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Review article

Human Coronaviruses: Genetics, Virulence Factors and Pathophysiology, Diseases' Epidemiology

Gnatoulma Katawa[*1], Banfitebiyi Gambogou [1,2], Christèle T. Nguepou [1], Essoham Ataba [1], Manuel Ritter [3], Eya H. Kamassa [1], Fagdéba D. Bara [1], Simplice D. Karou [1], Yaovi Ameyapoh [1]

[1]Advanced School of Biological and Food Techniques (ESTBA) / Laboratory of Microbiology and Food Quality Control / Research Unit in Immunology and Immunomodulation (UR2IM), University of Lomé, Togo
[2]Togolese Institute for Agronomic Research (ITRA), Togo
[3]Institute for Medical Microbiology, Immunology and Parasitology (IMMIP), University Hospital Bonn (UKB), Bonn, Germany

*Corresponding author: Gnatoulma KATAWA; *mahkatawa@yahoo.fr*

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Abstract

Coronaviruses are pathogens for both animals and humans. The recent Coronavirus Disease (Covid-19), caused by a novel *Coronavirus* (SARS-CoV-2), outbreak that took place in Hubei (Wuhan, China) from December 2019 aroused numerous questions regarding the nature and the origin of the SARS-CoV-2. Literature review of the main publications from scientific data bases was undertaken. These data revealed similarities of symptoms and identity of genome with the SARS-CoV. In this review, the genetics and virulence factors of coronaviruses, the disease pathophysiology and epidemiology were examined.

Keywords: ***Pathophysiology, epidemiology, coronavirus diseases, genome, SARS-CoV***

Introduction

Humanity has been struggling against pathogens. Theses pathogens cause parasitic diseases [1], bacterial infections and viral such us HIV [2], hepatitis B [3,4] and recent Covid-19 causes by SARS-CoV-2 [5]. *Coronaviridae* are single-stranded, positive-sense RNA viruses enveloped non-segmented, designated after their corona or crown-like on electron microscopy [6,7]. The International Committee on Taxonomy of Viruses (ICTV) established in 1975 the family of *Coronavirus*, which was divided into two genera in April 1992: the *coronavirus genus* and the *torovirus genus* [8]. Three genetically and serogically groups of *coronavirus genus* have been described [9]. Group I comprise Human CoV-229E (HCoV-229E), Human CoV-NL63 (HCoV-NL63) and Feline infectious peritonitis virus (FIPV). Group II includes Human CoV-OC43 (HCoV-OC43), Human CoV-HKU1 (HCoV-KHU1), Severe acute respiratory syndrome-CoV(SARS-CoV) and Mouse hepatitis virus (MHV). The group III contains bronchitis Infectious virus (IBV) [9-11]. The viral taxonomy has been regularly reviewed according to the following orders: the order of *Nidovirales*, created in 1996, which currently groups together three families (*Coronaviridae*, *Arteriviridae* and *Roniviridae*). These viruses have in common the organization of the RNA genome and the replication strategy but differ in their morphology, their capsid structure and the size of their genome which ranges from 13 000 nucleotides for *arterivirus* to 31 000 nucleotides for *coronavirus* [12]. Thus, group I and II coronaviruses infect mammals, including humans and group III coronaviruses are a group of avian viruses [13].

The classification of SARS-CoV has been much debated and the various phylogenetic analyzes proposed either to place it in a fourth group, or in a group II "extended". Finally, the latter solution was adopted and currently subdivided group II into 2a and 2b, and includes SARS-CoV as well as all the "SARS-CoV-like" or SL-CoV virus described in the different animal species [14,15]. In the 1960s, Human CoV (HCoV) comprised six strains: 229E, OC43 are most known than B814, OC16, OC37 and OC48. In 2003, the Chinese population was infected with a virus causing severe acute respiratory syndrome (SARS) in Guangdong province.

The virus was confirmed as a member of the Beta coronavirus subgroup and was named SARS-CoV [16]. On the thirteenth June, 2012, the first reported case of Middle East respiratory syndrome coronavirus (MERS-CoV) occurred in Jeddah, Saudi Arabia and caused an endemic in Middle Eastern countries. At the end of 2019, a novel coronavirus was discovered at Wuhan in China [17,18]. This virus was reported to be a member of the group 2b coronaviruses [19].

The ICTV named the virus as SARS-CoV-2 due to it's genetic similarity to SARS and the disease was named Covid-19 because of the year of the outbreak [20]. In total nine HCoV strains are now identified: 229E, OC43, B814, OC16, OC37 and OC48, SARS-CoV, MERS and SARS-CoV-2 [21]. HCoV-229E was isolated in 1966 from human embryonic kidney cells and has been adapted to several types of cells, including MRC5, cells widely used in virology laboratories. HCoV-OC43 was isolated in 1967 on culture of trachea after passages on mice brains to the line HRT18 (human rectal carcinoma). HCoV-NL63 (strain Amsterdam 1) was isolated in 2004 from the LLC-MK2 line and SARS-CoV on Vero E6 cells [22]. Only HCoV-HKU1 to date has never been isolated in cell culture but it has been characterized by molecular biology. It is important to note that apart from the prototype strains, the coronavirus remain very difficult to cultivate and there are few isolates [23]. Finally, it is important to remember that these viruses are class 2 agents except the three SARS-CoV, which require a level 3 containment laboratory for their handling. This literature review from main publications presents the genetics, the virulence factors, the etiology, epidemiology and pathophysiology of coronavirus diseases.

Methodology

Protocol: A systematic review of the published literature was undertaken from PubMed, Elsevier, Google scholar, HINARI, WHO, ECDC, and NCBI databases, in accordance with the preferred reporting elements for systematic reviews. Our initial objective was to carry out a systematic analysis and a meta-analysis to identify the relevant articles reporting on coronaviruses in order to analyze the genetics factors as responsible for virulence factors, epidemiology and pathophysiology of coronavirus diseases. However, the evaluation of the published studies was done using Endnote version X9 (Thomson Reuters) and it showed that the published papers related to the impact of coronaviruses on social and economic life or not answer the research question were excluded. All the literature found were discussed by the editorial team of this paper. Some articles have been included from others. The process of literature review is shown on **Figure 1**.

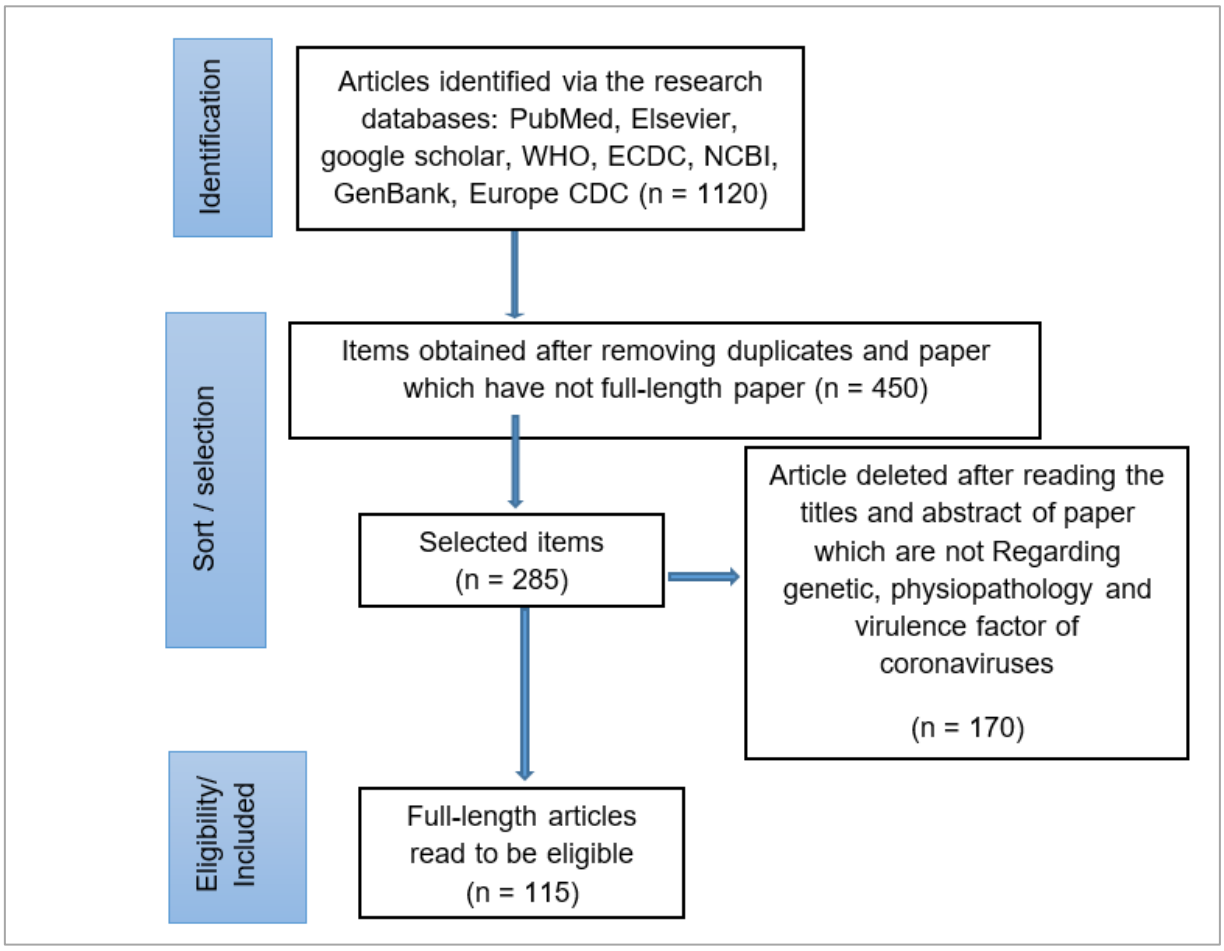


Figure 1: Process of data collection.

