Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

CHAPTER 1

Epidemiology, virology, and history of Covid-19 infection

NOHA S. SOLIMAN, MD • YOSRA M. HASSAN, MD • ADEL M. NADA, MD

(Dr. Prof. M Fadel Shaltout. Prof. of Obstetrics and Gynecology, Cairo University, Faculty of Medicine)

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INFECTION HISTORY

COVID-19 disease is a threatening infection that has appeared in December 2019 and has spread widely all over the globe to form a pandemic. According to the World Health Organization (WHO), it is considered the fifth pandemic since the Spanish flu 1918 pandemic (Liu et al., 2020a,b).

By the end of 2019, the Chinese government informed the WHO about the appearance of many cases of unfamiliar pneumonia subsequently causing outbreak in Wuhan city (Shereen et al., 2020). The events started in a seafood market located in Wuhan city, China, which frequently sells live animals such as frogs, bats, birds, snakes, and rabbits (Wang et al., 2020). It was reported that more than 50 people were rapidly infected and suffered from fever, dry cough, malaise, and dyspnea suggesting viral pneumonia as reported by the National Health Commission of China in January 2020. On the basis of genome sequencing of the virus, it was found that it is a novel coronavirus that belongs to group b of coronaviruses (Cui et al., 2019; Lai et al., 2020).

The newly discovered virus is considered the seventh among the coronaviruses that infect humans (Wu et al., 2020). The new virus was termed by the WHO as 2019 novel coronavirus (2019nCoV) in January 2020, and the infectious disease was officially named as COVID-19 in February 2020. The genomic characterization of the virus provided full analysis, and according to the International Committee on Taxonomy of Viruses (ICTV), it was named as SARS-CoV-2 (Coronaviridae Study Group of the International Committee on Taxonomy of Viruses).

Back to history, in the 1930s, several variants of coronaviruses were discovered, and since 1965, four human coronaviruses (HCoVs) have been identified to cause minor respiratory infection (Chauhan, 2020; McIntosh, 1974). The first two discovered human coronaviruses were HCoV-OC43 and HCoV-229E. The HCoV-NL63 and HCoV-HKU1 were other two human coronaviruses identified in the 1960s (Yesudhas et al., 2020). In 2003, a new virus that belonged to beta subgroup of coronaviruses infected Chinese population in Guandong province. The infected patients suffered from symptoms of severe pneumonia with expanded alveolar injury, which caused acute respiratory distress syndrome (ARDS), and the whole world witnessed the first appearance of severe acute respiratory syndrome (SARS) (Pyrc et al., 2007).

Initially, SARS coronavirus appeared in Guandong, China, and then disseminated all over the world rapidly to infect >8000 and kill 776 persons. Ten years later in 2012, another highly pathogenic member of coronaviruses emerged in Saudi Arabia (Shereen et al., 2020). The virus was considered the sixth among the emerged human coronaviruses that belongs to beta subgroup; however, it differs in phylogenetics from other human coronaviruses and was named as Middle East respiratory syndrome coronavirus (MERS-CoV). It emphasized the capability of coronaviruses to unexpectedly be transmitted from animals to humans (Zaki et al., 2012).

As reported by the WHO, about 2482 persons were infected with MERS-CoV with 838 deaths (Rahman and Sarkar, 2019). The infection by MERS-CoV varies from mild respiratory injury up to severe respiratory distress. Like SARS coronavirus, MERS-CoV exhibits symptoms of pneumonia that may reach up to acute respiratory distress and kidney failure (Memish et al., 2013). MERS-CoV started in Saudi Arabia and then spread to many Middle East countries (Shereen et al., 2020). Although MERS-CoV was relatively considered slowly spreading coronavirus, it recorded fatality rates of 36% (Yesudhas et al., 2020).

At current, the whole world is facing a battle with the pandemic caused by the seventh member of human coronaviruses (SARS-CoV-2). After its initial emergence in China, SARS-CoV-2 massively has spread to many countries all over the world and has reached almost all continents imposing a real global threat. The WHO raised a Public health emergency of international concern in January 2020 (Chan et al., 2020; Li et al., 2020a,b). In March 2020, it was finally declared by the WHO that COVID-19 can be defined as a pandemic (Liu et al., 2020a,b).

Prior to the emerged outbreaks by coronaviruses, the whole world previously suffered from various outbreaks by different strains of influenza viruses that reaped millions of human deaths as H1N1 (Spanish flu, 1918), H2N2 (Asian flu, 1957), H3N2 (Hong Kong flu, 1968), and H1N1 pandemic flu (Liu et al., 2020a,b).

The emergence of the latest SARS-CoV-2 pandemic has put the world in a state of extreme confusion and has shed the light on the countless flaws in the health systems in modern societies and the unpreparedness of many governments to face this scenario of extensive spread of the virus specially with the exponential rise of infections beyond the capacity of public hospitals. Generally, the outcome of pandemics crucially depends on world cooperation that is considered imperative in containing infection and facing the devastating consequences of the pandemic (Häfner, 2020).

EPIDEMIOLOGY

Reservoirs and Hosts of Coronaviruses

Studying the origin and transmission of infections is of utmost importance to help break the chain of transmission and develop strategies to contain infections and prevent their spread (Shereen et al., 2020).

All human coronaviruses originally stemmed from animals that act as natural hosts. Mainly bats were considered the natural hosts of HCoV-NL63, HCoV-229E, SARS-CoV, and MERS-CoV. However, rodents were probably the animal origin for HKU1 and HCoV-OC43. Generally, bats are considered the key reservoirs for alpha and beta coronaviruses (Woo et al., 2012). Rhinolophus bats are claimed to be the natural hosts for SARS CoV, while recent researches detected MERS-CoV in *Perimyotis* and *Pipistrellus* bats (Annan et al., 2013).

The transmission of coronaviruses from natural hosts to human requires the presence of intermediate hosts. Mostly, domestic animals act as intermediate hosts, as they get diseased by the virus and then transmitted it to humans. For example, palm civets and camels played a key role in transmitting SARS-CoV and MERS-CoV to humans, respectively, by being intermediate hosts for the viruses (Haagmans et al., 2014). The whole-genome sequencing of these viruses showed 96.2% similarity at the full-length genome level to a coronavirus (Bat-CoVRaTG13) whose natural host was a bat named as *Rhinolophus affinis* that lives in Yunnan Province at a distance of 1500 km from Wuhan (Zhou et al., 2020).

The presence of an intermediate host facilitates the transmission of viruses from their natural hosts to humans. Similar to other coronaviruses, bats are claimed to be the natural hosts for SARS-CoV-2, which has been transmitted to human either through direct contact or via an intermediate host. The role of intermediate hosts in transmitting SARS-CoV-2 remains inconclusive and has no solid evidence, as no enough samples were taken from suspected intermediate hosts to be tested by the scientists in the beginning when infections appeared in wild life and sea food markets in Wuhan, as wild animals could be the source of zoonotic infections. However, many researchers of phylogenetic analysis still work on tracing sources of COVID-19 infection assuming that the infection had multiple sources in the beginning of its spread (Liu et al., 2020a,b).

It was highly suggested that pangolins act as intermediate hosts for SARS-CoV-2 that might have carried the virus from bats to humans, as the whole-genome sequencing showed that the coronavirus detected in samples taken from Malayan pangolins (*Manis javanica*) in Guandong, China, was highly identical to SARS-CoV-2 (Lam et al., 2020). Also, researchers suspected that raccoon dogs and palm civets had possibly transmitted SARS-CoV-2 infection to humans (Liu et al., 2020a,b). However, molecular tests previously showed positive results for corona-like viral RNA in samples taken from civets at the food market, suggesting that civet palm might act as intermediate hosts (Shereen et al., 2020).

Surprisingly, molecular analysis was performed in a study on samples taken from healthy individuals in Hong Kong in 2001 and showed a frequency rate of 2.5% for SARS-CoV, which suggests the circulation of SARS coronaviruses in humans before the first outbreak appearance in 2003 (Zheng et al., 2020)

Modes of Transmission

As agreed by the majority of researchers, SARS-CoV-2 outbreak initially started by transmission of the virus from a natural host to human either directly or through an intermediate host, and then subsequently, human-to-human transmission had been reported. The human-to-human transmission of SARS-CoV-2 virus can occur directly through exposure to respiratory droplets from infected patients generated by coughing, sneezing, or even talking at a distance of less than 1 m. Moreover, indirect transmission may occur through touching surfaces, clothes, or personal belongings contaminated by the virus. SARS-CoV-2 mainly spreads through big respiratory droplets. However, the accelerated exponential rise in the rates of SARS-CoV-2 raised the suspicions about the possibility of viral transmission through aerosols in air, yet no clear data is available to prove or disprove the theory of airborne transmission (Yesudhas et al., 2020).

