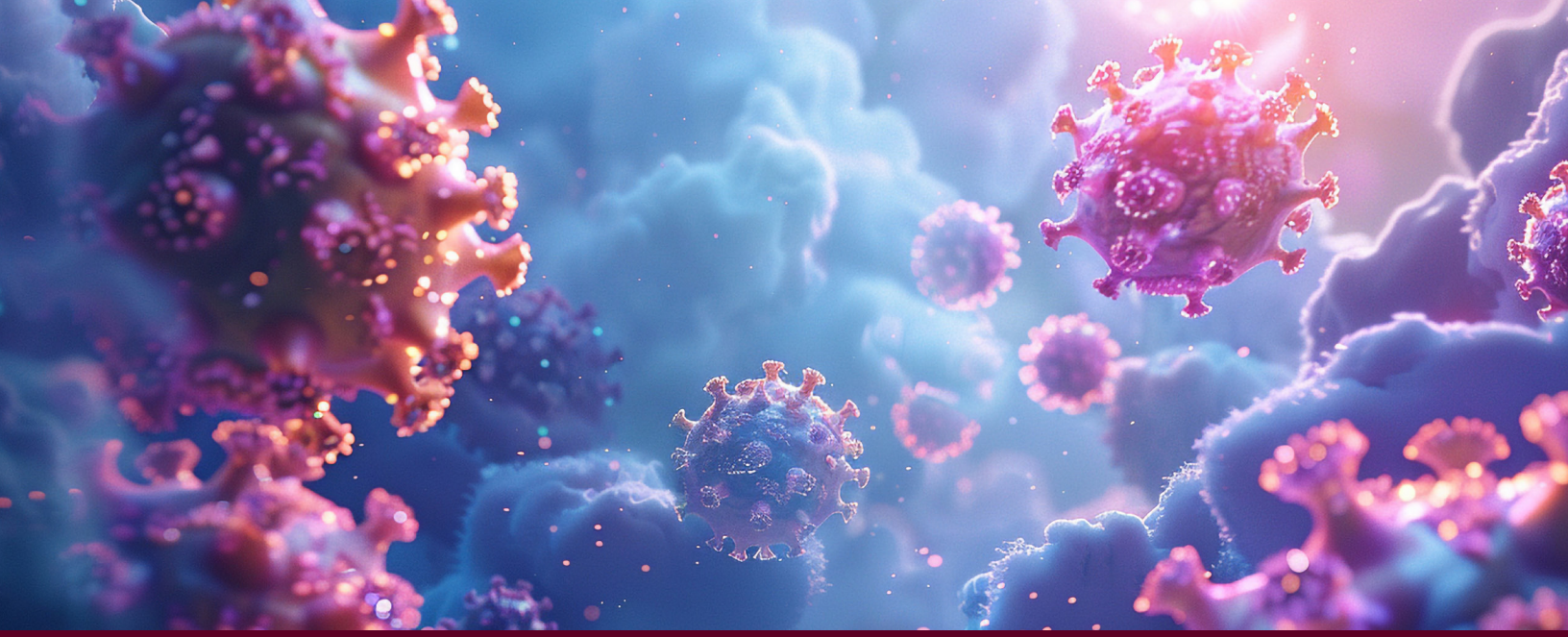

A CRITICAL REVIEW OF COVID-19 ORIGINS: "HIDDEN IN PLAIN SIGHT"

MUDDY WATERS UPDATE: SECOND INSTALLMENT

WRITTEN BY

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FOREWORD:

The following study is a years-long effort by the author, Dr. Kadlec, to find, synthesize, organize, and share information about the origins of SARS-CoV-2. It is one of the most thorough compilations of relevant information to date. While no definitive account exists of how SARS-CoV-2 first emerged in humans, this report assesses the likelihood of multiple scenarios based on the most up-to-date publicly available evidence, both previously known and newly identified.

The report finds that a research-related incident is the most probable origin of SARS-CoV-2. However, this does not imply the pandemic began with a deliberate act. Accidents are not conspiracies, which require human intent and purposeful action. Rather, accidents are a constant risk and, without extreme precaution, inevitable. Accordingly, the worldwide construction of ever more high containment laboratories warrants great caution and should be accompanied by a greater global adoption of strong biosafety standards. New facilities attract funding and attention, but maintenance and biosafety workforce development receive much less of either. While voluntary standards exist, there is no enforced system for safety measures at labs around the world, and in many cases, the leadership and funding for these facilities can be hindered by weak institutions in host countries.

The report further suggests the possibility of offensive biological weapons (BW) research occurring in China with links to the origins of SARS-CoV-2. This is the report's most provocative finding and one worth taking seriously. It is difficult to prove the existence of a BW program. If such a program is confined to early-stage research and development, possessing and experimenting with deadly diseases, even if military scientists are involved, can be explained as peaceful research to identify vulnerabilities and prepare defenses. Indeed, the U.S. military continues to conduct excellent research on dangerous pathogens to protect U.S. forces against them. The existence of a BW program then comes down to a question of intent, something notoriously hard to determine. Nonetheless, this report cites concerning writings by Chinese military strategists indicating an interest in biology's potential as a weapon. The report's findings are enough to justify placing a much greater priority on intelligence efforts aimed at possible Chinese BW activities. It bears repeating that, even if SARS-CoV-2 is associated with BW research, the report finds no evidence that the virus was deliberately released.

Deliberate suppression of public health information in China has been detrimental to international efforts to determine the origins of the pandemic. Since the initial outbreak in Wuhan, Chinese authorities have restricted the collection and publication of information about COVID-19, and several reports have concluded that the outbreak's origins can only be fully resolved with additional details known only in China. However, we should be wary of what conclusions we draw from this pattern of censorship. It may point to an attempt to cover up information about a research-related accident, but it could also result from a cover-up of a zoonotic origin (which would imply an embarrassing failure to control the wildlife trade) or attempts by Chinese officials to conceal their missteps during the COVID-19 response.

The report is among the first to compile new medical information about COVID-19's short-term and medium-term neurological effects. Research since 2020, including longer-term studies, has produced concerning new information about the damage SARS-CoV-2 causes to the brains of many patients, including those of children and people with only mild infections. COVID-19 remains with us and will continue to circulate for the foreseeable future, making it a public health imperative to understand its neurological implications. This should remain a central focus of future research regardless of the pandemic's origins.

Still, we believe it is important to understand how SARS-CoV-2 originated and entered the human population. We should invest in defending against both natural and human-caused public health risks, and many investments can address

threats regardless of their origin; however, the reality is that our resources are limited. In the current environment, both funding and public attention are scarce. Determining how the last pandemic began would better inform how to prioritize lessons learned and prevent the next one. This would impact the objectives of biomedical research, science diplomacy and policies intended to mitigate the risk of accidents in pathogen research while accelerating scientific advancement.

There is great value in identifying how experiments with pathogens could spark a pandemic, documenting gaps in our knowledge about COVID-19, and compiling biosafety concerns identified in reporting on SARS-CoV-2 since 2020. China has made great strides in life sciences research and continues to do so. Like the rest of the world, however, the zeal for new research and new facilities is not matched by a zeal for safety. Regardless of the pandemic's origins, the known handling of pandemic capable viruses under inadequate biosafety controls presents serious concerns. Many strong proponents of the zoonotic hypothesis agree on the importance of preventing incidents in infectious disease laboratories. A world in which the possibility of laboratory-caused pandemics has been eliminated would be a better one for us all. This report represents another small step toward realizing that future.

We appreciate Dr. Kadlec's extensive and dedicated efforts to analyze the origins and implications of the COVID-19 pandemic. It is our hope that this report will highlight three policy imperatives. First, we must improve our ability to rapidly detect and determine the cause of infectious disease outbreaks. Second, we must invest in medical and clinical research into the emerging effects of long COVID, especially for children. Third, we must create enforceable international biosafety standards for high-containment laboratory design and operations, including training requirements.

Finally, we feel this should be a conversation about facts, not about personalities, with an emphasis on forward-looking implications. Many discussions on the origins of the pandemic have focused on placing blame for the start of, spread of, or response to the pandemic. Some blame may be well-placed, but such a conversation does little to advance the policy, medical, and research needs highlighted in this report.

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PREFACE:

This study represents a continuation of research first begun as a bipartisan investigation by the Chairwoman, Senator Patty Murray, and Ranking Member, Senator Richard Burr, of the U.S. Senate Health Education Labor and Pension (HELP) Committee in the 117th Congress. The objective of the investigation was to evaluate available open-source information on the likelihood of a natural zoonotic origin versus a potential research-related incident as the proximate cause of the COVID-19 pandemic. It was ultimately released by Senator Roger Marshall in the 118th Congress as a minority member report. The original Muddy Waters report was compiled by many hands and diverse expertise. A small group of investigative lawyers, research assistants, a medical epidemiologist, a veterinary epidemiologist and a China area specialist formed the core team. Their efforts were supplemented by a larger group of virologists, physicians, veterinarians, epidemiologists, molecular biologists, China military experts and biosafety experts who provided technical assistance and reviewed the report. The original report found that a preponderance of open-source evidence supported the likelihood of a research-related incident over a natural zoonotic outbreak.

This Muddy Waters Update supplements the original report with new information that provides further evidence supporting a research-related incident. These new insights offer evidence associating this research with vaccine-related studies by the People's Liberation Army (PLA). This report also documents the acute and chronic neurological sequelae associated with COVID-19 infections. Based on unusual observed features of PLA vaccine research, pre-existing PLA writings, and the early publications on COVID-19 in China, the possibility exists that COVID-19's neurological consequences were either known or expected prior to the pandemic and a vaccine to protect against these effects was being developed.

These findings should be considered preliminary and do not reflect any classified information held by the U.S. Intelligence Community. The evidence supporting these findings is derived from open-source information, much of it from Chinese references; however, China's government has limited and censored information pertaining to COVID-19's origins that could provide further insight into the subject. Further information will likely continue to emerge. Declassified U.S. intelligence and data provided by China or published in peer reviewed literature could provide higher confidence to the findings contained in this report.

Comments or inquiries related to the report may be directed to muddy.waters.update@proton.me

EXECUTIVE **SUMMARY**:

While the COVID-19 pandemic is declared over, SARS-CoV-2 infections, along with their acute and chronic effects, have not ended. The pandemic continues to have "a profound impact on public health, disease burden, social and economic status, and quality of life" in the United States.[1] The legacy of the pandemic leaves millions globally afflicted with a variety of chronic cardiovascular, respiratory and neuro-psychiatric conditions.[2] An estimated 400 million globally, including 18 million American adults and 6 million children, continue to experience neuro-psychiatric symptoms of long COVID: fatigue and "brain fog."[3,4,5] In adults, neurocognitive testing and objective radiological scans indicate measurable decrements in cognition and observable defects in key regions of the brain associated with executive function.[6,7,8] Increasingly, enduring consequences of COVID-19 infection are seen in children. The annual economic impact of long COVID is estimated at $1 trillion, approximately 1% of the global economy.[9]

This update draws from findings from several published unclassified reports and additional new open-source evidence to address two outstanding issues concerning the SARS-CoV-2 pandemic. The first is the origin of the virus and the outbreak: Was SARS-CoV-2 a product of natural recombination and zoonotic spillover or possible lab manipulation? Was the pandemic the result of transmission from an infected animal host or the result of a research-related incident? The second is the possible nature of the research being conducted in Wuhan that may have resulted in a research-related incident: Could that research be part of a military biological weapons program as concluded by the House Intelligence Committee? Determining the origin of SARS-CoV-2, the COVID-19 pandemic and what relationship, if any, it may have with military biological research is essential for public health and national security. Regardless, there remains an imperative to prepare for and prevent the inevitable next pandemic.

In 2023, the Office of the Director of National Intelligence updated its assessment of SARS-CoV-2's origins. The U.S. Intelligence Community (IC) is unanimous in its assessment that SARS-CoV-2 was not a biological weapon but remains divided over the origins of the virus and the COVID-19 pandemic. The National Intelligence Council and several U.S. IC agencies assessed that SARS-CoV-2 resulted from a zoonotic (animal) source, which was documented in previous SARS-1 and MERS coronavirus outbreaks. The Department of Energy and the Federal Bureau of Investigation assessed that the SARS-CoV-2 emerged from a lab-associated incident.

In addition, several Senate and House congressional committees and members issued reports on the subject. The Senate Health, Education, Labor and Pension Committee and an individual member office issued reports by former Senators Richard Burr and Marco Rubio respectively.[10,11] The House Foreign Affairs and Intelligence Committees issued reports by Representatives Michael McCaul and Mike Turner respectively.[12,13] There was consistency in these reports' conclusions that the SARS-CoV-2 virus likely accidentally escaped from the Wuhan Institute of Virology (WIV). The House Intelligence report, however, further concluded that "there are indications that SARS-CoV-2 may have been tied to China's biological weapons research program."[14]

The Genetic Sequence of SARS-CoV-2

SARS-CoV-2's genetic sequence provides some potentially relevant insights. The spike protein of the SARS-CoV-2 virus, particularly the receptor binding domain (RBD), is most similar to a virus reportedly isolated from Malayan pangolins smuggled into Guangdong Province. Outside of the RBD, this pangolin virus is less similar to the rest of the SARS-CoV-2 virus. Other than the RBD, several other coronavirus strains isolated from Yunnan province, Zhejiang province, and northern Laos, over 600 miles away, are more similar to SARS-CoV-2. It remains possible that SARS-CoV-2 itself, or a closely related precursor, could have arisen by natural recombination of these geographically distant strains in the wild, most likely originating in bats before circulating in a susceptible intermediate animal host. SARS-CoV-2 could have then entered the human population, from bats or from an intermediate animal host by a natural 'spillover' infection of a human near the site where it first arose, likely in southern China. It is also possible that SARS-CoV-2 originated from a natural recombination event and entered the human population in Wuhan—for example, a human could have been infected by a SARS-CoV-2-infected animal in or near the Wuhan wet market.

It is also possible that SARS-CoV-2 arose via a natural recombination event and then entered the human population because of coronavirus research. SARS-CoV-2 or a closer viral relative may have been found in nature and subsequently transported to Wuhan, which is an epicenter of global coronavirus research. Collected bat specimens from across China and Southeast Asia were routinely shipped to and then studied in several Wuhan labs. SARS-CoV-2's genetic components reflect extensive recombination of SARS-related viruses that are geographically distant. It is also possible, however, that SARS-CoV-2 might have arisen from more extensive lab manipulation. SARS-CoV-2 has a furin cleavage site (FCS) and at least one protein sequence that can bind to human integrins (cell-surface receptors) not seen in other SARS-related coronaviruses (subgenus sarbecovirus) before the pandemic.[15,16] In addition, SARS-CoV-2's ACE2 binding site is well adapted to human ACE2 receptors, which would not be expected in a newly emerged virus.

A recently published comprehensive analysis of coronavirus recombination events seems to argue against natural recombination producing SARS-CoV-2. Researchers determined that coronavirus recombination is common but only between strains of the same coronavirus species (e.g. SARS-related viruses (sarbecoviruses)) and where the bats harboring these viruses are overlapping in geographic proximity.[17] The condition of proximity is required to enable the physical exchange of genetic material (e.g. bats roosting in the same cave). These findings suggest that natural recombination resulting in SARS-CoV-2 would be unlikely given that the geographic distance between the bats that harbor SARS-related strains was several hundred miles, far exceeding their migratory range. The presence of both SARS-CoV-2's FCS and its integrin-binding sequence, not found in any SARS-related virus prior to the pandemic, makes natural recombination less likely. Finally, the

emergence of SARS-CoV-2 in Wuhan, where research with SARS-related coronaviruses occurs but none of the progenitor viruses are naturally found, further decreases the likelihood of such a natural event.

Other recent findings also challenge the natural origin theory of SARS-CoV-2, although they are disputed. SARS-CoV-2 contains a pattern of restriction enzyme sites that, while naturally occurring, are evenly distributed, suggesting a synthetic origin. These sites are commonly used lab techniques to enable genetic manipulation of coronaviruses.[18,19]

Possible lab manipulations that could have contributed to the initial SARS-CoV-2 genome include but are not limited to: 1) Directed evolution (serial passage) of precursor coronaviruses in cell culture to adapt them to primate cells; 2) insertion of a pangolin virus recombinant spike or the spike's RBD protein that includes a sequence for an FCS and an integrin-binding protein; 3) changing the sequence of precursor viruses to facilitate insertion of alternative sequences; 4) assembly of a full length DNA sequence clone that allowed assembly of a live chimeric RNA coronavirus; 5) directed evolution of the chimeric virus or the precursor viruses by serially growing them in human cell cultures; 6) directed evolution of chimeric viruses by serial passage in animal hosts, including in human ACE2 expressing mouse strains. Wuhan researchers published studies demonstrating manipulations #1, 2, 5, and 6. Manipulation #1, part of manipulation #2 (insertion of an FCS), and manipulations #3 and #4 were part of an unapproved 2018 EcoHealth Alliance DARPA proposal that intended to team with WIV researchers to perform many of these manipulations.

SARS-CoV-2 possesses many characteristics described in the DARPA proposal. The research intended to increase human affinity and transmissibility of SARS-related viruses by inserting specific nucleotides that code for spike and RBD proteins. Also mentioned was inserting an FCS, an important gain of function for human infection. No other previously known sarbecovirus has an FCS. Until the April 2020 publication of the Guangdong pangolin sequence, no previous SARS-related virus had an (RGD) integrin-binding protein sequence. Integrins are human cell-surface receptors, and the RBD's interaction with them could provide an additional way for SARS-CoV-2 to infect cells and disrupt cellular function. The genetic differences found in SARS-CoV-2 and its nearest relative identified before the pandemic, RaTG13, that include the pangolin RBD with its ACE2 receptor and the presence of an FCS is "equivalent to an average of 50 years (and at least 20 years) of evolutionary change."[20] The possibility of lab manipulation is also suggested by published studies by researchers in China who artificially inserted spike, RBD and FCS proteins into SARS-related and other coronaviruses. The genetic sequence alone, however, cannot determine the origin of SARS-CoV-2 or the pandemic.

Did the Pandemic Start in a Wet Market?

The absence of key supporting data challenges the likelihood of a zoonotic spillover outbreak. Despite plausible natural explanations, the weight of the available evidence does not support a zoonotic origin consistent with previous SARS-1 and MERS outbreaks. First, no animals, particularly SARS-susceptible intermediate hosts, known to be sold at any Wuhan animal market or supplied from farms in Hubei province tested positive for the SARS-CoV-2 virus or antibodies indicating previous exposure to or infection by SARS-CoV-2 at the time of or prior to the outbreak. No animal vendor in Wuhan or Hubei province tested positive for the SARS-CoV-2 virus or antibodies against it prior to or at the time of the outbreak. Significantly, the SARS-CoV-2 viral sequences from recovered market environmental samples were identical to human clinical cases collected at the outbreak's outset and did not show evidence of animal adaptation. The virus was already human adapted meaning it came from humans or, potentially, humanized mice.

Further, bats collected in Wuhan and Hubei province have not been found with SARS-related progenitor viruses similar to SARS-CoV-2. Bats harboring viruses similar to SARS-CoV-2 are located several hundred miles away, far beyond their migratory range.[21] Bats in Hubei province at the estimated time of the SARS-COV-2 outbreak in late October or early November were likely already hibernating. No bats or Malayan pangolins were sold in any of the several live Wuhan animal markets. Only bats subject to active coronavirus research at the Wuhan Institute of Virology (WIV), or possibly other

Wuhan institutes and public health labs, had SARS-related progenitor viruses similar to SARS-CoV-2. Published geospatial statistical analyses linking early outbreak cases to the Huanan Seafood market have been challenged as flawed. Independent statisticians determined that "the analysis of the cases cannot rule out that places near the wet market are a possible origin."[22] Finally, both the Director of China's Center for Disease Control (CCDC), Dr. George Fu Gao, and the WIV's Zhengli Shi assessed that the Huanan Seafood market was not the outbreak epicenter rather, it was more likely an amplifier of transmission or a "super spreader" site.[23,24]

Was the Pandemic a Consequence of a Lab Leak?

Unlike the zoonotic hypothesis, there are fact patterns and other supporting evidence favoring an accidental lab-related incident. In 2019, biosafety of highly pathogenic infectious disease research was a matter of concern at the WIV and the highest levels of the government of the People's Republic of China (PRC). At that time, there was limited national oversight of any high-containment pathogen research, including the genetic manipulation of coronaviruses in China. Specific concerns noted that publications from the WIV reported performing such research at inappropriate biosafety levels (BSL-2 instead of BSL-3). Biosafety hazards were cited that could lead to laboratory-acquired infections (LAIs) from "hidden dangers" such as undetected aerosols. The WIV leadership prioritized biosafety and implementing specific corrective patents and procurements. The PRC drafted legislation requiring provincial-level review and approval of high-level pathogen research.[25] Further, governmental security agencies were mandated to monitor and enforce both biosecurity and biosafety. These efforts were drafted and approved but not fully implemented before the pandemic's onset in the fall of 2019.[26]

The exact timing of SARS-CoV-2 emergence is still uncertain. The accumulation of media reporting, epidemiological data and genetic modeling supports a late October to early November 2019 onset. Two potential

biocontainment-related incidents correlate with this timeframe. The first was a November 19 procurement notice for an air incinerator to augment the exhaust of a biosafety autoclave at the WIV's original Wuchang district (Xiaohongshan) campus.[27] This notice coincided with reporting, analyses and observations of a spike in Wuhan influenza-like-illnesses in November 2019 by U.S. diplomats, Nanjing and Wuhan epidemiologists, and WHO experts.[28,29,30,31,32] The State Department also released declassified intelligence reporting that WIV researchers became ill with symptoms consistent with SARS-CoV-2 infection in early November.[33] The CCDC recorded a confirmed case of SARS-CoV-2 in Hubei province on November 17, 2019.[34] These events also overlapped with what appears to be out-of-cycle WIV biosafety lectures and training convened by the head of security at the Chinese Academy of Science beginning on November 19th and lasting until the 21st.[35] This Beijing security head would later replace the WIV's chief of biosafety and director of its BSL-4 lab.

A patent application submitted on December 11, 2019, hints at a second biocontainment problem.[36] This application cited inadequacies and corrosion of a HEPA filter assembly for an animal transport cabinet, likely used to transport live, potentially infected animals between the WIV Wuchang campus and the Wuhan University Institute of Animal Models.[37] The institute had previously performed and published SARS-related vaccine challenge studies on non-human primates (NHP).[38] Local Wuhan media reporting on November 15, 2019, indicated that the institute had historically performed such studies but stated that the facility had undergone renovations in 2015 and had yet to be recommissioned.[39] This media report was contradicted by published SARS-related vaccine NHP research in 2018 that the institute performed during the time it was supposedly inactive.[40] Later in December 2019, social media medical assistance requests for COVID-19 symptoms occurred in Wuhan's Wuchang District, in the vicinity of the WIV and this institute.[41]

While these potential biocontainment incidents could account for the release of the SARS-CoV-2 virus into the Wuhan population, there could be other causes. A laboratory-acquired infection could have resulted from aerosols or droplets generated from the WIV's inappropriate (BSL-2) biosafety isolation of field-collected bat coronaviruses, during genetic manipulation or directed evolution of coronaviruses.[42]

Further, People's Liberation Army (PLA) researchers from the Academy of Military Medical Sciences (AMMS) Institute of Military Cognition and Brain Sciences who were involved in one of the first SARS-CoV-2 vaccine patents and earliest published SARS-CoV-2 vaccine research wrote of two "black swan" biosafety events associated with a commonly used lab device (flow cytometer) and a sample mishandling incident.[43] During the pandemic, U.S. National Institutes of Health researchers demonstrated the potential risk of LAIs from unrecognized aerosols created by flow cytometry of the SARS-CoV-2 virus.[44] A recent study by researchers in China evaluated the risk of LAIs during experimental sample mishandling incidents in BSL-2 labs. They noted a significant risk for LAIs when pathogens are mishandled in BSL-2 settings outside of a biosafety cabinet.[45]

The WIV's patent applications, procurements, and recorded concerns about potential "hidden dangers" highlight extant biosafety problems. An LAI could also have resulted from an unrecognized aerosol leak caused by corrosion of other stainless-steel biocontainment equipment due to inappropriate use of liquid disinfectants.[46] A November 2020 WIV patent noted the need to modify the liquid disinfectant used in biosafety labs because of excessive corrosion. The patent noted that long-term use of such corrosive disinfectants could "lead to the escape of highly pathogenic microorganisms into the external environment of the laboratory, resulting in loss of life and property and serious social problems."[47] WIV leaders also expressed concern about inexperienced researchers and technicians operating a high containment lab.

The recognition of SARS-CoV-2 LAIs could be initially confounded by mild or asymptomatic disease. In historical studies, about 66% of viral LAIs occurred in research facilities.[48] Most documented research-related viral LAIs were associated with unrecognized aerosol exposures.[49] The cause of over 80% of LAIs was never conclusively determined and only 18% could be definitively attributed to accidents caused by carelessness

or human error.[50,51] A recent study evaluated LAIs and accidental escapes from laboratory settings between 2000 and 2021. This study noted that the majority were caused by procedural errors followed by unknown causes.[52] The risk of a lab-related incident also depends on the lab design, safety equipment, work practices and workforce. Younger workers, workers with less technical training and labs operating with fewer experienced technicians have more accidents than those with older workers, those with more training or labs employing a greater percentage of women.[53]

Was the Pandemic Related to Military Vaccine Research?

If the pandemic resulted from coronavirus research, the possibility that the research was vaccine-related remains open. PLA Brigadier General Yusen Zhou, an accomplished Academy of Military Medical Sciences (AMMS) vaccinologist, submitted one of the first SARS-CoV-2 vaccine patents on February 24, 2020.[54] He developed and patented a similar MERS vaccine in 2013 that took at least four months.[55] Using data contained in General Zhou's patent, there is likelihood that he began his work earlier, possibly in the summer of 2019. His published SARS-CoV-2 infection and vaccine challenge studies in wild-type and humanized mice and NHPs were a significant risk for a research-related LAI.[56] The location of his NHP challenge research was not identified or attributed to a specific high containment lab, a fact at variance with colleagues in China performing and publishing similar vaccine studies.

