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Chapter 1

Coronavirus pandemic: History, overview of different strains of coronaviruses and what went wrong

Peculiar Feenna Onyekere[1] and Uchechukwu Victor Nwankwo[2]
[1]*Department of Pharmacognosy & Environmental Medicine, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, Enugu State, Nigeria;* [2]*General Hospital Okuta, Baruten, Kwara State, Nigeria*

Chapter outline

1.1 Introduction

Coronavirus is a genus of viruses belonging to the family Coronaviridae in the order *Nidovirales*. Other families in the *Nidovirales* order include Arteriviridae, Roniviridae, and Mesoniviridae as depicted in Fig. 1.1. Coronaviruses of the Coronaviridae family, which is subdivided into *Coronavirinae* and *Torovirinae*, are of greater economic importance compared to the other

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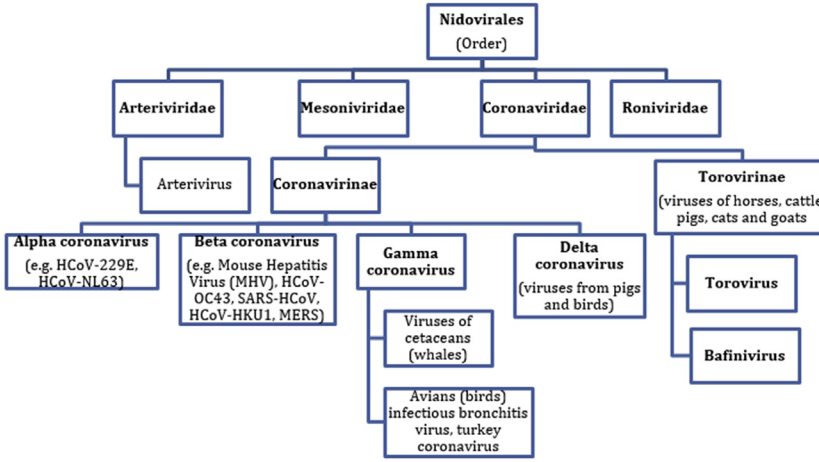

FIGURE 1.1 Phylogenic tree of coronaviruses.

families. They cause an array of diseases including pneumonia, enteritis, hepatitis, polyserositis, encephalomyelitis, pyelonephritis, bronchitis, reproductive diseases, and other cellular/physiological disorders [1]. Their nucleic acid material is composed of a single molecule of linear positive-sense, single-stranded RNA of 26−32 kbs in length [2]. They exist in the nano range size of 65−125 nm and are classified into three classical groups—group 1: HCoVs 229E and NL63; group 2: SARS coronaviruses; and group 3: coronaviruses including avian viruses (turkey coronavirus). Coronaviruses are further divided into four subgroups as depicted in Fig. 1.1—*alpha*, *beta*, *gamma*, and *delta* coronaviruses. The coronaviruses that affect humans are called human coronaviruses. The seven strains of human coronaviruses include five beta coronaviruses (SARS-CoV-2, SARS-CoV, MERS-CoV, OC43, and HKU1) and two alpha coronaviruses (229E and NL63) [3].

The virions of coronaviruses exist as pleomorphic spherical 80−222 nm enveloped with prominent club-shaped peplomers (spikes). Their helical nucleocapsid structure consists of three or four structural proteins (Fig. 1.2)—nucleocapsid protein (N), peplomer glycoprotein or spike protein (S), and transmembrane glycoprotein (M and E). Some *betacoronaviruses* also possess shorter spikes composed of hemagglutinin-esterase (HE) protein. Spikes are divided into two subunits S1 and S2. S1 is associated with binding or attachment to the host cell while S2 is responsible for penetration or fusion of the viral/cellular membrane. Moreover, the genomic structure of the virions of coronaviruses is highly infectious owing to its 5′ capped and 3′ polyadenylated sequence. The enveloped virions are released by the cellular exocytosis mechanism from the endoreticulum Golgi membrane complex where they are formed via budding [1].

