



# SARS coronavirus outbreaks past and present—a comparative analysis of SARS-CoV-2 and its predecessors

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## Abstract

The Coronavirus Disease 2019 (COVID-19), a pneumonic disease caused by the SARS Coronavirus 2 (SARS-CoV-2), is the 7th Coronavirus to have successfully infected and caused an outbreak in humans. Genome comparisons have shown that previous isolates, the SARS-related coronavirus (SARSr-CoV), including the SARS-CoV are closely related, yet different in disease manifestation. Several explanations were suggested for the undetermined origin of SARS-CoV-2, in particular, bats, avian and Malayan pangolins as reservoir hosts, owing to the high genetic similarity. The general morphology and structure of all these viral isolates overlap with analogous disease symptoms such as fever, dry cough, fatigue, dyspnoea and headache, very similar to the current SARS-CoV-2. Chest CT scans for SARS-CoV-2, SARS-CoV and MERS-CoV reveal pulmonary lesions, bilateral ground-glass opacities, and segmental consolidation in the lungs, a common pathological trait. With greatly overlapping similarities among the previous coronavirus, the SARS-CoV, it becomes interesting to observe marked differences in disease severity of the SARS-CoV-2 thereby imparting it the ability to rapidly transmit, exhibit greater stability, bypass innate host defences, and increasingly adapt to their new host thereby resulting in the current pandemic. The most recent B.1.1.7, B.1.351 and P.1 variants of SARS-CoV-2, highlight the fact that changes in amino acids in the Spike protein can contribute to enhanced infection and transmission efficiency. This review covers a comparative analysis of previous coronavirus outbreaks and highlights the differences and similarities among different coronaviruses, including the most recent isolates that have evolved to become easily transmissible with higher replication efficiency in humans.

**Keywords** COVID-19 · SARS-CoV-2 · Coronavirus · Pandemic · Outbreak · Virus

## Introduction

COVID-19 has affected the entire globe with more than 155,000,000 infections worldwide [1] accompanied by a fatality rate of 3.4% [1] and 3,250,000 associated deaths reported [2]. Contrary to the MERS-CoV and SARS-CoV outbreak believed to be associated with infected dromedary camel and bat reservoirs, the origin of SARS-CoV-2 to

date is still unknown and debated, with sources suggesting that it may have originated from bats, akin to the previous SARS-CoV [3, 4]. The first human coronavirus outbreak was caused by the SARS-CoV in November 2002, originating from Guangdong Province, China, which rapidly progressed to Hong Kong, Beijing, Singapore, Vietnam, and Canada by March 2003 [5, 6]. The MERS-CoV outbreak on the other hand, was first reported from Jeddah, Saudi Arabia in September 2012 [7, 8]. Prior to the SARS-CoV outbreak (2002) there have been 4 other human infections of coronavirus by the HCoV-NL63, HCoV-HKU1, HCoV-229E, HCoV-OC43 isolates [5, 9]. This makes the SARS-CoV-2 outbreak the 7th known infection of Coronaviruses in humans.

Coronaviruses are a well-known source of respiratory illness in humans [10–13]. It is the primary root for the common cold, manifesting as a mild illness, resulting in up to 20% of all common cold cases [14]. Coronaviridae (family) are zoonotic viruses, which are subdivided into four different genera: alpha, beta, gamma, and delta coronaviruses

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[15, 16]. Among all the genera, the beta-coronavirus is documented to be responsible for severe illness and death in humans [17]. To date, there have been many identified hosts for the coronavirus, including rodents, feline, canine, turkey, swine, and humans, with bats serving as the primary reservoir with the exception of MERS-CoV reservoir being dromedary camels [10, 18]. Being a beta-coronavirus, SARS-CoV-2 shares similar general morphology and structure as the other beta-coronavirus counterparts, albeit there are genetic and pathogenic differences which are described below. Another distinct feature of SARS-CoV-2 infections are the large numbers of asymptomatic cases in addition to patients with disease symptoms. Symptoms such as fever, dry cough, fatigue, dyspnoea, and headache are common to SARS-CoV-2, SARS-CoV and MERS-CoV infections [19]. Less common symptoms such as gastrointestinal discomfort, diarrhoea, conjunctivitis, skin discolouration or rashes, anosmia and dysgeusia have also been documented in SARS-CoV-2 infected patients with the latter two symptoms common in SARS and MERS-CoV patients [20, 21]. However, the multitude of asymptomatic infections for SARS-CoV-2 has been alarming and has contributed to the rapid spread of this pandemic [22]. An interesting case study by Chan et al. [22] reported a 10-year-old asymptomatic child having radiological bilateral ground-glass lung opacities similar to symptoms of SARS-CoV-2 infection however showed no symptoms of disease whereas, his family members were admitted to hospital upon clear symptoms like onset of fever, upper and lower respiratory tract symptoms and tested positive for SARS-CoV-2. SARS and MERS-CoV infected patients also show close resemblance to this however the large number of asymptomatic patients showing similar lung opacities is much more common in SARS-CoV-2 infected patients [23–25].

Like the SARS-CoV, the primary mode of SARS-CoV-2 transmission was reported to be via respiratory droplets [3, 4]. However, apart from the usual direct droplet transmission, multiple studies have also indicated the possibility of fomite transmission, as the stability of SARS-CoV and MERS-CoV in faecal waste for a considerable time has been shown [26, 27]. A study suggests that the percentage of patients with positive faecal samples in SARS-CoV and MERS-CoV are 97% and 14.5% respectively [27]. Similar to its beta-coronavirus counterpart, the SARS-CoV-2 also showed viability in stool samples albeit at a much lower percentage at 55% as compared to the previous SARS-CoV [27]. Therefore, the possibility of faecal transmission for SARS-CoV-2 cannot be ruled out and more evidence needed to support the aforementioned for this rapidly evolving pandemic [26, 27].