New evidence establishes that General Zhou's SARS-CoV-2 vaccine research, including submitting the patent, was a collaboration between several AMMS institutes, including the Institute of Military Cognition and Brain Sciences as well as General Zhou's Institute of Epidemiology and Microbiology. This kind of collaboration is unusual for early-stage vaccine research. Significantly, their published research provided limited, or no data of neuropathology observed in the experimental animals, or the neuroprotection afforded by the vaccine.[57,58] General Zhou's previously published SARS-1 and MERS vaccine research did not involve researchers from this institute. Coincidentally, the AMMS and its 11 associated institutes including General Zhou's were sanctioned by the U.S. Department of Commerce in December 2021 for allegedly using biotechnology "to pursue control over its people and its repression of members of ethnic and religious minority groups."[59] These AMMS organizations were subject to U.S. export controls limiting their access to prevent "medical science and biotechnical innovation to be diverted toward uses contrary to U.S. national security."[60]

Institute of Military Cognition researchers' involvement in such studies suggests an interest in the vaccine's protection against SARS-CoV-2 early in the outbreak before evidence of its neurological effects was widely known. The neuro-cognitive effects of SARS-CoV-2 were initially overshadowed by its prominent respiratory findings and concealed or censored by the PRC. Further, significant neuro-cognitive effects have since been documented in both young and old SARS-CoV-2 infected patients with both mild and severe disease.

PLA military scientists have shown interest in manipulating neurocognition since 2006 or earlier.[61] AMMS researchers cited advances in science and technology that could change the character of conflict, raising the concept of "biology-enabled" warfare. One theory described the PLA's interest in obtaining operational advantages from advances in biology to achieve "merciful conquest."[62] Success on the future battlefield would require achieving not only "biological" dominance but also "mental/cognitive" dominance.[63]

By 2015, this thinking had become a part of PLA military strategy and doctrine. Writings assert that the human brain will become a new combat space. PLA strategists believe that achieving "mental dominance" will be critical in future military competition across the peacetime to warfighting continuum.[64] As the speed and complexity of conflict increase, the criticality of the "cognitive domain," which involves "the field of decision-making through reasoning" also increases.[65] Achieving this military objective involves related research areas: brain monitoring (to measure and assess the military mental work); brain modulation (mind-controlling targets and effects); brain promotion (neuro-scientific training); brain damage and "interfering with the brain, causing brain dysfunction."[66] Nerve and body incapacitating agents

would be used to affect brain nerve potentials and the transmission of chemical neuro-transmitters.
In 2017, the PLA created a new military medical specialty devoted to this field. Military Brain Science was described as an emerging discipline of "cutting-edge innovative science based on the theories and technologies of clinical, basic, and military medicine, biology, physics, computer and military science[s] and multiple other disciplines."[67] The PLA's Fourth Military University published research showing an interest in the region of the brain associated with cognition, the anterior cingulate cortex.[68] The PLA's Academy of Military Science, whose vice chair is the former AMMS head, leads the scientific effort to pursue these goals.

There is historical military precedence for the use of chemical and biological agents to target cognition. The former U.S. and Soviet Union offensive chemical and biological programs developed incapacitating agents to affect an adversary's battlefield cognitive abilities.[69,70] The United States conceived that such agents could "open up a new dimension of warfare" causing effects including "extreme irritation, lethargy, discoordinated actions, temporary illness and lack of a will to fight."[71] Both nations developed Venezuelan equine encephalitis as a noncontagious neuro-incapacitating viral agent and made protective vaccines against it. President Richard Nixon unilaterally renounced the use of bioweapons and terminated the U.S. program in 1969.

Significant and Enduring Impact of COVID-19's Neurological Effects

Neurological effects were not prominent clinical manifestations noted in earlier SARS-1 and MERS outbreaks. The incidence of SARS-CoV-2 neurological findings seem to be at odds with these related viruses. The incidence of central or peripheral nervous system effects in SARS-CoV-2 occurred in 34 to 82% of cases in published clinical studies, which is a hundred or more-fold greater than in SARS-1 and MERS.[72,73] In the early stages of the pandemic, authorities in China censored aspects of the outbreak related to the virus' possible origin.[74] China's government strictly controlled "all research into its origins, clamping down on some while actively promoting fringe theories that it could have come from outside China."[75] The mention or inclusion of COVID-19's neurological effects in both clinical case reports and autopsies were underreported compared to similar studies published outside of China.

The acute and chronic ("long COVID") syndromes that involve fatigue, loss of smell, taste, headaches, muscle aches, brain fog that result in cognitive impairment and autonomic nervous system dysregulation are a constellation of neurological findings documented in COVID-19 infections.[76] Cognitive impairment is one of the most reported long COVID health effects, "potentially portending significant consequences for patient functioning and quality of life."[77] "Functional disability associated with long COVID has been characterized as the inability to return to work, poor quality of life, diminished ability to perform activities of daily living, decreased physical and cognitive function, and overall disability."[78] These findings are noted in mild and severe acute COVID-19 cases affecting both young and old patients. Since people with mild disease can also develop long COVID and given the much higher number of people with mild disease, "they make up the great majority of people with long COVID."[79] Recent studies noted that younger and middle-aged patients are "disproportionately affected" by long COVID compared to older patients. Younger and middle-aged patients have a higher burden of neurological problems such as fatigue, sleep disturbance and cognitive dysfunction than older patients do.[80]

Recent scientific studies provide greater insight into the pathophysiology of COVID-19. The presence of both the FCS and integrin sequence seems to have profound potential effects on the brain. Several studies showed that the FCS plays an important role promoting the free circulation of SARS-CoV-2's spike protein that causes generalized inflammation with neurologic effects.[81,82,83] The spike protein can acutely cause nerve injury and death and affect behavior. The persistence of the spike protein in the brain after acute infection is associated with the chronic findings of long COVID.[84] The integrin sequence found on SARS-CoV-2's spike protein promotes the inflammation of the lining of small blood vessels and activation of platelet cells that lead to the formation of clots that can disrupt the blood brain barrier further causing brain injury and cognitive impairment.[85,86,87,88,89]

PLA researchers from the Institute of Military Cognition and Brain Sciences involved in General Zhou's SARS-CoV-2 patent and vaccine studies later published on the SARS-CoV-2's direct toxic and indirect immune modulating effects causing neurological consequences. These effects cumulatively resulted in cognitive impairment. They described this impact and likely further neurocognitive decline comparable to HIV and Zika virus infections.[90] This progressive decline was documented by researchers in China who performed a longitudinal study of hospitalized severe and non-severe acute COVID-19 infection in adult survivors during the initial outbreak in Wuhan. The study evaluated the risk of cognitive decline in unvaccinated participants within 12 months of their illness. The study showed "severe COVID-19 was associated with an increased risk of early-onset, late-onset, and progressive cognitive decline.... 21% of individuals with severe cases in this cohort experienced progressive cognitive decline, suggesting that COVID-19 may cause long-lasting damage to cognition. These findings imply that the pandemic may substantially contribute to the world dementia burden in the future."[91]

Further, one of these PLA researchers from the Institute of Military Cognition and Brain Sciences contributed to another study in 2022 that determined the decrease in child intelligence in the United Kingdom was the result of SARS-CoV-2 infection rather than the lack of stimulation by missing school. He noted that "brain development of infants and children may be impaired by COVID-19 infection" and that "COVID-19 prevention in children is essential."[92]

In 2024, the American Academy of Pediatrics assessed that six million children in the United States suffer from long COVID.[93] In a longitudinal study from Bergen Norway, 35% of teenaged children infected with SARS-CoV-2 experienced neurocognitive effects persisting for at least four months.[94] As noted by a 2024 U.S. National Academies report, "limited data are available on long-term outcomes in children."[95] As described, "most children with long COVID recover slowly over time, but not all."[96]

Longitudinal studies conducted by the U.S. Department of Veterans Affairs on adult veterans who had documented COVID-19 showed that 20% of non-hospitalized and 25% of hospitalized veterans had evidence of neurocognitive deficits after two years.[97]

Objective tests, such as Positive Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) brain scans, showed acute and potentially enduring abnormalities. PET scans showed hypometabolism in both symptomatic and asymptomatic SARS-CoV-2 cases. These effects, while persistent, may be reversible over time: "At 6-12 months, patients showed a near-complete recovery of brain abnormalities, with residual limited hypometabolic clusters in the anterior cingulate cortex" among other frontal brain regions.[98] Children having lower initial severity of COVID-19 infection demonstrated a similar brain hypometabolism on PET scan as seen in adults, though an average of five months later.[99]

Brain MRI images in adults showed disruption of micro-structures and functional brain integrity in the recovery stages of COVID-19, suggesting the long-term consequences of SARS-CoV-2.[100] MRI imaging of patients "recovered" from mild-to-moderate SARS-CoV-2 infection showed significant brain alterations "commensurate with seven 'years of healthy aging."[101] A longitudinal study in adults conducted in the United Kingdom showed a "significant, deleterious impact associated with SARS-CoV-2."[102] Changes in specific areas of the brain, such as the atrophy of the cognitive lobule of the cerebellum, suggest that neurocognitive decline may be progressive.[103] A recent University of Washington MRI study in teenagers showed "unusually accelerated" brain aging that was attributed to chronic stress.[104] This study did not note or control for the prior history of COVID-19 infection in these adolescent subjects.

In children whose school attendance was interrupted by the pandemic, educational-related studies note that they continue to do poorly on standardized testing.[105] In some recently published studies, testing scores continue to decrease and are "worse than 'what [the researchers] had previously deemed as the low point.'"[106] *The New York Times* recently reported that "pandemic babies, toddlers and preschoolers are now school-aged, and the impact on them is becoming increasingly clear: Many are showing signs of being academically and developmentally

behind."[107] They score poorly on standardized testing and are noted to have behavioral problems thought to be associated with parental stress and social isolation.[108] The association between pediatric SARS-CoV-2 infection, neurocognitive effects and poor academic performance has not been firmly associated. The pandemic's negative impact on children's school testing was recently described by *The Washington Post* as growing.[109] As noted in one study, "it's as if the pandemic or some other factor is continuing to result in lower and lower performance."[110]

Vaccination in adults appears to lower the cumulative incidence of long COVID at one year.[111] A recent meta-analysis of 25 COVID vaccine efficacy studies suggests that two-dose pre-COVID vaccination and one-dose post- COVID vaccination are associated with a lower risk of long COVID.[112] A 2023 U.S. National Academies of Science study estimated that only approximately 7% of U.S. children younger than age five years have received COVID-19 vaccinations.[113] According to the U.S. Centers for Disease Control and Prevention, as of May 2024, only 14.4% of American children are effectively immunized against SARS-CoV-2 infection.[114] The findings noted by the PLA researcher about the "essential" nature of preventing infections in children have not been verified. The risk of reinfection and further neurocognitive injury, however, is possible and demands urgent further investigation and preventive intervention.[115] The prognosis for recovery or progression of neurocognitive injury in adults and children suffering from long COVID remains uncertain.

Further Concern Caused by Continued SARS-Related Research

More recently, in January 2024, researchers from the Beijing University of Chemical Technology (BUCT) and the Fifth Medical Center of the PLA General Hospital performed research on a different pangolin coronavirus SARS-related strain recovered from Guangxi province. One of the BUCT researchers, Yigang Tong, had previously been affiliated with the AMMS Institute of Microbiology and Epidemiology and first published with General Yusen Zhou in 2007 and as recently as 2016.[116,117] Tong with others conducted serial passage of this pangolin virus with the intent to create a live attenuated vaccine. The humanized mouse used to test this vaccine was the same one General Zhou used in an April 2020 study.[118] This

mouse closely mimicked human COVID-19 illness and showed brain infection.

Inoculating humanized ACE2 mice with this strain resulted in an unexpected outcome: "Surprisingly, all the mice that were infected with the live virus succumbed to the infection within 7-8 days post-inoculation, rendering a mortality rate of 100%."[119] The "attenuated" pangolin strain resulted in rapid brain infection and death of the mice. The biosafety level at which these experiments were conducted was not described. However, neither the BUCT nor the PLA Fifth Medical Center has known BSL-3 labs, so it may be surmised that this research was conducted at BSL-2 levels. The outcome of this experiment highlights the potential unpredictability and risk that accompanies SARS-related research and its dual-use nature. In this case, it resulted in a highly lethal neurological pathogen.

Conclusions

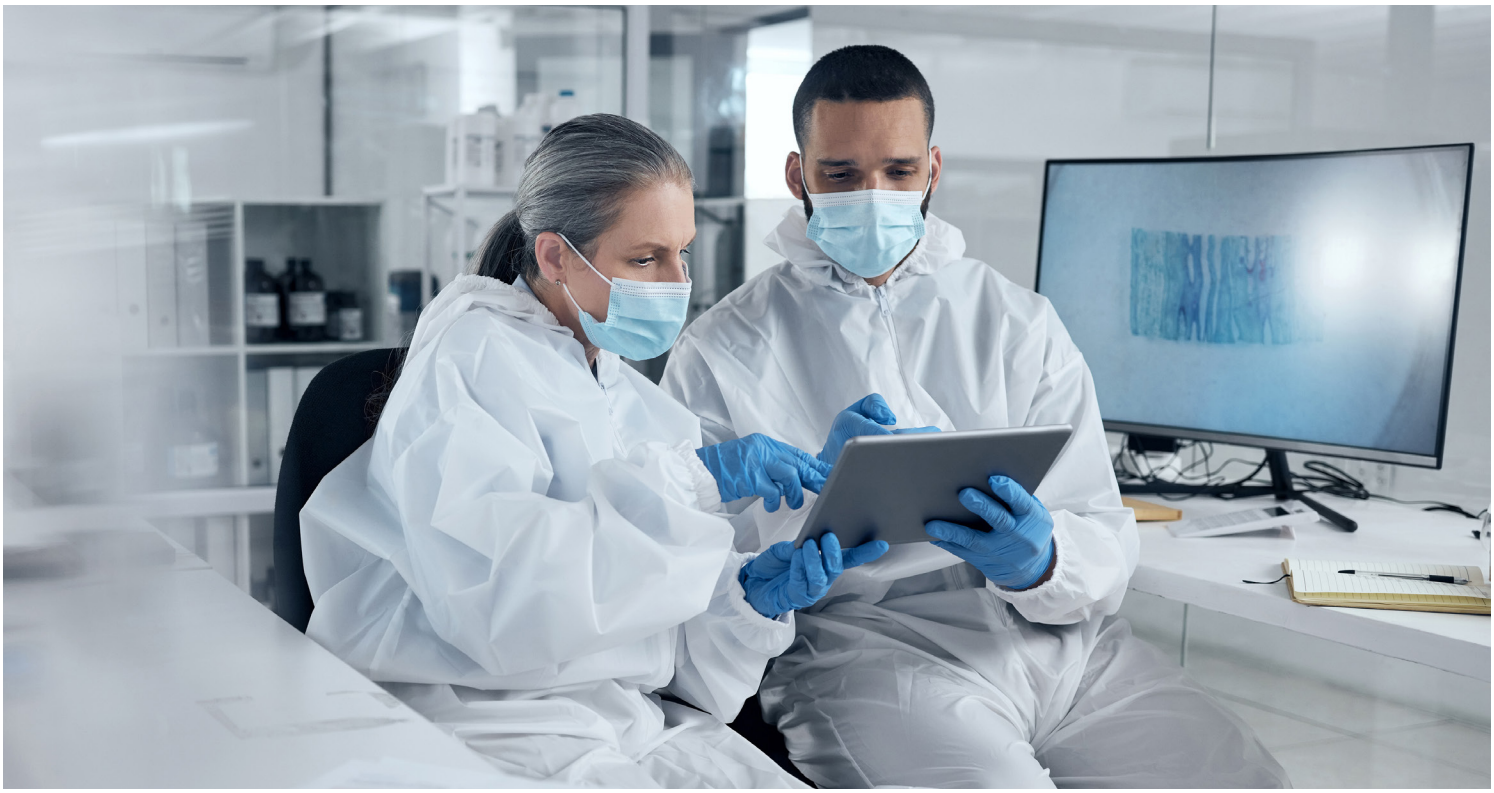
Despite China's lack of transparency, further insights and information will likely become publicly available over time. The case presented is not dispositive nor is all the information determinative or probative. **Evidence, however, supports the likelihood that a progenitor virus of SARS-CoV-2 was found in nature and subject to genetic engineering.** The presence of both a furin cleavage site and integrin binding sequence not previously found in other SARS-related viruses prior to the pandemic suggests gain of function insertions. The presence of restriction enzymes used in coronavirus-related genetic engineering further supports the likelihood of synthetic manipulation.

A preponderance of circumstantial evidence supports the likelihood of a lab-related accident associated with more than one biosafety or biocontainment failure over a zoonotic natural origin. Evidence of remedial procurements, patents and biosafety training beginning in mid-November 2019 shows a temporal relationship with epidemiological data and modeling coinciding with the likely start of the SARS-CoV-2 outbreak. Whether China knows all the details surrounding these incidents deserves further inquiry.

PLA writings indicate the aspiration and intent to develop military capabilities to achieve cognitive dominance during future conflicts. Pursuit of this objective is supported by published PLA research and a military medical specialty devoted to the topic. The involvement of AMMS neurocognitive researchers in the development of a vaccine for SARS-CoV-2, a respiratory pathogen, points to studies evaluating countermeasures to protect against a novel coronavirus' neurological effects in animals and by extension, humans. The human effects documented during and since the COVID-19 pandemic affirm its neurological and cognitive sequelae.

PLA researchers continue dual-use coronavirus research of concern which poses significant potential public health risks and may have national security and international treaty implications. Developing SARS-CoV-2 or any other agent for the purpose of inflicting harm would be subject to the Biological Weapons and Toxins Convention's prohibitions. This study presents information that casts doubt on the IC assessment that the SARS-CoV-2 virus was not part of a military weapons research effort.

Continued and expanded research is warranted into the prevention and mitigation of SARS-CoV-2's neurocognitive and other chronic effects. As recently published, "reinfection can trigger *de novo* long COVID or exacerbate the severity of existing long COVID. Cumulatively, two infections yield a higher risk of long COVID than one infection and three infections yield a higher risk than two infections."[120] Testing, antiviral therapies and vaccination appear to lessen the likelihood of subsequent long COVID.[121] Aggressive efforts should be pursued to screen, test and treat with antiviral drugs for COVID infections in children. Similar efforts should address low vaccination rates (14.4%) among children in the United States.[122] Regardless of SARS-CoV-2's origin, addressing the current and continuing risk of SARS-CoV-2 infection and its neurocognitive sequelae, particularly in children in the United States and around the world, is an urgent priority.



INTRODUCTION:

This paper presents a comprehensive update and review of open-source information, expert assessments and relevant publications concerning the origins of the SARS-CoV-2 virus with the intent to promote a fact-based discussion for the benefit of informing ongoing policy discussions regarding national security, public health, pandemic preparedness, biosafety and oversight of dual use research of concern.[123,124,125,126] While the declared COVID-19 pandemic is over, it continues to have "a profound impact on public health, disease burden, social and economic status, and quality of life" in the United States and globally.[127]

The central aim of this paper is to review—in an unclassified, open-source setting—the available evidence to assess whether the COVID-19 pandemic resulted from a research-related accident rather than a zoonotic source and whether it was part of a military research program. This latter assessment was first raised by a 2022 House Permanent Select Committee on Intelligence (HPSCI's) minority report that determined:

> Based on our investigation involving a variety of public and non-public information, we conclude that there are indications that SARS-CoV-2 may have been tied to China's biological weapons research program and spilled over to the human population during a lab-related incident at the Wuhan Institute of Virology (WIV).[128]

This report is organized into two parts. Part I summarizes and reviews the circumstances surrounding the emergence of SARS-CoV-2 to address the question of whether the pandemic originated from a zoonotic (animal) source or from lab-related research activities. Part I finds circumstantial evidence that the COVID-19 pandemic was most likely the result of at least two biosafety incidents. Several plausible events occurred at the Wuhan Institute of Virology (WIV) that could account for the escape of the SARS-CoV-2 virus in late October to mid-November when the outbreak likely started. This evidence supports the increasingly prevailing view that the virus emerged as a lab-related accident at the WIV.

Part I concludes with the observation that COVID-19-related vaccine challenge studies were likely conducted at the WIV during the same timeframe.

The second installment, Part II, attempts to address the first finding in the HPSCI's report's conclusion, "that there are indications that SARS-CoV-2 may have been tied to China's biological weapons research program." In doing so, Part II also tries to answer the question that logically follows from Part I's conclusion: Why would scientists be working on a SARS-CoV-2 vaccine before the pandemic? There is additional circumstantial evidence to support HPSCI's finding that military-related research intended to develop a vaccine to protect against the respiratory and neurological effects of a novel coronavirus, SARS-CoV-2.

Non-human primate studies and human autopsy findings indicate SARS-CoV-2 affects brain capillaries that disrupt the blood brain barrier and causes relative hypoxemia.[129] This localized lack of oxygen likely results in the "brain fog"' affecting cognition observed in acute SARS-CoV-2 infection and long COVID. The occurrence of observable neurological and cognitive deficits in both severe and non-severe COVID-19 illness is noteworthy. China obscured COVID-19's neurological effects in early clinical cases, autopsies and the likely neuroprotection afforded by the earliest vaccine the PLA was developing. The incidence of pediatric long COVID is particularly disturbing considering low vaccination rates in U.S. children. This paper suggests the possibility that poor performance noted in standardized academic testing may be caused by potential neurological injury rather than social isolation is a matter of urgent study and determination.

All the following observations are based on only publicly available, open-source information. Additional relevant information may exist in the Intelligence Community 's (IC) classified holdings to further support or refute the findings contained in this report. There remains a need to determine the origins of the COVID-19 pandemic to ensure the safety of future research with dangerous pathogens and to begin to build a comprehensive understanding of SARS-CoV-2's neurological effects, which may enable future preventive and therapeutic interventions.

Editorial note: Part I was initially released as a standalone "First Installment" on September 25, 2024. This document, the "Second Installment," includes both Part I and Part II along with an updated Executive Summary. Part I has been lightly edited since its original release.

PART 1
THE EMERGENCE OF SARS-COV-2:

U.S. Intelligence Community Assessments of COVID-19 Origins and China's Compliance with the Biological Weapons Convention

While the COVID-19 pandemic is over, SARS-CoV-2 infections have not ended, nor have their acute and chronic effects. An emerging legacy of the pandemic leaves hundreds of millions globally afflicted with a variety of chronic cardiovascular, respiratory, gastrointestinal and neuro-psychiatric conditions.[130,131] An estimated 400 million globally, including 18 million adults and 6 million children in the United States, suffer from neuro-psychiatric symptoms of long COVID: fatigue and "brain fog".[132,133,134] Brain fog is characterized by "diminished attention, concentration, memory, information processing and executive function."[135] Vaccination appears to lower the cumulative incidence of long COVID at one year.[136] Currently, the percentage of American children effectively vaccinated against SARS-CoV-2 is 14.4%.[137] For those suffering from long COVID, the prognosis for recovery or potential progression is uncertain.

Several Congressional Senate and House committees issued reports on COVID's origins. The Senate Health, Education, Labor and Pension Committee minority staff and an individual member office issued reports by former Senator Richard Burr and Senator Marco Rubio respectively. The House Foreign Affairs and Intelligence Committees issued reports by Representatives Michael McCaul and Mike Turner respectively. There was consistency in the conclusion of these reports that the SARS-CoV-2 virus likely accidentally escaped from the Wuhan Institute of Virology (WIV). The House Intelligence report, however, further concluded that "there are indications that SARS-CoV-2 may have been tied to China's biological weapons research program."

In June 2023, the Office of the Director of National Intelligence (ODNI) updated its assessment on the origins of the SARS-CoV-2 pandemic. The U.S. Intelligence Community (IC) is unanimous in its assessment that SARS-CoV-2 was not a biological weapon but remains divided over the origins of the virus and the COVID-19 pandemic. The National Intelligence Council and several IC agencies assessed that SARS-CoV-2 resulted from a zoonotic (animal) source, which was documented for previous SARS-1 and MERS coronavirus outbreaks. Two IC agencies, the Department of Energy and the Federal Bureau of Investigation, assessed that SARS-CoV-2 emerged from a lab-associated incident. The Central Intelligence Agency and one other agency were unable to make a judgment based on available intelligence.

Regarding the lack of consensus among different agencies, ODNI noted that "all [U.S. Intelligence] agencies continue to assess that both a natural and laboratory-associated origin remain plausible hypotheses to explain the first human infection."[138] As noted in the U.S. Intelligence Community's 2024 Annual Threat Assessment, "Beijing continues to resist sharing critical and technical information about coronaviruses and to blame other countries, including the United States, for the pandemic." Media reports indicate that some scientists in the intelligence community may have expressed greater confidence that SARS-CoV-2 emerged due to a laboratory accident than their agencies' published assessments.[139,140]

While the IC has determined that SARS-CoV-2 is not a Biological Warfare (BW) agent, the U.S. State Department 2024 Arms Control Compliance Report noted that "PRC military [PLA] medical institutions conducted toxin and biotechnology research and development with potential BW applications, which raises concern regarding the PRC's compliance with Article I of the BWC."[141] The U.S. Department of Defense (DoD) assesses that China "has engaged in research and activities with potential dual-use applications, which raise concerns regarding its compliance with the Biological and Toxins Weapons Convention (BWC) and the Chemical Weapons Convention (CWC).[142] The DoD in its 2023 Annual Report to Congress on the "Military and Security Developments Involving the

People's Republic of China" described China's relevant chemical and biological capabilities as "a threat to U.S., Allied, and partner forces, military operations, and civilian populations."[143] This report identifies specific information that calls into further question the potential intent of PLA-related novel coronavirus vaccine research at the time of the initial outbreak of SARS-CoV-2 that may have contributed to the occurrence of the pandemic.

Review of Evidence for the Wuhan Seafood Market as the Outbreak's Epicenter

Some Western scientists have favored the hypothesis that SARS-CoV-2 emerged because of wildlife animal sales at the Wuhan Huanan Seafood Market.[144,145] This hypothesis rests on the epidemiologic reality of pathogenic organisms crossing species lines under certain conditions (e.g., rising infection rates in the original species (animals in this case), close proximity to other susceptible species (humans in this case), and subsequent amplification in the new host species. This phenomenon is referred to as "zoonotic spillover," which is defined as cross-species transmission of a pathogen into a host species not previously known to be infected.[146,147]

The crux of their argument is based on the historical precedent of the 2002-2004 coronavirus outbreak when SARS-CoV-1 (SARS-1) first appeared in Foshan municipality in Guangdong province, China in November 2002.[148] Epidemiological investigations later determined that SARS-1 infected palm civets that were held in unhygienic conditions and sold at several animal markets.[149] Conditions described at the Wuhan Huanan market prior to the onset of the COVID-19 pandemic indicated that susceptible intermediate animal species were also held in poor hygienic conditions and sold there. Further, the stalls where these animals were kept were close to locations from which SARS-CoV-2 containing environmental samples were later collected.[150,151] Studies supporting the zoonotic origin of SARS-CoV-2 also included spatial statistical analyses. These analyses associated the proximity of early human COVID-19 cases and social media posts from Wuhan residents requesting medical assistance for COVID-19 to the seafood market outbreak in late January 2020.

