5% [6,15].

MERS-CoV

After nine years, another novel coronavirus that causes severe respiratory disease appeared in the Middle Eastern region of the world and named MERS-CoV. Similar to that of SARS-CoV the origin of MERS-CoV is also bats. Symptoms of MERS-CoV are mainly nonspecific, but many patients finally end up with severe acute respiratory distress. In all these patients, travel history is imperative, as all cases have been linked to the persons in or near the Arabian Peninsula. Very similar to SARS-CoV, health care professionals are at higher risk of getting this disease [15]. However, in comparison with SARS-CoV, MERS-CoV is still circulating among individuals, and the case fatality rate is very much higher (around 35%) compared to that of SARS-CoV [15,16].

COVID-19

The origin of source of the SARS-CoV-2 is also bat and the

intermediate host is suspected to be Malayan Pangolin, although the initial cases have been reported from the wet market of China. Though many of the early patients worked in or visited the market, none of the exported cases had contact with the market, signifying either human to human transmission or a more widespread animal source is the primary route of this disease [17]. In addition to seafood market, it is well reported on the social media that snakes, birds and other small mammals including pangolin, marmots and bats were sold at the Huanan South China Seafood Market. The WHO reported that various environmental samples taken from the market place for analysis recorded positive for the novel coronavirus, but no precise animal association has been identified as the primary source of this virus [17]. An early report regarding the primary source suggested that snakes might be the most likely source based on genetic analysis and codon usage [18], but this claim has been well rejected by other investigators through various scientific analysis [19]. Scientists are now presently working to identify the exact source of SARS-CoV-2 including possible intermediate animal vectors for transmitting the disease and now based on the scientific studies it is recorded that most possible intermediate host is Malayan pangolin [20,21].

MAJOR SIMILARITIES AND DIFFERENCES OF SARS- COV, MERS-COV AND SARS- COV-2

A zoonotic reservoir is a major source for the emergence of both SARS-CoV and MERS-CoV. SARS-CoV, the first highly pathogenic human CoV, emerged in 2002 with transmission from animals to humans which first occur in wet markets of China (Guangdong provinces). Investigations found the presence SARS-CoV viral RNA in both palm civets and raccoon dogs sold in these wet markets [22]; however, SARS-CoV was not yet all found in the wild, which signifies that those animal species sold in the wet market served as intermediate host reservoir where the virus undergoes certain adaptions to infect more efficiently against humans (Figure 2). Further research identified that this virus is highly related to CoVs found in bat species [23]. But further studies have confirmed that several bat CoVs are capable of infecting humans without a need for intermediate host adaptations [24,25]. Moreover, serology data shows the presence of bat CoV proteins in the samples and this indicates that low-level zoonotic transmission of SARS-like bat coronaviruses occurs outside of recognized outbreaks [26]. As stated earlier, MERS-CoV is also a zoonotic virus with most possible origins in bats [27,28], although camels are endemically infected with this virus. Moreover, close contact with camel is regularly reported during most of the primary cases of MERS-CoV [29]. In case of SARS-CoV, strict quarantine and the get rid of wet markets play a very important role in controlling the spread of the disease. Interestingly, the Asian continent played a major role in origination and ending of SARS-CoV outbreak. Due to the ethnic importance of camels in the Middle East, a similar approach for MERS-CoV was not an ideal option and periodic outbreaks continue in these areas still now. These findings from SARS and MERS highlight the importance of quickly finding the exact source for SARS-CoV-2 to control the ongoing deadly outbreak of this disease [14].

SARS-CoV was identified as a major human CoV that causes

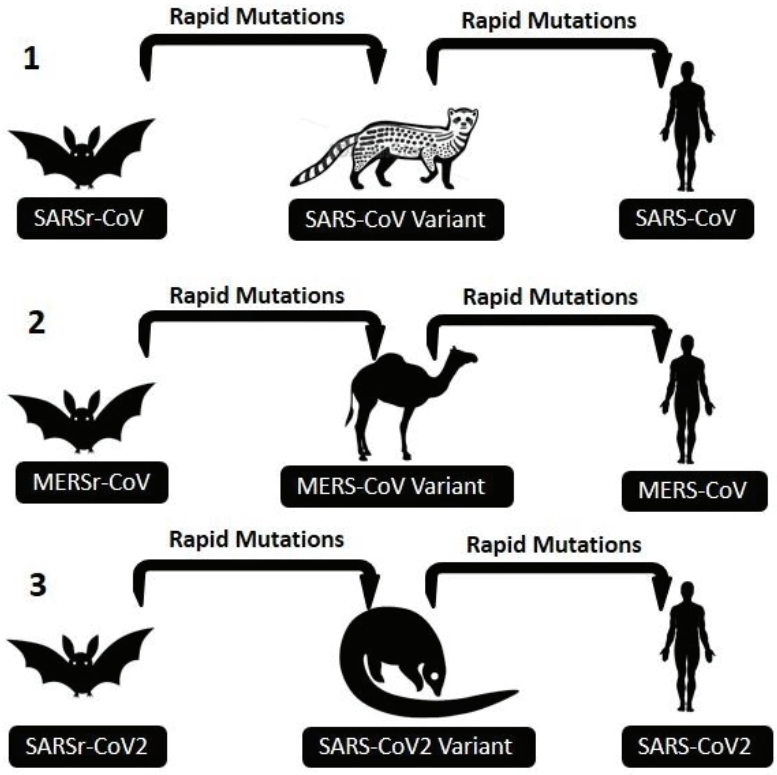

Figure 2: The primary source and further evolution of (1) SARS-CoV, (2) MERS-CoV, and (3) SARS-CoV-2 in different hosts during its infection period. All the above viruses originally present in bats as bat coronaviruses (SARSr-CoV, MERSr-CoV, and SARSr-CoV-2) before attaining rapid mutations and further adapted to live in intermediate hosts and finally infect the humans.

Severe Acute Respiratory Syndrome (SARS) in the 2002–2003 outbreak that occurred in the wet market of China and resulted in infected cases and death that were continued to infect over nine months (fatality around 10%) (Table 1) [5]. SARS-CoV was reported to infect unciliated bronchial epithelial cells and type II pneumocytes which resulted in high fever, cough, shortness of breath, and several other severe complications reported are pneumonia and kidney failure etc. [5,30]. The incubation period for SARS-CoV was assessed to range initially from 2 to 10 days and may extend up to 14 days (Table 1) [31]. Further research has recorded that CoVs found in bats are ancestral to SARS-CoV (Table 1) [32]. Civets and raccoon dogs sold at Chinese local wet markets were reported to harbour SARS-like CoVs (Table 1) [33]. The detection of SARS-related CoVs (SARSr-CoVs) in bats and small animals in retail wet markets may point to an interspecies transmission of this virus from bats to small animals especially mammals and finally to human beings (Figure 2). Studies on bats/bat samples from various regions of China have led to the identified several SARSr-CoVs [23]. The earlier studies specify that SARS-CoV has been circulating among the bats for a long period before undergoing various genetical changes through evolution and finally attack the humans. Later studies identified Angiotensin-Converting Enzyme (ACE) 2 was receptor gene for SARS-CoV and it is not surprising that SARS-CoV has adapted itself to bind human ACE2 and thus efficiently infect human cells [32]. That kind of adaptation in the receptor requires sequences of changes in the set of amino acid in the Receptor Binding Domain (RBD) region of SARS viruses S protein that was circulating in bats [32]. Hence, we conclude that the human-to-human transmission that was witnessed during the outbreak of SARS-CoV is recognised to the capability of SARS-CoV to adapt its S protein (particularly RBD) to proficiently bind to human ACE2 and finally infect airway epithelia (Table 1). The comparative studies between SARS-CoV, MERS-CoV, and the SARS-CoV-2, with respect to receptor usage, primary and intermediate hosts, incubation period, number of cases and deaths, and basic reproduction number

Table 1: General, biological and clinical characteristics of the three major human coronaviruses: SARS-CoV-2, SARS-CoV, and MERS-CoV infections.

