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REVIEW ARTICLE

SARS-COV-2/COVID-19: scenario, epidemiology, adaptive mutations, and environmental factors

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Abstract

The coronavirus pandemic of 2019 has already exerted an enormous impact. For over a year, the worldwide pandemic has ravaged the whole globe, with approximately 250 million verified human infection cases and a mortality rate surpassing 4 million. While the genetic makeup of the related pathogen (SARS-CoV-2) was identified, many unknown facets remain a mystery, comprising the virus's origin and evolutionary trend. There were many rumors that SARS-CoV-2 was human-borne and its evolution was predicted many years ago, but scientific investigation proved them wrong and concluded that bats might be the origin of SARS-CoV-2 and pangolins act as intermediary species to transmit the virus from bats to humans. Airborne droplets were found to be the leading cause of human-to-human transmission of this virus, but later studies showed that contaminated surfaces and other environmental factors are also involved in its transmission. The evolution of different SARS-CoV-2 variants worsens the condition and has become a challenge to overcome this pandemic. The emergence of COVID-19 is still a mystery, and scientists are unable to explain the exact origin of SARS-CoV-2. This review sheds light on the possible origin of SARS-CoV-2, its transmission, and the key factors that worsen the situation.

Keywords SARS-CoV-2 · Health threat · Origin · Epidemiology · Variants · Environmental factors

Introduction

Coronavirus disease 2019 (COVID-19) has been designated a public health emergency by the World Health Organization (WHO) because of the rising threat to global health (Ciotti et al. 2020). COVID-19 was initially discovered on December 30th, 2019, as a novel virus-associated infection (Ciotti et al. 2020; Wu et al. 2020a, b, c, d, e). As a result, millions of people became infected, and hundreds of thousands of people were killed throughout the globe by this novel coronavirus (Chakraborty and Maity 2020; Danese et al. 2020). It has been confirmed that a highly contagious new coronavirus known as SARS-CoV-2 is liable for the COVID-19 pandemic (Khan et al. 2020) and causes severe acute respiratory syndromes (Anderson et al. 2020).

SARS-CoV-2 is transferred to humans via inhalation of virus-laden liquid droplets (Fig. 1), intimate interaction with a diseased individual, or SARS-CoV-2-contaminated surfaces. Clinical observations in confined spaces have suggested aerosol transmission as an additional yet important pathway (Anderson et al. 2020; Ge et al. 2020; Zhang et al. 2020a, b, c, d). Airborne transmission is a common way for

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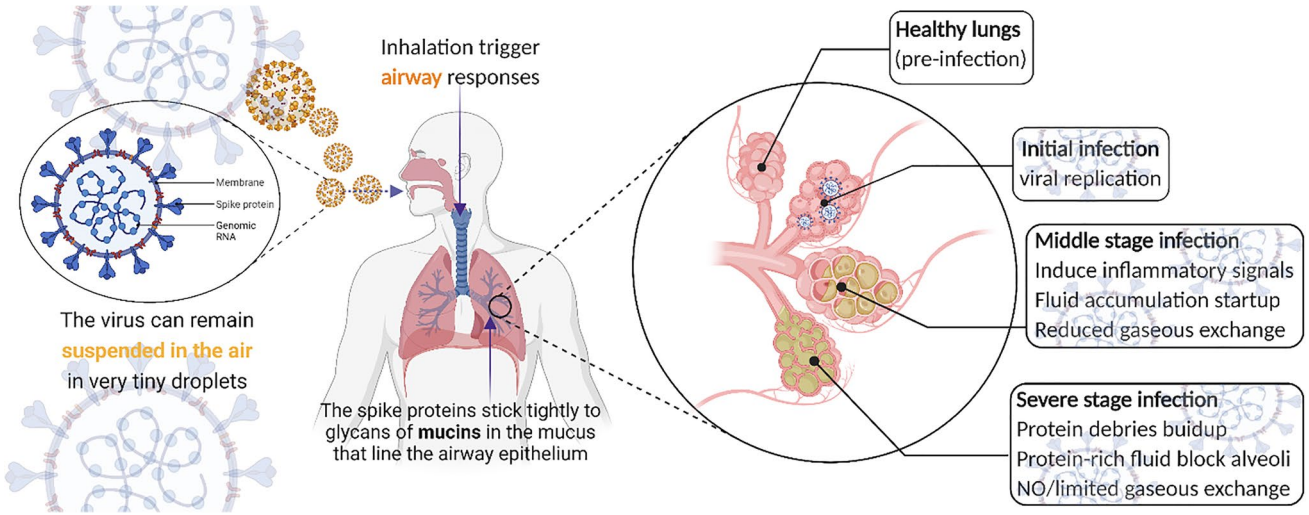

Fig. 1 SARS-CoV-2 transmission to humans via inhalation of virus-laden liquid droplets and various stages of lung damage. Created with BioRender.com and extracted under premium membership

respiratory illnesses like tuberculosis, measles, and chickenpox to spread (Tamm et al. 2015; de Vallavieille-Pope et al. 2000). Following the SARS outbreak in Hong Kong, one study found that airborne spread might have played a significant role in transmitting this disease. Because it is problematic to collect virus-containing aerosols in real-world settings and difficult to measure at low concentrations, there is a lack of SARS-CoV-2 aerodynamic characteristics and transmission pathways in aerosols (Farhangrazi et al. 2020). Of the four endemic human coronaviruses, SARS-CoV-2 has many similarities. Human coronaviruses are HCoV-OC43, HCoV-HKU1, HCoV-229E, and HCoV-NL63, all endemic in the USA and Asia (Holmes et al. 2021).

There are four structural proteins in the coronavirus virion: nucleocapsid (N), membrane (M), envelope (E), and spike (S). The S glycoprotein mediates the viral particle's entrance into the host cell, including attachment to the membrane and fusion (Lu et al. 2020a, b). The virion's membrane contains many copies of the S protein, which is assembled as a homotrimer, giving the virion its crown-like appearance. Many viruses, such as HIV-1, Ebola virus, and avian influenza viruses, have entry glycoproteins that split into two subunits—the extracellular and transmembrane subunits—in the infected cells before the virus is released (Lan et al. 2020). Some coronaviruses cleave their S protein in the infected cells into S1 and S2 subunits, whereas other coronaviruses do not. Furin, a proprotein convertase found in virus-producing cells, cleaves the S protein of SARS-CoV-2 and MERS-CoV (Hoffmann et al. 2020; Shang et al. 2020). S1 binds ACE2, and S2 fixes S protein to the membrane in a mature virion, thus having two non-covalently linked subunits on its surface. The fusion peptide and other machinery required to affect membrane fusion following infection of a new cell are included in the S2 subunit (Jackson et al. 2022).

For a virus to spread to a new species, the proteins' docking and entrance into the new host cells must be preadapted or rapidly evolved. Six amino acids in the spike protein's receptor-binding domain are essential for SARS-CoV-2's ability to attach to the host target receptor angiotensin-converting enzyme 2 (ACE2) and infect humans (Lan et al. 2020). This receptor binding site (RBD) of SARS-CoV-2 shows better efficiency at binding with human ACE2 (hACE2) than the original SARS-CoV RBD, making it easier for the virus to move into cells (Jackson et al. 2022). However, SARS-CoV-2's whole spike protein shows a comparable or lower total hACE2 binding affinity than SARS-CoV, suggesting that the SARS-CoV-2 RBD, despite its higher efficiency, becomes less accessible than the SARS-CoV RBD (Han et al. 2022). Because SARS-CoV-2 uses proprotein convertase furin to activate itself before entering target cells, it is less likely to be blocked by endosomal proteases (Jackson et al. 2022). The strong hACE2 binding affinity of the RBD, the preactivation of the spike by furin, and the presence of a hidden RBD in the spike may enable SARS-CoV-2 to enter cells efficiently while avoiding immune monitoring (Shang et al. 2020; Muus et al. 2021; Han et al. 2022).

Many studies were conducted to investigate the host reservoir of SARS-CoV-2, and bats were considered the main origin of this pandemic. Whereas these crucial spike protein residues are absent from the coronavirus collected from the horseshoe bat, RaTG13 (which has a 96% resemblance to SARS-CoV-2), they are present in the coronavirus sampled from the pangolin (Dejnirattisai et al. 2021). According to the SARS-CoV-2 genome sequence, no recent recombination

has ruled out a recombinant origin incorporating a pangolin. It is unknown what evolutionary modifications occurred before or during the human transition because of the inadequate coronavirus sampling from nature and the wide variety of animals with comparable ACE2 receptors (such as pigs, ferrets, cats, and non-human primates) (Yu et al. 2020). The emergence of COVID-19 is still a mystery, and scientists are unable to explain the exact origin of SARS-CoV-2. This review article sheds light on the possible origin of SARS-CoV-2, its transmission throughout the world (by epidemiological model and collecting data from published letters and reports), and the key factors responsible for COVID-19's transition from an epidemic to a pandemic.