The rate of infection (R0) is defined as the number of people acquiring microbial infection by an infected individual. For SARS-CoV-2, the R0 value was estimated in the range of 1.5−3.5, which was found to be close to the R0 value (2.75) of SARS pandemic in 2003. However, the R0 value of MERS-CoV-2 in 2012 was estimated to be around 1, and for H1N1 influenza in 2009 was 1.46−1.48. The difference in R0 values between various coronaviruses appears to be minimal (Phelan et al., 2020; Somsen et al., 2020).

The hardships faced with SARS-CoV-2 in controlling the high rates of infection are owed to various reasons as follows: (1) overlapping symptoms with other non-corona respiratory viruses, (2) inconsistency of clinical course of infection among various patients with uncertain incubation period, (3) many infected individuals

may not show symptoms; however, they are capable of transmitting the infection, and (4) variable risk predisposition to acquiring infection among different population. All of these factors need further researches to uncover more facts about the virus that may help in overcoming the challenges faced in controlling its spread (Yesudhas et al., 2020).

At-Risk Populations

People with underlying health problems such as diabetes, hypertension, cardiovascular, chronic respiratory, chronic renal diseases, cancer, and immune suppression are liable to acquire COVID-19 infection and most probably develop severe course of illness with poor or fatal outcome (European Center for Disease Prevention and Control, 2020).

In a European multicenter study, the most common risk factors for severe illness and intensive care unit (ICU) admission in adolescents and children were the presence of underlying health problems such as chronic lung disease, congenital heart disease, malignancy, and chronic kidney disease (European Center for Disease Prevention and Control, 2020).

People residing long-term care facilities specially those of old age (more than 60 years) with underlying medical problems are vulnerable to infection with high likelihood to adverse consequences and unfavorable outcomes. Other settings with medically vulnerable people include long-term care hospital wards, daycare centers, hostels, and home-based centers (European Center for Disease Prevention and Control, 2020)

The category of healthcare workers is considered of the highest risk of COVID-19 infection due to the high chance of exposure to infected patients. According to a study done in the United Kingdom, the risk of infection among the frontline healthcare workers is 3.4-fold higher than people living in the community. In china, it was recorded that 3.8% of SARS-CoV-2-infected cases were healthcare workers, and 14.8% of them had severe disease (European Center for Disease Prevention and Control, 2020).

In May 2020, it has been reported by the International Council of Nurses that about 90,000 healthcare workers have been infected with SARS-CoV-2 with more than 260 deaths during the pandemic. In June 2020, the Unites states reported 600 deaths due to COVID-19 among the frontline healthcare workers. Poor compliance and malpractice in dealing with personal protective equipment was considered the key factor for the elevated rates of infection among healthcare workers (European Centre for Disease Prevention and Control, 2020).

Asymptomatic patients infected with the virus are considered hidden sources that mediate transmission to healthy individuals. It was estimated in a systematic review that asymptomatic cases account for 6%–41% of SARS-CoV-2 positive patients. In asymptomatic cases, symptoms may start to appear later than in usual symptomatic cases, or they may remain without appearance of any symptoms or signs. However, in these cases, the SARS-CoV-2 viral shedding continues in gastrointestinal and respiratory tract samples carrying the risk of transmitting the virus to healthy individuals. Non- or late appearance of clinical symptoms and signs makes it difficult to trace asymptomatic transmission, which in turn may hinder the ability to estimate or quantify the actual number of infected cases (Byambasuren et al., 2020; Koh et al., 2020).

In terms of age, the available data showed that the chance of developing infection in children was 0.26 time slower than in old people (Jing et al., 2020). Children may contract SARS-CoV-2 infection from any gathering places such as schools, daycare centers, and sport clubs or through exposure to an infected family member at home. Publication data from Italy showed that 55% of infected children acquired the infection from a source outside family (Parri et al., 2020). However, a study in Italy reported that the majority of infected children (67%) acquired infection due to contact with at least one infected parent (Garazzino et al., 2020).

A matter of concern in children who go out for school or daycare centers is that many of children who get infected may be asymptomatic or exhibit mild nonspecific symptoms, which may not predict their infection with SARS-CoV-2. Nonapparent infection with SARS-CoV-2 makes it hardly suspected. Even the symptomatic children may continuously shed the virus in the early phase of acute illness before appearance of symptoms or before being confirmed of having SARS-CoV-2 by laboratory testing. The danger lies in the potential risk of transmitting infection to their parents or elderly family members who may have underlying medical problems ending into adverse consequences up to death (European Center for Disease Prevention and Control, 2020). It was reported from publication data in Germany that viral loads of SARS-CoV-2 in symptomatic children are comparable with middle-age and old-age persons (Wolfel et al., 2020; Jones et al., 2020). However, in another study, higher viral load was detected in symptomatic children (under and above 5 years of age), as well as adults (Heald-Sargent et al., 2020).

Occupational settings and work places with unfavorable environmental health conditions are considered epicenters for emergence of multiple outbreaks with COVID-19 infection. This is worsened by defective implementation of infection control measures and malpractices of workers inside these settings. Since the emergence of SARS-CoV-2, multiple outbreaks were reported in many occupational settings (Waltenburg et al., 2020). Several contributing factors are involved in occurrence of outbreaks in work settings such as (1) small working indoor spaces, (2) sharing same work tools and facilities in office and accommodation spaces, (3) inadequate compliance with the recommended social distancing, (4) shortage of personal protective equipment or improper use in donning and doffing, and (5) fear of losing job that may force some infected individuals with impaired awareness to ignore their illness, deny reporting, and continue going to their work exposing other employees to the risk of acquiring infection (Park et al., 2020; Baker, 2020).

In April 2020, the confirmed COVID-19 cases were estimated at 2,114,269 worldwide with about 60% of cases occurred mainly in Spain, Italy, Germany, France, and the United States as the distribution shown in Fig. 1.1. According to the WHO, as of December 8, 2020, the total number of reported cases all over