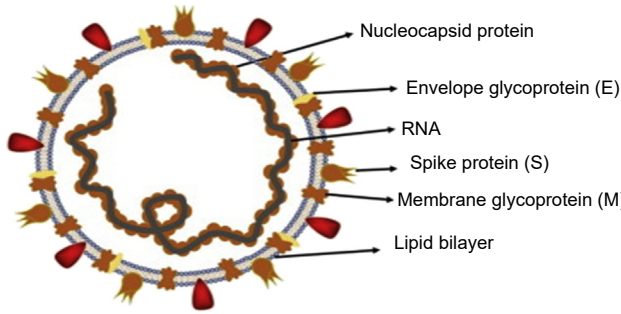

FIGURE 1.2 A structure of a typical human coronavirus. *Adapted from Muhammed AS, Suliman K, Kazmi A, Nadia B, Rabeea S. Covid-19 infection: origin, transmission, and characteristics. J Adv Res 2020;24:91–8.*

In 2003, the outbreak of severe acute respiratory syndrome (SARS) in China affected the population of the citizenry. The virus responsible for the infection was reported to be SARS-CoV, a member of the *betacoronavirus* [4,5]. In 2012, another member of *betacoronaviruses* was confirmed in Saudi Arabia and named Middle East respiratory syndrome coronavirus (MERS-CoV) which caused over 800 deaths. There are supporting evidence that confirm that SARS and MERS coronaviruses originated from ancestral bat viruses [6].

Novel coronavirus disease 2019 (COVID-19) is a recent upper respiratory disease caused by a strain of human coronaviruses, SARS-COV-2 [7,8]. It was first identified in Wuhan, China, in late 2019 [9]. Coronaviruses affect reptiles, dogs, rodents, cats, cattle horses, swine, and birds. In some cases, bats have been implicated as the hosts of coronaviruses. Currently, the specific animal host(s) that initially infected man with SARS-CoV-2 is yet to be identified. The symptoms of COVID-19 include fever, dry cough, and tiredness. They usually have a gradual onset, but later, they could be fatal, especially among the elderly and those with serious comorbidities, including diabetes, strokes, severe asthma, and chronic obstructive pulmonary diseases. COVID-19 is highly infectious and could be transmitted via the droplets of the nasal discharges of the affected person. When the affected person sneezes or coughs, the virus could be transmitted to the unprotected neighbor.

A good understanding of the types, origin of coronavirus, and what went wrong as regards the coronavirus outbreak are critical for the discovery of possible drug targets in the management and treatment of the COVID-19 disease. This chapter unveils the nature, type, origin of coronavirus, what went wrong as regards the coronavirus outbreak, and future projections on the possible ways to tackle the disease.

1.2 Origin of coronavirus

The word "coronavirus" was coined from two Latin words: *corona* (crown) and *virus* (slimy liquid or poison or venom). The *corona* part of the compound word corona-virus reflects the "fringe appearance" of coronavirus when viewed in the power of an electron microscope after negative staining [7]. Coronavirus is a genus of viruses belonging to the family Coronaviridae and the order *Nidovirales.* Coronavirus was first discovered in 1931 when infectious bronchitis virus (IBV) was implicated as the cause of severe acute respiratory infections in domesticated chicken. Later in the 1960s, precisely in 1965, the first human coronavirus (HCoV-229E) was discovered [7,10]. They are classified into three different groups as listed in Fig. 1.3.

1.2.1 Historical facts about SARS-CoV-2

In 2003, SARS first emerged in Guangdong province in China, and it spread across the globe infecting over 8000 people with 776 deceased [11−13]. SARS was confirmed to belong to the betacoronavirus group, and it was thereafter named SARS-COV [4,5,12,13]. People infected with SARS manifested pneumonia symptoms associated with some diffused alveolar injury, leading to acute respiratory distress syndrome (ARDS) [2,11].

