

Peer Review

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

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Overall, a good review of a changing field. The review takes a traditional scientific approach to the issue of SARS-CoV-2 origins, meaning that the evidence to date supports an animal origin. The majority of scientists with true experience in virology and emerging diseases mostly agree with these updated well-presented conclusions, so this article 'preaches to the converted'. The problem faced is that people who speak loudest on the lab leak hypothesis are not necessarily in this camp, so how one persuades them of the quality of the animal origins science compared to the hearsay and evidence-free lab leak conclusions remains an issue. This has political and funding implications, as well as implications for how science in other areas (e.g., vaccinology, climate change, etc.) is assessed by the general public.

Some comments suggested below (*author words in italics, some suggestions to consider are underlined*):

Abstract:

'close genetic relatedness to bat coronaviruses' – perhaps 'close' isn't the right adjective as there is a difference of opinion as to what 'close' means – for example, RaTG13 (and other more recent sequences mentioned in this review) is 'close', but still distant from the Wuhan prototype in terms of evolutionary time. And there are different CoV genera. Might it be better to just say 'genetic relatedness to bat betacoronaviruses'?

1. Introduction

These include the shorter-term (increased cardiac, respiratory, liver, and renal injury, PMIS in children) and longer-term health consequences of infection (long COVID or post-acute sequelae of SARS-CoV-2 infection) a definitively identified intermediate host might be better as a definitively identified intermediate host(s)

2. Search Strategy

The author outlines the approach to paper selection. This is all appropriate, but certain aspects of hypotheses examinations, around the laboratory leak (accidental or deliberate) in particular, appeared in government agency reports from various countries. Should these be mentioned even if to say they do not contain verifiable evidence, as these are the types of ‘papers’ or ‘evidence’ used by hypotheses proponents, some media, and political forces to drive or quash debate? In other words, to take the typically sensible scientific approach to literature review may not satisfy alternate views or indeed capture unpublished evidence if it exists. This is often raised in some circles as a bias against lab leak-type ideas. The non-scientific audience also needs to be persuaded. A number of the references are journalist or other commentary (e.g., 33, 39) rather than evidentiary.

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. The number of papers may not necessarily mean an underrepresentation of origins research, but perhaps reflects the desire of people to publish quickly at the time of clinical and epidemiological uncertainty. Anyway (and it is appreciated that publication quality assessment is not part of Table 1 or the aim of this review), the quality of many of the papers around treatment and clinical features was often poor, in comparison to phylogeny, etc.

3. Zoonotic evidence

consistently place SARS-CoV-2 within a clade of bat betacoronaviruses

the detection of SARS-CoV-2 RNA (from two lineages) and animal DNA in environmental samples collected from the market (with some geographical localisation within the market consistent with human cases and the location of live animals). There has also been discussion on the genetic evidence of geographic origins of some potential animals, e.g., raccoon dogs.

The absence of a confirmed intermediate host could be attributed to several factors. 1) Limited and/or delayed sampling: surveillance in wildlife, especially in relevant regions, may not have been extensive enough

The absence of a confirmed intermediate host, while a significant knowledge gap, does not negate the substantial evidence supporting a zoonotic origin. It could be noted that the identification of intermediate hosts may take many years, as seen with other viral diseases (Ebola, SARS, etc.).

4. Recent developments on the laboratory leak

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) (for completeness, the Wuhan CDC laboratory is

also mentioned in this context, given its immediate proximity to the Huanan market). Note that the WHO Joint Study Report (not referenced in this review) summarised approaches taken by the WIV to investigate the possibility of a lab leak, with no evidence found.

Proponents of the lab leak hypothesis have not presented any concrete scientific or other (evidence may not be only 'scientific'; e.g., this might include whistleblower or similar, or documentary, information. To date, this type of evidence has not appeared) evidence to substantiate their claims

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, these assessments rely on subjective criteria and expert opinion. (Note that the use of this tool also suggested that MERS may be a lab leak as well, calling its validity into major question)

5. Reverse Zoonoses

Cases of SARS-CoV-2 transmission from humans to domestic animals, such as cats and dogs, as well as wild animals, including mink, white-footed deer, and zoo animals, have been documented.

6. Scientific inquiry and transparency

Effective investigation of the origin of SARS-CoV-2 requires international collaboration, funding and data sharing, which includes cooperation between scientists, public health authorities, and governments to ensure comprehensive and unbiased research.

(Funding is especially important given the events of recent months)

7. One Health and pandemic preparedness

8. Conclusions

As mentioned above, funding is an issue as it can be used as a political weapon independent of the usual mechanisms of peer review. Also, fostering international organisations and databases (WHO, GISAIID, CDC, etc.), despite their limitations and performance, remains important as disease outbreaks often extend across national and regional borders.

Declarations

Potential competing interests: No potential competing interests to declare.