Scientific Advisory Group for the Origins of Novel Pathogens (SAGO)

Independent assessment of the origins of SARS-CoV-2

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List of abbreviations

APHIS	Animal and Plant Health Inspection Service
BSL	biosafety level
CDC	Center for Disease Control
CLIA	Chemiluminescence immunoassay
CNIC	Chinese National Influenza Center
CoV	Coronavirus
COVID-19	Coronavirus disease 2019
eCLIA	Electrochemiluminescence immunoassay
ELISA	Enzyme-linked immunosorbent assay
FCS	Furin cleavage site
GISAID	Global Initiative on Sharing All Influenza Data
HSM	HSM (also known as Huanan Seafood Wholesale Market, or Wuhan Wet Market)
ILI	Influenza-like illness
MERS	Middle East Respiratory Syndrome
NGS	Next generation sequencing
NHC	National Health Commission
NIC	National Intelligence Council
ODNI	Office of the Director of National Intelligence
PCR	Polymerase chain reaction
PPE	Personal Protective Equipment
RDB	Receptor-binding domain
RDT	Rapid diagnostic test
RT-PCR	Reverse Transcriptase PRC
SAGO	Scientific Advisory Group for the Origins of novel pathogens
SAR	Special administrative region
SARS-CoV-2	Coronavirus causing COVID-19
SNV	Single nucleotide variant
SSCP	Select Subcommittee on the coronavirus pandemic
USA	United States of America
USD	United States Dollars
VNT	Virus neutralization test
WHO	World Health Organization
WIV	Wuhan Institute of Virology
WOAH	World Organisation for Animal Health

Executive summary

The COVID-19 pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been one of the most severe health crises in the past century. Between December 2019, when the first cases of pneumonia of unknown etiology were reported from Wuhan, China, and May 2023, when the Director-General of the World Health Organization (WHO) declared that COVID-19 was no longer a public health emergency of international concern, more than 7 million deaths were reported to WHO. However, WHO estimates the true toll of the pandemic to be at least 20 million lives lost based on the excess deaths estimated in countries around the world. Underreporting of deaths directly attributed to COVID-19 because of pressure on healthcare systems during the pandemic, limited diagnostic testing, and deaths indirectly associated with COVID-19 contribute to the underestimation of reported deaths. The pandemic also caused severe disruption to societies and livelihoods (WHO, 2023a), with economic losses estimated to be at least USD 11–16 trillion, (GPMB, 2020) (Cutler and Summers, 2020).

In May 2020, the 73rd World Health Assembly adopted resolution 73.1 calling for a One Health approach to identify the source of SARS-CoV-2 introduction into the human population (WHO, 2020d). To date, there have been three scientific missions to China, with one specifically focusing on understanding the origins of COVID-19 in February 2021. In November 2021, the WHO Director General established the Scientific Advisory Group for the Origins of Novel Pathogens (SAGO) — a group of 27 independent international scientific experts — acting as an advisory board to WHO in this field; tasked with designing a framework to investigate the origins of emerging and re-emerging pathogens and to evaluate scientific evidence to determine the origins of SARS-CoV-2 (WHO, 2021a).

This is not solely a scientific endeavour it is a moral and ethical imperative. Understanding the origins of SARS-CoV-2 and how it sparked a pandemic is needed to help prevent future pandemics, save lives and livelihoods, and reduce global suffering. Ultimately, this pursuit underscores our collective responsibility to safeguard human health and well-being.

Despite the vast amount of research on SARS-CoV-2 and our increased understanding of its evolution and epidemiology, reports by scientists and governmental agencies have provided opposing views as to the virus' origins, without clear conclusions, and often without presenting the data underpinning those views.

SAGO provided initial findings and recommendations to better understand the origins of SARS-CoV-2 in a report published on 9 June 2022 (WHO, 2022). This current review updates its evaluation based on information from published scientific papers and reports, available intelligence statements and reports, scientific presentations provided to SAGO and expert discussions held by SAGO during closed meetings between November 2021 and June 2025.

It is important to note that SAGO did not have access to original raw data from any source in preparing this report. SAGO and WHO have requested further information from Member States, - including the Governments of China, Germany and the United States of America. Information was sought to clarify critical unknowns following the publication of the WHO-China March 2021 report and SAGO 2022 report, as well as data used to generate government reports. However, at the time of writing, all of the required information had not been provided to WHO. The focus of deliberations in this SAGO report is therefore predominantly based on available peer-reviewed scientific data. SAGO also reviewed preprint materials and private/government reports for any additional data, scientific information that could be used to better understand different hypotheses on the origins of SARS-CoV-2.

SAGO continues to articulate areas where the group feels scientific data is sparse, and what studies are needed to address limitations in our understanding of the origins of this pandemic. There have been several hypotheses proposed on the origins of SARS-CoV-2, some which had been discussed in the WHO-China 2021 mission report (WHO, 2020g) and further investigated in the SAGO preliminary report (SAGO, 2022).

SAGO evaluated the currently available scientific evidence that may support or dismiss these hypotheses in this report.

Hypotheses include:

1) introduction from a natural zoonotic source(s) as a spillover event(s) either directly to humans from wild animals or through an intermediate host;

2) an accidental laboratory-related event, which may have involved exposure to the virus during field research or a breach in laboratory biosafety procedures;

3) an introduction of SARS-CoV-2 into animal markets via cold chain processes and subsequent infection in humans through contact with products sold at markets, and

4) deliberate manipulation of the virus in a laboratory, followed by a laboratory biosafety breach.

Hypothesis #3 - an introduction of SARS-CoV-2 into animal markets in China from overseas via the importation of products through the cold chain was evaluated in the SAGO 2022 report (WHO, 2022). No additional evidence to support this hypothesis has become available to suggest that transmission of SARS-CoV-2 to humans from frozen products at the Huanan Seafood Market (HSM) or any other market in Wuhan occurred. SAGO will re-evaluate this hypothesis should additional evidence become available.

To evaluate hypothesis #4, of a deliberate manipulation of the virus in a laboratory and subsequent biosafety breach, SAGO analysed the genome structure of the virus and publications and reports addressing the likelihood of manipulation through reverse-genetics but did not find scientific evidence supporting this hypothesis over evidence that these mutations and recombination events also occur in coronaviruses in nature. This hypothesis also remains largely unsupported by other scientific and intelligence reports. SAGO will re-evaluate this hypothesis should additional evidence become available.

This report will focus on the two main hypotheses. While most available and accessible published scientific evidence supports hypothesis #1, zoonotic transmission from animals, possibly from bats or an intermediate host to humans, SAGO is not currently able to conclude exactly when, where and how SARS-CoV-2 first entered the human population. The closest known precursor strains were identified in bats in China (2013) and the Lao People's Democratic Republic (2020); however these strains are

too distantly related to SARS-CoV-2 to be the direct source of the COVID-19 pandemic. While available data support that the HSM played a significant role in early transmission and amplification, it is not conclusive that the HSM was where the virus first spilled over into the human population, or if it occurred through upstream infected humans or animals at the market. Metagenomic evidence identified several species of wildlife that were sold at the HSM in Wuhan, China, that should be investigated as potential intermediate hosts that may have infected early human cases. Currently, evidence needed to confirm this hypothesis is lacking, including comprehensive upstream investigations into wildlife species raised, traded and sold at the HSM and in other markets in and around Wuhan. This is needed to fully understand where, when and how the earliest humans were infected, which intermediate host(s) species were involved, and the conditions in which transmission(s) occurred leading to the earliest human cases.

Much of the information needed to assess hypothesis #2, of an accidental laboratory related event, either during field investigations or a breach in laboratory biosafety or biosecurity, has not been made available to WHO or SAGO. WHO has made several requests to the Government of China to provide health records of staff and documentation on biosafety and biosecurity practices and procedures in laboratories in Wuhan, including the Wuhan Institute of Virology (WIV) and the Chinese Centers for Disease Control in Wuhan as recommended in the 2022 SAGO Preliminary Report (SAGO, 2022). Without information to fully assess the nature of the work on coronaviruses in Wuhan laboratories, nor information about the conditions under which this work was done, it is not possible for SAGO to assess whether the first human infection(s) may have resulted due to a research related event or breach in laboratory biosafety. It can therefore not be ruled out, nor can it be proven until more information is provided.

SAGO reiterates its request to all governments — especially those where the earliest human cases were confirmed— to share information, data, and findings from investigations of the earliest human cases, interventions and testing in markets and sites of animal breeding including husbandry of captive wildlife, as well as any potential research-related accidents or breaches in biosafety including evidence regarding studies that may have involved culture and/or research on immediate genetic precursors to

SARS-CoV-2 in the laboratory. SAGO likewise reiterates its request for any researchers, scientists or governments with information on the origins of SARS-CoV-2 to make it available to WHO and SAGO. The work to understand the origins of SARS-CoV-2 remains unfinished.

To conclude, while a zoonotic origin with spillover from animals to humans is currently considered the best supported hypothesis by the available scientific data, until requests for further information are met or more scientific data becomes available, the origins of SARS-CoV-2 and how it entered the human population will remain inconclusive.

Background

More than five and a half years have passed since December 2019, when the initial human cases of a novel coronavirus, later named SARS-CoV-2, were reported in Wuhan, China. This marked the beginning of the most significant pandemic of this century. SARS-CoV-2 has infected billions of people globally and significantly affected all countries, communities and families. While reported deaths exceed 7 million (WHO, 2025), the actual number of deaths is estimated to range from 14.9 million (WHO, 2023a) to more than 18 million (Wang et al., 2022) by the end of 2021, based on various estimates of excess mortality studies during the initial years of the pandemic. Despite vast amounts of research conducted on this virus, the definitive route through which it entered the human population remains unknown. A deeper understanding of this emergence is crucial for mitigating future pandemics.

On 31 December 2019, the WHO China Country Office was informed of cases of pneumonia of unknown etiology detected in Wuhan City, Hubei Province, China (WHO, 2020c). Genetic sequencing and phylogenetic analyses of samples taken from early cases indicated that the virus belonged to the coronavirus family, specifically the *Betacoronavirus* 2B lineage within the *Sarbecovirus* subgenus. The virus first became known as '2019 novel coronavirus' (2019-nCoV) and was later named SARS-CoV-2 by the International Committee on Taxonomy of Viruses (Gorbalenya et al., 2020). While it is understood that partial and potentially full sequences may have been available in December 2019 and early January, the first full genome was made publicly available on 11 January 2020 (China National Center for Bioinformation, 2022). The closest related viruses to this novel coronavirus at the time was the known bat SARS-like coronavirus RaTG13 with a 96.1% genomic similarity, collected in China in 2013 (Zhou et al., 2020b), as well as Banal-52 (96.8% homology) collected in Lao People's Democratic Republic in 2018, and the sequence later reported (Temmam et al., 2022). More detail on closely related coronaviruses is provided in later sections of this report (Sections: Detection of SARS-CoV-2 in wild animals in China and South-East Asia and genomics investigations).

An initial WHO mission team—comprised of staff from the WHO Country office in Beijing and the Western Pacific Regional office in Manila—conducted a field visit to Wuhan from 20-21 January 2020. The mission aimed to gather epidemiological information and to understand response actions. They

provided their findings to WHO on a) the epidemiology of the outbreak known at the time, b) case definitions used by Chinese authorities, c) case management of patients, d) infection prevention and control in health facilities, and e) risk communication by Chinese officials, among other topics (WHO, 2020b).

From 16-24 February 2020, WHO and Chinese representatives conducted the first international joint mission to China (WHO, 2021c). The team included 25 national and international experts from China, Germany, Japan, the Republic of Korea, Nigeria, the Russian Federation, Singapore and the United States of America (USA). During the nine-day mission, the joint international-China team met with Chinese officials, agencies, institutions and hospitals involved in the COVID-19 response in several Chinese cities to better understand what was known about the virus, the earliest cases and their clinical severity, transmission dynamics of the virus, as well as prevention, control and response measures being adopted at national and local levels. The international mission team visited several field sites, including community centres and health clinics, county/district hospitals, designated COVID-19 hospitals, transportation hubs (air, rail, road), a wet market outside of Wuhan, warehouses for stocks of pharmaceuticals and personal protective equipment (PPE), research institutions, provincial health commissions, and local Centers for Disease Control (provincial and prefecture). A subset of the mission team also visited Wuhan, China, but their purpose was not to understand the origins of SARS-CoV-2, but rather to see first-hand the efforts to reduce the spread, care for patients and protect health workers. The full agenda of this mission is available in the report (WHO, 2020b).

The international team produced a report, published by WHO in February 2020 (WHO, 2020), outlining key findings of the mission, including a) virus characteristics, b) the timeline of the outbreak in different Chinese cities, as was known at the time, c) detailed transmission dynamics and secondary attack rates in different settings, d) disease progression and severity, e) details of response policies and actions by Chinese authorities, and f) critical knowledge gaps for which evidence was needed to guide prevention and control efforts in China and globally. The report provided recommendations for China, for countries with imported cases, for unaffected countries, for the public, and for the international community. At the time, there were approximately 75,500 COVID-19 cases reported in China. The

report commented on the importance of addressing knowledge related to the source of infection of the earliest cases needed for guiding control strategies (e.g., animal origin and natural reservoir of the virus, human-animal interface of the original event, early cases whose exposure could not be identified).

One year later, in February 2021, WHO and China organized a second international mission to China to work with government officials, technical partners and researchers in China specifically to investigate the origins of SARS-CoV-2. The terms of reference for this mission were agreed upon by China and WHO in July 2020 (WHO, 2020f) and the mission included international experts from Australia, Denmark, China, Germany, Japan, the Netherlands, the Russian Federation, Sudan, the United Kingdom of Great Britain and Northern Ireland, Viet Nam, and the United States of America. This mission produced a detailed report and annexes published by WHO in March 2021, which described specific information about the earliest cases, analyses of data from various disease and mortality surveillance systems as well as findings from early investigations that took place in China (WHO, 2021c).

The joint WHO international and China team advocated for further studies to better understand the origins of SARS-CoV-2 and its evolution. The report provided detailed information about the epidemiology of the earliest cases as well as data from different surveillance systems from Wuhan and the Hubei region, details related to animal and environmental studies and findings related to molecular epidemiology. The report concluded without being able to identify the origins of SARS-CoV-2, nor how the pandemic began (Koopmans et al., 2021; WHO, 2021).

