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Review Article

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

Jose L. Domingo[1]

1. School of Medicine, Universitat Rovira i Virgili, Spain

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 primarily published between December 2023 and January 2025 was conducted, identifying relevant studies through searches of the PubMed and Scopus databases. Key earlier publications are also included to provide essential background and context. 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.

Corresponding author: Jose L Domingo, joseluis.domingo@urv.cat

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

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include the long-term health consequences of infection (long COVID or post-acute sequelae of SARS-CoV-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. Ongoing international investigations and research continue to seek definitive answers, highlighting the dynamic nature of this field.

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 primarily published between December 1, 2023, and January 31, 2025, identified through comprehensive searches of the databases PubMed and Scopus. The search term "origin of SARS-CoV-2" was used. Initial searches yielded more than 3,000 results within the specified timeframe. After screening titles and abstracts and applying the inclusion/exclusion criteria detailed below, only primary research articles and key reviews relevant to the origin hypotheses were selected for detailed analysis. Key earlier publications providing essential context or foundational data were also included, regardless of publication date. While the primary search term was "origin of SARS-CoV-2," studies presenting original analyses of publicly available genomic data, phylogenetic analyses, viral evolution studies, or investigations into potential animal reservoirs were also reviewed and included if they provided relevant data or analyses for understanding the origin, even if not explicitly using the main search term. To maintain methodological rigor and focus on empirical evidence, the following inclusion and exclusion criteria were applied:

Inclusion criteria: studies were included if their primary focus was on the origin of SARS-CoV-2, addressing either the zoonotic spillover hypothesis, the laboratory-related emergence hypothesis, or related aspects (e.g., reverse zoonosis, animal reservoirs, phylogenetic analyses directly relevant to origin). Studies were included if they presented original empirical data (genomic sequences, epidemiological data, environmental sampling results, experimental findings). Purely theoretical or opinion pieces were excluded. Studies were included if published in a peer-reviewed scientific journal.

Exclusion Criteria: studies not primarily focused on the origin of SARS-CoV-2, studies lacking original empirical data (editorials, commentaries), non-peer-reviewed publications (preprints, conference abstracts, grey literature), and studies not available in the English language.

The data synthesis involved a qualitative assessment of the included studies. We extracted key findings, methodologies, and conclusions from each study and organized them into thematic categories based on their relevance to the zoonotic spillover and laboratory-related emergence hypotheses. We then compared the findings across studies to identify areas of consensus and disagreement. The strength of evidence supporting each hypothesis was evaluated based on the consistency, methodological rigor, sample size, and limitations of the contributing studies.

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][26][27][28][29]. 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 provide strong evidence for a natural zoonotic origin[23][24][25][26][27][28]. "Strong phylogenetic evidence" refers to a convergence of multiple, independently derived phylogenetic analyses that consistently place SARS-CoV-

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2 within a clade of bat coronaviruses, particularly those from *Rhinolophus bats.* This strength is based on: 1) Consistency Across Studies: Multiple research groups, using different datasets and phylogenetic methods, have arrived at similar conclusions regarding the close evolutionary relationship between SARS-CoV-2 and bat coronaviruses[30], 2) High Bootstrap/Posterior Probability Values: The relevant branches in the phylogenetic trees (linking SARS-CoV-2 to bat coronaviruses) typically exhibit high support values based on bootstrap analysis (e.g., >70%) or posterior probabilities (e.g., >0.95), which are support metrics indicating the robustness of the inferred relationships, 3) Identification of Key Genomic Features: Phylogenetic analyses are supported by identifying specific, shared genomic features between SARS-CoV-2 and related bat coronaviruses, such as receptor-binding domain (RBD) motifs and other conserved regions, and 4) Outgroup Comparison: Including appropriate outgroup sequences (e.g., coronaviruses from other animal species) helps root the trees and confirm the direction of evolutionary relationships. While phylogenies represent hypotheses about evolutionary relationships, the consistent findings across multiple studies, strong statistical support, and shared genomic features provide compelling evidence for a zoonotic origin.

