Chapter

Knowing Our Rival–Coronaviridae: The Virus Family

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Abstract

This chapter will describe the biological nature of viruses belonging to the Coronaviridae family. Coronavirus disease or COVID-19 which, with its ever-expanding attack around the globe has become the topic of discussion of the current era. The disease is caused by a SARS-CoV-2 virus which belongs to the Coronaviridae family. This family of the virus has a history of pandemic significance through its attacks of SARS and MERS since the year 2000. They are known to have affinity towards respiratory tract and any disease that erupts out of their group have caused mild and severe respiratory infections globally. Thus, understanding the virus by learning the characteristics of its familial strain will help us to combat their attack even after mutation in the future. This chapter also discusses the pathogenesis of each virus organism in this family, as well as their clinical characteristics and diagnostics, in order to understand their disease-causing pattern and the efficacy of vaccination in mitigating the worst outcomes of the disease.

Keywords: The Virus Family, Coronaviridae, SARS-CoV, Pandemics, Vaccination

1. Introduction

Coronaviruses have historically been the most common type of virus that has caused global pandemics. This virus family began its first outbreak as a mild endemic common cold in 1892 but quickly evolved into a viral pandemic that affected millions of people. The four major strains of human coronaviruses that have spread across the world, evolving from a common cold to a severe respiratory tract disease, are NL63, 229E, OC43, and HKU1 [1]. The majority of them are spread by zoonotic transmission from bats, cats, and camels through droplets or direct contact. However, SARS-CoV, MERS-CoV, and SARS-CoV-2 (a different strain of SARS-CoV) were the key causes of the three pandemics that occurred in the last two decades, and their similarities and variations in nature must be recognized in order to figure out how they attack and how to combat them effectively in the future.

2. Coronaviridae–the virus

The Family of Coronaviridae has two subfamilies named ***Coronavirinae*** and ***Torovirinae***, where the Torovirus family infects vertebrates and has been isolated with gastroenteritis while Coronavirinae affects mammals with respiratory and enteric infections. Torovirinae has unique doughnut-shaped nucleocapsids which distinguish them from Coronavirinae. The current classification of coronaviruses

recognizes 39 species in 27 subgenera, five genera, and two subfamilies that belong to the family Coronaviridae, suborder Cornidovirineae, order Nidovirales, and realm Riboviria [2].

The Coronavirinae family of viruses is widespread among mammals and is known to cause respiratory or enteric infections. This subfamily has four genus-group of viruses namely –

- Genus *Alphacoronavirus*
- Genus *Betacoronavirus*
- Genus *Gammacoronavirus*
- Genus *Deltacoronavirus*

Among the four genera, various disease affections by 60 virus species were found to belong to Genus *Betacoronavirus.* They were mostly isolated from bats but were also found to be from camels and sea species.

Members of the Coronavirinae family are mostly large, enveloped, single-stranded RNA viruses with genomes ranging from 25 to 32 kb and a virion of 118–136 nm in diameter. They are roughly spherical with large spike glycoproteins that extend 16–21 nm from the virus envelope. Almost two – thirds of the genome encodes a non-structural protein (nsp) required for transcription and genome replication and among the non-structural proteins, nsp – 12 forms a multiprotein complex with other CoV nsps which are synthesized as long precursor polypeptides. Ribosomes approaching the frame-shift site slip into the minus-1 reading frame almost 20–25% of the time, and a longer polyprotein called REP1b gets synthesized [3]. The RdRP (nsp12), a protein with helicase and phosphatase activities (nsp13), a protein with exonuclease and methyltransferase activities (nsp14), an endoribonuclease (nsp15), and a second methyltransferase (nsp16) are among the five additional proteins coded for by REP1b (**Figure 1**).

There are hundreds of coronaviruses of which most of them circulate among animals like pigs, camels, cats, and bats. Some of them have transmitted to humans as a result of spillover event, causing dreadful diseases.