Characteristics	SARS-CoV-2	SARS-CoV	MERS-CoV
General			
Disease	COVID-19	SARS	MERS
Distribution	Pandemic	Pandemic	Endemic
Origin	Hubei, China	Guangdong, China	Saudi Arabia
Global death	1,843,342 (as on 4th January 2021)	774	858
Biological			
Incubation period	2-14 (5.2) days	2-10 (7) days	2-10 (5.5) days
Median age of infected patients	59 years	65 years	50 years
Sex predominance	Male	Male	Male
Genetic nature of virus	Positive-sense single-stranded RNA	Positive-sense single-stranded RNA	Positive-sense single-stranded RNA
Mode of transmission	Animal to human Human to human Zoonotic disease	Animal to human Human to human Zoonotic disease	Animal to human Human to human (rare) Zoonotic disease
Transmission ways	• Respiratory droplets • Close contact with diseased patients • Possibly faecal-oral • Possibly aerosol	• Respiratory droplets • Close contact with diseased patients • Possibly faecal-oral • Possibly aerosol	• **Respiratory droplets** • **Close contact with diseased patients/camels** • **Ingestion of camel milk**
Contagious period	Not known	10 days after onset of disease	Once virus could be isolated from infected patients
Speed of spread	Very high	Moderate	Low
Seasonal occurrence	Winter (Dec-Jan)	Winter (Dec-Jan)	Summer (May-July)
Reservoir	Bat	Bat	Bat
Intermediate host	Malayan pangolin	Masked palm civets	Dromedary camels
Clinical			
Headache	*	*	*
Fever	**	**	**
Chills	**	**	**
Generalized myalgia	**	**	**
Malaise	*	*	*
Drowsy	*	*	*
Confusion	*	*	*
Lethal disease	Severe pneumonia	Elderly and persons with pre-existing conditions	Elderly and persons with pre-existing condition

*(Mild), ** (Moderate), *** (Severe)

(R_0) is depicted in the table 1.

MERS-CoV was first reported in 2012 as a novel CoV that also causes a severe respiratory disease in Middle Eastern region especially Saudi Arabia. As of January 2020, and since 2012, 862 of 2506 infected cases in 27 countries around the world have died (more than 35% fatality), which is more than three times the mortality recorded in SARS-CoV infections (Table 1) [34]. On the other hand, unlike SARS-CoV, human-to-human transmission of MERS-CoV is not very easy and has not been established except in a few cases of very close contact with infected persons with the health care professionals [34]. MERS-related CoVs (MERSr-CoVs) were identified in bats and this further suggests a potential bat origin for this virus (Figure 2 & Table 1) [35,36]. MERS-CoV was infected to humans from dromedary camels (Table 1) [37]. Various research has also revealed that MERS-CoV strains of camel are virtually identical to human MERS-CoV strains [38]. Thus, it was assumed that MERS-CoV that was existing in camels at least 30 years ago since antibodies to MERS-CoV was detected in samples that were collected from camels in early 1983 [39]. Sequence examinations have revealed that MERSr-CoVs' RBDs share only 60–70% sequence identity with that of human and camel MERS-CoVs [40]. Similar to the adaptation of SARS-CoV to human host, MERSr-CoVs that are circulating in bats have under gone a number of amino acid changes in S protein RBD to develop enough properties that have the capability of infecting both camels and humans [41]. From these informations we believe that the changes in the amino acid sequences in MERSr-CoVs' RBD led to the development of MERS-CoV strains that have the capacity to binds to human Dipeptidyl Peptidase (DPP4) with very high affinity, infecting humans, and finally end up with the 2012 MERS-CoV outbreak in the Middle Eastern regions (Figure 2).

Camels are suspected to be a reservoir of MERS-CoV since the virus has originated in the Middle East and some patients had close contact with camels prior to symptom onset [42]. Further research has concluded that the MERS CoV has been quite frequent among camels and has been spreading from camels to humans for at least the last 20 years, although it is not yet clear how the spreading process occur. Other camelid animals such as alpacas and Lamas is probably involved too [43].

As stated earlier, the SARS-CoV-2 was isolated from persons that presented symptoms of respiratory illness and pneumonia in Wuhan, China during December 2019 and its RNA were also sequenced. Thus SARS-CoV-2 is the third identified human CoV that can cause severe respiratory illness with incubation period and symptoms very similar to that of SARS-CoV and MERS-CoV infections (Table 1) [44]. Since December 2019, SARS-CoV-2 infection rates have been rising first in China and which then spread entire world [11]. Similar to SARS-CoV and unlike MERS-CoV, human-to-human transmission has been well confirmed in SARS-CoV-2 [11].

Initial cases of SARS-CoV-2 infections were some way connected to the Huanan seafood and wet market in Wuhan, in the Hubei province of China [45]. In this market, a number of non-aquatic animals were sold illegally, which includes birds, snakes, marmots, pangolins, bats, and rabbits [45]. Genetic analyses of viral samples from patients with SARS-CoV-2 infections revealed that the virus is a betacoronavirus that has 88% sequence identity to two earlier reported bat SARSr-CoV: 79% identity to SARS-CoV and only 50% identity to MERS-CoV [11]. The various research findings suggest that SARS-CoV-2 is a new virus that is distinct from both SARS-CoV and MERS-CoV. SARS-CoV-2 most probably originated in bats, which is very similar to SARS-CoV and MERS-CoV [11]. Another recent study confirmed that SARS-CoV-2 significantly clustered with a sequence from the bat SARS-like CoV that was isolated in 2015 [46]. To date, the fatality of SARS-CoV-2 appears to be less than that observed in SARS-CoV and MERS-CoV infections. However, enormous number of cases are reporting every day as we write this review, the fatality of this virus may keep changing drastically and will not be accurately calculated until after the end of this massive outbreak. The virus appears to be more fatal in elderly patients or patients with severe comorbidities [10]. However, it is important to note that there could be cases that went undetected, which makes it hard to accurately calculate the fatality of this new virus.

THE SPILLOVER (SPECIES JUMP) THEORY IN THE SPREAD OF CORONAVIRUS FROM BATS TO HUMANS

As happened with several viral diseases such as Measles, Rabies, Ebola, Dengue, HIV-1, Marburg and Lassa fever, Swine and avian Flu (H1-N1and H3-N7 respectively), the novel coronavirus diseases such as SARS in 2003, MERS in 2012 and SARS-CoV-2 in 2019 were also recognized as zoonotic origin [33]. Viruses from some animals (e.g. wild birds, bats, monkeys) have reached human beings through a special mechanism known as species jump or other ways known as spillover, *i.e.*, a biological mechanism linked to animal-human in transmitting the disease. Deforestation, changed ecosystems (which offer shelter for various wildlife), unlawful trading with wildlife/wet market (Bush meat), rigorous animal husbandry, and large-scale supply of uncontrolled animal origin food are the major factors that may have contributed to spillover process. World population explosion and increased intercontinental travel have also provided a major contribution on spillover process in spreading the pathogens from animals to humans [33].

The origin of SARS-CoV, still remains in a big question mark. SARS-CoV virus has been identified in palm civets, dogs, raccoons and Chinese ferret-badgers (Which act as major intermediary source) found in live animal markets from Guangdong region of China. Certain bats species (especially horseshoe bats) which are the primary reservoir of coronaviruses were found to be closely related to those responsible for the first SARS outbreak in 2003 [47]. MERS-CoV was also thought to originate in horse bats that reside in Middle Eastern regions and these infections were transmitted directly to humans from dromedary camels [47]. Extensive investigation on MERS-CoV led to the discovery of several MERS-like coronaviruses in bats which are very similar to SARS and likely to appear periodically in human beings due to frequent cross-species infections and occasional spillover processes. Furthermore, recent investigations specified that bats have certain unique defence mechanisms that allow them to be stubbornly infected with coronaviruses. Few recent outcomes have demonstrated that many coronaviruses associated with bats are highly talented to infecting humans without a need for intermediate host adaptation [48]. Since the mutation in the original viral strains could have directly triggered virulence activity towards human beings and it is not certain that intermediate hosts are exists in spreading the disease.