Data analysis: The extracted data were used for descriptive statistical analyzes. Further analysis was carried out in several stages. The Meta-analyzes as the gene fragments alignment, the phylogenetic tree construction, the identification of protein or gene similarities were performed with Blast, tBlast and Mega X v10.1.8. The cartographic representing full length genome sequence were done by Excel.

The collected data/information were classified into different groups: genome variability, virulence factor, physiopathology and epidemiology of human coronaviruses.

Genome similarity and conserved regions

The figure 2, 3, 4 and 5 represent the genome of *Coronaviridae*, the phylogenetic tree of *coronaviridae*, and *the* Human coronaviruses. The analysis of 33 full length publication papers and data GenBank analysis of all *coronaviridae* genome sequences and records how that coronaviruses' genome is a linear, non-segmented single stranded, positive-sense RNA, directly infectious RNA molecule. The main characteristic of this virus is the size of its genome, which is the largest known viral RNA (27000 to 30 000 nucleotides). The genomic organization is conserved among all coronavirus species and approximately 20 000 nucleotides (nt) consist of two open reading frames ORF1a and ORF1b over lapping and encoding two protein precursors which are cleaved

into 15 to 16 fragments and form the replication complex (**Figure 2**).

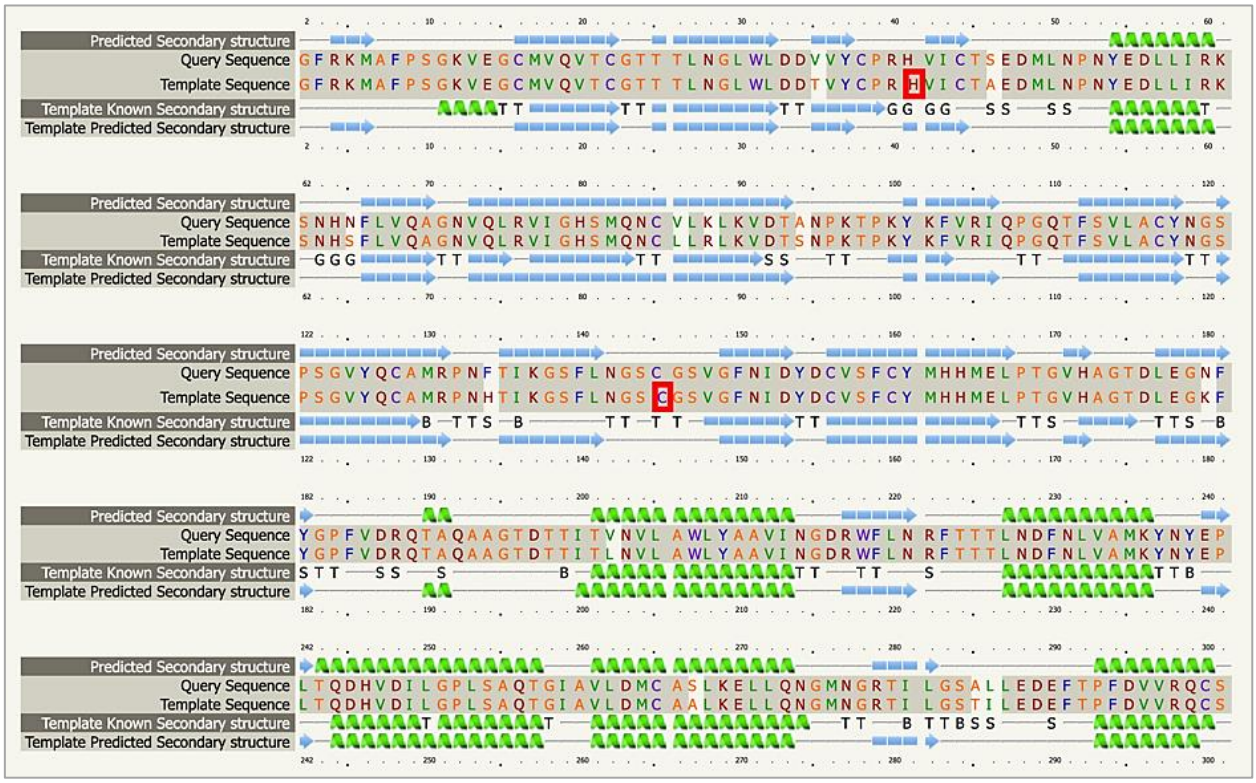


Figure 2: structure of coronaviridae genome (SARS-CoV 2) (Innophore technology).

The other conserved regions consist of four to five genes (HE-S-E-M-N) in a precise and conserved order and which encode the structural proteins. The figure 3 shows the phylogenic repartition among the human coronaviruses (HCoV) and show that the genome of the SARS-CoV-2 is mostly alike the previous human coronavirus (SARS-like bat CoV). Coronaviruses belong to *Coronaviridae* familly and fall into four distinct genera such us *alphacoronavirus* (1a, 1b) (blue), *betacoronavirus* (2a, 2b, 2c, 2d) (pink), *deltacoronavirus* (light green) and *gamma coronavirus* (deep green) [24,25]. This tree is adapted from the published trees of Coronavirinae [26] wich was reconstructed with sequences of the complete RNA- dependent RNA polymerase-coding region of the representative novel coronaviruses (maximum likelihood method using MEGA 7.2 software). *Severe Acute respiratory syndrome coronavirus* (SARS-CoV); SARS- related coronavirus (SARSr-CoV); the *Middle east respiratory syndrome coronavirus* (MERS-CoV); *Porcine entericdiarrhea virus* (PEDV); *Wuhan seafood market pneumonia* (Wuhan-Hu-1). Bat CoV RaTG13 Showed high sequence identity to SARS-CoV-2 [27].

