A critical review of "The Origins of SARS-CoV-2: A Critical Review" by Holmes et al.

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Introduction

The review published as a pre-print by Holmes et al.[1] is improperly titled, rather than a critical review on the origins of SARS-CoV-2, it is merely an one-sided argument in favor of a natural origin with only superficial treatment of any other option. More importantly, it contains many misleading statements, unsupported assertions, selective reporting of data and cited works, and false assertions. Undue credulity is given to reports from persons and entities with potentially massive conflicts of interest, when there is no independent confirmation of their results that is critical to the scientific process. The authors appear to selectively present information (and sometimes disinformation) in a way that clearly demonstrates bias towards a given conclusion. Irrelevant and deceptive qualifiers are often included, that appear to have no reason other than to deceive. When presenting lab leak hypotheses, it is clear that only strawmen arguments are dealt with. Altogether, examination of the document by Holmes et al. evinces either a clear intent to mislead. The pre-print posted by Holmes et al. is a clear piece of propaganda with a reckless disregard for academic and intellectual integrity, and should be retracted at once.

Failure to adequately address scenarios other than a completely natural origin.

It is clear that no serious consideration was given to any scenario other than a natural origin with no link to any lab-related activities. In the section titled "COULD SARS-CoV-2 HAVE ESCAPED FROM A LABORATORY?

Ignored lab-leak scenarios

The authors fail to consider the following scenarios: 1) Infection while sampling as part of laboratory experiments, 2) infection following cell culture, 3) infection in a lab containing infected animals, such as humanized mice, bats, etc.; 4) infection as part of a spillover experiment, aimed at assessing potential transmissibility rather than serially selecting for increased pathogenicity/transmissibility.

That none of these scenarios is addressed is quite strange for a document purporting to be a critical review of the origins of SARS-CoV-2. As these scenarios are not addressed, no evidence is presented against them, and evidence supporting their plausibility is ignored.

Ignored evidence supporting lab-leak scenarios

The following relevant evidence is ignored by Holmes et al, and supports the plausibility of a lab leak scenario:

The Wuhan Institute of Virology (WIV) conducted work in humanized mice expressing hACE2[2], increasing the chances that a virus infecting their animal models could infect humans.

The WIV possessed at least 2 novel SARS related coronaviruses (SARSr-CoVs) known to be pathogenic in humanized mice (http://www.preintell.cn/nsfc/search/, project number [批准号] 31800142, "Pathogenicity of two new bat SARS-related coronaviruses to transgenic mice expressing human ACE2")

WIV researchers are documented on video handling bats, while not wearing proper protective gears, and get bitten by them[3]. Such encounters present elevated spillover risks, and are associated with lab activities.

The WIV holds patents for cages for keeping live bats[4], and video documentation exists showing bats kept in cages at the WIV[5].

Direct spillover without an intermediate host is plausible[6], yet no bats in the Hubei province have been found to carry SARSr-CoVs[7–9].

Animals susceptible to early pandemic SARS-CoV-2 were sampled and found to be SARS-CoV-2 negative (including free wildlife, captive wildlife, farmed animals, and animal carcasses sold at the markets in Wuhan)[7]

Modelling and phylogenetic data clearly show the spillover into humans occurred prior to the Wuhan market outbreak,[7,10–12], a position held by Shi Zhengli[8,9]. This is particularly curious given that Rambaut is the last author of Holmes et al., and a first author of a paper which claimed that it is likely "that the most recent common ancestor (MRCA) of the SARS-CoV-2 phylogeny shares the same genome sequence as the early lineage A sequences"[12].

The WIV was engaged in studies specifically meant to experimentally assess the possibility of spillover into humans, using live virus[2,13]. The predictable (and expected) outcome of these experiments is the presence of a new SARSr-CoV capable of infecting humans, under only BSL-2 and BSL-3 conditions.