SARS-CoV-2 also cannot be excluded from the spillover process. In reality, several Chinese patients claim to have visited the Wuhan seafood and wildlife market in November 2019. Besides seafood, it was well reported that snakes, birds and small mammals including

marmots, pangolin and bats, were sold at the Wuhan Market illegally as we said earlier. To this end, the WHO has informed that various environmental samples taken from the Wuhan market for analysis were positive at PCR for the novel coronavirus, but no precise animal association has been recognised [14]. It also appears no bats were being sold at the Wuhan animal market, China, where the present outbreak is supposed to have begun and this suggests that an intermediate host species was likely involved in spreading the disease, which is so far unidentified. Although initially the snakes have been suggested as the intermediate host, but there is no pre-historic evidence of any coronavirus species being hosted by animals other than mammals and birds? But, based on the latest molecular phylogenetic data it is not unlikely that SARS-CoV-2 passed directly from bats to humans deprived of the intermediate host [49].

Whatever the intermediate animal, it cannot be excluded that the spillover effect may involve a mechanism similar to those in SARS or MERS, although there may be other animals involved. But now in case of SARS-CoV-2 pangolin was likely to be the intermediate host for spreading the disease and this supports the spillover mechanism similar to SARS and MERS.

SARS-CoV-2

Virology and genome: Coronaviruses are enveloped, non-segmented, positive-sense single-stranded RNA virus genomes with the size ranging from 26 to 32 kb (the largest known viral RNA genome). The virion has a nucleocapsid which composed of genomic RNA and phosphorylated nucleocapsid protein (N), which is concealed inside phospholipid bilayers of cell wall and this is covered by two different kinds of spike proteins: the (1) spike glycoprotein trimmer (S) which can be found in all types of CoVs, and the (2) hemagglutinin-esterase (HE) that exists in a few CoVs [50,51]. The membrane protein (M) which is type III transmembrane glycoprotein and the Envelope protein (E) are located among the spike glycoprotein trimmer S proteins in the envelope of virus. The name CoVs (Coronavirus) is given based on the characteristic crown like appearance. The general structure of CoV is revealed in the figure 3.

SARS-CoV-2 is an enveloped positive sense unsegmented single strand RNA virus that belongs to the Betacoronavirus genus (Figure 3) [52]. The whole SARS-CoV-2 genome sequences which is isolated from patients living in or visiting Wuhan wet market recorded a genome having a size of 29,844 to 29,891 nucleotides. The genome is encoding approximately 9860 aa and lacks the Haemagglutinin-Esterase (HE) gene [52]. The genome of SARS-CoV-2 has great sequence similarity which is about 89–96.3% with two bat coronaviruses, which is bat-SLCoVZC45 and bat-SL-CoVZXC21, and 79% to 82% with that of human SARS-CoV [12,52].

Coronaviruses are members of the subfamily *Coronavirinae* which come under the family *Coronaviridae* and the order Nidovirales. The *Coronavirinae* subfamily further divides into 4 genera which are alphacoronavirus, betacoronavirus, gammacoronavirus, and deltacoronavirus. To date, 6 coronaviruses are identified to cause diseases in human. Out of this, four coronaviruses are endemic in humans. These are known as human coronaviruses (HCoV) named 229E, OC43, NL63, and HKU1. Other two are epidemic human coronaviruses known as SARS-CoV and MERS-CoV. Alphacoronavirus includes HCoV 229E and NL63, and betacoronavirus includes HCoV OC43, HKU1, SARS-CoV, and MERS-CoV [30].

Inside the coronavirus, a Nucleoprotein (N) wraps the RNA genome to form a coiled tubular structure. The viral Eenvelop (E)

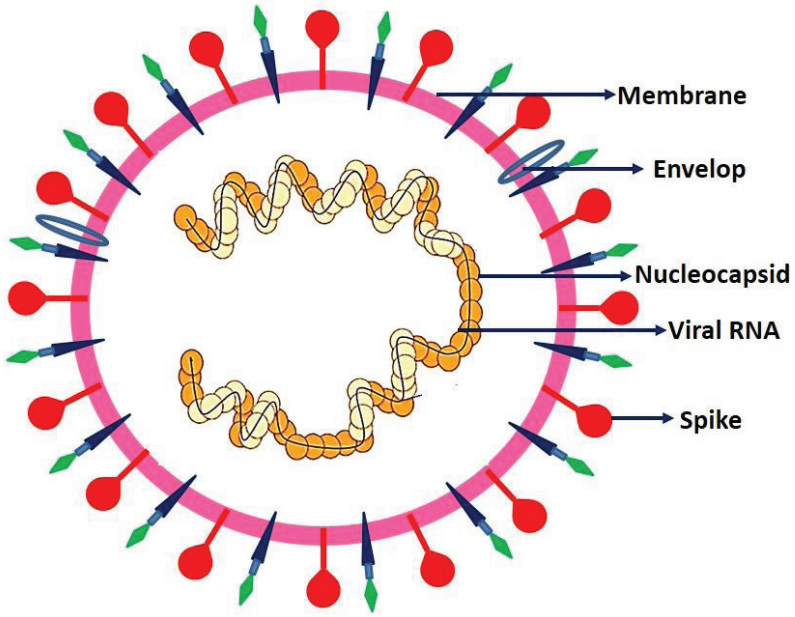

Figure 3: General structure of coronavirus. Coronaviruses are enveloped, non-segmented, positive□sense single□stranded RNA virus genomes in the size ranging from 26 to 32 kb. The virion has a nucleocapsid composed of RNA genome and phosphorylated nucleocapsid protein, which is concealed inside phospholipid bilayers and covered by the spike glycoprotein trimmer. The membrane protein and the envelope protein are situated among the spike glycoprotein trimmer proteins in the envelope of virus.

which mount this helical nucleocapsid. Additional 2 or 3 structural proteins are also associated with viral envelop. The Matrix protein (M) is embedded in this envelop. The Spike structural protein (S) attached in envelop is actually the target of various neutralizing antibody. The hemagglutinin esterase is also found in several types of betacoronaviruses [53]. The coronaviruses have 5 essential genes which are assigned for 4 structural proteins (named N, E, M, S) and for viral replication/ transcription (RNA dependent RNA polymerase known as RdRp). The genome organization is actually represented as 5'-RdRp-S-E-M-N-3'. The whole genome sequencing of SARS-CoV-2 clearly demonstrated that it is a new betacoronavirus which is far different from SARS-CoV [54]. The nucleotide sequence of SARS-CoV-2 recorded 79.0% and 51% identity with SARS-CoV and MERS-CoV, respectively and it is very closely related to bat-origin SARS-like coronavirus (bat-SL-CoVZC45) with 87.6%–89% identity [55,56]. This virus was originally called 2019-novel Coronavirus (2019-nCoV) upon its emergence, until the Study Group of International Committee on Taxonomy of Viruses named it as virus severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) based on the molecular phylogenetic analysis, on 11th February, 2020 [13]. On the same day, the WHO named the disease caused by the novel coronavirus as Coronavirus infectious Disease-2019 (COVID-19), in orientation with WHO best practices for naming of novel human infectious viral disease.

Based on the virus genome sequencing data, bats are expected to be the major reservoir of SARS-CoV-2, but the intermediate host was identified as Malayan Pangolin (further confirmation needed). Scientific data indicate that SARS-CoV evolved from bat coronavirus in horseshoe bats through civet cats or other intermediated animal hosts. MERS-CoV also likely evolved from bat coronavirus, with dromedary camels as intermediate hosts in spreading the disease to human [13].

SARS-CoV-2 epidemiology and transmission: During the past two decades China has witnessed the appearance of three main respiratory virus outbreaks that intern turned into major epidemics which includes avian influenza virus H5N1 in 1997 [57], SARS-CoV in 2003 [5] and the present SARS-CoV-2 during 2019–2020. Only the first reported SARS-CoV-2 cases had associations with the wet market of Huanan, China and the succeeding sources of SARS-CoV-2 infection is through the infected persons. Direct human-to-human transmission is supposed to be the leading route of worldwide spread of the COVID-19 [58]. The intermediate host for spreading SARS-CoV-2 in Wuhan was assumed to be pangolins. Frequent national/ international travel and importation played a major role in the spread of SARS-CoV-2 from China (Wuhan) to the entire world via Korea, Japan, the Middle East, entire Europe and finally USA and Brazil [59,60]. During the initial weeks of the epidemic, the basic Reproductive values (R_0) were calculated to be between 2 and 3.5, which were very much higher than SARS outbreak in 2003 [61,62].