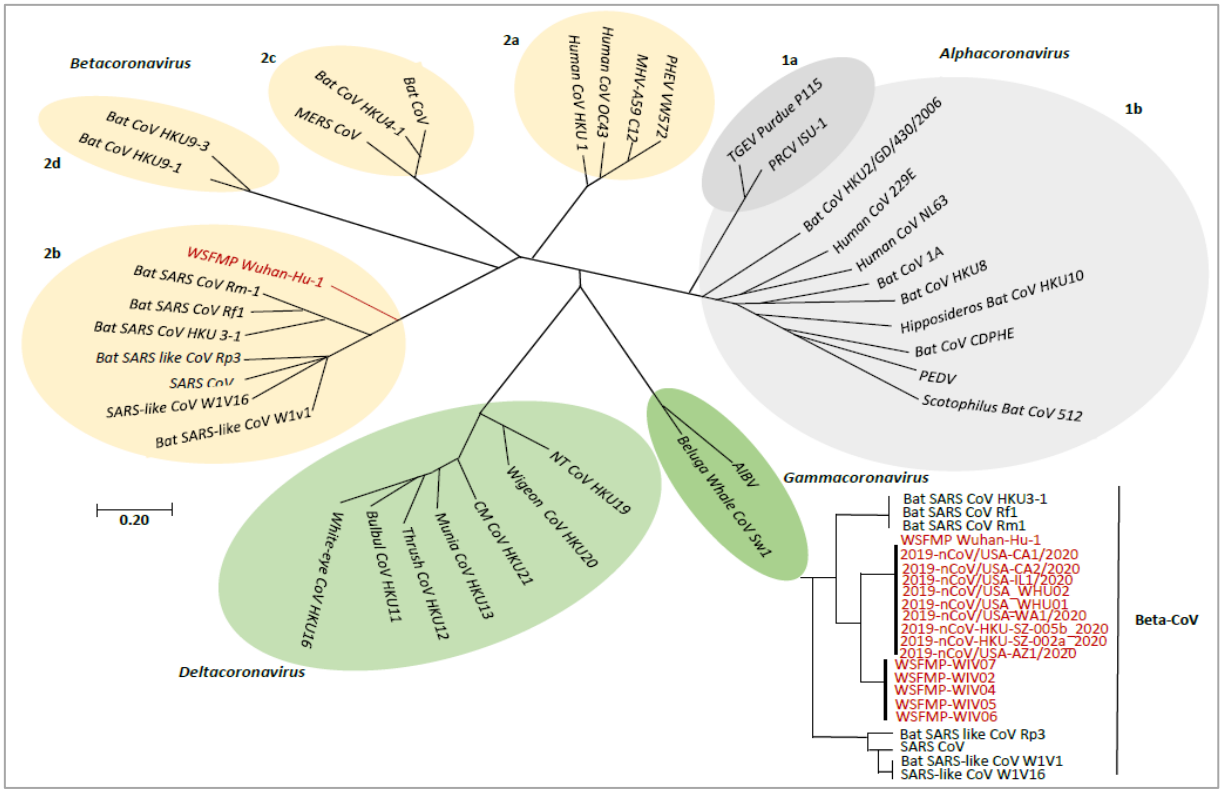


Figure 3: Evolutionary repartition of Coronaviridae (Adapted form [114])

Figure 4 shows the evolutionary relation among the human coronaviruses (HCoV). The novel acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new coronavirus that emerged through recombination of bat SARS-relatedcoronaviruses (SARSr-CoVs) with infected civets and humans and adapted to these hosts and became pandemic [8]. Middle east respiratory syndrome coronavirus (MERS-CoV) likely spilled over from bats to dromedary. HCoV-NL63 and HCoV-229E usually cause mild infections in immunocompetent humans [13]. HKU1 and HCoV-OC43 are alsomost harmless in humans [28]. The coronaviruses infecting humans (HCoVs) belong to alpha and beta coronaviruses genera. The alpha coronaviruses infecting humans are HCoV-229E and HCoV NL63, and the beta coronaviruses infecting humans are HCoV-HKU1, HCoV-OC43 (**Figure 4**). The Middle east respiratory syndrome coronavirus (MERS-CoV), SARS-CoV and SARS-CoV-2 are betacoronaviruses [29].

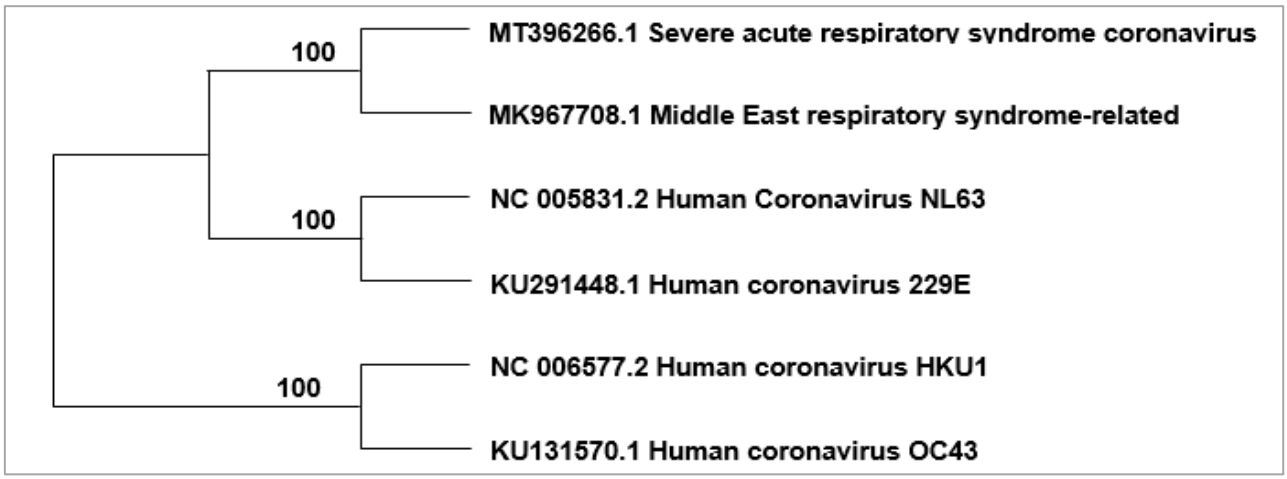
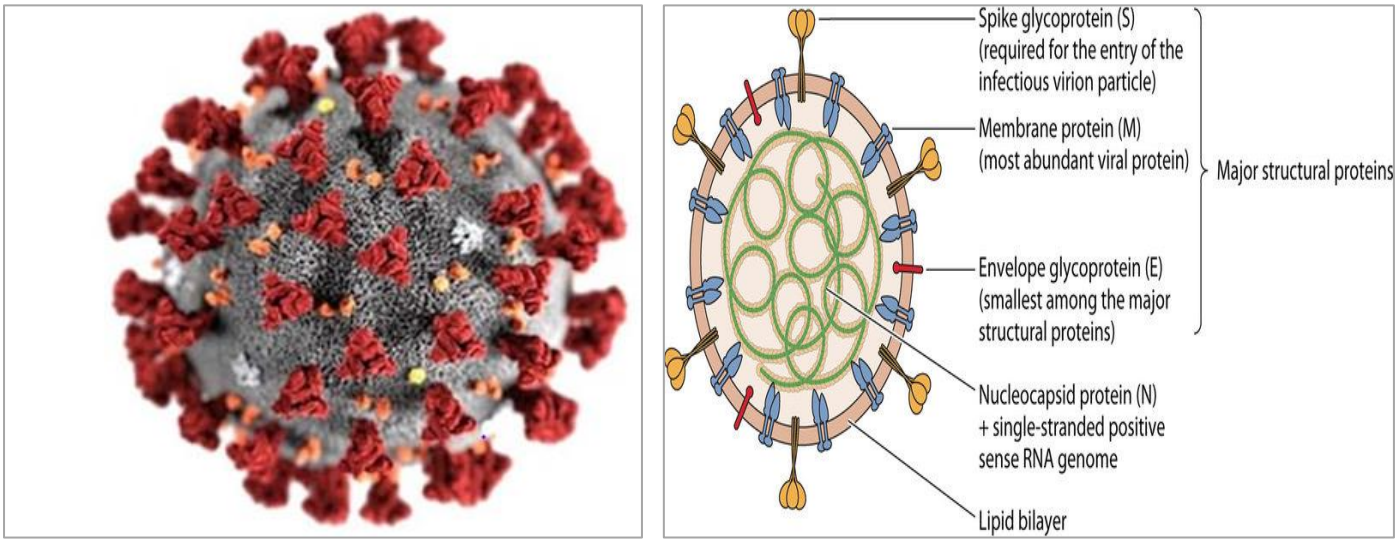


Figure 4: Evolutionary relationships of taxa of Human coronaviruses [103]

