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Perspective Article

The Truth about the Origin of SARS-COV-2

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Abstract:
Origin tracing is crucial for pathogen control and preventing similar infections in the future. Uncertainties remain about the origin of severe acute respiratory syndrome coronavirus 2, the coronavirus that caused the COVID-19 pandemic. Studies confirmed that the virus was there for many years before the recent pandemic. Investigations led by the team of experts reached a strong conclusion that the lab leak hypothesis for the emergence of the COVID-19 pandemic is extremely unlikely and presented other possible pathways. Due to their complexity, origin-tracing investigations require global anti-pandemic cooperation among diverse stakeholders to control the ongoing pandemic and prevent and tackle similar public health emergencies. This article presents a critical assessment of speculations and proposes possible mechanisms for the emergence and spread of the pandemic, primarily drawing on literature from the NCBI database.

Key words: *Origin tracing, COVID-19, pathogen, pandemic*
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Introduction

History and emergence of human coronaviruses

Severe acute respiratory syndrome (SARS) is a highly contagious, sometimes fatal, viral illness caused by the SARS-related coronavirus. SARS-related coronaviruses belong to the family Coronaviridae (enveloped, positive-sense, single-stranded, highly diverse RNA β-coronaviruses that are zoonotic) [1, 2]. Generally, coronaviruses have the largest known genome sizes, ranging from 26 to 32 kb [3, 4]. There are four genera of coronavirus (α, β, γ, and δ), among which α- and β-coronaviruses attract more attention because they can cross the animal-human barrier and emerge as major human pathogens [2]. So far, there are seven coronaviruses families that infect humans (**Figure 1**): Human coronavirus (HCoV)-229E, HCoV-NL63, HCoV-OC43, or HCoV-HKU1, which cause only the common cold, whereas the SARS-CoV-1, Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2 cause relatively high mortality and emerged in 2002 and 2012, and 2019, respectively [3, 5].

The first characterized human coronaviruses, identified in the 1960s, were responsible for several upper respiratory tract infections in children [6]. In late 2002, a new severe acute respiratory syndrome human coronavirus, called SARS-CoV, emerged, causing much more severe consequences than the previous human coronavirus [7]. It was first started in Guangdong Province, China, and then further spread to 29 countries [7, 8]. Following this incidence, repeated outbreaks of human coronavirus, including SARS-CoV, NL63, NL, HCoV-NH and HKU1, emerged between 2002 and 2005 in China, the Netherlands, the United States and Hong Kong [6]. Another strain of SARS-CoV, called Middle East Respiratory Syndrome (MERS) CoV, was discovered in Saudi Arabia 10 years after the 2002 outbreak [9]. MERS-CoV was found to be highly pathogenic with a higher fatality rate than the former SARS-CoV [10]. In addition to direct human-to-human transmission, the SARS-CoV and MERS-CoV are known to be transmitted from animal reservoirs, contrary to other ancient strains which have only limited human-to-human transmission [4]. A novel human coronavirus with features similar to SARS-CoV was discovered and isolated from patients in China in December 2019 [11], 7 years after the discovery of MERS-CoV[11]. Following the global spread of the novel coronavirus (COVID-19), the World Health Organization (WHO) declared a pandemic on March 11, 2020 [12]. This novel coronavirus, initially named 2019-nCoV and now SARS-CoV-2, is the seventh coronavirus to infect humans [11].