Due to this widespread nature, WHO declared SARS-CoV-2 to be a "Public Health Emergency of International Concern" on late January 2020 and as a "Controllable Pandemic" on 11th March 2020. According to the WHO statistics (as of 4th January 2021) most reported cases were in USA (confirmed: 20,639,219 & death: 351,580), India (confirmed: 10,340,469 & death: 149,649), Brazil (confirmed; 7,733,746 & death: 196,018), Russia (confirmed: 3,203,743 & death: 57,730), France (confirmed: 2,712,975 & death: 65,164), United Kingdom (confirmed: 2,662,699 & death: 75,134), Turkey (confirmed: 2,241,912& death: 21,488), Italy (confirmed: 2,155,446 & death: 75,332), Spain (confirmed: 1,928,265 & death: 50,837) and Germany (confirmed - 1,785,585 & death: 34,793) [63]. More than 55% of populations of the reporting countries are experiencing local transmission of the infection i.e. human to human transmission in a specified region [64]. Shockingly, more than 160000 confirmed cases were reported within the 10th–22ndMarch alone depicted the severity of SARS-CoV-2 [65]. Chinese Centre for Disease Control and Prevention (CCDC) reported that the major routes of human-to-human transmission are through respiratory droplets and contact by which people acquire this infection. So far, no trustworthy evidence of vertical (intrauterine) transmission has been reported in the literatures. Transmission of infection to healthcare workers is also a serious problem in many countries [66].

First report of SARS-CoV-2 as zoonotic infection from China in the late December 2019 and in the April 2020, we saw a rapid increase in the number of cases in USA, Brazil Italy, Spain, France, Germany and Iran which clearly recorded the pandemic nature spreading the entire world (Figure 4). Shockingly, by the end of 2020 the number of cases in the India was also rocketing like anything and reached 2nd place in the COVID-19 confirmed list published by the authorised agencies [63]. Currently almost all European countries are affected, and thousands of new cases are being reported daily, without known dynamics. Perhaps there is no previous immunity in the peoples against this virus and so all individuals are considered highly susceptible in nature to this disease. The chain of transmission might go unobserved during the incubation time of infected or asymptomatic individuals, who are very actively and unsuspectingly transfer the infection from one individual to another. An as yet unknown novel mutant type may be a main factor for the present devastating increase in cases despite the preventively implemented precautions and other counter measures taken by all the countries. Definitely, analysis of nearly 100 genomes derived from SARS-CoV-2 showed that almost all genomes fall into mainly one of two types: S (the ancestor) and L (the recent) types [67]. The L type was prevalent during early January 2020 but decreased in later weeks. Furthermore, recent studies support the evolution of the virus by successive mutations and recombination processes [68,69]. Comparative studies of genomes sequenced from cases of disease occurring in European subjects compared to previously sequenced genomes in China are needed to verify the previous findings.

By mid-March 2020 the number of new cases in China was decreasing with time; USA, Italy and Iran are now the hot spots from which new infections are dispersed to nearby countries. In the Middle East and Central Europe, the numbers of positive cases reported to the WHO are growing with time (Figure 4). In the European continent the total confirmed cases reached 151, 8251 with 174, 968 cases of death until 23rd June 2020 [70]. According to the epidemiologic data reported by the Italian Higher Institute of Health, the mortality rate in Italy is 5.4% which is much higher than China's (2.3%); total deaths in Italy exceeded the number reported from China. This increase may be accredited to the fact that most infected are elderly people, in addition to the ineffectiveness of Italy's healthcare system to manage with the quick increase of new cases [65]. Unfortunately, by the end of 2020 the number of cases in the India was rocketing like anything and the confirmed cases has reached 10,340,469, thus reached the second place after USA.

Population susceptibility and viral dormancy: An epidemiological investigation reported that elderly people are most susceptible to SARS-CoV-2 (median age at death 75 years), and

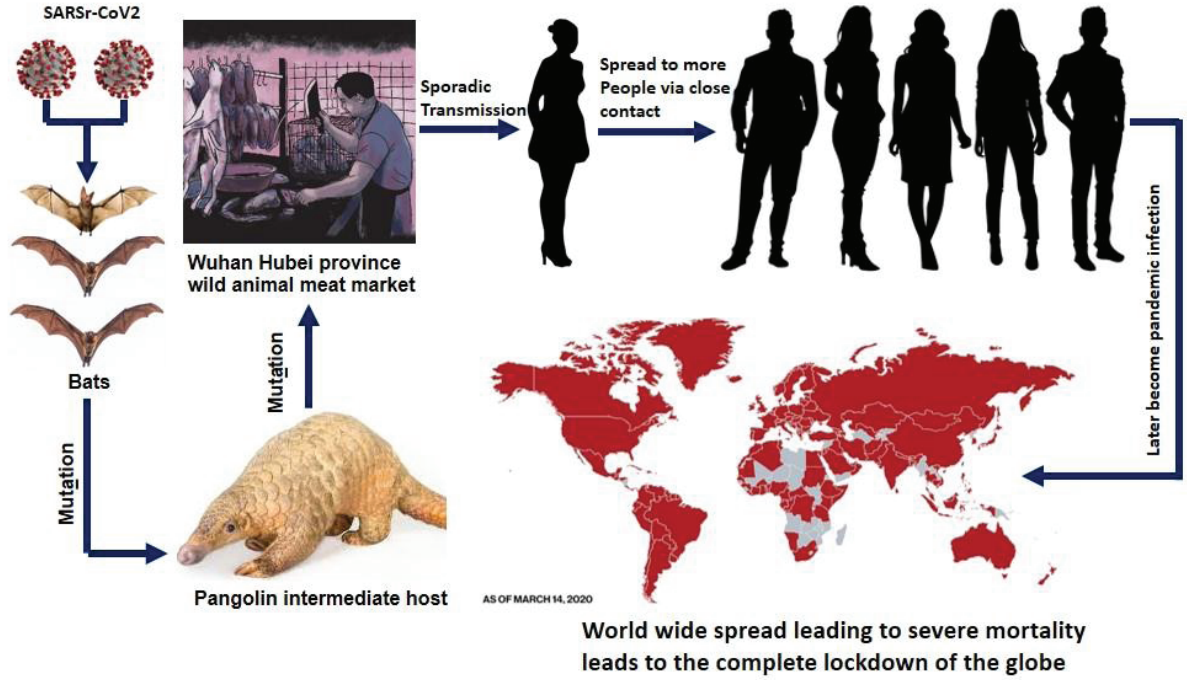

Figure 4: Spreading of SARS-CoV-2 from Wuhan to the rest of the world.

most of the patients who died had severe comorbidities or a history of surgery before admission [71]. For SARS-CoV infection, the median latency was 4 days, the average interval from symptom onset to hospital admission was 3.8 days, and the average interval from hospital admission to death was 17.4 days [72]. The median latency of MERS-CoV infection was 7 days [73]. The median incubation period for COVID-19 is shorter than that for SARS and MERS. However, the maximum latency of SARS-CoV-2 currently observed is as high as 24 days, which may increase the risk of virus transmission. Moreover, people aged ≥ 70 years had a shorter median interval (11.5 days) from symptom onset to death compared with patients aged < 70 years (20 days), demonstrating that disease progression is more rapid in aged people compared with younger people [74]. So, the health care officials should focus on aged people who might be more vulnerable to SARS-CoV-2 [75].