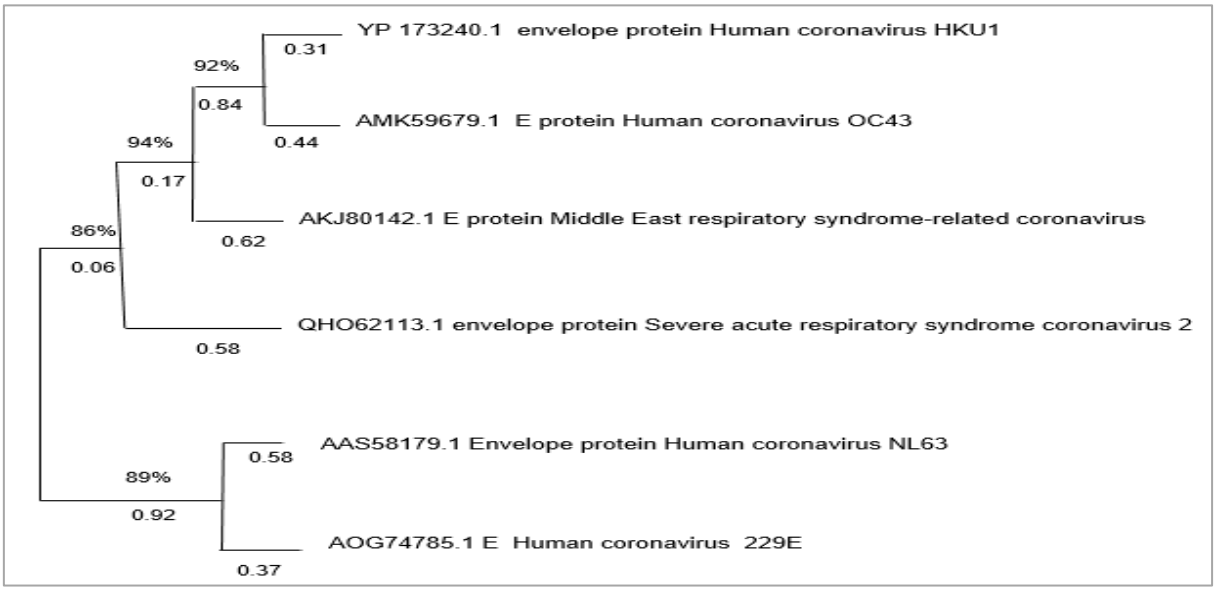
Coronavirus virulence factors

Figures 5 and 6 represent respectively the coronavirus structures, the host spectrum, the virulence factors similarity among HCoV and host factors. 6A show the similarity of Protein E, while 6B, 6C and 6D relate accordingly the similarity of Protein M, Protein S, and Protein N. Coronaviruses are enveloped pleomorphic viruses of 60 to 200 nm in diameter. The appearance in a crown visible by electron microscopy is due to the presence on the viral envelope of spicules in the shape of a club 20 nm high and made up of the surface protein S. The other envelope glycoproteins are the protein M, protein E and for group 2 coronavirus, hemagglutinin esterase (HE). The viral capsid is helical symmetry; it consists of the protein N, which is closely linked to genomic RNA. Protein S is a type I membrane glycoprotein, and plays a key role in the first stages of the viral cycle. It is responsible for the attachment of the virus to the target cell by its S1 subunit and largely determines the tissue tropism of the virus and its host spectrum. It is also responsible for the membrane fusion by its S2 subunit. In addition, it is the main target of the cellular and humoral immune response and induces the formation of neutralizing antibodies [29-34].

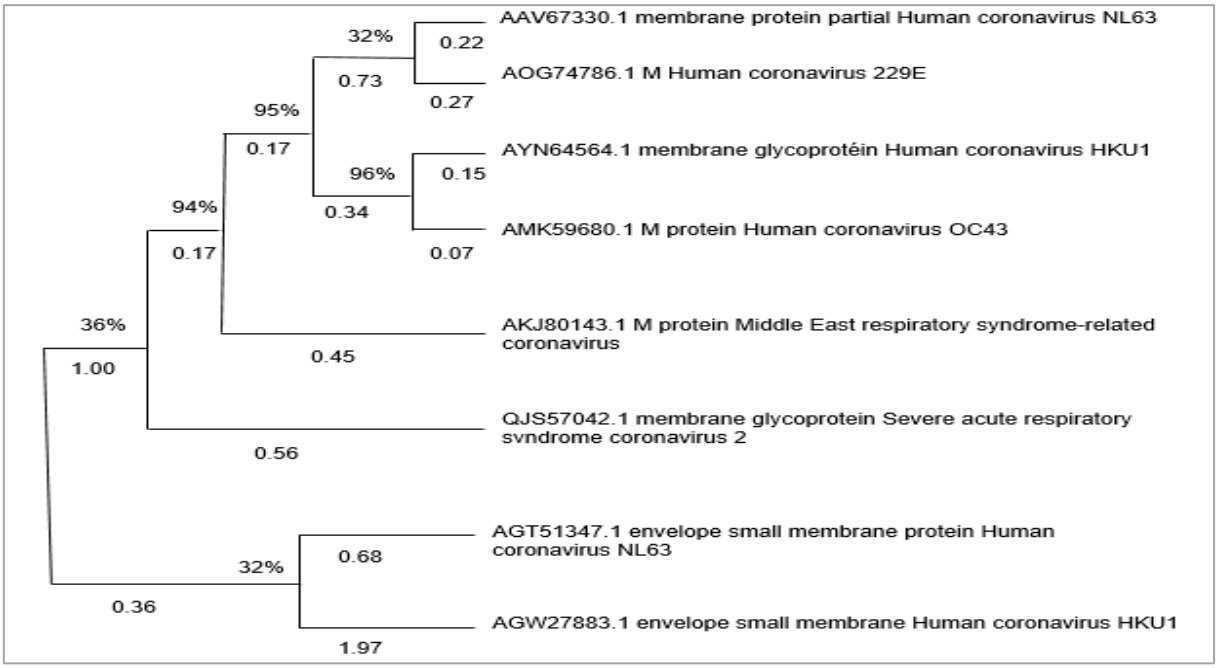


A B

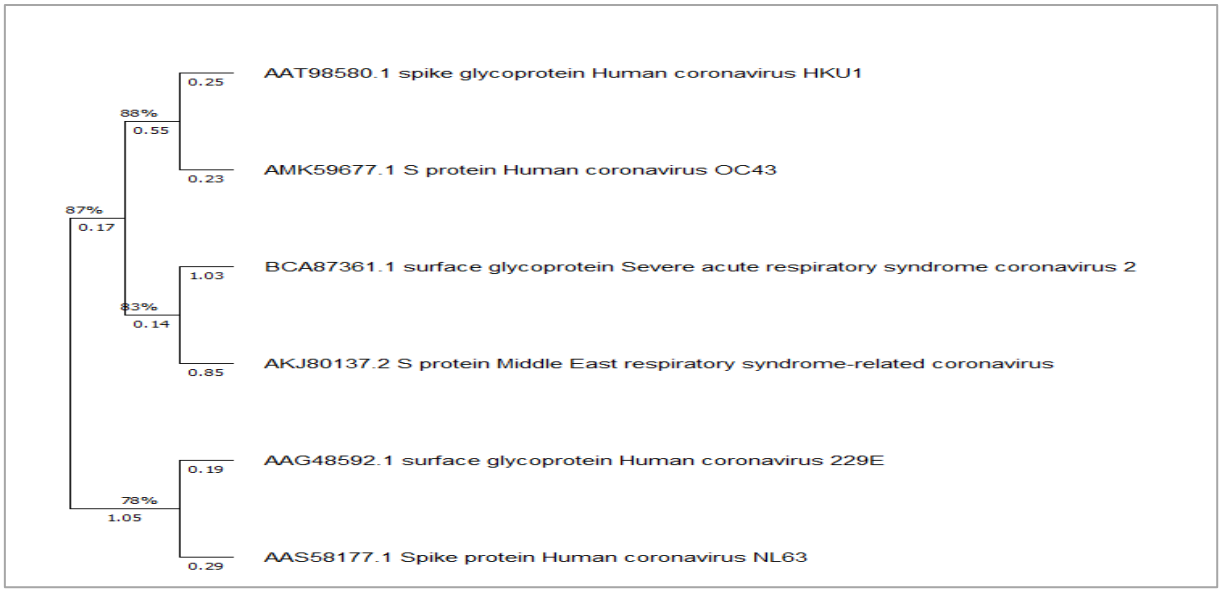
Figure 5: Structure of Coronaviridae (National Institute of Allergy and Infectious Diseases (NIAID), 2020. A: coronaviruses view in electronic microscope; B: structure of coronaviruses.


YP 173240.1 envelope protein Human coronavirus HKU1
0.31
92%
0.84
AMK59679.1 E protein Human coronavirus OC43
0.44
94%
0.17
AKJ80142.1 E protein Middle East respiratory syndrome-related coronavirus
0.62
86%
0.06
QHO62113.1 envelope protein Severe acute respiratory syndrome coronavirus 2
0.58
AAS58179.1 Envelope protein Human coronavirus NL63
0.58
89%
0.92
AOG74785.1 E Human coronavirus 229E
0.37