Origin of SARS-CoV-2

Animals

Human coronaviruses and most other viruses are descended from zoonotic sources. This new zoonotic virus, SARS-CoV-2, has many characteristics in common with other zoonotic viruses. The ancestor of SARS-CoV-2, i.e., coronaviruses, is reported to spread disease in animals, and animals transmit that disease to humans (Fig. 2). SARS-CoV viruses belong to the beta class of coronaviruses, and animals are their host reservoirs that transmit disease to humans. It bears striking similarities to SARS-CoV, which infected people twice, first in Foshan, China (in November 2002) and again in Guangzhou (in 2003) (Meyers et al. 2005). In 2019, live raccoon dogs and civets were sold in the Wuhan markets (Xiao et al. 2021) and were well-known to be vulnerable to SARS-CoV-2 contagion (Guan et al. 2003). These SARS-CoV emergence episodes have been linked to marketplaces selling live animals (Freuling et al. 2020).

Bats are considered the natural host for SARAS-CoV-2 (Zhou et al. 2020; Zhao et al. 2020). SARS-CoV-2 and RaTG13 (found in bats) have a phylogenetic relationship of 40 to 70 years, indicating a recent divergence (Zhao et al. 2020). Such a difference may also indicate the presence of more than one intermediary host in the chain of evidence. Although that theory has not been proven yet, some researchers believe the virus may be spread through pangolins (Zhou et al. 2020; Zhang et al. 2021). There was some doubt that SARS-CoV-2 arose from coronaviruses found in pangolins, but the research showed otherwise (Zhang et al. 2021). Snakes have also been proposed as possible intermediate hosts, but this concept seems to have been ruled out (Fam et al. 2020). In general, scientists believe that the SARS-CoV-2 virus results from animal origin (Fam et al. 2020), although no evidence of this has yet been found in the wild.

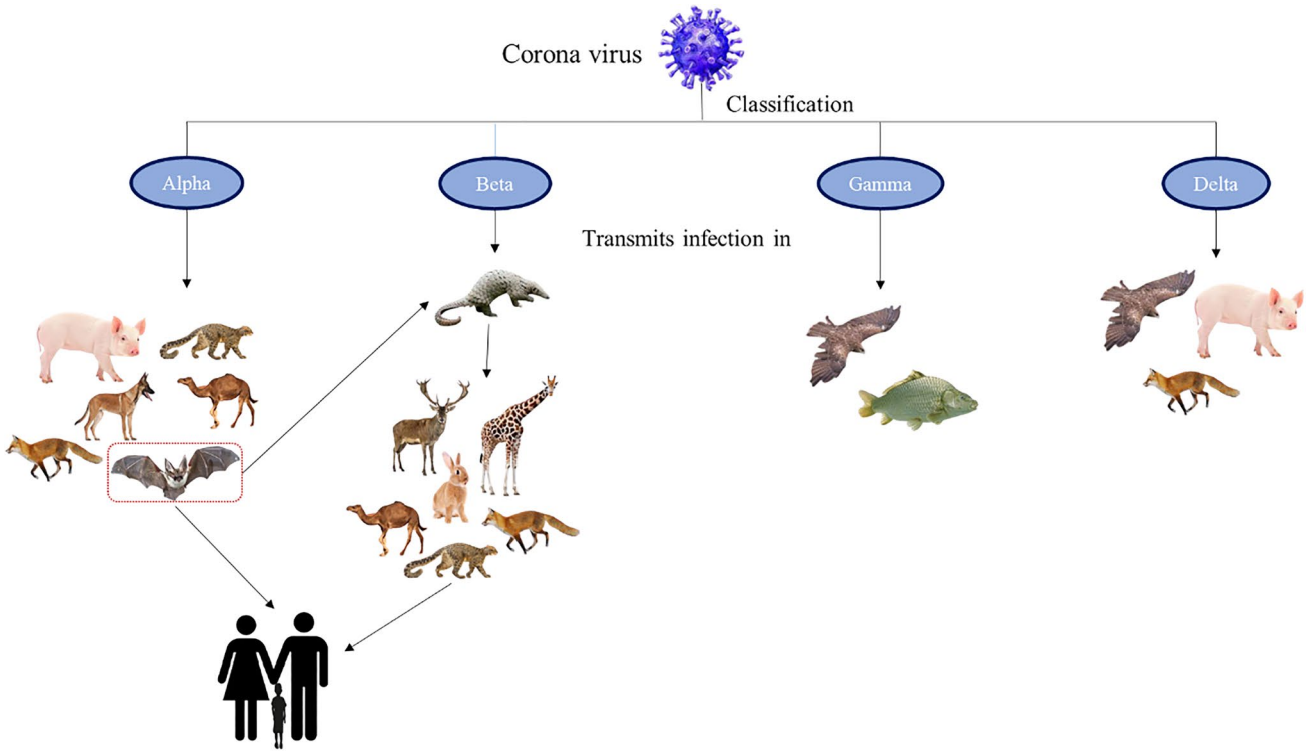

Fig. 2 Coronavirus classification and their reservoirs/host. There are 4 main classes of coronavirus (α, β, γ, δ). All four classes of viruses can infect animals, but only α- and β-class coronavirus can cause disease in humans and animals are the natural host of these viruses

Bats have drawn attention to studying their link with SARS-CoV-2 because previous SARS-CoV outbreaks emerged because of bats and serve as their natural and ancestral reservoirs (MacLean et al. 2021). Since the SARS outbreak in 2002, their mobility—gained via flying—has been recognized as a feature that may improve disease dissemination. As a result, researchers discovered more viruses in this population. A new study reveals that rats and bats, which are frequently identified as the "villains" in epidemics, are neither more nor less important as reservoirs of viruses. They have the potential to spread this virus to humans, then other species, as would be expected for the most diverse groups of mammals (Pereira et al. 2020). There is a link between greater viral transmission potential and more frequent interaction with animals, such as goats, pigs, and cattle, that humans keep (Mollentze and Streicker 2020). It is impossible to fully understand viral transmission dynamics from animals to people until we thoroughly search for viruses flowing in a larger taster group of all animal species. The following animals (bats and pangolin) are considered the origin of this disease because of the resemblance of the identified virus with SARS-CoV2. The details of this reported research work are as follows:

Bats

The COVID-19 epidemic has been accompanied by a torrent of data pointing to bats as the source. Despite this, no conclusive research to date links bats specifically to the SARS-CoV-2 virus, which resulted in the COVID-19 pandemic. Researchers started looking for a new host after sequencing the virus that causes SARS in humans (Wu et al. 2020a, b, c, d, e). As much as 96% of the SARS-CoV-2 genome is found in the genome of the coronavirus RaTG13, which was previously identified in Chinese *Rhinolophus affinis* bats (Zhou et al. 2020).

Fam et al. (2020) show that SARS-CoV-2 has evolved into a human-specific pathogen in recent years. Once a coronavirus has developed to the extent where it can traverse species barriers again, the competition to infect *Homo sapiens* and other species becomes even more ferocious, as new mutations and recombination drive the never-ending arms race between hosts and diseases. A situation like this illustrates how difficult it is for non-specialists to understand the procedure and the subject matter. This also contributes to inaccurate and hasty interpretations since diseases' transmission methods are not always fully and correctly communicated to the general population. For reasons of uncertainty or haste, bats were wrongly blamed for COVID-19 even though they had nothing to do with it. The outcomes have been disastrous for a group that already has a poor public image due to unjust stereotypes.

According to reports all across the globe, maltreatment, destruction, and ruin of bat perches and colonies have risen dramatically since the pandemic outbreak (Fenton et al. 2020; Zhao 2020). As a result of these actions, 1421 bat species that have been identified will be endangered, as well as the essential ecological services they offer (Zukal 2020). The pollination of thousands of plant species, comprising agronomic "pests" and infection trajectories for humans and viable animals, seed dispersion and territory rejuvenation, control of insect populations, and habitat regeneration are examples of such activities (Kunz et al. 2011; Ghanem and Voigt 2012).

As reported by Liu et al. (2021a, b), the SARS-CoV-2 spike protein receptor-binding domain (RBD) was found to bind to bat ACE2 (bACE2) from *Rhinolophus macrotis* (bACE2-Rm) with a lower affinity than human ACE2 (hACE2). Its infectivity to host cells expressing bACE2-Rm was revealed with pseudo-typed SARS-CoV-2 virus and SARS-CoV-2 wild virus. RBD binding manner comparable to hACE2 was found in the SARS-CoV-2 RBD with the Rm bACE2-Rm complex. The interaction network, including Y41 and E42 of bACE2-Rm, differed significantly from hACE2 based on examining binding specifics between SARS-CoV-2 RBD and bACE2-Rm. The RBD binding residues in the bACE2 receptor differed significantly across bat species, owing to their wide range of species. Since many bats are known to have the mutant allele, the bACE2-Rm binding capacity is significantly reduced, suggesting that the Y41H allele is critical to this interaction network.

