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Factors responsible for the emergence of novel viruses: An emphasis on SARS-CoV-2
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Abstract
Structural and genetic differences among various viruses play a significant factor in host infectivity and vulnerability to environmental stressors. Zoonoses of viruses require several re-combinations and mutations in their genetic material and among several viruses allowing them to switch hosts and infect new species. Additionally, the host genetics play a significant role in successful viral transmission among various hosts. For example, human immunodeficiency virus (HIV), Ebola virus and influenza viruses. In efficient zoonotic events, selective stresses in the host milieu-interieur are critical during viral infection of the first human host. The genetic rearrangement of the virus and the selective environmental pressure of the host immune system dominate the emergence of new viral disease outbreaks.

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Introduction
Viruses are one of the many evolutionary factors which play a part in both constructive and destructive evolution of species [32]. Viral evolution allows them to infect new hosts, thereby enabling genetic transfer among viruses and hosts [29]. Among other factors, environmental factors play a major role in the emergence and evolution of new strains of pathogenic viruses [19,22]. New viruses keep emerging end re-emerging with time and with changing environmental conditions, and their detection has been possible using high-throughput sequencing [36,47]. There have been 10 major regional and global viral outbreaks in the past two decades, as listed in Table 1. Viruses related to respiratory infections were responsible for almost half of the major outbreaks and had zoonotic transmission. The most recent and the biggest pandemic that we are facing today, coronavirus disease 2019 (COVID-19), is characterized as a respiratory tract infection caused by the 2019 novel coronavirus (2019-nCoV), also known as SARS-CoV-2 due to its remarkable resemblance to severe acute respiratory syndrome coronavirus (SARS CoV) and the Middle East respiratory syndrome (MERS) coronavirus [33]. It appears to have evolved from other coronaviruses. Moreover, considering the timeline of outbreak of both SARS CoV (November 2002) and SARS-CoV-2 (December 2019), the viruses could be related. Also, despite the fact that SARS-CoV-2 has lower fatality rates than other communicable viruses, such as SARS, MERS, and H1N1, it has surpassed all these viruses in terms of both infection rate and number of deaths caused (Callaway et al., 2020). Thus, it becomes important to analyze the factors which could lead to the evolution of newer viruses. In this review, we are trying to discuss the source of infection and plausible factors that lead to the evolution of viruses.

Source of the infection
Since all coronaviruses that have infected humans to date are zoonotic, there is a growing and alarming possibility that newer coronaviral strains can jump the species barrier and infect humans. RNA Sequence analysis of SARS-CoV-2 (MN908947) and the bat SARS related CoV, RaTG13 (MN996532), established a match of 96.2% while similar analyses with SARS-CoV (AY278741) and MERS-CoV established a match of about 79% and 50%, respectively [41]. This strongly indicates that the current SARS-CoV-2 originated from bats although the intermediate host is yet to be ascertained. Moreover, although the SARS-CoV-2 genome sequence shares significant similarities with the bat virus, the receptor-binding domain (RBD) region does not match with the same. The RBD region of SARS-CoV-2 S-protein exhibits sequence similarity to coronaviruses in pangolins, thereby pointing towards pangolins as the intermediate host [48]. While genetic analyses of 3 sets of smuggled Malayan pangolins that exhibited similar viral respiratory infections indicated significant genetic similarity with the
SARS-CoV-2 viral RNA, the zoonosis of this strain of virus from pangolins has not been conclusively proven [26]. Moreover, genetic analyses of the whole genomes of bat, pangolin and human COVID-19 coronaviruses indicated considerable divergence in the viral RNA across the whole genomes among the three species. This further strengthens the claim that pangolins may not be the intermediate host. Alternatively, the zoonotic event may have occurred via multiple host animals, which would be abundantly present in or around wet markets, where the outbreak could have been initiated [40]. This evidence, along with a big meat eating population [25], makes it difficult to pinpoint the source of COVID-19 in humans.