CLINICAL FEATURES OF COVID-19

The 5.1 days was the median incubation period of COVID-19 [76] ranged from 2–14 days [75]. An examination of household transmissions revealed that after exposure to this virus, fever and respiratory symptoms appear within 3–7 days. Commonly reported symptoms are fever, dry cough, and fatigue, however nasal congestion, rhinorrhoea, sore throat, and myalgia were found in rare cases [77], occasionally, non-respiratory symptoms such as palpitation, diarrhoea, or headache associated respiratory symptoms. Clinical spectrum of COVID-19 extended mostly from asymptomatic to deadly pneumonia. The degree of asymptomatic infection is yet to be well-defined, since most initial asymptomatic infections ultimately turned symptomatic. Whereas, SARS-CoV infection most frequently presents with high fever. The SARS-CoV infection initiate with systemic complaints or signs including myalgia, chills, or fatigue, which will follow by dry cough and dyspnea after a few days to a week. Symptoms of upper respiratory tract infection such as rhinorrhoea or sore throat are unusual in SARS-CoV cases. Watery diarrhoea may be accompanied in 15%–25% patients in later phase of the disease. Intensive care was mostly required in 20%–30% of patients, with nearly 10% fatality rate in the patients. In case of patients older than 60 years, the death rate was around 50%. Death will occur generally in the third week from the beginning of disease symptoms.

There is already certain evidence that COVID-19 can cause damages to tissues and organs other than the lungs. In an investigation of 214 patients with COVID-19, 78 (i.e. 36.4%) patients had neurological manifestations [78]. Moreover, there is evidence of ocular surface infection in certain patients with COVID-19 [79]. The SARS-CoV-2 RNA was also detected in secretions of eye from the COVID-19 patients [79]. Some patients with COVID-19 have had arrhythmia, acute heart injury, impaired renal function and abnormal liver function (50.7%) at the time of admission in hospitals [77,80]. A case history of the pathological manifestations of a patient with pneumonia displayed moderate microvesicular steatosis in liver tissue [81]. Surprisingly, tissue samples of stomach, duodenum and rectal mucosa have tested positive for SARS-CoV-2 RNA. The various organ involvement established by clinical features or biopsy in patients with SARS-CoV-2 are shown in figure 5.

In case of MERS-CoV infections, the disease course is particularly severe in patients with pre-existing conditions such as kidney damage and heart disease etc. complications such as cough and dyspnea appear within a few days after the onset of symptoms. In case of MERS-CoV patients if we examined the plain chest radiographs, which reveals infiltrations in unilateral or bilateral lung fields. The symptoms will worsen rapidly, and finally the patients require ventilator cares.

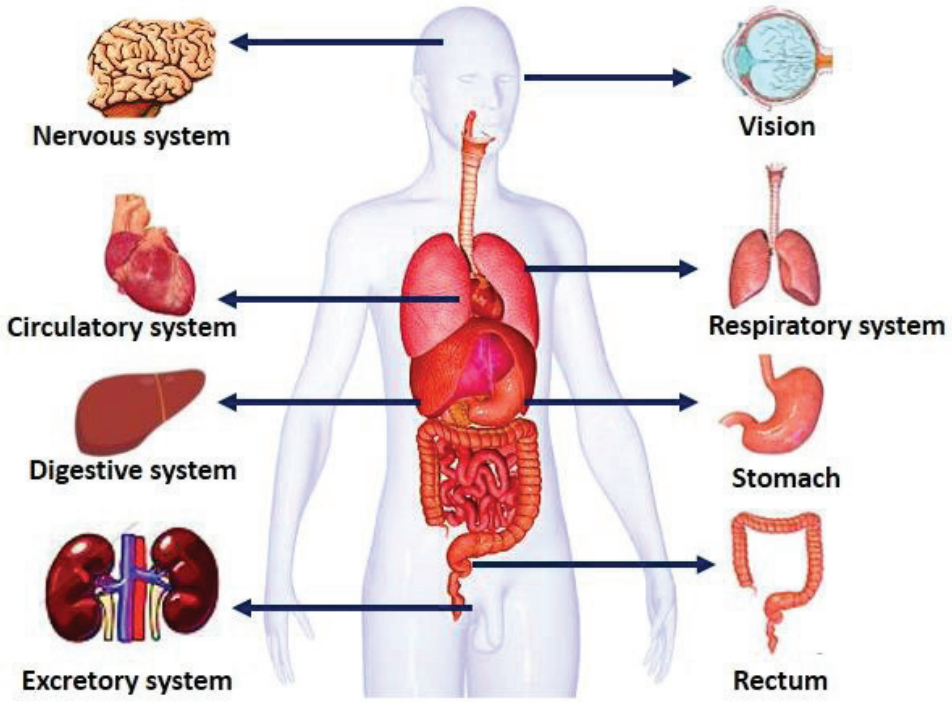

Figure 5: Various organ involvement established by clinical features or biopsy in patients with SARS-CoV-2.

Fatality rate of MERS-CoV is very high (35%) compared to SARS-CoV. Vomiting, diarrhoea, or abdominal pain was recorded in approximately 25% of cases.

The age-old people and those with underlying various disorders (i.e., hypertension, chronic obstructive pulmonary disease, diabetes, cardio-vascular disease), developed rapidly into acute respiratory distress syndrome, septic shock, metabolic acidosis very hard to correct and coagulatory dysfunction, which will finally lead to death [58]. In laboratory investigation results, most patients had normal or decreased white blood cell counts, and lymphocytopenia [58]. But the patients with severe condition, the neutrophil count, D-dimer, blood urea, and creatinine levels were significantly higher, and the lymphocyte counts continued to decrease. Additionally, various inflammatory factors (interleukin (IL)-6, IL-10, tumor necrosis factor-α (TNF-α) increase, which indicates the immune status of the patients. The data displayed that ICU patients had elevated plasma levels of IL-2, IL-7, IL-10, Granulocyte Colony-Stimulating Factor (GCSF), 10 kD interferon gamma- induced protein (IP-10), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein 1-α (MIP-1α), and TNF-α [58].

SCREENING OF SARS-COV-2

It is very necessary to establish a screening network in the health care centre (Figure 6). In the outpatient department, from the pre-examination and triage, the suspicious cases and ordinary cases are separated based on the epidemic history and patients' symptoms. The suspicious cases will be send to the special consulting room and been collected the medical history in detail, also have some relevant auxiliary examination. The team of experts will make consultation for the judgement whether these patients would be admitted to the hospital for further nucleic acid detection (RNA) through PCR. In the inpatient department, we also need to examine the epidemic history before admission to the hospital [82]. All the suspected cases should be admitted in the corona infectious ward directly. Only after the complete exclusion of the COVID-19 infection, these patients will be moved to the general ward. Since there is no effective therapy or vaccine, the best measures is to control the source of infection, early diagnosis, reporting, isolation, supportive treatments, and timely publishing epidemic information to avoid unnecessary panic [83]. More over complete quarantine is required for further spreading of the disease.

Clinical specimens collected for the analysis of SARS-CoV-2

The several types of clinical specimens can be collected from patients for checking SARS-CoV-2 and this includes: samples from lower respiratory (which includes bronchoalveolar lavage, tracheal aspirate and sputum), upper respiratory (nasopharyngeal swab and oropharyngeal swab, nasopharyngeal wash/aspirate or nasal aspirate) and serum specimens [84]. Before taking the specimen, patients mouth should be meticulously rinsed with sterile distilled water and then deep cough sputum should be carefully collected. Synthetic fibre swabs with plastic shafts must be used for collecting the specimen. Calcium alginate swabs or swabs with wooden shafts should not be used since they may contain several unwanted materials which may deactivate some viruses and this may also affect the PCR reaction. The health care workers who are involved in the sample collections must use the sterile containers for collecting and processing the specimens and further experiment must be performed under aseptic conditions as per CDC guidelines [85]. There should