Pangolin

SARS-CoV-2 has been found in bats and is transmitted to humans via the pangolin. According to reports, coronavirus infection has caused illness in pangolins, indicating that they are not a natural reservoir for the virus. However, this does not rule out the likelihood that the pangolin is helping to spread the disease to people. During the COVID-19 epidemic, researchers at Guangdong Wildlife Rescue Center in China identified a SARS-like CoV in the lung testers of 2 dead Malayan pangolins with foamy fluid in their lungs and pulmonary fibrosis. Following up on earlier studies, it was discovered that all the viral infections obtained from 2 human lung testers (lung07 and lung08) showed little similarities, varying from 80.24 to 88.93% for known SARS-CoVs (Abdelgawad 2020).

Pangolin lung samples have previously been studied by Zhang et al. (2020a, b, c, d) and contain SARS-CoV-like CoVs (2019). SARS-CoV-2-like CoV (called pangolin-CoV) was discovered in deceased Malayan pangolins, according to genomic and evolutionary data. Pangolin-CoV has 91% identity with SARS-CoV-2 and 95% identity with BatCoV RaTG13 at the whole-genome level. Only RaTG13 and

pangolin-CoV are more meticulously linked to SARS-CoV-2 than any other CoV. Pangolin-S1 CoV's protein has a significantly closer relationship to SARS-S1 CoV-2's protein than to RaTG13. RaTG13 contains four amino acid substitutions, while pangolin-CoV and SARS-CoV-2 share five essential amino acid residues interacting with human ACE2. Pangolin-CoV and RaTG13 lost the SARS-CoV-2-like supposed furin recognition sequence pattern at the S1/S2 cleavage site. This study's results also show that pangolins are a natural host for SARS-CoV-2-like CoV viruses.

Researchers found that the E proteins of coronaviruses isolated from Malayan pangolins had 99.6% amino acid identity with SARS-CoV-2, whereas the M proteins shared 98.6%, the N proteins shared 90.7%, and the S proteins shared 90.7% identity (Lau et al. 2020). There is just one non-critical amino acid difference between the receptor-binding domain of the pangolin-CoV S protein and that of SARS-CoV-2 (Zhang et al. 2020a, b, c, d). Xiao et al. (2020a, b) reported that SARS-CoV-2 was created when two viruses related to pangolin-CoV recombined with a virus associated with RaTG13 to form a new virus. One-third of the Malayan pangolins tested positive for pangolin-CoV. Clinical symptoms and histological abnormalities were seen in infected pangolins, and pangolins and circulating anti-pangolin-CoV antibodies reacted with the S protein of SARS-CoV-2. Pangolin coronaviruses are closely correlated to SARS-CoV-2, which means they may serve as intermediate hosts for the virus. If the illegal wildlife trade is not successfully regulated, this recently discovered coronavirus from pangolins—the most traded mammal—could potentially harm human health in the future.

Insects

Insects are a sustainable and innovative source of protein. Crickets, mealworms, and fly larvae are increasingly produced as food for humans or as feed for livestock. Like any other food ingredient, insects produced for food or feed must comply with the European Food Safety Authority (EFSA) regulations. Such compliance is controlled by national food safety authorities such as the Dutch Food Safety Authority (NVWA). WUR, UG, and UC scientists execute ongoing research programs on insects as a sustainable source of feed for circular agriculture and the diseases insects may contract during their production (Akhtar and Isman 2018). The virus responsible for COVID-19, SARS-CoV-2, requires living cells to replicate. The virus needs to bind to these living cells to enter the cell. The virus originates from bats and can reproduce in a limited number of mammalian species, including the pangolin and humans. Such "hosts" have receptors (ACE2) outside the cell that can bind the virus. In humans, cells high in the nostrils, lungs, and colon express an ACE2 receptor that can bind SARS-CoV-2. This ACE2 receptor is the same receptor that binds other coronaviruses, including the SARS virus that caused an epidemic in 2003 (Lange et al. 2020; Bosso et al. 2020; Zhang et al. 2020a, b, c, d).

The roles and substrate specificity of insect ACE-homologs have not been thoroughly studied, even though sufficient evidence has been discovered in many insect species on the significance of ACEs in proper growth and development. This suggests insect ACEs do not function as components of the renin-angiotensin systems seen in vertebrates since insects have an open circulatory system (Turner and Hooper 2002). Because they only have one domain, insect ACEs resemble vertebrate testicular ACEs. ACEs can be found in various insect tissues and cell types due to their widespread distribution. As a result, ACEs may have many biological roles. ACE is over-expressed in the testes of many insect species, which impacts male fertility in those species (Honda et al. 2006; Guo et al. 2017).

Insects have high ACE levels in their gut tissues, indicating that the ACE of the insect *Spodoptera littoralis* has a role in gut hormone production. Both neuropeptide processing and the neuropile areas, where ACE is found, are likely to be involved in the brain tissues of insects. The ACE transcripts in locust *Locusta migratoria hemocytes* were 10 times higher after an immune assault, suggesting that ACE is involved in cellular defense (Dicke et al. 2020).

In animals, the coronavirus first manifests itself or appears before affecting humans. Infected animals may spread these viruses to humans via direct contact with them or by eating meat or other items that have not been properly processed. For example, ticks, which may spread encephalitis, are mini-dangerous pests that killed over 150,000 people in 2015 since they are the most frequent carriers. Scientists have discovered the causal agent of encephalitis and many other viruses to persist for almost 13 years inside the tick insect shell. A tick insect can spread disease to both humans and other animals in its lengthy existence. Both viruses have the potential to spread noninvasively to new victims, perhaps infecting them repeatedly. Worldwide, more than 60 illnesses are linked to fly exposure. They infect both animals' food and skin, in addition to humans'. Additionally, dirt flies are mechanical disease vectors since their filthy bodies can transfer disease-causing bacteria to our meals, eyes, noses, mouths, and open wounds (Thyssen et al. 2015). From ancient times until the medieval ages, fleas were the primary vectors of the plague. These tiny parasites are very bouncy, allowing them to move long distances and enter almost any environment. Numerous diseases, such as helminthiasis, encephalitis, and others, can be transmitted to domestic animals and humans. Even though the Middle Ages are long gone, fleas that feed on bats could still carry the COVID-19 virus (Ismail et al. 2020).

Cockroaches are particularly hazardous due to their ugly appearance and ability to move quickly. They multiply at a breakneck pace and feast on everything in their path. In addition to leaving droppings and germs that may cause food poisoning, they are among the most infamous pests n premises. They transfer harmful microorganisms, such as bacteria, viruses, and fungus, to infected places, in addition to contaminating food (Portnoy et al. 2013). Their dirty, nocturnal lifestyles make them perfect carriers for many harmful bacteria. Cockroaches are tropical insects, and many pathogenic bacteria have been identified, including *Salmonella* spp., *Shigella* spp., and *K. pneumonia*. In addition, cockroaches have been discovered to have a variety of parasites and fungi on their exterior and interior surfaces (Kakumanu et al. 2018). Many dangerous and difficult-to-treat illnesses are spread by mosquitoes, including encephalitis, malaria, and other vector-borne diseases such as dengue fever. The virus infects approximately 200 million individuals annually across the world's most populous regions. Because of their limited lifespan, they may infect a large number of individuals with contaminated blood in their scrotums (Khah and Khoozani, 2020).

Blood-sucking arthropods like mosquitoes and lice have not been reported to transmit COVID-19 (Gomes 2020). The disease could be transmitted via contact with contaminated items and even the feces of sick individuals by cockroaches and houseflies, which are major disease mechanical vectors. Only a few instances of the live virus found in a patient's feces have been documented (Morawska and Milton, 2020). Up to 53.4% of COVID-19 patients had SARS-CoV-2 in their feces (Young et al. 2020; Tang et al. 2020a, b, c). Even though stool samples remained positive, respiratory samples from approximately 23% of patients no longer tested positive for the virus (Xiao et al. 2020a, b). In 98 COVID-19 patients, data revealed that virus shedding continued for almost 5 weeks in the stool (Wu et al. 2020a, b, c, d, e). According to another study, patients are still shedding the virus 30 days after infection. SARS-CoV-2 levels in the stool can be high in people who do not exhibit any disease symptoms (Xie et al. 2020).