Considered lab-leak scenarios

It seems only "straw-men" lab-leak arguments are presented, that is to say, the following scenarios are addressed: 1) isolation of novel viruses through serial amplification in Vero E6 cells, 2) "accidental infection in the course of serial passage of a SARSr-CoV" in wild-type mice, and 3) Gain of Function research intended to create a more pathogenic virus. These are all very specific scenarios, and immediately illustrate the aforementioned use of qualifiers that have the effect of deceiving the reader. With regards to:

Scenario 1: in addition to use of Vero E6 cells, the WIV is known to have used "primary or transformed bat cell lines that we have developed from Myotis davidii, Rhinolophus sinicus, Myotis chinensis, Rousettus leschenaultia and other bats of China"[2]. Arguments pertaining specifically to culture in Vero E6 cells do not necessarily apply to other isolation methods. Dismissing scenarios involving culture in VeroE6 cells can erroneously give the impression that other highly similar scenarios may be equally dismissed.

Scenario 2: While the authors initially mention only "passage in common laboratory animals", they only address this scenario in the context of wild-type mice, or gain of function experiments selecting for "increased pathogenicity and transmissibility" (to be discussed in Scenario 3). This completely ignores the possibility of accidental infection from virus in cell culture, or from laboratory animals other than wild-type mice. Dismissing scenarios involving passage in wild-type mice can erroneously give the impression that other highly similar scenarios may be equally dismissed.

Scenario 3: Research that could reasonably be expected to create a more pathogenic virus (even if that is not the goal) is often considered gain of function research as well. Addition of the assumption that the research is intended to increase transmissibility or pathogenicity allows certain scenarios to be dismissed, and can erroneously give the impression that other highly similar scenarios may be equally dismissed. Notably, attempts to adapt a SARSr-CoV for study in animal models should constitute Gain of Function research attempting to create a more pathogenic/transmissible virus within the animal model.

Arguments against the considered lab leak scenarios

As evidence against their scenarios, the following arguments are presented: 1) Chinese investigations have reported no links to laboratory work, 2) there is a lack of evidence that the WIV possessed a SARS-CoV-2 precursor prior to the pandemic, 3) there was no reason to hide work on a SARS-CoV-2 precursor prior to the pandemic, 4) that past outbreaks were not caused by labs, 5) Reports of illness during a period of high influenza transmission are not conclusive without further data, 6) Furin cleavage sites are lost in serial passage in VeroE6 cells, 7) the furin cleavage site in SARS-CoV-2 is suboptimal, 8) SARS-CoV-2 was not perfectly adapted to humans or mice when the outbreak started. 9) Some known viruses with part of their genome closer to SARS-CoV-2 were not collected by the WIV.

All these arguments are utterly unconvincing, for the following reasons:

Argument 1: There is a massive conflict of interest, and these results are impossible to verify.

Argument 2: Absence of evidence is not evidence of absence. Indeed, the WIV's virus database has not been available for inspection, it is known that the WIV extensively sampled the area containing the closest known viruses to SARS-CoV-2, the WIV has had full genome sequences of novel viruses for years before disclosure, and the WIV was working on undisclosed SARSr-CoVs causing pathogenic effects in mice expressing hACE2.

Argument 3: The lack of an apparent reason for hiding work doesn't change the fact that much of their work prior to the pandemic remained hidden for years (the RaTG13 genome sequence for instance), and much remains hidden to this day (such as the contents of the WIV database).

Argument 4: There was a lack of capacity in the past to grow and manipulate viruses. The lack of past events when capability was lacking is not relevant to the current situation where new pathogenic viruses are actively sought out for culture in labs, and new chimeras are routinely generated.

Argument 5: The lack of conclusive evidence for a hypothesis is not evidence for another hypothesis

Argument 6: Furin cleavage sites are strongly selected for via other propagation methods, such as Caco-2, Calu-3 and primary HAE cells[14].

Argument 7: The WIV has previously added a suboptimal cleavage site to a coronavirus spike protein[15], and a suboptimal cleavage site may be a tradeoff, as it enhances entry in some cell types, but not others[14].

Argument 8: There should be no expectation that the virus would be perfectly adapted before it spreads. Under any reasonable scenario, a sub-optimal progenitor is first present. It must be kept in mind that passage in cell culture or an animal model is not the same as transmission in real humans in the environment outside of the lab. There is also no comparing a limited duration of handling in a lab with the massive chances for mutation that result from the multitude of continuous transmission chains that are present during the massive spread of a worldwide pandemic. Notably, B.1.617.2, the most-fit strain to date, appeared more than a year after SARS-CoV-2 began spreading uncontrolled throughout the world-wide human population.