In 2012, 10 years after the emergence of the noisome pestilence of the 2002−03 SARS in China, another wave of coronavirus occurred in the Middle East. It was first identified among Saudi Arabia nationals [2,11]. Therefore, it was named MERS-CoV [11]. The symptoms of MERS-CoV range from mild

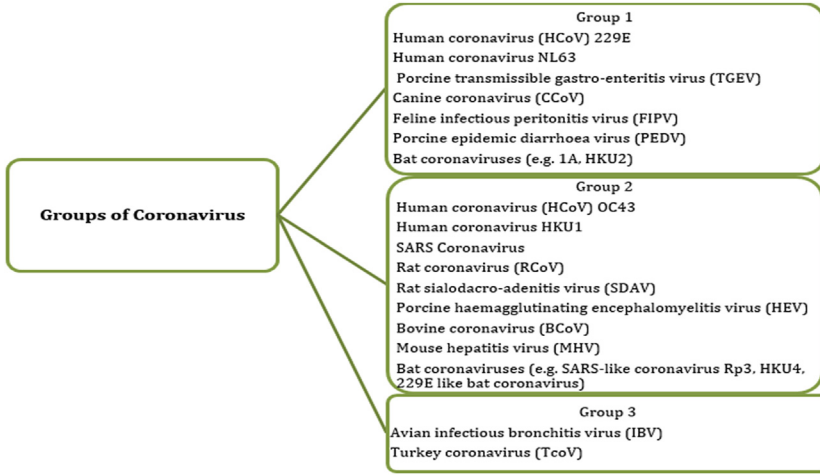

FIGURE 1.3 Groups of coronaviruses.

upper respiratory diseases to severe respiratory injuries, pneumonia, ARDS, and renal failure [11,14]. Between 2013 and 2018, MERS-CoV infected 2428 people and caused 838 deaths [11,15].

On December 31, 2019, the World Health Organization (WHO) was alerted of a disease outbreak associated with pneumonia-like symptoms of unknown etiology detected in Hubei province, Wuhan city, China [9,11,16]. On January 1, 2020, the Huanan Seafood Wholesale market was completely shut down for disinfection and sanitization purposes since viral pneumonia was associated with the market [16]. The Incident Management System of the WHO was activated on January 2, 2020. Then the Central Committee of the Communist Party of China, together with the State Council, launched a national emergency program, and between December 31, 2019, and January 3, 2020, 44 people were infected with SARS-CoV-2 in Wuhan, China [9].

The first imported case of SARS-CoV-2 outside Wuhan, China, was confirmed on January 13, 2020, in Thailand, followed by the second wave of the imported case confirmed in Japan on January 15, 2020. As at January 20, 2020, 282 cases from four countries had been reported as follows: China: Hubei Province—258, Guangdong province—14, Beijing municipality—5, Shanghai province—1; Thailand—2; Japan—1; Republic of Korea—1, bringing it to a total of 282 cases [9,17].

A traveller who returned from China on 15th January was discovered to have been infected with SARS-CoV-2 in Northwest State of Washington, USA (North America), on January 21, 2020 [18,19]. Meanwhile, the first COVID-19 case in South America was recorded on February 25, 2020, in Brazil [20–22].

Tedros Adhanom, the WHO Director-General, between Wednesday 22 (from 12:00 16:30, Geneva time, CEST) and from 12:00 to 15:10, CEST January 23, 2020, convened an Emergency Committee under the International Health Regulations (2005) to decide whether COVID-19 outbreak should be designated a Public Health Emergency of International Concern (PHEIC). The convened emergency health experts had divergent opinions, agreed on the urgency of the outbreak, and concluded on the need to reconvene a few days later for the final decision [9,21].

The first case in Australia was confirmed on January 25, 2020. Also, the first man in the Australian continent to die of COVID-19 was James Kwan who died on Sunday morning, March 1, 2020 [17].

On January 24, 2020, the first COVID-19 cases (3 cases) in the European continent were reported in France with their symptoms manifesting from 17, 18 and January 19, 2020, respectively. The first COVID-19 death in Europe was recorded on February 15, 2020, in France [23,24].

Africa was the second to the last continent hit by the COVID-19 pandemic after South America. It struck Egypt and Nigeria on February 14 and February 27, 2020, respectively, leading to the establishment of the Africa Taskforce for Coronavirus Preparedness and Response (AFTCOR). This joint task force

comprises Africa Center for Disease Control and Prevention (Africa CDC), WHO Regional Office for Africa (Afro), African Union Commission, African governments, and other stakeholders. An Italian patient who entered Nigeria was confirmed to be associated with the first imported case of COVID-19 in Lagos state, Nigeria, the most populated black nation of the world. Hundred days after the first COVID-19 case in Nigeria, a total of 11,844 cases and 333 deaths were confirmed, while 3696 patients were successfully treated and discharged [25,26]. The different dates of first cases and deaths in the various continents are listed in Table 1.1.