Recommendations from the international and Chinese team included conducting further studies inside and outside of China to trace the origin of SARS-CoV-2 These studies were multifaceted and aimed at detecting antibodies against SARS-CoV-2 in hundreds of thousands of human blood samples from June 2020 and onwards stored at the Wuhan Blood Service. These analyses would be conducted by both local and international laboratories using state-of-the-art serological methods. It was also agreed to re-do the review of approximately 76,000 medical files from individuals presenting with fever, severe acute respiratory illness, pneumonia of unknown etiology or influenza-like-illness as the first review outcome was hampered by the use of early case-definitions. Further recommendations targeted the

animal origin and included detailed upstream analyses of animal trade and serological sampling of humans and animals involved in farming and trading fur animals sold at the HSM, as well as the history of animal and product trade in various markets across Wuhan. Additionally, human serosurveys and surveys of susceptible animals on farms in China, South-East Asia and beyond were recommended to identify viruses related to SARS-CoV-2, with a particular focus on targeted surveys of geographical areas with fur farms.

In November 2021, the WHO Director-General established SAGO, pursuant to the World Health Assembly Resolution 73.1 (WHO, 2020d), to develop a Global Framework on identifying the source of emerging and re-emerging pathogens (including SARS-CoV-2) and the route of introduction to the human population (WHO, 2024a). This framework has been applied to the SARS-CoV-2 investigations and the outputs are outlined in this report.

Aim of SAGO's independent assessment of the origins of SARS-CoV-2

As provided in its Terms of Reference, the SAGO was established by the WHO Director-General to advise the WHO Secretariat on technical and scientific considerations regarding emerging and re-emerging pathogens, and is composed of experts acting in a personal capacity. SAGO was tasked by WHO to review all evidence (e.g., scientific peer-reviewed papers and reviews, available unpublished information, field investigations, interviews, and other reports including audit findings, and government reports) that evaluated early human COVID-19 cases, animal infections, and any other indicators relevant to the origins of SARS-CoV-2 in order to provide the WHO Secretariat with an independent assessment of what is known about the origins of the COVID-19 pandemic and recommend further studies to be conducted.

Its mandate was to provide an independent assessment of the origins of SARS-CoV-2 and evaluate all available evidence, including data from all field missions to China (WHO, 2021) and any data available since the first identification of SARS-CoV-2, notably studies published or otherwise made available since the publication of SAGO's preliminary report in 2022 (SAGO, 2022), that may support or dispute all reasonable hypotheses of the origins of the virus and its spillover into humans.

According to SAGO's Terms of Reference (WHO, 2021b), it was tasked to advise WHO on the development of a Global Framework to define and guide studies and field investigations required to investigate the origins of newly discovered, previously unknown pathogens with epidemic or pandemic potential ("Disease X"). The Global Framework, published in 2024 serves as a comprehensive reference for enhancing global programmatic and policy-related preparedness for 'Disease X' (WHO, 2024a, Venter, 2023). It provides Member States with comprehensive guidance on the studies needed to investigate the origins of emerging and re-emerging pathogens, offering a structured approach to evaluating and controlling future emerging health threats before they spread, and applied here for the investigation of the origins of SARS-CoV-2.

Methods

Since its establishment, SAGO (WHO, 2021a) has met 52 times – including 27 plenary sessions and 25 working group sessions — both in-person and virtually, to examine available evidence and review published and pre-print scientific reports related to the origins of SARS-CoV-2.

To ensure all available evidence was obtained, a comprehensive and multidisciplinary approach was used to assess a wide array of both published and unpublished studies, encompassing a diverse variety of data sources. SAGO relied primarily on peer-reviewed scientific publications for the majority of its deliberations. However, preprint materials, private research submissions, and governmental or government intelligence reports were also reviewed to identify novel scientific findings and to understand how these sources generated hypotheses related to SARS-CoV-2 origins. Where gaps in data were evident, SAGO has articulated those limitations and continues to recommend additional studies that may enhance our understanding of the pandemic's emergence.

Two systematic peer-reviewed literature reviews were conducted in 2022 and 2023, with regular updates in 2024 and 2025 to incorporate any new data. Original and review articles on SARS-CoV-2, COVID-19 and other coronaviruses were assessed, including, but not limited to, the following topics: surveillance in humans, animals and the environment; animal markets, early human cases, acute respiratory infection surveillance, pneumonia, severe acute respiratory infections; animal susceptibility to SARS-CoV-2, precursor virus strains; surveillance and research of bat coronaviruses in China and

South East Asia, potential intermediate hosts, reverse zoonoses, molecular epidemiology, evolution, serological surveys; laboratory biosafety, laboratory and farm biosecurity, field acquired infections, laboratory acquired infections, virus gain of function research, origins. Published scientific papers and pre-prints were reviewed and primarily was the focus of this review. However, while not treating the same as peer-reviewed literature, SAGO considered carefully as any relevant media reports or other data sources relevant to the origins of SARS-CoV-2. Data was sought from various databases where sequences and meta-data from early cases, animals or metagenomic data were deposited, including GenBank, GISAID and the Chinese National Genomics Data Center database (China National Center for Bioinformation, 2022). The WHO secretariat wrote to authors of published and pre-published (pre-print) literature to obtain further information about relevant studies, background data and/or reviews and contacted databases requesting access to sequences from early cases.

The WHO Secretariat arranged presentations for SAGO members from scientists representing a range of disciplines and institutions (see acknowledgements) including from the Chinese Center for Disease Control and Prevention (China CDC); Beijing Institute of Genomics, Chinese Academy of Sciences; National Health Commission of the People's Republic of China; Institute of Pathogen Biology, Chinese Academy of Medical Sciences; University of Arizona; University of California, San Diego; Technical University of Denmark, and the University of Sydney, Australia.

In addition to reviewing publicly available peer reviewed information, SAGO also considered pre-prints, interviewing authors of selected papers, unpublished data and findings provided through solicited and unsolicited communications to the Secretariat (through emails, reports and presentations to SAGO), as well as careful reviews and intelligence reports by governmental agencies, ensuring that all relevant information potentially related to the origins of SARS-CoV-2 was evaluated. This included discussions with journalists based in China during the start of COVID-19 who conducted interviews with people in and surrounding Wuhan involved in animal raising and trading.

Throughout this process, SAGO applied the *Global Framework for investigating novel pathogens* (WHO, 2024a) to ensure a systematic and transparent scientific review which underscores the importance of a collaborative, evidence-based approach to understanding and mitigating global health

risks. The results section in this independent assessment is structured according to the six elements outlined in the Global Framework (box 1).

Box 1. Elements of the WHO global framework to define and guide studies into the origins of emerging and re-emerging pathogens with epidemic and pandemic potential (WHO, 2024a)

- ***Early investigations*** *of the first identified cases/clusters/outbreaks to identify potential sources of exposure, collection of samples at the source, define the characteristics of the novel pathogen involved for establishment of diagnostic assays.*
- ***Human studies*** *to understand the epidemiology, including clinical presentation, modes of transmission, pathology and earliest presence in syndromic surveillance samples.*
- ***Human/animal interface*** *studies to identify potential animal reservoirs, intermediate hosts and reverse zoonoses.*
- ***Environmental and ecological*** *studies to identify insect vectors or other sources of infection as well as earliest presence in the environment.*
- ***Genomics and phylogenetics*** *studies to identify precursor strains, genomic characteristics, evolution in intermediate hosts and humans and spatial distribution over time.*
- ***Biosafety/biosecurity*** *studies to determine if a breach in laboratory or research activities may have been associated with the first cases.*

Results

Early investigations and human cases

Early studies reported varying dates for the earliest symptom onset. One publication cited the earliest reported case had symptom onset on 8 December 2019 (Li et al., 2020a), whereas others identified cases with symptom onset of 1 December 2019 (Huang et al., 2020; Allam, 2020). It was reported that the case with symptom onset of 1 December 2019 was linked to the HSM, whereas the case from 8 December 2019 was not. Using the initial case definition for novel coronavirus-infected pneumonia (NCIP) developed by China CDC, a suspected case was a patient meeting four criteria: a) pneumonia with fever; b) lung radiographic evidence (e.g. ground glass opacity); c) abnormal white cell count; and d) no improvement after three days of antibiotics. Alternatively, a case could meet the first three criteria and have an epidemiological link to the HSM or contact with a patient with similar symptoms (Li et al., 2020a). Li et al. (2020) reviewed 425 of the earliest laboratory-confirmed COVID-19 patients finding that 55% of the 47 cases with onset of illness before 1 January 2020 were linked to the HSM compared with only 8.2% of the subsequent cases reported between 1 - 22 January.

It was later recognised that SARS-CoV-2 infection may present with no symptoms or with mild illness, and therefore it is likely that early cases may not have been detected by early surveillance efforts. Li et al. (2020) concluded that the exclusion of cases not meeting the case definitions applied at the time, along with cases featuring mild or no symptoms, contributed to an underestimation of the number of cases, and that transmission could have occurred in the community, independent of the HSM, before 1 January 2020 (Li et al., 2020b; Wang et al., 2020). In support of the hypothesis that earlier cases with mild symptoms may have been missed, there was a case with an onset of mild symptoms of cough and fever on 1 December 2019, that was linked to the HSM. However, the case was later hospitalized on 26 December 2019 with palsy and related eye-movements suggesting CNS affection and interstitial pulmonary changes by CT scan of the lungs, but it was concluded by the review panel to have suffered from aspiration due to his CNS affection, possibly ignoring the early onset of cough and fever (2021c).

Early estimations of the basic reproduction number (R_0) in Wuhan in December 2019 and early January ranged from 2.24 to 3.77 (Zhao et al., 2020a; Zhao et al., 2020b; Lin et al., 2020).

In December 2020, Wuhan CDC reviewed the National Notifiable Disease Reporting System identifying 174 cases of COVID-19 with symptom onset in 2019 in Wuhan (100 laboratory confirmed, 74 clinically diagnosed). The case definition was iteratively revised based on findings regarding the transmissibility of SARS-CoV-2 (WHO, 2021). The members of the WHO-China Joint Mission in February 2021 were informed that 32.8% of the 174 early cases (for which information was available) were associated with the HSM in Wuhan, suggesting that the HSM played a significant role in the early phases of the epidemic, while 22.6% of cases had association with another market. Some 44.6% of the early cases had no history of market exposure, indicating unrecognized community transmission (WHO, 2021). This is consistent with a number of papers published in 2020, where 28-66% of early cases had documented links to the HSM, suggesting transmission of other cases was occurring outside of the market (WHO, 2021; Bosco-Lauth et al., 2021b; Xiao et al., 2021; Crits-Christoph et al., 2024).

Geospatial analyses of the earliest known 174 COVID-19 cases concluded that a disproportionate number of affected individuals had worked at or visited the HSM, and/or that an unexpectedly large proportion of 174 early cases were living close to the HSM (Worobey et al., 2022a). Although this suggests opportunity for human exposure to SARS-CoV-2 at the market, spatial epidemiological data and early human virus sequences from Wuhan infer the importance of the area in or around the market (Wu et al., 2022), but do not provide evidence of transmission from animals at the market, nor determine when nor where the virus first infected humans or began transmitting between humans. The same spatial focus on the HSM is apparent when using all reported early human cases (beyond the earliest 174 from December 2019), and also when those cases for which there was a known link to the market are excluded. Potentially, there was ascertainment bias due to the availability of clinical and laboratory data from certain sites closer to HSM, or this reflects treatment-seeking behaviour.

Using social media-derived case data, Worobey *et al.* also found the distribution of COVID-19 cases was similar to that of the spatial distribution of the population by February 2020 (Worobey et al., 2022a). Similar results were found by another group of researchers that analysed spatial distribution of

cases over January to February 2020 (Peng et al., 2020). This suggests the initial link to the market was lost after some weeks of the outbreak, consistent with secondary spread in the population.

During the first joint international mission in February 2020 (WHO, 2020), the team reviewed surveillance data related to the population of Wuhan, the epicentre of the outbreak at the time, and the surrounding Hubei Province. Discussions and review of routine surveillance data from official disease surveillance systems, including on severe acute respiratory illness, influenza-like illness (ILI), fever, and pneumonia of unknown etiology systems from 2015-2019, did not reveal evidence of earlier COVID-19 outbreaks in Wuhan or elsewhere in China. However, there were many questions unanswered, including the reasons behind the increase in ILI in children and adults at the end of 2019 in Wuhan, which could be due to other circulating pathogens like influenza and RSV (WHO, 2020). Furthermore, a review of official mortality data from Wuhan and Hubei Province provided to the WHO-China mission team of 2021 from week 14-2019 to week 14-2020 did not identify significant peaks in mortality prior to December 2019, contrary to the pneumonia-associated mortality that was evident in early January 2020, followed by a rapid rise of all-cause and pneumonia-specific mortality during week 3 of January 2020.

Chinese scientists followed the WHO-China joint-report recommendation to examine blood samples collected before 2020 in Wuhan, China and reported that no SARS-CoV-2-specific antibodies existed among 43,850 samples from 32,484 blood donors (Chang et al. 2022), indicating that there was no evidence of infection of SARS-CoV-2 before December 2019 within the study population area.

In summary, available evidence provided by China during the 2020 and 2021 missions did not identify unusual clustering or deviation from trends in the weeks and months preceding these first reported cases in early December 2019. However, it was noted then and remains relevant now that the stringent case definition, which included ‘COVID-19 specific pulmonary changes’ (e.g. ground glass opacity) on CT scans used for reviewing 76,253 medical files, limits the interpretation of these findings, with milder to moderately severe cases inevitably being missed.

Based on phylogeny and empirical mutation frequencies, initial and updated analyses considering all currently available sequence data, Pekar *et al.* proposed that a single introduction of SARS-CoV-2 into

the human population is “highly unlikely” (Pekar et al., 2022; Hensel and Débarre, 2025; Pekar et al., 2025). These findings suggest two slightly different but distinct genetic virus variants: lineage A and lineage B. Human infection with lineage B is estimated to have occurred around 18 November 2019 (range 23 October-8 December) and predates the initial infection of humans with lineage A by days to weeks. In view of the inferred extinction rate of early lineages, approximately eight precursor lineages (95% Bayesian confidence limits, 2 to 25 introductions) would be required to make the survival of two founding lineages likely (Tang et al., 2021).

