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Review Article

COVID-19 is a natural infectious disease

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Contents

1. Abstract	38
2. Accidental infectious disease outbreak	38
3. Deliberate infectious disease outbreak	39
4. So-called man-made virus	39
5. Real (cultured) virus versus putative (sequence only) virus	39
6. Genetically modified virus	39
7. SARS-CoV-2 is not a genetically modified virus	39
8. It is impossible that RaTG13 was used to generate SARS-CoV-2 as only the genome sequence of RaTG13 is available not the cultured virus	40
9. Behavior of the furin site varies among SARS-CoV-2 and pseudovirus RaTG13 S+PRRA	40
10. The first sites of detection and emergence for emerging pathogens	40
11. Possible animal origin of SARS-CoV-2	40
11.1. Bats	40
11.2. Marine animals	40
11.3. Mustelidae and other wild animals	40
11.4. Animals residing within glaciers, deep sea regions, polar regions, and plateaus	41
Declaration of Competing Interest	41
References	41

1. Abstract

Coronavirus disease 2019 is an infectious disease that has emerged naturally, not accidentally or deliberately. Similarly, Severe acute respiratory syndrome coronavirus 2 is not a man-made or genetically modified virus. Reverse genetic technology can only be used to produce infectious clones of a known virus. Phylogenetically, the RaTG13 genome sequence recovered from bats is the most closely related viral sequence to SARS-CoV-2; however, the corresponding RaTG13 virus is yet to be isolated or cultured in a laboratory. Therefore, the so-called bat coronavirus RaTG13 could not have been used as a starting strain or “backbone” for genetic modification. Furthermore, it would be impossible to generate SARS-CoV-2 by inserting the furin cleavage site into the bat coronavirus RaTG13. It is critical for the prevention and control of SARS-CoV-2 to investigate the animal reservoirs of SARS-CoV-2, and this work is ongoing.

From the prospective of biosafety and biosecurity, outbreaks of infectious diseases can be classified into three types: natural, accidental, and deliberate.^{1,2} There is a large body of evidence that COVID-19 is caused by a natural virus. It has no characteristics of an accidental or deliberate infection.³

2. Accidental infectious disease outbreak

An accidental infectious disease outbreak is defined as an outbreak caused by accidental exposure to a pathogen due to an inappropriate operation or management. It mainly includes the following cases: 1) pathogen leakage caused by the accidental breakage of a tube containing the pathogen; 2) laboratory infection caused by a sharp injury from a pathogen-contaminated tool; 3) infection caused by pathogen contamination in the laboratory or office environment; 4) laboratory and related personnel infection caused by pathogen exposure due to a relatively large-scale acci-

dent in a microorganism research or production unit. Accidental infections with Ebola virus, Bunya virus, *Yersinia pestis*, *Vibrio cholerae*, SARS-CoV, and other deadly pathogens have been reported within laboratories designated a high biological safety level in the USA, England, Germany, the former Soviet Union, and Singapore.^{4–10}

An accidental infectious disease typically meets the following three criteria: (1) storage and use of the causative pathogen by the laboratory before the accident, (2) a history of inappropriate handling by the laboratory personnel or a history of accidents (such as personal injury caused by pathogen-contaminated tools), and (3) genome level identity between the strain of pathogen isolated from both the patients and the laboratory or other unit where the pathogen is stored or cultured.¹¹

In recent decades, there have been a number of accidental infectious disease outbreaks due to pathogen exposure in laboratories worldwide.^{5,7,12–15} Leakage from a military bioweapons factory (Military Compound 19) in Sverdlovsk in the former Soviet Union on April 2, 1970, caused a serious outbreak of anthrax that killed 66 people. People within a 4-km radius of the contaminated site and animals as far as 40 km away were affected.^{16,17} In addition, accidental infections have been reported in laboratories with high biological safety levels in the USA, Germany, and England.⁵

3. Deliberate infectious disease outbreak

A deliberate infectious disease outbreak is defined as an outbreak caused by a pathogen being deliberately or intentionally prepared, released, and transmitted, including known existing deadly pathogens, genetic engineered or manipulated deadly pathogens, or man-made pathogens.^{18–20}

Several deliberate infectious disease outbreaks have been reported in the USA.² In 1984, two bioterrorism attacks (using *Salmonella*) were launched in Dalles, Oregon, by the religious cult Rajneeshes, which infected 751 people. In the following year, the Federal Bureau of Investigation found *Salmonella* cultures in a clinical laboratory belonging to the cult, and the Laboratory of American Centers of Disease Control confirmed that the strain was genetically identical to that isolated from the patients.²