The 2002 SARS-CoV-1 outbreak established the precedent for a zoonotic spillover origin for SARS-like viruses. A hallmark of this outbreak was that the human SARS-CoV-1 viral sequences were almost identical to sequences recovered from infected palm civet cats found in markets.[152] SARS-CoV-1 virus was identified in infected farmed civet cats sold in the market, but not those found in the wild. This finding and the rapid adaptive mutation of SARS-CoV-1 genomes identified in market civets all suggested that these caged animals might be intermediate hosts from which the virus entered the human population.

Identification of SARS-CoV-1 in civet cats and documentation of its spread was publicized within months of the initial outbreak. Later, it was suggested that the sale of live bats in Guangdong province and Hong Kong wildlife markets in close proximity to susceptible intermediate species in poor hygienic conditions led to bat-to-civet transmission that allowed later human infection from civet cats.[153] Identification of very proximal ancestors of SARS-CoV-1 in horseshoe (*Rhinolophus*) bats in Guangdong province and Hong Kong led to establishing *Rhinolophus* bats as the natural host for SARS-1 in 2015.[154]

The 2012 outbreak of the SARS-related Middle East Respiratory Syndrome (MERS) also followed this spillover precedent. The clinical spectrum of MERS is wide ranging from mild to severe fatal disease.[155] For MERS, the presumed intermediate host, dromedary camels (*C. dromedarius*), was quickly identified. Humans became infected by contact with camels or their products.[156] MERS cases have been linked to direct or indirect contact with camel nasal secretions, meat, feces, urine and milk. As for SARS-1, MERS strain sequences isolated from suspect camels were almost identical to those isolated from humans.[157] Unlike SARS-1, although many bat viruses bear sequence similarity to the MERS virus, the presumed ancestor progenitor bat virus has yet to be identified.[158]

So far, available data relating to the Wuhan Huanan market does not support a zoonotic origin for SARS-CoV-2. No human cases in workers selling live animals have been reported. No samples taken from any animals at the market, or from farms supplying the market or reported by the WHO, have tested positive for SARS-CoV-2. Finally, neither the SARS-CoV-2 viral sequences recovered from

humans, nor from environmental samples have shown the variation from the index case sequence that would suggest that the virus had become adapted to and was circulating in an intermediate animal host.

China's Center for Disease Control (CCDC) initially identified the Huanan Seafood Market in Wuhan as the epicenter of the outbreak. The CCDC closed the market on January 1, 2020. That same day, it was reported that the CCDC director, George Gao, called the director of the U.S. CDC, Robert Redfield, to inform him that the outbreak with the novel virus "had no human-to-human transmission, no hospital transmission," and that the cases were associated with the Huanan market. On January 4, 2020, Gao called Redfield again. In that call, Gao revised information he had conveyed earlier, stating, "the epidemic was out of control with cases everywhere, and it has nothing to do with the wet market."[159]

In its initial report of its investigation, the CCDC reported that of 198 patient cases, 22% had direct exposure to the Huanan Market before illness onset, 32% had contact with patients who had fever or respiratory symptoms, and 51% of cases had neither visited the market nor had contact with sick patients before their illness onset.[160] Eight out of the first 12 cases had no epidemiological link to the market.[161,162]

No human cases of SARS-COV-2 could be linked to live animal market vendors or handlers. The absence of human cases in such workers is in stark contrast with the origins of SARS-1 where it was a known occupational risk.[163] Serological studies detected anti-MERS antibodies in the blood of camel handlers, demonstrating a similar occupational risk of MERS exposure and infection.[164]

As described by the CCDC in January 2020: "Despite extensive searching, no animal from the market has thus far been identified as a possible source of infection."[165] This negative finding was later reconfirmed by the CCDC Director in May 2020 when he noted personally collecting samples from the Huanan market in early January. However, later when the pandemic was well underway, one apparent occupational SARS-CoV-2 infection was reported in October 2020. Analysis of a SARS-CoV-2 outbreak in Qingdao, China identified a COVID-19 case in a worker linked to exposure to packaged imported frozen fish.[166]

Zhengli Shi, the WIV's lead bat coronavirus researcher confirmed the CCDC's findings in a July 2020 *Science Magazine* interview. Shi noted that researchers from the WIV and Huazhong Agricultural University "detected SARS-CoV-2 nucleic acids only in the environmental samples such as roller shutter door handles, the ground and sewage, but not in the animals…[we] collected samples of farmed animals and livestock from farms around Wuhan and in other places in Hubei Province. We did not detect any SARS-CoV-2 nucleic acids in these samples… we did not detect any SARS-CoV-2 nucleic acids in frozen animal samples."

A joint WHO-China study conducted in 2021 stated, "there was no obvious clustering by the epidemiological parameters of exposure to raw meat or furry animals."[167] According to this study "more than 80,000 wildlife, livestock and poultry samples were collected from 31 species in China and no positive result was identified for SARS-CoV-2 antibody or nucleic acid (polymerase chain reaction (PCR)) before and after the SARS-CoV-2 outbreak in China."[168]

In a 2021 published study, researchers presented records collected between May 2017 and November 2019 of wild animal sales at all Wuhan's 17 animal vendors, including the seven at the Huanan seafood market.[169] The study's objective was to survey for possible zoonotic tick-borne viruses. The researchers stated that because they were scientists not associated with law enforcement, they were able to visit each market and each vendor monthly and document the wildlife species that were being sold for food or as pets, including quantities sold, and assess the vendor compliance with trading permits. The study reported the sale of 47,381 animals from 38 different species.[170] The study found that several susceptible intermediate species were sold at the market including palm civets, raccoon dogs and bamboo rats, however, no pangolins or bats (both proposed as possible reservoir species or intermediate hosts, and neither of which are typically eaten in central China) were traded at any of the Wuhan animal markets.[171] As expected from the report's timing, the study did not contain any data testing for SARS-CoV-2.

Once the outbreak began, early actions by the government complicated efforts to identify animals that may have been the source of or infected with SARS-CoV-2. The near immediate removal and killing of animals at the Huanan market and its disinfection impacted the ability to collect samples. Further, the farms that provided the wild animals to the Wuhan markets were closed, and the animals were killed but significantly not tested before being sacrificed.

As reported, the "government bought them up and had them all killed."[172] This practice was also followed during the first SARS outbreak in 2003-2004, except that susceptible market animals were only killed after civet cats tested positive.[173] As described, killing and disinfecting before testing "made it much harder—perhaps even impossible" to identify an animal origin.[174] This approach, at variance with historical precedence, seems to suggest deliberate efforts to obscure the absence of infected intermediate animal hosts.

In 2023, researchers from the Beijing CCDC's Key Laboratory of Biosafety, National Institute for Viral Disease Control and Prevention published a peer reviewed article on samples they collected at the Huanan market. The study noted, "no SARS-CoV-2 was detected" in 457 samples from 188 animals, representing 18 species collected at the Huanan market two weeks after the market was closed."[175] They tested the "unsold contents of refrigerators and freezers, swabs from stray animals, and the contents of a fish tank."[176,177]

This report stated that 73 environmental samples collected after the market was closed on January 1st tested positive for SARS-CoV-2 by PCR (rT-qPCR). Three live viral sequences were identified from these environmental samples. Those sequences showed a homology of 99.99% to 100% with the human clinical isolate HCoV-19/Wuhan/IVDC-HB-01/2019.[178] They also had 100% identity with one of the two lineages of SARS-CoV-2 (lineage A) assessed to be the two viral lineages that initially emerged in Wuhan within weeks of each other, likely in November 2019.[179,180]

This 2023 finding of environmental sequences nearly identical to the SARS-CoV-2 pandemic strain illustrates a point. One line of evidence that would support an animal origin of SARS-CoV-2 would be the identification of SARS-CoV-2 genetic sequences that differed, slightly from the human disease virus, demonstrating adaptation to an intermediate animal host, and genetic sequences showing subsequent evolutionary change as the virus became more adapted to humans. A notable characteristic of viral isolates recovered from initial human cases early in the 2002 SARS-CoV-1 outbreak was that they were more closely related to the palm civet isolates than those that had been recovered following multiple passages through human-to-human transmission.[181]

SARS-CoV-2 genetic adaptation has been seen in sequences recovered from human infected mink that then spread to other mink in Denmark.[182] The SARS-CoV-2 variant resulted in "four amino acid changes in the spike protein, that was identified in mink and isolated from 12 human cases."[183] As described, the changes in the mink SARS-CoV-2 variant "are very likely to be 'mink signatures', i.e. adaptation to the host… humans infected with a virus coming from minks are most likely to force the virus to mutate…. Mutations in humans will therefore be different from those in minks."[184] So far, there are no reports of such animal adapted SARS-CoV-2 sequences identified early in the 2020 outbreak that are less human adapted.

The possibility that the COVID-19 pandemic could have resulted from bat-to-human transmission was addressed by Zhengli Shi in her *Science Magazine* interview. She considered this "likelihood… very low."[185] Shi described studies conducted by the WIV in Hubei province that did not identify close coronavirus relatives to SARS-CoV-2 in the bats that carry such viruses. According to Shi, "we have done bat virus surveillance in Hubei Province for many years but have not found that bats in Wuhan or even the wider Hubei Province carry any coronaviruses that are closely related to SARS-CoV-2."[186] Further lowering the likelihood that bats were the direct source, binding studies of the SARS-CoV-2 virus show that it can bind to human and pangolin ACE2 receptors but only weakly to bat ACE2 receptors.[187] Further at the time of SARS-CoV-2's likely emergence in mid-October or early November, mosquito activity season (May to October) had ended and bats in Wuhan were likely already hibernating.[188]

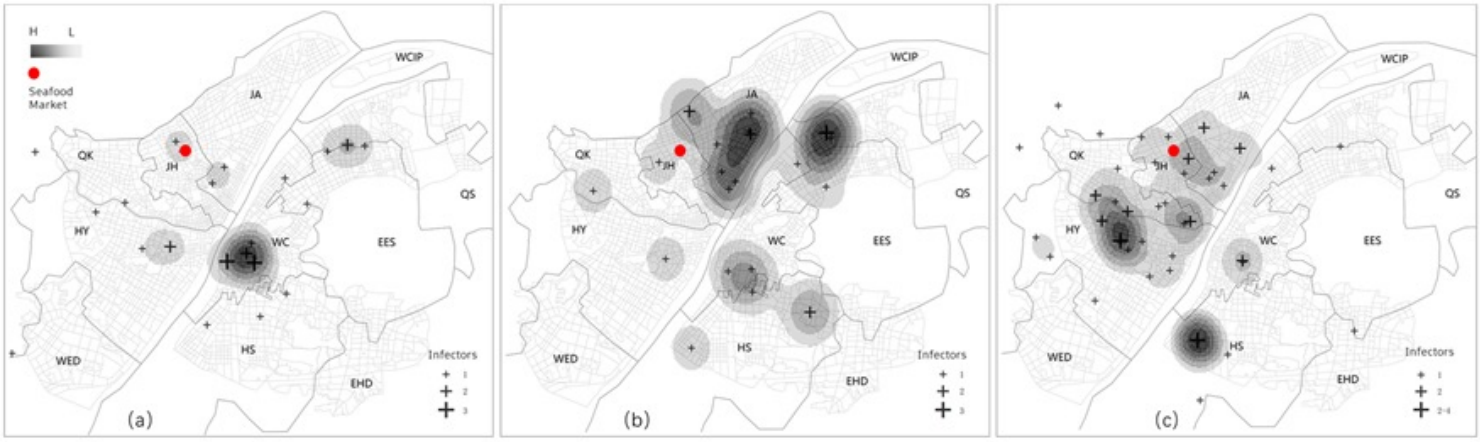
Review of Additional Spatiotemporal Evidence

As Zhengli Shi noted, "the Huanan seafood market may just be a crowded location where a cluster of early novel coronavirus patients were found."[189] CCDC Director George Gao noted that the market was where the outbreak was first recognized and that it likely occurred earlier than late December: "The market may have acted as an amplifier of transmission due to the high number of visitors every day, causing many of the initially identified infection clusters in the early stages of the outbreak."[190,191,192] His statements are consistent with the hypothesis that SARS-CoV-2 might have emerged earlier and at another location.

A 2022 *Science* article that asserted the Huanan market was the epicenter of the SARS-CoV-2 outbreak has recently come under criticism for its statistical analysis.[193,194] Statisticians from Germany and Hong Kong challenged its conclusion based on three considerations: the poor quality of the underlying data, the unproven method used to determine the center of the outbreak, and a flawed simulation that tested the hypothesis that no other location than the seafood market can be the origin.[195] Independent review of the statisticians' evaluation concurred that the statistical analysis in the *Science* study was "flawed in multiple ways." That same independent review noted that "the analysis of the cases cannot rule out that places near the wet market are a possible origin."[196] Further, neither spatial statistical analysis could support or refute the zoonotic hypothesis.[197]

The authors of the 2022 *Science* article referenced a 2020 study from the Wuhan School of Urban Design.[198] They also analyzed social media geotagged location requests for medical help on China's microblogging platform Sina Weibo.[199] The study's timeframe was from February 3 to 12, 2020, but included data beginning on December 20, 2019. Wuhan accounted for 99% of Weibo requests for medical assistance with a substantial number between December 20, 2019 and January 23, 2020. The spatiotemporal characteristics of disease transmission were based on the infection time of COVID-19 cases provided by Weibo data. The hot spots were regarded as the initial pathogen transmission, and areas with the highest density levels in each period were regarded as the areas with the fastest transmission of infection.

According to the study, "the COVID-19 transmission map of Weibo data shows a clear process of three stages: Scattered infection, community spread, and full-scale outbreak" (Figure 1). According to this study there were "multiple outbreak centers" across Wuhan in "high-density residential areas." Neighborhoods with large elderly populations had more requests for help.[200] The early outbreaks occurred in several neighborhoods nearly simultaneously.[201] The researchers noted the increased density of requests in Wuchang District in the earliest period of December 20, 2019, to January 18, 2020 (Figure 1a).



(a) December 20 to January 18th, 2020 (b) from January 19th to 20th, 2020 (c) from January 21st to 22nd, 2020

***Figure 1*. Spatial distribution of help seekers from December 20th, 2019, to January 22nd, 2020:** (a) before January 18th, 2020; (b) from January 19th to 20th, 2020; and (c) from January 21st to 22nd, 2020. Source: Peng et al. (2020).

The earliest reported social media requests for medical assistance for COVID-19-related symptoms in this study occurred during the period of December 20, 2019, to January 18, 2020. The "original" WIV Xiaohongshan campus and the Wuhan University Institute for Animal Models are in the section of Wuhan, the Wuchang district, where most early requests for assistance were clustered (Figure 2).[202]

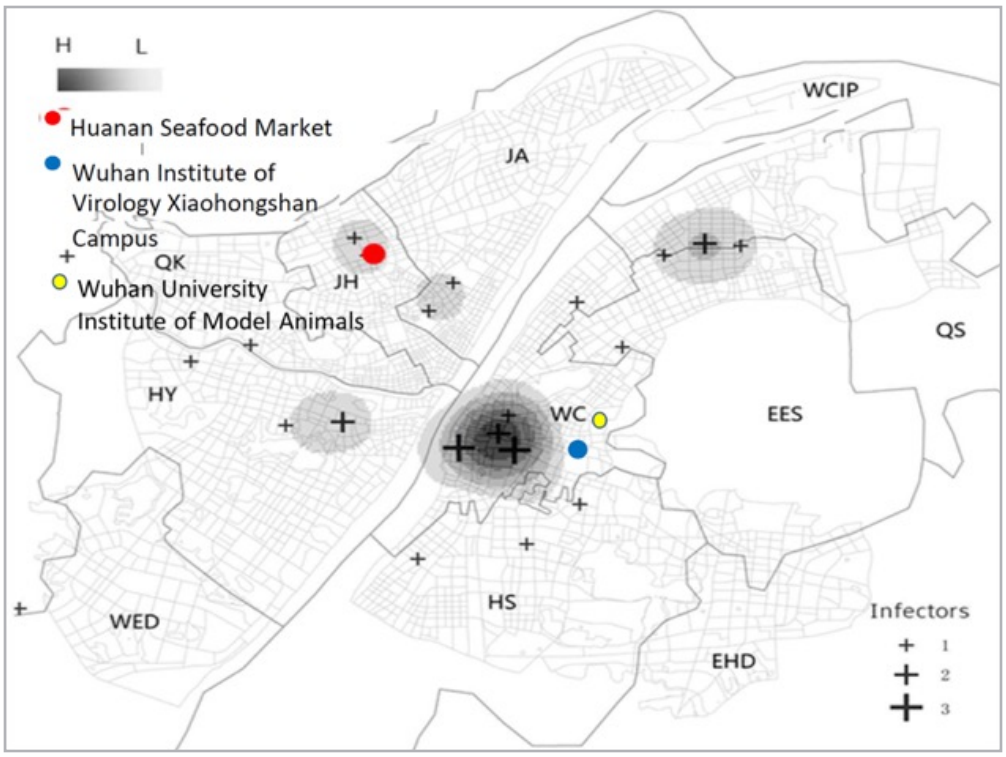
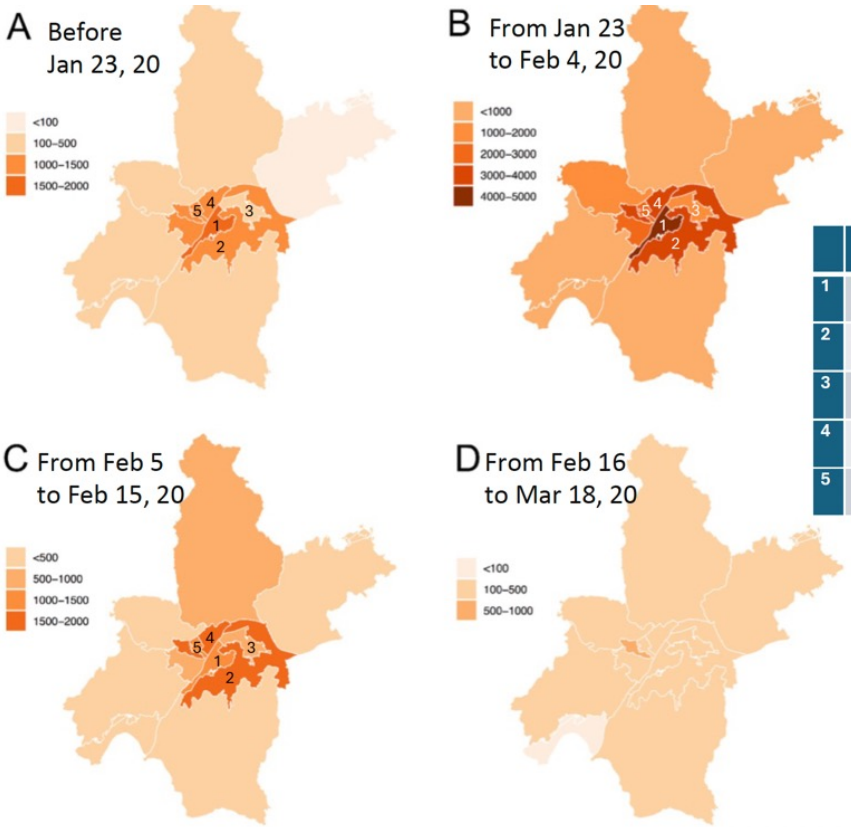


***Figure 2*. Chinese social media Begins to See an Increase in Requests for Help for Medical Treatments in Wuchang District, Wuhan December 20, 2019-January 18, 2020.** Density of social media requests and locations of the Huanan Seafood Market, WIV Xiaohongshan Campus and Wuhan University Institute of Model Animals. Source: Peng et al. (2020).

As suggested by Weibo reporting, the Wuchang district also seems to be where the preponderance of early COVID-19 cases occurred according to independent analysis by epidemiologists using China's National Health Commission data. Researchers from the Institute of Preventive Medicine Information, Hubei Provincial Center for Disease Control and Prevention and the School of Public Health of the Tongji Medical College analyzed a total of 49,973 confirmed COVID-19 cases in Wuhan. These cases were categorized based on time of onset into four periods: First period includes cases from the first case reported on December 8, 2019, to Jan 22, 2020, the day before Wuhan isolation (Figure 3A). The second period is from Jan 23 to Feb 4, 2020 (Figure 3B). The third period is from Feb 5 to Feb 15, 2020 (Figure 3C). The final fourth period is from Feb 16 to Mar 18, 2020 (Figure 3D).

According to the date of illness onset, the number of new confirmed cases was 8,841; 25,619; 11,583; and 3,930 for the first, second, third and fourth periods respectively. The top five districts of confirmed cases were Wuchang (7484, 15.0%), where the Wuhan Institute of Virology (WIV) Xiaohongshan campus and Wuhan University Institute of Animal Models are located; Hongshan (6990, 14.0%), Qiaokou (6863, 13.7%), Jiangan (6570, 13.2%) and Jianghan (5199, 10.4%), where the Huanan Market is located, and the last one was Xinzhou (1073, 2.2%).[203] The highest new cases occurred in Wuchang (new cases: 4240) and Hongshan (new cases: 3853) during the second period (Jan 23 to Feb 4).



Number of new cases recorded in the 5 highest Wuhan administrative districts before Jan 23 to March 18, 2020

	Wuhan District	# (%) new confirmed cases
1	Wuchang WIV & Institute of Animal Models	7484 (15.0%)
2	Hongshan	6990 (14.0%)
3	Qiaokou	6863 (13.7%)
4	Jiangan	6570 (13.2%)
5	Jianghan Huanan market	5199 (10.4%)

Note: The highest new cases occurred in Wuchang (new cases, 4240) and Hongshan (new cases, 3853) during the second period (Jan 23 to Feb 4).

***Figure 3*. The number of new confirmed cases of COVID-19 in Wuhan by administrative district:** A, before Jan 23, 2020; B, from Jan 23 to Feb 4, 2020; C, from Feb 5 to Feb 15, 2020; D, from Feb 16 to Mar 18, 2020. Source: Wang et al. (2020).

Timing of the Initial COVID-19 Outbreak

Evidence of early unrecognized coronavirus cases was first observed in the 2003 SARS-1 outbreak. Epidemiological investigations determined that the virus had been circulating in five other cities (Foshan, Heyuan, Zhongshan, Jiangmen, and Shenzhen) in Guangdong Province about two months before the large outbreak occurred in Guangzhou, the province's capital in February 2003.[204] Retrospective identification of cases and confirmation of clinical samples by sequence analysis were essential in determining the timing and origin of that outbreak.

According to a CCDC report from February 2020, the first SARS-CoV-2 case occurred on December 8, 2019.[205] Several lines of evidence are consistent, however, with the idea that the outbreak occurred earlier. In October 2020, epidemiologists at the Center for Global Health in Nanjing, using the same National Health Commission data set that CCDC did for its earlier February 2020 report, determined that the first symptomatic case occurred on December 1, 2019.[206] SARS-CoV-2's incubation period is estimated to be 6.5 to 14 days.[207,208] Using this estimate, this case likely became infected in mid- to late November 2019.

Consistent with an earlier date, a Wuhan University biostatistics professor gave a media interview in which he discussed compiling a nationwide database of COVID-19 cases. The professor noted several suspected cases predated the earliest official cases in December: "There were two patient cases in November, with onset on November 14 and November 21, 2019, and five or six cases before December 8, 2019."[209]

This timeframe also aligns with the earliest reported CCDC positive PCR SARS-CoV-2 test of a 55-year-old man from Hubei province (no other information provided) who

contracted the virus on November 17, 2019.[210] In addition, a 25-year-old British school teacher in Wuhan became ill with flu-like symptoms on November 25, 2019, developed pneumonia on December 6, 2019, and was treated at a Wuhan hospital. On January 16, 2020, he received a letter from the hospital telling him that he had been infected with the novel coronavirus.[211]

Some evidence is consistent with indications of an even earlier emergence. By mid-October 2019, American diplomats posted at the Wuhan U.S. Consulate knew that Wuhan "had been struck by what was thought to be an unusually vicious flu season. The disease worsened in November," recalled the Deputy Consular General.[212] In January 2021, the U.S. State Department published declassified intelligence reporting WIV researchers became ill with flu symptoms in the fall of 2019.[213] A veteran *Washington Post* columnist, Josh Rogin, provided further details of this report by stating that at least one of the WIV researchers became ill in early November 2019. This researcher exhibited symptoms highly specific to COVID-19, including the loss of smell and "ground-glass" opacities in his lungs seen on X-ray.[214]

Several scholarly articles have described other indicative events during this timeframe. Harvard University researchers found a significant increase in hospital traffic in Wuhan between October and November 2019. The increased hospital visits corresponded to increased web-based (Baidu) searches for symptoms of diarrhea and coughing that are associated with COVID-19 illness.[215,216,217,218] The Nanjing epidemiologists who identified the December 1st 2019 case recognized a significant increase of influenza-like-illness (ILI) cases in November to December 2019 compared to the previous 4 years. These authors suggested that COVID-19 cases may have occurred before December 2019 (Figure 4).[219]

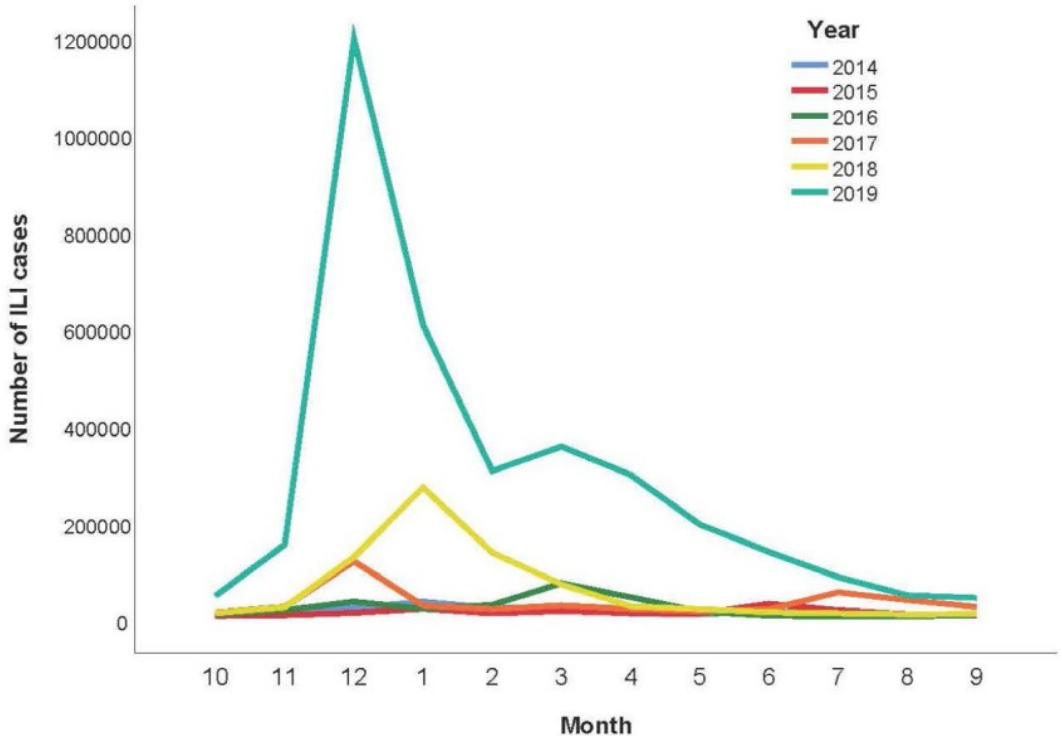


***Figure 4*. China National Health Commission (NHC) Reported influenza-like illness (ILI) cases during 2014-2019:** Comparison of monthly reported ILI cases in different years. Source: Dai and Wang (2020).