Argument 9: Given that we do not know what viruses the WIV or its personnel had or were exposed to, it seems quite irrelevant that some other labs collected viruses that had parts of their genome that were closer to SARS-CoV-2 – particularly given that these viruses were collected close to where the WIV extensively sampled.

Arguments for the natural origin scenario

The authors present a number of arguments for a vague natural spillover scenario, and do not present any arguments against it or evidence that would reduce confidence in the natural origin scenario without also presenting an excuse or explanation that would still be compatible with a natural origin. This is the complete opposite of their consideration of lab-leak scenarios in which they only consider highly specific scenarios, make no attempt to provide supporting evidence, and attempt to present and explation as to how the evidence would still be compatible with a lab-leak. This preferential treatment was apparently not enough, and the authors also resort to making false claims to pre-emptively dismiss any argument against a natural origin scenario (discussed ater). Their bias is thus laid bare.

In short, the authors argue/cite evidence that: 1) some early cases visited the markets, 2) early cases cluster near markets, 3) there was a wild animal trade present in Wuhan, and Wuhan is a big city, 4) wild animals host SARSr-CoVs and people in Yunnan have IgG antibodies reactive against SARSr-CoVs.

This all argues in favor of a natural origin being plausible, but it is certainly not sufficient to establish that it was a natural origin, and there is an utter lack of direct evidence showing a natural origin.

Regarding those arguments/evidence:

Argument 1: Only 1 case of lineage A was found to have a market link. No attempt was made to analyze the proportion of the population with market links and to determine if these links are relevant or simply by chance. One would expect many of the early cases to have links to cell phone possession, yet no one would reasonably suggest that such a link is relevant to the origin of the virus. Furthermore, as all cases come after the A and B lineage split, it must be regarded that the earliest verified cases do not represent the origin, a notion well known in their previously published and cited papers[10,12,16,17].

Argument 2: Early cases also cluster near labs that worked on SARSr-CoV, with BSL-2 or BSL-3 facilities, particularly the Wuhan CDC[18,19], although the early cases discussed are still too late to represent the actual origin point. The authors use a highly deceptive figure to illustrate their point, in which labs close to the earliest verified cases are simply not shown (see figure 1).

Argument 3: Trade in wild-animals is present in many large cities in many countries, this is not sufficient to establish that Wuhan would be a probable location where a new virus would emerge.

Argument 4: That coronaviruses may emerge from wild animals is not in dispute. Yet, there is no evidence of IgGs reactive to SARS-CoV-2 in the cited areas, and all tests have been negative.

Ignored evidence against the natural origin scenario

All sampled Bats in Wuhan/the Hubei province have been negative for SARSr-CoVs[7–9]. Absence of evidence can be evidence of absence when the evidence is sought and would expected to be found if it were present.

The wild animal trade in Wuhan is less extensive than larger, closer cities (to Yunnan) in southern China (particularly Guangdong)[20,21], which is where both previous SARS-CoV-1 outbreaks occurred. Wuhan is only the 9th largest city in China, and only 6.1% of the population of the population of the 20 largest cities[22]. It lies 1500km away from Yunnan. An outbreak natural occurring first in Wuhan is thus improbable (although not impossible), and was recognized as such by Shi Zhengli[23].

When SARS-CoV first spilled over into humans, the positive selection rate was observed to be high, particularly in the S-gene, and then slowed as the epidemic progressed and the virus adapted to

humans[24,25]. This is not the case with SARS-CoV-2, the positive selection rate is much lower than what was observed when SARS-CoV first spilled over into humans[26,27] and is under overall purifying selection[28]. While mutations have increased the fitness of SARS-CoV-2 in humans, particularly in the Spike protein, aside from D614G, these appeared relatively late in the pandemic after a period of relative stasis lasting about 11 months [29], many appear to be selected for by pressure to escape adaptive immunity, such as E484K[30].

False and deceptive statements, unsupported assertions

While the treatment of the arguments for and against natural or lab-related origins was clearly biased and meant only to support one side, numerous false or otherwise deceptive statements were made by the authors that must be commented on.