Hence, it becomes important to understand and revisit the information on other Coronaviruses like the SARS-CoV and MERS-CoV and other related Coronaviruses that have

successfully infected and caused disease to humans. With this approach in mind, many overlapping features and distinctions between the Coronaviruses listed above can provide insights into interim or long-term therapeutic solutions to effectively treat the current SARS-CoV-2 isolate.

## Comparative analysis of different coronavirus and SARS-CoV-2

### Morphology and general structure

In the past, the SARS-CoV and MERS-CoV have scored a significant 9.6% and 40% fatality rate, respectively [4, 6]. Albeit having a lower estimated fatality rate at 3.4%, the SARS-CoV-2 is progressing more quickly at a global scale and more infectious as compared to SARS-CoV and MERS-CoV. The rapid mutation in genomic context, especially the S protein in SARS-CoV-2 as compared to the previous SARS-CoV, renders the use of previous vaccines and antiviral therapeutic interventions ineffective. Hence, the study of viral morphology and pathogenesis play a pivotal role to identify the key features of SARS-CoV-2 with its similar counterpart, the SARS-CoV, to facilitate the drug repositioning progress, especially during these urgent times of need.

The general structure and genomic configuration of SARS-CoV-2 closely resemble the other coronaviruses, such as the SARS-CoV and MERS-CoV [10, 19]. The most prominent structure found in coronaviruses is the club-shaped spike projections on the virion surface. This structure gives the virus a crown-like appearance, which gives rise to the name, Coronavirus [15]. Coronavirus is the largest group of non-segmented positive-sense RNA viruses and is known to have an enveloped, spherical shape with a diameter of 65–125 nm in approximate [18, 28]. Under the envelope, coronavirus possesses atypical helical and symmetrical nucleocapsids, rare amongst the positive-sense RNA virus [15]. The current SARS-CoV-2 consists of an RNA genome with a size of approximately 29.9 kilobases (kb) [29]. The genome contains a typical 5' cap and a poly (A)-3'tail, which mimics an mRNA, granting it the ability to undergo translation [16]. Two-thirds of the viral RNA genome, starting from the 5' end, contains the open reading frame (ORF) 1a and 1b genes which primarily encode a large array of non-structural proteins (NSPs). The NSPs (nsp 1–16) are known to aid in viral replication [11, 18]. The remaining one-third of the genome encodes for structural proteins, a common feature for all coronaviruses. The structural proteins encoded by the ORF at the 3' end include the spike protein (S), envelope protein (E), membrane protein (M) and nucleocapsid protein (N) [11, 16].

The SARS-CoV-2 consists of 13–15 open reading frames (ORFs) containing ~30,000 nucleotides [30]. The typical

general layout of the SARS-CoV-2 genome is as follows [5'-leader-UTR-replicase-S-E-M-N-3'-UTR-poly (A) tail], with the accessory genes scattered between the structural genes at the 3' end of the genome [16, 30].

### The genetic constitution and possible origin of the SARS-CoV2

The beta-coronaviruses can be subdivided into four lineages: A, B, C and D [31]. Several notable examples of beta coronaviruses include OC43 and HKU1 from lineage A that were discovered in 1967 and 2005, respectively [5]. SARS-CoV and the present SARS-CoV-2 are both categorized under lineage B [6, 9, 32], whereas MERS-CoV belongs to lineage C [4, 8, 33]. To date, lineage D beta coronaviruses have only been reported in bats, such as the *Rousettus* bat coronavirus (Ro-BatCoV HKU9) [34]. Several theories revolve around the origin of SARS-CoV-2. Possible explanations include natural selection in humans after zoonotic transfer and natural selection in animal reservoirs prior to zoonotic transfer [3]. Yet, for a significant natural selection to occur, a larger animal population density is required and angiotensin-converting enzyme (ACE-2) encoding gene homologous to human ortholog must be present in the animal host [35]. Wu et al. and Guo et al. proposed another viewpoint, which states that the virus evolved to its pathogenic state prior to zoonotic transfer [23, 36].

SARS-CoV-2 was suggested to be genetically more closely related to SARS-related coronavirus (SARSr-CoV) than the MERS-CoV. The (SARSr-CoV) is a species of enveloped positive-sense single-stranded RNA virus that enters its host cell by binding to the angiotensin-converting enzyme 2 (ACE2) receptor. The SARSr-CoV has multiple strains which are of bat-related coronavirus, in which includes the Bat SARS-like coronavirus WIV1 (Bat SL-CoV-WIV1), Bat coronavirus RaTG13, SARS-CoV and many more [37]. A genome sequence similarity of 96.2% between SARS-CoV-2 and Bat CoVER aTG13 was observed through full-length sequencing of the short region of RNA-dependent RNA polymerase (RdRp) [19]. When compared to bat derived SARS-like CoV (bat-SL-CoVZC45, MG772933.1), a nucleotide similarity of 86.9% was reported [10]. On the other hand, SARS-CoV-2 has been reported to share 79% and 50% genetic similarity to SARS-CoV and MERS-CoV, respectively [38]. The SARS-CoV-2 possesses a 94.4% similarity in the amino acid sequences of the seven conserved replicase domains in the ORF1ab when compared to SARS-CoV. Under the same study, an 87.1% sequence matched between SARS-CoV-2 with several SARSr-CoV sequences were revealed via next-generation sequencing [19]. Interestingly, there was a 93.1% nucleotide similarity of receptor binding spike protein encoded by S gene between SARS-CoV-2 and bat coronavirus (BatCoV RaTG13). This

