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Review

Viral, host and environmental factors that favor anthroponotic spillover of coronaviruses: An opinionated review, focusing on SARS-CoV, MERS-CoV and SARS-CoV-2



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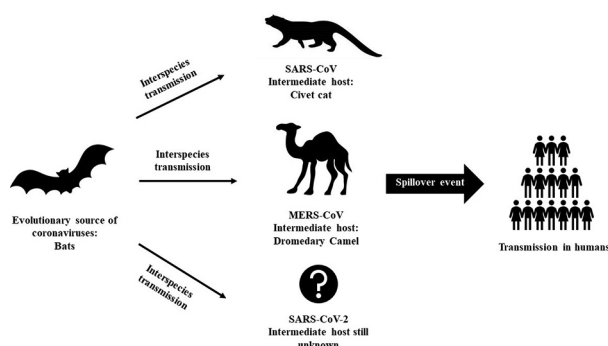
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HIGHLIGHTS

- Environmental factors play a key role in the zoonotic transmission of emerging.
- Ability for host switching and interspecies infection is often attributed.
- Bats are the main reservoir hosts for a lot of coronaviruses like SARS-CoV-2.
- SARS-CoV-2 uses the same ACE2 cell receptor and entry mechanism as SARS-CoV-1.

GRAPHICAL ABSTRACT



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ABSTRACT

Environmental factors play a key role in the zoonotic transmission of emerging pathogenic viruses as mankind is constantly disturbing wildlife's ecosystems usually by cutting down forests to build human settlements or by catching wild animals for food, which deprives the viruses of their natural hosts and gives them opportunity to infect humans. In December 2019, a new coronavirus emerged from bats and was named SARS-CoV-2 by the International Committee for Taxonomy of Viruses, and the disease it causes named COVID-19 by the World Health Organization. Disease outbreaks such as SARS in 2002–2003, MERS in 2012 and the current COVID-19 pandemic are the result of higher mutation rates of coronaviruses and their unique capacity for genetic recombination, resulting in adaptations that make them more suitable to cross the species barriers and infect other species. This ability for host switching and interspecies infection is often attributed to the great diversity of these viruses, which is a result of viral and host factors such as the low fidelity of their RNA-dependent RNA polymerase, the high frequency of their homologous RNA recombination, and the adaptation of the S protein to bind host receptors like the angiotensin converting enzyme 2 (ACE2) in the case of SARS-CoV and SARS-CoV-2, and dipeptidyl peptidase 4 (DDP4) in MERS-CoV. This review presents an overview of the zoonotic transmission of SARS, MERS and COVID-19, focusing on the viral, host and environmental factors that favor the spillover of these viruses into humans, as well as the biological and ecological factors that make bats the perfect animal reservoir of infection for these viruses.

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Contents

1. Introduction	2
2. The zoonotic origins of SARS-CoV, MERS-CoV and SARS-CoV-2.	2
2.1. SARS-CoV	3
2.2. MERS-CoV	3
2.3. SARS-CoV-2	3
3. Viral and host factors that favor transmission	3
3.1. The low fidelity of RNA-dependent RNA polymerase (RdRp)	3
3.2. The high frequency of homologous RNA recombination	4
4. Environmental factors that favor transmission	5
5. Why are bats the main reservoirs of infection for emerging viruses?	6
6. Conclusions and perspectives for the future	6
Funding	6
CrediT authorship contribution statement	6
Declaration of competing interest	7
Acknowledgements	7
References.	7

1. Introduction

Coronaviruses are enveloped, positive-sense, single-stranded RNA viruses that can infect both animals and humans (Duffy et al., 2008; Guo et al., 2020). They comprise the largest group of viruses under the order *Nidovirales*, which includes the families *Coronaviridae*, *Arteriviridae*, *Roniviridae* and *Mesoviridae*. The *Coronaviridae* family consists of two subfamilies: *Coronavirinae* and *Torovirinae*. The *Coronavirinae* are classified into four genera: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus* (Lefkowitz et al., 2017; Lu et al., 2015). Four coronaviruses have been identified to cause infections in humans so far, namely the alphacoronaviruses HCoV-NL63 and HCoV-229E, and the betacoronaviruses HCoV-OC43 and HCoV-HKU1, which are endemic and known to cause common colds and severe lower respiratory tract infections (Ahmad et al., 2020; Ye et al., 2020). Together, these four coronaviruses are responsible for 15 to 30% of all common colds (Mesel-Lemoine et al., 2012). The genus *Betacoronavirus* is further classified in four subgenera: *Embecovirus*, *Sarbecovirus*, *Merbecovirus* and *Nobecovirus*. (Gorbalenya et al., 2020; Li et al., 2019).