However, SARS-CoV-2's capacity to survive little is understood; the virus can stay intact in the environment for days, leading to fecal–oral transmission. This study was conducted by Zhang et al. (2020a, b, c, d). In a report, 15 cockroach surface swabs were examined by nested RT-PCR for the presence of the SARS coronavirus, and nested RT-PCR obtained only one questionable positive result for the cockroach surface (Forni et al. 2017). Feces can be a significant source of COVID-19 transfer, although the function and significance of this pathway remain unknown. The virus's long-term survival in the environment means that any creature that comes into contact with or feeds on human excrement could play a part in COVID-19 transmission, even if the organism tests negative. It follows that insects' involvement in COVID-19 transmission is critical. Because these insects feed on various foods, they touch a wide range of human remains, including food, excrement, and vomit, as well as a variety of water droplets and catarrhs, and they spread these contaminants throughout their habitat and into the surrounding area. There is a good chance that insects may spread the SARS-CoV-2 virus, which could speed up an infection or extend clinical trials because of the virus's large size and prevalence in feces, droplets, and surfaces (Ismail et al. 2020). Through these investigations, it is concluded that insects also have ACE receptors, but their function is different compared to hACE receptors due to the open circulatory system. Hence, they cannot be the host reservoir for SARS-CoV2, but due to their contact with households, feces, foodstuffs, etc., they might be the carrier of virus transmission.

Laboratory escape

Accidentally laboratory escaped viruses have been reported in the literature. Examples include SARS-CoV and laboratory incidents that resulted in single illnesses or short-term transmission chains (Kirchdoerfer and Ward 2019). There have been no known laboratory escapes of viruses capable of infecting people other than the Marburg virus (Bray and Chertow 2017), and all of them have been related to long-term work in high-titer cultures (Adenowo et al. 2015; Lashley 2004). Only one human epidemic or pandemic has been recorded due to scientific activity: the A/H1N1 influenza pandemic of 1977, most likely caused by a large-scale vaccination challenge experiment (Sutton 2018). Before the COVID-19 pandemic, no epidemic was sparked by the emergence of a new virus, and there is no indication that the Wuhan Institute of Virology (WIV)—or any other laboratory—was studying SARS-CoV-2 or any other virus closely enough to serve as an antecedent before it spread. When RNA is extracted, viruses are inactivated; thus, regular viral genome sequencing deprived of cell culture at the WIV offers a minimal risk (Yan et al. 2020). There have been no reported viral samples escaping the lab after sequencing.

Known laboratory epidemics have been linked to index cases' coworkers and family members and the lab where they originated (Sallard et al. 2021; Ristanović et al. 2020). While the early instances of the COVID-19 pandemic were extensively traced, no cases have been linked to the WIV's laboratory personnel, and all employees at Dr. Shi Zhengli's laboratory were claimed to be seronegative for SARS-CoV-2 when tested in March 2020 (Koopmans et al. 2021), with the laboratory adopting proper biosafety procedures throughout their coronavirus work (Frutos et al. 2021). SARS-CoV-2 disease reports must be confirmed during high influenza

spread and other respiratory viral transmissions before they can be considered viable (Liu and Wu 2020).

Bat-derived samples are abundant at the WIV (Starr et al. 2020), and three SARS-CoVs have been successfully grown from the bat—WIV1, WIV16, and Rs4874—according to the WIV's report (Wu et al. 2020a, b, c, d, e). All three viruses are more relatable to SARS-CoV than SARS-CoV-2 (Zhou et al. 2020; Chen et al. 2020). RaTG13 has never been isolated or cultured, and the unique nucleotide sequence is derived from short sequencing reads of the WIV bat virus (Rahalkar and Bahulikar 2020). In Vero E6 cells, it was found that the SARS-CoV-2 furin cleavage site was missing during serial amplification, making it unable to culture the three fecal viral isolates (Cantuti-Castelvetri et al. 2020; Cele et al. 2021; Sasaki et al. 2021; Wong et al. 2020a, b). Using these methods; a SARS-CoV-2 progenitor virus with a completely intact furin cleavage site would be very difficult to isolate. Alternative techniques, such as developing new reverse genetics systems to spread contagious SARS-CoVs recognized in bats' sequencing records, have not been documented at the WIV. To conduct gain-of-function research, scientists will likely need a known SARS-CoV genomic mainstay or, at the very least, a virus that has already been identified via sequencing. WIV researchers have utilized a genetic mainstay (WIV1) distinct from SARS-CoV-2 in previous coronavirus recombinant research (Zhou et al. 2020), and SARS-CoV-2 shows no indication of genetic markers one would anticipate from laboratory studies (Cascella et al. 2021). The WIV (Wu et al. 2020a, b, c, d, e) has never published or researched a SARS-CoV-2-like virus, and there is no proof that the WIV sequenced a virus that is more relatable to SARS-CoV-2 than RaTG13.

One possible scenario for laboratory egress is accidental infection during serial transit of a SARS-CoV in communal laboratory animals, such as mice. SARS-CoV-2 isolates from the commencement of the epidemic could not infect mice of the wild type (Graham and Baric 2020). While the hACE2 transgenic mouse model is convenient for studying contagion in vivo and testing vaccinations, it frequently results in slight or atypical disease in the animals. There is no confirmation to support the theory that this virus was chosen for its enhanced virulence and transmissibility by passing through susceptible rodents repeatedly. Even though SARS-CoV-2 has been created (Corbett et al. 2020) and serially transmitted to mice (Hu et al. 2021), specific mutations in the spike protein, particularly N501Y, are needed for such adaption in mice (Li et al. 2021). Consider that N501Y has occurred in many human SARS-CoV-2 variants of concern, indicating that it was selected to enhance the affinity of ACE2 for the virus (Kuzmina et al. 2021). For example, mutations like N501Y are required for SARS-CoV-2 replication in an animal model. However, there is no indication that mutations like N501Y occurred early in the epidemic. Based on the low pathogenicity of frequently employed laboratory animals and the lack of genetic markers related to rodent adaptation, it is very unlikely that laboratory workers acquired SARS-CoV-2 during viral pathogenesis or gain-of-function investigations (Holmes et al. 2021).

Transmission

Epidemiological model

In order to develop predictions regarding pathogen evolution, we must consider the possibly complicated interplay between epidemiological and evolutionary dynamics. Thus, developing an appropriate model of SARS-CoV-2 epidemiology is a critical first step. According to data collected from different regions, the median duration between contagion and the commencement of symptoms is 5 days (Lauer et al. 2020). In addition, it has been shown that infectiousness begins 2.5 days before the development of symptoms, with increased spread occurring before signs. Viral loads then fall following the symptoms' start and are reduced by half within 2–4 days (Miura et al. 2021). These findings indicate that there is a non-infectious exposed stage as well as a highly infectious presymptomatic period. Once infected, people may get well on their own or develop a more serious illness with a greater death ratio. The total case mortality for symptomatic people is predicted to be 1–2% (Giordano et al. 2020). The typical duration of a death warning is about eighteen days (Verity et al. 2020). Lastly, some diseased people show no symptoms throughout the illness. Buitrago-Garcia et al. (2020) estimate that 29% of patients still show no symptoms. However, they caution that this might be an exaggeration because of publication unfairness and the need for a minimum of one person with no symptoms in most studies. In terms of the origins of novel contagions, their research indicates that presymptomatic cases account for 40–60% of new contagions, with 10% coming from people with no symptoms and the rest from those with symptoms. As they emphasize, these figures remain unclear. COVID-19 is depicted in Fig. 3 and may be employed to study the epidemiology and development of SARS-CoV-2 under a variety of realistic conditions.

Published reports

Within China

The WHO was notified on December 31 of a cluster of pneumonia in Wuhan, China, with an unclear cause (Wu et al. 2020a, b, c, d, e). A new coronavirus (SARS-CoV-2) was quickly discovered and described by Chinese officials as the outbreak's causal pathogen only days afterward (Zhou