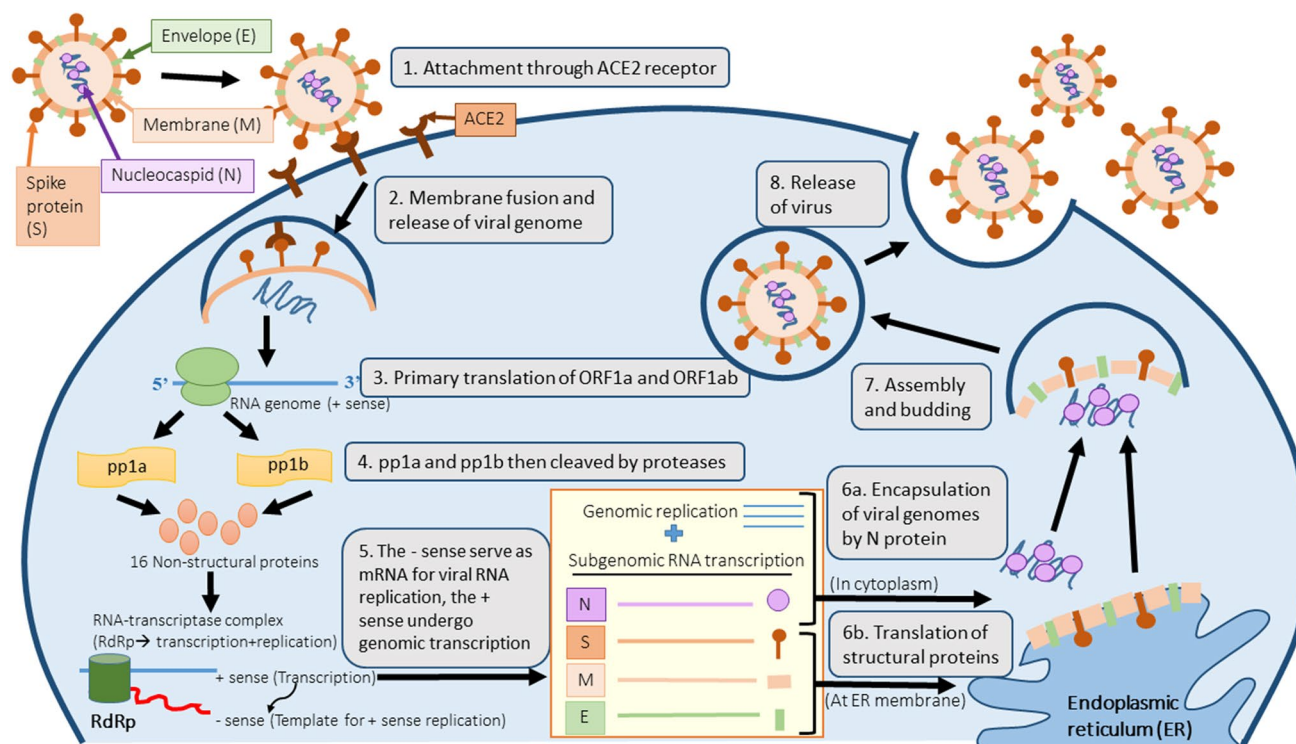
result is in line with similar studies where matching of 87.2% to 83.9% in S protein to minimal receptor-binding domain were demonstrated between the SARS-CoV-2 and the previous SARS-CoV [39]. As SARS-CoV-2 is highly similar to the bat coronavirus, bats were suggested to be the reservoir host for the ancestor of SARS-CoV-2 and subsequently transmitted to humans through an unrevealed intermediate host.

Albeit the aforementioned RaTG13 from *Rhinolophus affinis* bats having high genetic similarity index of 96% with the SARS-CoV-2 [3], the Malayan pangolins (*Manis javanica*) was reported to have a higher genetic similarity index in all six major receptor-binding domain residues [40, 41]. In the past, cleavage sites were only described in low pathogenicity avian influenza virus but absent in bat and pangolin beta-coronaviruses [35, 42]. Interestingly, the distinct cleavage site in SARS-CoV-2 was reported to be similar to several bird flu strains which transmit easily among humans [19]. Therefore, by conducting retrospective serological studies and studying banked human samples could potentially aid in understanding whether such spread had occurred for this current pandemic [43]. Based on the aforementioned above, such as the 79% genetic similarity between SARS-CoV-2 and SARS-CoV, 94.4% amino acid sequence similarity from the seven conserved replicase domains in the ORF1ab between SARS-CoV-2 and SARS-CoV, 87.1% matched sequence between SARS-CoV-2 and SARS-CoV and many more, strongly suggests that the SARS-CoV-2 are much more akin to the previous SARS-CoV than the MERS-CoV [19, 38] (Fig. 1, Table 1).