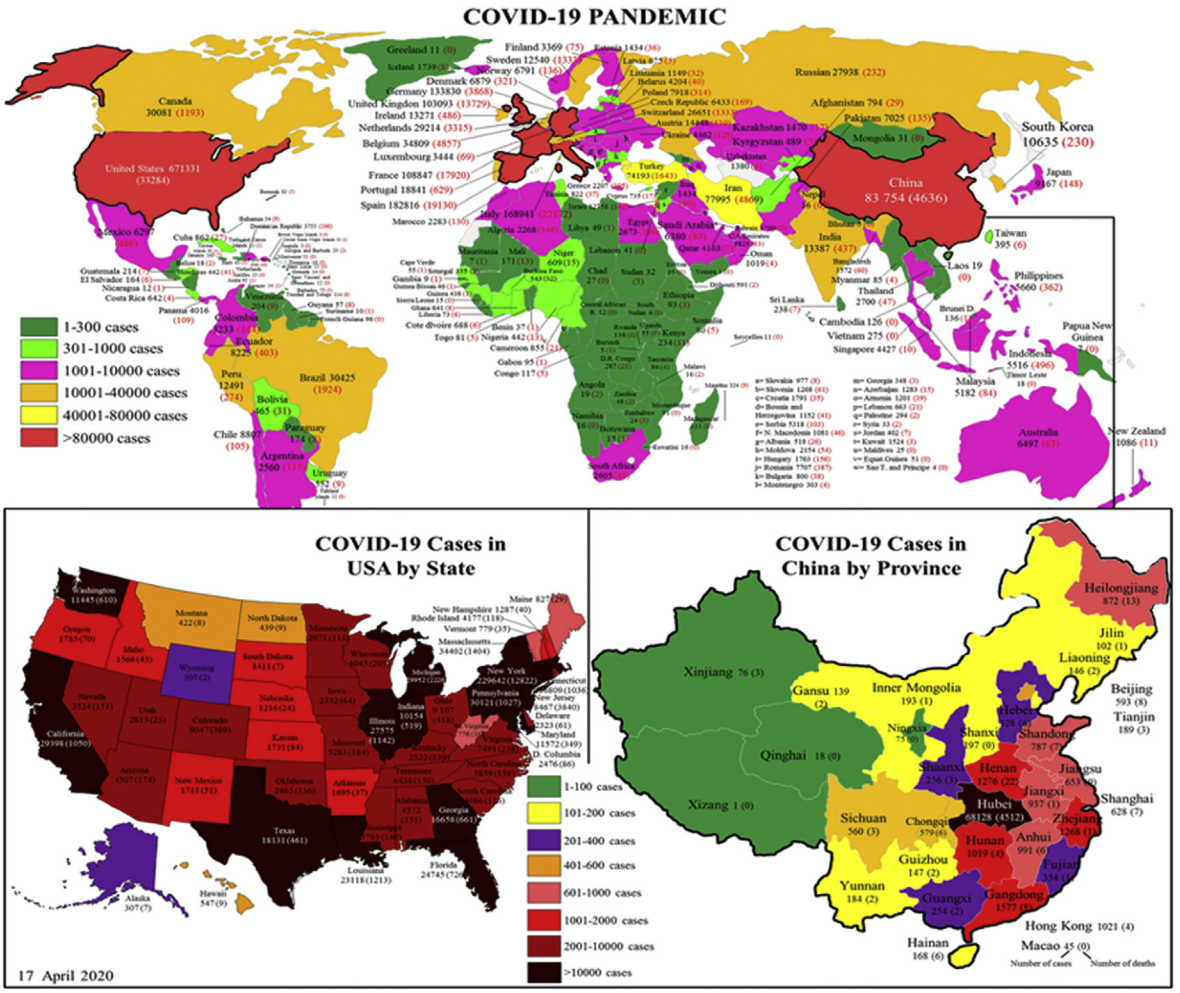

FIG. 1.1 The geographical distribution of SARS-CoV-2-infected cases according to the European CDC in April 2020 (https://www.ecdc.europa.eu/en/geographical-distribution-2019- ncov-cases). *CDC*, Centers for Disease Control and Prevention; *SARS*, severe acute respiratory syndrome coronavirus-2.

the world reached 65.8 million with 1.5 million deaths in 220 countries all over the globe (da Costa et al., 2020).

In respect to previous outbreaks by coronaviruses, Fig. 1.2 demonstrates the count of cases for SARS and MERS coronaviruses and their geographical distribution worldwide. In 2003, the SARS outbreak caused 8096 cases with774 deaths. In April 2012, the laboratory-confirmed cases for MERS-CoV were 2519 with a fatality rate of 34.3% (da Costa et al., 2020).

VIROLOGY

Viral Taxonomy

The Coronaviridae family belongs to Nidovirales order. The name of "corona" refers to crown-like spikes on the surface of the virus. The Coronaviridae family is classified into alpha, beta, gamma, and delta groups of coronaviruses. The alpha and beta coronaviruses can infect animals. On genetic basis, human coronaviruses mostly belong to beta coronavirus genus (B-CoV). The B-CoVs are further classified into four different lineages: A, B, C, and D. SARS and SARS-CoV-2 belong to the lineage B, whereas MERS-CoV is grouped in lineage C (Letko et al., 2020). As for other human coronaviruses, the alpha group includes HCoV-NL63 and HCoV-229E, whereas beta coronavirus includes HCoV-OC43 and HCoV-HK1 (Wan et al., 2020). The phylogenetic analysis showed that SARS-CoV-2 has 80% similarity with that of SARS coronavirus and is 96% identical to BatCoV-RaTG3 coronavirus (Zhou et al., 2020). However, MERS-CoV showed 54% relatedness to HKU4 Tylonycteris bat coronavirus. The sequence of spike protein showed about 76%−78% similarity between SARS-CoV-2 and SARS coronavirus. This sequence similarity is the root cause behind the capability of both viruses to bind to the same angiotensin-converting enzyme 2 (ACE2) host cell receptor (Yesudhas et al., 2020).

Viral Structure

The coronaviruses are enveloped spherical particles about 120 nm in diameter containing genetic material of single-stranded RNA. The outer surface is made of membrane (M), envelope (E), and spike (S) proteins. The envelope and membrane proteins are involved in the virus assembly, while the spike protein is the key element for host cell recognition and virus entry (Li, 2016).

The spike protein is structured as peplomers that form protrusions on the surface of the virus giving it the shape as if the coronavirus carries a crown, hence the name "corona," which is a Latin word that means a crown. The spike protein is divided into three segments: (1) ectodomain that consists of S1 and S2 receptor-binding subunit, (2) transmembrane domain, and (3) intracellular domain (Yesudhas et al., 2020).

The SARS-CoV-2 RNA genome contains 29,903 nucleotides with a 50-methyl-guanosine cap and poly(A)-tail (Wu et al., 2020). The SARS-CoV-2 has nine transcribed subgenomic RNAs, and its genome contains a 50-untranslated region that includes a 50 leader sequence, an opening reading frame (ORF)1a/ab that encodes nonstructural proteins (nsp) needed for replication: four structural proteins (spike, membrane, envelope, and nucleocapsid); accessory proteins (ORF3a6,7a/b and 8); and a 30-untranslated region. The polyprotein pp1a/b is broken down into 16 nonstructural proteins including nsp3 and nsp5 (proteases), nsp13 (helicase), and nsp12 (RNA-dependent RNA polymerase) (Liu et al., 2020a,b).

Pathogenesis and Viral Life Cycle

There are two pathways for coronaviral entry into host cells: endocytic and nonendosomal pathways (Zumla et al., 2016). The endocytic pathway (clathrin-dependent endocytosis) was demonstrated through various studies for MERS-CoV and SARS-CoV viral entry. It has been reported that the same mechanism is used for SARS-CoV-2. The exact mechanism of viral entry is dependent on the type of both virus and host cell (Yesudhas et al., 2020).

In viral infection, the spike protein is cleaved by the proteases of host cell into S1 receptor binding and S2 membrane fusion subunits. The S1 subunit is divided into N-terminal (NTD) and C-terminal (CTD) domains. The CTD of S1 has high affinity to human ACE2 receptor. The affinity of receptor-binding protein domain (RBD) in CTD of SARS-CoV-2 to human ACE2 receptor is higher 10−20 folds than RBD of SARS coronavirus (Wrapp et al., 2020). The putative cycle of SARS-CoV-2 inside host cells starts with binding of viral spike protein and human ACE2 receptors (Liu et al., 2020a,b). The S1 subunit of the viral spike protein binds to sugar and ACE2 receptors on the surface of host cell, while the S2 subunit is subjected to conformational changes that mediate the fusion of the viral envelope with cell membrane. During this state, the trimeric S2 conforms a six-helical bundle structure, and the hidden fusion hydrophobic peptides become exposed and entangled into the host cell membrane facilitating viral and host cell membrane fusion (Gui et al., 2017). This process requires large amount of energy, which is needed to accelerate the membrane fusion. Proteases such as elastases and transmembrane protease serine 2