The positive-strand RNA genome contains 7–10 open reading frames (ORF) with additional 7–10 frames lying downstream of the replicase-associated genes. The largest of these encodes is the spike protein (S) and the order of the structural proteins of the coronavirus genome is well conserved. The additional small ORFs thus lie in between or overlap the structural protein genes and are called accessory proteins which are encoded by the shortest mRNA. Previous studies on virus mutations have stated that these accessory proteins are not essential for coronavirus replication in cell culture. However, mutating the accessory protein has had a profound effect on the ability of the virus to replicate in their hosts and influence the viral pathogenesis [4].

2.1 Structural proteins of coronavirus

Viruses belonging to the family of Coronavirinae encode four structural proteins namely –

- Three membrane-associated proteins (S, M, and E)
- A single nucleocapsid (N) protein.

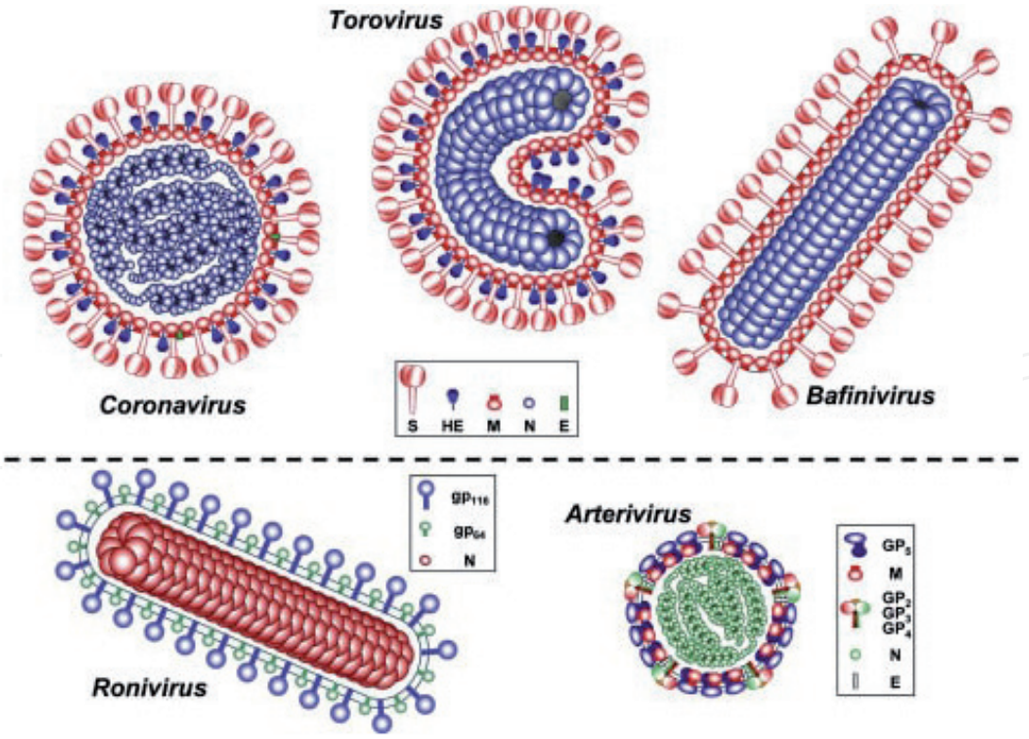

Figure 1.
Coronaviridae family. (reprinted from: Coronaviridae (Chapter-24) by MacLachlan NJ, Dubovi EJ, editors; science direct [4]).

However, some virus species belonging to the genus beta coronavirus have an additional membrane protein with Hemagglutinating and Esterase activities, called HE. Thus the order of the structural genes on the CoV genome is (HE) S, M, E, N [4].

S – CoVs have a distinctive appearance due to the **spike protein**, which forms a conspicuous projection from the virus envelope. S is glycosylated and becomes the attachment and fusion protein. Among the CoVs, there are some variations in the way S is processed (cleaved into S1 and S2 fragments) where it is often ER-associated and is altered by N-linked glycosylation.

S is partially or completely cleaved by host furin-like proteases in the ER (before an assembly of new virions) in many beta and gamma coronaviruses. The extent of proteolysis correlates with the number of highly basic residues at the S1/S2 cleavage site. The S1 (N-terminal) and S2 (C-terminal) products remain noncovalently associated.