SAGO discussed and considered the importance of retrospective investigations on clinical samples bio-banked in other areas of the world in 2019 to identify potential circulation of SARS-CoV-2 prior to the official reports of cases in Wuhan, China. As noted in SAGO’s preliminary report published in June 2022, (SAGO, 2022) retrospective detection of early SARS-CoV-2 from clinical samples were published from Italy (Lombardy) in October and November 2019 and France in December 2019 using IgG serological assays, followed by serum neutralisation assays (Apolone et al., 2021; Carrat et al., 2021). As a result of these initial findings, the WHO Secretariat arranged for further testing of the remaining clinical samples and verification in independent laboratories. The results could not be reconfirmed by an independent laboratory (Erasmus University Rotterdam, Netherlands) using IgG ELISA and virus neutralization test (VNT) (WHO, 2021). Other reports of early SARS-CoV-2 detections in clinical samples that tested positive by RT-PCR on respiratory samples or ELISA, on serum samples that could not be confirmed by VNT, were reported from Italy (September 2019-March 2020), France (November 2019-January 2020), Spain (unpublished) and the USA (no positive samples could be confirmed before December 2019). Table 1 summarises published studies of pre-pandemic samples tested for SARS-CoV-2. However, these have not been confirmed by other laboratories; positive RT-PCRs should be confirmed by sequencing.

Table 1: Pre-pandemic samples tested (published studies)

Country	Study period of the samples	Sample type	Results for samples	Number of positive samples (date of earliest detection)	Number of samples tested	Technology used to analyse samples	References
Italy	September 2019 - March 2020	Blood	Positive for SARS-CoV-2 antibodies	111 of 959 showed SARS-CoV-2 antibodies (September 2019). 6 of 111 positive through microneutralization test (October 2019)	959 111	RBD-ELISA microneutralization assay	(Apolone et al., 2021)
	November 2019	Skin biopsy	Positive	1 (November 2019)	1	RNA fluorescence *in situ* hybridization (FISH) (positive) RT-PCR (negative);	(Gianotti et al., 2021)
	November 2019 - March 2020	Plasma	Positive	11 (November 2019)	290 (234 liver diseases, 56 blood donors)	Antibody RDT + CLIA No neutralization assay	(Gragnani et al., 2021)
	September 2019– February 2020	Throat swab	Positive	1 (December 2019)	39	RT-PCR	(Amendola et al., 2021)
France	November 2019 -March 2020	Serum samples	Positive	13 (4 November 2019)	9,144	ELISA microneutralization assay	(Carrat et al., 2021)
	December 2019 – January 2020	Respiratory samples	Positive	1 (December 2019)	14	RT-PCR	(Deslandes et al., 2020)

Country	Study period of the samples	Sample type	Results for samples	Number of positive samples (date of earliest detection)	Number of samples tested	Technology used to analyse samples	References
USA	Oct 2019 - March 2020	Nasopharyngeal swabs	Positive	7 (mid-January 2020)	2,321	RT-PCR	(Hilt et al., 2022)
	January 2020 - March 2020	Blood	Positive	9 (January 2020)	24,079	ELISA	(Althoff et al., 2021)
	December 2019 -January 2020	Blood	Positive	106 (reactive) of 7389 samples (mid-December 2019). 84 of 90 had neutralizing activity (mid-December 2019).	7,389 total blood donations collected 90 further tested (ELISA/micro-neutralization	ELISA microneutralization assay	(Basavaraju et al., 2021)
	2011-2020	Serum samples from wild deer	Positive	3 – (2020 samples) 1 – (2019 sample - at limit of detection, not confirmed by another virus neutralization test) 0 (from 2011 – 2018)	239	Surrogate virus neutralization assay	(Chandler et al., 2021)
Norway	December 2019 - December 2020	Serum samples from pregnant women	Positive	36 (1 from December 2019)	6,520	eCLIA + CLIA No neutralization assay	(Eskild et al., 2022)

Testing for SARS-CoV-2 in animals and the environment at the Huanan Seafood Market

The 2021 WHO-China report and multiple studies have suggested that the HSM played an important role in SARS-CoV-2 transmission, either through the sale of animals known to be susceptible to SARS-CoV-2 infection, amplification of human transmission (spillover having occurred elsewhere), or as a possible site of spillover via contact with infected animals sold at the market (WHO, 2021c; Liu et al., 2023; Xiao et al., 2021; Pekar et al., 2022; Worobey et al., 2022a; Crits-Christoph et al., 2024).

The HSM was supplied with farmed wildlife from farms located in the prefectures of Tianmen, Xiaogan, Jingmen, Suizhou, Xiangyang, and Huangshi, also at the county level in Jianli, Wuxue and Jingshan - within Hubei Province. Outside Hubei province, source farms were in the provinces of Heilongjiang, Jilin, Shanxi, Henan, Hunan, Jiangxi, Guangdong, Guangxi and Yunnan (WHO, 2021). SAGO's ability to fully understand the significance of the HSM in the origins of SARS-CoV-2 is limited by the fact that no precise information, including on the quantity, species and source locations, of the animals sold at the HSM or other markets in Wuhan has been made available to WHO or SAGO to date or published. It is important to note that the wildlife trade in wet markets is prohibited under Chinese law. As a result, tracing the specific origins of animals sold at the HSM presents logistical and regulatory challenges. These circumstances may also complicate the systematic documentation and sharing of related information with WHO and international partners. It is also important to note that Xiao *et al* reported on animals that were sold at the HSM from May 2017 and November 2019, including 38 live animal species, including racoon dogs (*Nyctereutes procyonoides*), red foxes (*Vulpes vulpes*), mink (*Neovison vison*) and masked palm civets (*Paguma larvata*), all of which are known to be susceptible to SARS-CoV-2 infection (Xiao et al., 2021).

According to information provided to the international team in 2021, it is understood that on 30 December 2019, local Chinese public health authorities entered the HSM market and collected the first environmental samples from the market stalls and environments, and that on 31 December 2019, a joint team consisting of experts from four levels of China CDC conducted the investigation of HSM and initiated epidemiological studies around the market. On midnight 1 January 2020, Chinese authorities,

following standard public health biosafety procedures in response to the outbreak of COVID-19, closed the market for disinfection.

Between 1 January and 30 March 2020, Chinese authorities reportedly conducted interviews with market sellers, collected samples from 457 animals in and around the market (including live rats, mice, stray weasels, cats, and dogs, as well as from the carcasses of sheep, wild boars, bamboo rats, badgers, muntjacs, hedgehogs and rabbits) and 923 environmental samples (e.g., from equipment, stalls and drains) (Liu et al., 2023). Published reports and presentations to SAGO stated that all samples from animals collected at the market tested negative for SARS-CoV-2. However, 73 environmental samples collected from various locations and from surfaces inside the market were RT-PCR positive (Xiao et al., 2021, Worobey et al., 2022a; Liu et al., 2023; Bosco-Lauth et al., 2021a; Crits-Christoph et al., 2023; Wu, 2023). Further analysis by Crits-Christoph *et al*. (2024), using data shared by Liu *et al.* (2023), performed spatial risk mapping based on SARS-CoV-2 RT-PCR and metagenomic sequence detections in swabs from animal cages and other surfaces, as well as samples from sewage drains, pinpointing specific market stalls (Liu et al., 2023; Crits-Christoph et al., 2024). The authors refined the taxonomic comparison of animal genetic material by partially re-assembling sequence-read contigs. At the HSM stalls, mitochondrial DNA hits from several susceptible species to SARS-CoV-2 were detected, including from raccoon dog, hoary bamboo rat, and palm civet, with genetic traces of the former two species particularly abundant across the wildlife market area, and some of these samples containing high amounts of SARS-CoV-2 sequencing reads. Based on mitochondrial gene SNP typing, geographic origins of the detected raccoon dogs were mapped to central or southern China. Liu *et al.* (2023) confirmed presence of bat and pangolin DNA, but subsequent comparisons of detected nucleic acids with the Barcode of Life Data System COX1 gene database by international scientists failed to confirm the presence of bat or pangolin nucleic acids in market samples (Liu et al., 2023; Crits-Christoph et al., 2024). These findings suggest that some animals, particularly raccoon dogs, known to act as *Sarbecovirus* intermediary hosts, were present at the market before its closure on 1 January 2020, though it cannot be concluded that the virus was introduced via these animals (Liu 2023b).

The report by Liu *et al*. (2023) confirmed the presence of two SARS-CoV-2 lineages; A and B, in environmental samples from the HSM, and with a higher frequency of lineage B over A, consistent with lineage B´s earlier inferred emergence (Liu et al., 2023).

Detection of SARS-CoV-2 in wild animals in China and South-East Asia

According to the 2021 WHO-China joint report, 2328 samples from wildlife were collected in December 2019 — using non-structured, convenience sampling — all tested negative for SARS-CoV-2. Additionally, 2995 samples from Hubei province (February-March 2020), and 27,000 samples for PCR and 1914 sera were taken from other parts of China also yielded negative for SARS-CoV-2 (Annex C6 Reports Annexes) (WHO, 2021c).

The WHO Secretariat invited a number of scientists from China, including from the Centre for Infection and Immunity Studies, School of Medicine, Sun Yat-Sen University, Guangzhou, China; Chinese National Influenza Center (CNIC), National Institute for Viral Disease Control and Prevention, Chinese Center for Disease Control and Prevention (CDC), China, to present research associated with testing animal samples from Chinese provinces. In these presentations, the invited scientists reported that all testing undertaken in animals in China did not detect the presence of SARS-CoV-2 virus (nucleic acid) or antibodies.

The most detailed of these surveys was presented to SAGO in January 2022 by the Beijing Institute of Genomics, Chinese Academy of Sciences, and Clinical Laboratory Center, National Health Commission (NHC), who reported that by 30 November 2021, 32,479 animal samples had been collected from 18 provinces including Hebei, Inner Mongolia, Liaoning, Jilin, Heilongjiang, Shanghai, Jiangsu, Henan, Hubei, Hunan, Sichuan, Guizhou, autonomous region of Tibet, Gansu, Shaanxi, Jiangxi, Ningxia and Qinghai. The scientists reported that no SARS-CoV-2-related nucleic acid were found in 218 species from 13 orders including Rodentia, Carnivora, Artiodactyla, primates, Lagomorpha, Pholidota and Erinaceidae. Furthermore, 1311 serum samples from livestock and poultry (in Hubei and seven other provinces), and 2837 serum samples from dogs, cats, mink, foxes, and raccoon dogs (collected in Henan, Shandong, Hebei and Hubei in autumn 2020 - precise dates were not included in the presentation) all tested negative for SARS-CoV-2 antibodies. However, further details

about sample sizes, sampling schemes, specific animal species and numbers of animals tested, methodology of laboratory testing, locations of farms, markets, and sources of animals were not provided during this presentation (unpublished information presented to SAGO by Chinese Scientists).

Scientists in the Mekong Delta and South-East Asia (China, Thailand, Myanmar, Cambodia, Lao People's Democratic Republic, and Viet Nam) presented regional coronavirus research in various bat species at a WHO regional technical surveillance workshop held in Bangkok, Thailand (October 2022). Findings from the surveillance activities in Thailand (which is home to one third of all members of the Rhinolophidae family) included partial sequences of new species of SARS-CoV-like coronaviruses found in *Rhinolophus* bats. Researchers from Cambodia presented serological investigations which indicated seropositivity to coronaviruses, filoviruses, and henipaviruses across diverse bat populations and specifically in pteropid bats. Some gaps highlighted from these countries were the regional lack of technology and capacity in labs to detect and characterize novel viruses, including a lack of funding to conduct whole genome sequencing of the viruses, as well as biosafety capacities and training. These limitations hamper the ability for researchers to characterise novel SARS-CoV related viruses identified in bats and mammals in the region.

While the intermediate host(s) for SARS-CoV-2 has (have) not yet been determined, it is widely accepted that precursor viruses for coronaviruses originate in bats (Zhou et al., 2021). Sixteen bat species have been identified as potential sarbecoviruses carriers (Wu et al., 2022). Shortly after the reports of the first cases of SARS-CoV-2, phylogenetic analyses identified the closest related precursor strains to SARS-CoV-2, in bats detected from China (RaTG13; 2013; 96.1% identity) and later in Lao People's Democratic Republic (BANAL-52; 2020; 96.8% identity) (as seen in Table 2) (WHO, 2024a; Temmam et al., 2022; Zhou et al., 2020b). Wu *et al.* (2022) tested 4270 bats pertaining to different Rhinolophus species across China that yielded 146 novel Sarbecovirus genomes. None of the genomes were closely related to SARS-CoV-2 (680 members of the highly relevant species, *R. affinis* were included in the sample). Zhou *et al.* (2021) tested 283 bats from at least five Rhinolophus species and also *Hipposideros larvatus* identifying novel Sarbecoviruses but none closely related to SARS-CoV-2 (Zhou et al., 2021). These are discussed further in the genomics section of this assessment.

Variability of virus prevalence and species distribution makes it difficult to define virus endemicity. For instance, Wu *et al.* 2022 noted that the closest relatives to SARS-CoV-2 – BANAL-52, BANAL-103 and RaTG13 – stem from *Rhinolophus malayanus*, *R. pusillus*, and *R. affinis*, respectively (Table 2 summarises the closest known coronavirus relatives to SARS-CoV-2, including their host species, genome similarity, and geographic origin) (Wu et al., 2022).While some of these species may live predominantly outside China, they also exist within China, but few samples have been tested to date. Moreover, since the direct precursors to SARS-CoV-2 may have passed through an intermediate host, bat distribution alone may not indicate the site of spillover. A recent paper (Havens et al., 2025) analysed the hypothesis that zoonotic viruses require adaptation prior to zoonosis to sustain human-to-human transmission. Based on Ebola, Marburg, influenza A, SARS-CoV-1 and SARS-CoV-2, there was no change of selection immediately prior to a host switch. This implies that closely related precursor viruses from bats might have transmitted directly to humans and subsequent evolution occurred in humans. Nevertheless, the currently known precursor viruses are still too distant from SARS-CoV-2 to have been the source of the early cases in Wuhan as discussed under the genomics section.