According to some research groups, the current pandemic causing SARS-CoV-2 virus is more distinct than all other SARS-like viruses and especially the SARS-CoV virus [17,30]. Notable genetic variations between SARS-CoV and SARS-CoV-2 include the longer spike protein-encoding region and a distinct RNA dependent RNA polymerase gene in the latter [30]. Recent studies also point towards the evolution of SARS-CoV-2 through natural selection in bats before zoonotic transfer to pangolins and ultimately to humans. CoVs, in general, are rapidly mutating strains, mainly via recombination and genetic reassortment. Studies indicated the presence of multiple lineages of MERS-CoV strains circulating simultaneously in camels, leading to continuous mutations and resulting in a dominant MERS-CoV strain that could attack humans [39]. Such findings may be used also to explain the highly recombinant yet specific traits of SARS-CoV-2. For instance, it has been demonstrated that six amino acid residues in the RBD of SARS-CoV are responsible for its interaction with ACE2 receptor, which is the determinant of host range in viruses similar to SARS-CoV [43]. Mutations in this region of the SARS-CoV-2 makes its interaction even stronger with Angiotensin converting enzyme 2 (ACE2), as is evidenced by structural and biochemical studies [24,43]. Another novel feature specific to SARS-CoV-2 is a polybasic furin cleavage (RRAR) site in the S1–S2 junction of the viral S protein.

In contrast, both the RaTG13 (bat CoV) and the SARS-CoV have a single amino acid (R) in the S1–S2 junction [46]. Several studies in influenza, Ebola, HIV, and yellow fever viruses have established that the presence of a polybasic cleavage site is a strong determinant of pathogenicity [7,9]. In addition, SARS-CoV-2 S-protein sequences have been predicted to contain O-linked glycosylation motifs that are responsible for glycanshielding of epitopes [1,2]. In other attributes, however, SARS-CoV-2 shows high similarity to the pangolin RBDs, while other genetic features remain conserved among SARS-CoV and bat-CoVs. Therefore, the intermediate host may be harbouring multiple lineages and serving as a ‘mixing vessel’, which may have been a factor that is overlooked.

### Issues with containment of the infection

One of the issues faced during efforts to contain the present COVID-19 infection is the inability to identify the intermediate host [23]. In retrospect, the first case of SARS-CoV-2 infection was identified to be in November 2019, although an actual patient zero was never identified [1]. While the initial cases of patients who showed the symptoms of COVID-19 infection were all in some way associated with the wet market of Wuhan in Hubei Province, China, even the WHO has been unable to pinpoint to a patient zero or the actual ‘cause’ of the disease [44,45]. This suggested a presumable unrecognised and unknown transmission period to humans from the initial zoonotic event from the hitherto unconfirmed intermediate host animal(s). This poses the issue of accurately predicting the onset and tracking the extent of the spread of this disease. With this information unavailable, containment measures that were eventually taken by the world nations may have been delayed.

### Table 1

| Outbreak/disease | Causative agent | Intermediate host | Year |
|------------------|----------------|-------------------|------|
| COVID-19         | SARS CoV-2     | Bat/civet         | 2019 |
| Chikungunya     | Chikungunya virus | Ae. aegypti Ae. albopictus | 2019 |
| Nipah virus disease | Nipah virus | Bat and pig      | 2018 |
| Zika virus disease | ZIKA virus | Ae. aegypti Ae. albopictus | 2015 |
| Ebola virus disease | Ebola virus | Bat              | 2014 |
| Avian influenza/bird flu | H7N9 | Chicken          | 2013 |
| Middle East respiratory syndrome | MERS CoV | Camel            | 2012 |
| Swine flu       | H1N1           | Pig              | 2009 |
| Marburg virus disease | Marburg virus | Green monkeys   | 2008 |
| Severe acute respiratory syndrome | SARS CoV | Bat/civet       | 2002 |
Identifying the source, intermediate host and patient zero in epidemic events can expedite containment and surveillance for future outbreaks. Following the MERS outbreak, systematic surveillance of other camel species imported into Saudi Arabia, mainly from African countries, helped identify camel species and people at maximum risk of infection [12,21]. This ensured constant surveillance of the MERS-CoV viral strains in camels for alterations in virulence or infectivity [12]. This may also prompt governments and veterinarians to ensure the proper health of camels and provide preventive protection to people in close contact with these animals. Post containment, these issues are very well documented and similar viral attacks are then avoided by frequent surveillance of the enzootic populations during import [12] and even in zoos and wildlife sanctuaries [20]. Of course, this may prove to be a Herculean task as it is next to impossible to keep every wildlife animal under constant surveillance.