Just seventeen years ago, the Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) emerged in southern China in 2002 and caused the SARS epidemic of 2002–3, that affected 33 countries, resulted in 8422 confirmed cases and 916 deaths. Currently, there is no known SARS-CoV transmission anywhere in the world. The latest human cases of SARS-CoV infection were reported in China in April 2004 in an outbreak that resulted from laboratory-acquired infections (Centers for Disease Control and Prevention (CDC), 2004). About a decade later, the Middle East Respiratory Syndrome coronavirus (MERS-CoV) emerged as a dangerous human disease in the Arabian Peninsula in 2012 ((WHO), 2020a; LeDuc and Barry, 2004; Li et al., 2019; Sheahan et al., 2020). At the end of January 2020, a total of 2519 laboratory-confirmed cases of Middle East respiratory syndrome (MERS) had been reported globally, including 866 deaths with a case-fatality rate of 34.3%. The majority of these cases were reported from Saudi Arabia (2121 cases), including 788 deaths with a case-fatality rate of 37.1% (World Health Organization (WHO), 2020). In December 2019, a new coronavirus emerged and was named SARS-CoV-2 by the International Committee for Taxonomy of Viruses, and the disease it causes named COVID-19 by the World Health Organization ((WHO), 2020b; Gorbalenya et al., 2020). Phylogenetic analysis showed that this novel coronavirus has 79–79.5% genetic similarity with SARS-CoV, and 50% with MERS-CoV, being sufficiently different from SARS-CoV to be classified as a new *Betacoronavirus* belonging to the *Sarbecovirus* subgenus (Contini et al., 2020; Lu et al., 2020; Rothan and Byrareddy, 2020; Zhou et al., 2020).

Studies on the modes of transmission of SARS-CoV-2 have shown that it is primarily transmitted through close personal contacts with respiratory droplets or aerosols from an infected person, which can be generated during sneezing, coughing, and exhalation (Nabi et al., 2020; Shereen et al., 2020). This is why frequent hand-washing and maintaining a distance of at least one meter are considered the main precautions against contracting the infection ((WHO), 2020c; Morawska and Cao, 2020). In addition to that, several studies have reported that SARS-CoV airborne transmission was the main transmission route in indoor cases studied in Hong Kong’s Prince of Wales Hospital (Y. Li et al., 2005; Xiao et al., 2017; Yu et al., 2005), health care facilities in Canada (Booth et al., 2005) and in aircraft (Olsen et al., 2003). Considering the many similarities between the two SARS viruses and the evidence on virus transport in general, it is highly likely that the SARS-CoV-2 virus also spreads by air (Morawska and Cao, 2020). A recent study by van Doremalen et al. (2020) supports this hypothesis by showing that SARS-CoV-2 remained viable in aerosols for 3 h (the duration of the experiment), confirming that aerosol and fomite transmission of the virus is plausible as the virus can remain infectious and viable in aerosols for hours.

Another suggested transmission route is the fecal-oral one, as viable SARS-CoV-2 has been detected in stools of COVID-19 patients (Wang et al., 2020; Wu et al., 2020; F. Xiao et al., 2020) and virus RNA has been found in sewage (Ahmed et al., 2020; La Rosa et al., 2020; Medema et al., 2020; Randazzo et al., 2020), which may be overlooked in a hospital setting because it is not a commonly discussed source of pathogenic aerosols (McDermott et al., 2020). This could be used to identify the early-warning signs and scale of an outbreak, as monitoring wastewater could provide better estimates for how widespread the virus is than testing due to the fact that wastewater surveillance can account for those who have not been tested and have only mild or no symptoms (Mallapaty, 2020).

Next, we will discuss viral, host and environmental factors that favor SARS-CoV, MERS-CoV and SARS-CoV-2 zoonotic spillover and transmission to humans.

2. The zoonotic origins of SARS-CoV, MERS-CoV and SARS-CoV-2

The concept of species barrier in infectious diseases comes from the fact that the relationship between infectious agents such as viruses and their host species is restricted by genetic adaptations that develop through co-evolution of the virus and its host species, and when spillover of these viruses occur, development of severe disease in the new hosts might occur, as the virus is not adapted to the new host (Wong et al., 2009). Alphacoronavirus and betacoronaviruses infect only mammals, whereas gammacoronavirus and deltacoronavirus infect mainly

birds (Arora et al., 2020; Banerjee et al., 2019). Bats and birds are the main animal reservoirs of infection of coronaviruses (Woo et al., 2012), from which they can be transmitted to other animals that live near or in close contact with humans, such as domestic pets or exotic animals sold in Chinese wet markets destined for human consumption (Chan et al., 2013; Wong et al., 2009). During this journey, they either undergo genetic mutations and acquire new genes, or modify existing genes through recombination mechanisms (Woo et al., 2006). These changes in their genomes result in adaptations that make them more suitable to cross the species barrier, such as the changes in the Spike protein (S) in the receptor-binding domain (RBD) that contributed to the adaptation of SARS-CoV (Qu et al., 2005; Wu et al., 2012) and MERS-CoV to human cells (Cotten et al., 2014; Forni et al., 2015).