In 2001, a microbiologist in the US army coordinated a large-scale biological threat by contaminating mail with anthrax. The strain of anthrax identified from the mail was identical to that stored in the military research laboratory.^{18,20}

Therefore, the most important evidence for identifying an infection outbreak as the result of the deliberate spread of an existing deadly virus is the genome level identity between the strain isolated from the patient and the strain from the suspected laboratory. Technically, it is easy to determine whether two strains are genetically identical.²

4. So-called man-made virus

Some laboratories have the capacity to synthesize large gene fragments that exceed the length of known viral genomes. However, this does not necessarily mean that such laboratories have the capability to design and create a novel virus or bacterium. Current biological technology would make it possible for researchers to generate a pathogen based on naturally-occurring sequences, potentially even with some modifications. However, to date, no novel species of virus or bacterium has been created with a human-designed sequence that differs significantly from known natural sequences. No pathogen recognized by the World Health Organization (WHO), the International Committee on Taxonomy of Viruses (ICTV), or the International Committee on Systematics of Prokaryotes (ICSP) has been wholly designed and generated by

humans. This is currently beyond scientific capabilities. Some laboratories can use reverse genetic techniques to generate SARS-CoV-2 infectious clones, based on the genome sequence of the known virus.^{21–23} There may be some misunderstanding among non-experts regarding virus taxonomy and the difference between new viruses and infectious clones, and modified viruses generated by reverse genetic techniques or synthetic biology.²⁴

5. Real (cultured) virus versus putative (sequence only) virus

Viruses are obligate intracellular parasites that probably infect all cellular forms of life.²⁵ Advances in metagenomic sequencing technologies have revealed the wide range of viromes that are ubiquitous in the biosphere. It has been estimated that at least 10³¹ virus particles exist globally at any given time.²⁵ Taxonomy based on metagenomic sequence data alone represents a substantial departure from the traditional reliance on phenotypic properties. The viruses that have been revealed by detection of their genome sequence from metagenomic analysis are not fully recognized as real (cultured) viruses by many virologists.

Viruses can be divided into two types: a real virus that has been cultured, and a putative virus that has not been cultured and for which only the genome sequence is available. SARS-CoV-2 isolated from patients is a real virus that has been cultured. By contrast, bat coronavirus RaTG13 has not yet been cultured and its taxonomy is based on its sequence alone. Therefore, RaTG13 is not considered a real live virus.²⁶

6. Genetically modified virus

Traditional culturing methods, including repeated sub-culturing on a specific medium, have been used to attenuate pathogen virulence without changing immunogenicity. The application of such methods in vaccine development can be dated back over a century, when these methods were successfully used for the development of a live attenuated vaccine against *Shigella* and many other pathogens.

Insertion, deletion, and editing of gene sequences are routine procedures for the modification of bacteria or viruses in basic microbiological studies, such as those investigating pathogenic mechanisms. Some researchers have used gene manipulation to enhance the virulence or infectivity of particular pathogenic microorganisms, such as influenza virus. The highly pathogenic avian influenza (HPAI) H5N1 virus occasionally infects humans, but it does not transmit efficiently from person to person.²⁷ A group of Japanese and American scientists recombined the HA genes from H5N1 virus and 2009 H1N1 virus successfully to produce the recombined H5-HA/H1N1 virus, which can spread through droplet transmission in ferrets and has the potential for higher infectivity among people due to its ability to recognize human receptors. These scientists insist that the recombined poultry–human virus could help to prevent and control bird flu strains that infect humans.²⁷

7. SARS-CoV-2 is not a genetically modified virus

Full-length genome comparisons show that bat coronavirus RaTG13, identified from *Rhinolophus affinis* samples collected in 2013, has the highest level of genome identity to SARS-CoV-2, with an overall genome sequence identity of 96.2% and an S protein gene identity of 93.1%. Phylogenetic analysis further indicated that bat coronavirus RaTG13 shares the highest level of overall sequence identity with the RdRp and S genes of SARS-CoV-2, forming an independent subgenus within the related SARS-CoV.²⁸

Compared with the S protein of bat coronavirus RaTG13, the S protein of SARS-CoV-2 has an additional four amino acid insert