Additional research is consistent with the idea that the outbreak centered in Wuhan in Hubei province.[220] More than three quarters of the first 1099 patients with laboratory-confirmed SARS-CoV-2 from 552 hospitals in 30 provinces, autonomous regions, and municipalities in mainland China through January 29, 2020, were either residents of Wuhan, had visited the city or had contact with city residents.[221] Among nonresidents of Wuhan who contracted SARS-CoV-2, 72.3% had contact with Wuhan residents, including 31.3% who had visited the city. Only 1.9% of the patients had a history of direct contact with wildlife.[222]

Several published peer reviewed molecular clock and epidemiological models concluded that the initial outbreak of SARS-CoV-2 occurred sometime mid- to late October to mid-November.[223,224,225] A 2022 study assessed that SARS-CoV-2's entry into the human population "most likely began with at least two separate zoonotic transmissions starting in November 2019," resulting in two identifiable genetic lineages.[226] This study specifically calculated that the first emergence likely occurred "around 18 November 2019."[227]

Likewise, in February 2020, a Yunnan conservation biology group performed a full comparative genome sequence analysis of 93 SARS-CoV-2 strains and concluded the virus was already circulating widely among humans in Wuhan before December 2019, probably beginning mid- to late November. Furthermore, they determined that the "genomic evidence" from the Huanan Market did not support it being the "birthplace" of SARS-CoV-2. These researchers then independently assessed that: "The crowded market boosted SARS-CoV-2 circulation and spread it to the whole city in early December 2019."[228]

The WHO Scientific Advisory Group on Origins of Novel Pathogens (SAGO) preliminary report identified an "unexplained increase in Influenza Like Illness (ILI) in Wuhan adults during the 46th week of 2019" (November 11 to 17) (Figure 5 Left). These cases were evaluated at the Wuhan #1 General Hospital that participated in WHO's adult influenza surveillance program. This increase preceded recorded ILI cases that occurred with the recognized emergence of SARS-CoV-2 in late December 2019 (weeks 51 and 52) (Figure 5 Left).[229]

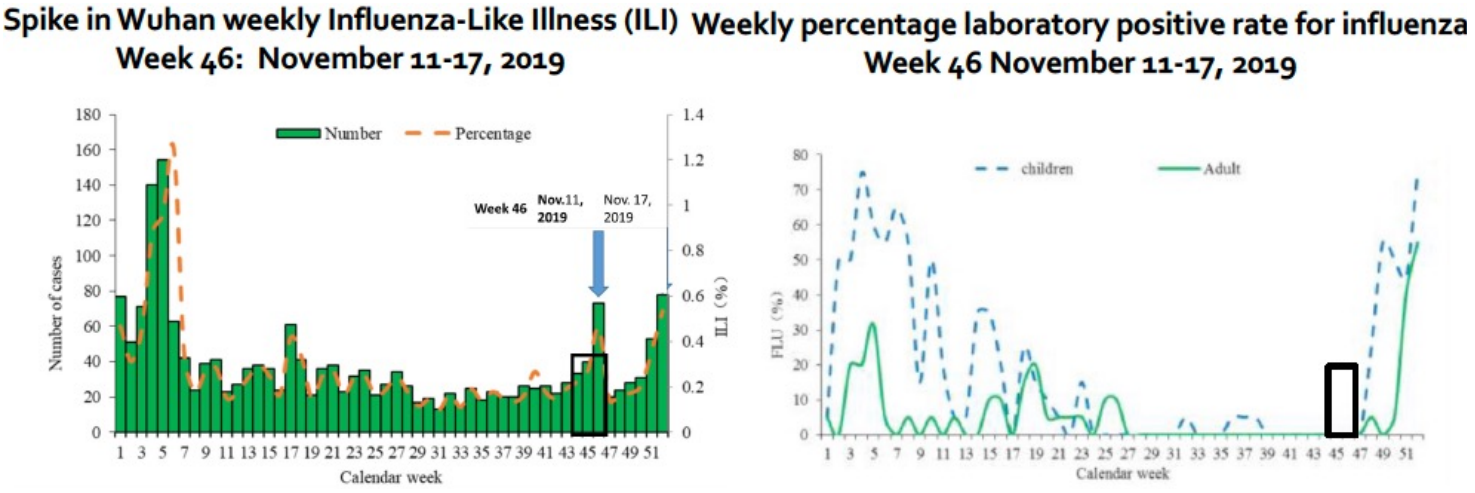


***Figure 5*. Left: Weekly number of ILI cases in adults in the sentinel surveillance in Wuhan in 2019** (and percentage of outpatient visits categorized as ILI, [ILI %]). **Right: Weekly percentage of ILI cases with laboratory-confirmed influenza** [FLU %] in the sentinel surveillance in children and adults in Wuhan in 2019. The black rectangle illustrates that there were no reported positive influenza cases in children or adults during week 44, 45, and 46. Source: World Health Organization (2022).

All week 46 (November 11-17) ILI cases tested negative for influenza (Figure 5 Right). This epidemiological outlier—observed ILI cases with a negative influenza (PCR) test—was also observed in other countries' WHO influenza surveillance data from the early pandemic. In 2022, researchers at the University of Washington analyzed information from 28 countries with high levels of data completeness for influenza surveillance and reported COVID-19 cases during 2020. In 16 countries, these researchers identified the first week in 2020 as a week when this positive outlier, influenza-negative ILI was observed.[230] China was not a country included in this study. In countries studied, however, peak incidence of SARS-CoV-2 infections followed on average 13.3 weeks after the detection of this outlier.[231] Wuhan follows this pattern. The reported peak incidence of SARS-CoV-2 cases in Wuhan occurred during week 6 (February 3 to 9, 2020), 13 weeks after the identified epidemiological outlier that occurred during week 46 (November 11 to 17, 2019).

Origins Implications of SARS-CoV-2's Genome Sequence

SARS-1 and SARS-CoV-2 are in the genus of the coronavirus family called betacoronaviruses and are both part of the subgenus sarbecoviruses. Other betacoronaviruses viruses in this genus include MERS-CoV, bovine coronavirus (BCoV), bat coronavirus HKU4, and human coronavirus OC43. Sarbecoviruses are positive-stranded RNA viruses. Their large viral RNAs (~30kb) can be translated directly into proteins.[232] The SARS-CoV-2 genome consists of 14 functional Open Reading Frames (ORFs) that encode for nonstructural, accessory, and structural proteins.[233,234] There are four structural proteins: nucleocapsid, envelope, membrane and spike proteins.[235] The spike protein receptor enables the virus to bind and infect the cell. For SARS-1 and SARS-CoV-2, the receptor is angiotensin converting enzyme 2 (ACE2), while for MERS-CoV, the receptor is different and called dipeptidyl peptidase 4 (DPP4).[236,237]

Sarbecovirus research is enabled by the ability to work with full length reverse transcribed viral RNA as DNA. Cloned viral genomes are often replicated in Bacterial Artificial Chromosomes, or BACs, or on plasmids in yeast. Live viruses can be recovered from these BACs or yeast constructions if they also carry the necessary promoters (such as the Cytomegalovirus or CMV promoter) that transcribe the full-length RNA genome when infected into mammalian cells. An alternative is to use an RNA (phage T7) polymerase promoter that can synthesize a full-length RNA which then can be introduced directly into mammalian cells by electroporation. The ability to mutually swap cloned DNA into virus and virus back into DNA allows experiments using the full range of DNA-based analysis and manipulation tools. These would include genome sequencing, genomic analysis by other means such as restriction mapping, engineered mutations, expression of individual viral proteins and protein derivatives, construction of modified and chimeric genomes from small pieces of DNA, directed evolution by growth and serial passaging on cell lines, and directed evolution by serial passage through infected animals.

In 2019, researchers at the Wuhan Huazhong Agricultural University published on their use of this reverse genetics approach using CRISPR/Cas9 technology and a BAC vector to make an infectious clone of an alphacoronavirus called porcine epidemic diarrheal virus (PEDV).[238] This approach and use of these tools permitted researchers to create recombinant viruses with defined genetic changes. As noted, they could "generate such recombinant viruses within a week, thus establishing a rapid and efficient platform for manipulation of not only the PEDV genome, but also other RNA viruses."[239]

For most portions of the SARS-CoV-2 genome, no virus has yet been discovered or described that is so closely related as to be an obvious ancestor. Outside of the spike gene, the SARS-CoV-2 genome bears sequence similarity to three previously reported strains: RaTG13, RmYN02, both reportedly isolated in Yunnan province in southern China, and ZC45/ZXC21, from Zhejiang province, in eastern China (Figure 6).[240] Of these, RaTG13 had the greatest similarity to SARS-CoV-2, until reports described the "Banal" series of SARS-related viruses found in northern Laos in late 2020 and early 2021.[241] One of the Laotian strains, BANAL-52, bears slightly more similarity to SARS-COV-2 (96.8%) than RaTG13 (96.1%).[242] Results of horizontal gene transfer and recombination analysis suggest that SARS-CoV-2 "could not only be a chimera virus resulting from recombination of the bat RaTG13 and Guangdong pangolin coronaviruses but also a close

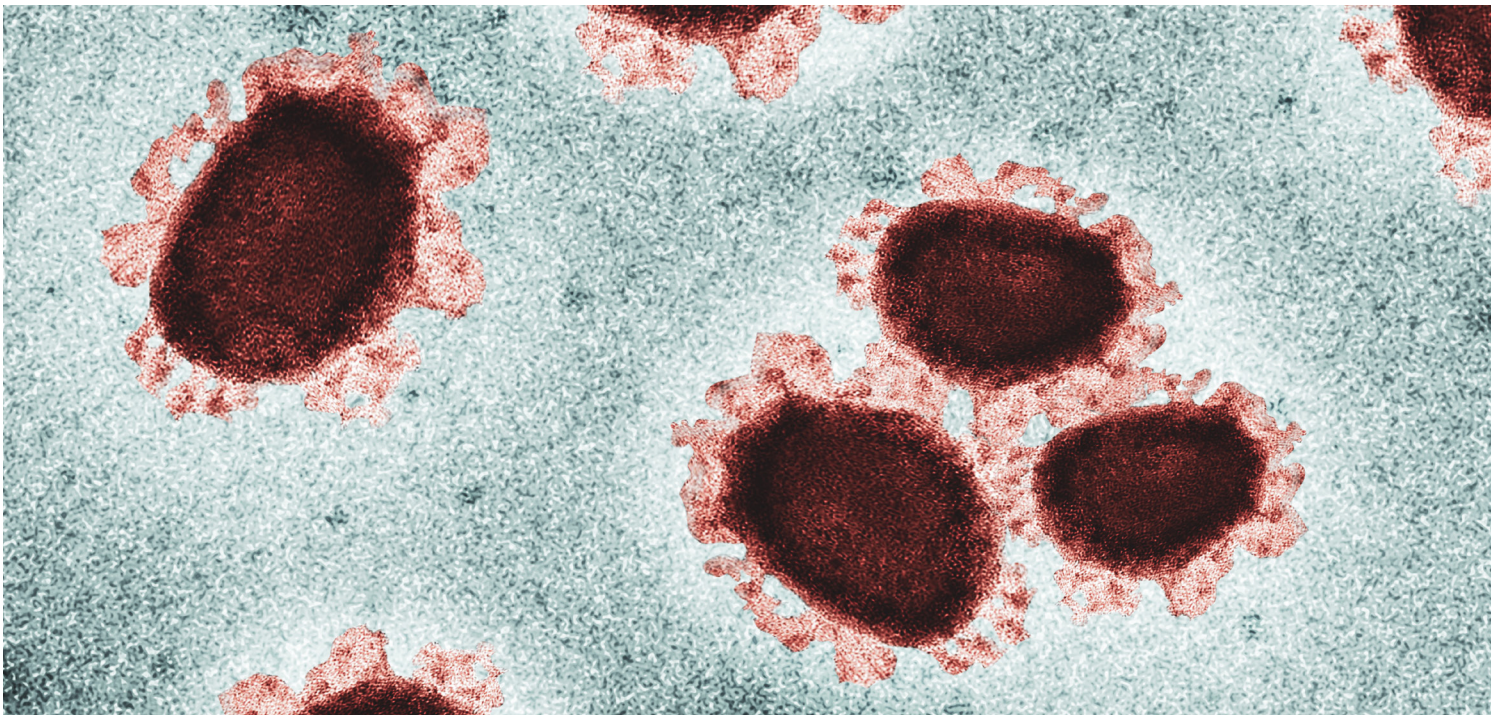
relative of the ZC45 and ZXC21 strains."[243]

The exception to the statement that there is of yet no plausible close relative or ancestor for most of the SARS-CoV-2 genome is the virus's spike protein. The spike protein consists of two subunits, S1 and S2, connected by amino acids that provide a site for the cell surface protease furin. The S1 subunit contains the receptor binding domain (RBD), the part of the protein that binds human ACE2.[244] The nucleotide and protein sequence of the spike protein and the S1 subunit are quite dissimilar to the genetic sequences of the closest related strains RaTG13 and BANAL-52.

However, the nucleotide sequence of the SARS-CoV-2 RBD is 86.64% identical to that of the Pangolin-GD strain.[245] For these two RBDs the amino acid identity is even greater, at 96.8% (4 out of 121 amino acids are different). Most of the binding with the ACE2 receptor is made by a smaller part of the RBD, called the receptor binding motif or RBM.[246] The protein sequence of the Pangolin-GD RBM differs by a single amino acid from that of SARS-CoV-2. The SARS-CoV-2 and Pangolin-GD strain also share an integrin-binding protein at the distal end of the RBD. This sequence is novel and was not identified in a previous SARS-related virus or coronavirus prior to the pandemic. As noted by U.K. researchers, "only the pangolin GD strain was to share 100% amino acid sequence identity with all of the potential integrin-binding motifs, including the RGD sequence, from SARS-CoV-2."[247]

The S2 fragment of the SARS-CoV-2 spike protein is highly conserved and shares 99% identity with the SARS-related ZC45 and ZXC21 strains and SARS-1.[248] The two bat SARS-related coronavirus ZC45 and ZXC21 are closest to SARS-CoV-2 after Banal-52 and RaTG-13. PLA researchers isolated these two strains from bats from Zhoushan city Zhejiang province in 2015 and 2017.[249]

This and other evidence is consistent with the idea that different portions of the SARS-CoV-2 genome might be derived from different ancestral viral strains. The Pangolin-GD genome was not similar to the genome of SARS-CoV-2 and RaTG13, except for the sequence identity in one portion of the spike gene RBD. The Pangolin-GD strain, however, appears to have donated the RBD of its spike protein to SARS-CoV-2. In the region of nucleotides 1-914, the Pangolin-GD is more similar to the bat SARS-related coronaviruses ZXC21 and ZC45. Overall, the SARS-CoV-2 genome might have originated from the recombination of a virus similar to Pangolin-GD and a virus similar to RaTG13.[250]



SARS-CoV-2 might be a chimera, or a mosaic, with most of the virus derived from a still unidentified close ancestor, while the spike protein, or perhaps just least its spike protein's RBD may have been donated by a virus related to the Pangolin-GD strain. The identical RBMs of SARS-CoV-2 and the pangolin strain GD have led some to suggest that SARS-CoV-2 resulted from recombination of a Pangolin GD strain with RaTG13.[251] Because of substantial sequence differences from SARS-CoV-2, the Pangolin-GD strain is unlikely directly linked to the current outbreak.[252] At least one other study also does not support that SARS-CoV-2 evolved directly from an infected pangolin.[253] Such a chimera, however, could result from naturally occurring recombination between closely related RNA viruses infecting the same bat (in a cave or in a cage in captivity). Alternatively, it may be the by-product of lab genetic engineering with recombinant DNA assembly and directed evolution using strains known to be in the possession or published on by the WIV and People's Liberation Army (PLA) researchers.

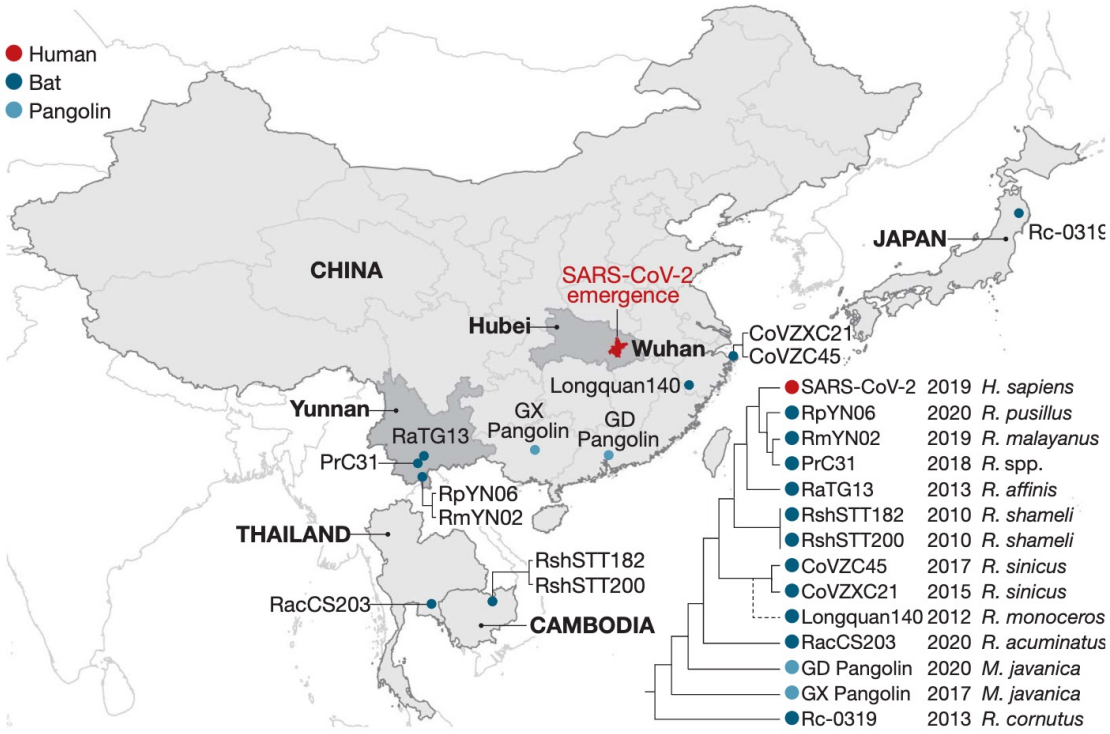


***Figure 6*. Distribution of bat species from which SARS-CoV-2 and SARS-related viruses have been found.** Source: Lytras et al. (2021).[254]

Viruses with a Close Match to the Non-Spike Protein Coding Regions of the SARS-CoV-2 Genome

SARS-CoV-2 is notably different from other SARS-related viruses in that the reported viruses most similar to different parts of its genome come from geographic locations that exceed the expected migratory flight range (1.86 to 17 km) of bat genera (eg. *Rhinophilus*, or horseshoe bats) that carry these viruses.[255] Approximately 2.7% of people living in southern China within six kilometers of caves harboring SARS-related viruses showed possible infection.[256] This study suggests the risk of spillover to people living near bat colonies is a "relatively rare event."[257] SARS-CoV-2 emergence in Wuhan differs from previously observed recombination and spillover events between SARS-related strains from different geographical locations within the *Rhinophilus* bat's foraging range.[258]

ZC45 and ZXC21

The earliest reported viral relatives of SARS-CoV-2 were two novel SARS-like viruses (ZXC21 and ZC45) discovered

by PLA researchers during field bat sampling in 2015 and 2017 from bats collected from Zhoushan city in eastern Zhejiang province (Figure 6).[259] In early January 2020, strain ZC45 was initially reported as the closest relative to SARS-CoV-2 with 89.1% genetic similarity.[260] The S2 fragment of the SARS-CoV-2 spike protein which enables cell fusion is highly conserved and shares 99% identity with the SARS-related ZC45 and ZXC21 strains and SARS-1.[261] The two bat SARS-related coronavirus ZC45 and ZXC21, being closest to SARS-CoV-2 after Banal-52 and RaTG-13, when injected intracerebrally can infect suckling rats, cause inflammation in the brain tissue, and pathological changes in lung & intestines. As described, "the inflammatory reaction in the brain tissues was most evident. Of the ten suckling rats, four showed clinical symptoms, including drowsiness, slow action, and mental depression."[262]

RaTG-13 and Ra(BtCoV)4991

In late January 2020, WIV researchers published the existence of the SARS-related strain RaTG-13. It had 96.2% similarity to SARS-CoV-2, more than ZC-45.[263] RaTG13 is the closest relative to SARS-CoV-2 known to be in the WIV's possession prior to the pandemic.

RaTG13, previously called Ra(BtCoV)4991, was first isolated in bats from the Mojiang County copper mine in the town of Tongguan in Yunnan province in July 2013. This site was the location of the much-publicized 2012 illness of six workers.[264] Workers cleaning bat guano from this mine contracted a severe respiratory illness that killed three of the six affected. The illness's etiology was suspected to be viral. Initial throat and blood samples tested for SARS-1 were reportedly negative.[265,266,267] Oral swabs and blood from the mineworkers were initially tested for a panel of possible viral agents, including SARS-1, and were reportedly negative.[268] In 2012, researchers at the WIV analyzed the workers' blood. This report stated that one patient tested positive for IgM antibodies against SARS-1 and four patients had measurable IgG SARS-CoV-1 antibodies.[269] After the reported start of the COVID-19 pandemic, researchers at the WIV reported retesting relevant 2012 clinical samples using RT-qPCR methods that detected RNA-dependent RNA polymerases (RdRp) from Ebola virus, Nipah virus and bat SARSr-CoV, and use of an enzyme-linked immunosorbent assay (ELISA) to detect antibodies against the SARS-CoV-2 nucleocapsid. This report stated that the results of these retests were negative.[270] The preserved samples have not been made available to other laboratories for independent confirmatory testing.

At the time of its initial characterization, RaTG13 was originally designated Ra(BtCov)4991 and part of its sequence was uploaded. The name change from BtCoV4991 to RaTG13 was not noticed until after the start of the pandemic, when its full sequence was published. British journalists noted that the WIV "having listed a section of its BtCoV4991 genome sequence on an international database in 2016 — it changed the name to RaTG13, which meant it could not easily be linked to the Mojiang mine."[271] Zhengli Shi described the nomenclature change to be more descriptive than deceptive: "Ra4991 is the ID for a bat sample while RaTG13 is the ID [identification] for the coronavirus detected in the sample. We changed the name as we wanted it to reflect the time (year 2013) and location for the sample collection (Tongguan-TG)."[272]

Recombination certainly occurs among highly similar SARS-related coronaviruses within the sarbecovirus subgenus.[273] Dissimilar viruses do not recombine.[274] Recombination in nature takes place when related viruses simultaneously infect the same animal. In bats, this happens when the bats are physically close, within inches or feet of each other. When bats roost in the same cave or inhabit nearby cages, they can transmit viruses and become infected indirectly "through droplets or aerosols of viruses excreted in urine or feces."[275] As described, the reported viruses most like different parts of the SARS-CoV-2 genome arose from geographic locations separated by thousands of kilometers, far exceeding the expected migratory flight range of bats that carry them. If SARS-CoV-2 arose from natural recombination, viruses initially carried by the different bat species in which they were initially isolated must have shared the same proximate space. It is unlikely that those different bats could fly to reach that space.

Alternatively, some suggest that inadequate sampling of coronaviruses may result in an incomplete geographic representation of other strains that may be genetically

closer to SARS-CoV-2. As described, coronavirus "field sampling [in China was] often carried out opportunistically in response to concerns about spillover, and capacity for systematic sampling [was] financially or logistically constrained."[276] Such sampling could lead to "substantial geographical bias."[277]

The DEFUSE Proposal

In March 2018, the nonprofit organization EcoHealth Alliance submitted a grant proposal to the Defense Advanced Research Projects Agency (DARPA). The proposal was titled "Project DEFUSE: Defusing the Threat of Bat-borne Coronaviruses." EcoHealth served as the lead for the project. The project's major goals were to "identify and model [animal] spillover risk of novel SARS-related coronaviruses" and to use that knowledge to develop vaccines to immunize bats in the wild. The suggested benefit of this ecological intervention was to prevent emergence of viral pathogens from bat reservoirs, reducing the potential risk to U.S. troops in Asia by the spread of bat coronaviruses.[278]

The DEFUSE project intended to collect SARS-related viruses found in four natural sites. Researchers from the United States and China would use proven technology to assemble, engineer and evolve novel coronaviruses, characterizing them for their ability to grow in cell culture and evaluate their "ability to cause SARS-like disease" in humanized mice. The data obtained from these studies would be used to create a predictive model for viruses naturally circulating in bat reservoirs permitting estimates of "evolutionary rates [and] rates of recombination." This data would be used in a machine learning approach to form predictions about which could "generate novel strains capable of human infection."[279]

These predictions would be used to create coronavirus chimeric spike proteins. Researchers would use these recombinant proteins to first vaccinate captive bats. The concepts to be tested included infecting bats with poxviruses, applying transdermal nanoparticles and feeding captive bats with edible adhesives. These approaches would either express, transmit or be infused with chimeric coronavirus spike proteins, respectively. Another concept would develop a novel "filament extension atomization" technology that generated aerosol vaccine droplets to be released in caves for the bats to breathe in.