According to the WHO situation report on the COVID-19 outbreak, 495,760 deaths and 9,843,073 cases have been reported globally with America and Europe topping the chart between December 31 and June 28, 2020 (Fig. 1.3) [17].

1.2.2 How COVID-19–causing coronavirus was first identified

The virus causing COVID-19, SARS-CoV-2, was first identified by lung washing of the patients with pneumonia of unknown etiology in Wuhan, China [9,27]. Using tissue cultures and electron microscopy, the virus was amplified, and the pictures from the electron microscopy showed virions (spikes) at the periphery of the virus. This feature is generally common among the conventional coronavirus [9,27]. Multiplex polymerase chain reaction (PCR) also revealed similar characteristics of coronavirus: RT-PCR showed a positive reaction for the pan-*betacoronavirus* [27]. The virus was then linked to the *betacoronavirus* 2B lineage using bioinformatics. However, there was no specific type of coronavirus that was identified at this point.

Consequently, deep sequencing, 30,000 base pairs per genome, which were large for viruses, was revealed to be associated with the COVID-19–causing coronavirus [9]. An alignment of the full genome and sequencing showed a

TABLE 1.1 Summary of the first cases, first deaths in different continents of the world.

Continents/country	Date of first case(s)	Date of first death(s)
Asia/China	November 17, 2019	December 1, 2019
North America/USA	January 21, 2020	February 29, 2020
Europe/France	January 24, 2020	February 15, 2020
Australia	January 25, 2020	March 1, 2020
Africa/Egypt	February 14, 2020	March 8, 2020
South America/Brazil	February 26, 2020	March 16, 2020

very close relation of 96% similarity between the virus and the bat SARS-like coronavirus strain BatCov RaTG13 [27]. Several cell isolations were done using Vero E6 and Huh-7 [27]. After the isolations, and based on the unique features of the new virus, Chinese authorities on January 7, 2020 identified and designated the virus a novel coronavirus [9].

1.3 Life cycle of SARS-CoV-2 and nomenclature of the strains of coronavirus

1.3.1 Nomenclature and strains of coronavirus

Unlike bacteria and parasites, the naming of viruses and the diseases they cause do take different shapes. Viruses are named according to their genetic structures in order to enhance the discovery and development of diagnostic tests, vaccines, and medicines [8]. The International Committee on Taxonomy of Viruses (ICTV) assumes the responsibility of naming the viruses. But, WHO publishes the names of diseases in their International Classification of Diseases (ICD) in such a manner as to enable discussions on disease prevention, transmissibility, severity, and treatment [8]. It is very possible for a layman to know the name of a viral disease without knowing the virus causing the disease. Therefore, on February 11, 2020, ICTV named the COVID-19—causing virus SARS-CoV-2 because it is genetically related to the SARS outbreak of 2003. The WHO, in communication with the ICTV, officially announced COVID-19 as the name of the disease caused by SARS-COV-2 on February 11, 2020 [8].

There are about 50 strains of coronaviruses (Fig. 1.4) including seven human coronaviruses—human coronavirus 229E (HCoV-229E); human coronaviruses HKU1 (HCoV-HKU1); human coronaviruses NL63 (HCoV-NL63); human coronavirus OC43 (HCoV-OC43). Others include KSA-CAMEL-363, KSA-CAMEL-363 isolate of Middle East respiratory

