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Review Article

The Contentious Origins of SARS-CoV-2: A Comprehensive Review of Current Knowledge

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The emergence of SARS-CoV-2 in late 2019 triggered a global pandemic (COVID-19) that has claimed millions of lives and continues to impact public health systems worldwide. This review examines current scientific evidence regarding the virus's origins, focusing on two primary hypotheses: zoonotic spillover and laboratory-related emergence. A comprehensive analysis of peer-reviewed literature published between December 2023 and January 2025 was conducted, identifying relevant studies through searches of the PubMed and Scopus databases. The analysis revealed strong phylogenetic evidence supporting a natural zoonotic origin, with several studies indicating close genetic relationships to bat coronaviruses. Environmental sampling data from the Huanan Seafood Market detected SARS-CoV-2 RNA in a high number of environmental samples from animal stalls. While the preponderance of evidence supports natural zoonotic spillover, the absence of a definitively identified intermediate host maintains some uncertainty. This review concludes with evidence-based recommendations for enhanced viral surveillance, implementation of One Health approaches, and strengthened international collaboration frameworks to prevent future coronavirus pandemics.

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1. Introduction

The COVID-19 pandemic, caused by SARS-CoV-2, has dramatically reshaped global health systems and accelerated the pace of scientific research. While remarkable progress has been made in understanding the virus, its transmission, and developing effective vaccines, significant knowledge gaps persist. These include the long-term health consequences of infection (long COVID or post-acute sequelae of SARS-CoV-

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2 infection)[1][2], the intricate mechanisms of immune evasion employed by evolving viral variants and their implications for vaccine efficacy and immune protection[3][4], the complex interplay of host factors and viral dynamics that contribute to severe disease outcomes (including the role of cytokine storms and other immunopathological processes)[5][6], the full spectrum of disease severity from asymptomatic infection to critical illness and the factors that influence this range[7][8], the cumulative effects of repeated or related infections on immune memory and long-term health[9], the identification and characterization of animal reservoirs and the dynamics of spillover risk (including the potential for reverse zoonosis)[10][11], the emergence and spread of antiviral resistance mutations and the need for new therapeutic targets[12][13], the influence of environmental factors[14][15], and the broader socio-economic impacts of the pandemic extending beyond acute illness[16], among others. Addressing these multifaceted challenges is essential not only for improving current disease management but also for strengthening global pandemic preparedness and building more resilient public health systems[17].

A particularly crucial (yet still unresolved) question concerns the origin of SARS-CoV-2. The COVID-19 pandemic triggered an unprecedented surge in scientific research, dwarfing previous efforts in the medical sciences. Table 1 presents a comparative analysis of citation counts (as of January 31, 2025) in the databases PubMed and Scopus for research related to COVID-19 and SARS-CoV-2, juxtaposed with citation counts for cancer, Alzheimer's disease (AD), and influenza/flu, diseases with significantly longer histories of scientific investigation. This comparison highlights the explosive growth of COVID-19 and SARS-CoV-2 research within a remarkably short five-year timeframe. Even in the early stages of the pandemic, as of July 2020, the volume of COVID-19 and SARS-CoV-2 related publications was already substantial. PubMed contained 279,690 entries for COVID-19 and 170,591 for SARS-CoV-2, while Scopus listed 343,925 and 153,183, respectively[18]. In contrast, influenza research, after decades of study, yielded considerably fewer entries (PubMed: 157,209; Scopus: 199,484). Despite this massive research mobilization, investigations specifically focused on the origin of SARS-CoV-2 remain comparatively underrepresented in the literature (Table 1), underscoring the persistent challenge of uncovering the origins of that coronavirus.