SARS-CoV, on the other hand, does not have S cleaved during assembly or release. Instead, during entry/penetration, it is cleaved in an acidified endosome. A cleavage at the S1/S2 boundary and a second cleavage within S2 (called the S2′ cleavage site) tend to be two crucial cleavage events that function in concert to mediate fusion [5].

Also within several isolates of a single type of coronavirus, comparison of S1 sequences show that they diverge widely and are not strongly conserved, leaving us with a fair assumption that the sequence divergence is a result of host immune response. However, unlike S1, the S2 product is highly conserved across the sub-family Coronavirinae subfamily.

M – The **membrane protein** is the most abundant protein in the virion containing three hydrophobic domains and thus tightly associated with the virus envelope. It has a short ectodomain (extracellular domain) that is modified by glycosylation and plays a major role in promoting membrane curvature. Expression of M in Human Corona Virus (HCoV) – SARS (in the absence of other viral proteins)

results in self-assembly and release of membrane-enveloped vesicles. M also interacts with the N and E proteins and virus-like particles are released when M is co-expressed with either N or E [6].

E – The **envelope protein** is present in the virion in very small quantities (about 20 molecules per virion), however larger amounts of E are present in infected cells. During particle formation, different CoVs have varying requirements for E, ranging from mandatory to optional. In fact, virus titres close to 1 × 106 pfu per mL have been reported for HCoV-SARS lacking the E protein. Studies show that E is a viroporin as it assembles in membranes to form ion channels and they influence the electrochemical balance in subcellular compartments [7].

N – The only protein found in the ribonucleoprotein particle is **nucleocapsid protein**. N forms homodimers and homo-oligomers and binds genomic RNA, packaging it into a long flexible nucleocapsid. In the infected cell, N localizes to the cytoplasm, and for some CoVs, N is also found in the nucleolus. N has a role in the assembly and binding as it interacts with other CoV structural proteins. It also co-localizes with replicas–transcriptase components and is required for RNA synthesis [8]. Other roles for N include modulating cell cycle (promoting cell-cycle arrest) and inhibiting host cell translation (**Figure 2**).

2.2 Viral replication

The first event in the replication cycle is the translation of the viral genome by the ribosomes in the host cell. REP1a and REP1b are translated from genomic RNA and some of the other REP1a products have transmembrane domains that serve to anchor the replication-transcription complex to cell membranes and become a pre-requisite for the synthesis of additional viral RNAs. This interaction causes the remodeling of host cell membranes to form structures for viral RNA synthesis.

The next event after translation comes the synthesis of RNA by RNA-dependent RNA polymerase (RdRP). A primer, specifically a short RNA oligonucleotide, is required by the CoV RdRP. It just so happens that the CoVs encode two separate RdRP-active proteins. The product of the nsp8 gene is thought to be a primase that can synthesize short oligonucleotides while nsp12 is the elongating polymerase. Cap synthesis is carried out by other viral nsps in the replication–transcription complex.