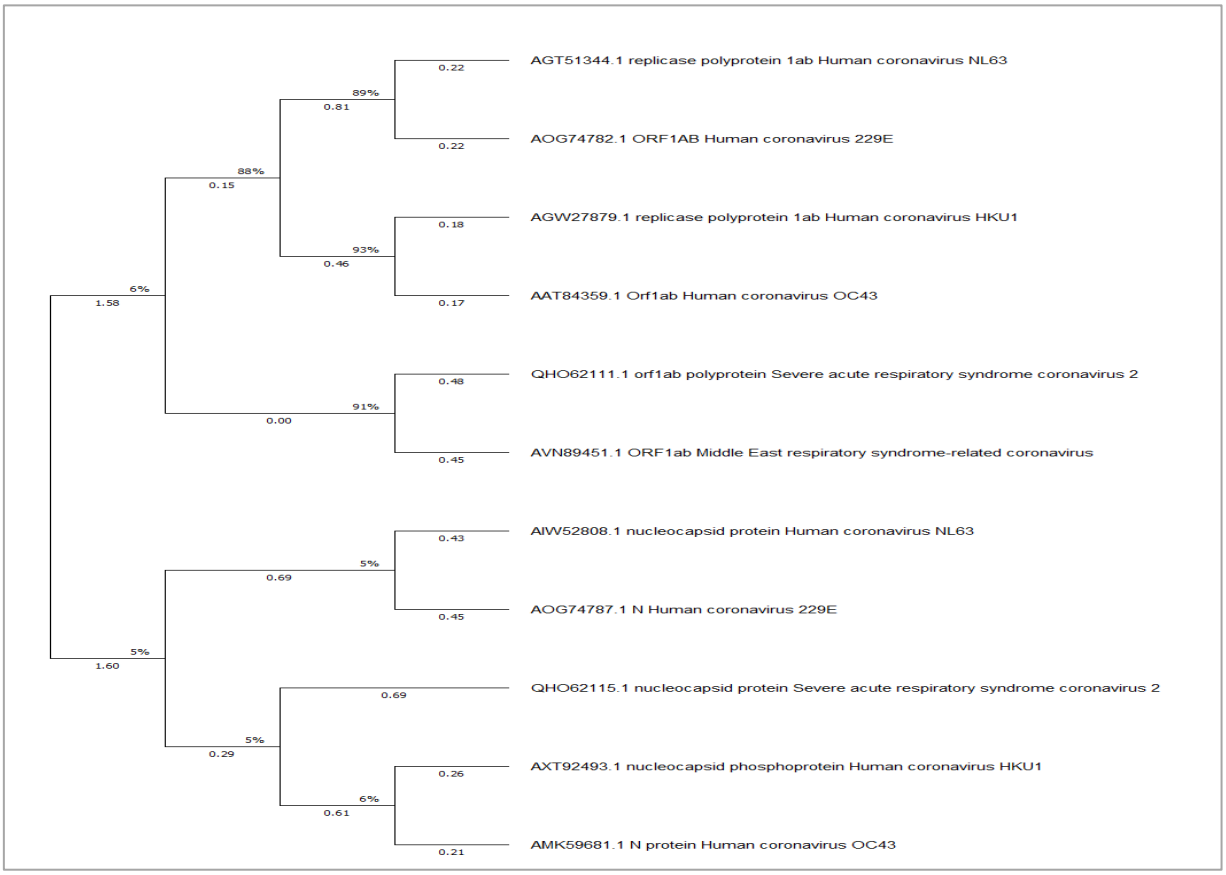
(A)


AAV67330.1 membrane protein partial Human coronavirus NL63
32%
0.22
0.73
AOG74786.1 M Human coronavirus 229E
0.27
95%
0.17
AYN64564.1 membrane glycoprotéin Human coronavirus HKU1
96%
0.15
0.34
94%
AMK59680.1 M protein Human coronavirus OC43
0.17
0.07
36%
AKJ80143.1 M protein Middle East respiratory syndrome-related coronavirus
1.00
0.45
QJS57042.1 membrane glycoprotein Severe acute respiratory syndrome coronavirus 2
0.56
AGT51347.1 envelope small membrane protein Human coronavirus NL63
0.68
32%
0.36
AGW27883.1 envelope small membrane Human coronavirus HKU1
1.97

(B)


0.25
AAT98580.1 spike glycoprotein Human coronavirus HKU1
88%
0.55
0.23
AMK59677.1 S protein Human coronavirus OC43
87%
0.17
1.03
BCA87361.1 surface glycoprotein Severe acute respiratory syndrome coronavirus 2
83%
0.14
0.85
AKJ80137.2 S protein Middle East respiratory syndrome-related coronavirus
0.19
AAG48592.1 surface glycoprotein Human coronavirus 229E
78%
1.05
0.29
AAS58177.1 Spike protein Human coronavirus NL63

(C)



(D)

Figure 6: phylogenetical Analysis of HCoV Envelope (E), Spike (S), Membrane (M) and Nucleocapsid (N) protein. A: Similarity of Protein E, B: Similarity of Protein M, C: Similarity of Protein S, D: Similarity of Protein N.

Host factors

Figure 7 shows the host spectrum of the different coronavirus species. The species represented in blue are group 1 coronaviruses, those in red are group 2 coronaviruses and group 3 coronaviruses in black (avian coronavirus). The arrows indicate the hypothetical crossing of monetary barriers with emerging success. Although human viruses, HCoVs have at some point emerged from an animal reservoir, with the original viruses being chiropterans (HCoV-229E, HCoV-NL63) or rodents (HCoV-OC43, HCoV-HKUl), with the putative intermediate hosts being cattle for HCoV-OC43 and camelids for HCoV-22928 [28]. In addition Malnutrition has been reported as a virulence factor for the SARS-CoV-2 infection. The malnutrition (hyponutrition and hypernutrition) is associated with immune dysfunction. The hyponutrition which is mainly protein deficiency is associated with low immuno-reactivity that lead to T cell function reduction, induction of IL4 and IL10 production, vitamins (A, B, D and E) deficiencies, hence the anaemia and micronutriment deficiencies. These conditions are surely associated with increased SARS-CoV-2 virulence.

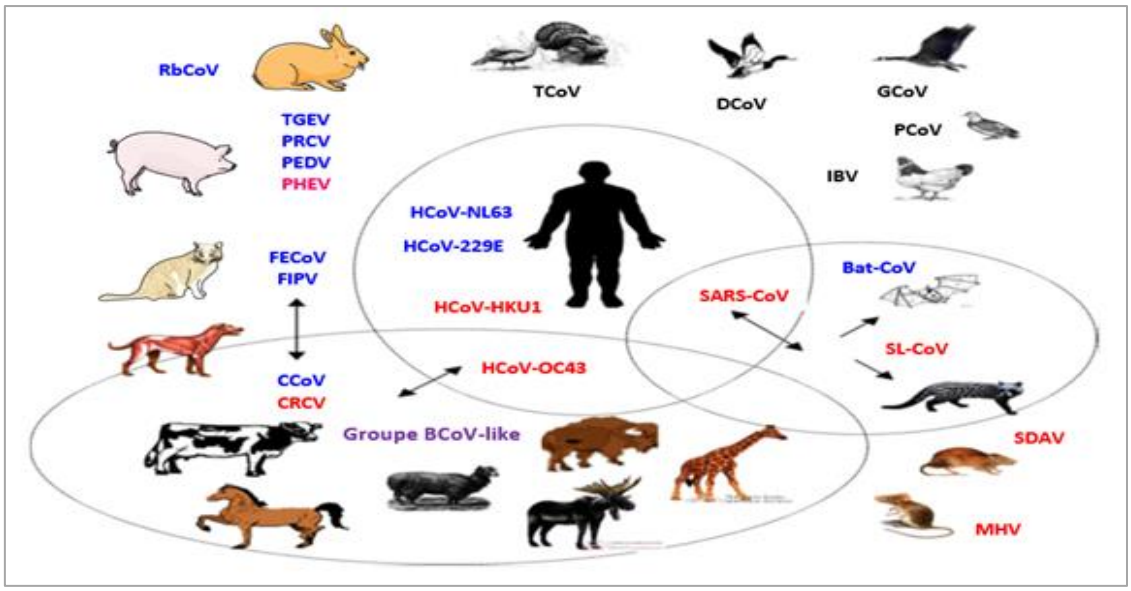


Figure 7: Host spectrum of different coronavirus species. Group 1 coronaviruses are written in blue, group 2 coronavruses in red, and group 3 coronaviruses (avian coronaviruses) in black. The arrows indicate the hypothetical crossing of cash barriers with emergent success.

The hypernutrition which is essentialy do to sedentarism has the reverse effect. The immune dysregulation that exists in malnutrition and obesity can ahance the susceptibility to SARS-CoV-2 infection (**Figure 8**) [35-37]. Malnourished people may have an immune deficiency to adequately fight against the virus. Malnourished individuals may be more susceptible to SARS-CoV-2 infection. Nutritional support is there for vital in severe Covid-19 patients [36]. The most relevant co-factor of SARS-CoV-2 is immune disfuntion. Also older age, comorbid conditions and poli pharmacotherapy are the essential factors that increased the disease susceptibility.