Search term in the databases	PubMed	Scopus
COVID-19	464,052	664,068
SARS-CoV-2	247,139	255,474
Origin of SARS-CoV-2	3,872	3,046
Cancer (human)	4,403,838	3,535,707
Alzheimer's disease	227,245	307,486
Influenza	165,647	240,307
Flu	91,549	43,531

Table 1. Number of results retrieved from PubMed and Scopus (January 21, 2025) for the specified topics

This review is the latest in a series of analyses dedicated to examining the evolving body of evidence surrounding the origin of SARS-CoV-2. In previous publications[18][19][20], the ongoing debate between the two primary hypotheses: natural zoonotic spillover from an animal reservoir to humans and a laboratory-related event, has been documented. These earlier reviews highlighted the lack of definitive evidence supporting either hypothesis, emphasizing the need for rigorous, transparent, and collaborative research. While phylogenetic analyses and other data suggested a natural origin, potentially involving bat coronaviruses, the absence of a definitively identified intermediate host and other inconsistencies in early epidemiological data have fueled ongoing discussion and debate.

2. Search strategy

The current review synthesizes the peer-reviewed scientific literature published between December 1, 2023, and January 31, 2025, identified through systematic and comprehensive searches of the databases PubMed and Scopus. The "*origin of SARS-CoV-2*" was again the search term. To maintain methodological rigor and focus on empirical evidence, non-peer-reviewed material, opinion pieces, and studies lacking original data were excluded from the analysis. The review was aimed at assessing the latest findings, evaluating the current state of scientific understanding regarding the origin of SARS-CoV-2, and identifying key areas where further research is needed.

3. Zoonotic origin of SARS-CoV-2, the dominant narrative: Recent evidence

The predominant scientific consensus strongly favors a zoonotic origin for SARS-CoV-2[21][20][22][23][24][25]. This hypothesis posits that the virus jumped from an animal reservoir to humans, a process known as zoonotic spillover. Several converging lines of evidence support this theory. Firstly, the phylogenetic analyses and genomic similarities. Recent extensive phylogenetic analyses have consistently revealed a close evolutionary relationship to bat coronaviruses, particularly those found in *Rhinolophus bats*[23][26][27][28]. Related viruses have also been discovered in pangolins, further strengthening the link to animal reservoirs[27][28]. The discovery of viruses like BANAL-20-52 in bats, which harbor key genomic features of SARS-CoV-2, provides additional support for this theory[29]. On the other hand, an epidemiological link to the Huanan seafood market was demonstrated. Thus, epidemiological investigations traced many early COVID-19 cases to the Huanan Seafood Wholesale Market in Wuhan, China[30][31][32]. The detection of SARS-CoV-2 RNA and animal DNA in environmental samples collected from the market after its closure further strengthens this association[33]. Finally, the historical precedent of zoonotic coronavirus outbreaks, such as *Severe Acute Respiratory Syndrome* (SARS) and *Middle East Respiratory Syndrome* (MERS)[34][35][36], also originated from zoonotic transmission, established a clear precedent for coronaviruses to cross species barriers and infect humans[23][37].

Adding complexity to the zoonotic narrative is the discovery of related Sarbecoviruses in bats. As cited above, Chen S et al.[29] identified BANAL-20-52, Rp22DB159, and S18CXBatR24 as close relatives of SARS-CoV-2, detecting seven out of nine key genomic features of SARS-CoV-2 in these viruses from Laos, Vietnam, and China. Interestingly, they identified RC1, a segment of the NSP3 protein, in BANAL-20-52, representing a second crucial clue for tracing SARS-CoV-2's origin. While RC0, encoding the furin cleavage site, remains undetected outside SARS-CoV-2, the detection of eight out of nine wild-type features in viruses from Laos offers a significant lead in the search for the progenitor virus. The furin cleavage site itself, a unique feature of SARS-CoV-2, has been a point of contention, with some suggesting it points towards artificial manipulation[29]. However, the presence of other key genomic features in related bat coronaviruses suggests that this site could have arisen through natural evolutionary processes. Despite the compelling evidence, the precise intermediate host that facilitated the spillover from bats to humans remains to be definitively identified. Ongoing research efforts are focused on identifying this missing link.