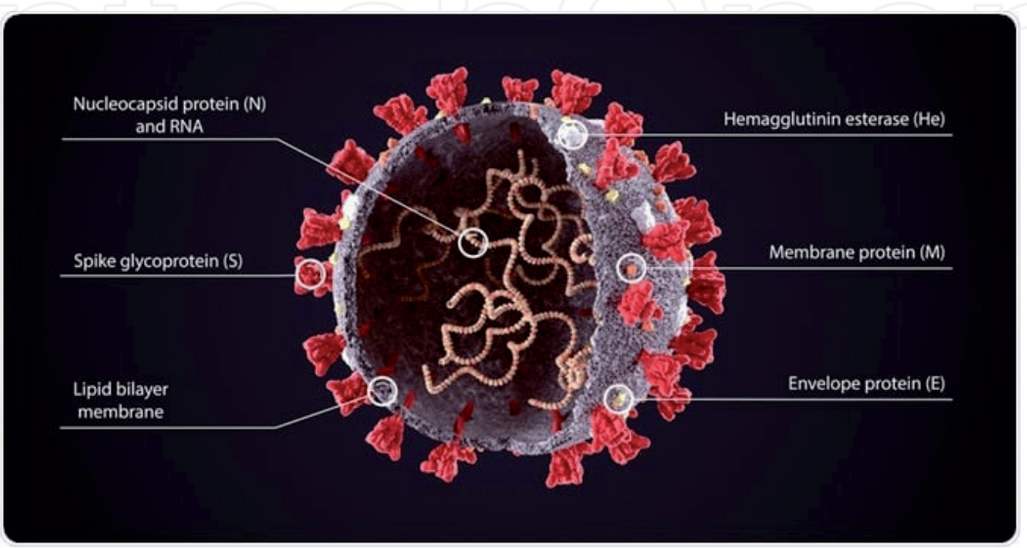

Figure 2.
Structural proteins. (reprinted from: The week: X-rays size up coronavirus protein structure at room temperature [9]).

The other two ribonucleases that are encoded are nsp14 and nsp 15, where nsp 14 is a 3′–5′ exonuclease while nsp 15 is a Nidovirales endonuclease that cleaves both single- and double-stranded RNA, cutting downstream of uridylate residues. Infected cells contain a set of subgenomic (sg) mRNAs in addition to genome-length RNA. The structural and accessory proteins are expressed using the sg mRNAs. They're all capped and polyadenylated, and all have the same 3′ end, creating a "nested set" of mRNAs. A closer examination of the sg mRNAs shows that they all have the same 70–100 nucleotides (nt) leader sequence at the 5′ end. These sequences are identical and though found on all sg mRNAs, they are found only once in the genome.

The transcription regulating sequence is formed when these leader sequences fuse with downstream sequences at short 8–9 nt motifs (TRS). A TRS is located upstream of the structural protein-coding ORFs (these are called TRS body or TRS-B). In the 5′ UTR, a TRS has been found just downstream of the leader chain. These results shed light on the unique strategy used for CoV mRNA synthesis [4].

The high degree of CoV genome recombination is most likely due to discontinuous transcription, and this form of RNA virus genome recombination is known as a copy-choice mechanism. The presence of cRNAs (negative-sense RNAs with 5′ oligo (U)) in infected cells is 0.1–0.01 times lower than that of "positive-sense" genomes and mRNAs, according to a study. This shows that the recombinants are more likely to occur during the synthesis of negative strands.

2.3 Release

Virion assembly takes place on membranes, where the N protein binds genomic RNA, which then interacts with M protein and buds into ER/Golgi membranes. M protein intends to induce the membrane curvature that drives budding by packing tightly into membranes. S and E are also Membrane proteins and are acquired during the budding phase. E protein has the ion channel activity of a viroporin, which changes cell secretory pathways to facilitate virus release. One of E's functions may be to raise the pH of the transport vesicles. The virus particles that are found in membrane-bound vesicles are released from cells by exocytosis [4].

3. Pandemics and coronaviridae

In concern to Infectious Diseases and Global Healthcare, Pandemic is a worst-case scenario spreading beyond country borders. Communicable diseases have escalated to a pandemic situation since the time of origin of the human race, where the first disease that spread across borders affecting millions of people was the Plague. Our world witnessed the spread of the Bubonic Plague, which started in Egypt and spread all over the Middle East, Roman, and Mediterranean regions.

This was then followed by other diseases like Leprosy, Small Pox, Cholera, Measles, AIDS, and Influenza draining out the health care for decades and centuries. The new addition to this series of diseases that are causing nightmare to global healthcare is SARS, MERS, and COVID-19, all caused by the family of coronavirus.

This large family of viruses is known to cause mild to moderate upper respiratory tract illnesses from the common cold to respiratory distress and failure. Among the group, three coronaviruses have emerged from animal reservoirs over the past two decades and spilled over to humans, causing three serious pandemics – SARS, MERS, and COVID-19.