The winning vaccine delivery technology would be tested in the field, in caves in Yunnan province, and the ability of the vaccine to cause changes in the local viral ecology to suppress potential emergent strains monitored. Researchers at several U.S. universities, other research entities and the Wuhan Institute of Virology (WIV) would carry out the field collection, the genetic engineering, directed evolution, vaccine testing, field deployment of the bat vaccination technology and conduct surveillance of the viral ecology in the bat caves. According to early draft comments, the role of non-U.S. researchers was deliberately de-emphasized so it would not be perceived as a "negative."[280]

The reverse genetic and directed evolution methods described in the proposal followed those published by U.S. researchers in 2015. This study was co-funded by NIH and USAID.[281,282] Work was completed prior to the 2014 pause in federally funded gain of function research on influenza, MERS and SARS coronaviruses mandated by the Obama Administration. In the work, researchers introduced the spike protein from one SARS-related coronavirus onto the genome of another to create a new chimeric SARS-related coronavirus, SCH014.[283] The reverse genetic studies (spike protein swapping and directed evolution) that created the new SARS-related strain were performed under enhanced biosafety (enhanced BSL-3 standards).[284,285,286] Researchers were required to wear Powered Air Purifying Respirators (PAPRs).[287]

Researchers anticipated that the chimeric virus, SCH014, should have diminished pathogenicity. Surprisingly, however, the chimeric virus showed an increased binding to human lung cells, increased pathogenesis and evaded existing therapeutics and potential vaccines.[288] As described by these U.S. researchers, "[on] the basis of these findings, scientific review panels may deem similar studies building chimeric viruses based on circulating strains too risky to pursue, as increased pathogenicity in mammalian models cannot be excluded.... The potential to prepare for and mitigate future outbreaks must be weighed against the risk of creating more dangerous pathogens."[289]

As described, the proposed laboratory splicing of RBDs and spike proteins into SARS viruses can mimic naturally occurring recombination which, in the past, may have allowed coronaviruses to evolve into new pandemic strains. Again, natural recombination occurs among highly similar but not dissimilar SARS-related coronaviruses.[290,291] In nature, recombination takes place when related viruses simultaneously infect the same bat(s) in close physical proximity.[292]

In the 2018 EcoHealth *DEFUSE* proposal, the spike proteins and entire genomes from viral isolates would be sequenced. Researchers would then splice spike proteins and RBDs onto SARS-related backbone viruses. The result would be chimeric viruses with spike proteins and the other parts of viral genomes from different SARS-related strains. As noted, these would be further engineered, evolved by directed evolution and passaging by serial infection of humanized mice, to identify those viruses that might pose the greatest danger of emergence into the human population and potentially cause pandemics.

DARPA did not approve or fund the EcoHealth DEFUSE proposal. DARPA reviewers noted that "the proposal does not mention or assess potential risks of gain of function research."[293] However, it is possible that some of the work described in the proposal might have been carried out anyway. Anecdotally, in the United States, it is common practice, at least for NIH proposals, for researchers to have completed at least some of the work before the proposal is submitted.

Proposed Viral Evolution Methods

The methodology described in the unfunded DEFUSE proposal to generate new viruses and new chimeric spike proteins was well established. Researchers would splice spike proteins and RBDs onto SARS-related backbone viruses. The result would be chimeric viruses with spike proteins from many different SARS-related strains. Researchers from the United States and China were competent to carry it out.

WIV researchers had previously recovered SARS-related coronaviruses that represented the "building blocks of SARS" (i.e. SARS-CoV-1) from caves in Yunnan province about 2000 km away.[294,295] Their five-year longitudinal study in a single cave affirmatively demonstrated that SARS-related viruses recombined among roosting bats, making it plausible that a virus arising from such an event might cause a pandemic.[296] The DEFUSE proposal included isolating bat coronaviruses from intensive field collections from Yunnan province and three additional ecological reservoirs: cave sites in Southern China and Southeast Asia. Partial viral sequences recovered from collected samples would be subject to "reverse genetic" methods.

As outlined in the DEFUSE proposal, the creation of the new viruses would be performed by a U.S. researcher.[297] EcoHealth's principal investigator of the proposal commented, however, "if we win this contract, I do not propose that all of this work will necessarily be conducted by [U.S. researchers], but I do want to stress the U.S. side of this proposal so that DARPA are comfortable with our team. Once we get the funds, we can then allocate who does what exact work, and I believe that a lot of these assays can be done in Wuhan as well."[298] This statement and a body of WIV's published research affirms their competence to perform reverse genetics, viral engineering, viral evolution, and study viral biology.[299,300]

In 2018, EcoHealth Alliance submitted a progress report for year four of an NIH grant (June 1, 2017- May 31, 2018). WIV researchers "successful[ly] rescue[d]" coronaviruses using reverse genetic methods. They repeated the SCH014 study performed by U.S. researchers in 2014. They constructed chimeric viruses with spike proteins for three SARS-related viruses (SHC014, WIV16 and Rs4231) into different SARS coronavirus (WIV1) backbones that had been isolated and tested at the WIV. They tested these chimeric viruses in BSL-3 containment for their ability to infect humanized ACE2 receptor mice. WIV researchers also reported and confirmed the increased lung affinity and pathogenicity of the SCH014 strain.[301]

The 2018 DEFUSE proposal anticipated that about three to five full length viruses and 15 to 30 bat SARS-related spike proteins would be collected per year.[302] The proposed work would also take advantage of 180 sequenced SARS-related viruses already in the WIV's possession that had not yet been assessed for risk of zoonotic transmission. Those viruses would be tested

for their ability to bind to human angiotensin converting enzyme (hACE2) receptor and infect animal and human cells. Viruses demonstrating these qualities would then be used to infect humanized mice to assess pathogenesis.[303]

The unfunded 2018 EcoHealth DEFUSE project also noted that other pathogenic viruses such as avian influenza and Ebola viruses have cleavage sites that are split by the human enzyme (protease) furin. The presence of a furin cleavage site (FCS) increases these viruses' infectivity and transmissibility, allowing them to infect additional cell types and cause more serious disease.[304] FCSs exist in the spike proteins of other sub-genus coronaviruses such as MERS, and in avian infectious bronchitis virus. None of the sarbecoviruses mentioned in the unfunded DEFUSE proposal had an FCS.

The DEFUSE plan proposed that sarbecoviruses might acquire furin cleavage sites in the wild by recombination with currently unknown FCS-containing sarbecoviruses. Project DEFUSE proposed to "analyze all [SARS-related spike protein] sequences… for the presence of potential A cleavage sites."[305,306,307] To understand the effects of FCSs, researchers intended to "introduce appropriate human specific cleavage sites" into chimeric SARS viruses to "evaluate [their] growth potential" in monkey kidney [Vero] and human lung [HAE] cells.[308]

Consistency of the SARS-CoV-2 Genome with Methods in the DEFUSE Proposal and Well-Practiced Techniques

SARS-CoV-2 has a significant number of features consistent with the hypothesis that it might have been modified in the lab. Some of these offer stronger arguments for this hypothesis than others, and in the aggregate, they are not dispositive.

A Furin Cleavage Site in the Spike Protein

A distinguishing feature of SARS-CoV-2 is the presence of an FCS on the spike protein at the junction where it cleaves into two fragments after it attaches to a cell. University of Nankai researchers in China "first reported a very important mutation on the S protein" on January 21, 2020.[309] They noted the FCS in SARS-CoV-2 was "more similar to that of murine hepatitis coronavirus, HIV, Ebola virus and some avian influenza viruses.[310] The FCS is essential to SARS-CoV-2's ability to infect human lungs. Thus, the FCS contributes to COVID-19's pulmonary morbidity and mortality, such as pneumonia.[311,312] SARS-CoV-2 strains losing the FCS have significantly less pulmonary pathology.[313,314]

No sarbecoviruses' spike proteins except SARS-CoV-2's have an FCS. BANAL-52 and RaTG13, with 95% and 93% SARS-CoV-2 spike protein nucleotide sequence similarity, respectively, do not have an FCS. The spike proteins from the ZXC21 and ZC45 SARS-related viruses do not have an FCS, nor do the spike proteins from the two related pangolin coronavirus strains Guangdong [GD] or Guangxi [GX].[315] Of the 1,500 known sequences of sub-genus sarbecoviruses, none has an FCS. It has been asserted, perhaps hyperbolically, that the presence of this site constituted a potential "smoking gun" providing probative evidence of artificial insertion.[316]

The FCS is defined by four specific amino acids—Proline (P), Arginine (R), Arginine (R) and Alanine (A). It has been claimed that the RNA code (codon: CGG) for arginine in the SARS-CoV-2 S FCS is rarely found in coronaviruses. This arginine code only comprises 3% of the nucleic acid in SARS-CoV-2 itself.[317,318] This arginine codon (CGG) in the SARS-CoV-2 FCS has consistently been found the least favored codon across coronaviruses infecting a variety of hosts, including bats. This finding suggests that the likelihood of direct zoonotic spillover of SARS-CoV-2 from bats to humans is unlikely.[319]

The Nankai researchers performed bioinformatic sequence analyses of the prevalence of arginine CGG codons in animals reportedly sold in the Wuhan South China Seafood market. Their analysis indicated that the likely intermediate hosts of the SARS-CoV-2 was "especially, deer, foxes and rats." Further, they concluded these codons were present in the virus before being transmitted to humans.[320]

However, several SARS-related viral strains found in nature (RmYNO2, BANAL-52 and BANAL-236) have a partial FCS sequence. Directed evolution experiments to evolve a complete FCS in a sarbecovirus closer in genetic similarity to SARS-CoV-2 (BANAL-236) via serial passage in mice expressing the ACE2 receptor failed.[321] But in 2015,

Wuhan researchers used point mutagenesis to insert a functional FCS in the alphacoronavirus Porcine Epidemic Diarrhea Coronavirus.[322]

The combination of widespread availability of long stretches of double stranded synthetic DNA with assembly methods that are scarless permits insertion of sequences encoding an FCS into any protein coding sequence of the assembled DNA clone used to generate the RNA viral genome.[323] In 2020, researchers in Shanghai published experiments on the effect of variants in the SARS-CoV-2 FCS and other changes introduced into the spike protein, for "plasmids that were synthesized... in our laboratory," presumably by such a route.[324] Researchers in China demonstrated inserting an FCS into SARS-1 and RaTG-13 betacoronaviruses in early 2020.[325]

Perhaps notably, the back-to-back arginine CCG codons in the PRRA of the SARS-CoV-2 FCS create a cut site for a restriction enzyme (FauI). Restriction enzymes cleave DNA sequences at specific sites. For almost half a century, restriction enzymes have been commonly used, and they remain critical for recombinant DNA research. Restriction mapping has provided a means to characterize recombinant DNA constructs. The presence or absence of this restriction enzyme site would provide a low-tech means to determine whether a recombinant DNA clone of a passaged SARS-CoV-2 virus had retained an FCS in the gene encoding the spike protein.

Low Probability Restriction Sites

The SARS-CoV-2 genome contains five sites for two restriction enzymes (BsaI and BsmBI) that would facilitate *in vitro* assembly from smaller fragments. This fact was noted by researchers who analyzed methods used in coronavirus labs.[326] Restriction sites occur naturally and randomly. These researchers noted that the restriction sites in SARS-CoV-2 were distributed evenly. No fragment would be longer than eight kilobases. All the three or four nucleotide single stranded ends of the restriction fragments made by the type IIs enzymes would be unique. The existence of these restriction sites supports the idea that the SARS-CoV-2 genome permitted "efficient dis- and re-assembly of the viral genome characteristic of synthetic viruses... [and] is anomalous for a wild coronavirus and more likely to have originated from an infectious clone designed as an efficient reverse genetics system."[327]

These researchers also noted that the genome contains more cut sites for type IIs restriction enzymes (BsaI, BsmBI, BglI) than expected, allowing it to be cut into (or reassembled from) five to eight fragments. All the restriction sites would be created using different codons than those found in related viruses. Stretches of SARS-CoV-2 viral genome flanked by two unique restriction sites would identify regions for which further manipulation could be performed. Finally, all the engineered restriction sites might be chosen to allow the same codons in homologous proteins in related viruses to be mutated, facilitating the swapping of segments among related viruses. The researchers asserted that the SARS-CoV-2 genome possessed all these characteristics, while the related viruses RaTG13 and BANAL-52 did not and the probability of the number of evenly spaced cut sites of an un-engineered virus was "one in a million."[328]

The idea that these restriction (BsaI and BsmBI) sites might have been engineered into SARS-CoV-2 recently received some corroboration. Investigative journalists analyzed documents obtained under the Freedom of Information Act, including detailed communications among the participating scientists before they submitted their unfunded DEFUSE proposal.[329,330] The journalist's review of these communications revealed that the researchers intended to insert furin cleavage sites at the S1/S2 junction in the spike protein, to identify coronaviruses up to 25 percent different from SARS, to select for spike proteins RBD with higher affinity for the human ACE2 receptor and to assemble synthetic viruses from six Bsa1 and BsmB1 restriction fragments. Those documents contain an order or quote from one of the researchers on the proposal to purchase the BsmB1 enzyme from New England Biolabs.

Restriction Sites Flanking the Receptor Binding Motif

The portion of the SARS-CoV-2 spike protein that binds to the human ACE2 receptor is the receptor binding domain (RBD). As mentioned, the non-RBD portion of the SARS-CoV-2 S1 spike protein is similar to that reported for the RaTG13 S protein (96% identity within S1), but only 76%

identical in the RaTG13 spike RBD. On the other hand, the sequence and structure of the RBD of SARS-CoV-2 S is remarkably similar to that of Pangolin-CoV-GD (97% identity).[331] The portion of the RBD that actually touches human ACE2 is the receptor binding motif (RBM). The "acquisition of a complete functional RBM by a RaTG13-like CoV through a recombination event with a [Pangolin-CoV-GD] virus enabled it to more efficiently use ACE2 for human infection."[332] In addition, the S2 fragment of SARS-COV-2 spike protein is 99% similar to the two SARS-related ZXC21 and ZC45 strains. The near perfect identity match of RBMs and the S2 between Pangolin-GD and ZXC21 and ZC45 with SARS-CoV-2 RBMs (one amino acid difference) and S2 fragment suggests that this portion of their spike proteins is derived from closely related ancestors that contributed that at least these portions to the spike protein of SARS-CoV-2. Interestingly, in both the Pangolin-CoV-GD and SARS-CoV-2 genes, the portion of the spike protein gene that encodes the RBM is flanked by type II restriction sites (EcoRI and BstEII) that would facilitate insertion or substitution.[333]

The RBM's 66-amino-acid protein sequence encoded by this 198-nucleotide fragment spans the part of the SARS-CoV-2 spike protein that makes contact with the target cell. In SARS-CoV-2, this region makes contact with the human ACE2 receptor protein.[334] The size of the nucleotide fragment makes it particularly amenable to further genetic manipulation that can use a particularly powerful method perfected over the last 12 years called "Deep Mutational Scanning."[335] Mutant versions of the RBM could be reintroduced into the RBD that would be facilitated by the presence of the restriction enzyme sites. The larger altered spike protein could then be attached to a backbone virus that would permit testing the chimera for binding affinity to target cells and pathogenesis. This characteristic of the SARS-CoV-2 genome was not noted in the DEFUSE proposal. There is no direct evidence to support the speculation that such experiments might have been carried out.

The Receptor Binding Domain's Integrin-Binding Protein Sequence

A finding made by Swiss researchers in May 2020 showed that SARS-CoV-2 contained a three amino acid sequence: Arginine (R)-Glycine (G)-Aspartate (D). This tripeptide is coded as RGD. This protein can bind to integrins, which are human cell-surface receptors. Integrin protein sequences are found in several other viruses responsible for human illnesses, such as Human Metapneumoviruses, Adenoviruses, Rotaviruses, Epstein-Barr and cytomegaloviruses for example.[336] They play a role in cell adhesion. Its discovery was notable because this binding protein had not previously been identified in SARS-related viruses or any other coronaviruses.[337,338] The DEFUSE proposal did not mention inserting such receptors from other non-coronaviruses.

Integrins are associated with a variety of cell types including lung, brain, blood vessel (endothelial) and platelets. They are involved in regulation of cellular growth, migration, signaling, and cytokine activation and release that is critical to inflammation and infection and coagulation.[339,340] Integrins provide alternative ways for a virus to infect different cells and interfere with host signaling pathways.[341] Analysis by U.K. researchers showed that the SARS-CoV-2 spike protein, in addition to the RGD, contained sequences of other potential integrins that could bind to multiple cell receptors or interfere with normal cell functioning.[342] Among the specific integrins the SARS-CoV-2 spike protein can bind to are *alpha5beta1* and *alphaVbeta3*.[343] These integrins are found in brain (neuron and glial) and cardiovascular (heart and blood vessel) cells.[344] As these researchers noted, "only the pangolin GD [Guangdong] strain was to share 100% amino acid sequence identity with all of the potential integrin-binding motifs, including the RGD sequence, from SARS-CoV-2."[345]

Recently, researchers from the University of California San Francisco found that the SARS-COV-2 spike protein binds to fibrinogen promoting not only blood clot formation but "infection-induced [clot] inflammation and neuropathology." [346] Their analysis showed a causal role of this mechanism for the neuropathology seen in COVID-19 disease.

This pangolin strain with the identical RBD to SARS-CoV-2's was reportedly isolated from Malayan pangolins seized by officials in Guangdong province, near Hong Kong in March and July of 2019.[347] These researchers determined that SARS-CoV-2 did not, however, "directly"

evolve from the GD pangolin strain.[348] Outside of the RBD, the spike protein of the coronavirus isolated from Guangdong pangolins is less similar to the SARS-CoV-2 spike protein and also lacks a furin cleavage site. The significance of these observations is that SARS-CoV-2's spike protein is a result of recombination between several human, pangolin and bat strains: RaTG13, ZXC21/ZC45, and Pangolin-GD and the acquisition of a novel furin cleavage site that none of the named strains possessed.[349]

Other Information About Betacoronaviruses

On February 1, 2020, senior NIH scientists convened a conference call of international virologists including evolutionary biologists to discuss the nature of the SARS-CoV-2 published sequence. In an email memorializing the conversation, the group expressed concern:

> About the fact that upon viewing the sequences of several [SARS-CoV-2] isolates… there were mutations in the virus that would be most unusual to have evolved naturally in the bats and that there was a suspicion that this mutation was intentionally inserted. The suspicion was heightened by the fact that scientists in Wuhan University are known to have been working on gain-of-function experiments to determine the molecular mechanisms associated with bat viruses adapting to human infection, and the outbreak originated in Wuhan.[350]

One evolutionary biologist commented on his assessment of the FCS: "And when I'm saying the genome is inconsistent with expectations from evolutionary theory, it's a bit of a fancy way of basically saying, like, look, guys, I think this could be engineered."[351] The participating scientists did not reach consensus on the issue and suggested it be referred to the WHO.[352]

A January 15, 2021 U.S. State Department Fact Sheet included declassified intelligence reporting that "starting in at least 2016 – and with no indication of a stop prior to the COVID-19 outbreak – WIV researchers conducted experiments involving RaTG13, the bat coronavirus identified by the WIV in January 2020 as its closest sample to SARS-CoV-2."[353] In July 2023, British journalists likewise reported, "investigators spoke to two researchers working at a U.S. laboratory who were collaborating with the Wuhan institute at the time of the outbreak. They said the Wuhan scientists had inserted furin cleavage sites into viruses in 2019 in exactly the way proposed in [EcoHealth's] failed funding application to DARPA."[354]

As mentioned, natural events could account for the chimeric nature of SARS-CoV-2. The virus might have arisen by natural recombination between the virus or viruses that contributed the spike gene and the virus or viruses that contributed the rest of the viral genome. Single or multiple recombination events could have occurred among different parent viruses that had been able to infect the same cells in the same animal host, in this case, the same bat, or even series of recombination events occurring in different bats. By such means, recombination among coronaviruses within the spike gene could result in RBDs with increased binding to human and animal cells, a substitution of a single amino acid in the RBD resulting in an integrin-binding protein, and the acquisition of an FCS on the spike protein between its S1 and S2 segments.[355] However, SARS-COV-2 recombination had to have resulted in an S2 fragment 99% identical to SARS-related strains ZXC21, ZC45 and SARS-1.[356]

As one prominent virologist stated, "you can't distinguish between the two origins from just looking at the sequence…you want to know were there people in the virology laboratory in Wuhan who were manipulating viral genetic sequences? It's really a question of history: What happened?"[357] The remainder of this report attempts to learn what one can from other available information.

Biosafety Practices at the WIV 2018-2019

On January 19, 2018, U.S. diplomats cabled concerns about the training of personnel and biosafety conditions after visiting the WIV's newly constructed Zhengdian BSL-4 laboratory complex. According to published excerpts, "during interactions with [U.S.] scientists at the WIV laboratory, they noted the new lab has a serious shortage of appropriately trained technicians and investigators needed to safely operate this high-containment laboratory."[358] The State Department cable further cautioned that the WIV's work with bat coronaviruses potentially posed a risk of a SARS-related pandemic.

The BSL-4 lab in Wuhan was the first of five to seven BSL-4 labs to be constructed in China.[359] It became fully operational in 2018.[360] At that time, during a visit to Wuhan, an NIH official noted that the WIV had no previous experience operating a high containment BSL-4 lab and had had to "learn everything from zero."[361] The WIV struggled to develop enough expertise among its staff and had to "rely on those scientists who have worked in P4 [BSL-4] labs outside China to train the other scientists how to operate."[362]

U.S. researchers were also aware that WIV researchers often conducted coronavirus research in BSL-2 labs.[363] A February 2018 draft of Ecohealth Alliance's DEFUSE proposal made explicit mention of this practice.[364] In the final version of this unfunded proposal, reference to the WIV's ability to work under BSL-2 biocontainment was changed to BSL-3, presumably in response to one U.S. contributing researcher's note on an early draft stating that if the proposal referred to conducting these virological experiments under BSL-2 conditions "U.S. researchers... [would] likely freak out."[365]

Acknowledged Need to Improve the WIV's Safety and Security Practices Prior to the Pandemic

The concerns about biosafety voiced by U.S. government researchers were echoed by their counterparts in China. A March 2019 article by researchers in Beijing (the State Key Laboratory of Pathogens and Biosecurity, the Academy of Military Medical Sciences (AMMS), and the Institute of Pathogen Biology of the China Academy of Sciences) noted the importance of biosafety to national security.[366] The authors cited the specific risks of emerging diseases, bioweapons and bioterrorism, antimicrobial resistance and laboratory accidents. About lab accidents, the authors noted that:

> Laboratory infections not only endanger the health of laboratory staff but may also cause the accidental leakage of organisms. This may cause an epidemic in the area surrounding the laboratory, which may endanger the health and safety of the general population and may even have a serious global impact on public health.... Unexpected disasters can occur in the event of a bio-accident leak, especially from a high-level biosafety laboratory.[367]

That month, on March 1, 2019, the WIV issued a maintenance procurement solicitation for its newly constructed BSL-3/ABSL-3 labs at the Zhengdian campus where the newly BSL-4 lab was located, on the outskirts of Wuhan.[368] The procurement solicitation closed on March 12, 2019. These new labs were built to expand the existing capacity of older BSL-3/ABSL-3 ones at the WIV's Xiaohongshan campus in Wuhan's central Wuchang district. The aging WIV buildings were characterized as ones "where scientists wore coats indoors in winter because of scant heating."[369] The opening of these new WIV Zhengdian BSL-3 labs was expected to come after the opening of the BSL-4 lab, but by the end of 2019.

On March 25, 2019, George Fu Gao, the Director of the Chinese Center for Disease Control (CCDC) published an editorial warning about potential natural, accidental and deliberate biological threats. He specifically identified laboratory risks:

> Man-made biological threats exist in many countries. A potential major risk stems from stocks of concentrated infectious pathogens stored in laboratories and the absence of adequate biosecurity measures. Non-compliance of approved biocontainment and biosafety protocols could result in accidental or deliberate release of pathogens into the environment.... Advances in biomedical technologies, such as genome editing and synthetic biotechnology, have the potential to provide new avenues for biological intervention in human diseases.... However, the proliferation of such technologies means they will also be available to the ambitious, careless, inept, and outright malcontents, who may misuse them in ways that endanger our safety.... CRISPR-related techniques provide revolutionary solutions.... Similarly, genetic modification of pathogens, which may expand host range as well as increase transmission and virulence, may result in new risks for epidemics. For example... synthetic bat-origin SARS-like coronaviruses acquired an increased capability to infect human cells.[370]

On April 3, 2019, the WIV held its annual lab security and safety conference. WIV senior leadership asked workers to embrace the "imperative to manage safety while managing professional work, and the imperative to manage safety while managing production." They were also asked to "launch self-inspections of safety and rectification of hidden dangers."[371] The term "hidden dangers" was not defined and its meaning in this context is not obvious.

Also in April, the WIV filed 13 of a total of 17 patents in 2019 pertinent to biosafety. Many apparently had to do with lessons learned constructing the BSL-4, BSL-3, and ABSL-3 labs. They covered improvements in physical containment (hermetically sealed doors), wastewater treatment, decontamination (autoclaves), and maintenance of negative air pressure in the high-containment labs (exhaust air management). The texts of some of the patents were associated with specific procurement actions (e.g., renovation of the hazardous waste treatment system at the newly constructed Zhengdian Park National Biosafety Laboratory, their BSL-4 lab) for example.[372]

On April 26, 2019, WIV personnel who were members of the China Communist Party (CCP) received training: "national security education" on the importance of protecting state secrets.[373] Later, on May 10th, the WIV's CCP party secretary required all the WIV's professional research personnel, postdoc researchers and graduate students to attend a similar national security training session. More than 170 people attended that second session. All attendees signed pledges to protect classified information pertaining to their WIV research. The incoming class of WIV graduate students received similar training on September 3, 2019.[374]

In mid-2019, U.S. Department of Energy officials warned an NIH official that "the coronavirus research the [United States] was helping to fund at the WIV risked being misappropriated for military purposes."[375] Consistent with the state secrets training previously noted, the U.S. State Department reported that the WIV had worked on classified projects, including animal experiments, with China's military since at least 2017.[376,377]

Further biosafety concerns were echoed in May 2019 by the WIV's Deputy Director of the Office of Safety and Security, Yuan Zhiming. As WIV's safety director, he published concerns about uncertain funding for laboratory construction, operation and maintenance.[378] He cited the risks of neglected maintenance, insufficient operational funds and the lack of specialized managers and engineers to operate BSL-3 labs. He noted that regulatory enforcement pertaining to pathogen waste and laboratory animal management needed to be strengthened. Zhiming specifically warned that uneven implementation of regulations put "biosafety at risk." To address this risk, he urged authorities to "promptly revise the existing regulations, guidelines, norms, and standards of biosafety and biosecurity."[379]

In August 2019, the CCDC's lead biosecurity expert, Guizhen Wu, advocated that the "manipulation of highly pathogenic microorganisms should be performed in high-level biosafety laboratories, namely BSL-3 or BSL-4." She identified several challenges in China's biosafety posture including "the [laboratory biosafety] management system in China.... [A] comprehensive system of legal and regulatory standards is lacking for BSL-2 laboratories in China.... [There are] not enough well-trained and experienced [laboratory biosafety] specialists."[380]

Also in the summer of 2019, WIV leadership held several internal meetings focusing on biosafety including accessing foreign manufactured biosafety equipment ("stranglehold problem"), "understand[ing] and recogniz[ing] the shortcomings and foundational [problems] limiting the institute's development" and "improving biosafety theory and biosafety technological training, and the system for screening and managing hidden safety dangers."[381,382,383] Again, the "hidden dangers" were not defined.