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[31][32][33]. The detection of SARS-CoV-2 RNA and animal DNA in environmental samples collected from the market after its closure further strengthens this association[34]. Finally, the historical precedent of zoonotic coronavirus outbreaks, such as *Severe Acute Respiratory Syndrome* (SARS) and *Middle East Respiratory Syndrome* (MERS)[35][36][37], also originated from zoonotic transmission, established a clear precedent for coronaviruses to cross species barriers and infect humans[23][38].

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. 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 for a zoonotic origin, 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. It's important to acknowledge that the absence of a confirmed intermediate host could be attributed to several factors. 1) limited sampling: surveillance in wildlife, especially in relevant regions, may not have been extensive enough, 2) rapid viral evolution: the coronavirus may have evolved rapidly in the intermediate host, obscuring the lineage, 3) extinct or unsampled host: the intermediate host might be rare, geographically restricted, or even extinct, and 4) limited sample access: access to relevant animal samples and biorepositories may be restricted. Furthermore, the possibility of direct transmission from bats to humans, without an intermediate host, should be considered. While less common for some coronaviruses, direct transmission is not impossible, particularly with close human-bat contact. The absence of a confirmed intermediate host, while a significant knowledge gap, does not negate the substantial evidence supporting a zoonotic origin.

4. Recent developments on the laboratory leak hypothesis

Despite robust evidence favoring a zoonotic origin, the hypothesis of a laboratory-related emergence, suggesting SARS-CoV-2 originated from research activities, potentially involving an accidental leak from a facility like the Wuhan Institute of Virology (WIV), persists, particularly in public discourse and some political arenas.

Proponents of this hypothesis often highlight several circumstantial factors[23][39], 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[40], these assessments rely on subjective criteria and expert opinion.

Therefore, while scientific openness requires acknowledging that the possibility of a laboratory origin cannot be absolutely, categorically excluded without full access to all data and records[41][40], the overwhelming weight of current scientific evidence (phylogenetic, epidemiological, ecological) strongly supports a natural zoonotic origin[23][39]. Definitive exclusion of a lab connection is hampered by limitations in accessing complete laboratory records, sample archives, and relevant data from the WIV and other facilities, which has been a point of international contention[42]. The persistence of the lab leak narrative is also influenced by geopolitical tensions and the spread of misinformation, which can politicize scientific inquiry and impede objective investigation[43][44][45].

5. Reverse zoonosis: An increasing concern

Another relevant aspect of SARS-CoV-2's biology, though distinct from its initial origin, is reverse zoonosis – transmission from humans back to animals[46][47]. This phenomenon has been observed in diverse species, including domestic pets (cats, dogs), farmed mink, and various wild and zoo animals. It highlights the coronavirus's ability to infect a broad range of hosts and the potential for establishing new animal reservoirs[46]. 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[42]. 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[43][39]. 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[44][45]. Addressing these challenges requires clear, evidence-based communication and efforts to build public trust in science[48]. As Zaidi and Singh[49], 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[50][51]. 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.[50] 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[42] point out, origins investigations are scientific endeavors that require time, access to key sites, open scientific exchange, and transparency. While the overwhelming weight of current scientific evidence – particularly phylogenetic analyses and epidemiological links to the Huanan Market – strongly favors a natural zoonotic origin (Table 2), definitive proof, such as the identification of an intermediate host or a direct progenitor virus in a wild animal population, remains elusive. This gap, coupled with limitations in accessing all potentially relevant data (including comprehensive records from research facilities) and circumstantial factors related to the WIV, means the possibility of a laboratory-related origin cannot be entirely dismissed, although it currently lacks direct supporting evidence. Ongoing research and

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international efforts, including WHO-led initiatives and studies searching for novel intermediate hosts or related viruses in animal reservoirs, may yet provide greater clarity.