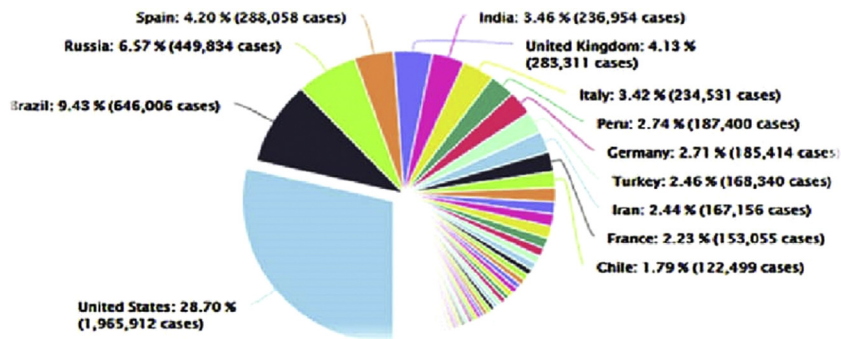

FIGURE 1.4 Geographical distribution of COVID-19 cases worldwide. *From World Health Organization (June 22—2, 2020).*

syndrome coronavirus; SARSr-CiCoV; and SARS-related palm civet coronavirus. There are three groups of coronaviruses: group 1: HCoV-229E and HCoV-NL63; group 2: HCoV-OC43 and HCoV-HKU1; and group 3. Genetic transformations enable coronaviruses to move from one host to another, breaking their species barriers. OC43, HKU1, NL63, and 229E are common human coronaviruses affecting people across the globe. But, SARS-CoV-2, SARS-CoV, and MERS-CoV which originally affected animals started affecting humans after genetic transformations [2,3] (Fig.1.5).

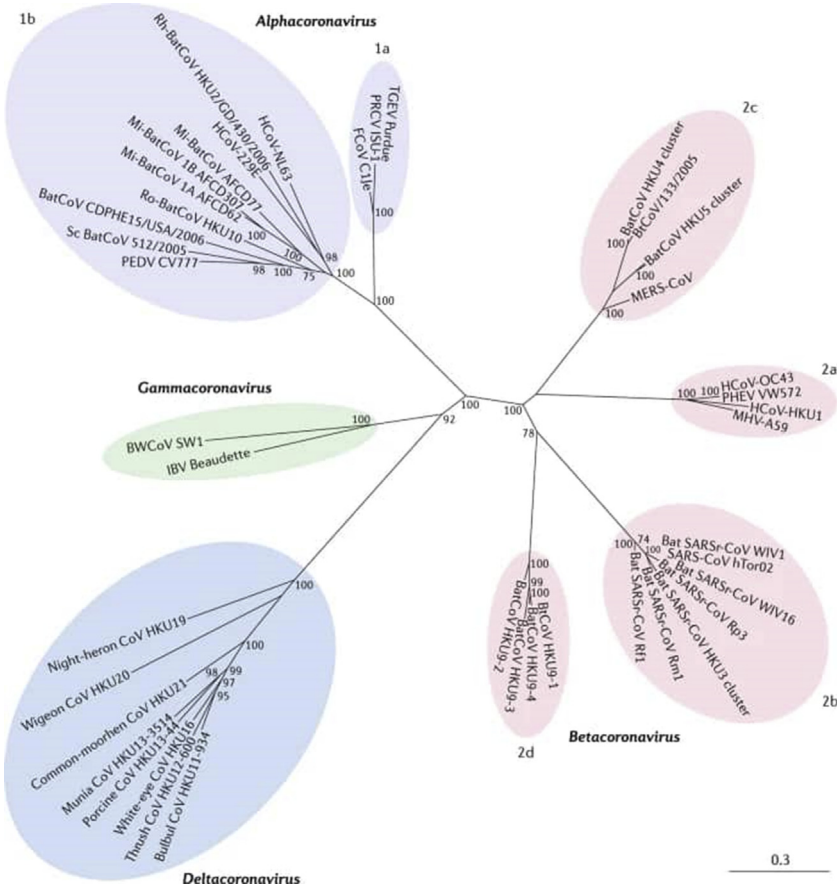

FIGURE 1.5 Phylogeny of 50 different strains of coronaviruses. Major human viruses are shown in red: human coronavirus 229E (HCoV-229E); human coronaviruses HKU1 (HCoV-HKU1); human coronaviruses NL63 (HCoV-NL63); human coronavirus OC43 (HCoV-OC43); KSA-CAMEL-363, KSA-CAMEL-363 isolate of Middle East respiratory syndrome coronavirus; SARSr-CiCoV, and SARS-related palm civet coronavirus. (For lack of space, the major human viruses have been highlighted). *Adapted from Christopher JB, Colin RH, Frederick AM. Coronaviruses. Fenner and White's medical virology. 5th ed. 2020. p. 437–46.*