WIV BSL-4 workers posted on their internal website their concerns about high containment safety as early as 2018. WIV lab workers noted the challenge of accessing western biosafety technology to operate the BSL-4. They described the challenge as the "stranglehold problem" limiting their access to key and core technologies.[384] Stranglehold refers to the "direct [deleterious] effects created by cutting off the supply of foreign key and

core technologies" that China "must import because it is unable to produce them domestically in sufficient quality or quantity."[385] Therefore, China's government placed a premium on developing their own biosafety equipment.

On October 26, 2019, at a time when the SARS-CoV-2 outbreak was likely emerging, PLA authors from the Academy of Military Sciences, Institute of Medical Service Technology, noted that "developed countries have formed a relatively perfect technological and industrial chain of key biosafety equipment for high containment laboratories. However, research and development (R&D) of biosafety equipment in China did not start until the late 1980s, lagging far behind the developed countries. Due to the lack of relevant standards and biosafety concepts in China at that time, only a small amount of biosafety equipment was developed, with slow R&D progress."[386] These authors further noted that since the 2003 SARS outbreak, China has made steady progress. They note that a variety of biosafety equipment has been developed (e.g. biosafety HEPA filtration devices, airtight doors, airtight isolation dampers) that are "widely" used in high containment laboratories in China and BSL-3 labs in Sierra Leone and Kazakhstan.[387] Though progress was made on biosafety equipment, they also noted challenges remained in the number of trained personnel operating such equipment:

> Although technical performance of most biosafety equipment developed in China has reached the similar level of the correspond[ing] products made in other developed countries, there are still gaps in product processing technology. Although containment laboratories are built and have been developed rapidly, most laboratories lack personnel trained in equipment operation and maintenance. The operation of facilities or equipment is no assurance of protection unless the operators are trained and are able to operate the equipment properly. The personnel involved must have the necessary understanding, training and skills to complete the operation procedures safely. Similarly, all users must understand the properties of the agents being handled and the implications for occupational safety.[388]

In response to publicized concerns about the WIV's state of biosafety and the nature of its coronavirus research, Zhengli Shi stated in her July 2020 *Science* Magazine interview:

> The coronavirus research in our laboratory [was] conducted in BSL-2 or BSL-3 laboratories.... We performed in vivo experiments in transgenic (human ACE2 expressing) mice and civets in 2018 and 2019 in the Institute's biosafety [BSL-3] laboratory. The viruses we used were bat SARS-[related coronaviruses] close to SARS-CoV-[1]. Operation of this work was undertaken strictly following the regulations on biosafety management of pathogenic microbes in laboratories in China. The results suggested that bat SARS-[related coronaviruses] can directly infect civets and can also infect mice with human ACE2 receptors. Yet it showed low pathogenicity in mice and no pathogenicity in civets. These data are being sorted and will be published soon.... After the COVID-19 outbreak, our country has stipulated that the cultivation and the animal infection experiments of SARS-CoV-2 should be carried out in BSL-3 laboratory or above.[389]

As of August 2024, Shi and the WIV have not published results from these 2018 and 2019 transgenic mice and palm civet studies. The observation that civets infected in these studies showed no overt evidence of illness may have potential significance to the speculation that "used" experimental animals might have been sold to wet markets.

Infectious Chimeric Betacoronavirus Research Conducted by the WIV at BSL-2

As noted by the U.S. Intelligence Community's June 2023 assessment, "China used biosafety practices that increased the risk of exposure to viruses. Academic publications from 2016 and 2017 suggest that WIV researchers did not use adequate biosafety precautions at least some of the time, increasing the risk of a laboratory-associated incident."[390] The laboratory manipulations included construction of reverse genetic systems that rescued SARS-related (WIV1 strain) viruses from cloned DNA and used such systems to construct infectious chimeric viruses based on WIV1 backbones

that carried spike proteins from different coronaviruses previously described by the institute.[391,392,393] This research was performed at the WIV under BSL-2 containment.

At BSL-2 containment, laboratory personnel can be infected by direct contact with cultures and infectious materials from samples (environmental, animal and human) and inhalation of infectious aerosols or droplets generated during their manipulation using lab equipment like centrifuges.[394] There are numerous documented occurrences of lab-acquired infections (LAIs) at this containment level resulting from manipulations including viral isolation, viral culture and centrifuging of viral cultures.[395,396,397]

A 2024 study by researchers in China evaluated the risk of LAIs during experimental sample mishandling incidents in BSL-2 labs. They noted a significant risk for LAIs when pathogens are mishandled in BSL-2 settings outside of a biosafety cabinet.[398] According to their data, 70% of all bioaerosols caused by mishandling incidents are deposited on surfaces such as walls, equipment, and humans.[399]

A 2023 study by two AMMS Institute of Military Cognition and Brain Sciences researchers, who collaborated with AMMS Fifth Institute director General Yusen Zhou in one of the earliest SARS-CoV-2 vaccine patents and animal challenge studies noted that "many 'black swan' incidents occur in the field of biosafety."[400] The authors cited as examples the SARS-CoV-2 pandemic and the monkeypox outbreak. They also noted, "biological weapon threats, and laboratory biosafety concerns including the potential risks associated with not only cytometry instrumentation and samples, but also the people working with them" required "urgent prevention or intervention strategies."[401]

The mention of flow cytometry is particularly noteworthy. Flow cytometry has been used for decades in lab and field research on a variety of diseases like cancer, malaria, tuberculosis and HIV. It is used to develop treatments and therapies for various chronic and emerging infectious diseases.[402]

Benchtop flow cytometers have historically been considered low risk devices commonly used in pathogen research. The low perceived risk has resulted in variability across different facilities in how they are handled during biosafety risk assessments.[403] This "low risk" presumption is supported with little empirical evidence. These devices have been underrepresented in risk assessments and their potential hazards are not well documented.[404] Operating an analytical cytometer involves routinely handling potentially biohazardous fluids, such as those found in its waste tank or the automated plate loader, for example. This risk is magnified when running samples in configurations where the fluidics system is not fully enclosed and appropriate Personal Protective Equipment (PPE) is not employed, such as in BSL-2 settings.

As described by a 2021 NIH sponsored SARS-CoV-2 study, aerosol and/or droplet hazards were detected on all benchtop cytometers predominantly during operation in "failure modes." These "benchtop analytical cytometers present a more complicated set of risks than are commonly appreciated.... If [certain potentially biohazardous components] produce biohazardous material, then the instrument may facilitate pathogen transmission."[405] Why this specific potential risk was cited by these PLA researchers involved in some of the earliest SARS-CoV-2 vaccine work is not known. Whether the device may have contributed to a laboratory-acquired infection (LAI) or why it was included in a review paper about SARS-CoV-2 neurocognitive decline is not known. The reference does echo the points PLA authors made about biosafety risks associated with inadequately trained persons in October 2019.

According to published research, the causes of over 80% of LAIs are never conclusively determined and only 18% of LAIs could be definitively attributed to accidents caused by carelessness or human error.[406,407] Moreover, the recognition and isolation of a new infectious agent, which represented a substantial amount of the WIV's known coronavirus BSL-2 research, could result in an LAI caused by the new isolate that may go unrecognized.[408]

As alluded to by the PLA researchers, who performs this research is another potential contributing risk factor. The profile of the workforce is an important biosafety risk factor in and of itself. Younger workers, workers with less technical training and laboratories operating with

fewer experienced technicians have more accidents than those with older workers, those with more training or laboratories employing a greater percentage of women.[409] In sum, the risk of exposure to infectious agents is a function of safety training, safe work practices, safety equipment and laboratory design.

Infectious agent research, like that conducted at the WIV, results in greater potential exposure to higher concentrations of infectious agents than work in clinical diagnostic laboratories.[410] The common routes of exposure are ingestion, needle-sticks, cuts, animal scratches and bites, and inhalation.[411] Inhalation is the most insidious because aerosols and droplets are often invisible and difficult to detect. They represent the hidden danger of high containment lab infectious disease research. As described by Shi in her 2020 *Science* interview, the WIV conducted SARS-related research in BSL-2 and BSL-3 labs prior to the pandemic, and only after the outbreak were they required to perform SARS-CoV-2 viral cultivation and animal infection experiments in BSL-3 labs or above.[412]

General Secretary Xi's Calls to Address Gaps in China's Biosecurity Laws

In early 2014, Xi Jinping noted the strategic importance of China's first state laboratory BSL-4 high-containment lab. Xi stated that "the construction of the [WIV's] P4 [BSL-4] laboratory [was] of vital importance to Chinese public health."[413] While the Wuhan BSL-4 lab was the first constructed, at least three others have been built, are under construction or are planned (Harbin, Kunming and Guangzhou, respectively). In 2020, there were at least 112 BSL-3 (including animal BSL-3) labs at 62 sites, up from 12 labs at three sites in 2002, and more than 1,000 BSL-2 labs in China.[414] The rapid increase in high-containment labs was government mandated. It reflected lessons learned after the 2002 SARS outbreak as well as the priority the CCP placed in pursuing dominance in global life science research. In 2018, Xi identified biotechnology as one of several "great changes unseen in a century," revolutionary technologies, like artificial intelligence, that could enable China's global leadership.[415]

By January 2019, there was evidence that the highest levels of China's government were concerned about risks associated with biotechnology and other scientific research. China central media reported on an early-January speech by General Secretary Xi Jinping about major risks and the need to "pay special attention to the strategic positioning of state laboratories," "speed up the establishment of an early warning and monitoring system for scientific and technological safety" and "accelerate relevant legislative work in areas such as... gene editing... [and] medical diagnosis."[416] At the time of the speech, the WIV was among the most high profile state laboratory and the only one with an operational BSL-4 lab. On February 25, Xi Jinping called on the National People's Congress (NPC) "to use legislation to ensure high-quality development and accelerate the economy's sustainable and healthy development." A biosecurity bill was among the items Xi identified as legislative priorities.[417]

A biosecurity bill was included in the NPC Standing Committee's 13th Legislative Plan approved in September 2018 but was originally categorized as the lowest priority for consideration.[418] On March 26 and 27, 2019, the NPC met to discuss its legislative agenda for the upcoming year. At that meeting, the biosecurity bill was re-designated a top priority. It was placed on an accelerated course for drafting, review, and passage, with the objective of completing the draft in 2019.[419]

In June 2019, The WIV's Deputy Director for Safety and Security, Yuan Zhiming, and authors from Wuhan's Chinese Academy of Sciences and Wuhan's University of Science and Technology submitted an essay for publication in the *Journal of Biosafety and Biosecurity*. The subject of their article was "our nation still lacks a law solely dedicated to biosafety regulation, and the supervisory system is incomplete." They documented the current challenges, including "no laws or regulations dedicated to dual-purpose biotechnologies.... Few biosafety legislations are issued by the National People's Congress or its standing committee... [and] a national or industry standard dedicated to bio-risk assessment is lacking in China and there is no professional agency in place to guide the establishment and operation of a bio-risk assessment system." They advocated criminalizing "biotechnology abuse" and creating a uniform risk-assessment system and mechanisms to identify risks and provide early warning.[420]

On July 10, 2019, the third highest ranking member of the Chinese Communist Party (CCP) Politburo Standing Committee, who was also the Chairman of the National People's Congress (NPC) Standing Committee, Li Zhanshu, chaired a symposium to discuss drafting the biosecurity law. He framed the task as a mission to "deeply carry out the instructions and requirements of General Secretary Xi Jinping, insist on the necessity and urgency of the biosecurity law based on a full awareness of the holistic view of national security, use legislation to establish a basic system and principles for the realm of biosecurity, give prominence to risk prevention, [and] use the law as a weapon to defend the biosecurity of the state and guarantee healthy lives for the people."[421] This symposium was not apparently associated with any known domestic infectious disease outbreak, although it did occur seven days before the WHO declared a Public Health Emergency of International Concern (PHEIC) for the Ebolavirus outbreak in the Democratic Republic of Congo.[422]

Key WIV Capabilities Offline, Biosecurity Law Advancing, and Preparations Made for Possible Novel Coronavirus Outbreaks in September 2019

On September 12, 2019, between the hours of 2:00 and 3:00 AM local time, a week before the draft law was passed out of the National People's Congress committee, the WIV blocked public access to its online data repository of viral sequences, the Wildlife-Borne Viral Pathogen Database.[423] The database reportedly contained more than 2,000 entries consisting of sample and pathogen data, including full and partial genomic sequences, collected from bats and mice.[424] This database had previously been accessible to researchers worldwide, with the exception of a password protected section, which held unpublished sequence data accessible only to WIV personnel.

On September 16, 2019, three days before the NPC committee's review of the draft biosecurity law, the WIV issued a notice on a PRC government procurement website seeking consultation for a "central air conditioning renovation project" at the newly constructed WIV Zhengdian National Biosafety Laboratory campus.[425] The procurement contract award was announced on September 30, 2019. Work for this approximately $550k (USD) renovation project was estimated to take 210 days.[426] Air handling and conditioning play a "critical role" in the control of infectious hazards in a biocontainment lab.[427] A failure or malfunction of the HVAC system may subject personnel to exposure to infectious aerosol hazards. As described in U.S. technical manuals, "air supply and air exhaust systems are essential to maintain proper air flows and [negative] pressures." For example, maintaining negative pressure in animal rooms, meaning less pressure than in other parts of the laboratory and less than in the surrounding corridors, is essential to prevent escape of possible infectious aerosols.[428] The renovations noted in the procurement likely made the WIV BSL-4 lab inoperable until they were completed.

On September 18, 2019, a day before the biosecurity law was passed out of the NPC, Wuhan Tianhe International Airport conducted two "emergency response drill activities" in advance of the Military World Games to be held in Wuhan in October.[429] One exercise was a response to a radiological threat, a radiation source in luggage. The other drilled a response to a novel coronavirus outbreak at the airport. State-run media described the exercise: "The drill simulated in real combat style... the whole process of handling the discovery of one case of a novel coronavirus infection at the airport customs lane.... [W]e drilled an epidemiological investigation, medical examination, real-time set up of a quarantine area, isolation and testing, the transfer of cases [to hospitals], hygiene management, and other stages [in the process]."[430]

The draft biosecurity bill reviewed on September 19, was read by the NPC Standing Committee on October 21, 2019. As described by NPC leadership, preventing and prohibiting the use of biological agents and biotechnology to harm state security was the legislation's "main point."[431] The chairman of the NPC Environmental Protection and Resources Conservation Committee explained the purpose of the legislation and summarized its key points. The leakage of biological agents from laboratories was a threat to state security that warranted the passage of the law.[432] He described the "biosecurity situation in our country [as] grim. Bio-warfare and traditional biological threats from major emerging and sudden outbreaks

of infectious diseases represented by SARS, Ebola, and African Swine Fever, as well as animal and plant epidemics, are occurring as frequently as ever before. Non-traditional biological threats, [such as] bioterrorist attacks, the erroneous use and deliberate misuse of biotechnology, and laboratories that leak biological agents, are clear and obvious."[433]

The law established a national biosecurity monitoring and early warning system—one of General Secretary Xi's objectives. It mandated safety review. High-containment laboratories engaged in research on highly pathogenic or suspected highly pathogenic microorganism experiments were required to seek approval of such studies by provincial or higher (health or agriculture) authorities. It also mandated oversight by public security organizations. Laboratories were required to abide by "supervision and guidance of public security organs and other departments on laboratory safety and security and strictly prevent the leakage, loss, theft and robbery of highly pathogenic microorganisms."[434] One curious provision included the explicit prohibition of selling "used laboratory animals into the market."[435] In January 2020, a noted researcher, Li Ning, was sentenced to jail for 12 years for selling a variety of used experimental animals.[436] How this incident factored into the inclusion of this prohibition in the legislation is not known. The Standing Committee passed the bill, but it did not officially become law until a year later on October 17, 2020.

Development of a COVID-19 Vaccine Likely Beginning Before the Announced Start of the Pandemic

No later than November 2019 and likely earlier, a senior PLA researcher began developing one of two early SARS-CoV-2 vaccines. Brigadier General Yusen Zhou from the Beijing Academy of Military Medical Sciences' (AMMS) Institute of Microbiology and Epidemiology collaborated with the WIV prior to the pandemic.[437] General Zhou was an accomplished coronavirus vaccinologist, who had published extensively on vaccines related to SARS-CoV-1 and MERS. General Zhou was likely conducting coronavirus vaccine-related research at the WIV no later than the Fall of 2019. He coauthored a paper with WIV researcher Shi Zhengli in November 2019 on adverse effects associated with SARS-related vaccines and antibody treatments.[438]

On February 24, 2020, General Zhou submitted, with colleagues from the Institutes of Microbiology and Epidemiology and two researchers from the AMMS Institute of Military Cognition and Brain Sciences, one of the first patent applications for a COVID-19 vaccine.[439] The candidate vaccine was a fusion of the SARS-CoV-2 spike protein RBD to an antibody segment (IgG Fc). As noted earlier, the SARS-CoV-2 RBD contains the part of the virus that touches and binds to the human cell to infect it. The RBD, as noted, is identical to that of the Malayan pangolin strain found in Guangdong. Notably, the sequence used by General Zhou and his colleagues also included the RGD protein sequence that binds with integrins and potentially other cell-surface receptors that may increase SARS-CoV-2's human cell binding affinity and pathological effects.[440,441] In theory, immunizing with this protein could afford protection from SARS-CoV-2 infection by creating antibodies directed against parts of the virus that contact and potentially infect human cells. This would include the ACE2 receptor, the RGD integrin-binding sequence and other potential integrin binding sites.

The work described in the patent application required access to SARS-CoV-2's spike protein sequence and access to live SARS-CoV-2 virus. Work described in the application was based on a published two-step approach used to develop his MERS RBD vaccine in 2017 (Figure 7).[442] That initial MERS effort took approximately four months to produce a similar RBD-Fc vaccine construct from a genetic sequence, as General Zhou described in the 2020 SARS-CoV-2 vaccine patent application.[443]

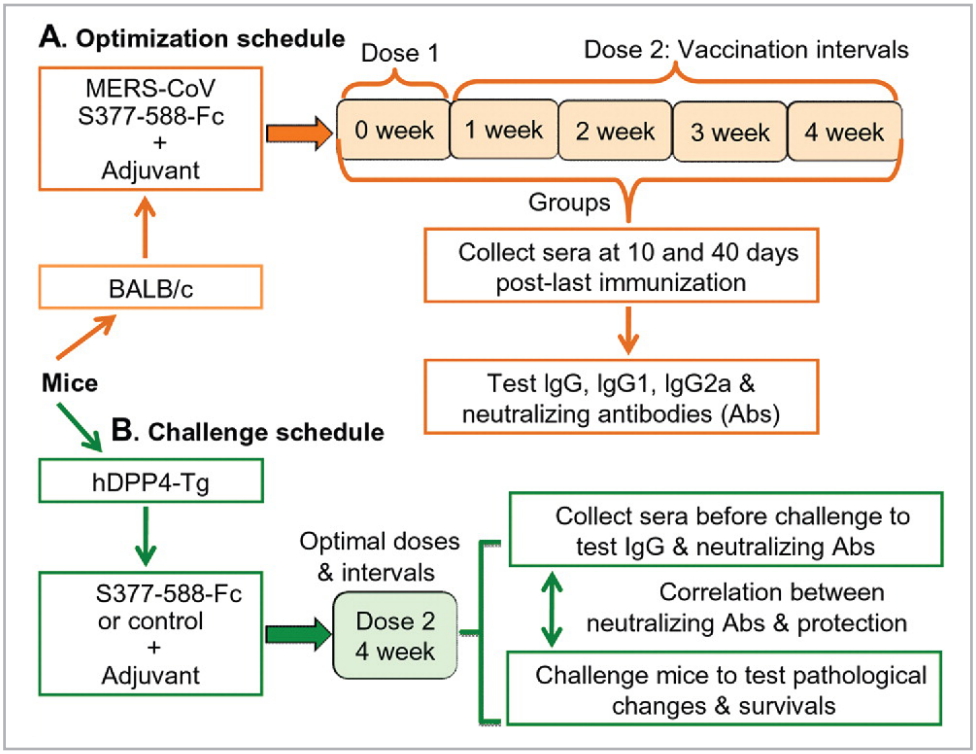


***Figure 7*. Vaccination optimization and challenge schedules for the RBD-Fc MERS vaccine challenge studies.** (A) Optimization schedule BALB/c mice (5 groups) were immunized with S377-588-Fc and either boosted once at 1-,2-,3-, or 4-week intervals, respectively. Sera were collected from the immunized mice at 10 and 40 days after the first immunization and tested for IgG, IgG1 and Ig2a, as well as neutralizing antibodies. (B) Challenge schedule. The hDDP4-Tg mice were first immunized with RBD-Fc candidate (S377-588-Fc-protein), or PBS control, at the optimal doses and interval. Next sera were collected before challenge for testing neutralizing antibodies and the challenged mice were evaluated for pathological effects. Source: Wang et al. (2017).

In May 2020, General Zhou and his AMMS coworkers from the Institutes of Microbiology and Epidemiology and Military Cognition and Brain Sciences submitted for publication part of this vaccine work.[444] They described how they evolved, by serial passage through wild-type (BALB/c non-human ACE2) mice, a mouse-adapted SARS-CoV-2 strain (MASCp6). This strain was infectious and mildly pathogenic. Its spike protein contained the N501Y substitution. This mutation lies in the receptor binding motif (RBM) of the spike protein RBD. It increased the affinity of the RBD for both human and mouse ACE2. This mutation would later emerge during the pandemic, when it was first observed in the Omicron strains and later in the B.1.1.710 variant.[445,446,447]

General Zhou initially tested his vaccine construct by challenging vaccinated wild-type mice using this mouse adapted MASCp6 strain to determine the appropriate dose and immunization schedule (Figure 7).[448,449,450] He then challenged vaccinated humanized ACE2 mice and controls with human SARS-CoV-2 virus.[451] Based on his previous MERS vaccine work and in order to be able to submit a patent in February 2020, General Zhou would have had to begin his work on a COVID-19 vaccine no later than early November of 2019 but likely earlier.[452,453] The efficacy of this vaccine was demonstrated in preventing the respiratory condition and associated pathology observed in the control mice who did not receive vaccination.

When his BALB/c mouse adapted study was published in July 2020, General Zhou was listed as "deceased." In the later published humanized mice and NHP vaccine challenge study using Zhou's vaccine, the deceased General was memorialized as contributing to the project and article design.[454] He was also memorialized in a later study evaluating the mechanism of MERS brain infection in specialized humanized DPP4 mice.[455] This MERS study conspicuously did not include researchers from the Institute of Military Cognition and Brain Sciences. One of the enigmas of General Zhou's efforts was the email from one of his collaborators, Shibo Jiang, who noted that when General Zhou died his research disappeared.[456]

Neither the PLA nor the Government of China seems to have formally acknowledged General Yusen Zhou's death. Such acknowledgement would typically be protocol for a senior PLA officer with a distinguished research career. Further, there seems to be no mention of his vaccine in any COVID-19 vaccine reviews published by researchers in China, including one by the PLA.[457,458,459,460,461]

General Zhou's studies had been reviewed by the AMMS's Animal Experiment Committee of Laboratory Animal Center. The NHPs came from that AMMS laboratory animal center in Beijing, and the humanized ACE2 mice from the Beijing National Institutes for Food and Drug Control. It seems possible that these experiments were performed in BSL-3 facilities at the Beijing AMMS Institute of Microbiology and Epidemiology, as later SARS-CoV-2 vaccine studies with mice and hamsters were also conducted there.[462]

However, and perhaps significantly, General Zhou's AMMS team did not identify where they conducted these animal vaccine challenge studies (with humanized mice and NHPs) as other vaccine study groups have.[463,464,465] The requirement for animal BSL-3 facilities and BSL-3 labs that could test primates would limit the locations where such work could be safely performed. Whether any of these challenge studies were performed at the WIV's Wuchang campus BSL-3 labs or at the Wuhan University Institute of Animal Models ABSL-3 primate facility is a matter of conjecture. What is not conjecture is the risk posed by conducting such animal vaccine challenge studies. As described by PLA engineers who designed and built China's high containment labs and biosafety equipment, infected animal research, such as vaccine challenge studies, will fill biosafety facilities with high-dose hazardous aerosols of highly pathogenic biological agents.[466]

Limited Opportunities for Vaccine Challenge Experiments in WIV BSL-3 or BSL-4 Facilities

During the fall of 2019, in Wuhan, evidence suggests that the new high-containment labs were unavailable.[467] At the WIV's new Zhengdian National Biosafety Laboratory campus, the 210-day BSL-4 HVAC renovation began in early to mid-October 2019 and the BSL-3/ABSL-3 labs were undergoing final construction. If any of the published AMMS animal vaccine challenge studies were

performed in Wuhan, the mouse studies would likely be conducted in the existing BSL-3/ABSL-3 labs at the original Xiaohongshan campus. The NHP vaccine challenge studies that the AMMS conducted and published would have likely been conducted at the Wuhan University Institute of Animal Models, also in Wuchang District, where previous NHP SARS vaccine challenge studies were performed (Figure 8).[468]

The anticipated use of WIV's Wuchang district BSL-3/ABSL-3 labs may have been foreshadowed by an August 14, 2020 WIV procurement notice for environmental air (vaporized hydrogen peroxide) disinfection and scalable automated sample storage management systems for the older Wuchang campus. The budget for the project was approximately $1.3 million USD.[469] A gaseous vaporized hydrogen peroxide system is an effective, less corrosive means to sterilize a laboratory conducting infectious agent research.[470] The scalable automated sample storage management system referenced is a key component of research sample integrity, which contributes to improved experiment reproducibility. This system is used when large numbers of biospecimens are handled. Automated handling and storage are preferred methods to maintain and improve sample viability and ensure experimental validity.[471]

***Figure 8*. Map of Wuhan showing the relative proximity of the Wuhan Institute of Virology, Xiaohongshan campus, and the Wuhan University of Medical College Animal Experiment Center and Institute of Animal Models** located in the Wuchang District of Wuhan. Distance measured on Google Maps is approximately one mile. Source: Google. (n.d).[472]

Rapid Production and Clinical Trials of a Vaccine Candidate from a Second PLA Research Group

One of China's other early 2020 vaccine candidates seemed noteworthy. This one was published by researchers in Beijing and Harbin. The development was led by PLA researchers at the Beijing AMMS Institute of Biotechnology and tested by BSL-4 researchers at the State Key Laboratory of Veterinary Biotechnology in Harbin. This vaccine contained the entire spike protein expressed from a human adenovirus (type 5 Ad5-nCoV). This is the same approach that these researchers had used previously to make an Ebola vaccine. It was also subject of a February 2020 preprint study that demonstrated the suitability of this adenovirus platform for SARS-1.[473] The group published animal challenge and human clinical studies showing that the SARS-CoV-2 vaccine was protective when administered by intramuscular injection or by nasal mucosal administration.[474,475,476,477]

The senior author of the paper describing this second vaccine candidate, Wei Chen, is also a PLA officer, with the rank of Major General, who led the AMMS Institute of Biotechnology. The vaccine was produced in collaboration with General Chen's AMMS institute and the state-owned biopharmaceutical company CanSinoBIO in Tianjin, China.[478] This team performed vaccine challenge experiments with humanized mice, ferrets and NHP at the Harbin veterinary BSL-4 research laboratory in northern China.[479] Photos of vials of the CanSinoBIO adenovirus-based vaccine showed that they were filled on February 26, 2020.[490] Human clinical trials began on March 17, 2020.[481] General Wei Chan, the senior PLA officer, submitted a patent application for this vaccine the next day on March 18, 2020.[482]

Isolation of SARS-CoV-2 was announced on January 8, 2020. The sequence was released on January 11th by an accomplished virologist at the Institute of Pathogen Biology of the Chinese Academy of Medical Sciences in Beijing, China.[483] Given that start date, progress from sequence to filled vials of manufactured recombinant vaccine on February 26, 2020, was astonishingly rapid. However, recent Congressional investigations have established that a complete SARS-CoV-2 sequence was posted on NIH's GenBank on December 28, 2019, which extends the possible timeline from known sequence to manufactured recombinant vaccine by another two weeks.[484]

Even such timing still seems extraordinary. General Chen's team's vaccine development would have been faster than Astra Zeneca's. Astra Zeneca developed a similar adenovirus vaccine to General Chen's that took 103 days, which was the fastest recorded time for a COVID-19 vaccine to begin Phase 1 clinical trials. If the Chen-CanSinoBIO team began vaccine development on December 28, 2019, this group would have beaten the time Astra Zeneca took by 24 days. General Chen's time is the fastest for any COVID-19 vaccine including those developed in Operation Warp Speed.[485] Unlike her AMMS colleague General Yusen Zhou, however, General Chen's efforts appear to have started after his. Moreover, there is no evidence that her vaccine research efforts were conducted in Wuhan, involved the work of cognitive scientists, occurred where the outbreak started or was associated with the timing of the initial COVID-19 outbreak.