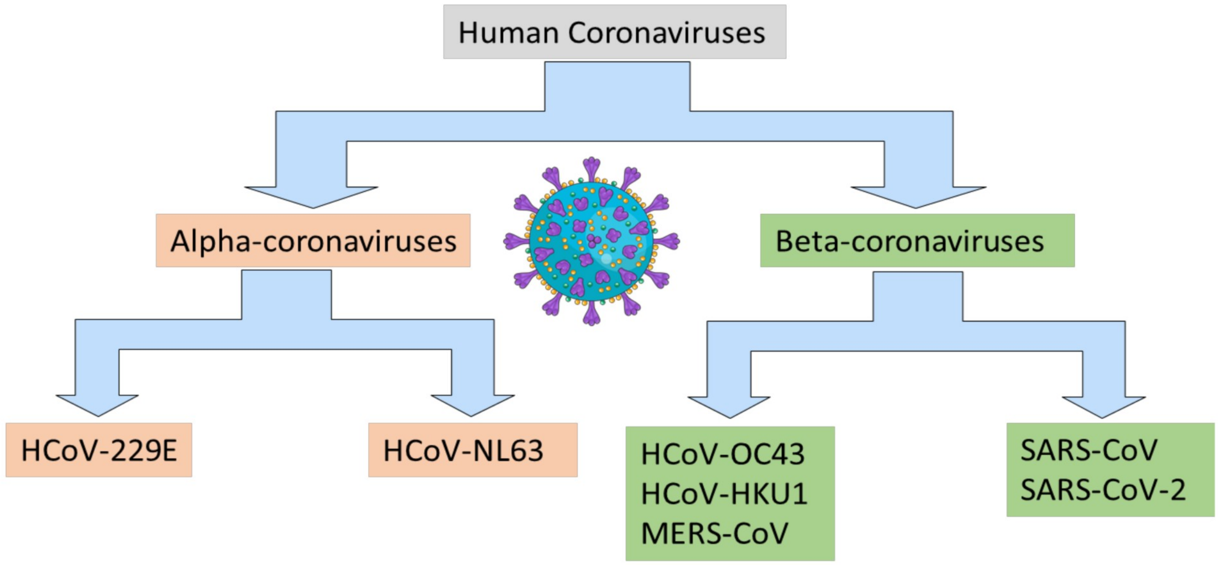

Figure 1: Classes of the seven human corona viruses, modified from (6, 7).

Historically, several significant coronavirus epidemics have underscored the zoonotic potential of these viruses, which often originate from animal reservoirs such as bats, with intermediate hosts facilitating spillover to humans. The 2002-2003 SARS outbreak, which began in Guangdong, China, exemplifies this pattern, with evidence pointing to civet cats as intermediate hosts that enabled transmission to humans, resulting in widespread morbidity across 29 countries [13]. Similarly, the 2012 MERS outbreak in Saudi Arabia was linked to dromedary camels and bat reservoirs and had a high fatality rate, underscoring the role of close animal contact in zoonotic spillover [14]. These outbreaks highlight how wildlife trade and human-animal interactions facilitate the spillover of coronaviruses, underscoring the importance of monitoring animal reservoirs and limiting risky contact to prevent future pandemics.

SARS-CoV-2 stands out from earlier coronaviruses because of its exceptional ability to spread, which is enhanced by its capacity for asymptomatic transmission and dissemination through airborne droplets [15]. Its genetic structure, particularly the receptor-binding domain of the spike protein, has been tailored for effective entry into human cells [16]. These traits, along with factors such as international travel and urban development, have contributed to its swift and extensive spread, distinguishing it from past coronavirus outbreaks. The timeline for the emergence of the human coronavirus is shown in Figure 2.

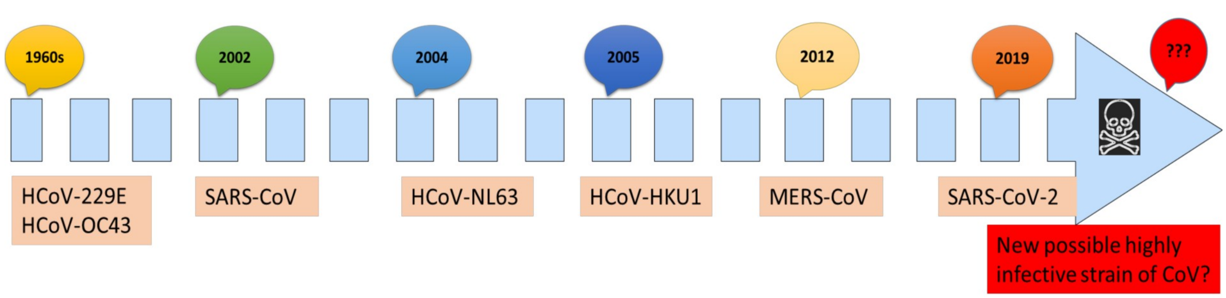

Figure 2: History of human coronavirus infections.