Severe Acute Respiratory Syndrome (SARS) caused by SARS coronavirus emerged in 2002 and spread over all major continents affecting thousands of

people which later came down and disappeared in 2004. This was followed by Middle East Respiratory Syndrome (MERS) which emerged in 2012 was caused by MERS Coronavirus, which originated from an animal reservoir in camels in Saudi Arabia. This caused severe sporadic and localized outbreaks across 27 countries, namely Algeria, Austria, Bahrain, China, Egypt, France, Greece, Germany, Islamic Republic of Iran, Italy, Jordan, Kuwait, Lebanon, Malaysia, the Netherlands, Oman, Philippines, Qatar, Republic of Korea, Kingdom of Saudi Arabia, Thailand, Tunisia, Turkey, United Arab Emirates (UAE), United Kingdom (UK), United States of America (USA), and Yemen. The disease affected millions of people across the world and continue to report its prevalence in some parts even today.

The third coronavirus that emerged out of the family is SARS-CoV-2, a novel virus that is quite similar to the SARS coronavirus. This emerged in the China Sea market in 2019 as an upper respiratory tract infection, which later spread rapidly across more than 200 countries and was soon declared as a global pandemic. The disease continues to affect millions of people, causing thousands of deaths even today.

3.1 SARS

In early 2003, a new pneumonic disease emerged as a life-threatening pandemic from the family of coronaviruses, SARS, caused by SARS – CoV virus. The disease originated in South China as an endemic upper respiratory tract infection and soon spread over various countries affecting millions of people in the United States of America, Europe, and other countries with approximately 10% mortality. The pathogenesis of the SARS CoV virus is quite complex where the genomic characterization is less similar to other known coronaviruses than the rest [10].

SARS-CoV involves a large viral RNA genome encompassing 29,727 nucleotides predicted to contain 14 ORF. The two large 5′-terminal ORF - 1a and 1b, constitute the replicase gene encoding the proteins required for viral RNA transcription and replication [9]. The remaining twelve ORFs encode the four key structural proteins, the spike (S) protein, the nucleocapsid (N) protein, the membrane (M) protein and the small envelope (E) protein, and other eight accessory proteins that are not likely to be essential in tissue culture but may provide a selective advantage in the infected host [11].

Polyprotein pp1a and pp1ab are cleaved extensively by a papain-like cysteine protease (PL2pro) and another chymotrypsin-like protease ($3CL^{pro}$) to yield a multi-subunits protein complex called "viral replicase-transcriptase". 3CLpro functions as a pivotal protease in coronavirus polyproteins processing and controls the activities of coronavirus replication complexes [12].

Coronavirus Spike (S) protein is a type I membrane glycoprotein that has an N-terminal ectodomain, a C-terminal hydrophobic anchor and an unusual cysteine-rich domain bridging the putative junction of the anchor and the cytoplasmic tail. SARS-CoV S protein is 1255 amino acids long glycoprotein [13]. It is predicted to possess a 13 amino acid signal peptide at the N-terminus, a single ectodomain (1182 amino acids) and a transmembrane region followed by a short cytoplasmic tail (28 residues) at the C-terminus. The protein is translated as a large polypeptide, which is subsequently cleaved by virus-encoded or host-encoded proteases to produce two functional subunits, S1 and S2. S1 is known to be the peripheral fragment and S2 is the membrane-spanning fragment. Both the S1 and S2 subunits appear to cause cell fusion when expressed individually suggesting their biological activity. The N, M and E proteins also play a vital role in SARS-CoV replication and infection mechanism [14].

The virus was isolated from a variety of species, including civet cats and raccoon dogs, but none was considered to be the true source. Certain bat species were later identified as possible natural reservoirs. Direct touch, droplets, and airborne routes are all used to spread SARS to and from humans. Additional routes are suggested by viral isolation from feces and urine samples [9]. Thus, SARS began to spread through droplet transmission or contact with fomite from person to person, affecting more than 70% of patients with shortness of breath or fever and 30% of patients with severe illness that required mechanical ventilation for survival.

3.2 MERS

The first case of MERS occurred in 2012 in Jordon, UAE as a mild upper respiratory tract illness caused by MERS CoV. The virus sequence was found to be in bats and dromedary camels which soon transmitted to humans and caused one of the most dreadful pandemics of the century. Thousands of laboratory-confirmed cases and hundreds of deaths due to the disease are reported even today in the Middle East [11] and the zoonotic transmission of the virus from animals to humans was caused by a common entry receptor named dipeptidyl peptidase 4 (DPP4).