### The key distinctions and features of SARS-CoV-2, SARS-CoV and MERS-CoV

#### Receptor recognition

The SARS-CoV and SARS-CoV-2 possess the same host cell surface receptor—the ACE2 protein. However, the SARS-CoV-2 possesses a higher binding affinity compared to SARS-CoV attributed to a single mutation at N501T in the Spike (S) protein [40, 46, 47]. Besides, a study has also revealed a large protein interaction surface with high binding-affinity between SARS-CoV-2 and ACE-2 receptors at 18 interactions, compared to only 8 interactions between SARS-CoV and ACE2, amounting up to 15-fold stronger interaction in SARS-CoV-2 [48]. The same study has also illustrated strong multi-epitope synapse adhesion between spike protein (amino acid position 471–486, 496–505, 404–416 & 446–456) in SARS-CoV-2 and human ACE-2 receptor, contributing to a strong viral surface-host's epithelial adhesion, suggesting the need for multi-epitope high affinity antibodies for antiviral therapeutics as compared to SARS-CoV [48]. This is also evident in the past when



**Fig. 1** The replication cycle of SARS-CoV-2. The attachment and entry of the SARS-CoV-2 are mediated by the S, or “spike” surface glycoprotein [44]. The S protein can be subdivided into S1 receptor binding domain and S2 fusion domain [44]. Upon proteolytic activation by the host cells, the S proteins bind to the cellular receptor, angiotensin-converting enzyme-2 (ACE-2), which facilitates membrane fusion with host cell membrane through the endocytosis, leading to the subsequent release of viral RNA genomes in the host cytoplasm. Both co-terminal polyproteins, pp1a and pp1b, produced from the translation of ORF1a and ORF1b are cleaved by proteases

to form non-structural proteins (nsps). These nsps will assemble into a replicase-transcriptase complex (RTC), which encodes for many enzymes such as RNA-dependent RNA polymerase (RdRp). During replication, RdRp will produce negative-sense RNA copies to serve as templates for replications of positive-sense RNA genomes. Then, a series of subgenomic mRNAs is produced during transcription and translated into respective viral proteins, which will be further assembled and packaged at respective sites. Following that, the resulting virion will undergo budding and release of virions through exocytosis

studies were done on combination of two monoclonal antibodies, CR3022 + CR3014, is much more effective in neutralizing SARS-CoV via the interaction with S2 domain of SARS-CoV S protein than CR3022 or CR3014 alone [49]. This gives a strong indication where one antibody may not be sufficient in hindering the already stronger affinity from SARS-CoV-2. Hence, this highlights the need for multiple multi-epitope high affinity antibodies that targets different sites of adhesion synapse in passive immunisation for COVID-19, to provide strong antiviral response [48].

Apart from the aforementioned above, other SARS-CoV-2 variants (B.1.1.7, B.1.351 & P.1) have also shown various spike protein mutations (N501Y, P681H, K417N, E484K and K417T), concomitantly enhancing binding affinity of S protein for human ACE-2 receptor to a greater extent.

The B.1.1.7 (20I/501Y.V1, VOC 202012/01) variant, B.1.351(20H/501Y.V2) variant, and the P.1 variant (B.1.1.28 subclade) have been described following viral genome sequencing. The most prominently identified mutations

between all variants lie within the spike (S) proteins [50]. The B.1.1.7 mutation was first identified in Denmark, United Kingdom and Northern Ireland in December 2020. Differ from the original variant, the B.1.1.7 variant carries a mutation in the S protein, an amino acid change from asparagine to tyrosine at position 501 (N501Y) in the receptor-binding domain of the spike protein, which increases the binding affinity to human ACE-2 receptor [50, 51]. Also, another mutation in the S protein, an amino acid change from proline to histidine at position 681 (P681H) in the spike protein, one of the four residues that creates a furin cleavage site between S1 and S2 in spike has been shown to promote entry into respiratory epithelial cells and transmission in animal models. Apart from that, a deletion of 2 amino acids at positions 69 and 70 (del 69–70) in the S protein provides an evasion point, S-gene target failure (SGTF) in RT-PCR assay, inadvertently increasing false-negative results and hidden transmissibility [50].

Moving on to the next variant, the B.1.351 was first detected in Nelson Mandela Bay, South Africa in December



**Table 1** Characteristic features of SARS-CoV-2, SARS-CoV and MERS-CoV

	SARS-CoV-2 (COVID-19)	SARS-CoV	MERS-CoV
Origin	China Source: Unknown, possible bats	China Source: horseshoe bats	Saudi Arabia Source: dromedary camels
Year of Outbreak	Dec 2019-ongoing	2002–2004	2012-ongoing
Number of reported countries affected	> 190 (Ongoing)	26	27
Reproductive number/Transmissibility ( $R_0$ )	~ > 3*	~ 2*	~ 0.7*
Genera	Beta-coronavirus	Beta-coronavirus	Beta-coronavirus
Lineage	B	B	C
Common symptoms	Fever, cough, lower respiratory tract infection	Fever, cough, lower respiratory tract infection, diarrhoea, runny nose	Fever, cough, lower respiratory tract infection, diarrhoea, runny nose
Mode of transmission	Close contact with an infected individual or via respiratory droplets	Close contact with an infected individual or via respiratory droplets	Close contact with an infected animal and individual or via respiratory droplets
Receptor Recognition	ACE-2	ACE-2	DPP4/CD26
Incubation period	~ 2–14 days* [45]	2–7 days [45]	2–14 days [45]
Preferred detection method	Real-time quantitative reverse-transcription PCR (RT-PCR)	RT-PCR, Enzyme-linked immunosorbent assay (ELISA)	RT-PCR, serum test for antibodies targeting MERS virus
Clinical examination	Chest-CT (Bilateral ground-glass opacities)	Chest-CT (Numerous infiltrative patchy shadows)	Chest-CT (Extensive ground-glass opacities)
Reported cases	> 155,000,000**	~ 8000 [6]	> 2564 [30]
Reported death	> 3,250,000**	~ 774 [6]	> 881 [30]
Fatality rate	~ 3.4% (initial estimate)	~ 9.6%	~ 40%