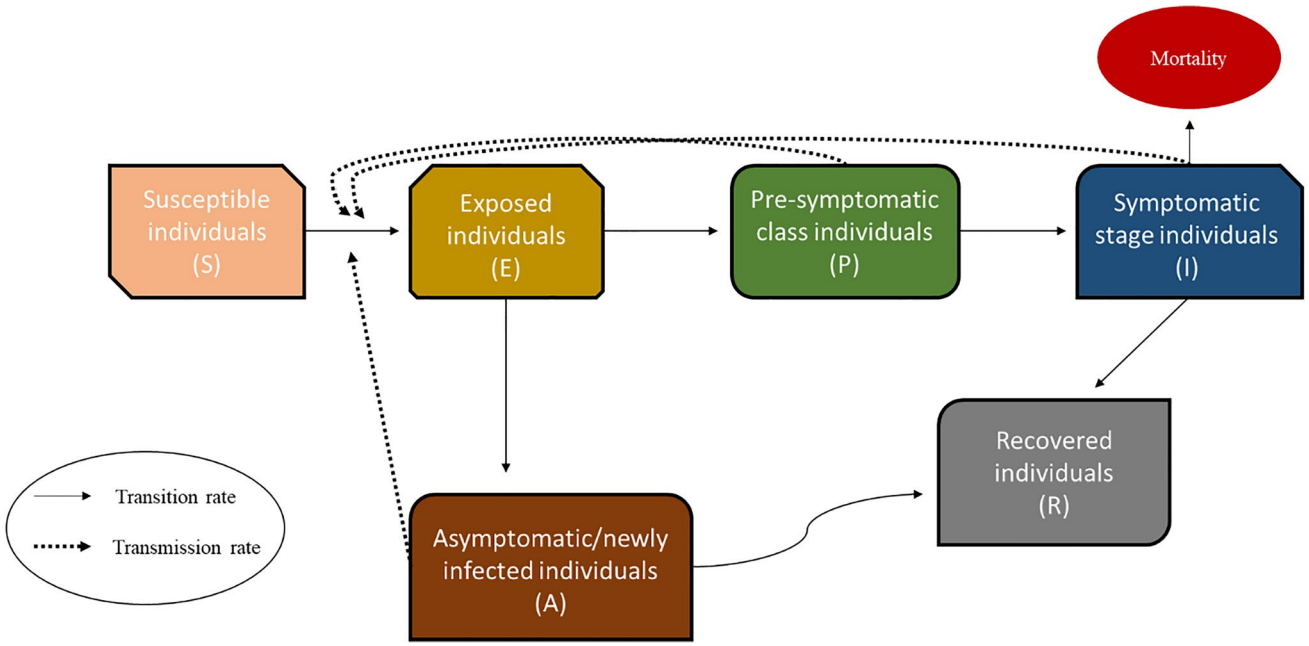

Fig. 3 A proposed epidemiological trend of SARS-CoV-2. Presymptomatic and asymptomatic stages are more contagious to the transmission of COVID-19

et al. 2020). The outbreak began with a solitary or several zoonotic transmission events at a wet market in Wuhan where wild animals and meat were sold, and by the 29th of January 2020, there had been 5997 confirmed cases in China and 68 confirmed cases in different foreign countries as a consequence of the pandemic (Riou and Althaus 2020).

Two key features influence the virus's potential to spread. In early epidemics, the basic reproduction number R0 represents the typical number of secondary cases produced by an infectious index case in a completely susceptible population. If R0 increases beyond 1, the human-to-human transmission will continue with long transmission chains. Second, the variation in the number of secondary cases across individuals reveals more about the epidemic's expected dynamics and the likelihood of superspreading occurrences (Keeling and Rohani 2011; Wu et al. 2020a, b, c, d, e; Van Doremalen et al. 2020). A limited number of primary cases could cause many secondary cases if the pathogen is not disseminated among a large number of individuals. Even though superspreading is very rare, it has the potential to cause a large-scale and rapid spread, which could have a major impact on the course of an epidemic. On the other hand, low dispersion would lead to a steadier spread of the disease, with a more homogeneous distribution of secondary cases per primary case. This significantly affects control efforts (Keeling and Rohani 2011).

The scientific community was concerned that the new coronavirus might transmit to former topographical areas comprising other nations via direct human-to-human contact, despite initial reports from Wuhan stating that there were only a few tens of cases in the cluster and no direct human-to-human spread had been detected (Yue et al. 2020). Hundreds of cases and a few household clusters have been documented since early January, when the epidemic quickly started to increase (Lai et al. 2020a, b; Tang et al. 2020a, b, c). There have been 830 instances in China as of 24 January 2020, with 549 being spotted in Hubei, 26 in Beijing, 20 in Shanghai, and 53 in Guangdong. Twenty-six people have died as a result of the epidemic (Lai et al. 2020a, b; Nishiura et al. 2020) and 13 cases have been transferred to Japan, Singapore, South Korea, Taiwan, Thailand, Vietnam, and the USA as of 22 January 2020 (Nishiura et al. 2020).

Some of the world's major and most compactly inhabited cities are in Guangdong Province and the Pearl River Delta Metropolitan Region. There are several major cities in Guangdong, comprising Guangzhou (12 million people), Shenzhen (10 million people), Dongguan (8 million people), and Foshan (8 million people). Hubei Province, where the first instances of COVID-19 were discovered, has good transit connections with the province. During the spring festival season, which began on the 10 of January 2020, the Wuhan-Guangzhou high-speed train is expected to transport between 0.1 million and 0.2 million people daily. Guangdong has the largest number of confirmed COVID-19 cases outside Hubei Province (1388) through the 19th of March 2020 (Lu et al. 2020a, b).

Following the initial reports of patients with undetected pneumonia on the 30th of December 2019, increased monitoring was implemented in all clinics in Guangdong Province. Patients with fever and respiratory symptoms and those who had traveled within 14 days after the start of their symptoms were first selected for screening and sampled for SARS-CoV-2. The first instance was discovered in Guangdong on the 1st of January and reported on the 19th of January 2020 (Ling and Leo 2020). The number of cases of COVID-19 in Guangdong increased till the beginning of February 2020 (when there were more than 100 cases per day), then decreased. In Guangzhou, no more than one locally infected case was recorded per day after the 22nd of February 2020. However, from the beginning of March 2020, there has been a rise in the number of COVID-19 instances introduced into Guangdong from other countries. A total of 102 imported cases from 19 different countries have been recorded as of the 26th of March 2020, indicating the danger of local COVID-19 emergence re-igniting in China (Lu et al. 2020a, b).

In Zhoushan, Zhejiang Province, China, Tong et al. (2020) examined a 2-family cluster of SARS-CoV-2-infected individuals in January 2020. It was determined that the illnesses were caused by interaction with a traveler from Wuhan, Hubei Province, who was already infected but had not yet shown symptoms. The Zhoushan Centers for Disease Control and Prevention Ethics Committee evaluated and approved our epidemiological study (CDC). One of the 1st two confirmed instances of SARS-CoV-2 was found in two professors from the same department at a university in Zhoushan, China, on 05 January 2020, after they attended an academic symposium organized by the university. Person W, a 45-year-old Wuhan teacher, came on 05 January for the conference and dined with people A and D on 06 January using the same serving plates as before. Person W became ill with a fever, cough, sore throat, and general malaise on 08 January after returning to Wuhan on 07 January. Based on the patient's self-report, he went to a nearby hospital and was diagnosed with COVID-19 by a Chinese CDC office. There was just one known exposure for individuals A and D to SARS-CoV-2, and that was during a feast and symposium with person W.

Wanzhou District is a 1.74-million-person Chinese city in Chongqing's municipality on Hubei Province's western border, where Wuhan is the province's capital. The COVID-19 epidemic in China, which originated in Wuhan, rapidly spread to Wanzhou, the city's entrance from Hubei Province. At the Spring Festival vacation in late January 2020, around 20,000 people came back to Wanzhou from Hubei Province. Wuhan and the surrounding regions were placed under quarantine on 23 January 2020, making Wanzhou an ideal location for epidemiological research (Shi et al. 2021).

Wanzhou recorded 183 confirmed SARS-CoV-2 instances and 1983 close interactions that were negative for the virus from 21 January to 10 April 2020. Of the 123 verified cases, 67.2% were symptomatic, and 32.8% were asymptomatic (including 5 instances not recorded in Wanzhou). Individuals with positive reverse transcriptase PCR (RT-PCR) findings who had signed before going to a hospital for the 2-week isolation period as a nearby interaction, throughout the hospital stay, or within 4 weeks after being released from the hospital were considered symptomatic cases. People with positive RT-PCR findings who had no indications before being identified and did not exhibit any signs during the isolation period and treatment, as well as for 4 weeks following release from the hospital, were considered asymptomatic cases since they did not show any symptoms. Nearby associates who were negative for SARS-CoV-2 had contact with the patients but were not infected with it themselves. People who had intimate contact with an infected person were infected, whether ill or not. Unconfirmed instances from Wuhan with no RT–PCR findings were removed from the study, but close connections between those patients were included. About 67.2% and 32.8% of patients were symptomatic and asymptomatic, respectively. Of the overall transmissions documented, 75.9% were asymptomatic or presymptomatic transmissions (Shi et al. 2021).

It is the 14th of January 2020, and a 56-year-old Chinese guy (the index patient) is flying from Guangzhou to Xuzhou, China, where he shows no symptoms after 6 h of transfer at Wuhan's Hankou Station (China). From the 14th to the 22nd of January, he was in close contact with his two daughters, a pregnant 32-year-old teacher (patient 1) and a 21-year-old undergraduate (patient 2). His 42-year-old son-in-law (patient 3, the spouse of patient 1) was admitted to the Affiliated Hospital of Xuzhou Medical University in Xuzhou on 15 January and was discharged on 23 January. As well, during the weeks of 2–19 January, patient 4 (a 62-year-old male) was in the hospital recovering after pancreatic surgery in the same ward as patient 3 (a 34-year-old woman) (patient 5). Patients 4 and 5 were in close contact with the index patient from 15 to 18 January, when he was asymptomatic. He was sent home on 19 January and kept in touch with his 56-year-old wife for the rest of the month (patient 6) (Li et al. 2020).