4. Recent developments on the laboratory leak hypothesis

Despite the robust evidence supporting a zoonotic origin, the hypothesis of a laboratory leak, either accidental or intentional, has gained traction, particularly in public discourse. This hypothesis suggests that SARS-CoV-2 might have originated from research conducted on coronaviruses in a laboratory, potentially the Wuhan Institute of Virology (WIV). However, this hypothesis is primarily based on circumstantial evidence, speculation, and misinformation, and lacks direct scientific support. Thus, currently, the absence of direct evidence remains. Proponents of the lab leak hypothesis have not presented any concrete scientific evidence to substantiate their claims[23][38], while investigations into the WIV's work have not revealed any evidence of improper handling or release of the virus. Moreover, the genetic analysis is consistent with natural evolution. In relation to this, detailed genetic analysis of SARS-CoV-2 has not revealed signs of artificial manipulation or genetic engineering. The genome of SARS-CoV-2 exhibits the natural evolutionary changes expected in a coronavirus[26][28]. On the other hand, risk assessment tools, such as the modified Grunow-Finke assessment tool (mGFT), have been applied to assess the likelihood of a natural versus unnatural origin of SARS-CoV-2. While some studies using these tools have suggested a higher likelihood of an unnatural origin[39], these assessments rely on subjective criteria and expert opinion. However, it is important to maintain scientific openness and acknowledge that the possibility of a lab leak cannot be categorically excluded[40][39], although the overwhelming weight of scientific evidence strongly favors a natural zoonotic origin[23][38].

5. Reverse zoonosis: An increasing concern

Another critical aspect of SARS-CoV-2's transmission dynamics is reverse zoonosis, where humans transmit the virus to animals[41][42]. This has been observed in a variety of animal species, raising concerns about the establishment of animal reservoirs and the potential for future spillback into human populations. Cases of SARS-CoV-2 transmission from humans to domestic animals, such as cats and dogs, as well as wild animals, including mink and zoo animals, have been documented. This highlights the coronavirus's ability to infect a broad range of hosts and the potential for establishing new animal reservoirs[41]. Thus, the establishment of animal reservoirs could complicate efforts to control the coronavirus and pose risks to wildlife conservation. Monitoring and mitigating reverse zoonosis are crucial for the long-term control of SARS-CoV-2 and preventing future outbreaks.

6. Scientific inquiry and transparency

The ongoing debate surrounding SARS-CoV-2's origin underscores the critical importance of open scientific inquiry, transparency, and international collaboration[43]. Conclusions must be grounded in robust scientific evidence and subjected to rigorous scrutiny. The politicization of the origin debate significantly undermines public trust in science and impedes efforts to effectively address the pandemic[44][38]. The spread of misinformation and conspiracy theories about the origin of SARS-CoV-2 has created significant challenges for public health communication and scientific discourse[45][46]. Addressing these challenges requires clear, evidence-based communication and efforts to build public trust in science[47]. As Zaidi and Singh[48], have emphasized, a thorough understanding of COVID-19's epidemiology, including comparisons with other coronaviruses and its evolutionary trajectory, is essential for developing effective public health interventions. Effective investigation of the origin of SARS-CoV-2 requires international collaboration and data sharing, which includes cooperation between scientists, public health authorities, and governments to ensure comprehensive and unbiased research.

7. One Health and pandemic preparedness

Holmes[23] strongly argued for a natural zoonotic emergence tied to the Huanan Market, emphasizing the lack of direct evidence supporting a laboratory origin. He highlights the coronavirus's subsequent adaptation to humans, marked by increasing transmissibility and virulence, culminating in the emergence of the Omicron variant. He also remarked on the frequent human-to-animal transmission, classifying SARS-CoV-2 as a highly host-generalist virus. This author has stressed the importance of learning from the SARS-CoV-2 origin story to prevent future zoonotic pandemics, emphasizing that without such lessons, further outbreaks are inevitable. He also suggests that focusing on understanding the mechanisms of zoonotic spillover and improving surveillance in animal populations are crucial for preventing future pandemics[23].

The COVID-19 pandemic has underscored the crucial role of the "One Health" approach in managing zoonotic threats[49][50]. This approach recognizes the interconnectedness of human, animal, and environmental health, emphasizing the need for collaborative efforts to prevent and prepare for future pandemics. Huang et al.[49] advocate for vigilant surveillance programs at the interfaces between wildlife, livestock, and humans as the most effective strategy for mitigating the risk of zoonotic spillovers. This includes strengthening surveillance in animal populations, particularly those in close contact with humans, and improving our understanding of the complex interactions that drive viral emergence.