The search for viral precursors in potential intermediary hosts suffers from similar challenges, based on limited sample size and geographic coverage in currently published studies. For example, He *et al.* (2022) tested 1941 individual game animals (samples collected after February 2020) typically sold in Chinese markets, including from the orders Rodentia, Carnivora, Lagomorpha, Eulipotyphla, and Pholidota (pangolins), but none were reported as positive for *Sarbecovirus* (He et al., 2022). However, in these analyses, only 95 raccoon dogs and 425 masked palm civets were tested – both known susceptible species. Additionally, animals in this study were mostly from natural habitats and not targeting the animal production sites that had been recommended for testing in the 2022 SAGO report (SAGO, 2022). Despite raccoon dog fur farming being legal in China, the sale of raccoon dogs in live animal markets was halted (precise dates were not included in the presentation in which this information was shared), and almost all samples that have been tested were collected after February 2020 (Xiao et al., 2021). No results of surveillance studies on upstream wildlife value chains and wildlife farms have been published or made available to SAGO, following the publication of the WHO-China 2021 report despite requests (WHO, 2021c).

Table 2: Coronaviruses identified with highest similarity to SARS-CoV-2

Animal Species	Virus strain	Genome Identity to SARS-CoV-2	Originating region, country	Year identified	References
Bat *R. malayanus*	BANAL-52	96.80%	Laos	2020	(Temmam et al., 2022)
Bat *R. affinis*	RaTG13	96.10%	Yunnan province, China	2013	(Zhou et al., 2020a)
Bat *R. pusillus*	BANAL-103	95.20%	Laos	2020	(Temmam et al., 2022)
Bat *R. marshalli*	BANAL-236	95.20%	Laos	2020	(Temmam et al., 2022)
Bat *R. pusillus*	RpYN06	94.48%	Yunnan province, China	2019	(Zhou et al., 2021)
Bat *R. malayanus*	RmYN02	93.30%	Yunnan province, China	2019	(Zhou et al., 2020a)
Bat *R. malayanus*	BANAL-116	92.90%	Laos	2020	(Temmam et al., 2022)
Bat *R. malayanus*	BANAL-247	92.20%	Laos	2020	(Temmam et al., 2022)
Bat *R. shameli*	RshSTT182	92.90%	Cambodia	2010	(Delaune et al., 2021)
Bat *R. shameli*	RshSTT200	92.90%	Cambodia	2010	
Malayan pangolin *Manis javanica*	PCoV-GDC	92.40%	Unknown (seized during anti-smuggling operation in China)	2019	(Xiao et al., 2020) (Liu et al., 2020) (Zhou et al., 2020a)
Bat *R. acuminatus*	RacCS203	91.15%	Thailand	2020	(Wacharapluesadee et al., 2021)
Bat *R. pusillus*	PrC31	90.70%	Yunnan province, China	2018	(Li, 2021)
Malayan pangolin *M. javanica*	PCoV-2020	90.32%	Unknown (seized during anti-smuggling operation in China)	2019	(Liu et al., 2020)
Malayan pangolin *M. javanica*	MP789	90.20%	Unknown (seized during anti-smuggling operation in China)	2019	(Liu et al., 2019)

After the SARS epidemic in 2002-2003, Chinese authorities discovered a second animal-to-human spillover of SARS-CoV (referred to as SARS-CoV-1 in the remainder of this report) at the end of 2003 (Wang et al., 2005; Ye et al., 2020), and they ordered the destruction of civet cats and raccoon dogs in the Xinyuan market in Guangdong province. During this process, culled animals were swabbed and tested for SARS-CoV-1, identifying 14 of 18 as positive at the Xinyuan market, as well as identifying antibodies to SARS-CoV-1 in masked palm civets in one of the four supplier farms in Guangdong province.

From January to September 2004, breeding facilities for masked palm civets in 12 Chinese provinces supplying animals to the Xinyuan market were systematically visited and the animals tested – results from 1107 samples tested negative (Kan et al., 2005). Detected viruses were sufficiently characterized to enable the retrospective reconstruction of genomic changes that occurred during the emergence of SARS in 2002 in humans. As of June 2025, no additional data outside of the information provided in the 2021 WHO-China report (WHO, 2021c) (refer to pages 99-106) has been made available to SAGO or WHO on SARS-CoV-2 testing conducted on raccoon dogs and other susceptible species that were commercially bred and had trade links to the HSM, or any markets in Wuhan city, Hubei Province or within China, prior to December 2019.

Also, data has also not been made available from SAGO-recommended studies (SAGO 2022), including the systematic random sampling of animal farms, hunters, animal traders, markets or market sellers to and from the HSM. There is a need for more information, particularly from source farms trading animals to wet markets, in order to determine the existence of early circulation and spillover (WHO, 2022).

Animal infection experiments and reverse zoonoses

Reverse zoonosis of SARS-CoV-2 from humans to animals has been documented in wild, farmed, zoo, and domestic animal species. As of October 2023, the World Organisation for Animal Health (WOAH) reported 775 outbreaks in animals, across 29 species in 36 countries (World Organisation for Animal Health, 2023). Susceptible species to SARS-CoV-2 infection belong to the families: Bovidae, Canidae, Cebidae, Cercopithecidae, Cervidae, Cricetidae, Felidae, Hominidae, Hyaenidae, Mustelidae,

Procionidae, Viverridae, Hippopotamidae, Myrmecophagidae, Atelidae, Rhinocerotidae, Suidae, Agamidae, Phasianidae, Anatidea, Castoridae, Muridae, Chlamyphoridae, Leporidae, Vespertilionidae, Sciuridae, Didelphids and Procyonidae, with spillover potential from one animal species to another**.** **(**Food and Agriculture Organization of the United Nations**,** 2023) (Annex 1 Table 1). In addition, laboratory experiments have been conducted on animals to identify potential susceptible species that could be considered in search of the SARS-CoV-2 reservoir and/or have the potential to create new SARS-CoV-2 variants (Food and Agriculture Organization of the United Nations, 2023) (Annex 1 Table 2).

Although most SARS-CoV-2 zoonotic transmission documented has been from humans to animals, some transmission has included spread among animals, and spillback to humans (Zhou and Shi, 2021; Yen et al., 2022). Farmed mink exhibit both symptomatic and asymptomatic SARS-CoV-2 infections and have been affected by large outbreaks before mass culling in several European countries in 2020 (Pomorska-Mól et al., 2021). In Denmark, culling of mink was recommended following the discovery of the "cluster 5" SARS-CoV-2 variant, which infected 12 people during November 2020 (EFSA Panel on Animal Health and Welfare et al., 2023). Outbreaks on mink farms in Poland were linked to a two-year-old human strain of the B.1.1.307 lineage that carried mutations typical of mink adaptation, suggesting undetected circulation in a previously unknown animal reservoir (Domańska-Blicharz et al., 2023). SARS-CoV-2 transmission from hamsters to humans was also documented in China, Hong Kong Special Administrative Region (SAR) when infected animals transmitted the virus to a pet shop owner, as well as probable cat to veterinarian transmission in Thailand (Yen et al., 2022 ; Chandler et al., 2021; Kuchipudi et al., 2022 ; Marques et al., 2022 ; Hale et al., 2022; Palermo et al., 2022 ; Caserta et al., 2023).

Another example is white-tailed deer (*Odocoileus virginianus*), where SARS-CoV-2 has spread widely. The Animal and Plant Health Inspection Service (APHIS) reported virus in 12.2% and antibodies in 31.6% of white-tailed deer in the USA (APHIS, 2023) – which thus could act as a reservoir for nearly extinct SARS-CoV-2 variants. (Chandler et al., 2021; Kuchipudi et al., 2022 ; Marques et al., 2022; Hale et al., 2022; Palermo et al., 2022; Caserta et al., 2023).

Environmental investigations

The presence of SARS-CoV-2 RNA was reported in wastewater/sewage samples taken in Milan and Turin, Italy, in December 2019 (La Rosa et al., 2021). Positive signals for SARS-CoV-2 were obtained by nested RT-PCR and further confirmed by sequencing of the amplicon, but results could not be verified by an independent laboratory at the Erasmus Medical Centre, Netherlands, a collaboration which was facilitated by WHO. Further next-generation sequencing (NGS) and metagenomic studies on those positive samples may yield more sequencing data, as near-complete genome sequences may determine if there was any genetic variation from the SARS-CoV-2 strains circulating in China during that period – noting that it is challenging to obtain full genomes from wastewater.

Following the publication of the SAGO preliminary report in 2022, a further study of wastewater samples obtained from Brazil in November and December 2019 provided sequences covering about 25% of the SARS-CoV-2 genome using NGS (Fongaro et al., 2021). The results from these samples should also be confirmed by an independent laboratory. Additional sequencing data may be useful to determine the phylogenetic relationship to the Wuhan strain. Wastewater samples from various additional countries at the time did not yield positive results (WHO, 2022).

Related to the 'cold chain' hypothesis, one more recent paper by Li et al published since the SAGO preliminary report results of a large surveillance study of the cold chain from July 2020 to July 2021, finding 1455 positive in more than 55 million samples taken across China (positivity of 0.26 per 10,000) (Li, 2022). This demonstrated a low risk of contamination of frozen products even with high incidence (and virus shedding) in humans, it should be noted that this surveillance did not cover the late 2019 period.

Genomic Investigations

As stated above, SARS-CoV-2 belongs to the *Betacoronavirus pandemicum* species in the *Sarbecovirus* subgenus of *Betacoronavirus*. The genome organization of SARS-CoV-2 includes a cap structure at the 5' end, a poly-A tail at the 3' end, and 13-15 open reading frames in different variants, flanked by 5'.

and 3' untranslated regions critical for viral RNA synthesis (Kim et al., 2020; Parker et al., 2021). The S protein is essential for receptor binding and viral entry. Two features distinguish the SARS-CoV-2 genome from SARS-CoV-1 and SARS-CoV-like bat viruses: 1) mutations in the receptor binding domain (RBD) that appear to optimize its binding to the human ACE2 receptor (as well as that of other susceptible species), and 2) insertion of 12 nucleotides in the spike protein that result in a functional polybasic furin cleavage site (FCS) RRAR at the S1–S2 boundary of the spike protein and predicted acquisition of three O-linked glycans around the site (Andersen et al., 2020). This may create a 'mucin-like domain' that shields epitopes and enhances immune evasion.

One of the viruses currently known to be closest to SARS-CoV-2 (RaTG13) was described along with an original characterization of SARS-CoV-2 by Zhou et al. (Zhou et al., 2020b) An addendum to this paper mentions that the virus material had been available since 2012/2013 at the Wuhan Institute of Virology in the form of an uncultured original animal stored sample (ID4991) with published partial sequence characterization in 2016, amended to near full sequence characterization in 2018, renamed RaTG13 and published on GISAID (accession number EPI_ISL_402131) on 24 January 2020 (Zhou et al., 2020b; Ge et al., 2016).

After the first identification and sequencing of SARS-CoV-2, comparison of the partial sequence led researchers to complete sequencing of the full genome of RaTG13. However, the RaTG13 genome has a low similarity with SARS-CoV-2 in the critical RBD of the spike protein (only 11 of 17 receptor contact residues are conserved). Three progenitor bat viruses described from Northern Lao People's Democratic Republic in 2022 have both the ability to enter human cells via the ACE2 receptor and a very high similarity in the RBD with SARS-CoV-2 (Temmam et al., 2022). BANAL-52 and BANAL-103 show only one amino acid difference against SARS-CoV-2 in the RBD. BANAL-52 also has high homology on full genome level (96.8%; compared to RaTG13 at 96.1%). However, these viruses are too distant to be considered direct progeny of a common ancestor with SARS-CoV-2 but rather represent mixed populations of viruses stemming from recombination and mutation events in a common ancestor (Xiao and Whitney, 2021; Patiño-Galindo et al., 2021).

Sarbecoviruses have mosaic genomes that result from multiple recombination events in virus populations existing mainly in *Rhinolophus* bats, while individual viruses may spill over into other animals, where they are in isolation from the original reservoir population. SARS-related viruses discovered in pangolins may be one example of many (Lam et al., 2020; Xiao et al., 2020). Genetic recombination causes genomes to be similar in certain parts, while other parts are less similar and appear less closely related. Genome recombination makes the tracing of genetic lineages difficult, as the number of differences between two given genomes no longer reflects the same time distance from common ancestors given the disruption recombination poses for molecular clock analysis. Recombination is also a possible source of novel gene elements such as the FCS present in SARS-CoV-2, which is not found in any of the known closely related genomes (Zhou et al., 2021).

Furin cleavage site elements - similar but not identical to those in SARS-CoV-2 - are commonly found in S proteins of members of the subgenera *Embecovirus*, *Hibecovirus* and *Merbecovirus* such as HKU1, OC43, and MERS-CoV that typically contain 2-3 arginine and optionally an additional lysine moiety (Andersen et al., 2020; Stout et al., 2021). A polybasic FCS with an additional arginine moiety has also evolved upon repeated serial passaging in mice in MERS-CoV, termed MERS-CoV MA-30 (Li et al., 2017; Lisewski, *2024)*. The FCS in this virus (PRRVR) resembles that in SARS-CoV-2 (PRRAR), but the nucleotide coding of identical amino acids is different between these viruses. PRRVR-containing viruses have occurred sporadically during the SARS-CoV-2 pandemic in humans, but these were never fixed in the population and have no evolutionary link to early SARS-CoV-2 strains or hypothetical precursors, making them less relevant for understanding the origin of the FCS in SARS-CoV-2. In 2025, a merbecovirus HKU5-CoV lineage 2 virus was identified in Pipistrellus bats in China that can use human ACE2 as a cell entry receptor and exhibits a broad host tropism. Extensive and additional studies of HKU5-related, ACE2 engaging viruses revealed a distinct interaction site and receptor binding domains that make any cross-immunity following SARS-CoV-2 contact unlikely. Several merbecoviruses possess FCS with two or three basic residues (Park et al., 2025). The ability of HKU5-CoV lineage to infect human ACE2-expressing cell lines and human respiratory and enteric organoids underscores its zoonotic potential (Chen et al., 2025). Several studies by Damas (2020), Conceicao (2020), and Briggs (2023) have found that SARS-CoV-2 exhibits a broad ACE2 receptor-binding

spectra using SARS-CoV-2 isolates or pseudo-virions, including in various bat species (e.g. little brown bat, Egyptian fruit bat), domestic and wild animals (e.g. pangolin, fox, civet, camel, ferret, rat and squirrel); Bovidae and Cricetidae; and marine animals (e.g. sea lion, minke whale) (Damas et al., 2020; Conceicao et al., 2020; Briggs et al., 2023). Affinity binding assays formerly suggested that pig ACE2 receptors were highly susceptible to transduction by SARS-CoV-2 S pseudo-virions, but recent reports suggest pigs have low levels of ACE2 expression in their respiratory tract and therefore may not be susceptible to infection (Carossino et al., 2024). This evidence expands on the list of animals that are capable of being potential intermediate hosts of the virus. However, further substantial evidence is required, including virus detection and isolation from these species to confirm their role/importance as intermediate hosts.