1.3.2 Life cycle of SARS-CoV-2

The life cycle of SARS-CoV-2 follows the following sequences: attachment, penetration, biosynthesis, maturation, and release. The invasion of a host cell by SARS-CoV-2 starts with the virus binding to the host receptor (attachment). Once the virus attaches itself to the host receptor, it undergoes endocytosis as it finds itself into the host cell (Penetration). Inside the host cell, the single-stranded RNA virus locates the nucleus of the host cell where it uses mRNA to synthesize proteins (biosynthesis). The produced new particles (maturation) are then released [28]. Further details on the life cycle of SARS-CoV-2 were described in subsequent chapters.

1.4 What went wrong in the history of COVID-19

Prior to the emergence of SARS in 2002, human coronaviruses (HCoVs) 229E and OC43 were the only two recognizable human pathogens (coronaviruses) causing mild common cold and other insignificant symptoms. These friendly viruses did not attract the attention of scientific research activities [7]. The sudden appearance of the deadly, and sometimes, fatal SARS, in China around November 2002, renewed scientific research-based interests in the field of coronaviruses, leading to the discovery of another two HCoVs: NL63 and HKU-1, which were associated with respiratory diseases [7]. Further research opened up the possibility of coronaviruses crossing the species barriers, hence the belief that coronaviruses can leave their original hosts to infect new animal species.

After the first cases of coronavirus in Wuhan, China, in November 2019, there was a lag of several weeks before WHO declared COVID-19 a Public Health Emergency of International Concern (PHEIC) on January 30, 2020. Usually, based on the recommendations of the emergency committee, the Director-General of WHO would pronounce an outbreak as PHEIC. These recommendations are evaluated based on the unexpectedness of the outbreak and whether the outbreak spreads internationally and would require some global efforts to stop it. The process of constituting an emergency committee specific for a particular outbreak may take some time as the six WHO regions would have to send a list of public health experts from their respective countries within each region. From the list, the WHO Director-General would select the global experts to constitute the emergency committee specific for the outbreak.

Moreover, in the case of COVID-19, the emergency committee for COVID-19 lacked enough initial evidence needed to declare the outbreak a PHEIC. The nature of human-to-human transmission was not reasonably clear at the time of the first meeting of the WHO Emergency Committee on COVID-19. And it is important to have relevant evidence about the criteria for declaring COVID-19 a PHEIC, especially when considering the restrictions that arise following such declarations.

Different unaffected countries did not close their borders on time. Most countries like the United States and Canada closed their borders in March. People moved freely from China to any other part of the world, exporting COVID-19 to their destinations. Strict measures at the country levels were not implemented until those countries started recording their first cases of coronaviruses. Between January 1 and January 30, 2020, three additional continents of the world, including North America, Europe, and Australia, got invaded by SARS-CoV-2. The designation of an outbreak a PHEIC alone is not enough to curb the spread of SARS-CoV-2. After the declaration of COVID-19 a PHEIC on January 30, 2020, Africa and South America were later afflicted by COVID-19 on February 14 and February 26, 2020, respectively. If all countries closed their borders against international flights at the appropriate time, it would have been the safest measure to contain the outbreak.

While the WHO worked assiduously, and in collaboration with scientists around the world to prothe duce evidence needed to declare COVID-19 a PHEIC, several unfounded conspiracy theories filled the air, thus affecting the precautionary measures at the individual levels even in the already affected countries.

1.4.1 Possible theories to explain why adults are more susceptible than infants and young children to SARS-CoV-2

Generally, infants, young children, and adults have high hospital admissions due to respiratory diseases [28]. In the case of COVID-19, there is a huge difference. Adults are more susceptible to SARS-CoV-2 than infants and young children. Pediatric COVID-19 is "*more friendly*" than adult COVID-19. First, there is a strong correlation between the viral load of SARS-CoV-2 and the severity of the disease that it causes, i.e., COVID-19 [29]. Children might possibly have lower viral loads of COVID-19 [28]. So, we consider the possibility of the pediatric population having less expression of ACE2 than adults. Precisely, the more differentiated the epithelial cells of the airways, the higher the expression of ACE2 [28,29]. This follows the logic that the human lungs, as well as other human organs, advance with age. Since ACE2 is the receptor for SARS-CoV-2, it follows that the host with higher ACE2 would have a higher viral load and consequently more severe COVID-19.