2.1. SARS-CoV

The initial studies investigating animal sources of the virus from wet markets in the Guangdong province of China suggested that Himalayan palm civets (*Paguma larvata*) and raccoon dogs (*Nyctereutes procyonoides*) were the probable hosts responsible for human transmission (Guan et al., 2003) because genetically similar coronaviruses were isolated from them. However, it has been reported that masked palm civets from the wild or farms without exposure to the live animal markets were mostly negative for SARS-CoV (Leung et al., 2009), suggesting that masked palm civets only served as the intermediate amplifying host (Ye et al., 2020). It has also been demonstrated that SARS-CoV can infect macaques, ferrets and cats, however it only produced disease in the first two (Fouchier et al., 2003; Martina et al., 2003).

On later studies, a SARS-like coronavirus (BatCoV RaTG13) that closely matched the human SARS-CoV was isolated from the Chinese horseshoe bat (*Rhinolophus affinis*) and was able to replicate in HeLa cells expressing the angiotensin-converting enzyme 2 (ACE2) receptor from humans, civets and bats (Ge et al., 2013). This RaTG13 and other bat SARS-CoV-related coronaviruses (Lau et al., 2005; W. Li et al., 2005) share 88–92% nucleotide sequence homology with SARS-CoV-1 (Ye et al., 2020), leading scientists to believe that SARS-CoV was transmitted directly to humans from wet market civets, with bats as the main reservoir hosts (Cui et al., 2019; Hu et al., 2017).

2.2. MERS-CoV

Dromedary camels are thought to be the primary zoonotic reservoir for human transmission, with strong evidence that bats are the evolutionary source of this coronavirus (Anthony et al., 2017; Chastel, 2014; Guan et al., 2003; Widagdo et al., 2017). Furthermore, it was demonstrated that MERS-CoV can infect bat cells by exploiting the dipeptidyl peptidase-4 (DPP4), the same receptor used to infect human cells (Raj et al., 2013; Salata et al., 2020).

It is not known when MERS-CoV spread from bats to camels, but widespread exposure to the virus in the Middle East and North/East Africa dates back as early as the 1980s, suggesting that camels have served as a zoonotic reservoir for MERS-CoV for at least 30 years (Alshukairi et al., 2018; Corman et al., 2014; Cui et al., 2019; Müller et al., 2014; Reusken et al., 2014, 2013). However, questions still remain as many confirmed cases of MERS have no contact history with camels before developing symptoms (Samara and Abdoun, 2014), most likely being a result of human-to-human transmission or unknown transmission routes involving unrecognized animal species that carry MERS-CoV (Ye et al., 2020).

2.3. SARS-CoV-2

Up until recently, the main suspect of being the intermediate host for SARS-CoV-2 was the pangolin, as several studies have identified SARS-CoV-2-related viruses in Malayan pangolins (*Manis javanica*) (Lam et al., 2020; Liu et al., 2019; Wong et al., 2020; Xiao et al., 2020a,

2020b; Zhang et al., 2020), but genetic analyses did not find any conclusive proof (Cyranski, 2020; Lam et al., 2020; Zhang et al., 2020). SARS-CoV-2 that was isolated from infected individuals showed a higher similarity to the BatCoV RaTG13 virus than to the ones that were isolated from the pangolins (X. Li et al., 2020). In addition to that, the Guangdong pangolin coronaviruses have a higher amino acid identity (97.4%) with SARS-CoV-2 than the bat coronavirus RaTG13 (89.2%) in the RBD (Han, 2020; Lam et al., 2020; Liu et al., 2019; Wong et al., 2020; K. Xiao et al., 2020a; Zhang et al., 2020). In the rest of the genome, RaTG13 possess a higher sequence identity with SARS-CoV-2 than the Guangdong pangolin coronaviruses, with phylogenetic analysis based on the synonymous sites of the RBD showing that RaTG13 is more closely related to SARS-CoV-2 than Guangdong's pangolin coronaviruses (Han, 2020; Lam et al., 2020; Liu et al., 2019; Wong et al., 2020; K. Xiao et al., 2020a; Zhang et al., 2020). Based on these evidences, three hypotheses were suggested for the link of pangolins with SARS-CoV-2: (i) pangolins are the intermediate host, and SARS-CoV-2 emerged from the spillover from pangolins to humans once; (ii) pangolins are the intermediate host, and SARS-CoV-2 emerged from the spillover from pangolins to humans multiple times; (iii) SARS-CoV-2 and pangolin CoVs originated independently through cross-species transmission from bats (Han, 2020).

Information about the SARS-CoV-2 virus in other animals is scarce until this date, with SARS-CoV-2 being isolated from dogs, cats, tigers and minks in only a few sporadic cases (World Organisation for Animal Health, 2020). Other cases have been reported in other countries such as Belgium, the Netherlands, France, Germany, Russia, and Spain, affecting different domestic animals or mink farms. These reported episodes evidence that while felines and dogs can be infected by SARS-CoV-2, only felines can develop symptoms. However, it remains unclear if any domestic or livestock species can spread the virus to humans (Hernández et al., 2020). Moreover, the susceptibility of ferrets and other domestic animals to SARS-CoV-2 has also been demonstrated in experimental infections (Kim et al., 2020). SARS-CoV-2 cannot replicate well in dogs, pigs, chickens, and ducks, but it can replicate efficiently in ferrets and cats, and be transmitted between cats via respiratory droplets (Shi et al., 2020).