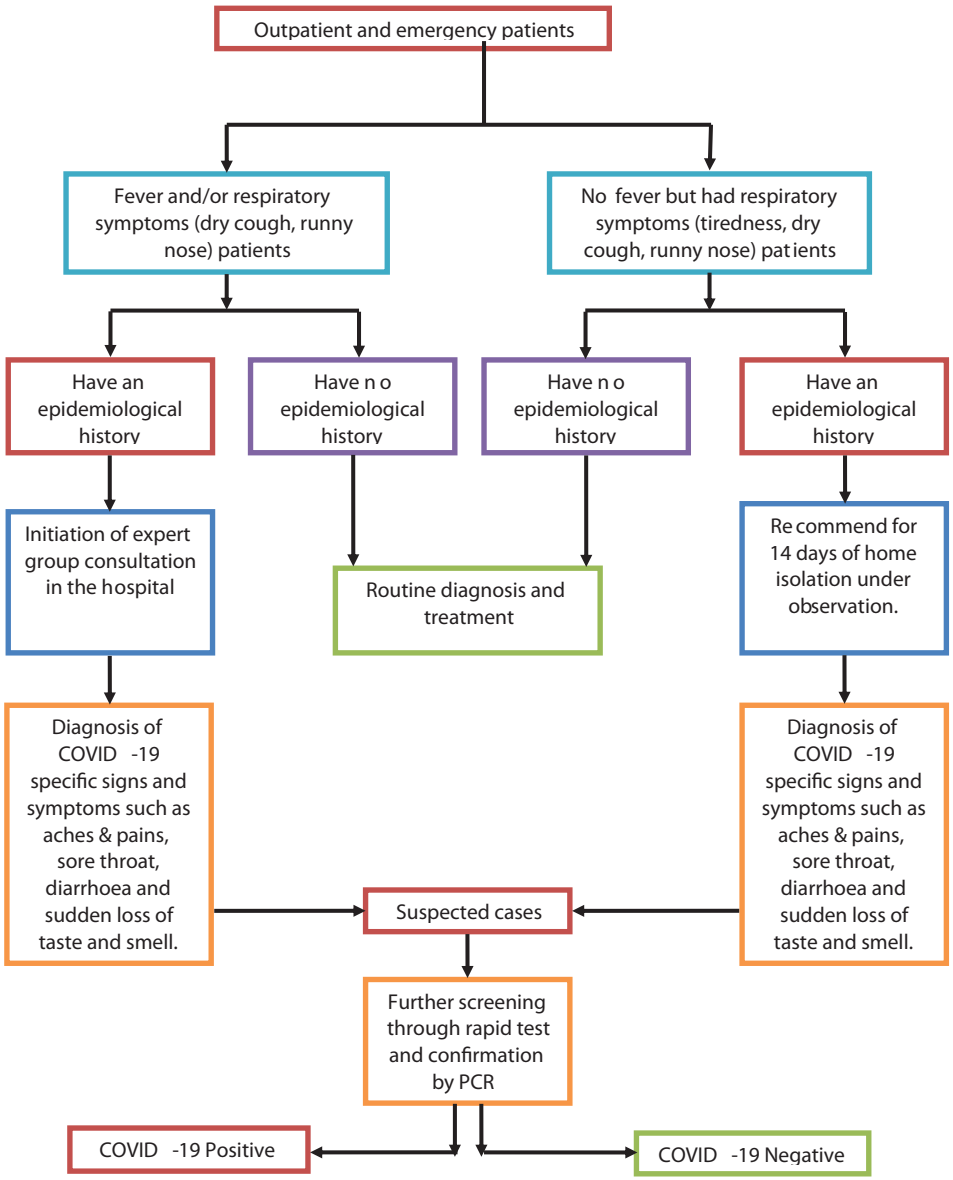

Figure 6: Rapid screening chart for COVID-19 cases.

be quick collection of the samples irrespective of symptoms onset and it should be guided by well-trained medical laboratory experts. Institutional or local guidelines should be followed regarding patient or guardian's informed consent for sample collection, testing and future experiments [86].

Various management process of SARS-CoV-2

Prevention of SARS-CoV-2: SARS-CoV-2 is well known to spread from one person to another via an airborne route. Air disinfection of communities is presently not known to be effective in further viral transmission and spread. Human-to-human transmission should be partial in order to prevent transmission amplification events. The large-scale use of personal protective equipment should be sensibly considered since these resources are at present in short supply. Surgical/normal cotton masks are utilised extensively within the general public but have not been clinically proven to decrease or prevent the spreading of COVID-19. Within the hospital setup, however, high-filtration masks including N95, goggles, and protective gowns must be worn by all healthcare persons working in direct contact (within 1–2 m) of COVID-19 patients. If a COVID-19 positive individual has been identified, rapid isolation and the management of optimised care should be provided without wasting time. Suspected patients should also be provided with a medical mask and placed in an isolation room if available in the hospital. Wherever possible, adequately ventilated single rooms should be used while performing aerosol-generating procedures.

All patients should be well instructed to cover their nose and mouth during coughing or sneezing with tissue paper which should be properly disposed according to the strict medical guidelines. Hand hygiene with the help of sanitiser after contact with respiratory

droplets should be strictly imposed. If possible, use either disposable or highly devoted equipment (e.g. stethoscopes, blood pressure cuffs, and thermometers) for suspected individuals. Moreover, avoid contaminating environmental surfaces in the room (e.g. door handles, window etc.) and all the accessories in the room.

In middle of January 2020, Chinese authorities executed an array of unprecedented control strategies, which includes the restriction of human movement, complete lockdown of Hubei province, and the complete suspension of flights, trains and other public transport systems. These time-critical actions have contributed greatly in the decline in reported cases. For these spectacular actions WHO have congratulated China on a "unique and unprecedented public health response that reversed escalating cases" [87]. Moreover, between 16th and 30th January 2020, the number of people infected by a single individual host considerably dropped to an estimated 1.05 range [88], and data from other cities having implemented complete lockdown measures reported approximately 37% less cases in comparison to those cities without lockdown [87]. Remarkably, the implementation of various strict control measures a week earlier could have prevented approximately 67% of all Chinese cases according to a model simulation proposed by University of Southampton, UK [87]. Various Non-Pharmaceutical Interventions (NPIs) have been well addressed in an attempt to suppress and/or mitigate the disease, with suppression defined as a reduction in the Reproduction Number (R_0) - the average number of individuals one infected person can infect - to less than 1, and mitigation defined as a reduction of the effects of the pandemic on health, which ultimately reducing mortality and morbidity. NPIs encompasses strict social isolation through quarantine measures and this includes the following procedures:

- **Case isolation at home**

Symptomatic individuals should remain at home for at least 7 days which is likely to reduce the number of contacts outside the household by 75% during this timeframe [89]. All forms of social contact must be avoided by symptomatic individuals in order to avoid the further spreading of this disease [87].

- **Voluntary home quarantine**

If a symptomatic individual is identified in the household, the entire members in the house must remain at home quarantine for 14 days. This is supposed to decrease contacts outside of the household by 75% and household contact to increase two-fold [89].

- **Social distancing for the individuals above 70 years old**

Individuals above 70 years of age should practice social distancing i.e. must maintain a 2 m distance from other individuals where ever possible. They should avoid gatherings or congregations in any means. These measures will definitely reduce the contacts by 50% in the workplace and decrease other contacts by 75%, while involuntarily increasing household contacts by 25% [89].

- **Social distancing for the entire population**

All individuals must practice social distancing as explained above and through this we can reduce all household contacts by 75% and workplace contacts by 25%. Contact in school rates remain the same and household contacts increase by 25% [89]. Non-essential usage of public transport must be avoided and provisions to work from home should be implemented where ever possible [87]. Individuals must use modern technologies to keep in touch with friends and family members. All large and small gatherings must be avoided. Mobile phone and various online services should be used to contact healthcare experts and other essential services [87].

- **Complete closure of schools, colleges and universities**

All schools and colleges to remain closed in essence increasing household contact for families of students by 50% and community contacts by 25% during the time of closure [89]. More over classes can be conducted through online platform which will further stop the contacts.

The overall consequences of these measures are exemplified in figure 7. In addition to this, strict hand washing habits through soaps/ideal sanitisers and respiratory hygiene must be followed by all individuals to restrict the spread of all respiratory viruses, including deadly COVID-19 [87]. Ferguson, et al. [89] predict that without strict control measures, the deaths in the UK and USA will reach 510,000 and 2.2 million respectively due to the coronavirus alone with 81% of the UK and USA populations becoming infected (R_0 = 2.4). As on today (i.e. 23rd June 2020), USA remains the top with respect to the number of infected case and death. To overcome this, the number of Intensive Care Unit (ICU) beds required is expected to reach more than 30 times the available number in both countries. With an aim to reach R_0 less than or equal to 1, the study recommends a combination of social distancing and case isolation in combination with household quarantine or complete closures of school and University for a duration of 5 months, with maximum effects felt if all four interventions plus complete lockdown (i.e. individuals prevented from going to work) are strictly implemented. Such control measures are predicted to result in a decrease in number of critical beds required by two-thirds, a figure which equates to 8 times the number of available ICU beds at present. With the above measures, they also estimate that the number of deaths will decrease by one-half - 250,000 and 1.1–1.2 million deaths in the UK and US, respectively.