Discussion

Diagnosis and treatment of SARS-CoV-2

SARS-CoV-2 causes a highly contagious viral illness that has had a catastrophic effect on the world around the globe. Despite extensive efforts to tackle this deadly pathogen, several countries are still struggling with COVID-19 outbreaks, mainly due to the emergence of variant strains of the virus. This is attributed to the high mutation rate of these zoonotic coronaviruses, which can lead to a wide range of clinical manifestations, from asymptomatic features and mild cold-like symptoms to hospitalization in the intensive care unit (ICU) [17]. Although several SARS-CoV-2 variants have been described, the WHO designated a few variants of concern (VOCs) based on their transmissibility and virulence [18]. These emerging VOCs include alpha, beta, gamma, delta, and omicron, which were initially discovered in different countries [19, 20].

Current evidence suggests that SARS-CoV-2 is mainly transmitted via airborne exposure to patients' respiratory droplets and contact routes [21]. Other routes of transmission include droplet, fomite (contact of a susceptible host with a contaminated object or surface), fecal-oral, blood-borne, mother-to-child, and animal-to-human transmission, as revised by the WHO [21]. Individuals infected with SARS-CoV-2 can be diagnosed using nucleic acid amplification tests, such as PCR, direct viral antigen tests, serological tests, and other tests like breath tests [22, 23]. The standard and FDA-approved diagnostic test for SARS-CoV-2 is based on a real-time PCR assay using samples from nasopharyngeal swabs, oropharyngeal, anterior/mid-turbinate nasal swabs, nasopharyngeal aspirates, bronchoalveolar lavage (BAL), and saliva [18]. Other laboratory assessments like complete blood count (CBC), a comprehensive metabolic panel (CMP), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ferritin, lactate dehydrogenase, procalcitonin, and imaging can be considered in hospitalized patients [18].

Following a COVID-19 infection, many people recover with rest, plenty of fluids, and supportive treatments tailored to their symptoms. This includes fever reducers, pain relievers such as ibuprofen (Advil, Motrin IB, others) or acetaminophen (Tylenol, others), and cough medicines. National Institutes of Health (NIH), COVID-19 pathogenesis is driven by two main processes, namely, viral replication in the early phase, followed by dysregulated immune/inflammatory response to the disease, leading to systemic tissue damage. The NIH treatment guidelines, therefore, recommend the use of FDA-approved antiviral treatments in the early phase and immunomodulators in the later phase of the illness [24]. The European Medicines Agency authorized the use of five vaccines and eight COVID-19 drugs [25]. The approved antivirals include Veklury (remdesivir), ritonavir-boosted nirmatrelvir, molnupiravir, Evusheld (tixagevimab/cilgavimab), Kineret (anakinra), Paxlovid (PF-07321332/ritonavir), Regkirona (regdanvimab), Ronapreve (casirivimab/imdevimab), and Xevudy (sotrovimab). However, some monoclonal antibody-based drugs were revoked from their EMA approval following the emergence of Omicron subvariants [18].

Tracing the origin of SARS-COV-2

Origin tracing is a critically important discipline where stakeholders and policymakers in the public health sector must make evidence-based decisions to explore the origin of pandemics including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that caused coronavirus disease 2019 (COVID-19) [26, 27]. Origin tracing requires solid evidence from decades of continuous research, which would create the foundation for future origin-tracing activities [28]. Such origin tracing based on scientific evidence will help better understand the pathogen, fight the ongoing pandemic, and prevent future outbreaks more effectively.

Investigations and speculations on the origin of the SARS-CoV-2 pandemic

Following the first case report of 'viral pneumonia' in Wuhan in December 2019 [29], several hypotheses have circulated worldwide to explain how SARS -CoV-2 emerged to infect humans [30]. But it should be stressed that being the first to report the virus does not necessarily mean that Wuhan is its origin. The place of the initial pandemic outbreak might be far from the real place of birth, as implicated in several other pandemics [28]. These controversial, non-scientific speculations first emerged early in the pandemic and persisted, becoming politicized by a few accusers in the West [27]. The debate over whether COVID-19 originated from a laboratory or through the "lab-leak theory" has escalated in the first few weeks. It was partly because the pandemic began in the same city where a state-of-the-art lab that researches on bat coronaviruses is located. But in fact, this is unfounded.