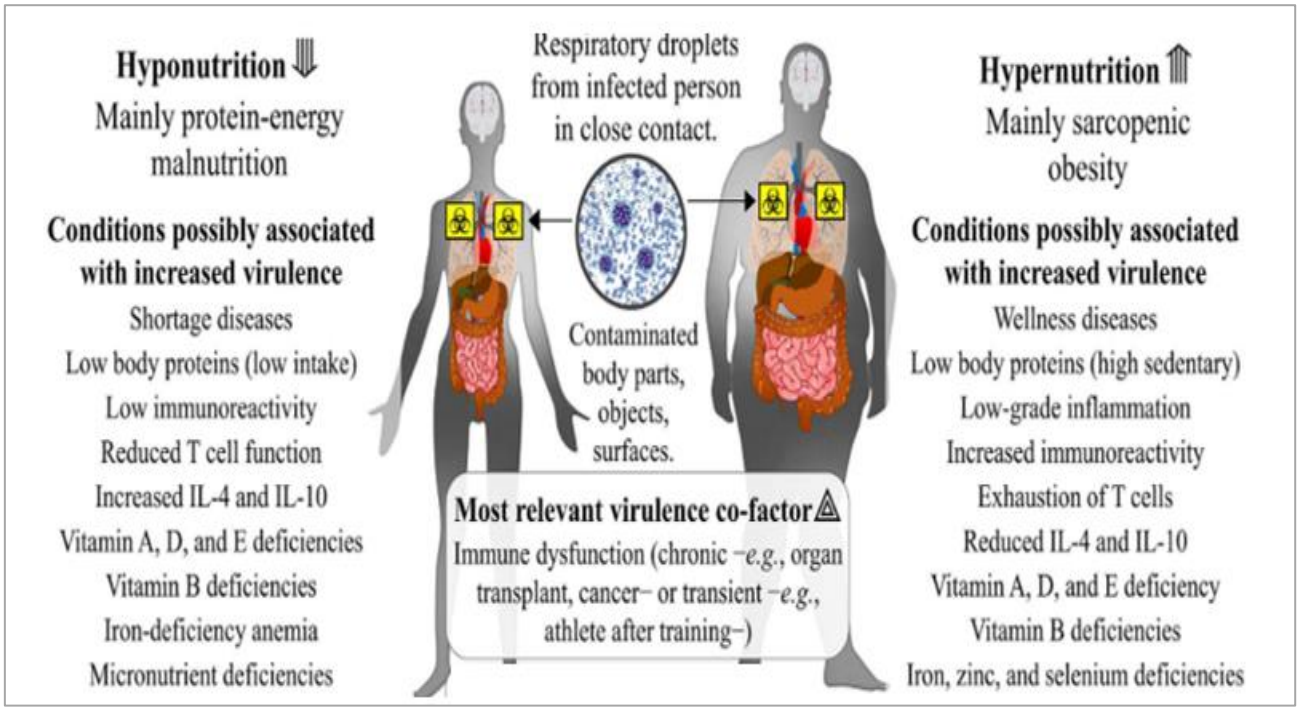


Figure 8: Malnutrition as virulence factor to coronavirus disease 2019 (Adapted from 115).

Pathophysiology

The pathophysiology of HCoV is linked to the function of both the nsp and the structural proteins. Some studies underlined that nsp areable to block the host innate immune response [38]. Coronaviruses starting the synthesis of polyprotein 1a/1ab (pp1a/pp1ab) in the host [16,39], of both pp1a and pp1ab polypeptides that are processed by virally encoded chymotrypsin-like protease (3CLpro) or main protease (Mpro), as well as one or two papain-like proteases for producing 16 non-structural proteins (nsp) [40]. In addition, other ORFs encode structural proteins, such as spike, membrane, envelope, nucleocapsid proteins and accessory protein chains [41-43].

Non-structural protein 1 (Nsp1) from severe acute respiratory syndrome coronavirus suppresses host cell protein synthesis by binding to the 40S ribosomal subunit and endonucleolytically cleaving host mRNA [44]. This slows down translation in the infected cells and prevents, the proper expression of host factors that may be involved in the fight against the virus and its subsequent clearance by the innate immune. While Nsp1 prevents the expression of host proteins, viral protein synthesis continues unimpeded [45].

The function of nsp2 is not fully understood. It is thought to be associate with the host endosome and host cell stability [46]. It is reported to be one of the conserved proteins of coronaviruses play a key role in viral replication in culture. Nsp2 and nsp3 of SARS-CoV are detected not only as mature processed proteins but also as precursors of nsp1 and nsp3, which conferred them a role as precursors in replication. These results suggest that nsp2 may be involved in the regulation of nsp1 and nsp3 functions [47].

It has been reported that nsp3, nsp4, and nsp6 contain trans membrane domains and are likely to be involved in membrane anchoring of the replication complex [48,49]. Np3, also known as papain-like protease (PLPro), is the largest non-structural protein encoded by the coronavirus (CoV) genome, with an average molecular mass of about 200 Kdand the second most promising vaccine candidate besides S protein [50]. It has different domain organization according to each Corona virus genera. The nsp3 releases nsp1 and nsp2 from polyproteins and interacts with not only the other viral nsps but also RNA to form a replication/transcription complex. nsp3 interacts with host protein translation to block host innate immunity, promote cytokine expression and is also responsible for the survival of the virus within the host by interfering with host proteins [51]. nsp3 interact with nsp4 to playa key role in the replication of SARS-CoV inside the infected cells[52]. Nsp6 alone has membrane proliferation properties. As for Nsp5, it is a cysteine protease wich is also called, the main protease (Mpro). Nsp5 plays a major role in the virus replication making MPro a potential and safe target for anti-CoV drug design. Nsp7 and nsp8 form an exadecameric complex. The both act as RNA polymerase primase and forms a replicase complex for replication and transcription of the viral RNA genome [53]. It was found that there is an inter connection between the major nsp of SARS-CoV. Thus, nsp12 bound to nsp7/nsp8complex and play a central role in the viral replication [54]. It is the most conserved protein in coronaviruses and an RNA-dependent RNA polymerase (RdRp) wich is the key enzyme in the viral replication/transcription complex. The nsp7/nsp8 complex increases binding of nsp12 to RNA [55]. Nsp9 is a single-stranded RNA-binding protein wich is also implicated in the virus virulence. It ha been reported that nsp9 also interact with Nsp7/Nsp8 complex and is essential for the viral replication and potential target of drug development against the SARS-CoV-247. Nsp10 is a small, single-domain protein having 99% sequence identity with SARS-CoV Nsp10. Nsp10 acts as a scaffold protein to form the mRNA cap

methylation complex with Nsp14 (exonuclease and N7-methyltransferase) and Nsp16 (2′-O-methyltransferase). It's there for a cofactor of nsp14 and nsp16 which enhance their activities [56]. Nsp 13 is the 1 helicase superfamily with plays an essential role in viral replication and conservation across all CoV species [57]. Nsp15 is a nidoviral RNA uridylate-specific endoribonuclease (NendoU) belonging to Endo U enzymes family. Firstly, nsp15 was thought to be able to bind RNA and involved in viral replication, then it was shown that it's rather responsible for the protein interference with the innate immune response. Other studies suggested that Nsp15 mediate the virus evasion of the host immune system. Recent data proved that this mechanism is not regulated by NendoU activity [58,59]. The Non-Structural Proteins (nsp) of Coronavirus and their biological functions are resumed in **Table 1**.

NAB nucleic acid binding, PL Pro papain-like protease, SUD SARS-unique domain, DMVs double-membrane vesicles, Mpro main protease, RdRp RNA-dependent RNA polymerase, MTase methyltransferase, Exo N viral exoribonuclease, Nendo U viral endoribonuclease, MDA5 melanoma differentiation associated protein 5, Ublubiquitin-like, Acacidic, 2′-O-MT 2′-O-methyltransferase, ADRP ADP-ribose-1′-phosphatase.