"While animal carcasses retrospectively tested negative for SARS-CoV-2, these were unrepresentative of the live animal species sold, and specifically did not include raccoon dogs and other animals known to be susceptible to SARS-CoV-2"

The only carcasses mentioned in the WHO report were those of 6 Badgers[7], which are mustelids. Badgers were sold at the Wet market[31] and thus are representative of the live animal species sold. Furthermore, live ferrets, also mustelids, were captured near the wet market and tested in February or March 2020. Mustelids, and ferrets in particular, are known to be susceptible to SARS-CoV-2 infection[32,33]. Furthermore, 27 cats, which are known to be susceptible to SARS-CoV-2[34], from in and around the market were tested. Thus, **the claim that tests specifically did not include animals known to be susceptible to SARS-CoV-2, is demonstrably false.**

"No published work indicates that other methods, including the generation of novel reverse genetics systems, were used at the WIV to propagate infectious SARSr-CoVs based on sequence data from bats" * ie. methods other than "serial amplification in VeroE6 cells"*

This statement is unequivocally false. First, SARSr-CoVs were propagated in Hela cells expressing human ACE2, based on sequence data from bats[35]. This remains a case of mere cell culture, and may be taken as a minor falsehood.

Additionally the qualifiers "*published work"* and "*based on sequence data from bats"* are unnecessary and deceptive. The qualifier "published work" excludes other suitable records that could provide evidence of novel reverse genetic systems. Furthermore, there seems to be no relevance to the qualifier "*based on sequence data from bats"*, as is not relevant to the question of whether a novel CoV was being propagated – indeed a new virus may be cultured from a sample, and thus propagated, before being sequenced. There are *records* showing that other methods were used to propagate infectious SARSr-CoVs, including infection of humanized mice. There were also projects [13] describing the use of "S protein sequence data, infectious clone technology, in vitro and in vivo infection experiments", suggesting the use of "sequence data from bats" and "propagat[ion] of infectious SARSr-CoVs". **The claim's use of qualifiers is thus deceptive, and would lead readers to have an understanding quite different from the facts, and appears to be an obvious attempt to deceive.**

"Examination of the locations of early cases shows that most cluster around the Huanan market, located north of the Yangtze river"

The figure provided by Holmes et al. is highly deceptive, and example of cherry-picking data. Only the location of the P4 campus of the WIV is shown. Notably, according to diplomatic cables from 2018, the WIV was not authorized to work on SARS-CoV at this facility[36]. Work on bat-CoVs was performed under BSL-2 (cell culture) and BSL-3 (animal experiments) conditions. Notably, the Wuhan CDC has BSL-2

facilities, the main WIV campus in the center of the city has BSL-2 and BSL-3 labs, and BSL-3 experiments were also done with bat-CoVs at the Wuhan Center for Animal Experimentation. Furthermore, a shuttle operates to take researchers/workers from the main campus of the WIV to the P4 campus on the outskirts of the city, thus any person infected at the WIV P4 campus may pass through the WIV main campus. Also note that the home addresses of the cases are shown, which does not indicate where they were infected.