\*The reproductive number ( $R_0$ ) varies across different countries and regions, the given values in the table are based on the few cited sources in this manuscript. The incubation period for COVID-19 in Table 1 was obtained from the CDC on 20 February 2021, the value is uncertain as the pandemic is still ongoing [45]

\*\*The associated values for COVID-19 vary across time as the pandemic is still on-going at a rapid pace at the time of this writing. (May 6, 2021)

2020. Apart from the similar N501Y mutation found in the B.1.1.7 variant, this variant has two distinct mutations in the S protein (K417N, E484K, and N501Y) [52]. The K417N mutation on the RBD of S protein interacts with the D30 ACE-2 protein residue, contributing to significant enhancement of binding affinity to human ACE-2 receptors. Besides, there have been reports on the likelihood of K417N mutation towards the abolishment of key interactions with class 1 neutralising antibodies, contributing towards immune evasion [52]. Apart from that, the E484K mutation in S protein interacts with the K31 human ACE-2 protein residues, enhancing the binding affinity with the receptor [52, 53]. Furthermore, the E484K mutation has been shown to reduce neutralization by convalescent sera and monoclonal antibodies, leading to reinfection cases in Brazil [50].

The variant P.1, a subclade of B.1.1.28 variant was first identified in Tokyo, Japan in January 2021 by the National Institute of Infectious Disease (NIID). This lineage contains the usual N501Y spike protein mutation found in other variants in addition to two other S protein mutations (K417T, E484K, and N501Y) [54]. Apart from the aforementioned

roles for E484K and N501Y S mutations, the K417T spike protein mutation might be playing a significant role in this variant. Given that it is a very recent discovery, not much is known about this variant, however, there is evidence suggesting that the P.1 variant may affect the ability of antibodies to recognize and neutralize the virus [54].

An interesting similarity was also found across these three emerging variants where D614G mutation in S protein is consistent across the variants, increasing the binding affinity for ACE-2 receptor [50]. The D614G mutation denotes an amino acid change from aspartic acid to glycine at position 614 in the S protein, leading to reduced S1 shedding and increased total S protein incorporated into the virion [50]. However, given that there are different mutations across the different emerging SARS-CoV-2 variants, vaccines were found to be effective against all these mutations. As such, the Pfizer-BioNTech BNT162b2 vaccine has successfully induced neutralisation against the panel of the aforementioned spike protein mutations across different SARS-CoV-2 variants [55].

Besides, differing from SARS-CoV, SARS-CoV-2 has three short insertions in the N-terminal domain along with distinct 4/5 key residues in the ACE-2 receptor-binding motif [19]. MERS-CoV, on the other hand, recognises host dipeptidyl-peptidase 4 (DPP4)/CD26 receptor. Apart from that, SARS-CoV-2 has also been reported to have gained a polybasic cleavage site at the S1–S2 boundary in the spike protein with an insertion of 12 nucleotides, which was not observed in SARS-CoV. The insertion of these nucleotides is predicted to provide three O-linked glycans which are believed to involve in the immune-evasion [46, 47]. Numerous cases of aggressive COVID-19 progression in hypertensive and diabetic patients have been reported post renin–angiotensin–aldosterone system (RAAS) inhibitor administration. Such inhibitors disrupt RAAS and subsequently increase ACE2 levels thus, resulting in the rapid progression of COVID-19, further indicating the correlation between levels of host ACE2 and COVID-19 disease progression [47, 56] (Table 2).

### Attachment and entry

The S1 receptor binding domain of the spike protein is the same across the different coronaviruses (SARS-CoV-2, MERS-CoV and SARS-CoV), utilizing the S1-C terminal (S1-CTD) [57]. However, only 64% similarity has been reported in the S1-CTD when compared to SARS-CoV [63]. In addition, the S2 spike protein fusion domain in SARS-CoV-2 showed a 90% identity with respect to SARS-CoV [63]. There are generally four different modes of proteolytic activation of coronavirus spike proteins, including the proprotein convertases, extracellular proteases, cell surface proteases and lysosomal proteases. The three latter modes are involved in the activation of SARS-CoV spike proteins, including extracellular protease (elastase), cell surface proteases (TMPRSS2) and lysosomal proteases (cathepsin

L/B) [44, 57, 61]. However, it has been reported that SARS-CoV-2 uses all four modes of proteolytic activation, which includes Proprotein convertases (Furin) [46, 47, 64]. On the other hand, the MERS-CoV utilises Proprotein convertases (Furin), Cell surface proteases (TMPRSS2) and Lysosomal proteases (Cathepsin L) [46, 57]. Furin is highly expressed in the human lungs, hence it may be playing a key role in enhancing the infectivity of SARS-CoV-2 in the human lungs thus, allowing increased exploitation of the host as compared to the SARS-CoV [46, 47, 64]. Apart from that, the ability to exploit four different modes of proteolytic activation might confer an infectivity advantage for SARS-CoV-2 compared to the SARS-CoV and MERS-CoV, in which both uses only three modes. It was also found that SARS-CoV-2 is more susceptible to furin cleavage, as compared to the SARS-CoV [64].