Fig. 1 shows the zoonotic origins as well as the intermediate hosts for SARS-CoV, MERS-CoV and SARS-CoV-2.

3. Viral and host factors that favor transmission

Disease outbreaks such as the 2002–2003 SARS epidemic and the current COVID-19 pandemic are the result of several factors, including higher mutation rates of RNA viruses and the unique capacity for genetic recombination of the positive-sense RNA genomes of coronaviruses (Chan et al., 2013; Khan et al., 2020; Shereen et al., 2020).

Coronaviruses encode the largest single-stranded positive-sense RNA genomes among RNA viruses (27–32 kb), with at least six open reading frames (ORFs), namely ORF1ab, spike, envelope, membrane and nucleocapsid (Graham and Baric, 2010; Mousavizadeh and Ghasemi, 2020; Perlman and Netland, 2009; Smith and Denison, 2012; Woo et al., 2009). These large genomes account for their diversity, leading to greater plasticity and greater chances to adapt to different hosts, being an advantage for host switching and interspecies infection (Woo et al., 2009). Their diversity has been attributed to two main factors: the low fidelity of their RNA-dependent RNA polymerase (RdRp) and the high frequency of their homologous RNA recombination (Duffy et al., 2008; Jenkins et al., 2002; Woo et al., 2009).

3.1. The low fidelity of RNA-dependent RNA polymerase (RdRp)

Coronaviruses have high genetic variability and this is mainly due to their high mutation rates resulting from the low fidelity of the RdRp, which is associated with the capacity of these viruses to adapt to many different hosts and their rapid evolution (Sexton et al., 2016;

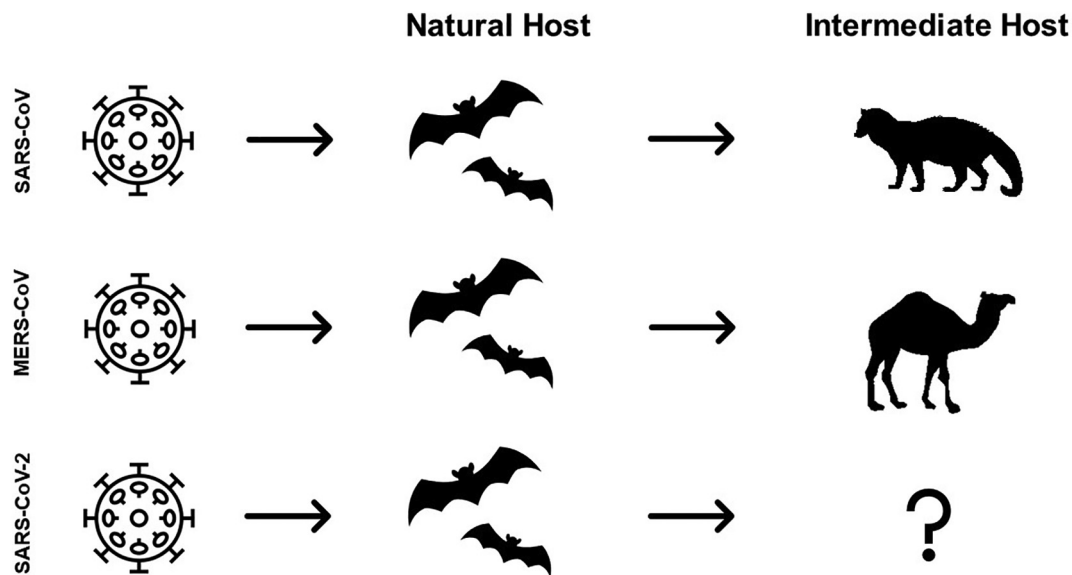


Fig. 1. The zoonotic origins and intermediate hosts for SARS-CoV, MERS-CoV and SARS-CoV-2.

Simon-Loriere and Holmes, 2011). The low fidelity of the RdRp results in unusually high mutation rates, generally estimated as 10^3 to 10^5 , giving coronaviruses plasticity to adapt to new environmental pressures and host changes (Bolles et al., 2011; Chan et al., 2013; Woo et al., 2009).

In contrast to other positive-sense RNA viruses, coronaviruses replicate with higher fidelity, and all larger members of the *Nidovirales* order encode a 3'-to-5' exoribonuclease (ExoN) domain that is required for replication fidelity and is a probable RNA-dependent RNA proof-reading enzyme (Denison et al., 2011; Lai, 1992). This might have allowed for genome expansion and may also be responsible for fast virus evolution in face of changes in ecological settings and maintenance of RNA transcription fidelity (Denison et al., 2011; Perlman and Netland, 2009; Sexton et al., 2016). When ExoN is inactivated in engineered SARS-CoV genomes, viruses can exhibit a 10-fold or higher increase in mutation frequency, up to 18 times higher than those tolerated for fidelity mutants of other RNA viruses, suggesting that ExoN probably acts as a proof reading enzyme and is required for fidelity regulation and maintenance of these large genomes (Duffy et al., 2008; Graham and Baric, 2010; Sexton et al., 2016). The discovery of ExoN's function as a regulator of replication fidelity might indicate that RNA genome replication fidelity can adapt to different environmental settings and selective pressures, which would allow for rapid virus evolution in changing ecologic conditions (Bolles et al., 2011; Denison et al., 2011; Graham and Baric, 2010).