Table 1: Coronavirus non-structured proteins and their biological functions

Protein	Functions
nsp1	Promotes cellular mRNA degradation and blocks host cell translation, results in blocking innate immune response
nsp2	No known function, binds to prohibiting proteins
nsp3	Large, multi-domain transmembrane protein, activities include
	• Ubl1 and Ac domains, interact with N protein
	ADRP activity, promotes cytokine expression
	PLPro/Deubiquitinase domain, cleaves viral polyprotein and blocks host innate immune response
	Ubl2, NAB, G2M, SUD, Y domains, unknown functions
nsp4	Potential transmembrane scaffold protein, important for proper structure of DMVs
nsp5	Mpro, cleaves viral polyprotein
nsp6	Potential transmembrane scaffold protein
nsp7	Forms hexadecameric complex with nsp8, may act as processivity clamp for RNA polymerase
nsp8	Forms hexadecameric complex with nsp7, may act as processivity clamp for RNA polymerase; may act as primase
nsp9	RNA binding protein
nsp10	Cofactor for nsp16 and nsp14, forms heterodimer with both and stimulates ExoN and 2-O-MT activity
nsp12	RdRp
nsp13	RNA helicase, 5′ triphosphatase
nsp14	N7 MTase and 3′-5′ exoribonuclease, ExoN; N7 MTase adds 5′ cap to viral RNAs, ExoN activity is important for proofreading of viral genome
nsp15	Viral endoribonuclease, NendoU
nsp16	2′-O-MT; shields viral RNA from MDA5 recognition

Epidemiology of coronavirus disease

In 2003, an epidemic of severe respiratory disease, severe acute respiratory syndrome (SARS), occurred in Guandong Province, China which quickly spread to other provinces in China. Intensive international research identified the new virus and see that it has the same morphological characteristics as and genetic characteristics of coronaviruses [60] and was called SARS-CoV. Recommendations for travel and measures to control the spread of the epidemic (rapid detection of cases, isolation, wearing of masks, etc.) were quickly issued by the WHO and quickly stopped the transmission of the virus [61,62]. At the beginning of July 2003, no further transmission of the virus was observed and transmission was no longer observed and the WHO considered that the epidemia was contained. Some isolated cases, were identified between September 2003 and January 2004, with no other transmissions. It was then established that the natural host of the virus that causes SARS-CoV was a bat [63]. In 2012, Middle East Respiratory Syndrome Coronavirus (MERS-CoV) was identified in a patient with died of pneumonia in Saudi Arabia and a wave of severe pneumonia had occurred like previously in Jordan due to the same MERS-CoV [64]. Coronaviruses genetically very similar to MERS-CoV have been identified in bats that represent the virus reservoir. Humans become infected through contact with dromedaries, which are intermediate hosts. Human-to-human transmission was not really established, the few cases observed were nosocomial infections [65].

The occurrence of severe pneumonia has been observed in December 2019 in the city of Wuhan, China. A new coronavirus associated with this outbreak was identified in early January 2020 [66] and the disease, which emerged in 2019, was named Covid (**Co**rona**vi**rus **d**isease)-19. The epidemic has spread rapidly outside China and all over the world. It is reported that the rapid emergence of SARS-CoV-2 and its pandemic spread are a proof that this virus is far more contagious than SARS-CoV-1 and MERS-CoV [26].

From MERS-CoV to SARS-CoV-2, the transmission has been identified as airborne droplet transmission [67]. The human coronavirus infection's incubation periods are short. It is around three days for conventional CoV (HCoV-229E and HCoV-OC43), two to ten days for SARS-CoV (SARS-CoV and MERS -CoV) and two to fourteenth days for SARS-CoV-2 [68] (**Table 2**).

The duration of the viral excretion in the respiratory tract is less well known, the RNA of conventional HCoV is detectable for about 14 days in the respiratory tract [69,70]. SARS-CoV RNA can be detected by reverse transcriptase – polymerase chain reaction (RT-PCR) in the patient's respiratory secretions, stool, and urine up to approximately 30 days after the onset of the clinical signs [71].

Table 2: Epidemiology of Human coronaviruses. ARE: acute respiratory illness, CoV: coronavirus, ILI "influenza-like illness", MERS "Middle East respiratory syndrome", SARS "severe acute respiratory syndrome

	SARS-CoV 2	MERS-CoV	SRAS-Cov1	HCoV-HKU1	HCoV-NL63	HCoV-229E	HCoV-OC43
Discovery	2019	2012	2004	2004	2003	1960	1960
Source of infection for humans	-	Dromedarie, human	leather mouse, crawling cats, human	human	human	human	human
Transmission	Airborne droplet	Airborne droplet	Airborne droplet	Airborne droplet	Airborne droplet	Airborne droplet	Airborne droplet
Infection period	-	Spring	Spring	Winter - Spring	Winter - Spring	Winter - Spring	Winter – Spring
Focus of geographic distribution	Worldwide	Arabian Peninsula	No more human cases since 2004 (previously East Asia)	Worldwide	Worldwide	Worldwide	Worldwide
Typical clinic	Viral pneumonia	Viral pneumonia	Viral pneumonia	ARE, ILI	ARE, ILI	ARE, ILI	ARE, ILI
Case fatality rate (CFR)	~ 7.1%[a]		9.6–11%	-	-	-	-
Incubation time	2–14 days	2–7 days	2–7 days	2-3 days	2-3 days	2-3 days	2-3 days

Genome similarity and conserved regions

The size of the genome and the complexity of the replication mode of coronaviruses granted them a high evolutionary potential.

The two major modes of evolution of coronaviruses are mutations and recombination [37,72]. The mutation is due to an RNA dependent RNA-polymerase (RdRp), devoid of error correction system and generating many mutants replicates of RNA genomic. As with all RNA viruses, the viral population is heterogeneous and has a distribution in quasi-species. This distribution can be seen as an optimization strategy, being a structure allowing having a reservoir of variants with the capacities to cope with environmental changes.

It has been described for several coronaviruses not only in the context of persistent infections, but also in acute infections [73-76]. The best-known example is the emergence of respiratory porcine coronavirus (PRCV) in the 1980s, which is a spontaneous variant (deletion of 672 nucleotides (224 amino acids) in the gene encoding the protein S1) of enteric porcine coronavirus (TGEV). One of the biological consequences of this great deletion is the change in the tropism of the virus, from the TGEV to respiratory for PRCV [77].

The other evolutionary mode of coronaviruses is genetic recombination. This phenomenon is frequent in positive RNA viruses and seems to be favored in coronaviruses by the discontinuous mode of transcription. Recombination is the exchange of genetic material, which can be homologous if it takes place between two coronaviruses genomes, or heterologous if it involves other viral or cellular genes. Many recombinant forms have been described *in vitro* and *in vivo* in coronaviruses.

For example, feline coronavirus type II is the result of a double recombination between feline coronavirus type I and canine coronavirus, following a crossing of a species barrier in the dog-cat direction [78]. The important evolutionary capacity of coronaviruses was highlighted by the emergence of SARS-CoV [79]. The complete sequencing of HCoV-OC43 genome in 2005 by Vijgen*et al.* has further shown that this coronavirus is very close to bovine coronavirus, with more than 90% of nucleotide identity and on the other hand the E gene would have been acquired following a recombination with the porcine coronavirus of group 2 and hemagglutination encephalitis virus (HEV) [12,80]. These data strongly suggest an emergence of HCoV-OC43 in the human population, secondary to an interspecies transmission in the bovine - human sense, which would have occurred at the end of the XIXth century [81,82].

Several coronaviruses belonging to group 2a and with the same molecular lineage as HCoV-OC43 and BCoV have been recently described in elk, buffalo, giraffe, horse, and dog [83,84]. It therefore seems that this group 2a "BCoV-like" coronavirus has a very broad host spectrum in wild and farmed mammals and has a high potential for interspecific passage [85]. Otherwise, the comparison of SL-CoV genomes from civets with the human SARS-CoV sequences shows approximately 30 000 nucleotides (a total of 212 positions of variation) of which 209 in a protein coding region (73 of these 209 are silent) [85,86].

The SARS-CoV sequences of the early period (November 2002 to January 2003) are close to the SL-CoV sequences of civets, in particular the existence of a sequence of 29 nucleotides located at the level of ORF8, which has then disappeared when the virus adapted to humans (deletion of 29 nucleotides) [65,87]. During the evolution of SARS-CoV, the mutation of amino acid residue 487 (from serine in civets to threonine in humans) of protein S seems to have contributed significantly to the adaptation of SARS-CoV to the human receptor angiotensin-converting enzyme 2 (ACE2) [88-90]. The percentage of similarity of sequences in six bat SL-CoV genomes has shown 89 to 90%, and around 87 to 92% with the civet sequences SL-CoV and SARS-CoV. The most variable regions are the S gene (76 – 78% similarity) and ORF8.

The 29 nt region found in SL-CoV civets and early stage human strains is also found in SL-CoV bat [91]. Sequence analysis of SARS-CoV-2 has shown a typical structure to other coronavirus and its genome has been linked to a previously identified coronavirus strain, SARS-CoV that caused the SARS outbreak in 2003 [92]. Structurally, the SARS coronavirus (SARS-CoV) has a well-defined composition comprising 14 binding residues that directly interact with human ACE2. Of these amino acids, eight have been conserved in SARS-CoV-2 [93].

Although the exact pathophysiological mechanisms underlying the emergence of SARS-CoV-2 are unknown, genomic similarities to SARS-CoV could help to explain the resulting inflammatory response that may lead to the onset of severe pneumonia [94].