Host immune response and immunopathology along with special biomarkers: The immune response by our body is very important for the control and resolution of CoV infections, but it can also lead to various immunopathogenesis, associated with the immune response out of control. The S proteins of coronavirus binds to the host cells by ACE2, binding and fusing to the membrane and release the viral RNA. The viral RNAs, as Pathogen-Associated Molecular Patterns (PAMPs), are usually detected by the Pattern Recognition Receptors (PRRs). Generally, Toll-Like Receptor (TLR) 3, TLR7, TLR8, and TLR9 sense viral RNA and DNA in the endosome [90,91]. The viral RNA receptor retinoic-acid inducible gene I (RIG-I) [90], cytosolic receptor Melanoma Differentiation-Associated gene 5 (MDA5) and nucleotidyl transferase cyclic GMP-AMP synthase (cGAS) [58] are responsible for the recognition of viral RNA and DNA in the cytoplasm of the cell. These complex signalling recruit various adaptors, including TIR-domain-containing adaptor protein including IFN-β (TRIF), Mitochondrial Antiviral-Signalling Protein (MAVS) [58] and Stimulator of Interferon Genes Protein (STING) to trigger down regulating cascades molecules, involving adaptor molecule MyD88 and lead to the activation of the transcription factor nuclear factor-κB (NF-κB) and Interferon Regulatory Factor 3 (IRF3) and the production of type I Interferons (IFN-α /β) and an array of various pro-inflammatory cytokines [58]. From this time onwards, virus-cell interactions produce a diverse set of immune mediators against the invading virus. Innate immunity is needed in

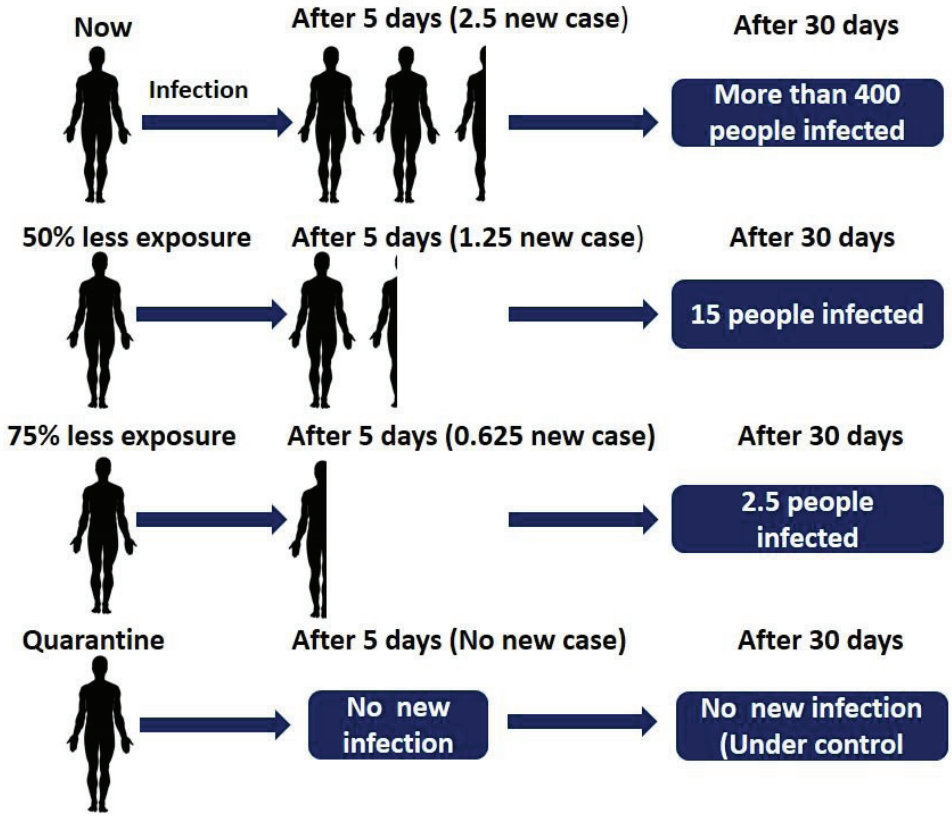

Figure 7: The power of quarantine/social distancing in avoiding the mass spreading of COVID-19.

a precise regulation to eliminate the virus, otherwise will end up in immunopathology. A few plasma cytokines and chemokines were observed arisen in COVID-19 patients, which includes IL-1, IL-2, IL- 4, IL-7, IL-10, IL-12, IL-13, IL-17, GCSF, Macrophage Colony-Stimulating Factor (MCSF), IP-10, MCP-1, MIP-1α, hepatocyte growth factor (HGF), IFN-γ and TNF-α [51,61]. Importantly, an anatomy report of COVID-19 pneumonia corpse [61] indicated that COVID-19 caused an inflammatory response in the lower airway and which further led to lung injury (Figure 8). Collectively, the virus initially invades the respiratory mucosa and then infect other cells, which will trigger a series of immune responses and this will lead to the production of cytokine storm in the body. This cytokine storm may be associated with the critical condition of most of the COVID-19 patients (Figure 8).

Most of the patients with severe COVID-19 exhibit significantly elevated level of pro-inflammatory cytokines in serum which includes IL-6 and IL-1β, as well as IL-2, IL-8, IL-17, G- CSF, GM- CSF, IP10, MCP1, MIP1α (also known as CCL3) and TNF, characterized as cytokine storm [92]. Also, C- reactive protein and D-dimer are found to be abnormally high in patients. Elevated levels of pro-inflammatory cytokines may finally lead to severe shock and tissue damage in the vital organs such as heart, liver and kidney, along with failure of respiratory system or multiple organ failure. They also facilitate extensive pulmonary pathology, which will lead to massive infiltration of neutrophils and macrophages, diffuse alveolar damage with the formation of hyaline membranes and a diffuse thickening of the alveolar wall. Spleen atrophy and lymph node necrosis were also noticed, which is a clear indication of immune- mediated damage in dead patients. To further help our fight against COVID-19, prognostic immunological biomarkers need to be well identified for patients who are at higher risk of developing ARDS or multiple organ failure without no time.

Finally, we can look on the innate immune response and adaptive immune responses of CoV infection. CoV infects macrophages, and then macrophages present CoV antigens to T cells. This process leads to T cell activation and differentiation, including the production of cytokines associated with the different T cell subsets (mainly Th17), followed by a massive release of cytokines for immune response amplification. The continued production of these mediators due to viral persistence has a negative effect on NK, and CD8 T cell activation [50]. However, CD8 T cells produce very effective mediators to clear CoV. Virus-cell interactions lead to the strong production of immune mediators. The secretion of large quantities of chemokines and cytokines (IL-1, IL-6, IL-8, IL-21, TNF-β, and MCP-1) is promoted in infected cells in response to CoV infection. These chemokines and cytokines, in turn, recruit lymphocytes and leukocytes to the site of infection (Tay, et al., 2020). However, the potential role of Th17 responses has a number of implications in terms of the production and clinical development of COVID-19 vaccines.

