

WHO-convened Global Study of Origins of SARS-CoV-2:
China Part

Joint WHO-China Study
14 January-10 February 2021

Joint Report

LIST OF ABBREVIATIONS AND ACRONYMS

ARI	acute respiratory illness
cDNA	complementary DNA
China CDC	Chinese Center for Disease Control and Prevention
CNCB	China National Center for Bioinformation
CoV	coronavirus
Ct values	cycle threshold values
DDBJ	DNA Database of Japan
EMBL-EBI	European Molecular Biology Laboratory and European Bioinformatics Institute
FAO	Food and Agriculture Organization of the United Nations
GISAID	Global Initiative on Sharing Avian Influenza Database
GOARN	Global Outbreak Alert and Response Network
Hong Kong SAR	Hong Kong Special Administrative Region
Huanan market	Huanan Seafood Wholesale Market
IHR	International Health Regulations (2005)
ILI	influenza-like illness
INSD	International Nucleotide Sequence Database
MERS	Middle East respiratory syndrome
MRCA	most recent common ancestor
NAT	nucleic acid testing
NCBI	National Center for Biotechnology Information
NMDC	National Microbiology Data Center
NNDRS	National Notifiable Disease Reporting System
OIE	World Organisation for Animal Health (Office international des Epizooties)
PCR	polymerase chain reaction
PHEIC	public health emergency of international concern
RT-PCR	real-time polymerase chain reaction
SARI	severe acute respiratory illness
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SARSr-CoV-2	Severe acute respiratory syndrome coronavirus 2-related virus
tMRCA	time to most recent common ancestor
WHO	World Health Organization
WIV	Wuhan Institute of Virology

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SUMMARY

In May 2020, the World Health Assembly in resolution WHA73.1 requested the Director-General of the World Health Organization (WHO) to continue to work closely with the World Organisation for Animal Health (OIE), the Food and Agriculture Organization of the United Nations (FAO) and countries, as part of the One Health approach, to identify the zoonotic source of the virus and the route of introduction to the human population, including the possible role of intermediate hosts. The aim is to prevent both reinfection with the virus in animals and humans and the establishment of new zoonotic reservoirs, thereby reducing further risks of the emergence and transmission of zoonotic diseases.

In July 2020, WHO and China began the groundwork for studies to better understand the origins of the virus. Terms of Reference (TORs) were agreed that defined a phased approach, and the scope of studies, the main guiding principles and expected deliverables. The TORs envisaged an initial Phase 1 of short-term studies to better understand how the virus might have been introduced and started to circulate in Wuhan, China.

WHO selected an international multidisciplinary team of experts to work closely with a multidisciplinary team of Chinese experts in the design, support and conduct of these studies and to conduct a follow-up visit to review progress and agree upon a series of further studies.

The joint international team comprised 17 Chinese and 17 international experts from other countries, the World Health Organization (WHO), the Global Outbreak Alert and Response Network (GOARN), and the World Organisation for Animal Health (OIE) (Annex B). The Food and Agriculture Organization of the United Nations (FAO) participated as an observer. Following initial online meetings, a joint study was conducted over a 28-day period from 14 January to 10 February 2021 in the city of Wuhan, People's Republic of China.

The team agreed a workplan and established working groups to review the progress made in Phase 1 studies in the areas of: epidemiology; animals and the environment; and molecular epidemiology and bioinformatics. During the course of the discussions, the international experts gained deeper understanding of the methods used and data obtained. In response to requests during the visit, further data and analyses were generated, reflecting a productive iterative approach to refining the design and interpretation of complex studies in all areas.

In addition to group work, the team shared scientific and thematic presentations on relevant topics to help inform its work, undertook a series of site visits to important locations and conducted interviews with key informants.

The epidemiology working group closely examined the possibilities of identifying earlier cases of COVID-19 through studies from surveillance of morbidity due to respiratory diseases in and around Wuhan in late 2019. It also drew on national sentinel surveillance data; laboratory confirmations of disease; reports of retail pharmacy purchases for antipyretics, cold and cough medications; a convenience subset of stored samples of more than 4500 research project samples from the second half of 2019 stored at various hospitals in Wuhan, the rest of Hubei Province and other provinces. In none of these studies was there evidence of an impact of the causative agent of COVID-19 on morbidity in the months before the outbreak of COVID-19.

Furthermore, surveillance data on all-cause mortality and pneumonia-specific mortality from Wuhan city and the rest of Hubei Province were reviewed. The documented rapid increase in all-cause mortality

and pneumonia-specific deaths in the third week of 2020 indicated that virus transmission was widespread among the population of Wuhan by the first week of 2020. The steep increase in mortality that occurred one to two weeks later among the population in the Hubei Province outside Wuhan suggested that the epidemic in Wuhan preceded the spread in the rest of Hubei Province.

Both surveillance data and cases reported to the National Notifiable Disease Reporting System (NNDRS) in China were subjected to clinical review. The NNDRS was notified of 174 COVID-19 cases with onset of symptoms in December 2019. In an extensive exercise by 233 health institutions in Wuhan, some 76,253 records of cases of respiratory conditions in the two months of October and November before the outbreak in late 2019 were scrutinized clinically. Although 92 cases were considered to be compatible with SARS-CoV-2 infection after review, subsequent testing and further external multidisciplinary clinical review determined that none was in fact due to SARS-CoV-2 infection. Based on the analysis of this and other surveillance data, it is considered unlikely that any substantial transmission of SARS-CoV-2 infection was occurring in Wuhan during those two months.