Xuzhou Medical University's Affiliated Hospital admitted the index patient with fever, cough, and sore throat symptoms on 25 January. Testing revealed that the patient had COVID-19. His condition deteriorated quickly; he had a rapid respiratory rate of 38 breaths/min and a low saturation level on the oximeter of 93%. From January 26 to 31, six more members of the two households tested positive for SARS-CoV-2 using real-time fluorescence reverse transcription PCR on throat swab samples. These individuals'

medical situations were all unique in some respects (Li et al. 2020).

This cohort research studied a community COVID-19 epidemic in Zhejiang province. On 19 January 2020, 128 people traveled 100 min round trip on two buses to attend a 150-min worship service (60 [46.9%] on bus 1 and 68 [53.1%] on bus 2). A passenger on bus 2 provided the source patient. On the one hand, we looked at the risks of SARS-CoV-2 infection in those who took bus 1 or bus 2 ($n = 60$ (source patient omitted)); on the other hand, we looked at the risks in people who attended the worship service in general ($n = 172$). To compare COVID-19 risk, we separated the exposed bus seats into high- and low-possibility areas, depending on the patient's distance. The central air conditioners on both buses were set to indoor recirculation (Shen et al. 2020).

Other countries

The genetic sequence of a virus can tell us a lot about whether or not two different viruses, separated in time and location, are epidemiologically connected. Early SARS-CoV-2 epidemics in North America differed in timing, geographical origins, and transmission patterns, according to genomic data from Washington State (Worobey et al. 2020; Bedford et al. 2020), the East Coast (Fauver et al. 2020; Gonzalez-Reiche et al. 2020), California (Deng et al. 2020), and British Columbia (BC), Canada (Worobey et al. 2020; Moreno 2021). Virus strain ("WA1") identified in Washington state was firstly reported in a tourist returning from Wuhan, China, on 15 January 2020, and seemed to be 1st reported case in the USA (Holshue et al. 2020a, b; Worobey et al. 2020). Following the discovery of genetically identical viruses to WA1 in Washington, Connecticut, California, British Columbia, and elsewhere, it was speculated that WA1 might have begun a cryptic transmission chain on 15 January and remained undiscovered for many weeks. This introduction may predate other known SARS-CoV-2 communal spread networks elsewhere on the continent, making Seattle the hub of the North American pandemic if it is accurate (Worobey et al. 2020).

According to Holshue et al. (2020a, b), the 1st instance of SARS-CoV-2 infection was discovered in the USA in January of that year, and reports of community transmission quickly followed (Spellberg et al. 2020). The coronavirus disease 2019 (COVID-19) pandemic continues to have a substantial influence on the USA, with more than 9 million illnesses and 230,000 fatalities being recorded as of 01 November 2020 (Christie et al. 2021). Thus, SARS-CoV-2 infections are being underreported due to limited testing options and mild and asymptomatic illnesses (Yousaf et al. 2020). Therefore, seroprevalence studies are critical for improving estimates of infection and transmission (Havers et al. 2020).

Between 27 July and 24 September 2020, Bajema et al. (2021) collected leftover patient sera from samples for monotonous screening (e.g., cholesterol, thyroid) or clinical management in 50 US states, Washington DC, and Puerto Rico and examined them in two commercial labs (laboratory A and laboratory B). Laboratory A gathered samples from seven states (Arizona, Indiana, Maryland, Pennsylvania, New Jersey, New York, and Virginia), while laboratory B, which had previously participated in a CDC-led seroprevalence study, supplied residual sera from 45 other states. SARS-CoV-2 antibodies were detected using chemiluminescent immunoassays, and de-identified data on patient age, sex, condition, and specimen collection date were submitted to the CDC.

Of the 177,919 serum samples analyzed, 103,771 (58.3%) came from women, 26,716 (15.0%) from people 17 years old or younger, 47,513 (26.7%) from people 65 years old or older, and 26,290 (14.8%) came from people living outside of major urban areas. The seroprevalence at the jurisdictional level varied from less than 1% to 23% throughout four collecting periods. Fewer than 10% of individuals developed detectable SARS-CoV-2 antibodies in 42 out of 49 countries with enough data to assess seroprevalence over time. Prevalence estimates vary by gender, age group, and metropolitan/nonmetropolitan location. Seroprevalence estimates in all jurisdictions show that the changes from period 1 to period 4 were less than 7 percentage points, and they varied by location. According to the results of this cross-sectional research, most people in the USA did not have prior serologic evidence of SARS-CoV-2 infection as of September 2020, but prevalence varied greatly depending on the jurisdiction.

On 23 January 2020, a tourist from Wuhan brought SARS-CoV-2 into Singapore for the first time. COVID-19 has been detected among additional tourists and returning passengers, with some local transmission occurring (Wong et al. 2020a, b). The Singapore Ministry of Health issued a health warning on 02 January 2020, after the initial reports of an unusual pneumonia epidemic in Wuhan, China, recommending that patients with pneumonia and contemporary tourism to Hubei Province be tested for SARS-CoV-2 infection. All patients with probable SARS-CoV-2 infection were quarantined using airborne and connection safeguards.

Twenty-eight SARS-CoV-2-infected individuals were identified in Singapore between 23 January and 03 February 2020, with symptoms appearing between 14 and 30 January 2020, according to a study by Young et al. (2020). All patients had visited Wuhan, China, during the previous 14 days before becoming sick. Contact tracing method found four patients (22%), while border screening identified three (17%). There were 18 patients, with 16 (89%) Chinese and 2 (11%) Singaporeans. There were five groups of close

people: family members, friends, or coworkers. Eighteen patients traced their contact information, resulting in 264 close Singaporean connections. On 25 February 2020, no illnesses were found in health care professionals who had treated COVID-19 patients.

Over 300,000 people died, and over 13 million people were infected in Brazil during the COVID-19 epidemic, according to official figures as of March 2021. The state of Amazonas in northern Brazil has been the most severely impacted due to SARS-CoV-2 infection and illness burden varying greatly across the country (Menezes et al. 2021). By October 2020, serological monitoring of blood donors in Manaus, Amazonas' capital and the region's biggest city, suggests cumulative attack rates of > 67% (Buss et al. 2021). Many other towns and cities in the surrounding area have similar but slightly lower seroprevalences. As a result, the city's health care system has been under considerable strain since late 2020 and early 2021 as an outcome of a prompt resurgence of SARS-CoV-2 transmission and mortality (Fongaro et al. 2021).

Despite previously high infection levels, cases of SARS-CoV-2 infection resurfaced in Manaus, Brazil, by the end of 2020. According to genome sequencing of viruses collected during that time, a new SARS-CoV-2 variant has appeared and is circulating in Manaus, Brazil, between November 2020 and January 2021. A trio of spike protein mutations (K417T, E484K, and N501Y) found to be correlated with increased binding to the human ACE2 receptor was acquired by lineage P.1, which included 17 mutations. The emergence of P.1 was predated by a period of accelerated molecular evolution, according to a Molecular Clock analysis conducted in the middle of November 2020. Based on genomic and mortality data, we anticipate that P.1 could be 1.7 to 2.4 times more transmissible than non-P.1 and that prior infection with non-P.1 offers 54 to 79% protection against P.1 infection. Improved worldwide genomic monitoring of potentially more transmissible and immune-evading variations is essential for speeding up the response to a pandemic (Faria et al. 2021).

The first Austrian case was found in Kühtai, Tyrol, on 24 and 26 January 2020, in a person exposed to the virus by a Chinese teacher in Starnberg, Germany, on 20 and 22 January. Since her diagnosis was fully confirmed on 28 January in Munich (Germany), this qualifies as a German case. Two instances were diagnosed in Innsbruck on February 25th, imported from Italy, but no further cases were found in Austria. On the 27th of February, three illnesses among Austrian citizens were discovered in Vienna. There were 6 instances in the first cluster (from an unknown source) and 61 instances in the second cluster (from a recognized source). The latter cluster was most likely spawned in Italy. After returning from a voyage ship tour of Italy, a 69-year-old Viennese man was identified with COVID-19 and died on 12 March in a Vienna hospital. On the 6th of March, the Tyrol reported three locally acquired cases, all linked to the ski resort of Ischgl. In Ischgl, 11 of the 14 Islandic COVID-19 cases had returned to Iceland by the 29th of February (Kreidl et al. 2020).

