

**United States Government Expert Analysis on the
WHO-Convened Global Study of the Origins of SARS-CoV-2
Joint China-WHO Report
April 5, 2021**

TOPLINE POINTS

- While the report includes some new relevant information potentially related to the origins of COVID-19, the report has not significantly improved our understanding of how the virus might have started circulating in Wuhan, which was called for in the study's Terms of Reference (TOR) for the investigation.
- Conclusions made by the joint expert team lack raw data and/or supporting information in the final report and annexes. In fact, some sections of the report appear to contradict or undermine conclusions in other parts of the report.
- The information and analyses presented in the report did not provide clear scientific support for any one hypothesis, and additional work is needed to identify the origins and circumstances leading to the emergence of SAR-CoV-2 in the hopes of reducing the probability of a similar event.
- The report does not provide substantive guidance for future investigations, such as prevention of new outbreaks/spillover events, design of studies of novel outbreaks of unknown origin, or lessons on treatments/risk factors for patients.

Methodology

- When reviewed by the international experts, Phase 1 studies appear to have needed additional data and analyses, and some of those analyses may still be underway. The need to refine the design of the studies and interpretation of the analyses suggests problems in the initial parts of the investigation.
- The report does not appear to have fulfilled the TOR, which lays out more extensive studies, such as comprehensive epidemiological analyses and mapping of supply chains of animals and products.
- Summary data were presented to the external panel, but raw data did not seem to be available for analyses, other than viral genome sequence data.
- The report revealed several types of tests and studies that were not yet completed, despite the long time elapsed and potential relevance to the origins of the virus, for example retrospective testing of all available clinical and surveillance samples from Wuhan.
- Some referenced articles have not been peer-reviewed and others appear to have been withdrawn. References claimed to support infectivity actually appear to describe stability.⁴

Key Findings

- The report lists four possible pathways of emergence, but it does not include a description of how these hypotheses were generated, would be tested, or how a decision would be made between them to decide that one is more likely than another. Therefore, it is difficult to understand how each of these could have a probability assigned to it.
- The qualitative risk assessment does not discuss the level of uncertainty associated with different classifications.
- The analysis of the possible pathways of emergence (p.115-123) does not link up well to the three sections presenting the analyses by the working groups. They are a blanket statement of likely versus unlikely, with no link to why the data presented in the report makes one more or less likely.
- The report only provides a cursory look at the laboratory incident hypothesis, and the evidence presented seems insufficient to deem the hypothesis “extremely unlikely.”
- The joint team’s assessment is that “introduction through cold/ food chain products is considered a possible pathway.” Although such a pathway is *theoretically* possible, there is no evidence presented in the report to indicate that it is, in reality, an actual pathway. The report notes the probability of a cold-chain contamination with the virus from a reservoir is very low, it is not emphatically stated in the up-front summary.
- Lack of key data and information on fomite transmission, such as infectious dose, undermines the conclusions about transmission via cold-chain products.
- Alternate explanations for contamination of containers or packaging, such by handling through a COVID-19 infected person, are not adequately explored.
- The three sections presenting working group analyses read more like generalized literature reviews without linkages to the possible pathways of emergence. The report does not bring the three analyses together or discuss how the data from across the analyses informed their conclusions. For example, data from the Huanan Seafood Market is examined by all three working groups, but at no point is that information all clearly brought together to make an overall statement about the role of the Huanan Seafood Market in the early spread of SARS-Cov_2.

Report Recommendations

- The report does not appear to prioritize among the various recommendations, and recommendations may have feasibility challenges at this stage of the pandemic. For example, results of farm surveys could be confounded by human to animal transmission over the past year.
- Phase 2 studies are not well laid-out, with specific, targeted questions to ask to resolve

origins questions.