Role of anthropogenic factors in triggering future pandemics

Zoonotic disease organisms are endemic in human populations or enzootic in animal populations with frequent cross-species transmission to people. Pathogens of zoonotic origin form two-thirds of all pathogens infectious to humans, including the newly emergent infections [11]. Of all the potential zoonotic threats, those from RNA viruses are the highest. Owing to their high reproduction number (> 2 for the SARS-CoV-2) [27] and even faster evolutionary trends [15], these viruses can breach species barrier more frequently and successfully than other infectious agents. Most zoonotic events have been reported initially to have occurred in wild animals before affecting humans. However, historically, wildlife diseases have been considered important only when there is a significant die-off in wild animal populations [20] or when they start affecting domesticated pets, agriculture (due to secondary impacts on soil and essential insect population) or human health [11]. This again leads to a lapse in understanding and predicting the onset of a likely zoonotic event.

Climate change

With rapidly changing global landscapes and local environments, SARS-CoV-2 may quickly adapt to and exploit varying conditions because of genetic variation (mutation, recombination and reassortment), environmental factors (including ecological, social, health care, and behavioural influences). These parameters may play an essential role, as have been seen in other viruses, especially with RNA as their genetic material [34]. Climate change such as alteration in the rainfall and temperature could drastically affect agricultural practices and yield. Such changes have been responsible for micro-alterations in the ecosystem, migratory patterns and food chains of several species, including bats, chimpanzees, pangolins and deer, which have been responsible for carrying several viruses. Two to threefold increase in the precipitation resulted in the explosion of rodents responsible for causing hantavirus pulmonary syndrome [4]. In the event of climate change, when crops fail to grow and livestock succumbs, hunger may trigger people to hunt and eat wild animals, as has been seen for Ebola virus transmission due to eating of wild chimpanzees [14]. Later researchers also linked this outbreak with eating fruit bats [16]. The devastation of the natural habitats triggered by climate change could intensify viral infections and increase the risk of viral zoonosis [18]. Increased rainfall in abandoned or poorly managed stagnant water bodies could provide a favourable place for vectors to grow. Specific examples include wet and humid conditions that have previously favoured breeding of Aedes aegypti mosquito yellow fever and dengue fever and frequent transmission. Additionally, climate change could provide suitable conditions for Aedes albopictus to grow by the end of this century, risking 30 million people vulnerable [37]. Similarly, the incidence of other mosquito-borne viruses such as the chikungunya virus, Zika virus, and West Nile virus could increase due to climate change. While warmer and humid conditions decrease the viability of respiratory viruses (Baker et al., 2019), frequent temperature fluctuation could additionally affect an individual’s immune responses adversely to fight against respiratory infections [28].

Rapid viral evolution can also lead to the formation of seed strains common to a geographic location, which can further establish and evolve independently as spatially separated strains, increasing the risk of spontaneous or seasonal re-emergence of the disease. For instance, evolutionary divergence has been observed in influenza viruses concerning distinct geographical locations throughout the 7 continents of the world [38]. Although a variety of data on metagenomic analysis, surveillance of wildlife and cross-species pathogen outbreaks, such as the West Nile virus outbreak [20] are in place, methods to predict these threats remain largely underdeveloped, so much so that the SARS-CoV-2 has infected hundreds of thousands of people in over 200 countries, within a span of a few months. However, by incorporating climate change and other meteorological parameters in epidemiological models, uncertainty associated with future outbreaks may be significantly reduced [3]. Pollination can be affected by changes in humidity and temperature [10]. It can also act as efficient transmitters of viral load as has been demonstrated by testing the coexistence of airborne pollen with SARS-CoV-2. Similar approaches that include a more holistic and varying environmental factors and effects may be developed and used to study virus transmission and the influence of climate change on the same.
**Deforestation and poaching**

Deforestation and poaching have been listed as two of the reasons for increasing zoonotic events. In addition to coronaviruses, other viruses have also undergone adaptation as a need for their survival. For instance, the AIDS virus was originally carried by chimpanzees in west African rainforests but started infecting humans in the 1940s [40]. Similarly, bats carry a high number of viruses without developing the disease due to their unique, but low-grade immune system [8]. However, the severe acute respiratory syndrome (SARS) coronavirus epidemic in 2003 probably began when humans encountered the bats. Bats have been identified as the zoonotic origin of several coronaviruses (Beyer et al., 2021).