### Viral replication and genetic expression

The pp1a and pp1b, produced from the translation of ORF1a and ORF1b are cleaved by proteases to form non-structural proteins (NSPs). The NSPs assemble into a replicase-transcriptase complex (RTC), which encodes for many enzymes such as the RNA-dependent RNA polymerase (RdRp). The significant difference between the SARS-CoV-2 and SARS-CoV genetic expression is the absence of 8a protein and changes in the number of amino acids in 8b and 3c protein [28]. Another key difference between the SARS-CoV-2 compared to SARS-CoV, is the transmembrane helical segments in the ORF1ab encoding for NSP2 and NSP3 [65]. The study has reported that at amino acid position 501 (position 321 in NSP2), the SARS-CoV-2 encodes for glutamine residue instead of threonine residue found in the SARS-CoV [65]. With this substitution, the side chain now has a higher polarity and stronger ability to form hydrogen bonds (H-bonds), providing stability to the protein. Also, the same study

**Table 2** A summary of receptor recognition from different coronavirus

Coronavirus genera	Identified coronavirus	Receptor recognition	Source
Alpha ( $\alpha$ )	Human Coronavirus NL63 (HCoV-NL63)	Angiotensin-converting enzyme-2 (ACE2) Aminopeptidase N (APN)	[15, 57]
	Human Coronavirus 229E (HCoV-229E)	Aminopeptidase N (APN)	[15, 57]
	Porcine Transmissible Gastroenteritis Coronavirus (TGEV)	Aminopeptidase N (APN)	[15, 57]
	Canine coronavirus (CCoV)	Aminopeptidase N (APN)	[15]
Beta ( $\beta$ )	Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV)	Angiotensin-converting enzyme-2 (ACE2)	[57–60]
	Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2)	Angiotensin-converting enzyme-2 (ACE2)	[40, 60, 61]
	Middle East Respiratory Syndrome Coronavirus (MERS-CoV)	Dipeptidyl-peptidase 4 (DPP4)/CD26	[57, 58, 60]
	Mouse Hepatitis Coronavirus (MHC)	Carcinoembryonic antigen-related cell adhesion molecule 1 (CAECAM1)	[57, 58]
Gamma ( $\gamma$ )	Avian Infectious Bronchitis Coronavirus (IBV)	$\alpha$ -2,3 linked sialic acids	[57]
Delta ( $\delta$ )	Porcine deltacoronavirus (PdCV)	porcine-APN (pAPN)	[62]

reported that at amino acid position 723 (position 543 in NSP3), SARS-CoV-2 encodes a serine residue instead of a glycine as per in SARS-CoV. This substitution may lead to an increase in local stiffness of the polypeptide chain and increased ability to form H-bonds, affecting enzyme active sites [65]. In addition, at the amino acid position 1010 (position 192 for NSP3), SARS-CoV-2 encodes for proline instead of isoleucine, as found in SARS-CoV [65]. With proline in place for isoleucine, a steric bulge will be expected, providing stiffness to the molecular structure of the SARS-CoV-2 [65] (Table 3).

## The immune-response towards SARS-CoV-2 infection

In general, the human body has a few lines of defences to fend off virus, bacteria, and other microbes. The first line of defence (also known as the innate immunity) provides an initial defence against the infection. There are a range of first line barriers which includes the phagocytes, dendritic cells, natural killer cells, complement cells to the simplest epithelial barrier. The immune response for any viral infection is generally the adaptive immunity, in which generated by the white blood cells known as the “lymphocytes”, that entails the B cells and T cells. The humoral response or also known as the antibody-mediated response plays an

important role for antibody production to neutralize the viral antigen. Lymphocytes primarily reside in the lymph nodes and spleens [66]. Upon SARS-CoV-2 invasion, the foreign antigen presented by the SARS-CoV-2 drives the primary antibody (IgM antibody production) and secondary antibody response (IgG antibody production) from B cells, which ultimately increases the levels of several inflammatory cytokines for subsequent defence against viral invasion [67]. The released cytokines include the TNF- $\alpha$ , IL-1 and IL-6 which stimulate the CD4+ and CD8+ T-cells. The CD4+ T cells help to coordinate the immune response via stimulation of other immune cells, such as macrophages, B cells, and CD8+ T killer cells to clear the pathogen and destroy the infected cells [68]. However, in certain scenarios, a notable reduction of CD4+ and CD8+ T cells can be seen in severe cases at less than 800, and 400 cells/ $\mu$ L respectively due to T cells exhaustion, concomitantly leads to collapse in host immunity defence. This was contributed by the persistent stimulation of the virus, which enhances the production of IL-10 inhibitory cytokine in the body [69].

Immunoglobulin M (IgM) is commonly known to provide most of the primary antibody defence upon viral infections. On the other hand, the high-affinity IgG is tagged as a secondary antibody immune response that is vital for long-term immunity and immunological memory [70]. Hence, in the event of SARS-CoV-2 infection, IgM is often released in large amounts 3–6 days post-infection followed by IgG