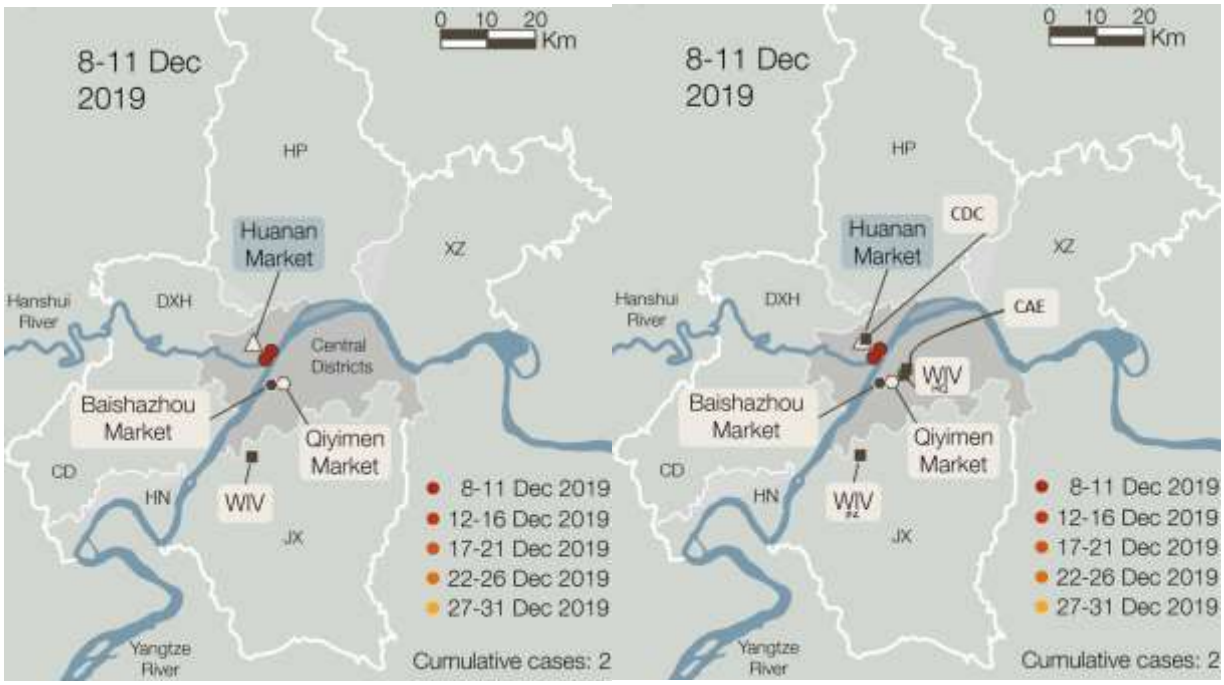

Figure 1: Left: the image shown by Holmes et al, displaying markets, cases, and the location of the WIV P4 campus. Right: A more complete image additionally showing the location of the main WIV campus (WIVHQ), the Wuhan CDC (CDC), and the Wuhan Center for Animal Experimentation (CAE). Note that the geographic association with markets is no stronger than the geographic association with labs working on bat-CoVs.

Omission of other labs in Wuhan from the original images is deceptive.

"The only previous studies of artificial insertion of a furin cleavage site at the S1/S2 boundary in the SARS-CoV spike protein utilized an optimal 'RRSRR' sequence in pseudotype systems"/"there is no evidence of prior research at the WIV involving the artificial insertion of complete furin cleavage sites into coronaviruses."

The fact is that there have been at least one other case of "artificial insertion of a furin cleavage site at the S1/S2 boundary in [a coronavirus] spike protein": notably it did not utilize "an optimal 'RRSRR' sequence". The sequence in question is RTFRF, and was done in the spike protein of HKU4-CoV, notably this addition was done at none other than the WIV[15].

It must be noted that this coronavirus spike protein was expressed in a pseudovirus, so technically it was not inserted into a coronavirus. Despite this, there is a clear pattern of moving to live viruses, particularly by the WIV, in recent years as seen by the studies using the WIV-1 backbone[35,37,38] and the published project descriptions[13].

Again, deceptive and unnecessary qualifiers are seen: Holmes et al. needlessly include the qualifier "SARS-CoV" when "a coronavirus" would suffice and be equally relevant – not even insertion of a furin cleavage site into RaTG13 would render the statement false, yet it would be more relevant to the origin

question than addition into SARS-CoV-1. ***Holmes et al. ignore that the WIV artificially added a suboptimal furin cleavage site into a coronavirus spike protein, and lead the readers to an opposite conclusion through the use of unnecessary qualifiers. This can only be taken as a dishonest attempt at misdirection.***

"no evidence nor mention of a SARS-CoV-2-like virus in any prior publication or study from the WIV" / "Under any laboratory escape scenario SARS-CoV-2 would have to have been present in a laboratory prior to the pandemic, yet no evidence exists to support such a notion"/ "there is no data to suggest that the WIV—or any other laboratory—were working on SARS-CoV-2, or any virus close enough to be the progenitor, prior to the COVID-19 pandemic."
First, RaTG13 is a SARS-CoV-2-like virus, was mentioned in a prior publication (as BtCoV-4991), and was clearly present at the WIV approximately 7 years prior to the outbreak[39], **this is sufficient to render the claim false**.