Events Consistent with a Potential Safety Incident at the WIV in Fall 2019

Coincident with the influenza-negative influenza-like-illness (ILI) outbreak in Wuhan noted by the WHO SAGO during the week of November 11 to 17, 2019, U.S. Government intelligence, internal WIV reports and additional media articles correspond with the likely emergence of SARS-CoV-2 in that time period. According to a U.S. State Department fact sheet, "the U.S. government has reason to believe that several researchers inside the WIV became sick in autumn 2019, before the first identified case of the outbreak, with symptoms consistent with both COVID-19 and common seasonal illnesses."[486] Further details about this information were later provided by several media outlets including *The Wall Street Journal*, *Public* and *The Washington Post*. As reported, three WIV researchers, including Zhengli Shi's deputy, became ill with symptoms that were consistent with COVID-19, such as loss of smell and ground glass opacities seen on chest x-ray. At least one of these researchers sought hospital care in November 2019.[487,488]

An internal WIV internet post that first appeared on August 30, 2019, was part of a Chinese Academy of the Sciences (CAS) story that featured WIV researchers who had to overcome challenges establishing their BSL-4 laboratory.[489] A reposted November 12, 2019 version that appeared on the WIV internal website included additional details not found in the August post. It first described risks of potential lab leaks. The subsequent report noted that the viruses the WIV worked on "come without a shadow and leave without a trace." The post also described the WIV BSL-4 lab's construction noting that it was airtight with laser welded stainless steel wall panels.[490,491] It also described the need "to operate very cautiously to avoid operational errors that give rise to dangers" and the possibility of past biosafety incidents involving "high pathogen microorganisms." The November 2019 post also indicated that the BSL-4's CCP members responded, "every time this has happened."

The WIV's Deputy Director of the Office of Safety and

Security, Yuan Zhiming, publicly "vociferously denied that the WIV had any part in the coronavirus pandemic's origin."[492] The same article noted that "the new P4 [Zhengdian National Safety Laboratory BSL-4] lab was not being used for researching coronaviruses, however, which are classified at lower security [biosafety: e.g., BSL-2, BSL-3] levels." Since the new Zhengdian BSL-3/ABSL-3 labs had not been commissioned by the fall of 2019, the likelihood is that any BSL-3 coronavirus research would have been conducted at the original WIV Xiaohongshan campus in the Wuchang district of Wuhan.

On November 15, 2019, a Wuhan daily newspaper and official local publication of the CCP Propaganda Department of the Hubei Provincial Committee, and the Information Office of the Hubei Provincial People's Government, published an article that appears deceptive in its content. It was titled, "explore the Institute of Model Animals of Wuhan University, which used to be one of the battlefields against SARS." It described the institute's historical SARS-related vaccine research. It also stated that the animal BSL-3 laboratory had undergone renovations in 2015 and was "currently" awaiting "final process of re-approval."[493] This media article contradicts a 2018 *Virologica Sinica* journal study describing the institute's SARS-related vaccine challenge experiment in Rhesus monkeys in 2017.[494] Further deception was likely contained in this story as it also noted that *Nature*, an "international authoritative journal," had published a "feature article" introducing the institute. In fact, *Nature* did publish an Advertisement Feature on November 7, 2019, paid for by the institute's Partnership & Custom Media Unit of Nature Research.[495] To place this advertisement in *Nature*, the order would have had to be submitted no later than October 30, 2019.[496] The advertisement described the research performed at the institute. It did not, however, mention its recent or historical infectious disease SARS-CoV-1 vaccine studies.

In March 2020, the South *China Morning Post* noted that the first CCDC confirmed case of COVID-19 was recorded on November 17, 2019. As described, the first person infected with SARS-CoV-2 may have been a 55-year-old Hubei province resident (see reference 210).

Later during the pandemic on May 6, 2020, a local Wuhan government internet notice post indicated Li Hongliang, who had been both Wuhan University's Director of the Institute of Animal Models and Director of the ABSL-3 laboratory since 2015, had been removed from these positions. Li also resigned rather than being removed from his position of Dean of the Wuhan College of Basic Medicine, held since 2017. The reasons for his dismissal and resignation were not noted in the May post.[497]

Safety- and Security-Related Visits to the WIV by High-Level Chinese Officials

At the WIV, two notable events occurred on November 19, 2019. The first was the visit by Ji Changzheng, the Director of the CAS Office of Technology Safety and Security. He had been dispatched from Beijing to personally oversee and administer a one-day senior level safety training seminar and two-and-a-half-day larger safety and security training symposium.[498] The seminars occurred seven months after the WIV's annual safety conference held in April. At the first session, he addressed senior personnel from the CAS Wuhan Branch as well as WIV department heads, and other "responsible personnel" from all WIV departments.[499] According to a WIV internal report, the Beijing visitor opened the training by conveying "important oral and written instructions" directly from Xi Jinping regarding a "complex and grave situation." His mention of "important written instructions" is a reference to an internal CCP system of written directives called *pishi*. *Pishi* are issued when a senior CCP leader receives a printed report on a specific issue, important development, or worrisome trend. The senior official then handwrites instructions on the report that is conveyed to lower-level officials who are responsible for the report's subject.[500,501] From the context, the report that General Secretary Xi Jinping received likely dealt with WIV "safety and security work."

The CAS Director's remarks were followed by the WIV's Deputy Director for safety and security, Yuan Zhiming, who "summarized several general problems that were found over the course of the last year during safety and security investigations, and pointed to the severe consequences that could result from hidden safety dangers and stressed that the rectification of hidden safety risks must be thorough, and management standards must be maintained."[502] The nature of the

"hidden dangers" were not specified.

Starting on November 20, 2019, the day after the senior leadership session, the Director of CAS Safety and Security led a separate two-and-a-half day "Training on Biosecurity Laboratory Management and Techniques for Conducting Experiments." More than 150 participants and personnel from WIV BSL-1, BSL-2 and BSL-3 labs and other Wuhan research institutes attended.[503] According to the WIV website, "the [training] course included the national biosecurity law [that had not yet been implemented], regulations, and standards, the management system for high-containment biosecurity laboratories, methods for assessing biosafety risks in laboratories, the storage of bacterial and viral strains, and the management of waste from animal experiments and laboratories."[504]

On December 5, 2019, four days after the first reported symptomatic COVID-19 case, the WIV hosted another high-level visitor. This was the Vice Governor of Hubei Province, Xiao Juhua, who visited one of the WIV campuses. The object of this visit is not clear. According to the Hubei Daily, Vice Governor Juhua "conducted a site investigation of the course of [the WIV's] construction, its current research, direction of development, etc. and immediately called a meeting [of lab management] to carry out support measures on site."[505] The nature of the issue requiring her visit or possible support measures required were not described. Her visit does suggest a high-level interest in the activities at the WIV, though it is not specific to the nature of those activities or which campus she visited.

On that same day, in Washington D.C., an emigre Chinese dissident, Wei Jingsheng, who still had extensive ties in China, shared with a U.S. colleague the news of a new "dangerous virus spreading in China."[506] According to the dissident, many people were becoming sick, and it seemed to be centered in Wuhan. This was five weeks before China publicly acknowledged the outbreak. On January 2, 2020, this dissident met again with his U.S. colleague to cast doubt on the reports from China implicating the animal market. He also shared concerns about the Wuhan laboratories and the role of the PLA conducting military-related research. He stated that "the virus is from the laboratory either through incompetence, accident, negligence, corruption or intention. The wet market theory is only likely, if the avaricious lab technicians sold the used and infected animals to the wet market."[507]

Contemporaneous Work Orders and Patent Applications Suggesting Multiple Concerns About Biosafety Containment Failures at the WIV

The other significant event occurring on November 19, 2019, was the issuance of a sole source, short suspense procurement for an air incinerator at the original WIV Wuchang (Xiaohongshan) campus.[508] The air incinerator was needed to sterilize exhaust gases from a biosafety autoclave. The procurement described the existing autoclave system as having a serial (two) high efficiency particulate air (HEPA) filter assembly. The incinerator would be added to the autoclave exhaust pipe after the HEPA filter assembly to incinerate all the media discharged.[509] The desire to obtain this device suggests that a WIV biosafety autoclave in central Wuhan may not have been completely sterilizing infectious contents or that the autoclave's HEPA filters were not filtering infectious exhaust gases.

A possible reason for this procurement is suggested by an April 22, 2019, patent application by inventors at the WIV. This application described methods researchers had devised to overcome problems with biosafety autoclaves used to sterilize waste generated by infectious pathogen studies.[510] The patent application cited three problems: 1) not being able to achieve required sterilization temperatures, 2) potential leaks around the autoclave doors, and 3) excessive condensation of and moisture from autoclaved infectious materials. To address these, the patent described inventive technical changes that allowed a different procedure to operate an autoclave. The new procedure involved intermittently opening the autoclave exhaust valve as the steam pressure and temperature were rising, then intermittently opening the exhaust once the operating pressure and temperature had been reached.

According to expert analyses, this autoclave practice is at variance with typical procedures. The process described could prevent achieving the temperature and pressure parameters required for effective sterilization. It seems

likely that intermittent exhaust of high-pressure steam through the serial HEPA filters downstream of the autoclave exhaust valve could degrade the filters and reduce their ability to filter out infectious particles.[511] If the HEPA filtering system was compromised, or if it was even a worry, such worry could account for the issuance of a short suspense procurement of the air incinerator, installed after the HEPA filters to sterilize the exhaust from the autoclave at the WIV Xiaohongshan campus.

On December 11, 2019, WIV researchers filed a second interesting patent application. This application indicates that a WIV biocontainment transfer cabinet may have sustained an initially unrecognized HEPA filter failure. The patent application was for a sensor to detect failure of HEPA filtration. Transfer cabinets are used to move infected lab animals to or from a BSL-3/BSL-4 laboratory and a holding ABSL-3/ABSL-4 facility, and to transfer them from animal holding rooms to a specific procedure room.[512] Infected animals create a variety of potentially hazardous infectious aerosols from urine, feces, fur and by respiration.[513] Transportation of an infected experimental animal requires ensuring sufficient air exchange to meet the animal's physiological needs while preventing the inadvertent release, including escape, of the animal or the infectious agent.[514] Biocontainment transfer cabinets pump HEPA filtered air in for the animals and pump twice HEPA filtered air out of the cabinets. As for autoclave exhaust, ensuring the exhaust from the biocontainment transfer cabinet is effectively HEPA filtered and sterile is a critical biosafety feature.

In its description of the existing inadequacies that the inventions described in the patent corrected, the inventors asserted "when an accident occurs in the transportation process, an effective monitoring device is not available for judging whether the equipment is [normally operating] or not."[515] This patent application described specific problems with a HEPA filter connection that resulted in "multi-stage" risks. To address this shortcoming, the patent described developing a sensor to detect when HEPA filters had failed or were not operating correctly. To also address the problem with a faulty "multi-stage" HEPA filter connection that resulted in the need for a sensor, the patent application also described that the HEPA filter holder should be "preferably made

of 7075 aircraft aluminum alloy which is corrosion resistant."[516]

From this patent application, it seems likely that previous HEPA filter holders in the biocontainment transport cabinets were made of corrosion-susceptible metal. China made extensive use of stainless steel in the design and construction of high-containment laboratories and equipment for cell-level and small- and medium-sized animal infection studies.[517] Stainless steel corrosion is a well-documented challenge in the food and pharmaceutical industries and biosafety laboratories.[518,519] The liquid disinfectant used in the WIV's high-containment labs was subject of a published study in 2018.[520] As described by the U.S. disinfectant manufacturer, the WIV used a more concentrated solution, more than double than recommended: "The higher… concentration, the more corrosive the solution will be."[521]

A third patent application from the WIV, filed November 13, 2020, by Yuan Zhiming, provides support for the idea the WIV was addressing potential failures in biocontainment related to stainless steel corrosion. This application described improvements to the liquid disinfectant used in their high-containment laboratories. The improved formulation "reduces the corrosion effect… on metal, particularly stainless steel." The patent echoed the manufacturer's warning that: "Long-term use [of the previous disinfectant] will lead to corrosion of metal components such as stainless steel, thereby reducing the protection of… facilities and equipment… shorten its service life and cause economic losses, but also lead to the escape of highly pathogenic microorganisms into the external environment of the laboratory, resulting in loss of life and property and serious social problems."[522]

The stainless-steel design and construction of China's high containment labs and supporting biosafety equipment put them at particularly high risk for corrosion using liquid disinfectants. In January 2019, engineers from the PLA's Academies of Military Science (AMS) and Military Medical Sciences (AMMS) and China's National Bio-Protection Engineering Center published two articles describing the design and construction of their BSL-4 lab and biosafety equipment.[523,524] As previously noted, China's biosafety programs lagged those of Western countries. Much of China's biosafety equipment was dependent on imports from foreign Western suppliers. Political demands for self-sufficiency prompted indigenous production of biosafety equipment that likely was slow to meet Western standards.[525,526]

Chinese researchers reported that they "independently designed and built a domestic high-level pathogenic microorganism model [BSL-4] laboratory" with supporting protective equipment for the first time in 2019.[527]

PART II
CHINESE MILITARY-CIVIL FUSION AND COVID-19'S NEUROLOGICAL EFFECTS:

Why would the PLA be working on a SARS-CoV-2 vaccine before the pandemic?

General Yusen Zhou's SARS-CoV-2 vaccine research was a collaboration between his Institute of Microbiology and Epidemiology of the Academy of Military Medical Sciences (AMMS) and other AMMS institutes such as the Institute of Military Brain and Cognition Sciences, Peking Union Medical College and Fudan University and Chinese Academies of Science. Collaborations are common practice in vaccine development. For example, General Zhou's previously published SARS and Middle East Respiratory Syndrome (MERS) vaccine research involved collaborations with outside institutions. The anomaly is that his previous coronavirus work did not involve researchers from the Institute of Military Cognition and Brain Sciences or researchers from those scientific disciplines.[528,529,530,531,532,533,534,535,536]

Scientists from the Institute of Military Cognition and Brain Sciences were named in the February 2020 patent of General Zhou's SARS-CoV-2 vaccine, and vaccine challenge studies using wild-type and humanized mice and NHPs. Their participation raises questions about their role and the objectives of these experiments. Their involvement suggests there was some neurological component to the patent and earliest experiments involving the development of a SARS-CoV-2 vaccine.* Neither the patent nor the studies these scientists contributed included findings that detailed the neurological effects of SARS CoV-2 or the protection afforded by the vaccine.

Part II attempts to explain why the People's Liberation Army (PLA), the armed wing of the ruling Chinese Communist Party (CCP), would be engaging in the early-stage development of a SARS-CoV-2 vaccine before the pandemic and why that research collaboration would involve scientists from an institute devoted to cognition and brain sciences. Congressional studies and media reports alluded to a possible explanation: "SARS-CoV-2 may have been tied to China's biological weapons research program and spilled over to the human population during a lab-related incident at the Wuhan Institute of Virology (WIV)."[537]

To evaluate whether "there are indications that SARS-CoV-2 may have been tied to China's biological weapons research program," Part II examines three questions.[538] First, whether China has an offensive biological weapons (BW) program beyond the defensive one it publicly admits. Second, whether the researchers and institutes identified in Part I as involved in pre-pandemic SARS-CoV-2 vaccine development work may have connections to China's BW program. Third, whether the coronavirus research trajectory of those scientists indicates involvement in a biological weapons research program. The evidence that answers these questions cannot be determinative—nor entirely probative.

*A recent study by the Tulane Brain Institute and University of North Carolina researchers adapted the SARS-CoV-2 virus to wild-type (BALB/c) mice to evaluate the virus' neurocognitive impact. They intranasally infected juvenile (10-week) and aged (1- year old) BALB/c mice. The resultant infection simulated the clinical symptoms of respiratory distress associated with SARS-CoV-2 infection. The mice were euthanized 60 days post-infection and the examination of their brains showing the long-term effects of the infection on brain pathology and neuroinflammation. This study provides relevant insights into the role neuroscientists likely played in General Zhou's patent and vaccine studies even though the published studies themselves were silent on the neurological effects or protection of the vaccine.

Military-Civil Fusion and AMMS's Role in "Biology-enabled Warfare."

The People's Republic of China's (PRC's) Military-Civilian Fusion (MCF) initiative was first introduced in 2007 by former General Secretary Hu Jintao and endorsed by his successor Xi Jinping in 2014. MCF is the PRC's priority effort to build the country into an economic, technological, and military superpower by fusing its military and civilian industrial, science and technology resources. Emerging technologies offer China "historic" opportunities to achieve strategic advantage over the United States. It became part of Beijing's official military strategy in 2015.[539] A recent U.S. Department of State report on biotechnology and China's MCF strategy noted, "the PRC's national biotechnology strategies blur the lines between public and private sector (creating competitive advantages for favored PRCbacked companies), programs, leveraging joint ventures and commercial power to support military objectives and enhance the capabilities of the PLA."[540]

PRC leaders believe emerging technologies offer China "historic" opportunities to achieve strategic advantage over the U.S. Beginning in 2005, published PLA medical writings described the theory of application of biotechnology in warfare to "create weapons more powerful and civilized."[541] The theory was first published in U.S. military medical journals by Ji-Wei Guo, a PLA physician at the Third Military Medical University. It states that "with the participation of modern military biotechnology, the military attack will obtain stronger directivity and deterrence, less casualt[ies], and lighter damage of the civilization, which will be a merciful conquest that can increase the benefit of war."[542,543]

This concept was repeated and refined in the intervening years so that by 2010, Guo, then a colonel and later a brigadier general, published *War for Biological Dominance*, a book emphasizing the role of biology in any future war.[544] PLA AMMS researchers highlighted advances in science and technology that could change the character of conflict, raising the concept of "biology-enabled" warfare.[545] This concept will be translated into the PLA's intent to achieve advantages by capitalizing on the revolution in military affairs in human performance using brain and biological sciences.

In 2015, then-president of the AMMS Major General He Fuchu claimed that biotechnology would achieve "strategic commanding heights" of national defense, from biomaterials to "brain control" weapons.[546] Since then, Major General He has become the vice president of the entire Academy of Military Sciences (AMS), which leads China's military science enterprise including the AMMS.[547] Since 2016, the Central Military Commission (CMC) has funded several projects that included military brain science, human performance enhancement, and "new concept" biotechnology.[548]

These concepts are incorporated into China's Science of Military Strategy (SOMS) which is considered "the most authoritative explanation of China's military strategy."[549] Akin to the U.S. National Military Strategy, the SOMS serves as a "foundational document and teaching tool" and represents the fusion of Chinese military thought by the AMS and National Defense University (NDU).[550] These two institutes are influential in advising CMC and educating general and senior military officers.[551] Both the 2017 and 2020 editions of SOMS highlight the importance of biotechnology, artificial intelligence and human cognitive enhancement as innovations that will impact future wars and require China to incorporate these advances in their military capabilities. Specifically, SOMS describes biotechnology as:

> (1) A new territory for the expansion of national security
>
> The biological field has become a brand-new territory for the expansion of national security. For example, the use of new biological weapons, bioterrorism, large-scale epidemic infections, specific ethnic genetic attacks, and purposeful genetic modification of the ecological environment, food and industrial products...can not only bring biological damage to specific targets and people, but also bring large-scale spreading effects and deterrent effects....
>
> (2) The core driver of the evolution of war patterns
>
> The great development and major breakthroughs in biotechnology will lead the new trend of military

> conflict development, cause major changes in the form of warfare, and the emergence of biological warfare. In the future battlefield, new biological weapons produced by military biotechnology such as genetic weapons, biological electronic equipment, bionic navigation systems, biological bombs, military bioenergy, military biosensors, military biomedicine, biological equipment, bionic power, and animal weapons and other new biological weapons and equipment produced by military biotechnology will become an important warfare force and will promote a series of new changes in the way of military conflict....
>
> (3) Multiplying factors for the improvement of combat capability
>
> Destroy the enemy's combat effectiveness. Biotechnology changes the traditional damage model, and directly targets the microscopic damage of specific physiological functions, which greatly weakens the enemy's combat effectiveness. It is predicted that in the future there may be genetic weapons targeting genes, genomes and proteomes, brain-controlled weapons that can control target behaviors, as well as targeting the cognitive and nervous system, energy metabolism and physical fitness, single or multiple physiological functions, and biotech weapons specific populations. These biological weapons damage the life function by changing the microstructure of the organism, or control the organism, thereby breaking through the traditional military killing mechanism and bottleneck and achieving the purpose of destroying the enemy's combat effectiveness.[552]

Chinese propaganda describes current U.S. research in both medical biodefense and human cognitive enhancement as a threat to China.[553] These provide justification for China's current assessment about U.S. intent to use offensive BW.[554] These views are likely grounded in current threat perceptions and China's experience during World War II when more than 10,000 of its citizens were used as experimental subjects in Japan's offensive BW research. PLA strategists contend the United States used nuclear weapons during World War II and granted amnesty to those involved in Japan's BW program in exchange for information on their research. These perspectives underlie the PLA's current assessment about the United States's intent to use offensive BW.[555]

Although the United States has renounced the use of BW weapons, the PLA fears that the United States is likely to use offensive BW weapons in any future conflict. The 2017 SOMS described, however, that the greatest perceived BW threat is from bioterrorism by rogue actors. The PLA has an announced policy of "active defense" against BW and chemical warfare. This concept has been described as defensive research and programs that can rapidly transition to offensive programs or weapons.[556] The ambiguity created by this approach may manifest their intent to deter U.S. BW use.

A 2019 analysis by the U.S. Defense Intelligence Agency noted that "China's biotechnology infrastructure is sufficient to produce some biological agents or toxins on a large scale."[557] The U.S. Department of Defense's 2023 Biodefense Posture Review noted that China is one of four countries that "probably maintain the knowledge and capability to produce and employ traditional pathogens and toxins" and "probably also retain the knowledge and ability to employ these agents if necessary."[558] Since there is no open-source discussion of China's potential for the use of chemical, biological or nuclear weapons, all that is known is derived from classified sources.[559]

China's commitment to use advanced biotechnology for military purposes is also reflected in a 2018 decision that seems to have merged the disciplines of biology and cognition into a new military medical specialty. The PLA describes "military brain science" as a new "cutting-edge innovative" discipline that "uses military application as the guidance."[560] Two of nine specified functions defining this new medical specialty indicate an offensive ilk:

> Injuring the brain—promoting the research and development of sound, light, explosion, magnetic and other new types of weapons. People are the key to victory or defeat in war, whereas the brain is the "headquarters" of the human body. Precisely attacking the "headquarters" is one of the most effective strategies for determining victory or defeat

> on the battlefield. When researching and finalizing various weapons and equipment, in addition to the killing energy of the arms and the destroying effect of an enemy's equipment, the biological killing effect of the combatants should also be considered.[561]
>
> Interfering with the brain—causing brain dysfunction and a loss of control with the "smokeless" method.... According to the physiological basis of the transfer of brain nerve potentials and the transmission of chemical transmitters, nervous system incapacitation agents and body incapacitation agents will be developed, including brainwave interference weapons.... The strategy of interfering with the brain can affect mentality, influence thinking, and affect decision making to create a whole new "brain war" combat style and redefine the battlefield.[562]

As the speed and complexity of conflict increase, PLA strategists write that achieving "mental dominance" will be critical in future military competition across the spectrum from peacetime to warfighting. This concept emphasizes the criticality of the "cognitive domain" which involves "the field of decision-making through reasoning."[563] The increased integration of human cognition with technology affords the opportunity to affect an enemy's perception by degrading that adversary's decision-making through technical, physiological, or psychological techniques. As noted, "the sphere of operations will be expanded from the physical... and information domain to the domain of consciousness, the human brain will become a new combat space."[564]

U.S. military analysts assess that "Chinese innovation is poised to pursue synergies among brain science, artificial intelligence (AI), and biotechnology that may have far-reaching implications for its future military power and aggregate national competitiveness. Chinese military leaders appear to believe that such emerging technologies will be inevitably weaponized."[565] Several interrelated research areas have been noted that include brain monitoring (measuring and assessing the military mental work); brain modulation (mind-controlling effects); brain promotion (neuro-scientific training) and "interfering with the adversary's capacity for cognition, whether through manipulation or outright destruction."[566]

An example of the kind of research likely conducted in support of this objective is a collaboration between PLA professors from the Fourth Military Medical University and the Broad Institute's Stanley Center for Psychiatric Research in Cambridge MA. Their published 2019 study showed the centrality of the brain cerebrum's anterior cingulate cortex in social behavior.[567] The cingulate cortex appears to be involved in affect-related cognition like decision-making and attention. This part of the cerebrum assimilates multiple neural signals—both task-relevant and task-irrelevant—necessary for the modulation of attention so that "difficult decisions can be made and action plans adapted when necessary."[568] Hyperstimulation of the cingulate cortex can result in "impair[ed] consciousness, alter[ed] affective state and expression, and [affect] skeleto[-]motor and autonomic activity." In rhesus monkeys whose cingulate cortices were ablated, their "vigor and vigilance... responding to threats over time and repeated [threat] presentations" were diminished compared to controls.[569]

In addition to MCF-related cognitive research, senior PLA officers and academics have also highlighted concerns about "national biological security (and) defense" in response to the threats of infectious diseases. Reflecting this concern, the PLA emphasizes defense and preparation in the event of the use of BW. The PLA has a large number of dedicated units for chemical, biological, and radiological defense "demonstrating genuine concern of an attack on China."[570] They also, however, emphasize the importance of exploring the military potential and even offensive applications of biotechnology. "As the weaponization of living organisms will become a reality in the future, non-traditional combat styles will be staged, and the 'biological frontier' will become a new frontier for national defense."[571] The 2017 SOMS describes biotechnology as an "emerging new form of strategic power."[572] A significant proportion of China's CRISPR gene editing research is occurring at military medical and research institutions, especially at PLA General Hospitals.[573] The role of PLA institutions in CRISPR-related gene editing research is concerning when juxtaposed with known programs and indications of military interest in

both human enhancement and infectious disease.