The SARS-CoV-2 infection killed a Vo', Italy resident on the 21st of February 2020, after developing pneumonia due to severe acute respiratory syndrome coronavirus exposure. As far as we know, this is the first fatality in Italy linked to COVID-19 since the SARS-CoV-2 outbreak in Wuhan, China. Local officials retaliated by placing the whole municipality under a 14-day lockdown. Later, during the two surveys, we obtained nasopharyngeal swabs from 2812 and 2343 study participants, respectively, representing 85.9% and 71.5% of the eligible study population. Age-specific percentages ranged from 57.1% to 95.4% in the first poll and 40.1% to 80.4% in the second poll, with a homogenous sample of all age groups. Surprisingly, the initial poll showed a 2.3%t (95% confidence interval (CI): 1.2–2.4%) of the 2812 people who tested positive for syphilis. According to the second survey, a total of 29 people tested positive (prevalence: 1.2%; 95% confidence interval: 0.8–1.8%), 8 of which were new cases (prevalence: 0.3%; 95% confidence interval: 0.15–0.7%) (Lavezzo et al. 2020).

To detect imported cases early and avoid secondary transmission, enhanced COVID-19 monitoring was introduced in France on the 10th of January 2020. To put things in perspective, the NRC at Institute Pasteur in Paris discovered Europe's first instance of the virus, which was later confirmed by the WHO. SARS-CoV-2 infections were initially identified at the NRC-associated laboratory in Lyon and subsequently at first-line hospital labs throughout France, with the Institute Pasteur's NRC concentrating on northern France, particularly Paris, which has a high density of people. Those who had symptoms (fever and respiratory difficulties) or had been to high-risk regions for infection were given special attention during screening and sampling for SARS-CoV 2. Asymptomatic infection or a mild illness was among the many possible clinical manifestations of COVID-19 infection as the virus propagated across the population (Stoecklin et al. 2020).

From 15 January to 04 April 2020, Furuse et al. (2020) examined clusters of COVID-19 patients and suspected primary cases in Japan. Some groups had more than 100 cases and were associated with healthcare and care institutions such as hospitals and nursing homes. Local transmission and an increase in the pandemic occurred after the second wave of imported COVID-19 cases hit Japan. Notably, clusters of COVID-19 cases in hospitals and care institutions predominated in epidemiologic weeks 11 (9–15 March) and 14 (30 March–04 April), which resembled around 3 weeks after the 2 waves of imported instances. A healthcare facility could be near the end of the native spread chain since clusters at these

institutions only appeared after community transmission had already been ongoing for many weeks.

Several COVID-19 clusters have been linked to events, such as singing at karaoke night festivities, encouraging clubs, conversing in pubs, and working out in gyms that involve deep breathing. According to other research, these activities may contribute to the spread of illness in communities. Japanese officials from the Prime Minister's Office and the Ministry of Health, Labor, and Welfare warned the public about three circumstances that might upsurge their risk of contracting COVID-19. They recommended that they avoid the "Three Cs": poorly ventilated enclosed spaces, crowded public places, and close-contact settings (Furuse et al. 2020).

A 68-year-old male with a severe acute respiratory infection (SARI), chills, and dyspnea was admitted to hospital A in Qom (Iran) on 12 February 2020. Iran's National Influenza Center (NIC) at the School of Public Health, Tehran University of Medical Sciences, took his throat swab sample on 15 February and submitted it to the center for influenza testing. It turned out he did not have influenza. His health worsened, and he passed away from respiratory failure on the 16th of February, 5 days after his symptoms appeared. On 18 February, the National Institutes of Health (NIC) detected SARS-CoV-2 in his sample, and on 19 February. On 07 February 2020, patient 2 (a 75-year-old male with SARI, chills, and dyspnea) became sick and was hospitalized. He died on 16 February due to a negative influenza virus test in NIC on a throat swab sample. As soon as the initial identification of SARS-CoV-2 was made on 18 February by the National Institutes of Health (NIC), the same test was run on his sample, and it came out positive for SARS-CoV-2 on 19 February. Samples were taken from all suspected patients hospitalized in Qom after the first SARS-CoV-2 cases were discovered on 19 February; five (5/16) tested positive for SARS-CoV-2 (Yavarian et al. 2020).

The Indian government published details on the first SARS-CoV-2 patient in Kerala, India, diagnosed in January 2020. The documented patient returned from China and infected everyone who had unprotected contact with them. SARS-CoV-2 cases with no symptoms have been recorded in significant numbers, making the possibility that asymptomatic patients remained unnoticed all but implausible. There is a wide variance in the number of people impacted throughout India, with Maharashtra reporting the most and Mizoram reporting the least (Gautam and Hens 2020).

According to Pakistan's Ministry of Health, there were 1179 instances of COVID-19 throughout the country as of 26 March 2020. Sindh had the most cases at 421, Punjab at 394, Khyber Pakhtunkhwa at 131, Gilgit-Baltistan at 84, Azad Jammu, and Kashmir at 25. Throughout the initial periods of the epidemic, most SARS-CoV-2 infections in Pakistan were linked to travel. Local viral transmissions are, however, on the rise. COVID-19 has been linked to the deaths of nine people as of the 26th of March 2020. The case fatality rate is 0.8%, lower than China, Italy, the USA, and Iran combined. According to epidemiological research using the Susceptible-Infected-Recovered (SIR) model, almost 90 million people will get infected in the next several days, with 5% of those cases necessitating the use of medical facilities (Raza et al. 2020).

Why is COVID-19 still a global health threat?

Mutations/Adaptations

The emergence of different mutated variants of SARS-CoV-2 worsened the situation and hindered the development of an effective vaccine. The phylogenetic divergence of a disease can reveal information about its past. The phylogeny of the SARS-CoV-2 virus in humans (Mavian et al. 2020) shows a star-like structure with numerous long-tip branches, which is anticipated in an expanding population. It is predicted that the substitution rate is 0.00084 per year based on genomic sampling throughout time (Day et al. 2020), which is 2 to 6 times lower than the substitution rate for influenza (Bedford et al. 2015). A genetic mutation occurs approximately every other week in SARS-30,000-basepair CoV-2's genome. Our ability to evaluate genetic variations quickly during an epidemic is made possible by genomic tracking technologies such as Nextstrain (Hadfield et al. 2018). As of 16 May 2020, there were 5380 genomes available for analysis. Nonsynonymous amino acid substitutions affect viral protein composition.

SARS-CoV-2 exhibits considerable genetic diversity. However, it is not apparent if these variations have any functional relevance. In many cases, the virus does not affect them (Tang et al. 2020a, b, c), and their numbers have increased due to the virus spreading to new vulnerable hosts. Mutations with no functional relevance vary in frequency, like genetic fingerprints, allowing researchers to monitor the viral geographic distribution and reconstruct epidemiological patterns. Long-term genetic studies across more distantly related coronavirus lineages show that detrimental mutations are anticipated to be eliminated (Boni et al. 2020). On the other hand, even harmful mutations may increase in huge numbers during an epidemic if their effective reproduction number is greater than one. The question of whether human nonsynonymous modifications enhance viral fitness is more contentious. The following data summarize the findings of four major research studies on possible adaptive SARS-CoV-2 mutations, along with warnings regarding their potential dangers.

Adaptive mutations in SARS-CoV-2

Scientists began looking for signs of adaptation to humans in the SARS-CoV-2 genomes only a few weeks after the first reports of a new respiratory disease arose from Wuhan, China, in December 2019. According to one of the first investigations, there were two strains of SARS-CoV-2 circulating in Wuhan (strains "L" and "S"), with the L being more "aggressive" (Guo et al. 2020). COVID-19 could become more severe as a consequence of evolutionary change, according to this assertion, which was extensively reported in the media. This conclusion was made only based on frequency data for the two variants, and random mutations can thoroughly explain the frequency data on the basal branches of a star-like phylogeny for a rapid dispersal disease (Kucharski et al. 2020). The original writers subsequently accepted this more frugal explanation (Tang et al. 2020a, b, c).

Korber et al. (2020) discovered that the non-synonymous mutation D614G in the spike gene has increased frequency in numerous nation-states. Normally, this pattern would be anticipated if the mutation was beneficial, but neutral sampling mechanisms can also explain it. A corresponding enhancement in the rate of mutations across states is expected even without selection if travelers first transmit novel disease epidemics from a geographical location with a low mutant rate (for example, China), trailed by travelers from a locality where the mutation is (by chance) at a high rate (such as Italy). This impartial explanation must be evaluated for plausibility before conclusions are drawn. Hospitalization rates were also examined by Korber et al. (2020), but the only viral load was related to genotype. Even then, variables like days from the start of symptoms (a key predictor of viral load) were not controlled and could have altered over time as more testing became available. Numerous organizations are presently studying the effect of D614G on SARS-CoV-2 at both the functional and epidemiological levels, and this will provide information on the particular significance of this mutation (He et al. 2020).

A 382-nucleotide loss in ORF8 has also been reported in Singapore's COVID-19 patients, which has attracted media attention. A comparable deletion was identified in several coronaviruses, including SARS variants that emerged during the 2003–2004 epidemic, despite the lack of clear evidence that this deletion was positively selected (Cui et al. 2019). Studies in cell culture showed that a previous SARS deletion slowed viral multiplication (Muth et al. 2018). The recurrence of these deletions is interesting, but more research is required to determine whether or not they are associated with illness outcomes or transmission rates.