Second, it must be considered what a prior "mention of a SARS-CoV-2-like virus in any prior publication" would be prior to the naming of the virus SARS-CoV-2. SARS-CoV-2 is a Bat coronavirus, of the SARS-like CoV lineage, using ACE2: any mention of such a virus would constitute prior evidence of a SARS-CoV-2 like virus. Thus project number 31800142, "Pathogenicity of two new bat SARS-related coronaviruses to transgenic mice expressing human ACE2" (http://www.preintell.cn/nsfc/search/), constitutes evidence of 2 SARS-CoV-2 like viruses under study at the WIV, rendering the claim patently false or dependent upon the vagueness of the term "like".

Third, there is evidence from publications that the WIV possessed samples from patients infected by a novel coronavirus, capable of infecting humans, located in the exact same cave where RaTG13 (undoubtedly a SARS-CoV-2 like coronavirus) was found[40,41]. There is thus evidence that there was a good chance that the Mojiang miner's virus was a SARS-CoV-2-like coronavirus.

Fourth, in 2014 alone, 171 samples were reportedly taken from the same location that RaTG13 was found[2]. There is data proving the sample of RaTG13 was repeatedly accessed prior to the pandemic. There is data proving that not all collected CoVs are disclosed[39,42]. Thus this evidence provides a good reason to expect that additional SARS-CoV-2-like viruses were found.

"A specific laboratory escape scenario involves accidental infection in the course of serial passage of a SARSr-CoV in common laboratory animals such as mice. However, early SARS-CoV-2 isolates were unable to infect wild-type mice"
This statement is extremely misleading, as multiple project descriptions from the WIV clearly report the use of humanized mice, not wild-type mice[43]. ***Holmes et al again add unnecessary qualifiers. While SARS-CoV-2 initially did not infect wild-type mice, it did infect mice expressing hACE2, which are known to be used at the WIV. This statement is apparently another dishonest attempt at misdirection.***

"Viral genomic sequencing without cell culture, which was routinely performed at the WIV, represents a negligible risk as viruses are inactivated during RNA extraction"
This statement is extremely misleading, as cell culture was carried out with novel CoVs. Public project descriptions mention the use of infectious clones, in vivo infection experiments, cell culture, when assessing SARSr-CoV spillover risk[13,43]. Holmes et al. later argue against a different point (referring to the loss of furin cleavage sites), and (in an apparent contradiction) acknowledge that cell culture of SARSr-CoVs was performed at the WIV.

"None of these closer viruses were collected by the WIV."

Without an audit of the WIV lab, or at least access to its database, this statement is impossible to confirm. It is also impossible to know if an even closer virus was present, although there are reasons to think one might for reasons previously mentioned. **It is also highly deceptive to refer to them as closer viruses when their sequence is only closer than RaTG13's in a minority of each of their genomes.**

"The WIV possesses an extensive catalogue of samples derived from bats and has reportedly successfully cultured three SARSr-CoVs from bats"
While this statement is not necessarily false, it likely understates the number of successfully cultured SARSr-CoVs. According to the grant reports obtained under a freedom of information act request, in year 2 (2015-2016) they "*obtained full genome sequence for **11 CoV isolates***"[2]. They go on to say "These SL-CoVs, ***including four others isolated previously from this colony, Rs3367, RsSHC014, WIV1 and WIV16***, are highly diversified in the S gene, but share similar sequence identity to SARS-CoV in ORFlab (Fig 4). Genomic phylogenetic analysis showed that the SL-CoVs detected in this colony are more closely related to SARS-CoVs from other geographic regions, especially three isolates, WIV16, Rs4874 and Rs4231 (Fig 5). Notably, **among *the 15 SL-CoVs***, two **isolates**, Rs4084 from Rhinolophus sinicus and Rf4092 from Rhinolophus ferrumequinum, are highly similar to SARS-CoV in the ORF8 region (Fig 5)."