3.2. The high frequency of homologous RNA recombination

It has been proposed that coronaviruses have a special random template switching mediated by a 'copy-choice' mechanism during RNA replication. This process is divided in two stages: genome replication and subgenomic RNA transcription (Bolles et al., 2011; Cheng and Nagy, 2003; Gallei et al., 2004; Kuge et al., 1986; R. Banner and Lai, 1991). In the first stage, the plus-strand genome RNA is transcribed into a full-length minus-strand template RNA, from which more plus-strand genome RNAs are synthesized. In the second stage, 3'-nested subgenomic RNAs are transcribed and used as templates for the translation of viral proteins (Denison et al., 2011). Due to the low capacity of the RdRp to copy the same template, the RNA replicase complex must pause and switch from the original template to the acceptor template during synthesis (Cheng and Nagy, 2003; Gallei et al., 2004). This acceptor RNA must be in close proximity for the switch to take place, and it also needs to present sequence similarity to allow the RdRp to bind

and continue RNA synthesis (Lai, 1992; Popov et al., 2014; Simon-Loriere and Holmes, 2011). In the case of coronaviruses, mRNA synthesis occurs in a discontinuous manner, in which the RNA replicase complex jumps between positions in the genome. This mechanism involves frequent template switching during replication, leading to frequent recombination events (Payne, 2017).

The viral RdRp recognizes the transcriptional regulatory sequences (TRSs) that are located upstream of each subgenomic ORF during negative strand synthesis (Denison et al., 2011; W. Li et al., 2005). The polymerase has two options at these points: it can read through to the next TRS or dissociate from the template strand and reassociate with the leader TRS that is in the 5' UTR (Denison et al., 2011; Graham and Baric, 2010). Then, it completes synthesis of a set of subgenomic negative strand RNA containing an antileader RNA sequence the same size as each viral mRNA. These subgenomic negative strand RNAs function as the main templates to produce subgenomic mRNAs that are 3'-coterminal with an ~70 nt 5' leader sequence. Therefore, alterations in TRS sequences can influence viral replication efficiency (Denison et al., 2011). Combined, all these factors have given coronaviruses more plasticity to accommodate and modify genes (Ye et al., 2020), which is evidenced by the numerous unique open reading frames (ORFs) and protein functions encoded towards the 3' end of the genome (Bolles et al., 2011; Pasternak et al., 2006; Woo et al., 2009; Ye et al., 2020).

Besides the low fidelity of coronaviruses RdRp, their high frequency of homologous recombination and genetic diversity, another key determinant of interspecies transmission and host specificity of SARS-CoV-like viruses is the interaction of the spike (S) protein with the host receptor angiotensin-converting enzyme 2 (ACE2) (F. Li, 2013; Wan et al., 2020). "The S protein of SARS-CoV, MERS-CoV, and SARS-CoV-2 has 1104 to 1273 amino acids and contains an amino (N)-terminal S1 subunit and a carboxyl (C)-terminal S2 subunit (Liu et al., 2020; Wrapp et al., 2020) (Fig. 2). In the S1 subunit, the receptor-binding domain (RBD), spanning about 200 residues, consists of two subdomains: the core and external subdomains (F. Li et al., 2005; Lu et al., 2013). The RBD core subdomain is responsible for the formation of S trimer particles (Yuan et al., 2017). The external subdomain contains two exposed loops on the surface, which bind with ACE2 (Letko et al., 2020)" (Liu et al., 2020).

Recently, it has been shown that SARS-CoV-2 has a polybasic cleavage site (RRAR) at the junction of S1 and S2, which allows effective cleavage by furin and other proteases and has a role in determining viral infectivity and host range (Nao et al., 2017). A leading proline is also inserted at this site in SARS-CoV-2 (PRRA), creating a turn that is