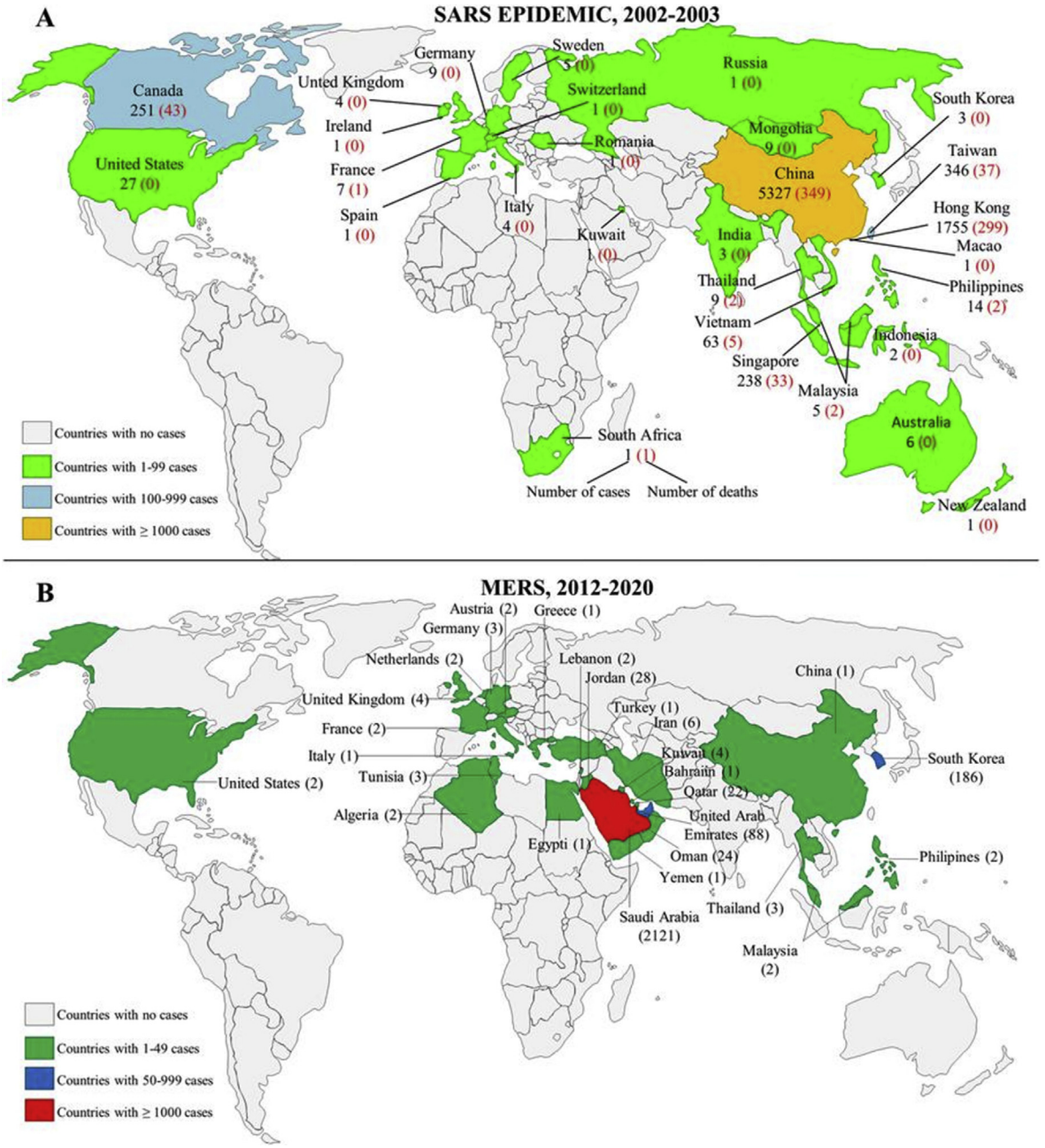

FIG. 1.2 The geographical distribution of SARS-CoV (**A**) and MERS-CoV worldwide **(B)** according to the World Health Organization (https://www.who.int/csr/sars/country/table2004_04_21/en/), (http://www.emro.who.int/health- topics/mers-cov/mers-outbreaks.html). *MERS-CoV*, Middle East respiratory syndrome coronavirus; *SARS*, severe acute respiratory syndrome coronavirus.

(TMPRSS2) on the surface of respiratory tract cells and lung cells play an important role in spike protein priming to activate membrane fusion (Fig. 1.3) (Yesudhas et al., 2020).

After membrane fusion, the viral genome is released into the cytoplasm and becomes translated into pp1a and 1ab replicase viral polyproteins. A group of subgenomic mRNAs undergoes transcription by polymerase enzyme; then membrane proteins enter the Golgi apparatus and endoplasmic reticulum, while the N protein binds to the genomic RNA forming nucleoprotein complex. The nucleoprotein complex, structural proteins, and viral envelope are assembled to form new viral particles, which are released from infected cells to enter new host cells repeating the same cycle (Liu et al., 2020a,b).

Viral Spike Protein Active and Inactive States

SARS-CoV S1 subunit of the spike protein is composed of beta strand structures, formed of three C-terminal

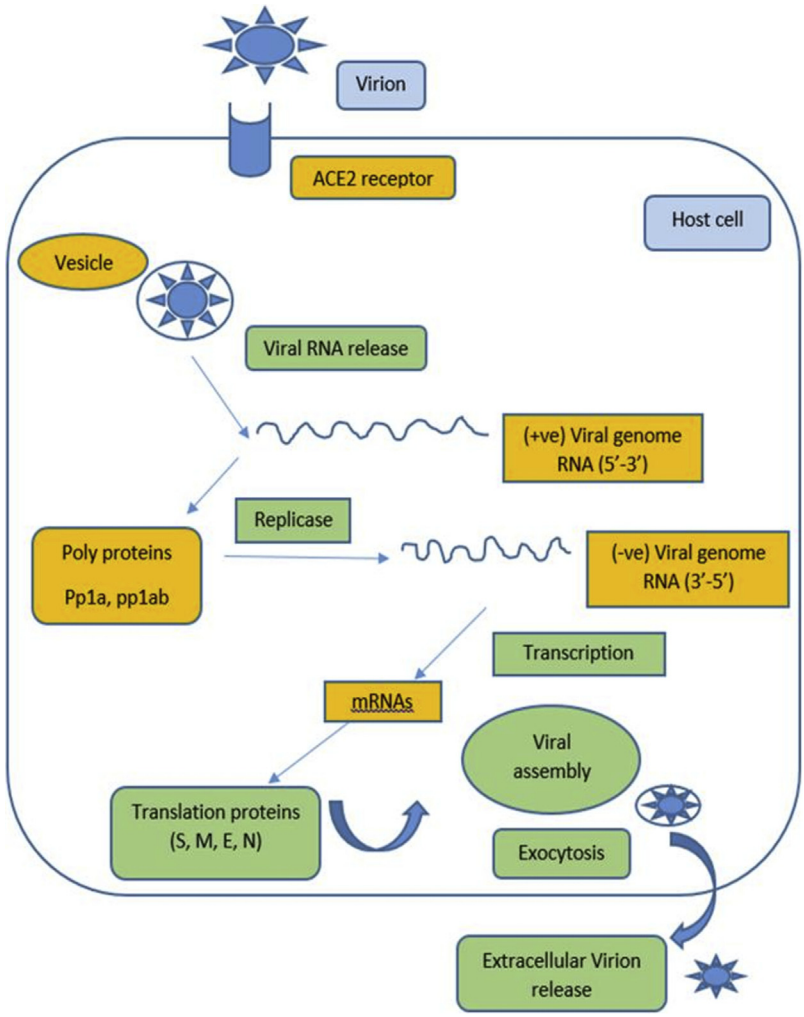

FIG. 1.3 The infection starts with the spike protein binding to ACE2 receptor. The viral RNA is released into the host cell and is translated into pp1a and pp1ab viral replicase polyproteins. The replicase enzyme uses the RNA genome positive strand as a template to produce copies of negative-strand viral RNA genome. In transcription phase, RNA polymerase enzyme produces subgenomic RNAs that become translated into viral proteins spike (S), membrane (M), envelope (E), and nucleocapsid (N). The viral RNA genome and proteins are assembled to be released into vesicles out of the cell.

domains (CTD1, CTD2, and CTD3) and N-terminal domain (NTD). The NTD is bound to CTD1 through 295–319 residues linker, where CTD1 acts as receptor-binding domain (RBD) for SARS-CoV-2 and binds with the ACE2 receptor (Yesudhas et al., 2020). All the conformations that occur to the spike glycoprotein depend on the position of CTD1. The three-monomer spike glycoprotein interlaces with each other and forms homotrimer. The head of this trimer is taken place by CTD1 and NTD of S1 subunits, where the CTD1s are placed in the center, while the NTDs are outside of this head. The S2 subunits constitute the stem of this trimer, which is then surrounded by CTD2 and CTD3 of the S1 subunit. When the spike protein is in the inactive state, the S2 subunit becomes covered by CTD1 (head portion), which takes "down" position causing steric clashes for binding between ACE2 and spike protein. In the active state, one CTD1 turns outward "up confirmation," which uncovers S2 subunit and thus allows the interaction between ACE2 receptor and spike protein (Fig. 1.4) (Yesudhas et al., 2020).

SARS-CoV-2 and SARS-CoV Key Residues

The similarity in the sequence of SARS-CoV and SARS-CoV-2 spike protein may support the theory of having the same ACE2 receptor in host cell (Wan et al., 2020). The sequence studies identified the key residues that are involved in spike–ACE2 receptor interactions. The key residue at 493 position in RBD of SARS-CoV-2 is Gln, whereas the corresponding 479 residues in SARS-CoV of humans and civets are Asn and Lys, respectively. As the 479 residue of RBD is near to the virus binding Lys31 residue of human ACE2 receptor, the Lys residue in civet leads to stearic clashes weakening binding to human ACE2 receptor. However, the Lys 479-Asn mutation showed that the Asn lying in 479 position of human SARS-CoV strengthens the binding of virus with human ACE2 receptor. The Gln493 residue in SARS-CoV-2 RBD is matching with hot spot Lys31 residue of human ACE2 receptor explaining the target cell identification (Wan et al., 2020). Likely, the 501 residue in the RBD of SARS-CoV-2 is Asn, while the corresponding residues at 487 position in civet RBD are Ser and Thr in humans.