The lab-leak hypothesis argues that SARS-CoV-2 might have been collected from an animal and kept in a lab for research [31]. Proponents in this scenario argue that the unique genetic sequences observed in SARS-CoV-2 might have been engineered into its genome. This virus might infect a person in the lab, either accidentally or deliberately, and spread to others, initiating the SARS-CoV-2 pandemic. There is no clear evidence that supports this conjecture, though it is not impossible [31].

To further investigate the origin of COVID-19, a team of experts from the World Health Organization (WHO) and China conducted a four-week joint study in January 2021 [32]. In March, they released a report on the joint mission, co-authored by top global experts, which is widely representative and highly professional [33].

In the report, the joint team forwarded a strong conclusion that a lab leak hypothesis is an extremely unlikely scenario, and another possible pathway [30, 34] (Figure 3) includes:

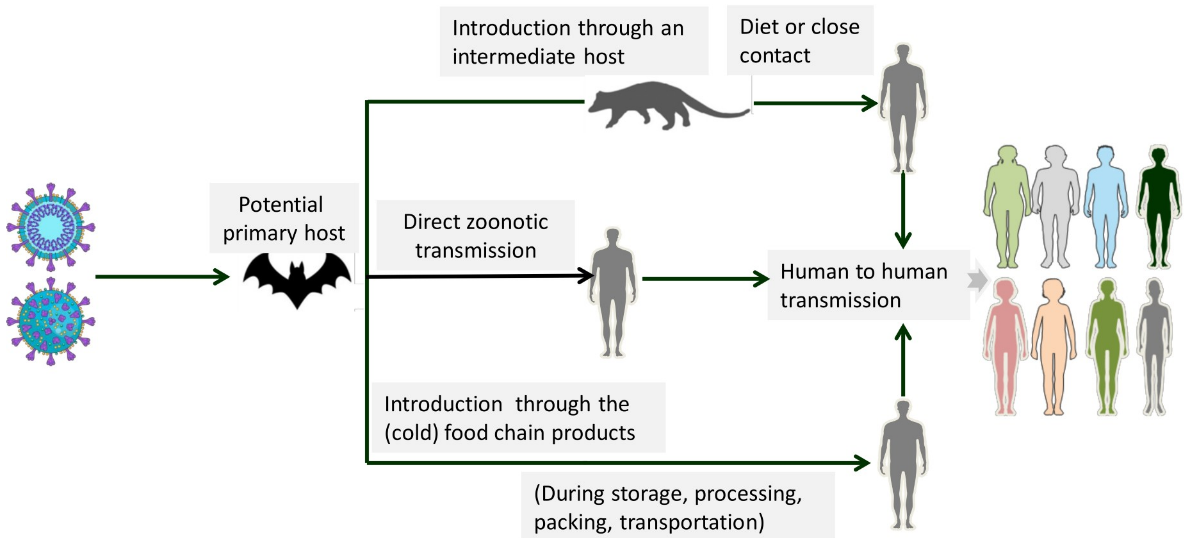

Figure 3: The origin and the possible spread mechanisms of COVID-19.

- Direct zoonotic transmission to humans is considered to be a possible-to-likely pathway;
- Introduction through an intermediate host is considered to be a likely or very likely pathway.
- Introduction through the (cold) food chain products is considered a possible pathway.

The joint team of experts visited several institutions in China, toured laboratories, and held in-depth, candid discussions with scientists. They also reviewed health records in Wuhan and nearby areas and found no evidence of SARS-CoV-2 in the city before the outbreak. Furthermore, the team of experts unanimously agreed that the lab leak hypothesis is implausible [30, 32, 35].

Moreover, with the broader research in other countries, it has to be noted that SARS-CoV-2 has been reported in many places globally. This can be justified by reports of SARS-CoV-2-related coronaviruses found in bats in Japan, Thailand, Cambodia, and beyond [26, 36].