**Table 3** The key distinctions and features of SARS-CoV-2, SARS-CoV and MERS-CoV

Receptor recognition	<p>SARS-CoV and SARS-CoV-2 utilises host angiotensin-converting enzyme (ACE2)</p> <p>SARS-CoV-2 has much higher binding affinity compared to SARS-CoV due to single mutation at N501T in the Spike (S) protein [40, 46, 47]. A study has also revealed a large protein interaction surface (18 interactions) with high binding-affinity between SARS-CoV-2 and ACE-2 receptors compared to SARS-CoV (8 interactions), amounting up to 15-fold stronger interaction in SARS-CoV-2 [48]</p> <p>Other SARS-CoV-2 variances (B.1.1.7, B.1.351 &amp; P.1) have also shown various spike protein mutations (N501Y, P681H, K417N, E484K and K417T), in which enhances the binding affinity of S protein for ACE-2 receptor at a greater extent [51–55]</p> <p>SARS-CoV-2 has three short insertions in the N-terminal domain along with distinct 4/5 key residues in the ACE-2 receptor-binding motif which is not present in SARS-CoV [19]</p> <p>Unlike SARS-CoV, the SARS-CoV-2 gained a polybasic cleavage site at the S1–S2 boundary in the spike protein with an insertion of 12 nucleotides to provide three O-linked glycans involved in immunoevasion [46, 47]</p> <p>MERS-CoV, on the other hand, recognises host dipeptidyl-peptidase 4 (DPP4)/CD26 receptor</p>
Attachment & entry	<p>The SARS-CoV-2 shows only 64% similarity in S1-CTD when compared to SARS-CoV [63]</p> <p>The S2 spike protein fusion domain in SARS-CoV-2 showed a 90% identity with respect to SARS-CoV [63]</p> <p>The SARS-CoV-2 uses 4 modes of proteolytic activation, including the Proprotein convertases (Furin) [46, 47, 64]. Furin is highly expressed in the human lungs, hence allowing enhanced infectivity of SARS-CoV-2 in the human lungs for increased exploitation compared to the SARS-CoV [46, 47, 64]</p> <p>The SARS-CoV-2 is more susceptible to furin cleavage, as compared to the SARS-CoV [64]</p> <p>On the other hand, the MERS-CoV also utilises Proprotein convertases (Furin), in addition with Cell surface proteases (TMPRSS2) and Lysosomal proteases (Cathepsin L) [46, 57]</p>
Viral replication and genetic expression	<p>The SARS-CoV-2 genetic expression showed changes in the number of amino acids in 8b and 3c protein and an absence of 8a protein as compared to the SARS-CoV [28]</p> <p>The SARS-CoV-2 encodes for glutamine residue instead of threonine residue found in the SARS-CoV at amino acid position 510 [65]. At amino acid position 723, the SARS-CoV-2 encodes for serine residue instead of glycine found in SARS-CoV [65]. In addition, at amino acid position 1010, SARS-CoV-2 encodes for proline instead of isoleucine, as found in SARS-CoV [65]</p>

antibody production, which may be detected 8 days after the onset of symptoms [70, 71]. A study has shown that SARS-CoV-2 leads to significant reduction of Bcl-6<sup>+</sup> T follicular helper cells (Bcl-6<sup>+</sup> T<sub>FH</sub>) and absence of germinal center B cells in lymph nodes, contributing to dysregulated humoral response. This was due to the interference on the production of high affinity pathogen specific antibodies, leading to impaired IgG response. Apart from that, the study has also observed B lymphopenia in COVID-19 patients, in which might be a contribution of excess TNF- $\alpha$  production which suppresses differentiation in Bcl-6<sup>+</sup> T<sub>FH</sub> and germinal center loss, concomitantly compromises the production of quality IgG antibodies [72].

Another study conducted on the avidity maturation of IgG antibody upon SARS-CoV-2 infection also highlights an incomplete maturation, low or intermediate avidity in IgG to receptor binding domain (RBD) [66]. In which, the binding strength between IgG and its epitope, and strength of the multivalent interactions where both antigen interacting with multiple IgG antigen-binding sites greatly reduced [66]. Besides that, the avidity maturation of the IgG antibody allows the differentiation of acute and past SARS-CoV-2 infection, albeit not completely certain [73]. Bauer and colleagues stated that low avidity of IgG antibody illustrate an acute sars-cov-2 infection, intermediate avidity IgG might indicate recent infection and high avidity IgG might indicate a past infection [74]. Therefore, the importance of antibody immune response, especially the levels, affinity, and avidity of IgG (Immunoglobulin G) towards SARS-CoV-2 infection cannot be overlooked.

## The transmission and stability of SARS-CoV-2 vs SARS-CoV

To contain the SARS-CoV-2, the reproduction number becomes crucial. The basic reproduction number ( $R_0$ ) is an important metric to measure the potential of a disease spread within a completely susceptible population [75]. For instance, if a disease has an  $R_0$  of 10, a person positive for the disease will transmit it to an average of 10 people within the community. For any given contagious infectious disease, if  $R_0 < 1$ , the few infected individuals introduced in a susceptible population have a low probability of infecting others, hence suggesting low disease spread and the possibility of the disease eventually dying out [76]. On the other hand, if  $R_0 > 1$ , then the infected individuals in a susceptible population will easily infect others thereby increasing the number of infected individuals in each generation [76].  $R_0$  can vary significantly depending upon a variety of factors such as the infectious period, probability, and the number of infecting a susceptible individual upon one contact per unit time [75]. The  $R_0$  value allows one to determine the efforts required to

prevent or contain an epidemic from a population. The  $R_0$  value allows health officials and governments to plan and design strategies to contain a viral outbreak effectively. In summary, a basic reproduction number indicates the risk of viral infection in a community.

The estimated  $R_0$  value for SARS-CoV-2 has been reported to be around 3.28 with a median of 2.79 and interquartile range of 1.16 according to a study conducted by Liu and colleagues [77]. Another study suggested an estimated  $R_0$  value of 2.43 to 3.10 across different cities in Italy [78]. On the other hand, an estimated  $R_0$  value of 2 was accessed during an early outbreak in Wuhan, China [79]. Comparing the  $R_0$  values across these different studies to the previous SARS-CoV outbreak, the estimated  $R_0$  values for SARS-CoV-2 was found to be slightly higher at  $\sim > 3$  as compared to the  $R_0$  values of  $\sim 2$  for the previous SARS-CoV outbreak [77, 80]. Greater  $R_0$  values indicate that the SARS-CoV-2 has higher transmissibility than the previous SARS-CoV in a susceptible population. The MERS-CoV showed the lowest  $R_0$  value at 0.7 among the three deadly coronavirus outbreaks, recorded in a study conducted by Petrosillo and colleagues [80]. However, with the ongoing pandemic, it is difficult to obtain an estimate of the SARS-CoV-2 basic reproduction number. Besides,  $R_0$  values are very subjective to population, data collection, counter preparations, and social customs across the globe as these are the key factors for virus transmission. Hence, the  $R_0$  values cannot fully represent the outbreak in every country but rather used as a tool to contribute towards an overall understanding of the virus spread.