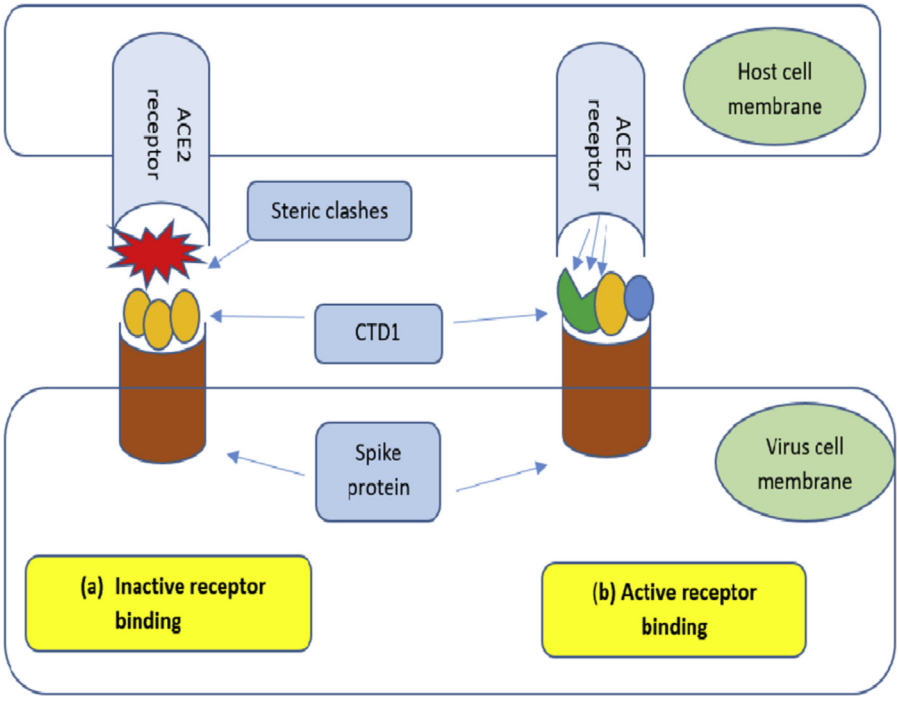

FIG. 1.4 Conformations of spike protein in active and inactive states. **(A)** The conformations in S2 subunit in the inactive state where CTD1s completely cover the S2 subunits "down position." This hinders the binding of the spike protein with ACE2 receptor. **(B)** Spike protein conformation in the active state in which one of the CTD1s (showed in green) is in an open state facilitating the binding of the spike protein with ACE2 receptor. *ACE2*, angiotensin-converting enzyme 2; *CTD*, C-terminal domain.

This residue plays a key role in mediating the interaction with Lys353 hot spot residue of ACE2 receptor. The analysis of Sr487-Thr mutation shows a significant role in human ACE2 receptor binding and in human-to-human transmission. Thus, interacting with Lys353 will be more favorable for human SARS-CoV threonine and SARS-CoV-2 Asn than civet serine (Wan et al., 2020).

The Lue455, Ser494, and Phe486 residues in SARS-CoV-2 RBD and Tyr442, Asp480, and Leu472 residues in human and civet SARS-CoV are also considered important for binding with the human ACE2 receptor. The interaction of Tyr 442 residue of civet and human SARS-CoV RBDs with Lys31 hot spot residue of ACE-2 receptor is considered unfavorable; however, Lue455 residue of SARS-CoV-2 shows favorable interactions. The Phe486 residue of SARS-CoV-2 RBD interacts more favorably with Lys31 residue of human ACE2 receptor than Leu472 residue of human−civet SARS-CoV. The Ser49 residue shows positive affinity for the hot spot residue Lys353 of human ACE2 receptors. Also, the Asp480 residue of SARS-CoV shows favorable interaction with the Lys353 residue (Yesudhas et al., 2020).

In describing the viral entry process, the Lys353 and Lys 31 are named as "hot spot" residues of human ACE2 receptors, which are made of salt bridge in a crypt of hydrophobic medium and contribute vitally for binding of virus and host cell receptor. This key residue comparison of human and civet SARS-CoV with SARS-CoV-2 emphasizes how SARS-CoV-2 can actively choose and bind with human ACE2 receptors, which subsequently can cause human-to-human transmission (Wan et al., 2020). The heterogenic amino acids in ACE2 receptors contribute for wavering the virus- and host-binding affinities. However, the variations in ACE2 host cell receptors can resist binding and entry of the invading pathogen. As reported by Hussein et al., S19P and E329G mutations in ACE2 receptor hinder interaction with viral spike protein. Therefore, resistance against infection by SARS-COV-2 can be attributed to variations in ACE2 receptor or viral spike protein (Hussain et al., 2020).

Intrinsically disorder regions in coronaviruses

The intrinsically disordered regions (IDRs) have a chief role in many biological functions such as protein binding and DNA/RNA binding, as they allow easy access to the corresponding sites. The protein−RNA recognition needs structural changes in both protein and RNA, which is mediated by flexibility in the structure of disordered residues. The IDRs have functional role in proteins transcription, translation, and cell. Studying the role of IDPs can help in identifying the viral life cycle and its pathophysiology (Yesudhas et al., 2020).

Evolution of SARS-CoV-2 virus

Coronaviruses being RNA viruses have high likelihood for genomic mutations that allow these viruses to accommodate new environments rendering them as long-term persistent threats. Mutations could be generated during replication of RNA viruses due to the low RNA-dependent RNA polymerase (RdRP) proofreading ability. These genomic mutations by viral RdRP allow an emerging virus to adapt to a new environment. The rate of synonymous substitution for coronaviruses is lower than that of some RNA viruses. During coronavirus replication, the mutation rate could be controlled by viral exoribonuclease (nsp14) (Denison et al., 2011). During the SARS-CoV-2 pandemic, viral evolution has been continuously occurring worldwide. The SRAS-CoV-2 was first collected from Wuhan city, China, in December 2019, and it was shown that the submitted sequences in databases varied from the latest sequence submitted in North America in April 2020. In the light of the continuous variations in viral genomic sequence, establishing a phylogenetic network is considered vital to investigate the capability of the virus to adapt in different environments and populations (Liu et al., 2020a,b).

It was claimed by a recent study that there are three genetic types of SARS-CoV-2 globally (Forster et al., 2020). The study demonstrated the genotypes in correlation to geographical locations; however, still the sample size and the analytical method are argued in the field of research (Mavian et al., 2020). Therefore, it will be still early to confirm if the evolution of SARS-CoV-2 is correlated to varied genetic and immunological factors in different human populations. Investigating SARS-CoV-2 variation among different geographical areas can provide useful information to develop vaccines for different populations. Moreover, regular sequencing is considered crucial to update information about viral evolution.

Clinical Features of SARS-CoV-2 Viral Infection

Generally, coronaviruses can affect different body systems (gastrointestinal, respiratory, and central nervous system). The clinical features are overlapping between different coronaviruses; however, they vary in intensity from mild to severe and in the most dominating symptoms and signs (da Costa et al., 2020). SARS-CoV-2 is characterized by variable wide range of incubation period from 1 to 12 days, with a median of 4 days (Guan et al., 2020). What is remarkably noted about the SARS-CoV-2 is the extreme variation in clinical presentation, severity, course of disease, prognosis, and clinical outcome among exposed individuals, a matter

that renders consequences of infection unpredictable. Some of SARS-CoV-2-exposed individuals experience no symptoms (asymptomatic) or very mild symptoms (subclinical infection), which may be mistaken for other respiratory viral infections. Mostly, these cases are accidentally discovered by screen testing. Even the symptomatic patients vary in their clinical presentation between gastrointestinal, respiratory, and neurological symptoms according to the dominant affected body system (da Costa et al., 2020). SARS-CoV-2 infection most commonly presents with fever (85%), cough (58%), fatigue (29%), dyspnea (17%), pharyngitis (13%), diarrhea (7%), headache (7%), nausea and vomiting (4%), and abdominal pain (2%) (da Costa et al., 2020).