The MERS-CoV genome is 30119 nt in length and contains 10 predicted ORFs. The single-stranded, positive-sense polyadenylated RNA genome has 5′ and 3′ UTR of 278 and 300 nt in length, respectively [12]. The 5′ end of the genome is translated to yield a large polyprotein, which gets co-translationally cleaved in cis by two viral proteases into 16 functional non-structural proteins, which then work together to shape the complex machinery for viral RNA synthesis and recombination. The region downstream of ORF1b is distinguished by the presence of a diverse set of structural proteins, including the spike and envelope proteins.

The case fatality rate of MERS seemed to be higher than SARS, which is reported to be due to the high virulence of the virus and its increased attacks on the lower respiratory tract that resulted in respiratory distress and failure.

3.3 COVID-19

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the virus behind the current global pandemic COVID-19 has unique variants that result in a change in transmissibility, clinical presentation, and severity causing greater impact in diagnostics, therapeutics, and vaccine measures. The disease that started as a case of flu in the city of Wuhan, China soon caught up with the global population affecting millions of people and killing thousands every day.

The first affection of COVID-19 that emerged in December 2019, was caused by a strain of beta-coronavirus. The virus showed a high nucleotide sequence homology with two bat-like - severe acute respiratory syndrome:

- bat-SL-CoVZC45
- bat-SL-CoVZXC21 (88% homology)

This strain, however, has 79.5% homology with SARS-CoV, and with MERS-CoV, it has 50% homology. SARS-CoV-2 contains a single-stranded positive RNA of 30 kilobases that encodes 10 genes. The virus enters cells by binding the angiotensin-converting enzyme 2 (ACE2), through its receptor-binding domain in the spike protein [13].

The initial strain, soon on community transmission, began to endanger the novel mutation and gave rise to a new variant, D614G substitution in the gene

encoding the spike protein. This variant soon replaced the initial strain and became the dominant form of the virus circulating globally. Almost all strains of D614G mutation have a mutation in the protein responsible for replication (ORF1ab P4715L; RdRP P323L). Due to mutations in the spike protein's receptor binding domain, these variants are unlikely to reduce ACE2 binding affinity, since this would reduce the virus's fitness. V483A and G476S are mostly found in US samples, while V367F is found in samples from China, the Hong Kong Special Administrative Region, France, and the Netherlands [14].

In the evolution of SARS-CoV-2, phylogenetic research suggests population structuring. The results provide an independent test of the major clades we discovered, as well as the variants' regional expansions. Although the earliest samples from the United States seem to be from China and belong to the basal or L84S clades, clades such as D614G/Q57H, appear to be from Europe. D614G was discovered in late January in China and quickly rose to the top of the clade hierarchy. The mutation rate of $1.12*10^{-3}$ mutations per site-year is comparable to the SARS-CoV-1 mutation rate of $0.80*10^{-3}$ to $2.38*10^{-3}$ mutations per site-year [15].

From the present shreds of evidence, we can conclude that the SARS-CoV genome has evolving nature that causes serious implications to human lives. Due to this nature, the number of people with confirmed COVID-19 has been on a continuous increase for the past few months with no sign of decline and the site of affection has also been changing with every new strand. Thus, the major challenge for drug developers against COVID-19 will be to understand the biological reservoirs carrying coronaviruses and the modes of contact with the human population through trade, travel, or recreation to anticipate future risks for novel infections.

3.4 Clinical picture

Knowledge of viral dynamics and host response is essential to understand the clinical picture of any viral disease and its transition after mutations. With regard to COVID-19, this analysis holds more importance due to its serious pandemic attack in the current era.

A cohort study on 23 patients admitted to the hospital with COVID-19 reported that the viral load peaked during the first week of illness and gradually declined in the second week. This may be due to the high transmissibility of SARS-CoV-2 and the increase in IgG and IgM antibody levels [16]. The high viral load in elderly patients was also found to be associated not only with low immunity but also with high expression of the ACE2 receptor (the cell-entry receptor for SARS-CoV-2). From this study, we can conclude that the analysis of serial viral load and antibody profile is essential to understand the viral and host interactions and their transition over the virus mutations [17].