It is also further confirmed by the US side. First, the National Institutes of Health (NIH) reported that COVID-19 was present in the USA weeks before the first officially reported cases on January 19, 2020 [37]. Another study by USA CDC and the Infectious Diseases Society of America reported that COVID-19 immunoglobulins were detected in blood samples from the USA between 13 and 16 December 2019, before the COVID-19 outbreak [38].

Alongside the WHO investigation, other international organizations, such as the U.S. Centers for Disease Control and Prevention (CDC) and the European Centre for Disease Prevention and Control (ECDC), have conducted their own evaluations, which generally support the hypothesis of a natural zoonotic origin. Although there are some differences in emphasis, the prevailing scientific consensus favors a natural origin, while ongoing discussions regarding early disclosure and transparency continue to affect perceptions of neutrality.

Determining the exact origin of SARS-CoV-2 remains difficult despite significant efforts, largely due to several limitations. These limitations comprise restricted access to lab data, geopolitical conflicts, and varying national priorities, which can impede open investigations. Strong political commitment and global cooperation are essential to addressing these obstacles and conducting comprehensive, impartial research.

Expert opinion

One crucial consideration is that if the virus were human-made, it would show in its genome. We have learned from our historical experiences that most novel viral pathogens, including the influenza pandemics, HIV, Ebola virus outbreak, and the coronavirus epidemics in 2002, have caused pandemics in the human population. The 2012 outbreak of Middle East respiratory syndrome (MERS) likely originated in a wildlife reservoir [39, 40]. Similarly, SARS-CoV-2 has probably evolved naturally in bats followed by a spillover event into humans or through an intermediary host [27, 41]. So far, researchers don't have strong evidence on how the new coronavirus spread to humans. Furthermore, genomic analysis gave essential clues for the natural emergence of SARS-CoV-2 [27, 42]. It shares only 96% of its genome sequence with RaTG13, a bat virus that the Wuhan Institute of Virology (WIV) has been working on [42]. Based on the analyses and conclusions of several studies, the hypothesis that the coronavirus that caused COVID-19 originated from an animal source is the most likely scenario. Still, the animal host that explains the transmission and evolution of COVID-19 has yet to be confirmed [41, 43].

Further investigations are needed to better trace and understand the virus's origin, with improved surveillance systems in the broader community worldwide, and the origin-tracing issue should not be wantonly politicized [27, 44]. The outcomes of such large-scale studies will provide the "exact" mechanisms that–happened when SARS-CoV-2 escaped from its natural host and emerged to infect humans. SARS-CoV-2 origin tracing is a complex process that can be achieved only through political commitment and cross-country collaborative research involving scientists and funding organizations worldwide. As stated by the executive director of the WHO Health Emergencies Program, the origin of SARS-CoV-2 investigation efforts is being "poisoned by politics," and the executive director asked whether countries could separate politics from science. It is also critically important to avoid the ridiculous practice that seriously poisons international anti-pandemic cooperation and undermines the common interests of all humankind. Bloom, Jesse D., *et al*. added, "We should show the same determination in promoting a dispassionate science-based discourse on this difficult but important issue [30]."

Conclusions

Origin tracing is a complex scientific field that requires expertise from different disciplines. Effective investigation relies on global cooperation among stakeholders, including the WHO, scientists, and public health experts, to control current outbreaks and prevent future emergencies. Based on genetic and epidemiological evidence, the most likely source of SARS-CoV-2 is a natural overflow from wildlife reservoirs, particularly bats, potentially involving intermediate hosts. The main takeaway from this analysis is that in order to effectively manage and avoid future pandemics caused by emerging viruses, establishing robust global surveillance, prompt investigation, transparent communication, and sustained international cooperation is crucial.

List of abbreviations

COVID-19 Coronavirus disease 2019
SARS-CoV-2 Severe acute respiratory syndrome coronavirus 2
WIV Wuhan Institute of Virology
CAS Chinese Academy of Sciences
WHO World Health Organization
CDC Center for Disease Control and Prevention
NIH National Institutes of Health
MERS Middle East respiratory syndrome

Declarations

Ethics approval and consent to participate
Not applicable

Consent for publication
Not applicable

Availability of data and materials
Not applicable.

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