Since the start of the pandemic, SARS-CoV-2 continues to evolve, resulting in the emergence of a significant number of variants of interest and of concern (WHO, 2020e). With millions of SARS-CoV-2 genome sequences published in publicly available databases (over 15 million in GISAID as of 30 April 2025), thousands of single nucleotide variants (SNVs) have been identified. Variants that differed significantly from previous variants gave rise to new waves of infection (WHO, 2020e).

The emergence of SARS-CoV-2 variants of concern (WHO, 2020e) through mechanisms such as reverse zoonoses or spillover of novel coronaviruses from animals to humans requires continued surveillance and investigation of any novel SARS-CoV-2 or other SARS-CoV-like variants that may give rise to renewed waves or to new epidemics or pandemics (WHO, 2020; Chatterjee et al., 2023).

WHO has made requests to the Chinese government from the onset of the pandemic to release publicly and/or provide WHO and SAGO with available sequences related to early SARS-CoV-2 infections. While the initial SARS-CoV-2 genome was released quickly and allowed for the development of diagnostic assays, other essential sequences only became available much later, with additional SARS-CoV-2 metagenomics data from samples collected at the HSM in January 2020 only released by China CDC in 2023 when an earlier preprint around investigations at the HSM was being prepared for final publication in Nature (Liu et al., 2023). SAGO was made aware of this additional evidence only upon its release by international researchers who analysed host DNA data from HSM previously

generated but not previously released by Chinese researchers. SAGO released a statement on the importance of sharing genomic data rapidly and for international researchers to engage with the owners of the data to ensure optimum analysis and timely release of data after emergence of novel pathogens (WHO, 2023c). The WHO Secretariat contacted the China National Center for Bioinformation requesting access to 508 SARS-CoV-2 sequences from patients in January-February 2020 uploaded to the National Genomics Data Center by authors investigating early cases (China National Center for Bioinformation, 2022). To date this sequence data has not been released.

Biosafety & Biosecurity Investigations

Laboratory-acquired infections and accidental pathogen release due to breaches in laboratory biosafety and biosecurity have occurred in isolated but well-documented events throughout history and remain a concern worldwide (Blacksell et al., 2024; Ristanović et al., 2020; Pedrosa and Cardoso, 2011; Weinstein and Singh, 2009; El Jaouhari et al., 2022; Wurtz et al., 2016). Strict biosafety standards published by international and national bodies work to minimise the risk of such events (WHO, 2020a; Government of Canada, 2025; Centers for Disease Control and Prevention, National Institutes of Health, 2020). WHO has published guidance to support laboratories and research institutions in implementing these standards effectively, such as the WHO Laboratory Biosafety Manual (4th edition), which provides comprehensive frameworks for risk assessment and mitigation in handling infectious agents (WHO, 2020a).

Additionally, national biosafety guidance for laboratories has been published by authorities in several countries including Australia and New Zealand, Canada, and the USA, as well as the European union which provide detailed protocols for containment, equipment usage, and personnel training, ensuring safety and compliance with international norms.

To date, no official information or documentation has been provided to WHO or SAGO to analyse the biosafety and biosecurity practices and procedures in laboratories in Wuhan, including the WIV and the Wuhan Centers for Disease Control. Representatives of the WIV laboratory provided verbal assurances that appropriate procedures were and are being followed correctly, although no physical inspections

were done by the WHO-China international team in 2021 (WHO, 2021). No access has been approved or provided to enable the independent verification or investigation of biosafety and biosecurity measures in either laboratory, such as occupational health records, results of previous audits (including biosafety reviews or biosafety evaluations), and any documentation of potential biosafety and biosecurity breaches occurring in the months or years leading up to the first reported cases, as recommended in the SAGO preliminary report (SAGO, 2022). In the biosafety statement published for the recently identified bat merbecovirus, BtHKU5-CoV-2-023, that can utilize human ACE2 receptors for cell entry, the authors state that "the experiments related to virus isolation and cell assays of BtHKU5-CoV-2-023 were performed in a BSL-2 plus negative pressure laboratory following standard operating procedures with necessary personal protection and approved by the WIV Institutional Biosafety Committee according to a bio-risk assessment procedure (including the viral genome sequence and its phylogenetic relationship to known human viruses, human receptor utilization, cell tropism, prevalence in domestic animals and humans, and pathogenicity and transmission in animal models) (Chen et al., 2025). Whereas SARS-CoV-2 has now been reclassified as risk group -2 in view of its endemic status with widespread distribution and population immunity, countries should consider classification of animal-derived coronaviruses with known or likely zoonotic potential, including bat-derived CoV, as higher risk group pathogens. SAGO recommends that biosafety and biosecurity measures for work involving potential zoonotic bat coronaviruses should be guided by a comprehensive risk assessment, following the WHO Laboratory Biosafety Manual (4th edition) (2020) and the WHO Laboratory Biosecurity Guidance (2nd edition) (WHO, 2024a).

A number of reports have also been published by government agencies (see later section for review of these reports), which have evaluated the possibility of a laboratory leak at the start of the COVID-19 pandemic. WHO has requested access to the source materials and data used by government agencies in the development of these reports, but these requests have not been granted. WHO received a response from the German government the preparation of the report was ongoing and would revert once this process is finished.

SAGO continues to recommend the investigation of all reasonable hypotheses for the origin of SARS-CoV-2 as outlined in their preliminary report[2] (SAGO, 2022).

SAGO continues to recommend: on-site laboratory assessments through interviews with laboratory staff and officials from facilities in and around Wuhan; a review of all laboratory work and materials documentation and digital inventories, biosafety and biosecurity records; risk assessments for activities with pathogens (risk group 2 or higher) and review of risk control strategies; and a review of all laboratory staff absenteeism reports and/or health complaints during 2019 (SAGO, 2022). In line with this recommendation, WHO Secretariat wrote to the Government of China to request further investigations, audits and other relevant documentation and interviews with staff at the WIV and Wuhan CDC laboratory. However, this has been refused, no audit files have been made available for review and, to date, no scientific data or evidence has been made available to SAGO or WHO to evaluate whether a laboratory incident could have initiated the COVID-19 pandemic. The Government of China has instead proposed that similar investigations be conducted in laboratories in other countries where coronavirus research or reverse genetics studies have been carried out (State Council Information Office, 2025).

Since information needed to assess the hypothesis of a lab related event, either during field investigations or a breach in laboratory biosafety - has not been made available to WHO or SAGO, it was not possible for SAGO to evaluate this hypothesis. Therefore, this possibility cannot be confirmed nor eliminated. SAGO remains open to any new information that may further the evaluation of any reasonable hypothesis grounded in science.

[2] It is noted that one author of this report (Dr Maria Guzman) does not agree with the inclusion of evaluating the possibility of introduction of SARS-CoV-2 to the human population through a laboratory incident.

SAGO's Evaluation of other reports on the hypotheses of the origins of SARS-CoV-2 spillover into the human population

SAGO relied primarily on peer-reviewed scientific publications for the majority of its deliberations. However, SAGO also reviewed available reports and government-produced intelligence reports to understand how these sources generated hypotheses related to SARS-CoV-2 origins.

To date, there have been several groups (both scientific and non-scientific) and governmental agencies convened to evaluate the origins of SARS-CoV-2. SAGO has reviewed and considered published peer reviewed scientific reports from the most relevant groups and governmental or intelligence agencies with the aim to seek out novel scientific evidence or intelligence that may help guide the discovery of SARS-CoV-2 emergence into the human population. SAGO regarded scientific investigations that were grounded in science and peer reviewed as the basis of our deliberations. More comprehensive summaries of the most notable scientific reports were reviewed and are provided in Table 3A.

Secondary to this, SAGO evaluated governmental or intelligence reports to identify any novel scientific evidence and to understand how their hypothesis was generated, however we recognise potential political bias that may have driven some of these reports. More details are summarised in Table 3B.

Finally, SAGO evaluated a few reports, by civil movements, some that were co-authored by scientist, that were sent directly to SAGO and publicised in the media, to provide a scientific perspective by SAGO experts.

Published Scientific Reports (Summarised in Table 3.A)

In October 2022, several members of the Lancet COVID-19 Commission presented a brief analysis to SAGO of their findings of the origins of SARS-CoV-2 (Sachs et al., 2022), as well as a separate analysis by Keusch et al. (Keusch et al., 2022). While no new evidence was presented to SAGO that could support either hypothesis, the Lancet report focused on the genomic structure of the virus (specifically the furin cleavage site), and encouraged that WHO and governments should intensify the search for the origins of SARS-CoV-2 and investigate both the possibilities of a zoonotic origin and research-associated origin (Sachs et al., 2022). The zoonotic spillover hypothesis was presented in detail with options of natural spillover from a bat reservoir, via an intermediate animal host to human, followed by

human-to-human transmission or direct bat-to-human transmission. The authors also noted that similar SARS-CoV-like viruses have been identified in several bat species across China. However, they question whether the HSM was the initial site of spillover (as there were no animals identified from the market testing positive for SARS-CoV-2) or whether it was a site of amplification. The Lancet report outlines a possible pathway of a research- or laboratory-associated release of a pathogen – either through accidental exposure in the field or within a laboratory setting involving a genetically modified virus during research activities. The Lancet report emphasises that further investigation is required to investigate both hypotheses and that this will require unbiased, independent, and transparent work led by international scientific teams supported by governments.

The review by Keusch et al. (2022) covered RNA virus outbreaks, spanning from Marburg virus in 1967 through to SARS-CoV-2, underscoring the recurrent theme of viral origins in avian, bat, and other mammalian reservoirs and intermediate hosts (Keusch et al., 2022). This brief commentary on SARS-CoV-2 origins concludes, without presenting original or direct evidence, that the virus is likely of zoonotic origin, transferred from wildlife to humans via wildlife farming and trade and concludes that the virus could have evolved to contain a furin cleavage site naturally.

In summary, although both Keusch et al. (2022) and Sachs et al. (2022) papers review published research, the conclusions were largely opinion-based and did not present any new evidence to support claims regarding the origins of SARS-CoV-2 (Keusch et al., 2022; Sachs et al.,2022). Similarly, a commentary by a group of North American scientists also did not introduce novel data but raised concerns regarding promoting anti-science sentiment and the disproportionate emphasis on a laboratory origin hypothesis over consideration of a natural spillover (Alwine et al., 2023).

The 2021 review by Holmes provides an overview of the available information regarding the zoonotic spillover and laboratory origin hypotheses of SARS-CoV-2 (Holmes et al., 2021b). Based on the available studies and his personal expertise, he described the facts supporting the spillover from bats to animals and then to humans via an unidentified secondary host. Supporting evidence of early occurrence in the HSM and wild animals present are explained in detail. The review also offers views regarding various hypotheses for unnatural origin of SARS-CoV-2 including potential release from a laboratory but highlights the lack of compelling evidence other than circumstantial elements regarding the work

at the WIV, Wuhan CDC and the presence of a furin-cleavage site. His conclusion is that most evidence points to the HSM as an epicenter, similar to the emergence of SARS-CoV-1 in 2002.

On 2 April 2025, the French National Academy of Medicine published its report entitled '*From the Origin of SARS-CoV-2 to the Risks of Zoonoses and Dangerous Virus Handling'*, which analysed two hypotheses: 1) SARS-CoV-2 is a zoonosis and 2) the origin of SARS-CoV-2 is linked to a laboratory accident. The Academy did not reach any firm conclusions on the subject, which it has taken as a starting point for reflection on possible recommendations and proposals for action to better anticipate and react to emerging diseases (Académie Nationale de Médecine, 2025).

While we are aware of several additional reviews, none provided additional scientific evidence and have not been detailed here further.

Intelligence Reports/Reports from Governments (Summarised in Table 3.B)

In addition to articles in peer-reviewed literature, there have also been reports released by individual Member State government-related agencies, including from the U.S.A., Germany and China. Seven reports have been issued by the U.S. government entities and are summarized in Table 3.B. WHO has requested access to the underlying data these entities used to make their assessments, but, to date, this access has not been granted; thus SAGO has reviewed what is publicly available.

The U.S. National Intelligence Council (NIC) and the Office of the Director of National Intelligence (ODNI) issued a report in October 2021 (Office of the Director of National Intelligence, 2021), followed by an updated report in June 2023 (Office of the Director of National Intelligence, 2023). Both reports state their findings came from 'available intelligence reporting and other information', without stating the nature of this other information or agreeing to share any of the primary data or intelligence with SAGO or WHO. The reports include a mix of factual observations, speculative assertions, and calls for further investigations. Still, neither of the two reports presented any new or conclusive evidence to support either zoonotic or laboratory origins of SARS-CoV-2.

The NIC/ODNI (2021) report stated that four Intelligence Community elements[3] assessed with low confidence that the initial SARS-CoV-2 infection was most likely caused by natural exposure to an animal infected with SARS-CoV-2 or a close progenitor virus (Office of the Director of National Intelligence, 2021). One element assesses with moderate confidence that the first human infection with SARS-CoV-2 most likely was the result of a laboratory-associated incident, probably involving experimentation, animal handling, or sampling by the Wuhan Institute of Virology. Despite a lack of consensus between agencies on these two hypotheses, areas of agreement between all agencies included: that the first known cluster of COVID-19 cases occurred in December 2019 in Wuhan, China; that the virus was not developed as a bio-weapon; that the virus was not genetically engineered; and that Chinese officials were not aware of the virus before it emerged (Office of the Director of National Intelligence, 2021). These findings underscore the complexities and uncertainties surrounding the origins of COVID-19, highlighting the need for further investigation and international cooperation to determine the virus' source, close remaining evidence gaps, and align on approaches to obtain information which might clarify current hypotheses and inferences on origins. Although not citing specifics, SAGO observes that different US government agencies concluded different probability rankings for current hypotheses of the origin of SARS-CoV-2. While suggesting areas for additional research, the assessments highlighted the ongoing disagreement within the intelligence community and their analysts about the origins of SARS-CoV-2, with some favouring a natural origin caused by zoonotic transmission and others a laboratory-origin hypothesis.