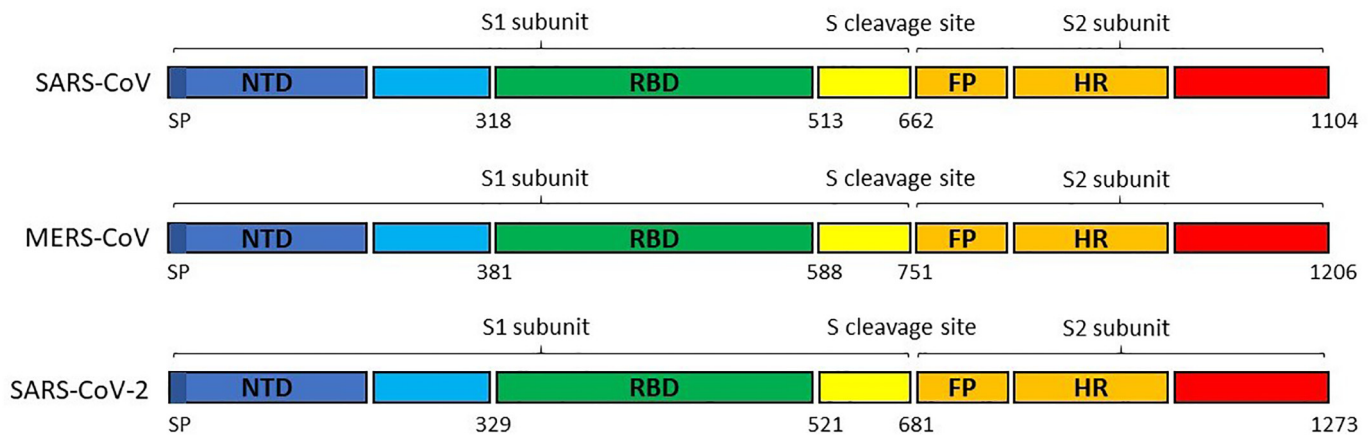


Fig. 2. Structural diagrams of S (spike) glycoproteins of SARS-CoV, MERS-CoV, and SARS-CoV-2. The spike proteins contain S1 and S2 subunits, which are divided by the S cleavage sites. FP: fusion peptide; HR: heptad repeat 1 and heptad repeat 2; RBD: receptor-binding domain, contains core binding motif in the external subdomain; SP: signal peptide. Image adapted from Liu et al. (2020). *Journal of Medical Virology*, DOI: (<https://doi.org/10.1002/jmv.25726>).

predicted to result in the addition of O-linked glycans to S673, T678 and S686, which flank the cleavage site and are unique to SARS-CoV-2 (Andersen et al., 2020). The functional implications of this polybasic cleavage site and the addition of O-linked glycans is still unknown. Previous experiments with SARS-CoV have shown that insertion of a furin cleavage site at the S1–S2 junction enhances cell–cell fusion without affecting viral entry (Follis et al., 2006), and efficient cleavage of the MERS-CoV spike enabled MERS-like coronaviruses from bats to infect human cells (Menachery et al., 2020). Regarding the addition of O-linked glycans, it has been suggested that it might play a role in protein folding and immune evasion (Andersen et al., 2020; Bagdonaite and Wandall, 2018; Watanabe et al., 2020).

The infection of humans by SARS-CoV-like viruses depends on specific genetic changes in the S1's RBD. These changes are thought to have been achieved by continuous evolution independent of recombination, in which the bat-CoV ancestor virus ability to bind human ACE2 was acquired or improved by point mutations when it infected intermediate hosts before it could efficiently infect humans, which is supported by the existence of at least 3 discontinuous highly variable genomic regions between SARS-CoV and SARS-CoV like viruses (Wang et al., 2006). To enter host cells, a defined RBD in the S1 subunit of the S protein needs to specifically recognize the host receptor's ACE2 for docking and entry, thus making the RBD and the ACE2 the key determinants of cross-species and human-to-human transmission of SARS-CoV-like viruses (Li, 2015; Li et al., 2003; Wan et al., 2020).

The S protein of the SARS-CoV-2 is thought to be modified via homologous recombination, being the result of a mixture of bat SARS-CoV and an unknown betacoronavirus (B. Li et al., 2020; Shereen et al., 2020). It has been shown that SARS-CoV-2 uses the same ACE2 cell receptor and entry mechanism as previously described for SARS-CoV (Gralinski and Menachery, 2020; B. Li et al., 2020; Xu et al., 2020), the latter being capable of recognizing and binding to the ACE2 receptors of other animal species including bats, palm civets and raccoon dogs, giving us a lead on how the events leading to SARS-CoV-2 interspecies transmission might have taken place (Chan et al., 2013).

Major species barriers between humans and mice, rats or bats have been recently reviewed by. By using human ACE2 as the reference molecule, key residue changes in these animal's ACE2 molecules that disfavor SARS-CoV binding were identified. Mice have been found to support SARS-CoV infections inefficiently, rats have showed to be resistant to SARS-CoV infections and the Daubenton's bat (*Myotis daubentonii*) supports SARS-CoV infections at low levels, showing that critical residue changes between human ACE2 and mouse, rat, or bat ACE2 pose as major species barriers for SARS-CoV infections (F. Li, 2013).

Similar to SARS-CoV-2 and SARS-CoV, host cell entry in MERS-CoV is mediated by binding of the S protein to another cell receptor, namely

the host dipeptidyl peptidase 4 (DDP4) receptor, and variation in this receptor has been shown to block cell entry in host cells (van Doremalen et al., 2016, 2014). Viral adaptation of MERS-CoV to the bat species *Desmodus rotundus* DPP4 was shown by demonstrating that the S protein of MERS-CoV can make use of multiple paths to rapidly adapt to novel species, once again highlighting the capacity of coronaviruses for host-switching (Letko et al., 2018).