Even if it is assumed that they misused the term "isolate" and they actually meant "genomes" or "genomic sequences", when describing the 11 new isolates in year 2, it seems clear that they had 4 cultured isolates before this (Rs3367, RsSHC014, WIV1 and WIV16). Curiously, there is no mention of new isolates (or isolates at all) after year 2. ***It is likely that Holmes et al. are understating the number SARSr-CoVs successfully cultured from bats by an order of magnitude or more.***

"There is no rational experimental reason why a new genetic system would be developed using an unknown and unpublished virus"
Far from being no rational explanation, such an explanation is readily derived from one of the WIV's project descriptions: that novel coronaviruses will be identified, and that reverse genetics will be used to test spillover potential based on the S protein mutations. Spillover risk of a virus might not be adequately assessed merely by placing the S protein of a virus into the backbone of another virus, and thus there is an obvious rational to generate new backbones for the novel viruses, in which S gene substitutions can be tested. Were this not the case, there would seem to be no rational reason to use the WIV-1 backbone, instead of a common and mild human coronavirus such as NL-63.

"This phylogenetic pattern is consistent with the emergence of SARS-CoV-2 involving one or more contacts with infected animals and/or traders, including multiple spill-over events, as potentially infected or susceptible animals were moved into or between Wuhan markets via shared supply chains and sold"
The pattern is more consistent with the emergence from one spillover event. The proposed scenario is exceedingly improbable speculation, with no evidence favoring it over a single spillover event. Indeed, the proposed scenario would suggest multiple infected animals, likely carrying multiple lineages of the precursor virus, causing multiple spillover events that would be expected to result in a multitude of different identifiable early lineages, rather than just lineage A and B with very minor differences between them. **The data are hardly consistent with multiple spill-over events.**

"It displays clear similarities to SARS-CoV that spilled over into humans"
It also displays clear differences, such as the distance to the nearest animal reservoir, and the viral fitness in the first detected human cases. Notably, the article cites multiple factors that are quite different between the SARS-CoV and SARS-CoV-2 outbreaks, such as:

“Both these SARS-CoV emergence events were associated with markets selling live animals” – Data does not suggest that the emergence of SARS-CoV-2 had anything to do with a wet market selling live animals, as previously discussed, the wet market outbreak was likely just an early super-spreader event. Furthermore, many suspected early cases were not allowed to be investigated by researchers outside of China, and attempts were made to delete sequence data (from unknown dates) from early cases[7,11].

“involved species, particularly civets and raccoon dogs, that were also sold live in Wuhan markets in 2019 and are known to be susceptible to SARS-CoV-2 infection” – This ignores the distinction that extensive infection by SARS-CoV was found in the animals after the SARS-CoV outbreaks[44], but has not been found after the SARS-CoV-2 outbreaks[7].

“Animal traders working in 2003, without a SARS diagnosis, were documented to have high levels of IgG to SARS-CoV” – No such similar findings are apparent for SARS-CoV-2[7,9]

“For both SARS-CoV and SARS-CoV-2, there is a considerable geographic gap between Yunnan and the location of the first human cases” – The gap is considerably larger for SARS-CoV-2, and a wet market provides a direct transport method, but as previously noted, spread via the wet market appears to have been ruled out be phylogenetic data.

There are clear differences, and the only real similarity is that they are both coronaviruses that can spread in wet markets there is no evidence pointing towards a wet market being the origin of SARS-CoV-2 – this is pure speculation with no data backing it.

Conclusion

This pre-print contains many misleading statements, is overly credulous of sources with potentially severe conflicts of interest, and makes numerous demonstrably false statements. It further neglects to even mention the fact that WIV researchers were conducting in vivo experiments with humanized mice and novel SARS-related coronaviruses. Such an oversight is inexcusable in a document purporting to be a critical review on the origins of SARS-CoV-2. It furthermore adds unnecessary or irrelevant qualifiers to statements multiple times that have the effect of giving readers an impression contrary to the facts – this appears *prima facie* to be a dishonest attempt at misdirection.

This work displays clear signs of bias and falls well short of being a critical review of the origins. Indeed, the bias and dishonesty may rise to the level of scientific misconduct. Inappropriate exclusion and manipulation of data (“cherry picking” and “faking” data, respectively) would be inexcusable scientific misconduct in a research article. Such practices in a review article should be equally egregious. The paper by Holmes et al. should be immediately retracted, yet it has already being cited by new sources world-wide. Every author listed on the Holmes et al. article should face condemnation from the scientific community for publishing such a biased and inaccurate piece of propaganda, despite their previously high reputations in the scientific community.

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