Several treatment options of COVID-19

Current clinical therapies: Due to the absence of effective antiviral therapy against COVID-19, current treatments normally focused on symptomatic and respiratory support according to the Diagnosis and Treatment of Pneumonia Caused by COVID-19 (updated to

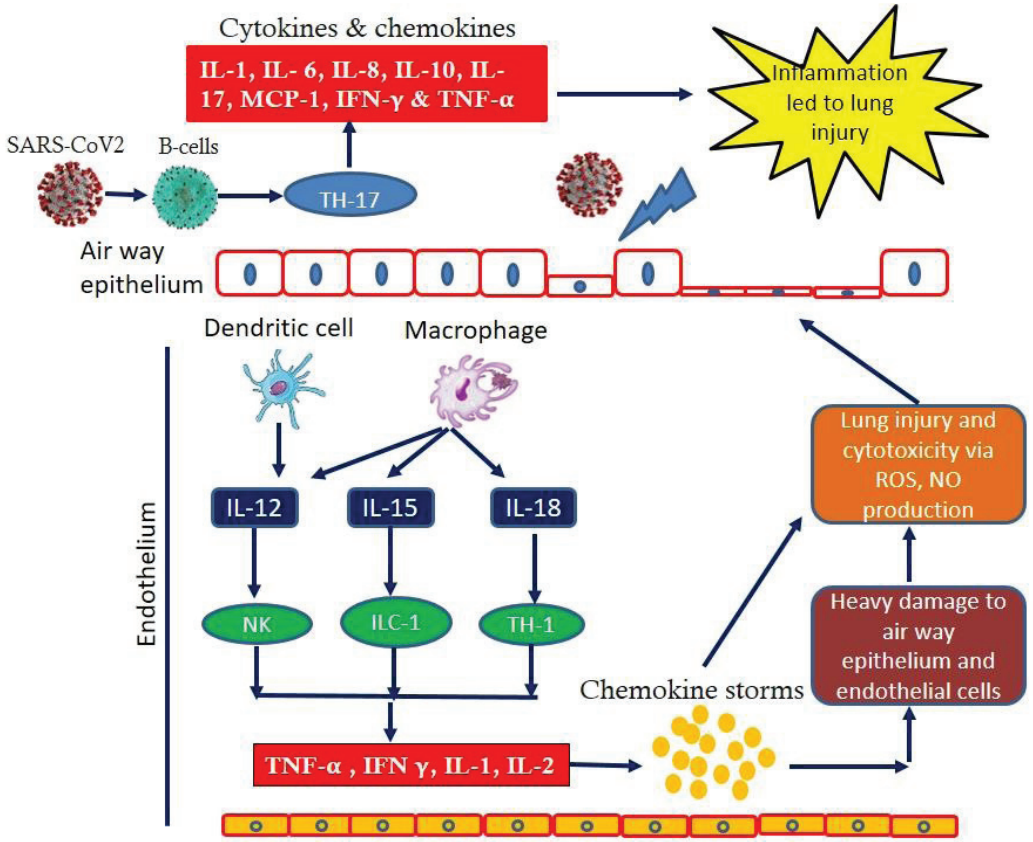

Figure 8: Virus-induced inflammation pathway in the lower airway and which will lead to severe lung injury followed by respiratory failure.

version 6) conveyed by National Health Commission of the People's Republic of China. Most of the patients accepted oxygen therapy as this virus severally affects the respiratory system. WHO further recommended Extracorporeal Membrane Oxygenation (ECMO) to patients with refractory hypoxemia [94]. Further rescue treatment with convalescent plasma and immunoglobulin G are administered to certain very critical patients according to the conditions [83].

Antiviral treatments

According to the previous understanding of fighting the epidemic SARS-CoV and MERS-CoV, we obtain specific lessons for some treatment strategies to control coronavirus [95]. Antiviral drugs and systemic corticosteroid treatment are commonly employed in clinical practice earlier. This includes drugs that inhibits neuraminidase (for example oseltamivir, peramivir, zanamivir, etc.), ganciclovir, acyclovir, and ribavirin, besides methylprednisolone [96] for controlling influenza virus. But all these drugs are really worthless for COVID-19 and are not recommended to use against them. Remdesivir (GS-5734) is a 1'-cyano-substituted adenosine nucleotide analog pro-drug, which recorded significant broad spectrum antiviral activity against several RNA viruses. Based on the data obtained from *in-vitro* cell line studies and mouse animal model experiments, remdesivir may interfere with the NSP12 polymerase even in the setting of intact ExoN proof reading activity [97]. Remdesivir has been reported to treat the first US case of COVID-19 successfully [98]. Chloroquine is a repurposed medicine with great potential to treat COVID-19. Chloroquine has been successfully used to treat malaria for several years [99], with a mechanism that is not well explained against some viral infections. A number of possible mechanisms are considered: first one is chloroquine can inhibit several viral replications through pH-dependent steps [100], may also be an effective drug against the SARS-CoV infection and spread [100]. Moreover, chloroquine has immunomodulatory properties, which will suppress the production/release of TNF-α and IL-6 and which intern enhance the natural immunity. It also works as a new class of autophagy inhibitor [101], which may inhibit the viral infection and further replication in host cells. Several studies have found that chloroquine interfered with the cellular glycosylation of receptors of SARS-CoV [100] and worked at both entry and at post-entry stages of the COVID-19 infection in Vero E6 cell lines [102]. The chloroquine and remdesivir combination was established to inhibit effectively novel SARS-CoV-2 in *in-vitro* condition. Many researchers earlier confirmed that the protease inhibitors lopinavir and ritonavir can be used to treat infection with Human Immunodeficiency Virus (HIV) [103] and this might also improve the outcome of MERS-CoV [104] and SARS-CoV [105] infected patients. It is well reported that coronavirus viral loads of a COVID-19 patient in South Korea significantly reduced after the treatment of lopinavir/ritonavir (Kaletra®, AbbVie, North Chicago, IL, USA) [106]. Moreover, certain clinicians combined Chinese and Western medicine for the treatment which includes lopinavir/ritonavir (Kaletra®), arbidol, and Shufeng Jiedu Capsule (SFJDC, a traditional Chinese medicine) and which gained significant enhancement in pneumonia associated symptoms of patients in Shanghai Public Health Clinical Centre, China [107]. The other

antiviral drugs include nitazoxanide, favipiravir, nafamostat, and several others may also be used to control SARS-CoV-2. Through the literature survey, it is highly evident that a proper drug is not available till dated to control this deadly disease. So, our prime importance is to find a best drug from nature/synthetic route or ideal human vaccine to control the spread of this deadly disease. But unfortunately, no significant progress can be made in this.

CONCLUSION

The recent SARS-CoV-2 epidemic outbreak is an ongoing crisis that is causing global uncertainty on an extraordinary scale. The COVID-19 pandemic represents the greatest global public health crisis of present generation and, potentially, since the pandemic influenza outbreak of 1918. Within 3 months since the discovery of a novel coronavirus in patients with pneumonia of unknown origin in Wuhan City, China, COVID-19 has spread rapidly throughout the world and is beating SARS-CoV and MERS-CoV in the number of confirmed cases and deaths and thus emerges as a leading coronavirus in the last two decades. Its main initial symptoms include fever, cough and fatigue which are similar to those of SARS. The most likely source of origin of SARS-CoV-2 is bats. This virus is highly infectious and can be transmitted through droplets, secretions and close contact.

Internationally, the number of confirmed reports has continued to rise, and is currently placed at 85,136,586 laboratory-confirmed cases with over 1,843,342 deaths worldwide. This perhaps clear that quarantine alone may not be sufficient to prevent the spread of COVID-19, and the global impact of this viral infection is one of heightening concern. Further studies are undoubtedly required to help define the exact mechanism of human-to-human and animal-to-human transmission to facilitate the development of a virus-specific vaccine. Obviously, the pandemic nature of COVID-19 demands rigorous surveillance and on-going monitoring measures to accurately track and potentially predict its future host adaptation, evolution, transmissibility, and pathogenicity.

The morbidity, mortality, mental health impact and psychological effects due to the new COVID-19 are currently difficult to predict. Additionally, COVID-19 is now a pandemic, careful surveillance is essential to monitor its future host adaption, viral evolution, infectivity and transmissibility. Other critical issues include identifying reservoirs, defining exactly the incubation period, characterizing the clinical spectrum of the disease, exploring the potential for long-term health effects and understanding sensitive populations. Reducing the spread and transmission of the infection for this new coronavirus is today the best preventive strategy we can have in the absence of vaccine or specific drugs. We sincerely hope that our world will overcome the epidemic as fast as possible.

DECLARATION OF COMPETING INTEREST

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

AUTHOR'S CONTRIBUTIONS

HNJ and SS conceived and designed the review; KNA, AR, NKS and SS performed the literature survey for the review preparation; KNA and NKS wrote the manuscript. All authors read and approved the final manuscript.

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