Before fusion, the S protein also needs to be cleaved by host cellular proteases (Bolles et al., 2011; Lu et al., 2015), such as the human airway trypsin-like protease (HAT), cathepsins and transmembrane protease serine 2 (TMPRSS2) (Bertram et al., 2011; Shereen et al., 2020). These cellular factors are also important in defining host specificity and must also be taken into consideration. Other factors such as the innate immune response, metabolic characteristics and restriction factors of host cells that either increase or decrease viral replication still need to be elucidated for complete understanding of SARS-CoV-2's mechanisms of infection and pathogenicity. The divergence of these host factors between humans and the natural and intermediate hosts of coronaviruses might elucidate how cross-species infections occur and what might be the barriers to cross-species transmission (Ye et al., 2020).

4. Environmental factors that favor transmission

Mankind has already been through three epidemiological disruptions (Morand and Figuié, 2017). The first one goes back to when humans were hunter-gatherers many thousand years ago. We were never in one place long enough and settlements were not large enough to sustain the transmission of infectious diseases, but this changed with the advent of the agriculture and the arrival of permanent settlements in the Middle East during the Neolithic revolution (Hershkovitz and Gopher, 2008). This led to the domestication of animals and the establishment of larger permanent human settlements, which in turn facilitated the spread of bacteria and viruses between cattle and humans (Fournié et al., 2017). The next two disruptions are linked to urbanization and commercial trade and resulted in pandemic influenzas, viral hemorrhagic fevers in animals and humans, and antimicrobial resistance – all of which are linked to environmental and socioeconomic factors and frequent contact between humans and animals (Alirol et al., 2011; Morand and Figuié, 2017; Neiderud, 2015).

Because humans are now living in an interconnected and globalized world, greater human mobility is leading to an increase in the frequency and reach of infectious diseases epidemics. People can go from one location to virtually any other point on the planet in only 1–2 days, bringing with them the diseases they carry and potentially causing the dissemination of emerging and re-emerging infectious diseases that may pose

a threat to global health security (Findlater and Bogoch, 2018), as seen with the current global spread of COVID-19.

Just like SARS-CoV and MERS-CoV, SARS-CoV-2 also emerged in China. The reasons China seems to be the hotspot for emerging viral diseases are the increase in population and mobility, as well as the increased cultural demand for food and animals in wildlife trade (Liu et al., 2014). The presence of many different species of animals in cages near one another in wet-markets and the fact that these markets are located near residential areas in most parts of China allow frequent contacts between humans and these animals that might be carrying new viral diseases, providing an ideal scenario for the emergence of novel viruses that can cross the species barriers (Chan et al., 2013; Liu et al., 2014; Woo et al., 2006).

Other factors that contribute to interspecies infections are deforestation and altered ecosystems (which result in viral deprivation of their natural hosts, therefore providing the basis for human infection), illegal wildlife trading, intensive domestic animal husbandry, and large-scale distribution of uncontrolled food of animal origin (Capua and Munoz, 2013; Contini et al., 2020; Guan et al., 2003).

5. Why are bats the main reservoirs of infection for emerging viruses?

Bats seem to be the main reservoir hosts for a lot of coronaviruses like SARS-CoV, MERS-CoV and SARS-CoV-2. First of all, bats are a very diverse order of mammals (Order Chiroptera), with approximately 1240 species (20% of the nearly 5000 known species within Mammalia) (Han et al., 2020; Turmelle and Olival, 2009). One in every four species of mammals on earth is a bat, and they can be found in every continent with an exception of the polar regions and some oceanic islands, which means there is a good chance that a virus would come from a bat just because they are so diverse and have a broad geographic distribution (Wong et al., 2009). A bat can also live up to twenty years, and this can facilitate the persistence of infectious agents, thereby increasing the chance of spreading these infectious agents by natural or accidental dispersal of bats into new geographical areas, as they can fly over a relatively large distance from their roosting sites in search for food or during migration (Wang et al., 2006; Wong et al., 2009).

Another important aspect is the fact that they live in large communities (ranging from 10 to 200,000 bats) in very close proximity to one another, which in addition to their social habits creates the perfect environment for passing viruses within their communities (Wong et al., 2009). In addition to that, their immune system seems to be less able to clean viruses, leading to asymptomatic infection and viral persistence (Chan et al., 2013; C. Li, 2013; Wang et al., 2006), which is indicative of a highly evolved relationship between bats and the viruses they carry (Wang et al., 2011). Some bat species also have the habit of hibernating over winter to save energy (George et al., 2011). With a reduced body temperature and lower metabolic rates, they may temporarily fail to create an antibody response to infection, leading to delay in virus clearance from their organisms (Chan et al., 2013; Han et al., 2020; Wang et al., 2011).

It has been suggested that early control of viral replication by the innate immune response of bats through IFN responses followed by a generally slower peak of T-cell response might be the key mechanism to explain the absence of symptomatic disease in infected bats (Baker et al., 2013). Another special feature of their immune system relies in the fact that bats have more T cells than B cells in the blood and spleen (Banerjee et al., 2020), and their antibodies have been shown to have lower avidity and form a weaker association with antigens (Chan et al., 2013), which would explain the absence or low titers of neutralizing antibodies following infection with certain viruses, as in the case of wild-caught *Epitesicus fuscus* bats that were positive for *Epitesicus fuscus* gammaherpesvirus (EfhV) but did not contain neutralizing antibodies against the virus (Subudhi et al., 2018). All of this suggest that the antibodies produced by bats may control viral infections via an unknown

mechanism that does not involve virus neutralization (Baker et al., 2010; Banerjee et al., 2020) and still needs to be elucidated by future research efforts.