USG EXPERT ANALYSIS

Main Findings of Working Groups

- **Epidemiology**

- The report concluded that none of the data analyzed showed evidence of widespread circulation of SARS-CoV-2 in Wuhan before December 2019, although could not exclude the possibility of undetected low-level circulation, and suggested additional research to investigate this issue.
- Contrary to the TOR's mandate for the mission to analyze "in-depth reviews of hospital records for cases compatible with COVID-19 before December (page 6), most data analysis and interpretation has been performed on previously compiled assessments from limited sources (a few hospitals and centers). Data are primarily presented as already processed, summary data. It is not evident that raw data was made available to be examined or re-analyzed by the team, or that the team had access to ask for more information beyond what was presented. The data presented do not show the extensive mild/asymptomatic cases that should have been likely before the severe cases were detected. The selection of only two hospitals in Wuhan which show extremely low cases of influenza (e.g., Annex: Figure 3 shows only 20-60 adult confirmed influenza cases in peak influenza season) warrants further discussion.
- The epidemiologic data provided was difficult to follow and the different pieces didn't seem to be consistent with each other. For example, the trends in Influenza-like illness (ILI) data seemed relatively flat year-round in previous years and early in 2019, which was surprising given the seasonal nature of influenza (page 19, figure 1). The 2017-2018 influenza season was a severe epidemic in the Northern hemisphere (as documented by China in the peer-reviewed literature: e.g. <https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-019-4181-2>) and thus Wuhan data showing a flat baseline was inconsistent with previously published data, with the graphic presented in Annex: Figure 1 (page 137), and not expected. Furthermore, Figures 4 and 5 do not correlate to the data presented in Figures 1-3 reporting ILI cases and percent influenza in adults and pediatrics from one hospital each.
- Several types of disease surveillance and mortality data presented from Fall 2019 indicate no evidence of the early circulation of SARS-CoV-2, however the possibility was not excluded and follow-on studies were recommended to further explore this issue. It is unclear why some of the follow-on work is recommended. For example, it is suggested that next steps include further review of data on respiratory illnesses from on-site clinics at the Military Games in October 2019. However, in the discussion of the Military Games and other international events- it is noted that there are no clusters of fever or respiratory illness.
- Additionally, an increase in ILI and laboratory confirmed influenza cases was noted in December 2019, particularly in children. Details were not provided on which subtype(s) were present in these children or if samples were also tested for COVID-19. These results were also not consistent and did not correlate with data on deaths during the same time period, or in next month, as those were found to be in older adults. Without access to the raw data it is difficult to understand the trends in respiratory cases before and during December 2019, and into January 2020.
- Although early reported cases were linked to the Huanan market (or other markets), there were as many cases not linked to markets and also sporadic cases in the community earlier than the first markets cases. This suggests that the virus was circulating unnoticed in the community prior to the first clusters detected associated with the Huanan market.

- The report is not clear about which team considered the 92 cases to be compatible with SAR-CoV-2 infection, the team from 233 health institutions or the international team.
 - Investigation into possible earlier cases should have occurred and is still needed. This is another example of a missed opportunity to further evaluate the initial cases.
 - It is not clear how many “other cases” were reviewed and how they were excluded as incompatible. This appears to be a missed opportunity to thoroughly review the epidemiological studies to identify other possible exposures.
 - **USG Position:** The report’s conclusions are based on limited data sets which likely should be expanded. The recommendations to look further into details and an expanded data set derived from more hospitals and local, regional and national registers are reasonable and justified. However, it seems rather unlikely that new conclusions will be drawn from surveillance data. Thus, new approaches should be considered such as intensified testing of archived material and blood bank specimens (mentioned by the team) to find answers for the emergence of SARS-CoV-2.
- **Molecular Epidemiology**
 - Combining worldwide and early molecular epidemiology was well done. Overall, this section has the format of a manuscript/review article rather than an investigation report. Conclusions, such as linking genomic with epidemiological data, sequence quality control and studying closely related bat sequences, are supported and justified. Other conclusions, such as spreading event at the Huanan Market and unrecognized circulations/introductions, are rather hypothetical. Environmental sample sequences from other countries need to be further verified and supported by additional investigations. This seems very vague and lacks strategy/concept.
 - Some new genetic analyses were generated as part of this study, which is useful to the origin questions. One of the conclusions is that genetic sequences diversity indicates additional sources or unrecognized circulation, but that is not correlated with the epidemiologic data section.
 - Viral genome sequences from the earliest human cases in December 2019 were not included for analysis and comparison, only sequences available after January 2020. Based on sequences available to date, molecular analyses suggest the virus most likely emerged between September and November 2019.
 - The sequences available for analysis from January 2020 already showed different sequences clusters present in the infected people.
 - Access to viral genomes from the first cases in December, if they exist, would be more informative to better characterize the earliest sequences and cases, and perhaps better inform on timeline and source of emergence
 - **USG Position:** There is a need for more early sequences if material is still available/ accessible. This would include specimens from human cases (e.g., blood draws), animals (wildlife and domestic) and environment. A worldwide accessible database needs to be implemented with quality control at entering level. Data analysis needs to be performed by a team of international experts rather than local/national entities. A global effort seems possible on this topic if all countries and researchers agree to a joint concept/strategy.
 - **Animal and Environmental Studies**
 - The report concludes that coronaviruses that are phylogenetically related to SARS-CoV-2 have been identified in multiple animals, but did not identify a specific host. This section of the report includes material on possible cold chain transmission.
 - A significant amount of work has been summarized in this section, unfortunately, with little outcome in identifying the source/reservoir/intermediate host. Some of the

presentations, such as the presentation on SARS-CoV-2 in mink in the Netherlands, is odd and appears peripheral to information requested in the TOR. The link to bats has some evidence based on coronavirus diversity in bats (based on the literature, not findings from the investigation) but this report does not present sufficient data to make conclusions.