Given the genetic and structural similarities between the SARS-CoV and SARS-CoV-2, findings on the stability of SARS-CoV-2 are much needed to aid in the control of virus spread. A study has discovered that SARS-CoV-2 exhibits similar surface stability as the SARS-CoV [81]. Another study carried out on multiple TCID<sub>50</sub> (median tissue culture infectious dose) revealed the viral titers at which 50% of the cells were infected. In an aerosolized environment, both SARS-CoV-2 and SARS-CoV showed a similar reduction trend of infectious titre at  $10^{3.5}$  to  $10^{2.7}$  TCID<sub>50</sub>/L of air and  $10^{4.3}$  to  $10^{3.5}$  TCID<sub>50</sub>/L of air respectively after 3 h [81]. Also, the SARS-CoV-2 and SARS-CoV exhibited similar stability kinetics where both viruses were more stable on plastic and stainless-steel surfaces than on the copper and cardboard surfaces [81]. On plastic surfaces, both SARS-CoV-2 and SARS-CoV showed a significant reduction of virus titre from  $10^{3.7}$  to  $10^{0.6}$  TCID<sub>50</sub> and  $10^{3.4}$  to  $10^{0.7}$  TCID<sub>50</sub> after 72 h, respectively. A similar trend was also observed on stainless-steel surfaces after 48 h where the stability kinetics of SARS-CoV-2 and SARS-CoV reduced from  $10^{3.7}$  to  $10^{0.6}$  TCID<sub>50</sub> and  $10^{3.6}$  to  $10^{0.6}$  TCID<sub>50</sub>, respectively [81].



A recent study by van Doremalen et al. reported key differences in SARS-CoV-2 and SARS-CoV fomite transmission, which is the transmission of the virus from contaminated surfaces [81]. The viable duration of SARS-CoV-2 was found to be halved on copper surfaces and tripled on the cardboard surfaces compared to the SARS-CoV, at 4 h and 24 h viable duration, respectively, a significantly longer survival duration on cardboard surfaces for SARS-CoV-2. The same study also showed that both SARS-CoV-2 and SARS-CoV exhibited similar half-lives in aerosol and on plastic and stainless-steel surfaces [81]. These preliminary results indicate that SARS-CoV-2 has good aerosol and fomite transmission. However, it must be noted that the study was performed with only one SARS-CoV-2 strain. Further studies must be performed to validate the SARS-CoV-2 transmission ability in order to design effective control measures against the virus. Despite SARS-CoV-2 sharing similarities to its predecessor SARS-CoV, it is highly susceptible to mutation and has a much higher transmission capacity. Owing that the basic reproduction number ( $R_0$  value) and transmission stability of SARS-CoV-2 varies across different strains, regions, and continents, it cannot be concluded as a definite value. The effort on basic reproduction number and transmission stability of SARS-CoV-2 are utmost important to illustrate how a different basic reproduction number ( $R_0$  value) and transmission stability can affect the effort to contain the pandemic.

## Conclusion

Several explanations were suggested for the undetermined origin of SARS-CoV-2, in particular the idea of bats, avian and Malayan pangolins as reservoir hosts, owing to the high genetic similarity. As compared to the predecessors, SARS-CoV-2 is much similar to SARS-CoV regarding its general structure and morphology. Key distinctions between the two that contribute to the increased transmissions and severity of COVID-19 reside in the higher binding affinity in SARS-CoV-2 due to the single mutation at N501T in the Spike protein. Spike protein mutations are the most common occurrence among various SARS-CoV-2 strains (B.1.1.7, B.1.351 & P.1), contributing to enhanced binding affinity towards ACE-2 receptors. In addition, SARS-CoV-2 is known for its greater susceptibility to furin cleavage compared to SARS-CoV. Besides, the genetic expression of SARS-CoV-2 differs in the numbers of amino acids in 8b and 3c protein accompanied by the absence of 8a protein. Moreover, the SARS-CoV-2 encodes for different residues at amino acid position 510, 723 and 1010, unlike SARS-CoV. Despite the various SARS-CoV-2 strains that are associated with differences in transmission capacity across different continents and

regions, the values and data cannot be overlooked as it contributes towards an overall understanding of the virus spread, helping towards the effort to contain the pandemic. Akin to the predecessors, the common symptoms such as fever, dry cough, fatigue, dyspnoea, and headache are also present for SARS-CoV-2. Since SARS-CoV-2 can be largely or mildly asymptomatic upon initial contact, individuals who had close contact with an infected individual or residing in a COVID-19 red-zones should not be excluded for chest CT-imaging and laboratory testing such as RT-PCR. The common findings for COVID-19 are in close resemblance to its counterparts, the SARS-CoV, and MERS-CoV, in which pulmonary lesions, bilateral ground-glass opacities, and segmental consolidation are present in lungs on chest CT, a distinctive clinical diagnosis to characterize coronavirus infection.

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## Declarations

**Conflict of interest** All authors have read and agreed to the published version of the manuscript. All authors have declared that there is no conflict of interest.

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