Globally, the cases and deaths records for COVID-19 pandemic had exceeded those of SARS and MERS coronaviruses (European Center for Disease Prevention and Control, 2020). According to the recent reports from the European Centre for Disease Prevention and Control, there were estimates of 145,144 deaths. The distribution for most of deaths was recorded in the country order of the United States, Italy, Spain, France, and United Kingdom (European Center for Disease Prevention and Control, 2020). Usually the clinical outcome is related to the age and the presence or absence of underlying health conditions, which makes fatality rate is expected to be high among old-age patients with chronic illnesses. Unexpectedly, there were unexplainable deaths records among middle age and SARS-CoV-2 young individuals who had no history of underlying medical problems. It is noted that most of SARS-CoV-2-infected patients have clinical manifestations of moderate severity and well prognosis. However, some patients can progress to complicated cases who die of organ system failure as acute cardiac injury, acute renal injury, and shock (da Costa et al., 2020). So far, the pathophysiology behind the rapid deterioration and loss of SARS-CoV-2-infected patients with severe clinical course is not fully understood. However, recent studies primarily introduced a suggested theory of "cytokine storm," which may associate the severe cases of COVID-19. In cytokine storm, immunological proinflammatory cytokines, e.g., INFγ, IL1B, MCP, and IP10, are produced in large amounts and poured in circulation resulting into shock and organ failure. The role of cytokine storm in severe cases was evidenced by reporting higher levels of cytokines in COVID-19 patients who required ICU admission than other patients with mild or moderate severity of disease. In addition to the reported increase in the secretion of cytokines from T-helper1 cells, recently a similar increase was observed in production of T-helper2 cytokines (e.g., IL10 and IL4) (da Costa et al., 2020). In this perspective, more studies are needed in the research field to introduce detailed emphasis on the different patterns of immune response in SARS-CoV-2-infected patients, which in turn can help to trace the dynamics of virus pathophysiology (da Costa et al., 2020).

SARS-CoV-2 Viral Shedding

The shedding of viral RNA is the highest at the onset of symptoms and then reduces after days and weeks from the beginning of symptoms (Lavezzo et al., 2020). Nevertheless, the viral RNA can be detected in respiratory specimens during the incubation period (1−2 days before the appearance of symptoms) reaching the peak few days after, and it can remain positive for up to 8 days in mild patients and can extend for longer periods in severe cases (Wolfel et al., 2020). It has been reported that viral RNA shedding may extend for up to 67 days in nasopharyngeal specimens among adult cases and for >1 month in feces of pediatric cases (Perera et al., 2020).

The late clearance of viral RNA (≥15 days after disease onset) is more reported with cases with old age, severe course of illness, hypertension, or delayed hospital admission (Xu et al., 2020a,b,c). Not mere polymerase chain reaction (PCR) detection of viral RNA will necessarily confirm infectivity unless the infectious particles are recovered through the isolation of virus from cultured samples. Moreover, the viral infectivity correlates proportionally with viral load, which is also considered an index for the disease course and prognosis. It has been reported that the viral loads are 60 times higher in severe than in mild cases (Wolfel et al., 2020). The viral load profile of SARS-CoV-2 is found to be similar to that of influenza virus, as in both, the viral load reaches the peak at around the onset of symptoms (Cheung et al., 2020). In contrast, SARS-CoV viral load reaches the peak about 10 days after the onset of symptoms, whereas MERS-CoV viral load peaks at the second week after the onset of symptoms (Cheung et al., 2020). Reaching high viral load around the time of the onset of symptoms can predict high infectivity and easy transmission of SARS-CoV-2 in early stage of illness (Ackerman et al., 2020).

Respiratory infection with non-SARS-CoV-2 pathogen does not exclude having SARS-CoV-2. A study conducted in North Carolina that 20.7% of COVID-19 patients had coinfection with additional viral pathogens (Kim et al., 2020). The most common copathogens were rhinovirus, respiratory syncytial virus, and seasonal coronaviruses.

Pneumonia in pregnancy

Pneumonia was considered the third common cause for indirect maternal deaths in one study done in the United States between 1960 and 1968 (Visscher and Visscher, 1971).

It is the most common cause of nonobstetric infections in pregnancy, and for that, pneumonia of infectious origin is considered very important cause for maternal morbidity and mortality (Benedetti et al., 1982; Berkowitz and LaSala, 1990; Madinger et al., 1989).

It is estimated that 25% of pregnant females who developed pneumonia will need ICU admission and ventilatory support (Madinger et al., 1989).

As a rule viral pneumonia is more serious than bacterial pneumonia as regard maternal morbidity and mortality although bacterial pneumonia may be serious even with bacterial agents sensitive to antibiotics (Rigby and Pastorek, 1996).

Many etiologies stand behind increase risk of pneumonia in pregnancy as alteration in cell-mediated immunity and changes in pulmonary functions (Jamieson et al., 2006; Sargent and Redman, 1992; Nyhan et al., 1983; Weinberger et al., 1980).

There is historic evidence proved that pregnancy adversely affects the course of pneumonia especially in late pregnancy (third trimester); during influenza pandemic in 1918−19, the case fatality rate (CFR) for pregnant female was 27% and reaches 50% if pneumonia occurred in third trimester(Harris, 1919).

There was other proof during pandemic of Asian flu between 1957 and 1958, as the CFR was doubled in pregnant women than nonpregnant women, and pregnant deaths constituted 10% of all deaths (Eickhoff et al., 1961).

There were many reported adverse complications of pneumonia on pregnancy; they include premature labor or delivery, premature rupture of membranes (PROM), intrauterine fetal death (IUFD), and fetal growth restriction (Visscher and Visscher, 1971; Benedetti et al., 1982; Berkowitz and LaSala, 1990).

Severe acute respiratory syndrome and pregnancy

There were several case reports and small studies that described effects of SARS on pregnant females; those effects included severe maternal illness or death and spontaneous abortion or preterm labor (PTL) (Jamieson et al., 2006; Wong et al., 2003, 2004; Ng et al., 2003, 2004).

As usual, the complications were more, and clinical outcome was worse in pregnant female with SARS than nonpregnant female in Hong Kong (Maxwell et al., 2017).

During the period from February 1, 2003, and July 31, 2003, Wong et al. observed cohort of pregnant female infected by SARS, and they reported 60% abortion rate in those infected early in pregnancy and 80% PTL in those infected in third trimester (Wong et al., 2004).

Another case control study was done in Princess Margarit Hospital in Hong Kong; this study compared pregnant (10 patients) and nonpregnant females (40 patients), who all had SARS infection. The investigators reported three deaths in pregnant females (30%) versus no deaths in nonpregnant females ($P = .006$). The risk of renal failure was also more in pregnant females ($P = .006$), and also risk of disseminated intravascular coagulopathy was more in pregnant group ($P = .006$). Not only that ICU admission was more in pregnant females, but they also needed more intubation and ventilatory support (Lam et al., 2004).

In 2017, Maxwell and his colleagues studied seven pregnant females infected by SARS-CoV in SARS unit, and they reported two deaths out of seven (CFR = 28%) and that four out of seven needed ICU admission and mechanical ventilation (57%). They also reported better outcome on nonpregnant females with CFR about 10%, and 20% only needed ICU admission. For the remaining 5 recovered pregnant females, two of them had delivered babies with low birth weight due to intrauterine growth restriction, but none of those babies were infected by SARS-CoV, and their mothers were advised to cancel breast feeding to avoid vertical transmission of infection (Maxwell et al., 2017).

During the peak of SARS epidemic in 2003, Zhang and his colleagues, reported their clinical analysis for five primigravida females infected by SARS-CoV, and they found two out of five primigravida were infected in second trimester, while three were infected in the third trimester, and also two out of five had hospital-acquired infection, while three were community-acquired infection. All primigravidas developed fever and abnormal radiograph in chest X-ray or CT. Four of them developed cough, four of them developed hypoproteinemia, three developed elevated liver enzymes, namely, alanine transferase, three developed rigors, two out of five developed lymphopenia, and two developed thrombocytopenia. They reported also one ICU admission, but fortunately all pregnant females were recovered without any maternal deaths and also their babies were proved to be SARS free (Zhang et al., 2003).

Robertson et al. had reported detailed case report of American pregnant lady. She was 36 years old and

presented by intermittent cough and no fever. She had traveled to Hong Kong during SARS epidemic in 2003, and during her stay in Hong Kong, she was exposed to a person who was proved to be SARS-CoV positive, When she reached 19 weeks of her pregnancy, she developed fever, loss of appetite, continuous cough, headache, weakness, and dyspnea. When she had come back to the United States, she was hospitalized for pneumonia and tested for SARS-CoV and proved to be positive. Ultrasound was normal except of placenta previa; fortunately, she recovered and was discharged from hospital. Then after she was readmitted at 38 weeks for elective cesarean delivery due to placenta previa, she delivered healthy girl; after delivery, whole maternal blood, maternal serum, nasopharyngeal swab, rectal swab, placenta, cord blood sample, amniotic fluid sample, and breast milk sample were collected and tested by PCR, but no viral RNA was detected in all samples.

However, antibodies to SARS-CoV were detected by enzyme immune assay and indirect immunofluorescence assay in maternal serum, breast milk, and cord blood (Robertson et al., 2004; Schneider et al., 2004).