The HCoV structure has shown that there are most surface proteins, which have hypervariable regions, allowing it to escape immune pressure and, if necessary, to be able to enlarge its cellular tropism. Protein S of coronaviruses has a weak

hemagglutination activity and binds to sialic acids. However, entry into target cells appears to require interaction with a specific protein receptor. Thus, cellular receptors are identified for some coronaviruses: CEACAM1 molecule for the MHV, amino peptidase N (APN) or CD13 for several group 1 coronaviruses (HCoV-229E, TGEV and PRCV, canine coronavirus and felines), the ACE2 molecule for HCoV-NL63 and SARS-CoV [63,95]. The interactions between the protein S and its receptor seems complex and a large amount of data remains misunderstood.

The site of binding of the protein S to its receptor (receptor binding domain [RBD]) is located in different regions of the protein depending on the species of coronavirus, and its cleavage into its two subunits S1 and S2 is variable, depending on the coronavirus and the cell type [96]. Some experimental data are unexpected: despite the amino acid sequences conserved at the level of the S1 protein of HCoV-229E and HCoV-NL63, these two human coronaviruses use different receptors (APN and ACE2, respectively). Furthermore, SARS-CoV uses the same cellular receptor as HCoV-NL63 while the S1 sequences are far apart; however, the RBD of the two viruses seems to be close and absent in SL-CoV.

The hypothesis is posed of an acquisition of this domain by recombination between SARS-CoV and another coronavirus close to HCoV-NL63 during its evolution in humans [97,98]. The apparent plasticity of protein S and RBD would allow coronaviruses to adapt to different protein receptors or to heterologous receptors in different species and would be an advantage in emerging in new hosts. Group 2a coronaviruses are characterized by the existence of an HE protein, which forms a double row of small spicules of five nm high on the surface of the virus. It is a dimeric protein with hemagglutination activity and acetyl esterase. The gene encoding this protein is characteristic of group 2a CoVs. However, its expression is very variable.

Thus, in most MHV isolates, mutations, deletions or insertions have led to the loss of the open reading frameof this gene. Among the human coronaviruses, only the HCoV-OC43 and HCoV-HKU1 strains have the gene encoding HE [99,100]. There is approximately 28% homology between the HEF surface protein of influenza C virus and the HE protein of HCoV-OC43 and bovine coronaviruses (BCoV).

Since the influenza C and HCoV-OC43 viruses infect the same tissues in humans, this homology suggests the acquisition of this gene by recombination. It should be noted that the HEF protein of the Influenza C virus has a membrane fusion activity, which is absent in the HE protein of CoV [101,102]. This protein recognizes cell receptors containing acetylated 9-O sialic acids and induces the formation of neutralizing antibodies. Thus, it would have a function of attachment protein and of initiation of the infection, additive to that of protein S. However, its main function would be the acetyl-esterase activity. Many questions exist about the *in vivo* course of the first stages of the replication cycle for Group 2a CoVs. The HE protein required little attention, probably because it would not be present in the CoVs most studied so far (IBV, MHV, TGEV, SARS- CoV, HCoV-229E and HCoV-NL63) [103,104]. For all Group 2a CoVs studied so far, the binding of protein S to a sialic acid corresponds with the preferential substrate of HE. The HE protein would therefore allow optimal use of sialic acids as attachment factors.

The mode of entry of CoV expressing the HE protein would then be close to that adopted by the influenza A and B viruses, and the functional balance described between hemagglutinin and neuraminidase HA/NA could also exist between S and HE [85]. Protein S is the factor that determines the host spectrum and tissue tropism of coronavirus strains and is the carrier where the differences between HCoV, BCoV and civet coronavirus are concentrated [82]. Cellular protein receptors, in addition to binding to sialic acids have been described for a number of coronaviruses. However, some coronavirus, such as BCoV and HCoV-OC43, use only a sialic acid as the same used by the influenza C virus.

Epidemiology transmission of HCoV occurs mainly directly through droplets of oropharyngeal secretions dispersed by the cough of an infected or symptomatic person. During SARS, MERS and Covid-19, those infected are mainly person who had close contact with a positive case. Airborne viral spread appears to be infrequent as well as indirect "hand-carried" transmission. However, these transmission routes must be taken into account for the control of epidemics, especially in healthcare settings.

Studies of "survival" or maintenance of pathogenicity in air is rare and difficult. The number of secondary cases from index case was only studied within the framework of SARS in 2003. This virus is moderately contagious, with an average number of secondary cases estimated at 2.2 to 3.6. However, super-propagation events with several dozen secondary cases have been described, and have played an important role in the spread of the disease [105].

Concerning old outbreak of the human coronaviruses, among the classic coronavirus strains isolated in the 1960s, only HCoV-229E and HCoV-OC43 were studied and maintained in culture [106]. These studies have shown that HCoV represents a group of respiratory pathogens that infects all age groups and involves in lower respiratory infections (bronchitis, bronchiolitis, pneumonitis, exacerbations of asthma) [107]. The primary infections occur in the early years and re-infections are common throughout life. These reinfections are symptomatic in approximately 45% of cases. The infection rate is relatively uniform across all age groups.

This situation differs from other observed for respiratory viruses such as respiratory syncytial virus (RSV), for which infection rates decrease with age. The classic coronaviruses circulate in an epidemic mode, most often between January and May in areas with a temperate climate. The cyclical and alternative nature of HCoV-229E and HCoV-OC43 strains had been stressed as well as the probable existence of other serotypes. That suggested the combined use of several serological techniques such as complement fixation, inhibition of hemagglutination and sero-neutralization [80].

Regarding HCoV-NL63 and HCoV-HKU1, their recent identification reflects a reduced number of epidemiological data. HCoV-NL63 is a group 1 coronavirus that was discovered and identified by molecular techniques from a respiratory sample of a seven-month-old infant hospitalized for bronchiolitis in January 2003 and the prototype strain was called Amsterdam 1 [95]. The retrospective studies have shown that HCoV-NL63 is not an emerging virus but a virus already circulating in the human population and newly identified [108].

HCoV-HKU1 is a group 2a coronavirus, discovered in Hong Kong in 2005, in a 71-year-old patient hospitalized for pneumonia. This virus has been characterized on a molecular level and determined three different genotypes; A, B, and C of HCoV-HKU1, genotype C being a recombinant of genotypes A and B. In addition, this virus is not responsible for a new disease, only its knowledge is emerging [109]. HCoV-HKU1 has not been adapted to cell culture.

In 2006 and 2007, some studies were published on the circulation of the four HCoVs (HCoV-229E, HCoV-OC43, HCoV-NL63 and HCoV-HKU1). These studies have nonetheless

confirmed the epidemic nature of human coronavirus infections, at the winter - spring junction (peak in February). The four HCoV co-circulate with variations in the distribution of different species according to geography and years [110] . SARS is a special story in coronavirus infections.

According to the WHO, on March 12th, 2003, SARS-CoV made about 8000 probable cases and 800 deaths were declared, the great majority in China. The estimated fatality rate is 0% for subjects under 35 years of age, 7% for subjects 35 to 65 years of age, and 47% for subjects over 65 years of age. WHO declared the end of human-to-human transmission in July 2003 [8]. Since July 2003, several cases of laboratory contamination have been reported in Asia; finally, epidemiological reports from the Guangdong Center for Disease Control and Prevention have indicated that in January 2004, six months after the end of the epidemic, four patients were hospitalized for a mild SARS-CoV infection. The molecular study of these strains concluded that they derived from the same source as the epidemic strains from 2002 to 2003 [8,95].

MERS-CoV triggered an occurrence of respiratory illness in the Middle East with secondary spread to Europe, Africa, Asia, and North America. The diseases occurred mainly in the Middle East states with highest cases of 88% followed by 11% in Asia, 0.8% in Europe, 0.1% in Africa and 0.1% in USA. The age group with highest risk for acquiring as primary cases of infections is 50-59 years and high risk for acquiring as secondary cases of infections is 30-39 years. The total number of associated fatality rate is 858 (34.40%) [111].

Recent coronavirus outbreak was due to a novel SARS-CoV-2 coronavirus. In December 2019, reports of pneumonia-like conditions came in Wuhan, China. The viral spillover is believed to happen in a seafood market in Wuhan, Hubei Province, China [112]. WHO declared Covid-19 to be a public health emergency of international concern (PHEIC) on 30th January 2020 [113].

Conclusion

A new member of SARS-CoV species has emerged. SARS-CoV comprised now SARS-CoV, MERS-CoV and SARS-CoV-2 and the four seasonal circulating human coronaviruses (HCoV 229E, HCov-HKU1, HCov-NL63 and OC43) which represent the most circulating Human coronavirus detected. In addition, SARS-CoV-2 is the most pathogen HCoV and its outbreak locked down the world as never seen before. Scientists must focus on the mutation capacities of the coronavirus in order to predict the emergence of SARS-CoV epidemics.

Conflict of Interest

Submitting authors are responsible for co authors declaring theirs interest.

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