Members of the United States Senate issued three reports on the origins of SARS-CoV-2: An Analysis of the Origins of the COVID-19 Pandemic; (Senate Health Education Labor and Pensions Committee Minority Oversight Staff, 2022), Muddy Waters - The Origins of COVID-19; (Marshall, 2023), and A Complex and Grave Situation: A Political Chronology of the SARS-CoV-2 Outbreak. (Rubio, 2023). All three reports contain similar information. The Muddy Waters Group report is the most detailed as it relates to specific inputs used in the generation of its conclusions. They hint at potential sources that could lead to a containment breach, including biosafety and biosecurity enhancements at the WIV in

[3] Intelligence Community Element means any executive agency or unit thereof determined by the President under section 2302(a)(2)(C)(ii) of title 5, United States Code, to have as its principal function the conduct of foreign intelligence or counterintelligence activities.

late 2019. However, they stop short of directly suggesting a laboratory breach as the origin of the COVID-19 pandemic. These reports highlight periodic potential biocontainment and personnel security weaknesses at the WIV that could potentially result in biocontainment breaches; however, the reports do not provide any direct evidence. Speculations are made regarding engineering modifications and upgrades to the laboratories, staff training, but without concrete information and as such they remain conjecture. Collectively, these reports highlight the critical need for a thorough, unbiased investigation into the origins of SARS-CoV-2 to enhance global health security and prevent future pandemics.

In late 2024, the After Action Review of the COVID-19 Pandemic: The Lessons Learned and a Path Forward (Select Subcommittee on the coronavirus pandemic) SSCP report, **(**Select Committee on the Coronavirus Pandemic**,** 2024) was published. While it had a broader mandate than other US government agency reports, including review of financing and management of the COVID-19 pandemic within the USA, the report made claims regarding the possibility that SARS-CoV-2 emerged due to a laboratory- or research-related accident without providing any new evidence or factual scientific evidence to support such claims. The report provides no new specific data; in fact, most of the relevant section focuses on the initial development of the "Proximal origin of SARS-CoV-2" Nature Medicine paper (Andersen et al., 2020). The report focuses on how initial observations on the genomic structure of the virus identified unique features and speculates as to whether the final statements and conclusions of the manuscript may have been influenced by other than scientific reasoning.

In response to and countering the arguments of the SSCP report, the US Democrats published *Partisan Probes Over Pandemic Prevention and Preparedness (*U.S. House of Representatives Committee on Oversight and Reform (Democratic Staff), 2024); a report providing a concise review of available knowledge on potential origins of SARS-CoV-2, concluding that a zoonotic origin and laboratory accident are both plausible as is a 'hybrid' scenario reflecting a mixture of the two, though no new data to further assess virus origins is provided. A further report by the Central Intelligence Agency has been cited by media – but is not publicly available and thus has not been reviewed by SAGO.

The China White Paper 'Covid-19 Prevention, Control and Origins Tracing

China's Actions and Stance' was released in April 2025 by the State Council Information Office (State Council Information Office, 2025). It summarizes China's efforts in containment, cites both international (joint WHO-China) missions (WHO 2020g; WHO 2021c), and highlights key research conducted in China on the origins of COVID-19. Key conclusions of the report include that the government of China considers the work on the origins of COVID-19 in China is finished, which is not the opinion of SAGO; and that the original source of the infection in China was via the cold chain from products originating outside China, without citing any new evidence for SAGO to review.

Reports by Civil Groups

The SAGO takes note of reports by civil groups and had been approached by several including DRASTIC ('Decentralized Radical Autonomous Search Team Investigating COVID-19') who investigated the DEFUSE grant proposal by EcoHealth Alliance, previously rejected for funding a project on bat coronaviruses, which was released publicly following a Freedom of Information Act request by the organization US Right To Know. SAGO found that these reports did not provide additional scientific- or intelligence-based data that was not already presented in the above-mentioned peer-reviewed papers, scientific reviews or reports but include many speculations and theories that are not backed up by science and were therefore not included in this report.

A report entitled 'The Most Plausible Origin of SARS-CoV-2' was also shared with SAGO via email in late May 2025, summarizing a recent book by Haslam, which proposes a laboratory origin of SARS-CoV-2 and incriminating specific individual scientists in the USA, Singapore and China based on the DEFUSE proposal (Haslam and Haslam, 2024). There were several misconceptions, misinterpretations and speculations in this report, some that SAGO addresses here. While recombinant chimeric live vaccine technology has been patented by University of North Carolina (UNC), the DEFUSE proposal did not propose to vaccinate bats using this vaccine. The proposal instead involved recombinant antigen (synthetic protein) vaccine that would not replicate or spread. Implicated proposals by NIH involved vaccinating bats with vectored vaccine (Modified Vaccinia Ankara, Vesicular Stomatitis Virus) which similarly would not spread, and these proposals did not involve coronaviruses.

The SHC014 sequence provided by WIV to UNC is not closely related to SARS-CoV-2 but belongs to another sarbecovirus clade (Menachery et al., 2015). Recombinant vaccine vector genome elements including HKU3 do not belong to the clade to which SARS-CoV-2 belongs, so that SARS-CoV-2 cannot be derived from this vector. Animal experiments on SARS-CoV-2 in US laboratories do not allow conclusions regarding geographical origins of SARS-CoV-2. Several additional arguments put forward in the report and book appear to be caused by misunderstandings, misquotations or confusion of terms. These affect all elementary motifs of the overall theory put forward.

Table 3A: Published Scientific Reviews

The *Lancet* Commission on lessons for the future from the COVID-19 pandemic

Sachs et al. Lancet Commission. Published 2022. (Sachs et al., 2022)

- No new evidence was presented for either hypothesis: the virus emerged as a zoonotic spillover from wildlife or a farm animal, possibly through a wet market, in a location that is still undetermined; or the virus emerged from a research-related incident, during the field collection of viruses or through a laboratory-associated escape.
- The zoonotic spillover theory was presented in detail with potential natural spillover from a bat reservoir, via intermediate animal host to human, followed by human-to-human transmission or direct bat to human transmission.
- SARS-CoV-2 is thought to derive from a bat SARS-CoV-related coronavirus with a furin cleavage site that enhances the capacity of the virus to infect human cells.
- Questions the suggestion that the HSM was the primary site of spillover (given that no animals from the market tested positive for SARS-CoV-2) or if it served as a secondary outbreak location and site of amplification.
- Since 2006, following the emergence of SARS, furin cleavage sites have also been the subject of laboratory manipulation, including their insertion into coronavirus spike proteins.
- The presence of the furin cleavage site in SARS-CoV-2 therefore does not by itself identify the proximal origin of the virus, whether natural or laboratory.
- WHO, governments, and the scientific community should intensify the search for the origins of SARS-CoV-2, investigating both a possible zoonotic origin and a possible research-associated origin. The search for origins requires unbiased, independent, transparent, and rigorous work by international teams in virology, epidemiology, bioinformatics, and other related fields.

Pandemic origins and a One Health approach to preparedness and prevention: Solutions based on SARS-CoV-2 and other RNA viruses. PNAS.

Keusch, Gerald T. et al. Published 2022. (Keusch et al., 2022)

- Examined RNA virus outbreaks to highlight the recurring pattern of viral origins, with pathogens emerging from avian, bat, and other mammalian reservoirs, often involving intermediate hosts, in previous outbreaks.
- The increasing scientific evidence concerning the origins of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is most consistent with a zoonotic origin and a spillover pathway from wildlife to people via wildlife farming and the wildlife trade.
- This builds on the accepted spillover theory of SARS-CoV-1 from the masked palm civet (*Paguma larvata*) and perhaps raccoon dogs (*Nyctereutes procyonoides*) linked to a live animal market in Guangdong, China which led to the SARS outbreak in 2003.

The Emergence and Evolution of SARS-CoV-2.

Annual Review of Virology (Holmes et al., 2021b)

- The review provides an overview of the diversity, hosts and geographical distributions of Sarbecoviruses pointing to a distribution of SARS-CoV-1 and SARS-CoV-2-related sequences in southeastern Asia. *Rhinolophus* bats have been the host from which most closely related viral sequences were recovered. Sarbecovirus origins and evolution from pangolins are also discussed in relation to SARS-CoV-2.
- The review summarizes the information available regarding the HSM in relation to early occurrence and detection of SARS-CoV-2. A description of the geolocation studies of early COVID-19 patients is discussed, supporting the market as an epicenter or amplifying location, along with the documented presence of potential intermediate hosts such as wild mammals or farmed animals (presence documented by picture, metagenomic analysis and documentaries) permissive for an animal-human interface which could drive "cross species transmission".
- The review offers a summary table describing the various hypotheses for unnatural origin of SARS-CoV-2 including potential release from a laboratory but highlights the lack of evidence other than circumstantial elements regarding the WIV, Wuhan CDC and the presence of a furin-cleavage site. The author also cites personal communications that one researcher - implicated in some theories as "the researcher" infected with SARS COV-2 - tested negative by PCR and serology for COVID-19 in 2020.
- As an example of the evolution of SARS-CoV-2, the Omicron variant's possible origin is also described such as either undetected spreading, evolution in an animal host or within a chronically infected, likely immunosuppressed individual.

Table 3B: Government Reports/Assessments
1.**Updated assessment on COVID-19 origins** National Intelligence Council (NIC). Published 2021. (Office of the Director of National Intelligence, 2021)
• Four Intelligence Community (IC) elements and the National Intelligence Council assess with low confidence that the initial SARS-CoV-2 infection was most likely caused by natural exposure to an animal infected with it or a close progenitor virus, a virus that probably would be more than 99 percent similar to SARS-CoV-2. • **Emergence Timeline:** The NIC assesses that SARS-CoV-2, the virus responsible for COVID-19, probably emerged and infected humans through an initial small-scale exposure that occurred no later than November 2019, with the first known cluster of COVID-19 cases arising in Wuhan, China, in December 2019. • **Natural Zoonotic Origin:** Four intelligence agencies, along with the National Intelligence Council, assessed with low confidence that the initial SARS-CoV-2 infection was most likely caused by natural exposure to an infected animal or a close progenitor virus. • **Laboratory Incident Hypothesis:** One agency assessed with moderate confidence that the first human infection was most likely the result of a laboratory incident, likely involving experimentation, animal handling, or sampling in the Wuhan Institute of Virology. • **Uncertainty and Intelligence Gaps:** Three other agencies remained unable to agree on either hypothesis without additional evidence, with some favouring natural origin, others a laboratory origin, and some seeing the hypotheses as equally likely. Variations in analytical views were largely a result of differences in the way agencies have studied intelligence reports and scientific publications, as well as intelligence and scientific gaps. • **China's Cooperation:** Criticizing governmental authorities for continuing to hinder the global investigation and refusing to share information. It also stated that the Chinese government's actions reflected its own uncertainty about where an investigation could lead, as well as its frustrations that the international community was using the issue to exert political pressure on China. Cooperation with China is needed to reach a conclusive assessment on the origins of the disease • These findings underscore the complexities and uncertainties surrounding the origins of COVID-19, highlighting the need for further investigation and international cooperation to determine the virus' source. • The report identifies knowledge gaps, and approaches to obtain information which might clarify hypotheses and inferences on origins. • Although not citing specifics, SAGO observes that different US government agencies came to different ranking of hypotheses for the origin of SARS-CoV-2 and COVID-19.
2.Potential links between the Wuhan Institute of Virology and the origin of the COVID-19 Pandemic Office of the Director of National Intelligence - (ODNI). National Intelligence Officer for Weapons of Mass Destruction and Proliferation and coordinated with the IC. Published 2023. (Office of the Director of National Intelligence, 2023)

- Almost all U.S. Intelligence Community (IC) agencies concur that SARS-CoV-2 was not genetically engineered. Most agencies assess that SARS-CoV-2 was not laboratory-adapted; some are unable to decide. All IC agencies assess that SARS-CoV-2 was not developed as a biological weapon.
- U.S. IC has found no direct evidence of a "biosafety incident" or of the pre-pandemic presence of the virus that causes COVID-19 at a laboratory in Wuhan, China.
- The National Intelligence Council and four other IC agencies assess that the initial human infection with SARS-CoV-2 most likely was caused by natural exposure to an infected animal that carried SARS-CoV-2 or a close progenitor, a virus that probably would be more than 99 percent similar to SARS-CoV-2.
- The Central Intelligence Agency and another agency remain unable to determine the precise origin of the COVID-19 pandemic, as both hypotheses rely on significant assumptions or face challenges with conflicting reporting.
- The Department of Energy and the Federal Bureau of Investigation assess that a laboratory-associated incident was the most likely cause of the first human infection with SARS-CoV-2, although for different reasons.

3.An Analysis of the Origins of the COVID-19 Pandemic Interim Report

Senate Committee on Health Education, Labor and Pensions (HELP). Published 2022.
(Senate Health Education Labor and Pensions Committee Minority Oversight Staff, 2022)

- Reviews publicly available information to assess two prevailing theories regarding the origin of SARS-CoV-2:
  - Natural Zoonotic Origin: The virus emerged from an animal reservoir, such as bats or other wildlife, and transmitted to humans through an intermediate host.
  - Research-Related Incident: The virus accidentally leaked from a laboratory, such as the Wuhan Institute of Virology, due to inadequate safety protocols.
- The report emphasizes the need for a comprehensive, transparent investigation to determine the virus' origin and to inform future pandemic preparedness.

4.Origins of COVID-19 report

Muddy Waters Group (MWG). Published 2023 (Marshall, 2023)

- Describes the complexities and uncertainties surrounding the origins of SARS-CoV-2.
- It examines various hypotheses, including zoonotic spillover and laboratory-related incidents, and highlights the challenges in obtaining conclusive evidence.
- The report underscores the importance of international cooperation and transparency in scientific research to uncover the true origins of the virus.

5.A Complex and Grave Situation. A political chronology of the SARS-CoV-2 outbreak

Rubio State Senate. Published 2023. (Rubio, 2023)

- This document provides a chronological account of the political responses to the SARS-CoV-2 outbreak, both within the United States and internationally.