Exposures to infected urine has also been suggested as a possible route of transmission of some viruses from bats, as in the case of Hendra virus, in which the virus is likely transmitted to horses via ingestion of food, pasture or water contaminated with urine, saliva and feces of infected bats (Allocati et al., 2016; Wang et al., 2006), as well as Rabies virus, for which bat urine and feces have been suggested as a source of infection and a possible mode of transmission (Allendorf et al., 2012). They may also transmit viruses to human and other animals through bites and scratches like it happens with rabies (Ding et al., 2004). It is also worth mentioning that consumption and handling of undercooked bat meat is still practiced in China and some parts of Asia (Chan et al., 2013; Wong et al., 2009), increasing the possibilities of direct transmission from bat to humans.

6. Conclusions and perspectives for the future

We are now aware of the great genetic diversity of bat coronaviruses and the threat to public health these unknown viruses represent when they cross the species barrier and cause outbreaks of dangerous novel diseases such as COVID-19. It is therefore essential to understand in detail the distribution of bats as reservoir hosts, and the interaction between animals and between humans and animals. Research should be focused on the genetic diversity of bat-borne viruses to prevent future outbreaks, and efforts should also be made on real-time surveillance of potentially zoonotic viruses in bat populations and wet-markets as COVID-19 was neither the first nor the last disease to jump from animals to humans in these settings.

One of the lessons we have learned from SARS, MERS and COVID-19 is that detailed molecular analysis of their S protein, its RBD and host receptors will be the key to understand the whole molecular mechanism involved in cross-host transmission of these viruses. It is also important that more details about bats immune response to persistent viral infections are elucidated, particularly regarding adaptive immunity, as this would allow for a better understanding of the relationship between these viruses and their reservoir hosts and allow us to be better prepared or even prevent the emergence of novel diseases like this in the future.

Moreover, the world could benefit from implementing One Health approaches in aspects involving animals, the environment and humans. Taking into consideration that the last three major zoonotic spillovers of coronaviruses from wild animals to humans resulted from the close contact between humans and wildlife, we could say that human health is closely related to animal and environmental health. Which is why integrating the One Health approach to the mitigation strategies currently used in controlling new disease outbreaks could contribute substantially to the control of SARS-CoV-2, as well as many other novel infectious diseases that might emerge the near future.

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CrediT authorship contribution statement

Priscilla Gomes da Silva: Writing of original draft and methodology. **João Rodrigo Mesquita:** Supervision, review of the first draft, creation of the figure. **Maria de São José Nascimento:** Supervision, review of

the final draft. **Vanessa Andreia Martins Ferreira:** Conceptualization and methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Update

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Corrigendum

Corrigendum to “Viral, host and environmental factors that favor anthroponotic spillover of coronaviruses: An opinionated review, focusing on SARS-CoV, MERS-CoV and SARS-CoV-2” [Sci. Total Environ. 750 (2021) 141483]



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The authors regret that the printed version of the above article contained a number of errors. The correct and final version follows. The authors would like to apologise for any inconvenience caused. Please note that none of these changes impact on the conclusions made by the paper but are necessary to correct for accuracy.

Correction 1

In the second paragraph of Section 2.1, we note that we made a mistake regarding the information given in this part. We confused the information regarding the bat species and the bat-coronavirus strain related to SARS-CoV-2 with the bat species and the bat-coronavirus strain related to SARS-CoV-1. SARS-CoV-2 indeed shares 96.2% nucleotide homology with a bat-coronavirus (RaTG13) that was isolated from the bat species *Rhinolophus affinis* (Cui et al., 2019), not SARS-CoV-1. Moreover, the HeLa cells were used in a virus infectivity study with SARS-CoV-2, not SARS-CoV-1. In this study, HeLa cells that expressed or did not express ACE2 proteins from humans, Chinese horseshoe bats, civets, pigs and mice were used, and it was found that SARS-CoV-2 is able to use all ACE2 proteins (except for mouse ACE2) as an entry receptor to enter ACE2-expressing cells, but it could not enter cells that did not express ACE2, indicating that ACE2 is probably the cell receptor through which SARS-CoV-2 enters cells (Zhou et al., 2020). That being said, the reformulated paragraph with the correct information is as follows:

“On later studies, a bat-coronavirus closely-related to SARS-CoV-1, named SARS-related *Rhinolophus* bat CoV HKU3 (SARSr-Rh-BatCoV

HKU3), was isolated from Chinese horseshoe bats (*Rhinolophus sinicus*) (Lau et al., 2005). This and other bat-coronaviruses share 88–92% nucleotide sequence homology with SARS-CoV-1 (Ye et al., 2020), leading scientists to believe that SARS-CoV was transmitted directly to humans from wet market civets, with bats as the main reservoir hosts (Cui et al., 2019; Hu et al., 2017)”.

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