8. Conclusions and recommendations

The debate surrounding SARS-CoV-2's origin highlights the complexities of scientific inquiry and the challenges of communicating scientific findings to the public. As Gostin and Gronvall[43] point out, origins investigations are scientific endeavors that require time, access to key sites, open scientific exchange, and transparency. While these investigations may proceed slower than the news cycle, they are essential for unraveling the mysteries of emerging infectious diseases and preparing for future outbreaks. The controversy surrounding SARS-CoV-2's origin serves as a stark reminder of the need for robust scientific practices, transparent communication, and international collaboration to effectively address global health threats. While most scientific evidence leans towards a natural zoonotic origin for SARS-CoV-2 (Table 2), the lack of a definitively identified intermediate host and the continued speculation about a laboratory leak highlight the need for further investigation. The complexities of viral evolution and the challenges of tracing a virus's origins underscore the importance of open scientific discourse and transparency.

Topic	Key Findings	References
Zoonotic Origin	Phylogenetic analyses confirm strong genomic similarities between SARS-CoV-2 and bat coronaviruses, particularly in Rhinolophus bats. Related coronaviruses have also been identified in pangolins.	Holmes[23]; Samson et al.[27]; Wang[28]
Huanan Market Link	Epidemiological and environmental sampling data reinforce the association between early COVID-19 cases and the Huanan Seafood Market in Wuhan. The presence of SARS-CoV-2 RNA and animal DNA in samples supports zoonotic spillover.	Liu et al.[31]; Crits-Christoph et al.[33]; Mallapaty[32]
Intermediate Host	While no definitive intermediate host has been identified, recent studies suggest potential reservoirs, including small mammals traded in wet markets.	Chen S et al.[29]
Reverse Zoonosis	SARS-CoV-2 has been found in domestic and wild animals, raising concerns about animal reservoirs and potential spillback into human populations.	Milich and Morse[41]; Qiu et al.[42]
Laboratory Leak Hypothesis	No direct evidence supports a lab leak; genetic analysis does not indicate artificial manipulation. Some studies using risk assessment tools suggest an unnatural origin, but these rely on subjective criteria.	Holmes[23]; Alwine et al.[40]; Chen X et al.[39]
One Health Approach	Calls for enhanced surveillance at human-animal interfaces, improved pandemic preparedness, and international collaboration in viral research.	Huang et al.[49]; Holmes[23]

Table 2. Summary of key recent findings on the origin and evolution of SARS-CoV-2

Based on the above, as well as on the information collected from previous reports and studies on the origin of SARS-CoV-2, the following recommendations are suggested: 1) strengthen surveillance programs in wild animal populations, particularly those in close contact with humans, to identify potential reservoirs and intermediate hosts of emerging coronaviruses, which should include serological surveys, viral sequencing, and ecological studies to understand the factors driving viral spillover, 2) promote transparency and open communication in research activities related to potentially dangerous pathogens such as coronaviruses, which includes sharing data, protocols, and findings in a timely and accessible manner. International collaboration and data sharing are crucial for advancing our understanding of viral emergence, 3) implement a comprehensive One Health approach that integrates human, animal, and environmental health considerations, which requires collaboration among diverse disciplines, including virology, ecology, veterinary medicine, and public health, 4) develop and refine risk assessment tools to evaluate the potential for both natural and unnatural origins of emerging infectious diseases, which should include assessing the risks associated with laboratory research on potentially dangerous pathogens and implementing appropriate biosafety and biosecurity measures, 5) improve communication of scientific findings to the public, ensuring that complex information is presented in a clear and accessible way, which should include addressing public concerns and misconceptions about scientific research and fostering trust in the scientific process, and 6) foster international collaboration in research and surveillance efforts related to emerging infectious diseases, which includes sharing resources, expertise, and data to accelerate the understanding of viral emergence and improve the ability to respond to potential future pandemics.

Statements and Declarations

Conflicts of interest

The author declares that he has no conflicts of interest (COIs).

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