Previously, in the early 1990s, the yellow fever outbreak in the Kerio Valley in Kenya was linked to deforestation. Subsequently, between 2016 and 2018, South America reported the highest number of yellow fever cases, and the effect was severe in the Atlantic timberland of Brazil, where the forest cover was shrunk by 7%. Later, studies reported that deforestation had concentrated howler monkeys and primates, the major host for yellow fever in Kenya and Brazil, which further made the pathogens more prevalent and aided the mosquitoes that could transmit the virus to humans [5,31]. Similarly, several studies linked Ebola outbreaks between 2004 and 2014 with deforestation and forest fragmentation [35]. In addition to the possible concentration of Ebola wildlife hosts, forest fragmentation might have aided pathogens more prevalent and aided the mosquitoes that could transmit the virus to humans [5,31]. Similarly, several studies linked Ebola outbreaks between 2004 and 2014 with deforestation and forest fragmentation [35]. In addition to the possible concentration of Ebola wildlife hosts, forest fragmentation might have aided pathogens more prevalent and aided the mosquitoes that could transmit the virus to humans [5,31]. Similarly, several studies linked Ebola outbreaks between 2004 and 2014 with deforestation and forest fragmentation [35]. In addition to the possible concentration of Ebola wildlife hosts, forest fragmentation might have aided pathogens more prevalent and aided the mosquitoes that could transmit the virus to humans [5,31]. Similarly, several studies linked Ebola outbreaks between 2004 and 2014 with deforestation and forest fragmentation [35]. In addition to the possible concentration of Ebola wildlife hosts, forest fragmentation might have aided pathogens more prevalent and aided the mosquitoes that could transmit the virus to humans [5,31]. Similarly, several studies linked Ebola outbreaks between 2004 and 2014 with deforestation and forest fragmentation [35]. In addition to the possible concentration of Ebola wildlife hosts, forest fragmentation might have aided pathogens more prevalent and aided the mosquitoes that could transmit the virus to humans [5,31]. Similarly, several studies linked Ebola outbreaks between 2004 and 2014 with deforestation and forest fragmentation [35].

Rampant deforestation and poaching of wildlife led to a decrease in the availability of the natural host of this virus, could have led them to undergo essential mutations required for inhibiting humans. Even for the current scenario of SARS-CoV-2 infection, several scientists have suggested that a natural selection mediated essential mutation might have prompted the breach in the species barrier [1]. Furthermore, wildlife poaching, illegal smuggling, and environmental stressors, including but not limited to global warming, climate change, and pollution, may have attracted the animals severely. They can become stressed, resulting in adverse and non-reversible damage to their immune systems, making them easy prey for viruses, as [26] reported. The pangolins, which are suggested intermediate hosts to SARS-CoV-2 viruses were extremely ill and presented respiratory symptoms similar to COVID-19. Furthermore, such anthropogenic activities can also increase the contact between animals and humans, increasing the opportunities for a cross-species jump [13]. Coronaviruses, being opportunistic viruses, mutate rapidly to infect newer animal hosts (natural selection mechanism) to ensure their survival, and if a substantial number of the animal host is absent, CoVs rapidly mutate to infect humans. This mechanism is reported as a possible route of human infection for SARS-CoV-2 [1].

**Conclusions**

Most zoonotic viruses bear envelopes derived from the host cell membrane and thus also bear different envelope proteins. Undoubtedly, viruses have evolved themselves too, and they vary in shapes, sizes, genetic material, host specificity, mode of infection, and life cycle. Several factors, including climate change and deforestation, play a significant role in the evolution of novel viruses, including new serotypes that could compromise the vaccination programmes and jeopardise public health. Noteworthy in this regard is the fact that anthropogenic interferences inevitably increase unwanted interaction of humans with one or many hosts harboring infectious viruses. As states earlier, human interactions for many wild and untamed animals are a cause for major stress, which alters their milieu-interieur and favours viral infection, replication and subsequently, zoonotic events. While viral transmissions among and between species is rather common in wild animals, zoonotic events have increased mainly due to unnecessary human interference of natural habitats, be it climate change, industrialization, deforestation or poaching. Therefore, information regarding role of manmade changes and their effects on the environment, natural hosts and on zoonoses is required. This would ensure in developing robust and systematic approaches to enable and enforce stricter and scientifically sound regulations with respect to wildlife protection, trade and breeding. Pre-outbreak strategies need to be strengthened if catastrophic pandemics are to be avoided by developing artificial intelligence (AI) assisted surveillance systems from complex models that incorporate a wide array of variables. While development of pre-outbreak strategies are important, it is also of equal importance to ensure sustainable development with due importance to preservation of natural resources and habitats.

**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 article.
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