- Environmental sampling seems insufficient as it is largely related to the Huanan Market. The same holds true for frozen food and cold-chain products, as the portion of the report looking at cold-chain transmission is 2 pages long (p.110-111) and includes minimal data to analyze the possibility of infection as a result of frozen foods, nor citations to support the assertions. All laboratory evidence so far speaks against frozen food as a source, but current investigations seem insufficient for final conclusions.
- Samples (sample types not clear besides feces) were collected and tested from a number of different wild and domestic animal species, including rabbits, cats, dogs, rodents, porcupines, poultry, swine etc., from different locations and times (total numbers, timing and locations are a bit hard to follow and summarize). All samples tested as a part of this effort were negative for SARS Cov-2 and for antibodies to SARS CoV-2.
- Previous and other published data were also presented and summarize the SARS CoV-2 related viruses sequences detected in bats and pangolins to date. These data support the potential for bats and/or pangolins to be a potential part of the transmission chain of spillover of the virus from animals to people.
- **USG Position:** An area with little attention so far seems to be wildlife farms/traders and breeding farms of wildlife species (nearby or far-away) including illegal farming .If a potential animal source cannot be identified on the nearby consumer market, one should go up the trading and production line. This could be geographically far away as wildlife products are often brought in from long distances. Environmental sampling on different markets within and outside the province may be helpful. The identification of the origin is less likely to be determined through environmental sampling, but data could be supportive. While frozen food and cold-chain products have not been excluded by the current investigations, it is noteworthy that no evidence has been presented is occurring. Further investigations are warranted because viruses are rather stable in cold environments and while contaminated food products could theoretically be a source of infection, there remains no direct evidence of transmission of COVID-19 via cold chain products to date nor does the report present any such evidence. However, highest priority would be investigations into wildlife farms and breeding facilities around Wuhan and greater China, and discussion of frozen or cold-chain food products should differentiate between frozen wildlife products and commercial products. In addition, studies examining wildlife for potential reservoir/amplifying species in China should be expanded. Finally, a global effort should be initiated to look into reservoir/intermediate host species.

Possible Pathways of Emergence

- **Direct zoonotic transmission**
 - Data from this report did not shed any additional light on this hypothesis.
 - While the global scientific community agrees that this is a likely source, the studies documented in the report did not uncover much new information on the original virus reservoir—no analysis of new data, or visits to possible locations in Wuhan or elsewhere.
 - The published data to date show that the most closely related viruses, but not any sequences identical to SARS CoV-2, have been found in a number of *Rhinolophid* bats species in China, Japan Cambodia and Thailand. This is also the group of bats that has been shown to carry SARS CoV-1 related viruses. This is still the strongest evidence to

date based on the published literature that bats may be linked in some way to the emergence of SAR CoV-2.