Many of the early cases were associated with the Huanan market, but a similar number of cases were associated with other markets and some were not associated with any markets. Transmission within the wider community in December could account for cases not associated with the Huanan market which, together with the presence of early cases not associated with that market, could suggest that the Huanan market was not the original source of the outbreak. Other milder cases that were not identified, however, could provide the link between the Huanan market and early cases without an apparent link to the market. No firm conclusion therefore about the role of the Huanan market in the origin of the outbreak, or how the infection was introduced into the market, can currently be drawn.

The molecular epidemiology and bioinformatics working group examined the genomic data of viruses collected from animals. Evidence from surveys and targeted studies so far have shown that the coronaviruses most highly related to SARS-CoV-2 are found in bats and pangolins, suggesting that these mammals may be the reservoir of the virus that causes COVID-19. However, neither of the viruses identified so far from these mammalian species is sufficiently similar to SARS-CoV-2 to serve as its direct progenitor. In addition to these findings, the high susceptibility of mink and cats to SARS-CoV-2 suggests that additional species of animals may act as a potential reservoir.

To analyse the viral genomes and epidemiological data from the early phase of the outbreak, the team reviewed data collected through the China National Centre for Bioinformation integrated database on all available coronavirus sequences and their metadata. All sequence data from samples collected in December 2019 and January 2020 were subjected to deeper analysis to see the diversity of viruses in the first phases of the outbreak. For the cases detected in Wuhan, data on samples from cases with illness onset before 31 December 2019 were linked with epidemiological background data. Several samples from patients with exposure to the Huanan market had identical virus genomes, suggesting that they may have been part of a cluster. However, the sequence data also showed that some diversity of viruses already existed in the early phase of the outbreak in Wuhan, suggesting unsampled chains of transmission beyond the Huanan market cluster. There was no obvious clustering by the epidemiological parameters of exposure to raw meat or furry animals.

In addition, the time to the most recent common ancestor of the SARS-CoV-2 sequences in the final data set was estimated and compared with results from previous studies. Such analyses can be considered estimates but do not provide definitive proof of time of origins. Based on molecular sequence data, the results suggested that the outbreak may have started some time in the months before the middle of December 2019. The point estimates for the time to the most recent ancestor ranged from late September to early December, but most estimates were between mid-November and early December.

Finally, the team reviewed data from published studies from different countries suggesting early circulation of SARS-CoV-2. The findings suggest that circulation of SARS-CoV-2 preceded the initial detection of cases by several weeks. Some of the suspected positive samples were detected even earlier

than the first case in Wuhan, suggesting the possibility of missed circulation in other countries. So far, however, the quality of the studies is limited. Nonetheless, it is important to investigate these potential early events.

The animal and environment working group reviewed existing knowledge on coronaviruses that are phylogenetically related to SARS-CoV-2 identified in different animals, including horseshoe bats (*Rhinolophus* spp) and pangolins. However, the presence of SARS-CoV-2 has not been detected through sampling and testing of bats or of wildlife across China. More than 80 000 wildlife, livestock and poultry samples were collected from 31 provinces in China and no positive result was identified for SARS-CoV-2 antibody or nucleic acid before and after the SARS-CoV-2 outbreak in China. Through extensive testing of animal products in the Huanan market, no evidence of animal infections was found.

Environmental sampling in Huanan market from right at the point of its closing showed out of 923 environmental samples in Huanan market, 73 samples were positive. This revealed widespread contamination of surfaces with SARS-CoV-2, compatible with introduction of the virus through infected people, infected animals or contaminated products.

The supply chains to Huanan market included cold-chain products and animal products from 20 countries, including those where samples have been reported as positive for SARS-CoV-2 before the end of 2019 and those where close relatives of SARS-CoV-2 are found. There is evidence that some domesticated wildlife the products of which were sold in the market are susceptible to SARS-CoV, but none of the animal products sampled in the market tested positive in this study. In the early phase of pandemic, due to lack of awareness of the potential role of cold chain in virus introduction and transmission, the cold-chain products were not tested. These findings, however, do raise the possibility of different potential pathways of introduction. Preliminary sampling and testing of other markets in Wuhan and upstream suppliers to the Huanan market taken during 2020 did not reveal evidence of SARS-CoV-2 circulating in animals.

SARS-CoV-2 has been found to persist in conditions found in frozen food, packaging and cold-chain products. Index cases in recent outbreaks in China have been linked to the cold chain; the virus has been found on packages and products from other countries that supply China with cold-chain products, indicating that it can be carried long distances on cold-chain products.

Further analysis will examine spatial and temporal correlations and correct for underlying biases in sampling, and also to trace frozen products back to the Huanan market from suppliers.

The team suggested next-phase studies to help tracing the origin of SARS-CoV-2 and the closest common ancestor to this virus, including analysis of trade and history of trade in animals and products in other markets, particularly in markets epidemiologically linked to early human cases or sequence data, surveys of susceptible animals in farms in South-East Asia and further afield for viruses related to SARS-CoV-2, livestock farms where coronavirus-susceptible animals are present, and continued,

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