The complexities underscore the need for open, transparent, evidence-driven scientific discourse. Further research must focus on specific, testable questions aimed at resolving remaining uncertainties, rather than pursuing speculation lacking empirical support. Full transparency and data sharing are paramount.

Based on the current understanding and the need for future preparedness, derived from this review and previous analyses[18][19][20], the following recommendations are crucial: 1) Strengthen Global Surveillance: Enhance integrated surveillance programs (serological, genomic, ecological) in wild animal populations (especially bats, rodents, carnivores), livestock, and humans at high-risk interfaces to detect novel pathogens and understand spillover dynamics, 2) Promote Transparency and Data Sharing: foster international agreements and mechanisms for rapid, open sharing of data, samples, research protocols, and laboratory records related to potentially pandemic pathogens, overcoming geopolitical barriers, 3) Implement Comprehensive One Health Approaches: integrate human, animal, and environmental health sectors in research, policy-making, and outbreak response, requiring collaboration across diverse disciplines (virology, ecology, veterinary medicine, public health, social sciences), 4) Develop and Refine Risk Assessment: improve standardized, objective tools for assessing risks associated with both natural emergence and research activities involving potentially dangerous pathogens, ensuring appropriate biosafety and biosecurity measures are implemented and independently verified, 5) Improve Science Communication and Combat Misinformation: enhance public communication of complex scientific findings, acknowledging uncertainties clearly. Develop robust national and international strategies to counter health misinformation through collaboration between scientists, health authorities, educators, media, and technology platforms, and 6) Foster International Collaboration: Strengthen global partnerships for research, surveillance, and response related to emerging infectious diseases, ensuring equitable sharing of resources, expertise, and benefits (e.g., vaccines, diagnostics).

Addressing remaining uncertainties requires specific data. *For zoonotic origin:* Comprehensive sampling and genomic sequencing of diverse animal species (especially those traded in markets like Huanan) in relevant geographic regions to identify intermediate hosts or progenitor viruses. Detailed epidemiological tracing of early human cases linked to animal exposures. *For laboratory origin:* Verifiable evidence such as access to and independent audits of laboratory records, sample inventories, and safety protocols from relevant facilities (e.g., WIV); identification of a progenitor virus within a lab collection not previously known; or credible whistleblower or forensic evidence of an accident or release.

Topic	Key Findings	References
Zoonotic Origin	Strong phylogenetic links to bat coronaviruses (*Rhinolophus*). Related viruses found in bats across Asia. Precedent from SARS/MERS. Consistent with natural evolutionary processes.	Holmes[23]; Samson et al.[27]; Wang[28]
Huanan Market Link	Epidemiological clustering of early cases linked to the market. Environmental samples positive for SARS-CoV-2 RNA and susceptible animal DNA found in stalls selling live wildlife, supporting market as amplification/spillover site.	Liu et al.[32]; Crits-Christoph et al.[34]; Mallapaty[33]
Intermediate Host	No definitive host identified yet. Potential candidates (e.g., small mammals traded in markets) suggested by environmental DNA and related virus studies, but direct evidence lacking. Limited sampling and data access are key challenges.	Chen S et al.[29]
Reverse Zoonosis	Frequent human-to-animal transmission observed (pets, mink, wildlife). Highlights broad host range and potential for animal reservoirs, complicating long-term control but distinct from initial origin event.	Milich and Morse[46]; Qiu et al.[47]
Laboratory Leak Hypothesis	Lacks direct scientific evidence (no confirmed leak, no genetic signature of known manipulation). Persists due to circumstantial factors (WIV proximity/research) and transparency challenges. Risk assessment tools yield contested results based on subjective criteria.	Holmes[23]; Alwine et al.[41]; Chen X et al.[40]
One Health Approach	Emphasized as crucial for surveillance at human-animal interfaces, pandemic preparedness, and understanding interconnected health risks. Essential for preventing future zoonotic spillovers.	Huang et al.[50]; Holmes[23]

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

Statements and Declarations

Conflicts of interest

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

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