Another American pregnant female 38 years old was reported to have SARS; she traveled to Hong Kong at 7 weeks' gestation and had exposed to SARS-CoV-positive person at her stay in Hong Kong. When she had come back to the United States, her husband developed manifestations of SARS, and then after 6 days, she developed fever, muscle pain, headache, cough, expectoration, wheezy chest, and dyspnea. She was hospitalized for SARS, and later on, she recovered. Serum samples were taken 4 and 9 weeks postonset of her illness; both samples were proven to be positive for SARS-CoV by enzyme immunoassay and immunofluorescence assay. She had continued her pregnancy without any manifestations except high blood glucose. At 36 weeks' gestation, cesarean section was done due to preterm premature rupture of membranes and reported fetal distress, and she had delivered healthy boy baby. At time of delivery, serum sample was taken and reported to be positive for SARS-CoV antibodies, but samples from umbilical cord and placenta were negative. Breast milk was also negative for SARS-CoV antibodies, and it was tested twice: 12 and 30 days postdelivery. Samples from maternal blood, nasopharyngeal swab, stool, cord blood, infant blood, and infant stool were tested for SARS-CoV virus by reverse transcriptase–polymerase chain reaction (RT-PCR), and all were negative (Stockman et al., 2004).

Yudin and his colleagues observed a 33-year-old pregnant woman in Canada who was hospitalized at 31 weeks' gestation with fever, dry cough, and abnormal chest X-ray with patchy infiltrations; she had infected by SARS via contact to a person from her family. She had stayed in hospital for 3 weeks, but she did not need ICU admission or ventilatory support. After convalescence, she was positive for antibodies for coronavirus. Her pregnancy continued uneventful, and she delivered healthy normal girl baby with no evidence of infection (Yudin et al., 2005).

Shek and his colleagues studied that five neonates delivered from infected pregnant women had been proved to be positive for SARS-CoV during Hong Kong epidemic in 2003. Fortunately, serial testing by RT-PCR, viral culture, and antibodies assay for the infants were negative, and none of them had any respiratory manifestations so they were clinically and microbiologically free. From this study and other studies, it is proven that there is no vertical transmission from pregnant mother infected by SARS CoV to their infants during Asian epidemic in 2003 (Shek et al., 2003).

Pathological changes in placenta of SARS patients

Ng et al. studied the placentae of seven pregnant females infected by SARS-CoV; two out of seven were infected and recovered in the first trimester, and they found no pathological abnormalities in their placentae, other three placentae were delivered from mothers of acute SARS-CoV, and they found fibrin deposition subchorionic and intervillous. These findings are common with impaired placental blood flow, and the two placenta examined from pregnant women who recovered from SARS-CoV in third trimester were highly abnormal; they found extensive fetal vascular thrombosis, fetal hypo- or malperfusion, and avascular villi. These two pregnancies were also complicated by fetal growth restriction, oligo hydramnios, and poor fetal outcome, but it was strange that no signs of inflammation as villitis were found in those placentae (Ng et al., 2006).

Middle East respiratory syndrome with pregnancy

Unfortunately, we have few data about MERS and pregnancy as regards clinical course, fetal outcome, and postpartum period. It seems that alteration in cell-mediated immunity may increase risk of MERS and its severity in pregnant women (Malik et al., 2016).

As clinical outcome was much worse in pregnant females with SARS-CoV than nonpregnant females, so it is expected that related coronavirus causing MERS will have similar course and effect and from the

previous study of pregnant females with MERS 10 out of 11 had adverse complications (Malik et al., 2016).

From November 2012 to February 2016, the Ministry of Health in Saudi Arabia (MOH) had reported 1038 cases with MERS; only five pregnant females were reported to have MERS, and unfortunately, all of them had adverse complications. All five females were admitted to ICU, with two maternal deaths; although their ages were young from 27 to 34 years old, there are two perinatal deaths: one of them was IUFD and the other was early neonatal death shortly after cesarean delivery. Two of those females were nurses, and this confirmed that the healthcare workers are at risk for MERS (Assiri et al., 2016).

Then, Alserihi et al. described another case report of MERS with pregnancy; they observed a 33-year-old pregnant nurse that was working in critical care unit who got infected in her third trimester of pregnancy during hospital major outbreak. After admission to the hospital, the nurse's conditions deteriorated, and she was admitted to ICU and put on intermittent positive pressure ventilator. She received dexamethasone for lung maturity of her fetus; then emergency cesarean section at 32 weeks' gestation was done, and then she was readmitted to ICU. Fortunately, the mother had recovered, and her baby was admitted to neonatal ICU for observation, but he was discharged also after several days in good conditions (Alserehi et al., 2016).

It was supposed that her young age, immune response early delivery, and steroids therapy may contribute to the good maternal outcome.

Then; Alfaraj et al. reported two pregnant cases infected by MERS-CoV. The cases were recorded in PMBAH (Prince Mohammed bin Abdulaziz Hospital). The infection was confirmed by RT-PCR from nasopharyngeal swab samples. One of them was relatively young 29 years old, had no history of comorbidity, and was 6 weeks gestation, but the other one was 39 years old, with history of hypertension, renal failure, and repeated hemodialysis. Both patients were tested negative for MERS-CoV later on and then were discharged after several days. The young patient delivered a healthy baby but no report about the other one after discharge (Alfaraj et al., 2019).

Another report from Jordan in 2012 described a case of second trimester IUFD due to MERS CoV infection during outbreak in Al Zarqa region. The mother was presented by fever, abdominal pain, mild vaginal bleeding, fatigue, cough, and with history of exposure to MERS CoV. One week after onset of symptoms, ultrasound was repeated and confirmed IUFD. The infection was confirmed by antibody testing and history of contact to a known family member with MERS CoV. This was the first report of IUFD with MERS CoV (Payne et al., 2014).

Another report came from the United Arab of Emirates (UAE) in 2013. When Malik et al. reported that a pregnant female developed adult respiratory distress syndrome (ARDS), she got infected via community-acquired pneumonia. She was admitted to ICU and developed respiratory failure and hypotension. The mother was tested by RT-PCR for MERS CoV and proved to be positive. Emergency cesarean section was done to ameliorate her condition with delivery of healthy baby with good Apgar score. She received ribavirin and peginterferon-α. However, her condition deteriorated into septic shock and died despite vigorous treatment and ventilatory support. It was strange that viral shedding and chest radiograph improved on treatment despite the patient died (Malik et al., 2016).

MERS CoV was also reported outside Middle East in South Korea. Jeong et al., in 2015 described a 39-year-old pregnant female who was exposed to MERS CoV contact in during third trimester of her pregnancy. She was confirmed to be MERS-CoV by RT-PCR testing. This lady delivered a healthy baby by emergency cesarean Section despite placental abruption and sudden antepartum hemorrhage and premature rupture of membranes. Antibody testing of her baby was negative as regard MERS-CoV IgG, IgM, and IgA (Jeong et al., 2017).

Other coronaviruses with pregnancy

The alpha coronaviruses include HCoV 229E and NL63.

There are beta coronaviruses, and they include HKU1 and OC43. They can infect human and present by common cold symptoms. Gagneur et al. investigated the vertical transmission (from mother to infant) of all four mentioned viruses. They collected maternal samples from vagina and respiratory tract during labor and collected gastric aspirate from newly born babies. All the samples were evaluated by RT-PCR for HCoV 229E and NL63, HKU1, and OC43. From July 2003 to August 2005, the collected samples are from 159 pregnant mothers and their infants. The human coronavirus was detected in 12 samples; all were from only seven maternal–infant pairs.

Three pairs were positive respiratory samples, two were positive for respiratory and vaginal (total four), two were positive for vaginal-only, and the other

remaining three samples were positive from neonatal gastric samples. Fortunately, all babies were free of symptoms (Gagneur et al., 2007, 2008).

Vertical transmission of COVID-19 (SARS-CoV-2) from mother to infant

On January 13, 2020; the Wuhan Children's Hospital in Hubei Province reported delivery of a healthy baby. Then later on, his nursemaid was confirmed to be COVID-19 positive, and the mother also was tested few days later and was also COVID-19 positive. 16 days after delivery, the baby started to develop symptoms. It is not clear who infected who, but it supposed that the nursemaid had transmitted infection to the mother through direct contact, and then the mother transmitted it to her baby, but other scenario may be true.

On February 5, the hospital reported a delivery of a baby who was tested positive for COVID-19 after 30 h of his delivery; the mother was also known to be COVID-19.