A total of 31 mutations found in the SARS-CoV-2 genome, including the previously reported D614G mutation, were examined via sister clade comparisons by van Dorp et al. (2020). As a consequence of their findings, they conclude that little evidence exists for favorably chosen alleles since most mutations are located in clades linked with decreased transmission. On the other hand, sister clade comparisons lack sway and are skewed against identifying derived characteristics that help a lineage advance in the evolutionary process.

In mid-November 2021, a new SARS-CoV-2 strain (OMICRON) was discovered in Gauteng, South Africa. The sophisticated genome sequencing infrastructure in South Africa allows for the early discovery and reporting of novel variations to the rest of the globe. As of December 15, 2021, OMICRON instances have been reported in 77 nations, most occurring in the UK, South Africa, and the USA. OMICRON-positive instances have been reported in India as well. The first mortality caused by the novel COVID-19 strain was reported in the UK (Thakur and Kanta Ratho 2021). According to Wei et al. (2021), Omicron has gained 45 point mutations since diverging from the B.1.1 lineage. There was a more positive selection on the Omicron spike protein sequence than on any previously documented SARS-CoV-2 variants that have evolved in human hosts, suggesting a chance of host-jumping. There were considerable differences in the molecular spectrum (the relative frequency of the 12 base substitutions) gained by Omicron's ancestor from viruses developed in human patients, but they were similar to the spectra associated with viral development in mouse cells. Omicron spike protein changes coincided considerably with SARS-CoV-2 alterations, which are well-known for facilitating virus adaption to mouse hosts, notably via increased spike protein binding affinity to the mouse cell entry receptor. These findings imply that Omicron's progenitor crossed from humans to mice, collected mutations favorable to infection, and then leapt back into humans, demonstrating an inter-species evolutionary trajectory. Table 1 presents different variants of SARS-CoV-2.

Environmental factors

Researchers from the University of Pennsylvania discovered that absolute humidity (measured as the amount of water in the ambient air) and temperature were important environmental variables for the transmission of certain viral infections, in addition to inhabitant mobility and human-to-human interaction (Shaman et al. 2011). Influenza viruses, for example, are more likely to spread if they are exposed to cold, dry air or droplets. According to a recent study on COVID-19, high temperatures might have contributed to increased transmission in 122 Chinese cities, and there was no evidence to support the prediction that COVID-19 instance tallies would reduce as temperatures increase (Xie and Zhu 2020). Therefore, the genetic variations between SARS-CoV-2 strains collected from different regions may

Table 1 Different variants of SARS-CoV-2

Variants	Origin (country)	Reported date	Mutation	Position of mutation	Reference
B.1.1.7 (VOC-202012/01)	UK	14 December 2020	23 mutations with 17 amino acid changes	N501Y	Abdool Karim and de Oliveira (2021)
P.1 (B.1.1.28.1)	Brazil	12 January 2021	Approximately 35 mutations with 17 amino acid changes	N501Y, K417N/T, and E484K	Abdool Karim and de Oliveira (2021)
P.2	Brazil		Spike protein mutations	E484K	Annavajhala et al. (2021)
P3	Philippines		Spike protein mutations	E484K mutation	Liu et al. (2021a, b)
501Y.V2 (B.1.351)	South Africa	18 December 2020	23 mutations with 17 amino acid changes	N501Y, K417N/T, and E484K	Abdool Karim and de Oliveira (2021)
B.1.427	Southern California	20 January 2021	3 spike mutations	S13I, W152C, and L452R	Webb et al. (2021)
B.1.429 (CAL.20C or 452R.V1)	California	20 January 2021	3 spike mutations	L452R (receptor binding motif), W152C (N-terminal domain)	Shen et al. (2021)
B.1.525	Nigeria	Mid-December 2020		E484K mutation	Pereira et al. (2021)
B.1.526	New York		Spike protein mutations	L5F, T95I, D253G, E484K, D614G, and A701V	Annavajhala et al. (2021)
B.1.617.1 (Kappa)	India		Spike protein mutation	L452R and E484Q	Wilhelm et al. (2021)
B.1.617.2 (Delta variant)	India	May 2021	Spike protein mutations	E484K, E484Q, and L425R mutations	Alizon et al. (2021)
B.1.618	India, UK, Pakistan, and Ireland		Spike mutations	Tyr145 and His146 (N-terminal domain)	Khan et al. (2021)
B.1.1.529 (Omicron)	South Africa	Mid-November 2021	30 spike protein mutations and 15 RBD mutations	Spike deletions (H69 –, V70 –, G142 –, V143, Y144 –, N211) Spike substitutions (A67V, T95I, Y145D, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, and L981F) ORF1a (NSP6) mutations are K856R, S2083 –, L2084I, A2710T, T3255I, P3395H, L3674 –, S3675 –, G3676 –, and I3758V	Thakur and Kanta Ratho (2021)

be traced back to the countries where they were first discovered. This fast-evolving virus can quickly adapt to a variety of different environments. This new coronavirus's fast proliferation is a global health issue, and climate change may impact how quickly it spreads. COVID-19 transmission may be influenced by environmental conditions, with dry and cold temperatures increasing the likelihood of the virus spreading (Su et al. 2016).

Another study, however, discovered that when data from 429 cities around the world were analyzed, the greater transmission was seen in colder locations, indicating that temperature may affect COVID-19 transmission (Wang et al. 2020). A third study showed that the virus thrived in warm, dry conditions (Bu et al. 2020), whereas a fourth found that transmission decreased as spring and summer arrived (Oliveiros et al. 2020). Quantifying the link between COVID-19 transmission and meteorological factors is difficult, as described in a recent article (Cohen et al. 2020). First, analyzing the time course of COVID-19 transmission using information collected by a variety of public health organizations may give wildly divergent results about the timing of the epidemic. Estimating Rt using report dates rather than start dates will always lead to substantially different findings, as would utilizing instantaneous transmission rates rather than delayed reporting dates to estimate Rt. Third, the choice of techniques to calculate Rt, such as Cori's approach or Wallinga and Teunis' method, will lead to temporal changes that complicate the establishment of causal links between weather and transmission (Pan et al. 2020). Since then, non-pharmaceutical efforts in China to control COVID-19 have substantially decreased illness duration and outdoor transmission throughout the state. This may have overshadowed the environmental effect of transmission. The last consideration is that comparing weather and transmission connections from one place to another may be complicated by variations in reporting methods between regions (Lai et al. 2020a, b).

Kifer et al. (2021) argued that environmental variables have a vital influence on patients who have already been infected. This winter's COVID-19 severity and mortality are likely to worsen, as seen by the decline in seriousness with the arrival of spring. Patients in the early stages of illness may benefit from humidified air since many hospitals have dry air in the winter. The fast-spreading COVID-19 pandemic necessitates the promotion of active nasal hygiene and hydration and the humidification of dry air in all warm environments. This is because our mucosal barrier suffers, and a mucosal barrier is our first line of defense against infection (Principi and Esposito 2017). Because air-conditioning is an efficient dehumidifier, it is important to monitor humidity levels in cooled buildings with restricted access to fresh air. Basray et al. (2021) found that COVID-19 incidence was positively correlated with all temperature ranges (maximum, lowest, and average) and negatively correlated with humidity, DTR, and rainfall. There was a positive correlation between COVID-19 mortality rates and temperature and a negative correlation with humidity. For every unit increase in humidity, COVID-19 cases decreased by 3.345 per day, whereas in Karachi, the number of cases increased by 10.104 per day. In Gilgit-Baltistan, there was a considerable rise in daily cases of 0.534 and 1.286 for every unit increase in average temperature and rainfall.

Conclusion and future perspectives

The World Health Organization has confirmed a pandemic due to the fast global extent of the severe acute respiratory syndrome coronavirus 2. SARS-CoV-2 is spread through respiratory droplets produced by infected individuals when they cough or sneeze. The exact origin of SARS-CoV-2 is still unknown, and studies are being conducted to investigate its source of origin. Many people believe this pandemic is a hoax because the spread of such a disease was predicted in novels, movies, and cartoon shows. Later, however, scientific studies proved that SARS-CoV-2 is not a laboratory escape virus, confirming these rumors to be just a myth. Until now, scientific studies have shown that bats are the source of SARS-CoV-2 and pangolins are an intermediary source for transferring SARS-CoV-2 from bats to humans. The evolution of its various mutant variants and environmental factors (like temperature, humidity, etc.) worsen the condition and become a challenge to overcome this disease. This pandemic has shown both the critical nature of national efforts and the world's interconnectivity and the critical nature of global collaboration for pandemic containment. International health officials must remain alert about SARS-CoV-2's trajectory while also evaluating the tactics and approaches employed during the epidemic to create more effective structures and procedures to guarantee a more prosperous and equitable response in the future.

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