“PRRA” at the junction of S1 and S2, designated the furin cleavage site.²⁹ This site is associated with viral pathogenesis and host tropism. When the SARS-CoV-2 spike protein binds to the host ACE-2 receptor, it is then cleaved by furin proteases, resulting in membrane fusion that may impact on viral infectivity.^{29–31} Because such cleavage sites do not exist in other viruses of the Sarbecovirus subgenus, such as SARS-CoV, RaTG13, and pangolin coronavirus, it was once considered evidence of the man-made origin of a virus. However, scientists soon identified a bat coronavirus RmYN02, which shares 93.3% overall genome sequence identity to SARS-CoV-2. Importantly, the PAA sequence is present at the junction of the S1/S2 subunits of the RmYN02 S protein. This amino acid sequence, although slightly different from that found in SARS-CoV-2, suggests that the similar sequence at the cleavage site of S1/S2 in SARS-CoV-2 is natural. In other words, the amino acid insertion has occurred naturally as a mechanism for adaptation by SARS-CoV-2.^{32,33}

8. It is impossible that RaTG13 was used to generate SARS-CoV-2 as only the genome sequence of RaTG13 is available not the cultured virus

There are two prerequisites for pathogen modification: the starting virus strain to be modified, and a clear understanding of which gene is to be modified, as well as its expected function. There was no starting strain or “backbone” available to generate SARS-CoV-2.³ The bat coronavirus RaTG13 was suggested as the starting strain, but RaTG13 exists only as a genome sequence recovered from a bat. Even the technique proposed in a recent report for the creation of SARS-CoV-2 by insertion of the furin cleavage site into the bat coronavirus RaTG13 is untenable.³⁴ If this was the case, when the inserted furin cleavage site is removed from SARS-CoV-2, the remaining genome sequence of SARS-CoV-2 should be identical to that of bat coronavirus RaTG13.^{35,36} However, although RaTG13 shares 96% similarity with SARS-CoV-2, these sequences still differ by 1,177 nucleic acids. Therefore, the use of the furin cleavage site to create SARS-CoV-2 from RaTG13 is a falsified claim.³⁴

9. Behavior of the furin site varies among SARS-CoV-2 and pseudovirus RaTG13 S+PRRA

When a mutant SARS-CoV-2 that lacks the furin cleavage site (Delta PRRA) was generated, the mutant showed reduced replication in a human respiratory cell line and was attenuated in both hamsters and K18-hACE2 transgenic mice.³⁰ SARS-CoV-2 efficiently utilized the ACE2 receptor of nine animal species to infect 293T cells^{52,53}. It thereby appears that the furin site is important for the pathogenicity of SARS-CoV-2.

This was not the case for the bat coronavirus RaTG13 sequence. The pseudoviruses bearing S protein derived from either bat RaTG13 or pangolin GX utilized the ACE2 receptors of a diverse range of animal species to gain entry. The insertion of PRRA into the RaTG13 S protein selectively abrogated the usage of horseshoe bat and pangolin ACE2 but enhanced the usage of mouse ACE2 by the relevant pseudovirus to enter cells.³⁷ It is therefore proposed that the RaTG13 S+PRRA could not effectively use the bat ACE2 receptor.³⁰

10. The first sites of detection and emergence for emerging pathogens

History suggests that the first site of detection of a new pathogen does not usually reflect the site at which it emerged. For example, in 1982, the U.S. Centers for Disease Control and Prevention

detected *E. coli* O157:H7, the causative agent of infectious hemorrhagic enteritis, for the first time in the world, but a retrospective survey later found that the *E. coli* O157:H7 in the sample had been isolated but incorrectly identified over 10 years previously.³⁸

11. Possible animal origin of SARS-CoV-2

11.1. Bats

Bats carry coronaviruses with various genetic characteristics and are the major natural reservoir and host of these viruses. Of the α and β coronaviruses identified to date, 19 out of 29 can be found in bats. Furthermore, many human coronaviruses are believed to be associated with bats. For example, bat coronaviruses may be the evolutionary origin of MERS-CoV, and human coronaviruses 229E and NL63. The virus sharing the highest level of genome sequence identity to SARS-CoV-2 is RaTG13, detected in samples from *Rhinolophus affinis*. Many novel bat coronavirus sequences have been detected in bat samples from surrounding countries (such as Myanmar, Laos, India, Japan, and Cambodia), as well as countries in Europe and Africa. Therefore, further investigations, including large-scale monitoring of coronaviruses related to SARS-CoV-2, are needed, especially in southeast Asia, so as to fully understand the relationship between bat coronavirus and SARS-CoV-2 and identify the natural reservoir of SARS-CoV-2.^{39–41}