- It outlines key decisions, policy shifts, and diplomatic interactions that shaped the global response to the pandemic.
- The report offers insights into the interplay between political considerations and public health measures during the early stages of the outbreak.

6.After Action Review of the COVID-19 Pandemic: The lessons learned and a path forward.

Select subcommittee on the coronavirus pandemic. Published 2024. (Pandemic, 2024)

- Notes the possibility that COVID-19 emerged due to a laboratory- or research-related accident is not a conspiracy theory.
- It references a Fact Sheet released by the State Department in 2021 – which claims that the US government had reason to believe there were several researchers inside the WIV who became sick with symptoms in line with common seasonal illness or COVID-19.
- It also references the ODNI report which makes reference to WIV activities on SARS-like coronaviruses and its involvement with the Chinese military. It also states that the ODNI report claims "some WIV researchers probably did not use adequate biosafety procedures…". It references the DOE and FBI who made similar assessments that COVID-19 was likely the result of a lab incident (FBI with moderate confidence and DOE with low confidence.
- proposes that Ecohealth Alliance facilitated gain-of-function research in WIV and were unable to acquire copies of WIV notebooks in 2021 to understand the extent of recombinant bat-coronavirus virus work being done at WIV, and absence of receipt of that information.

7. Partisan Probes Over Pandemic Prevention and Preparedness – Democratic Final Report

Published 2024. (U.S. House of Representatives Committee on Oversight and Reform, Democratic Staff, 2024).**)**

- Democratic Party opinion based on the above Select Subcommittee Report.
- 'After hearings etc., … the Select Subcommittee remains in the same position in which it started: the origins of COVID-19 are unknown. A zoonotic origin and lab accident are both plausible, as is a "hybrid" scenario reflecting a mixture of the two'.
- Does not add any new evidence.
- Questions accusation by Select Subcommittee that NIAID director or EcoHealth Alliance 'created' SARS-CoV-2.

Discussion

Prior to the emergence of SARS-CoV-2, all known human coronaviruses that have emerged in past decades are believed to have originated in bats or rodents and spilled over to humans through an intermediate animal host (Corman et al., 2018; Mittal et al., 2020). SARS-CoV-1 (2003), for instance, has a precursor virus in bats, with masked palm civets and possibly raccoon dogs acting as intermediate hosts (Mittal et al., 2020). For the Middle East Respiratory Syndrome Coronavirus (MERS-CoV; 2012), dromedary camels have been identified as the intermediate host (Reusken et al., 2013; Mohd et al., 2016). While the initial SARS-CoV-2 strain is most closely related to the Laos BANAL-52 bat strains, an intermediate host has yet to be identified.

SAGO has reviewed available published and unpublished scientific evidence related to the origin of SARS-CoV-2, received presentations by scientists from China and elsewhere (institutions listed in methods section and acknowledgements); the joint international WHO and China teams' mission report from 2021 and had discussions with researchers and other groups conducting relevant work as outlined in this report. SAGO applied the Global Framework for investigation of the origins of novel pathogens (WHO, 2024a) to thoroughly assess the available scientific information covering the key elements for investigation of the emergence of novel pathogens including 1) early investigations around the first human cases and the HSM; 2) early human epidemiology and surveillance data globally, including in the months preceding 1 January 2020; 3) investigations at the animal/human interface including precursors strains from bats and potential susceptible hosts, 4) environmental surveillance data, 5) genomic analysis to understand the genome structure and evolution as well as 6) laboratory biosafety and biosecurity at laboratories where the initial cases were reported in Wuhan China.

SAGO has also reviewed scientific and non-scientific publications including reports by independent bodies and met with journalists who presented unpublished information from their work. SAGO reviewed this information and included what was deemed scientifically and factually relevant in this assessment (Keusch et al., 2022; Sachs et al., 2022; Senate Health Education Labor and Pensions Committee Minority Oversight Staff, 2022; Marshall, 2023; Rubio 2023; Office of the Director of

National Intelligence, 2021; Office of the Director of National Intelligence, 2023). The WHO Secretariat and SAGO members searched for and reviewed reviews, evidence and opinion pieces from January 2020 and up to April 2025. Any which did not provide any novel data and/or information were therefore not included in SAGO's review. Although evidence is still missing, making it difficult to conclude how exactly the SARS-CoV-2 virus spilled over into the human population, assessing currently available and accessible data affords the scientific community a better understanding about the origins of SARS-CoV-2.

To summarize, the evidence available for analysis remains the following:

1) Despite screening of animal and human samples using molecular and serologic testing from samples collected in the second half of 2019 in a number of countries globally, no animal or human clinical samples positive for SARS-CoV-2 have been identified and/or verified prior to December 2019; suggesting that SARS-CoV-2 did not circulate widely in humans prior to December 2019. It is possible that there were earlier human cases prior to December 2019, but currently there is no available evidence to confirm this. Serological screening of 43,850 blood bank samples from Wuhan prior to December 2019 yielded no reported positives suggesting the virus didn't circulate widely in the city prior to the detected cases on 1 December 2019, current data supports that the first cases occurred in Wuhan China in early December 2019.

Reports of molecular screening and genetic sequencing of wastewater samples and serological studies from human clinical samples from Italy, France and Brazil proposed that the virus may have circulated undetected as early as November 2019 in some countries. However, these reports have not been verified by external laboratories. The validity of the study from Italy was compromised by several factors: 1. the outcomes not exceeding the expected rate of false-positive samples occurring by chance 2. the lack of double IgM and IgG specimens as would have been expected at least in some of the cases 3. lack of negative control samples from previous years. A lack of clinical cases identified prior to early December or molecular confirmation suggests that circulation may have been at low levels and sporadic cases could have been asymptomatic or sub-clinical and, therefore, not severe enough to seek medical care nor require hospitalization or resulting in secondary infections. With the available information, it is

difficult to verify if earlier circulation, prior to December 2019, was taking place. Further investigations from stored respiratory disease surveillance samples, wastewater or clinical specimens in China and globally should continue to be tested to determine if there was indeed circulation or if any undetected outbreaks occurred before December 2019.

2) Although not all of the reported cases in December 2019 had a direct link to the HSM, analyses of available geospatial data, sequence data, clinical and environmental samples suggests that many of those without a reported direct link lived in the vicinity of the market, indicating that most individuals that tested positive had chances of contact with animals/animal products or visitors from the market (Worobey et al., 2022a). This supports the hypothesis that the market played an important role, either due to spillover from animals, though possibly not the first spillover events, or as an amplification site for SARS-CoV-2 from infected humans present at the market (Temmam et al., 2022).

With currently available information, questions remain on exactly when and where a) the first cases occurred and b) onward transmission into the human population began. There are considerable gaps in our understanding of the testing done in humans working at markets in and around Wuhan, at the farms or along trade routes for the animals that were sold at the HSM and/or at farms raising animals known to be susceptible to SARS-CoV-2 infection. This makes it currently not possible to determine whether spillover of SARS-CoV-2 occurred upstream from source farms providing animals to the HSM or at the market itself. The HSM was a site for amplification, which allowed the virus to spread further, but it is not possible to determine if the first infections occurred at the HSM. Further sharing of data on early investigations, if they have taken place is critical, as is all sequencing data of these early detections to determine the genetic distance to the original SARS-CoV-2 strains reported from Wuhan.

3) Analysis of available genomes provides evidence of two separate introductions of SARS-CoV-2 virus lineages - that led to the development of a sustained epidemic in humans has also been found after conducting analyses from environmental samples collected from the HSM in early 2020. (Crits-Christoph et al., 2024; Liu et al., 2023) These findings and evolutionary analyses suggest that these introductions occurred after November 2019 (Worobey et al., 2022a; Pekar et al., 2022).

4) Two other unique features of the SARS-CoV-2 genome have been the focus of debate on the origin of SARS-CoV-2. As described in the genomics investigations section of this report, evidence around the evolution of the virus suggests that these features likely developed through natural evolution in susceptible animals and humans due to a propensity for recombination and accumulation of mutations associated with coronaviruses, including SARS-CoV-2. Furin cleavage sites occur in other human coronaviruses and had been previously identified in nature, for example in animal-associated merbecoviruses. This suggests that it could also be acquired in sarbecoviruses through natural recombination events between related sarbecoviruses in humans or susceptible animals. Based on our knowledge on coronavirus evolution and biology, this and other features of SARS-CoV-2 are readily explained by natural evolution and provide no support to theories of a man-made origin (Keusch et al., 2022; Sachs et al., 2022; Senate Health Education Labor and Pensions Committee Minority Oversight Staff, 2022; Marshall, 2023; Rubio, 2023; Office of the Director of National Intelligence, 2021; Office of the Director of National Intelligence, 2023). However, the latter is also not refuted by biological data.

5) It has been reported to SAGO and WHO that no stored samples from animals in China taken before the first identified human cases of COVID-19 (January 2020) were SARS-CoV-2-positive (WHO, 2022). This has not been independently verified by SAGO. However, it seems unlikely that there have been no animal SARS-CoV-2 reverse zoonotic infections in China since the onset of the COVID-19 pandemic (aside from Syrian hamsters in Hong Kong Special Administrative Region), considering the many susceptible species present there, the reverse zoonoses events reported in various susceptible species around the world, and the possibility of exposure to potentially infected animals at source farms and the HSM. Despite some testing of the environment and animals sampled from the HSM, there was a limited number of susceptible species included in this testing, thus limiting the ability to make definitive conclusions. It is likely that many animals had already been removed due to public health measures imposed on 1 January 2020, when the market was shut down and disinfected; therefore, they were not traced for sampling. It remains the recommendation of SAGO that investigation of animals, animal vendors and source farms related to the HSM and susceptible species across Southeast Asia should have been conducted, and that if these investigations have already taken place, that these results

be shared (Liu et al., 2023). There would be value in tracing the movements of these animals from source to market, even 5 years later.

Currently, the most compelling evidence of a possible spillover from animals to humans comes from the independent metagenomic data analysis, which confirmed the presence of mitochondrial DNA of animals known to be susceptible in stalls at the HSM, and SARS-CoV-2 positive environmental swabs from the same stalls. The data confirms that these animals were present before the market was closed on 1 January 2020 and may have been a source for human infection. These species should be a focus of ongoing investigations into the identification of the intermediate host(s).

6) SAGO worked closely with the WHO Technical Advisory Group on Biosafety and Biosecurity (TAG-B), which provides expert advice and scientific and technical recommendations for evidence-based biosafety and biosecurity control strategies to improve the safety of pathogen laboratories worldwide (WHO, 2020a). Together, SAGO and TAG-B identified and outlined the critical areas for investigating potential breaches in biosafety and biosecurity to ensure a comprehensive assessment of risks and vulnerabilities in laboratory settings.

At the present, it is not possible to assess the possibility of an incident occurring in laboratories in Wuhan as SAGO has not had the opportunity to formally examine the biosafety and biosecurity protocols and measures that were in place, the activities conducted in those facilities, or the health status of staff from late 2019. SAGO notes that no evidence has been presented, other than speculation from scientific or intelligence reports, that supports a laboratory-related incident causing the spread of SARS-CoV-2 into the human population. Without the requested information, this hypothesis can however not be ruled out.

Conclusion

More than five and a half years have passed since the first reported cases of SARS-CoV-2 infection were reported in Wuhan, China in December 2019. Although evidence exists that has improved our understanding of the early and subsequent evolution of the virus in humans and animals, significant

data gaps remain which preclude SAGO from concluding with certainty how SARS-CoV-2 initially entered the human population.

Throughout the development of this independent assessment, it may be obvious to state that SAGO has only been able to analyze evidence made available to them and the public. However, SAGO and WHO are aware that more data exists. Some examples of this include requests for more information including:

a) the sharing of more than 500 sequences from individuals with COVID-19 early in the pandemic; (China National Center for Bioinformation, 2022).

b) more detailed information on the sources, locations, sampling and testing methods of animals sold at the HSM and other wet markets in Wuhan, including upstream farming or illegal trade; and

c) information on research and field activities in laboratories in Wuhan, including staff health records, biosafety and biosecurity information of the Wuhan Institute of Virology, and the Wuhan China CDC laboratory.

The weight of available evidence reviewed by SAGO suggests zoonotic spillover of SARS-CoV-2 into the human population, either directly from bats or through an intermediate host. However**,** SAGO cannot conclude with certainty where and when this occurred, nor if the HSM was indeed the first instance of spillover into the human population, or the site of further spillover and amplification. Susceptible infected animals (or animal products) could have acted as reservoirs and therefore exposed humans through different routes: (a) before the infected animals or humans arrived at the HSM, or (b) once the infected animal or animal product arrived at the HSM. However, irrespective of the precise spillover event or events, the HSM appears to be location for amplification of infection in humans leading to widespread transmission to surrounding areas in China, and eventually to other countries. Evidence for widespread infections or cases in any other countries prior to December 2019 is lacking, as well as evidence to support the cold chain hypothesis. Information and evidence is also lacking to assess the possibility of a laboratory origin - either the evidence is not available or has not been provided to the scientific community. As a result, SAGO has been unable to adequately assess this route for

human infection and therefore is not in a position to rule this out as a possibility. Hypotheses submitted to the SAGO or available in the public domain on intentional manipulation of the virus however, are not supported by accurate science, and not currently considered as the likely source.

Nevertheless, based on the recommendations in SAGO's preliminary report on COVID-19 (WHO, 2022), outcomes from the March 2021 WHO-convened global mission (WHO, 2021) and recent findings from scientific evidence related to SARS-CoV-2 origins, the scientific investigations and studies recommended in Table 4 remain to be conducted, in order for the scientific community to conclude with more certainty the origins of SARS-CoV-2.

The COVID-19 pandemic has caused so much suffering and devastation globally for the world not to know exactly how this pandemic started. SAGO urges China together with the global scientific community to prioritize further work on understanding the origins COVID-19 and for all countries to comprehensively study future emergences of unknown pathogens.

SAGO remains committed to science and will continue to evaluate any and all new sound scientific evidence and data as it is made available through public or private sources to clarify the origins of SARS-CoV-2. If provided with reliable evidence, SAGO is available to evaluate all possibilities to revise this report.

Table 4. Recommended investigations into the origins of SARS-CoV-2: The following are recommended studies that are outstanding from previous reports and the SAGO considers them to still be pertinent.