The bay had no fever or cough, but he developed tachypnea and abnormal chest radiograph and elevated liver enzymes.

So vertical transmission from mother to infant should not be excluded (Steinbuch, 2020; Woodward, 2020; Gillespie, 2020).

Immunological response to COVID-19 (SARS-CoV-2), SARS-CoV, and MERS-CoV

The most constant immune response to all mentioned coronaviruses infections is severe lymphopenia (Booth et al., 2003; Lee et al., 2003; Panesar, 2003; Ajlan et al., 2014; Arabi et al., 2015; Ko et al., 2016; Xu et al., 2020a,b,c; Zhang et al., 2020a,b).

Also decreases in CD4 and CD8 lymphocytes were noted in the early course of COVID-19 (SARS-CoV-2), SARS-CoV, and MERS-CoV and were associated with adverse complications. In SARS-CoV infection, lymphocyte involvement was detected by expression of CD25, CD28, and CD69. In MERS-CoV infection, the virus negatively regulates MHC-I, MHC-II, and CD80/86 in antigen-presenting cells, which results in inhibition of the T lymphocyte response. These events can further impair the function of B and T cells through negative regulation of DPP4 receptors by MERS-CoV (Yu et al., 2003; Cai et al., 2004; Josset et al., 2013; Chu et al., 2014; Ying et al., 2016).

MERS-CoV infection may induce T lymphocytes apoptosis, and this leads to the obvious immune suppression seen during infection. DPP4 (which is negatively affected during MERS-CoV) plays an important role in activating T lymphocyte during infection by MERS-CoV (Ishii et al., 2001; Manni et al., 2014).

Ying et al. reported that T CD4 helper cells are more affected during MERS-CoV infection through apoptosis by extrinsic and intrinsic pathways (Ying et al., 2016).

A significant increase in cytokines IL-17 was observed during MERS-CoV infection; thus, it is thought that MERS-CoV infection induces production of Th 17 cytokines. These Th17 cytokines recruit monocytes and neutrophils to the site of infection and inflammation and lead to production of many cytokines in serial reactions such as IL-1, IL-6, TNF-α, TGF-β, IL-8, and MCP-1 (Jin and Dong, 2013; Mahallawi et al., 2018).

Normally, the immune system can produce neutralizing antibodies to any viral infection, which block the viruses and prevent their entry to host cells. These antibodies appear in patient serum and thus are used as diagnostic method to confirm any viral infection or MERS-CoV infection. We can detect serum antibodies to MERS-CoV infection 14−21 days after infection, and this may continue up to 18 months. The antibodies for SARS-CoV may even last more up to 24 months and may take 6 years to disappear (Park et al., 2015; Corman et al., 2016; Alshukairi et al., 2016; Liu et al., 2006; Tang et al., 2011).

In patients recovered from SARS, specific memory $CD4^+$ T lymphocytes for HLA-DR08 and HLA-DR15 restricted epitopes of the SARS-CoV S protein have been identified. Virus-specific $CD4^+$ T lymphocytes mainly exhibited a central memory phenotype ($CD45RA^-$ $CCR7^+$ $CD62L^-$), while $CD8^+$ memory T lymphocytes were identified as memory effector cells ($CD45RA^+$ $CCR7^-$ $CD62L^-$).

These findings suggest that there is an activity of specific memory T lymphocytes in long-term protection against SARS-CoV infections. In addition, the response of memory B lymphocytes to SARS-CoV decreases significantly after 1−2 years of infection (Openshaw, 2004; Yang et al., 2006, 2007; Libraty et al., 2007; Martin et al., 2008).

The immune response to SARS-CoV-2 or COVID-19 needs time to be fully investigated. Some reported a decrease in CD4 T cells and CD8 T cells in the peripheral blood of infected patients (Xu et al., 2020a,b,c), a reduction in total lymphocytes (35%), and an increase of serum IL-6 (52%) and C-reactive protein (84%) (Peng et al., 2020).

Cytokines Storm

Many reports point to the pathology beyond the severe cases of SARS-CoV-2 or COVID-19 that need ICU admission and ventilatory support. Hence the

expression of cytokines storm went to force. There is an increase in humoral immunity in patients admitted to ICU, such as IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A, and TNF-α.

As mentioned before, there is a decrease in CD4 and CD8 T cells in peripheral blood of infected patients but with increased activation of remaining cells with marked expression of HLA-DR (CD4 3.47%) and CD38 (CD8 39.4%) double-positive fractions (Huang et al., 2020; Fang, 2016).

Clinical course of COVID-19 and other coronaviruses in pregnancy

Contact to MERS-CoV or SARS-CoV or SARS-CoV-2 (COVID-19) can trigger asymptomatic carrier state or common cold symptoms with or without fever. Unfortunately, symptoms may progress into severe pneumonia, adult respiratory distress, gastroenteritis, liver damage, septic shock, renal failure, multiple organ failure, and death. As regard severe cases of COVID-19, there we found multifocal nodules and ground glass opacity in lungs, for pregnant women. In addition to all mention manifestations, there is risk of vertical transmission and obstetric complications such as PTL and IUFD. As few reports about COVID-19 in pregnancy are available, but in general severe cases with pregnancy usually need ventilatory support and induction of PTL (WHO, 2020; Hui et al., 2018; ECDC, 2018; Kong and Agarwal, 2020; Santos, 2003; Alserehi et al., 2016; Assiri et al., 2016; CDC, 2013).

Cytokines produced by T-helper (Th) lymphocytes regulate immunity and inflammation. Th1-type cytokines are antimicrobial and proinflammatory and mainly include interferon-γ (IFN-γ), interleukin (IL)−1α, IL-1β, IL-6, and IL-12, but Th2-type cytokines are antiinflammatory and comprise IL-4, IL-10, IL-13, and transforming growth factor-β (TGF-β).

In pregnancy, the attenuation in cell-mediated immunity by Th1 cells due to the physiological shift to a from Th1 to Th2 dominant environment contributes to overall infectious morbidity by increasing maternal susceptibility to intracellular pathogens such as viruses (Nelson-Piercy, 2015; Berger, 2000).

The CFR in pregnant females with COVID-19 (SARS-CoV-2), SARS-CoV, and MERS-CoV are 0%, 18%, and 25%, respectively. The disease looks milder in pregnant COVID-19 than in SARS and MERS pregnant. The explanation is not fully understood. However, in COVID-19, a range of immune responses has been described, and early adaptive immune responses may be predictive of milder disease severity. We postulate that changes in the hormonal milieu in pregnancy, which influence immunological responses to viral pathogens together with the physiological transition to a Th2 environment favoring the expression of antiinflammatory cytokines (IL-4 and IL-10) and other unidentified immune adaptations, may serve as the predominant immune response to SARS-CoV-2, resulting in the lesser severity of COVID-19 compared with that in nonpregnant individuals. These immune responses should be further characterized in gravidas and nongravidas with COVID-19 of different disease severities (Wong et al., 2003; Assiri et al., 2016; Thevarajan et al., 2020).

Fetal complications of COVID-19 include miscarriage (2%), intrauterine growth restriction (IUGR; 10%), and preterm birth (39%). Fever, with a median temperature of 38.1−39.0°C, is the prevailing symptom in COVID-19. Cohort studies in patients with other infections have not shown increased risks of congenital anomalies from maternal pyrexia in the first trimester, although childhood inattention disorders are more common, possibly related to hyperthermic injury to fetal neurons (Sass et al., 2017).

There is a theoretical risk of vertical transmission, similar to that seen in SARS, as the ACE2 receptor is widely expressed in the placenta, with a similar RBD structure between SARS-CoV and SARS-CoV-2.

Most recently, two neonates from COVID-19-infected mothers are said to have tested positive for SARS-CoV-2 shortly following delivery, casting concerns about the possibility of vertical transmission (Levy et al., 2008; Woodward 2020; Murphy, 2020; Li et al., 2020a,b; Liu et al., 2020a,b).

However, there have been no confirmed instances of vertical transmission among the 46 other neonates born to COVID-19-infected mothers reported thus far, supported in turn by evidence demonstrating an absence of viral isolates in the amniotic fluid, cord blood, breast milk, and neonatal throat swabs in a subset of these patients.

It is notable, however, that the overwhelming majority of these women acquired COVID-19 in the third trimester; there are currently no data on perinatal outcomes when the infection is acquired in early pregnancy. Regardless of the risk, it is reassuring that COVID-19 appears to manifest as a mild respiratory disease in the pediatric population (Zhu et al., 2020; Zhang et al., 2020a,b; Chen et al., 2020a,b,c; Xu et al., 2020a,b,c; Cai et al., 2020).

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