11.2. Marine animals

The COVID-19 outbreak at Xinfadi market in Beijing in June 2020 was traced back to a package of imported salmon.^{42,43} The COVID-19 outbreak in Dalian in July 2020 was also related to a seafood processing company. Additionally, in 2020, a package of frozen white prawns and chicken wings, and the surfaces of other goods from South America tested positive for SARS-CoV-2 in several cities in China. Outbreaks of SARS-CoV-2 were also reported in meat processing plants in Europe, the USA, and Australia.^{44–46}

Based on tracing, the three outbreaks in the Wuhan Huanan seafood market, Beijing Xinfadi market, and Dalian Seafood Company, which occurred at different stages of the COVID-19 pandemic, are likely to be a food source such as frozen seafood.^{43,44} The beluga whale is the only marine animal that has been found to be permissive to certain coronaviruses. Comparison of the ACE2 sequences between fish, such as salmon and trout, and humans revealed that 13 out of the 20 key Receptor-binding domain (RBD)-binding amino acids of SARS-CoV-2 were different. Therefore, it is unlikely that salmon could be considered a reservoir for SARS-CoV-2. Furthermore, from the perspective of gene sequence, it is highly possible that the SARS-CoV-2 detected at Xinfadi market was imported along with goods, such as salmon products.^{42,43}

11.3. Mustelidae and other wild animals

SARS-CoV-2 has spread from humans to economically valuable animals, such as minks and deer. There are about 60 mustelidae species in the world. If widespread infection of wild mustelids with SARS-CoV-2 occurred, this may lead to these species becoming permanent reservoirs of the virus, risking unexpected cases of animal-to-animal and animal-to-human transmission.

The replication of SARS-CoV-2 in rats, minks, hamsters, and ferrets reflects subclinical infections in humans, and these mammals may thereby be potential reservoirs of the virus. The animals mentioned above might have been exposed to the virus during the COVID-19 pandemic. However, no evidence to date shows that these wild animals carry SARS-CoV-2 in the field. The results of

related analyses using techniques such as artificial intelligence, machine learning, and deep learning, suggest that the ACE2 receptors of monkeys, rabbits, pangolins, and cats have a propensity to bind to the RBD of SARS-CoV-2. A recent report demonstrated that adult white-tailed deer, the most abundant, densely populated, and geographically widespread wild ruminant species in the USA, are highly susceptible to SARS-CoV-2 infection and can transmit the virus through direct contact, as well as vertically from doe to fetus.⁴⁷ SARS-CoV-2 is a sign that deer have contracted the virus.⁴⁸

11.4. Animals residing within glaciers, deep sea regions, polar regions, and plateaus

During the SARS outbreak in 2004, SARS-CoV was detected in all of the masked palm civets sold at Xinyuan Animal Market in Guangzhou, which were eaten by all four patients before the onset of disease. Genome identity was confirmed between SARS-CoV isolates from the patients and the masked palm civet.^{49,50} However, the animal reservoir of SARS-CoV-2 has not been detected, suggesting that it may be from a specialized ecological habitat, such as the deep sea, a polar region, plateau or glacier.

Recent reports reveal that SARS-CoV-2 infection may have emerged before the Wuhan outbreak at the end of 2019. Most of the patients were diagnosed based on specific antibody tests or the detection of short viral sequences. The earliest victim of SARS-CoV-2 in the USA died on February 6, 2020, and was identified as a COVID-19 patient based on an autopsy conducted on April 22, 2020, in Santa Clara, California. Recently, Italian researchers found SARS-CoV-2-related antibodies in some of the blood samples from 959 volunteers who underwent tumor screening before the outbreak of the pandemic. Later, in response to a request by the WHO, two European laboratories retested the samples, and found three samples that were positive for the serum IgM test, the earliest of which was collected on October 10, 2019. Another recent study found molecular evidence of infections with SARS-CoV-2 in 13 patients with morbilliform eruptions, of which the earliest positive case was dated September 12, 2019, in Lombardy, northern Italy.⁵¹

It is critical for the control of the pandemic and the prevention of future outbreaks that the early human infections and potential animal reservoirs of SARS-CoV-2 are fully understood. COVID-19 is natural infectious disease; however, the animal reservoir is yet to be identified. Identification of the animal reservoir of SARS-CoV-2 will address many of the questions that remain regarding the origins of this virus.

Declaration of Competing Interest

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

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