Another reason for the increased susceptibility of the elderly to SARS-CoV-2 compared to the younger children is the difference in response to the virus, assuming the child finally gets infected with COVID-19. Usually, adults have more proinflammatory cytokines, which could lead to the development of multi-organ dysfunction syndrome (MODS) and ARDS. Research also shows that severe COVID-19 is associated with ARDS and MODS [28].

Another possibility is the inhibition arising from the competitions among different viruses which are more simultaneously present in the airways of the younger children. More scientific evidence is needed to further prove this, but

there is a logic that when many viruses occupy (or cohabit) a niche, there will be some levels of competition for survival [28,30].

A combination of the above possibilities and more could help us understand better why adults are more susceptible to severe COVID-19.

1.5 Future projections: possible ways to tackle COVID-19

There are research works in the area of molecular biology, computational chemistry, and natural product pharmacology for the development of drug targets against SARS-CoV-2. One of the areas of interest and target sites for drug development against SARS-CoV-2 would be the spikes (S1 and S2) of the virion's structural proteins. The S1 which is associated with binding or attachment to the host cell and S2 which is responsible for penetration or fusion of the viral/cellular membrane would serve as interesting receptor sites for possible drug targets [28]. Interestingly, research revealed that angiotensin-converting enzymes, ACE2, which was proven to be the functional receptor for SARS-CoV, also bind the spikes of SARS-CoV-2 [31,32]. More importantly, molecular modeling showed that the SARS-CoV-2 receptor-binding domain (RBD) of the spike glycoprotein (S1/S2) has more affinity for ACE2 than the RBD of SARS-CoV [32]. Since it has been established that ACE2 can be found in fish, birds, amphibians, reptiles, and mammals, it strongly suggests that the above could be considered the natural hosts of SARS-CoV-2 [32,33].

Furthermore, ACE2 is greatly expressed in the kidneys, lungs, heart, intestines, and testis. Therefore, faecal-oral, respiratory droplets, among other routes could be possible routes of transmission of SARS-CoV-2 [32]. The possibility of faecal-oral route of transmission resonates with the recent detection of SARS-CoV-2 in untreated wastewater in Australia [34]. The development of some antibodies and inhibitors that can prevent any potential or actual interactions between the ACE2 of the host body (human body) and the RBD of the SARS-CoV-2 could hold some promising future in an attempt to discover and develop effective therapies for COVID-19 [31–34].

1.6 Conclusion

Coronaviruses cause a wide spectrum of diseases in humans, mammals, and birds. They are associated with high mortality rates in neonates of pigs, chickens, and other animals and have recently become a global threat to the human population. A lot of apocryphal conspiracy theories concerning SARS-CoV-2 and COVID-19 have beguiled people around the world. Some of these specious theories have continued to dwindle as science-based findings and postulations have recently emerged, thereby replacing some of the spurious theories. COVID-19 is both a fact and a reality. The existence of conspiracy theories does not affect the authenticity of COVID-19. The WHO, individual governments, and scientists around the world have intensified their efforts,

with the optimism to provide solutions to the COVID-19 scourge. Nevertheless, there is still a need to enforce some preventive measures, especially at the individual levels. COVID-19 eradication requires global, local, and personal efforts to prevent its spread. Wearing personal protective equipment, such as face masks and hand gloves (for the medical professionals handling the infected patients), regular washing of hands, and social distancing can effectively reduce the rate of COVID-19 transmission.

List of abbreviations

HKU1 Human coronavirus
IBV Infectious bronchitis virus
MERS Middle East respiratory syndrome
MERS-CoV Middle East respiratory syndrome coronavirus
OC43 Human coronavirus (HCoV)
RNA Ribonucleic acid
SARS Severe acute respiratory syndrome
SARS-CoV-2 Severe acute respiratory syndrome coronavirus 2

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