- **USG Position:** The evidence provided in the report does not support this hypothesis over others; however, the published data fit best with the hypotheses of either a direct zoonotic transmission or transmission via an intermediate animal host.
- **Introduction through intermediate host followed by zoonotic transmission**
 - Data from this report did not shed much additional light on this hypothesis. There is some evidence to support an intermediate animal host or hosts may be linked to transmission to people.
 - Published data to date show that pangolins also carry viruses related to SARS CoV-2 (90% similarity). Additionally, also from the literature and/or experimental studies, other species have been shown to be susceptible to COVID-19 infection.
 - Introduction via an intermediate host is not well separated from “direct zoonotic transmission,” and it is not clear what evidence would distinguish these two hypotheses.
 - **USG Position:** The evidence provided in the report does not support this hypothesis over others; however, the published data fit best with the hypotheses of either a direct zoonotic transmission or transmission via an intermediate animal host.
- **Introduction through the cold/food chain**
 - The joint team’s assessment is that “introduction through cold/ food chain products is considered a possible pathway.” Although such a pathway is *theoretically* possible, the evidence presented in the report does not suggest that it is, in reality, an actual pathway.
 - Currently, there are no data to support the hypothesis that the introduction came through foodborne transmission; therefore, it is not likely that the introduction came through foodborne transmission. However, this route of transmission cannot be excluded either at the moment.
 - Not only is infection via frozen food items considered low likelihood, for this to be the source of the original Wuhan infections, there would need to be a high level of SARS-CoV-2 infection in another community for food products to carry enough virus to provide an infectious dose. It seems unlikely that such a high rate of infection in any other city or country would have been missed.
 - This section included discussion of environmental sampling and description of vendors at the Huanan market, a description of the supply chain for and sampling of animals at the market (in Jan – March, 2020), domestic animal testing, and further testing of livestock and captive wildlife for SARS-CoV-2. It also includes discussion of what is termed the “study on cold-chain products”. However, it does not appear to be a well-designed study, but rather some opportunistic surveillance; the sampling design and any rationale for it is not discussed.
 - They present data from China that indicate that some imported cold-chain samples have tested positive and that some workers at import facilities had Covid-19 which demonstrates an association, but not causality.
 - Furthermore, they do not provide any details about the analytical methods or provide any details of the handling of the product before it was sampled to control for potential contamination within China. Note that from our understanding the imported products are sampled at a special warehouse that the products are moved to after they clear Chinese customs and many of the positives were from samples collected on the outside packaging, leaving opportunity for contamination from workers to have occurred.

- Lastly, they do not discuss the false positive rate of the tests used (or provide data on the performance of positive and negative controls). Note that we heard at one point, only about 40 samples of imported cold-chain product out of about 1.5 million samples tested positive (or < 0.003%).
 - The report does not discuss the temporal relationship between tests and cases or any potential confounding factors (e.g., person-to-person spread, or transfer of RNA from already infected, asymptomatic cases to the packaging), which are key considerations for drawing conclusions about causality rather than associations.
 - Documented evidence or peer-reviewed scientific publications are needed to support these statements.
 - This paragraph points to the potential for other exposures besides cold-chain seafood.
 - The report focuses a great deal on the exterior packaging of frozen products. More information is needed about the potential for the shipping container itself to serve as the point of contamination. More information is needed to document the traceability of particular shipping containers. Consideration needs to be given to the point at which the shipping container may have become contaminated, such as when it was in a shipping yard in China.
 - This is noteworthy, as there is a recommendation to conduct further testing of stored product. It is also interesting that no domestic products were sampled and tested.
 - There is no further information about these “index cases” and how they were evaluated for other exposures.
 - This supports the argument against this theory and is the same conclusion many other countries, including the United States has reached.
 - ***USG Position:*** Although it might be theoretically possible that the cold-chain could be involved in transmission of CoV-2, there is no credible evidence presented in the report to support that it actually occurred. If contaminated food entered markets such as the Huanan Market, one would likely have to assume that clusters/outbreaks would have occurred in another location, which has not yet been detected.
- **Introduction through a laboratory incident**
 - The main report does not describe sufficient investigation into a potential laboratory incident, and there are no data presented in the report on this scenario. In the Annex, there are short visits described to Hubei CDC, Wuhan CDC and Wuhan Institute of Virology (WIV), though there is limited discussion of potential laboratory accidents or examination of records to dismiss the possibility. Possibilities for a lab-associated origin could include: direct infection of a laboratory worker; infection of a field worker collecting animal specimens; or improper disposal of an infected animal from a laboratory resulting in a human being infected.
 - The report reveals that WIV leadership said none of the staff tested positive for the virus or antibodies to the virus, however there were few details provided on employee health monitoring, dates of antibody and PCR screening, and numbers of lab members tested on those dates.
 - Data presented regarding laboratory visits by the team to investigate possible sources of the outbreak also does not include adequate data to examine possible exposure by laboratory workers in the field while sampling bats or other animals, which could have led to the first case.
 - ***USG Position:*** There was minimal investigation into this possibility. The assessment of this hypothesis being extremely unlikely is justified based on the narratives provided by the labs, however one should not give the impression that this is based on data derived from a forensic investigation of the laboratory.

Recommendations for Next Steps

The lack of definitive conclusions in the report is not surprising given the mandate of the team and the circumstances in interacting with the Chinese colleagues and the difficulty tracing the origins of emerging infectious diseases.