The clinical picture of the disease thus began to vary from its initial attack to the current day from simple respiratory affection to multi-system illness. However, the most common signs and symptoms even today includes –

- Fever/chills
- Cough
- Shortness of breath/breathing difficulty
- Fatigue
- Muscle/body aches

- Headache
- Loss of taste/smell
- Sore throat
- Congestion/runny nose
- Nausea
- Vomiting
- Diarrhea [18]

According to WHO, CDC, and ICMR, the signs and symptoms of COVID-19 that may appear 2–14 days after exposure to the virus are classified into different stages namely mild–moderate, severe, and critical [19].

Mild–Moderate Stage:

- Fever
- Dyspnoea
- Gastrointestinal troubles like Nausea, Vomiting
- Nasal congestion
- Sore throat
- Loss of smell
- Mild gasping for breath with Pneumonia

Severe Stage:

- High Fever
- Cough with gasping for breath
- Severe respiratory distress [SpO_2 < 90% on room air]
- Bloody expectoration
- Delirium

Children with clinical signs of Pneumonia and Central Cyanosis.

Critical Stage:

- Acute Respiratory Distress Syndrome
- Pulmonary Oedema
- Fluid overload leading to Cardiac Failure

- Sepsis with weak pulse, cold extremities.
- Reduced urinary output
- Thrombocytopenia, Hyperbilirubinemia
- Septic shock with Hypothermia and Collapse [20]

While most people with COVID-19 develop only mild (40%) or moderate (40%) disease, approximately 15% develop the severe stage that requires oxygen support, and 5% have the critical disease with complications such as respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism, and/or multiorgan failure including acute kidney disease and cardiac failure [21].

However, this clinical picture is found to be similar to the previous pandemic attacks of this century by the same family of viruses. SARS-CoV and MERS also started as upper respiratory tract infections and rapidly progressed towards respiratory failure, septic shock, and multi-organ failure resulting in death [22]. The incubation period for both SARS-CoV and MERS was around 2–10 days with a mean incubation period of 6.4 and 5 days respectively. Also, the meantime from the onset of illness to the hospitalization in both diseases is 4 days [23]. This shows the similarity of affection and rapidity in the progression of illness caused by any type of virus from the Coronaviridae family.

4. The future of coronaviridae

Howard Markel, a medical historian once quoted "The most predictable thing about this coronavirus is its unpredictability" when describing several pandemic outbreaks. Historically, the occurrence of a viral outbreak and its transition from a mild endemic disease to a global pandemic has been a great challenge to public health researchers and global healthcare. Apart from disease, the geography, host response, and treatment procedures have been influential in viral mutation and its pathogenicity. This is notably important to understand the future attacks of viruses from the Coronaviridae family [24].

Some infectious disease researchers, on the other hand, foresee a healthy future in which virus transmission is reduced due to increased vaccination among people. Experts are hopeful that as vaccinations reach more people, the effect of the COVID phase will lessen and help protect them from the worst possible outcomes of the disease. Current vaccination developed has proven to provide complete and effective protection against most variants of coronavirus and thus, as more people develop specific immunity on vaccination, scientists hope any attack of illness caused by this family of the virus will be of no threat more than an endemic common cold.

5. Conclusion

Since the first pandemic, which was caused by human coronavirus OC-43, one of the four coronaviruses, the existence of disease attacks by them has remained a mystery to medical professionals. The viral organism and its variants, on the other hand, have often evolved after each attack, resurfacing as a new variant of the same Coronaviridae family. To predict the emergence of any viral attack from the family Coronaviridae that has caused serious illness in the global population in the future, it is essential to understand the nature of each organism from the family Coronaviridae.

Furthermore, achieving full immunity by vaccination would aid in the fight against the disease without causing any harm to the global population.

Conflict of interest

There are no conflicts of interest.

Ethical considerations

Not Applicable.

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