Aim	**Outstanding recommended studies (what is still feasible)**	**Status** **(to the best of our knowledge – has not been done)**
Identification of potential previously unrecognized COVID-19 cases prior to December 2019	Wastewater and clinical samples surveillance, from influenza-like illness (ILI) and Severe Acute Respiratory Infections (SARI) and polio surveillance from East and Southeast Asia from September to November/December 2019 that may identify earlier cases with an expanded case definition, in order to capture milder cases and younger individuals.	Not conducted or if done not made publicly available. Still feasible where archived samples exist in research and public health institutions.
Investigation of animals, animal vendors and source farms related to the HSM and susceptible species across Southeast Asia	Focused serological and genetic testing and increased surveillance of animals and/or wildlife associated with the HSM in live animal markets and upstream supply farms are essential to monitor high-risk potential host species. Testing sick or dead animals, particularly those from susceptible species, and conducting sequencing to monitor virus evolution is recommended. (EFSA Panel on Animal Health and Welfare et al., 2023) Mammalian species susceptibility to SARS-CoV-2 and potentially levels of virus shedding, including raccoon dogs, civets, bamboo rats, Malayan porcupines, and hedgehogs, as well as minks and bats throughout Southern China and South-East Asia, can shed light on the animal trade networks that may have led to the emergence of SARS-CoV-2 as previously recommended. (WHO, 2022) Archived samples from prior to Jan 2020 should be traced from research, veterinary or public health laboratories, and other sources to be tested to identify the presence of SARS-CoV-2 infection prior to December 2019. Systematic random sampling of wildlife farms, hunters or animal traders in and around the Wuhan region is still outstanding. There is a need for more	Some wildlife surveillance was conducted by Chinese researchers, but the sampling strategy and methods were unclear, as the numbers of samples/species tested, which were limited, did not include sampling from source farms, targeted wildlife value chains or all appropriate susceptible species. If this data or stored samples are available from research or veterinary labs this may still be carried out. Testing of current samples or animals should be prioritized to prevent future spill over events even if it is unlikely to yield the source of the COVID19 pandemic.

	information, particularly from source farms trading animals to wet markets in Hubei Province, China prior to Jan 2020.	
	Continued syndromic and genomic surveillance in humans and animals in the East and Southeast Asia region may detect continued circulation of early human strains in animal reservoirs or emerging variants of concern. Specifically, those who enter caves and communities in the vicinity where precursor strains circulate including RaTG13 in China and Banal-52 strain in Lao People's Democratic Republic and recent SARS-CoV-like bat viruses (that can infect human cells). In addition, SARS-CoV-like viruses detected in bats by Southeast Asian researchers that had not been sequenced yet should be subjected to whole genome sequencing.	Not conducted or if done not publicly available; only partial sequences of bat SARS-CoV-like strains are available.
Biosafety and Biosecurity investigations	An independent review of the laboratories in the proximity of the HSM should be conducted, including the research conducted in the years prior to the outbreak of SARS-CoV-2, the biosafety and biosecurity practices and procedures in place at the end of 2019, and the health of staff before and after the recognition of the outbreak. Independent international investigations and/or follow-up of any suggested evidence from laboratories in other parts of the world that worked on coronaviruses should also be investigated for SARS-CoV-2 activities prior to December 2019.	Not conducted despite numerous advocacy attempts.

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Annex

Annex 1. Table 1. Animal species naturally infected (RNA detection) by SARS-CoV-2

(Reference**:** Food and Agriculture Organization of the United Nations, 2023)

Animal species	Scientific name	Country/Territory	Site	Year reported & number of epi units affected [4]
Domestic cat	*Felis catus*	Argentina, Belgium, Brazil, Canada, Chile, Croatia, Ecuador, Egypt, Estonia, France, Finland, Germany, Greece, Hong Kong SAR., Hungary, Iran, Italy, Japan, Latvia, Mexico, Netherlands, Nigeria, Portugal, Republic of Korea, Russia, Spain, Switzerland, Thailand, United Kingdom of Great Britain and Northern Ireland, United States of America, Uruguay	Household	2020 (76) 2021 (94) 2022 (31) 2023 (2)
Domestic Dog	*Canis lupus familiaris*	Argentina, Bosnia and Herzegovina, Brazil, Canada, Chile, Colombia, Croatia, Denmark, Ecuador, Egypt, Finland, France, Hong Kong SAR, India, Italy, Japan, Jersey, Mexico, Myanmar, Netherlands, Nigeria, Portugal, Republic of Korea, Spain, Switzerland, Thailand, the United Kingdom of Great Britain and Northern Ireland, United States of America, Uruguay	Household	2020 (76) 2021 (76) 2022 (93) 2023 (7)
Domestic American Mink	*Neovison vison*	Bulgaria, Canada, Denmark, France, Greece, Italy, Latvia, Lithuania, Netherland, Poland, Spain, Sweden	Farm	2020 (349) 2021 (32) 2022 (2) 2023 (1)
Domestic Ferret	*Mustela furo*	Slovenia, United States of America	Household	2020 (1) 2021 (1) 2024 (1)
Wild American Mink	*Neovison vison*	Spain, United States of America	Free range	2020 (no data) 2021 (2)
Western lowland Gorilla	*Gorilla gorilla gorilla*	United States of America, Spain, the Netherlands, Brazil	Zoo	2021 (12) 2022 (5)

[4] individual animal cases or production or marketing units such as farms or markets

Animal species	Scientific name	Country/Territory	Site	Year reported & number of epi units affected [4]
White-tailed deer	*Odocoileus virginianus*	Canada, United States of America	Natural Park Wild habitat (hunted)	2021 (350) 2022 (625) 2023 (1) 2024 (7)
Binturong	*Arctictis binturong*	United States of America	Zoo	2021 (1)
Coatimundi	*Nasua nasua*	Brazil, United States of America	Zoo Urban Park	2021 (3)
Fishing cat	*Prionailurus viverrinus*	United States of America	Zoo	2021 (1)
Tiger	*Panthera tigris*	Argentina, Denmark, Indonesia Sweden, United Kingdom of Great Britain and Northern Ireland, United States of America	Animal sanctuary Zoo Wild animal exhibitor facility	2020 (1) 2021 (24) 2022 (4) 2023 (1)
Lion	*Panthera leo*	Croatia, Colombia, Estonia, Japan, the Netherlands, Puerto Rico, Singapore, South Africa, Spain, Sweden, United States of America	Zoo	2020 (2) 2021 (26) 2022 (3) 2023 (1)
Puma	*Puma concolor*	Argentina, South Africa, United States of America	Wild animal exhibitor facility Rescue center	2020 (2) 2021 (1)
Snow Leopard	*Panthera uncia*	United States of America	Zoo	2020 (3) 2021 (2)
Indian Leopard	*Panthera pardus fusca*	India	Free range	2021 (1)
Canada Lynx	*Lynx canadensis*	United States of America	Zoo	2021 (1)
Spotted hyenas	*Crocuta crocuta*	United States of America	Zoo	2021 (2)
Asian small-clawed otters	*Aonyx cinereus*	United States of America	Aquarium Zoo	2021 (9)
Hamster	*Mesocricetus auratus*	Hong Kong SAR, China	Pet shop Warehouse of pets	2022 (2)
Wild Eurasian River Otter	*Lutra lutra*	Spain	Free range	2021 (1)
Hippopotamus	*Hippopotamus amphibius Unspecified*	Belgium, Viet Nam	Zoo	2021 (1) 2022 (2)
Black-Tailed Marmoset	*Mico melanurus*	Brazil	Free range	2022 (1)

Animal species	Scientific name	Country/Territory	Site	Year reported & number of epi units affected [4]
Mule deer	*Odocoileus hemionus*	United States of America	Natural Park	2022 (1) 2023 (2)
Antillean manatees	*Trichechus manatus manatus*	Brazil	Captive	2020 (2)
Giant anteater	*Myrmecophaga tridactyla*	Brazil	Free range	2022 (1)
Mandrill	*Mandrillus sphinx*	United States of America	Zoo	2022 (1)
Monkey Squirrel	*Saimiri sciureus*	United States of America	Zoo	2022 (1)
Red fox	*Vulpes vulpes*	Switzerland	Zoo	2022 (1)
Cattle	*Unspecified*	India, Nigeria, Republic of Korea	Animal-rearing pockets Unspecified	2021/2022 (32) 2023 (1)
Buffalo	*Unspecified*	India	Animal-rearing pockets	2021/2022 (13)
Goat	*Unspecified* *Capra hircus coreanae*	Nigeria Republic of Korea	Unspecified	2021/2022 (46) 2023 (1)
Black-and brown headed Spider Monkey	*Ateles fusciceps*	Ecuador	Captive	2022 (20)
Common woolly monkey	*Lagothrix lagothricha*	Ecuador	Captive	2022 (1)
White rhinoceros	*Ceratotherium simum*	Senegal	Natural reserve	2023 (1)
Duck[a]	*Unspecified*	Nigeria	Households and backyard farms	2021/2022 (2)
Chicken[a]	*Unspecified*	Nigeria	Households and backyard farms	2021/2022 (10)
Turkey[a]	*Unspecified*	Nigeria	Households and backyard farms	2021/2022 (1)
Sheep	*Unspecified*	Nigeria	Households and backyard farms	2021/2022 (50)
Pig	*Unspecified*	Nigeria	Households and backyard farms	2021/2022 (4)
Lizard	*Agama agama*	Nigeria	Households and backyard farms	2021/2022 (19)
Eurasian beaver	*Castor fiber*	Mongolia	Farm	2021 (1)

Animal species	Scientific name	Country/Territory	Site	Year reported & number of epi units affected [4]
White-fronted capuchin	*Cebus unicolor*	Peru	Captive	2022/2023 (9)[b]
House mouse	*Mus musculus*	Mexico	Urban	2020 (4)
Brown rat	*Rattus norvegicus*	Mexico	Urban	2020 (3)
Big hairy armadillo	*Chaetophractus villosus*	Argentina	Captive	2022 (3)
Pantanal cat	*Leopardus braccatus*	Brazil	Captive	2021 (1)
Gray brocket	*Subulo gouazoubira*	Brazil	Captive	2022 (1)
Red deer	*Cervus elaphus*	Brazil	Captive	2022 (1)
Manned wolf	*Chrysocyon brachyurus*	Brazil	Captive	2022 (2)
European fallow deer	*Dama dama*	Brazil	Captive	2022 (1)
Eastern deer mouse	*Peromyscus maniculatus*	United States of America	Natural habitat study	2023 (8)
Raccoon	*Procyon lotor*	United States of America	Wildlife center and natural habitat	2023 (4)
Eastern cottontail	*Sylvilagus floridanus*	United States of America	Wildlife center	2023 (3)
Eastern red bat	*Lasiurus borealis*	United States of America	Natural habitat	2023 (1)
Groundhog	*Marmota monax*	United States of America	Wildlife center	2023 (3)
Virginia opossum	*Didelphis virginiana*	United States of America	Wildlife center and natural habitat	2022 (1) 2023 (3)

Annex 1. Table 2. Animal species susceptibility to SARS-CoV-2 based on experimental infection studies

(Reference: Food and Agriculture Organization of the United Nations. (2023)

Animal species	Scientific name (wild animals)	Susceptibility	Transmission[5]
Raccoon dogs (reference)	*Nyctereutes procyonoides*	Yes	Yes
Red Fox (reference)	*Vulpes vulpes*	Yes	Not specified
Coyotes (reference)	*Canis latrans*	No	-
Deer mice (reference)	*Peromyscus maniculatus*	Yes	Yes
Bank voles (reference)	*Myodes glareolus*	Yes	No
Bushy-tailed woodrats (reference)	*Neotoma cinerea*	Yes	Not specified
Laboratory BALB/c mice (reference)		Yes	Yes
White-tailed deer (reference)	*Odocoileus virginianus*	Yes	Yes
Ferret (reference)	*Mustela furo*	Yes	Yes
Egyptian fruit bat	*Rousettus aegyptiacus*	Yes	Yes
Striped skunks (reference)	*Mephitis mephitis*	Yes	Not specified
Zebra fish (reference)	*Danio rerio*	Yes	Not specified
Zebra mussel (reference1) (reference2)	*Dreissena polymorpha*	Yes	Not specified
Syrian hamsters	*Mesocricetus auratus*	Yes	Yes
Tree shrews (reference1) (reference2)	*Tupaia belangeri chinensis*	Yes	Not specified
Rhesus macaques (reference)	*Macaca mulatta*	Yes	Not specified
The crab-eating macaque (reference)	*Macaca fascicularis*	Yes	Not specified
Baboons (reference)	*Papio hamadryas*	Yes	Not specified
Common marmosets (reference)	*Callithrix jacchus*	Yes	Not specified
Cynomolgus macaques (reference)	*Macaca fascicularis*	Yes	Not specified
African green monkeys (reference)	*Chlorocebus aethiops*	Not susceptible	Not specified
Mosquitoes (reference1) *(reference2)*	*Aedes aegypti, Aedes. albopictus, Culex tarsalis and Culex quinquefasciatus*	Not susceptible	-

Midge (reference)	*Culicoides sonorensis*	Not susceptible	-
Chicken – Duck – Geese – Turkey – Quail and Pigeon (reference)	-	Not susceptible	-
Pig (reference1) (reference2) (reference3)	-	Yes (Low susceptibility)	No
Cattle (reference1) (reference2) (reference3)	-	Yes (Low susceptibility)	No
Horse (reference)	-	No	-
Sheep (reference)	-	Yes (Low susceptibility)	No[1]
Goat (reference1) (reference2)	-	Yes (Low susceptibility)	Not specified
Alpaca (reference)	-	No	-
Rabbit (reference)	-	Yes	Not specified
Cat (reference)	-	Yes	Yes
Dog (reference)	-	Yes (Low susceptibility)	No
Sprague Dawley rats (reference)	*Rattus norvegicus*	Yes	Not specified
Elk (reference1) (reference2)	*Cervus canadensis*	Yes (ancestral virus) (Low susceptibility to Delta VOC)	No
Mule deer (reference)	*Odocoileus hemionus*	Yes	Yes
Mexican free-tailed bats (reference)	*Tadarida brasiliensis*	Yes	No
Little brown bats (reference)	*Myotis lucifugus*	No	

[5] to co-housed animals of same species

END OF REPORT.