On a positive note, the report summarizes a tremendous amount of data (published or unpublished) and provides reasonable and justified recommendations for second-phase investigations. It also lays out many deficiencies as well as needs for future investigations. Finally, it provides two likely (not surprising) scenarios for the emergence of SARS-CoV-2 in the human population. Future investigations should be more timely and better prepared with direct involvement of the team leading the investigation and countries/laboratories performing it. On a negative note, the report does not exclude any of the four scenarios or provide support for any scenario beyond what was known previously. There was no direct investigation into the scenario of a laboratory incident – something that the investigation was not set up to allow. One could view the report as a decent start into a second-phase investigation. Future studies need to focus on broader searching for virus hosts (e.g., expanding animals sampled), more coherent hypothesis testing, and specific targeted questions that refine details about the origins of the virus/outbreak. Every recommendation for Phase 2 work should specify joint review to ensure the WHO team has access to data it needs to conduct thorough analyses.

Identifying the source of an epidemic/pandemic is not an easy task and success is not a given. The biggest lesson learned from the investigation/report is that transparency and real-time information/data sharing is key in the fight against infectious disease events of global dimension. It is also important to acknowledge that trying to do these "origin" studies after outbreaks/epidemics/pandemics start is never going to be easy. For many outbreaks, the source and spillover mechanism were not conclusively identified during or after the outbreaks, or the understanding of the origins came many years later. We must understand that expanded efforts to understand new pathogens and where they come from *before* there are widespread outbreaks is needed. Otherwise, we will continue to do the same thing over and over again—that is, wait until after outbreaks start while hoping for better results on sources of the pathogens.

Origins Review USG Expert Group

Mara Burr, JD, LLM

Director, Multilateral Relations
Office of Global Affairs
US Department of Health and Human Services
Mara.Burr@hhs.gov

Ray Arthur, PhD

Director, Global Disease Detection Operations Center
Emergency Response and Recovery Branch
Division of Global Health Protection, Center for Global Health
US Centers for Disease Control and Prevention

rca8@cdc.gov

Hillary H. Carter, PhD

Senior Advisor
Office of Countering Weapons of Mass Destruction
Department of Homeland Security
hillary.carter@hq.dhs.gov

Michelle Catlin, PhD

International Coordination Executive
Food Safety and Inspection Service
U.S. Department of Agriculture
michelle.catlin@usda.gov

Clara Davis, PhD

Foreign Affairs Officer
US Department of State
DavisCL@state.gov

Erika Elvander, PhD

Director, Asia and the Pacific
HHS Health Attaché Designee to China
Office of Global Affairs, HHS
Erika.Elvander@hhs.gov

Heinz Feldmann, MD, PhD

Chief, Laboratory of Virology
National Institute of Allergy and Infectious Diseases, National Institute of Health
Healthfeldmannh@niaid.nih.gov

Jose A. Fernandez, PhD

Deputy Director, Office of Pandemics and Emerging Threats
Office of Global Affairs
U.S. Department of Health and Human Services
Jose.Fernandez@hhs.gov

Tracey Goldstein, PhD

Division Chief, Emerging Threats Division
Office of Infectious Disease, Bureau for Global Health
USAID
tgoldstein@usaid.gov

Adrienne Keen, Ph.D.

Bureau of Intelligence and Research
U.S. Department of State

keenAR@state.gov

Larry Kerr, PhD

Director, Office of Pandemics and Emerging Threats
Office of Global Affairs
US Department of Health and Human Services
lawrence.kerr@hhs.gov

Paul Kiecker

Administrator
Food Safety and Inspection Service
U.S. Department of Agriculture
paul.kiecker@usda.gov

Robin M. Moudy, PhD

Senior Science Advisor and Team Lead
Office of Global Affairs
U.S. Department of Health and Human Services
Robin.Moudy@hhs.gov

Amy Norris

Senior Global Health Advisor
Bureau of International Organizations Affairs
U.S. Department of State
NorrisAB@state.gov

Donald A. Prater, DVM

Acting Assistant Commissioner for Food Safety Integration
Office of Foods and Veterinary Medicine
Food and Drug Administration
Donald.Prater@fda.hhs.gov

Kis Robertson Hale, DVM, MPH

Deputy Assistant Administrator, Chief Public Health Veterinarian
Office of Public Health Science
Food Safety and Inspection Service
U.S. Department of Agriculture
kis.robertson@fsis.usda.gov

Collin Weinberger, MPH

Senior Advisor and Team Lead, Influenza and Pandemic Preparedness
Office of Global Affairs, Pandemics and Emerging Threats
U.S. Department of Health and Human Services
collin.weinberger@hhs.gov