Concerns About AMMS Institutes and China's PLA Military-Civil Fusion Brain Control Research

In December 2021, during the pandemic, the U.S. Department of Commerce added the AMMS and its 11 associated institutes to the "Entity List" for intending to misuse biotechnology. "The 'Entity List' is a U.S. government compilation of foreign individuals, companies, and organizations deemed a national security concern, subjecting them to export restrictions and licensing requirements for certain technologies and goods."[574] Commerce Secretary Gina Raimondo issued a public statement explaining the rationale for invoking this sanction: "Unfortunately, [China] is choosing to use these technologies to pursue control over its people and its repression of members of ethnic and religious minority groups. We cannot allow U.S. commodities, technologies, and software that support medical science and biotechnical innovation to be diverted toward uses contrary to U.S. national security."[575]

A Commerce Department spokesperson stated, "under China's 'military civil fusion' strategy, Beijing is seeking to use emerging biotechnologies to support future military applications, including sponsoring research on gene editing, human performance enhancement, brain machine interfaces and biological materials." The AMMS and 11 of its Institutes, including General Yusen Zhou's Institute of Microbiology and Epidemiology that was involved in SARS-CoV-2 research, were cited.[576] However, the Institute of Military Cognition and Brain Sciences was not named on the Commerce Entity List.[577] The failure to list it may have been caused by the Institute changing its name sometime between November 2020 and January 2021 to the Institute of Basic Medical Sciences. The name change was also noted on the preprint version of the humanized mouse and NHP SARS-CoV-2 vaccine study submitted for publication by General Zhou's AMMS research team on November 20, 2020. The affiliation of three researchers, who were originally listed as belonging to the Institute of Military Cognition and Brain Science, was changed to the Institute of Basic Medical Sciences in the version published on March 17, 2021.[578,579] There is no indication that this represented anything than a name change. The institute remains a part of the AMMS.

Questions About China's Adherence to the Biological Weapons Convention

The Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction (BWC) opened for signature in 1972 and entered into force in 1975. The BWC supplements the 1925 Geneva Protocol, which prohibits only the use of biological weapons. Article I of the BWC outlines a State Party's obligations: "never in any circumstances to develop, produce, stockpile or otherwise acquire or retain: 1. microbial or other biological agents, or toxins whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes; 2. weapons, equipment or means of delivery designed to use such agents or toxins for hostile purposes or in armed conflict."[580]

A state biological warfare program is defined by the U.S. government as "a leadership-approved effort intended to acquire, develop, modify, produce, or retain biological warfare agents for use or potential use as a weapon. A biological warfare program would probably include one or more of the following: researching, acquiring, developing, modifying, producing, retaining, or testing biological weapons (BW) agents and/or BW agent dispersal devices for use as a weapon; facilities producing or intended to produce BW agents and/or BW agent dispersal devices for use as a weapon; training, doctrine, or plans for use of BW agents as a weapon; and, use or attempted use of a BW agent as a weapon."[581,582]

The PRC officially declared the AMMS Institute of Microbiology and Epidemiology or the AMMS Fifth Institute as part of its defensive biological weapons program under the BWC Confidence Building Measures. In 2005, the U.S. State Department publicly stated its assessment that China operates an offensive biological weapons program and specifically implicated the Fifth Institute as one of the two entities likely involved. A heavily redacted August 2020 declassified Department of State cable that was released after a formal Freedom of Information Act request indicated that the AMMS was a BW research institute. This cable also suggested that

there was "robust cooperation between the WIV and PLA AMMS" and that there was "cyber" evidence that the PLA operated "shadow labs" at the WIV.[583]

In a 2006 declaration of compliance with the BWC, China acknowledged that the Fifth Institute specifically conducted research on SARS-related coronaviruses. A review of academic research on the PubMed database maintained by the U.S. National Institutes of Health shows Fifth Institute scientists had extensively published research on coronaviruses, including collaborative work with WIV researchers. In short, the AMMS's Fifth Institute is likely a constituent part of China's historic offensive bioweapon efforts, as well as current biodefense and collaborative coronavirus research with the WIV.

Questions and concerns regarding China's BWC compliance have been reported since 1993.[584] China became a BWC State Party in 1984 and has submitted Confidence Building Measures each year since 1989, including in 2023. China never disclosed its historic offensive BW program. It reportedly weaponized ricin, botulinum toxins, and BW agents for anthrax, cholera, plague, and tularemia. The U.S. State Department's 2024 Arms Control Compliance Report noted that "PRC military [PLA] medical institutions conducted toxin and biotechnology research and development with potential BW applications, which raises concern regarding the PRC's compliance with Article I of the BWC."[585]

PLA Research Interest in SARS-Related Viruses Began with the 2003 SARS-1 Outbreak

As early as 2000, human coronaviruses causing respiratory illness were linked with neurotropism, neuro-invasion and possible neuropathology including an association with multiple sclerosis.[586,587] Yet, the PLA involvement with published coronavirus-related research appears to begin with the first SARS outbreak in 2003. Early on, PLA AMMS researchers, including General Yusen Zhou, showed interest in SARS clinical effects such as the possible role of reovirus coinfection in SARS-1 cases resulting in higher morbidity and mortality.[588,589] They also noted that some cases during the 2003-2004 SARS outbreak showed brain involvement and potential long-term neurological sequelae.[590,591]

Autopsy findings in early SARS-1 cases that showed brain involvement were first reported by PLA pathologists from the Nan Fang Hospital, First Military Medical University in Guangzhou, Guangdong Province. Two of three fatal cases showed slight brain swelling (edema) and evidence of immune cell infiltration of small intracranial veins with focal nerve cell degeneration and demyelination.[592] A larger autopsy study of 18 suspected SARS cases by Peking University pathologists confirmed the presence of SARS in neurons of the brains of all eight PCR positive patients.[593] The effects on specific neurons appeared to occur in two parts of the human brain: the hypothalamus and cortex.[594] In 2010, researchers from the Tongi University School of Medicine in Shanghai published their SARS-1-related autopsy observations: "Proliferation, swelling, and apoptosis [death] of endothelial cells, and edema, inflammatory cell infiltration, and fibrinoid necrosis… [was seen] in the walls of small blood vessels in specimens from the lungs, heart, liver, kidneys, adrenal glands, and brain" as well as other organs.[595]

A pregnant woman who successfully gave birth while infected with SARS developed a generalized seizure on day 22 of her infection. Her "cerebrospinal fluid tested positive for SARS-[1] by reverse transcriptase–[PCR]." The authors concluded that "SARS-[1] may have caused an infection in the central nervous system [CNS] in this patient." The hospital that treated this patient had treated 577 SARS-1 cases, they concluded that the "involvement of the CNS in SARS-[1] is rare."[596]

Neuropsychiatric findings were also reported during the first SARS outbreak. Researchers in Hong Kong identified ten cases of depression and psychosis in patients hospitalized with SARS. Four patients treated with steroids for the acute phase of their disease developed psychosis when the steroid treatment was tapered. While the onset of psychosis has been associated with the initiation of high dose steroids, depression rather than psychosis is typically associated with the tapering or reduction of steroid dosing, suggesting that the psychosis noted in some SARS patients was not linked to their steroid treatment.[597,598]

A case-control study performed at the Chinese University of Hong Kong Hospital suggested psychosis and manic

behavior in SARS patients may be associated with high dose steroid treatment and a family history of mental illness. These authors referenced, however, unpublished data that reported that ~40% of 148 patients with SARS-1 had been given a diagnosis of one or more psychiatric [*DSM-IV*-defined] disorders during the acute and/or convalescent phases of their illness.[599] Psychiatric disorders would be re-encountered during the COVID-19 pandemic and recognized as neuropsychiatric manifestations of SARS-CoV-2 CNS involvement.[600,601]

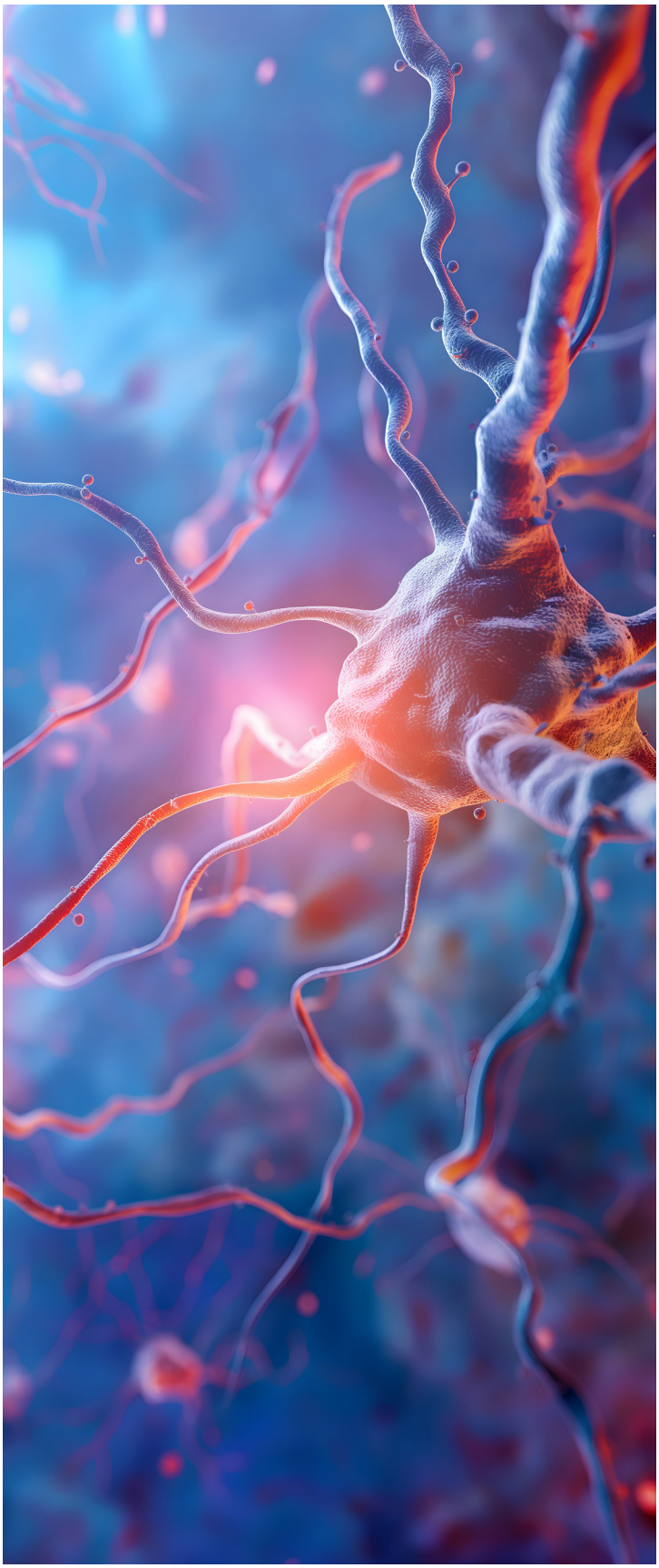
Researchers in Taiwan reported neurological findings in only 13 (1.9%) of the 664 SARS-1 cases documented there. Eight cases had neuro-muscular findings thought to be associated with their critical illness, though further study would be required "to determine the relationship between SARS coronavirus and neuromuscular problems."[602] Additionally, strokes were observed in five SARS patients with poor prognoses. "Multiple factors contributed to [these] vascular insult[s] [that] included hyper-coagulable status related to both SARS[-1] coronavirus and the usage of intravenous immunoglobulin, septic and cardiogenic shock, and possible vasculitis [inflammation of blood vessels]. The relationship between SARS[-1] and above neurological problems still needs further clarification."[603] Taiwan reported a single documented case of acute loss of smell (amsonia) 3 weeks after the onset of SARS-1 illness in a 27-year-old female.[604]

During and after the SARS-1 outbreak, animal models became an important window into the clinical effects caused by SARS. Because previous studies infecting wild-type mice (BALB/c or C57BL/6) with an unadapted SARS virus resulted in minimal, non-lethal disease, a humanized mouse model was needed.[605,606] U.S. researchers from the University of Iowa showed that transgenic mice with human ACE2 receptors caused fatal SARS-1 disease that mimicked the lung pathology seen in human cases. These infected mice also had high levels of SARS-CoV-1 virus in the brain.[607] In 2008, a study showed this transgenic human ACE2 mouse inoculated with SARS-1 virus that had minimal lung infection died from extensive brain infection with early nerve cell death in the cerebral cortex (cingulate cortex, thalamus and hypothalamus) of the infected mice.[608] The researchers postulated that the mice's deaths were potentially caused by high levels of inflammatory cytokines or infection of the brain, especially in regions that regulate the cardiorespiratory system.[609,610]

Relevant to findings of brain infection during the SARS-1 outbreak in 2005, PLA researchers from the Fourth Military Medical University and the AMMS Institute of Basic Medical Sciences identified a CD147 protein receptor on SARS-1 nucleocapsid (N). The study noted that this protein played "a functional role in facilitating invasion of host cells by SARS-[1-]CoV" in addition to the ACE2 receptor found on the spike protein.[611] The researchers identified a three-way interaction between the N protein, CD147, and another protein, Cyclophilin A. Researchers suggested that this interaction with CD147 might somehow play a role in viral entry, although the mechanism by which this might occur is not clear. The role of CD147 in the pathology of SARS-CoV-2 would be noted by PLA researchers after the pandemic started.

The CD147 receptor has been reported to play an important role in human immunodeficiency virus type 1, hepatitis B virus, hepatitis C virus, and Kaposi's sarcoma-associated herpesvirus infections.[612] CD147 also plays a pivotal role in traumatic or ischemic brain injuries that promote the production of messenger chemicals (matrix metalloproteinases) that disrupt the blood brain barrier, damaging nerve (astrocytes) cells, affecting brain immune cells (microglia), and releasing inflammatory mediators (cytokines).

Microglial cells act as immune sentinels and are distributed throughout the brain. They protect the brain from potential threats such as injury and infection and play a role in both innate and adaptive immunity.[613] They play a protective function by removing harmful protein and if impaired can lead to excessive residual protein aggregates such as amyloid beta and neuroinflammation that can result in neurodegeneration.[614] Direct effects (disrupting the blood brain barrier) and indirect ones (inflammatory cytokines) can impair microglial cells and increase the severity and extent of brain injury.[615,616]



Limited Neurological Effects Described in General Zhou's Mouse and Primate Studies

In April 2020, after General Zhou filed his patent but before he published any of his vaccine-related animal studies, he submitted for publication a SARS-CoV-2 infectivity and pathogenesis study in specialized humanized mice.[617] The mice were created by a research group at the PRC National Institutes for Food and Drug Control in Beijing using CRISPR-related technology to cleanly replace the mouse ACE2 gene with a human ACE2 gene to create a "knock-in" mouse. The resulting ACE2 humanized mice were developed in 2018 at the same time as MERS-susceptible humanized DPP4 mice. The DPP4 mice were first disclosed and published on in 2018.[618] The existence of this specialized new SARS mouse model, however, was first published only in February 2020 after the SARS-CoV-2 pandemic had begun.[619]

The advantage of this humanized ACE2 mouse model over existing transgenic mice was that it could be infected with SARS-CoV-2 through either the respiratory or gastrointestinal tract. The intranasally infected mouse showed robust viral growth in the lung and brain.[620,621] As described, "both young and aged hACE2 mice sustained high viral loads in lung, trachea, and brain upon intranasal infection (Figure 9). Additionally, immunostaining of brain sections from the intranasally infected hACE2 mice showed that robust viral spike protein expression was detected in neurons, astrocyte and microglial cells." Mice orally infected did not show brain involvement but developed robust pulmonary findings comparable to the intranasally infected mice. The study also showed the higher inflammatory cytokine responses in aged compared to young hACE2 mice. The pathological and inflammatory changes observed in the aged hACE2 mice more closely resembled those observed in COVID-19 patients. According to the researchers, "thus, the use of hACE2 mice described in our manuscript provides a small animal model for studying the transmission and pathogenesis of SARS-CoV-2 and for the understanding of unexpected clinical manifestations of SARS-CoV-2 infection in humans."[622]

General Zhou's pathogenesis study was one of the earliest to document the potential neurological effects of the SARS-CoV-2 virus. He noted that the brain findings in

his mouse studies were at variance with earlier published studies by other Chinese researchers who evaluated SARS-CoV-2's affinity in different human tissues.[623,624] He stated that "this inconsistency between human and mice deserves further investigation." The two studies he cited did not test for SARS-CoV-2 virus in brain or neurological tissues.

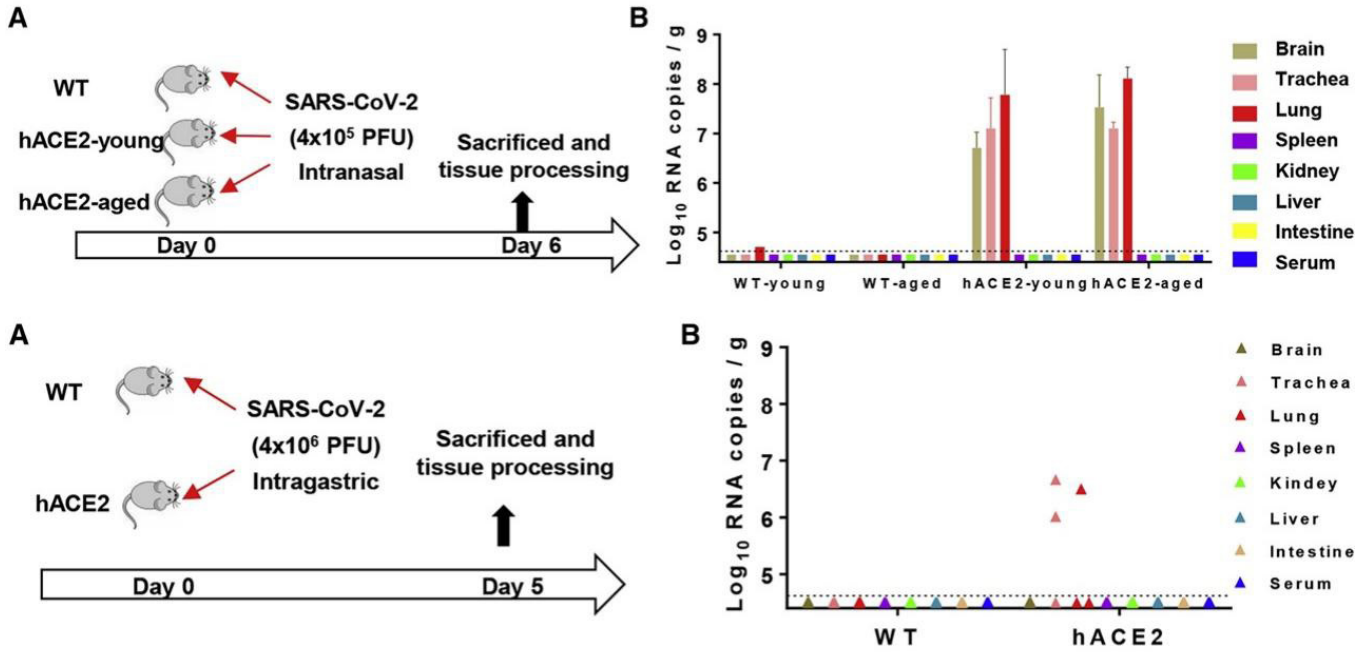


***Figure 9*. Intranasal & Intragastric Infection with SARS-CoV-2 in hACE2 Mice.** Top: WT C57BL/6 mice, young (4.5-week-old), and aged (30-week-old) hACE2 mice (n = 3) were intranasally infected with 43105 PFU of SARS-CoV-2, and all mice were sacrificed on 6 dpi for tissue collection. Bottom: WT C57BL/6 mice and hACE2 mice (n = 3) at 4.5 weeks old were infected with 4 3 106 PFU of SARS-CoV-2 through intragastric administration, and all mice were sacrificed on 5 dpi for main tissues and serum collection. Source: Sun, Chen, et al. (2020).

There are a few other aspects of General Zhou's mouse study that deserve scrutiny. He used two mice cohorts: 4 to 5 weeks old (juvenile) and 30 weeks old (aged). To submit this study in April 2020, the aged mice would have been conceived 33 weeks earlier, no later than August 2019. The typical gestation period of this type of mouse is 18 to 22 days.[625] Given the constraints of this timing, the ability to conduct studies of SARS-CoV-2 infection and effects using large numbers of humanized ACE2 mice is consistent with the idea that researchers may have been aware of, and possibly experimenting with, SARS-CoV-2 before August 2019.

Another curious aspect of this study is the SARS-CoV-2 strain (AMMS01) it used. It was described as "SARS-CoV-2 strain BetaCoV/wuhan/AMMS01/2020 [that] was originally isolated… from a patient returning from Wuhan." The provenance of this strain cannot be determined. The patient's identity, when he or she became infected and when it was isolated is not known. It suggests, however, that someone, possibly a researcher from General Zhou's AMMS institute, may have become infected and that may have prompted General Zhou's research and vaccine work in 2019.

As described in Part I of this study, accidental laboratory acquired infections (LAI) are not uncommon during the isolation or discovery of a new or novel virus.[626] If the virus was part of a long-term research interest or perceived public health risk, such incidents could be the impetus for developing a vaccine to protect researchers or the public. In light of the PLA's involvement, it could

also indicate a military interest in such a pathogen as either a potential natural or BW threat.

In March 2019, public writings and statements by PLA and WIV researchers and George Fu Gao, then Director of the Chinese Center for Disease Control, cited concerns about high pathogen lab biosafety and related research.[627] Gao specifically mentioned coronavirus research that "may expand host range as well as increase transmission and virulence, [that] may result in new risks for epidemics."[628] These public references would be followed in early April by the WIV's annual biosafety conference notable for prioritizing mitigation of "hidden dangers" such as undetected hazardous aerosols and filing 13 new patents addressing a range of biosafety issues.[629]

Whether these collective activities reflect a reaction to an earlier incident is not known. These actions also coincide with the initiation of efforts by the Government of China in late March 2019 to prioritize legislation to address biosafety and biosecurity of high pathogen research.[630] The possibility that General Zhou's vaccine research began in the summer of 2019 seems like a logical response to an earlier incident resulting in a lab acquired infection in a researcher involving a pathogen with pandemic potential.

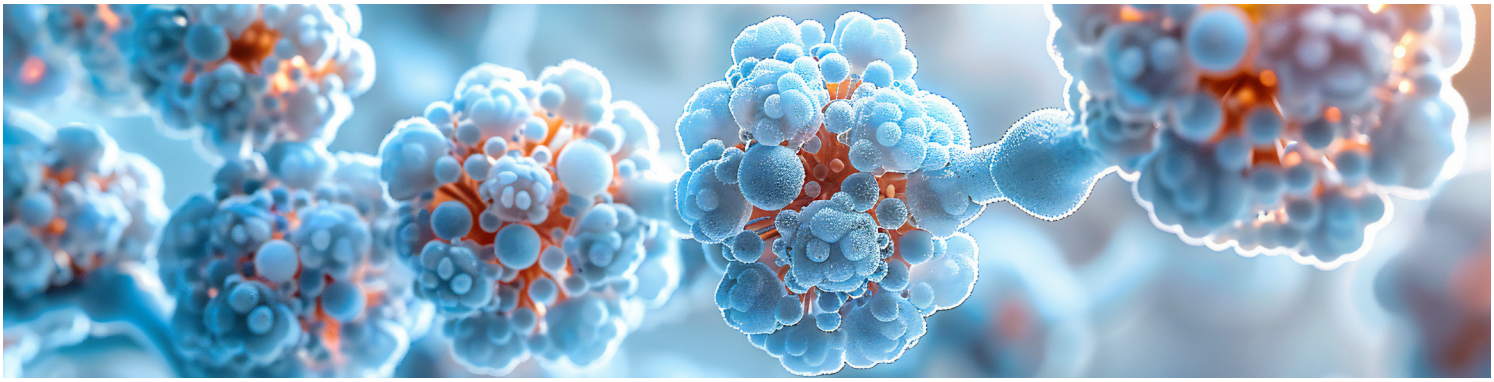
The AMMS01 strain would also be referenced in the May 2020 preprint version of General Zhou's study adapting the SARS-CoV-2 virus to BALB/c mice and assessing the efficacy of a candidate protein subunit vaccine.[631] This strain reference would be changed when the study was formally published in July 2020 to "SARS-CoV-2 strain IME-BJ05 (BetaCov/human/CHN/Beijing_IME-BJ05/2020) [that] was originally isolated from a COVID-19 patient."[632]

The July article would also note General Zhou's death, which occurred sometime after the late May 2020 release of the preprint version. The cause of General Zhou's death was never publicly disclosed and never officially acknowledged.

Two researchers, Gencheng Han and Yan Li named on the February 2020 vaccine patent did not participate in General Zhou's April 2020 transgenic mouse pathogenesis study but were named in this BALB/c mice and later SARS-CoV-2 humanized mice and NHP vaccine challenge studies. These two later studies were qualitatively different than General Zhou's April study for including limited or no data reflecting SARS-CoV-2's neurological effects. In the first study published in July 2020, SARS-CoV-2 was described being serially passed in wild-type (BALB/c) mice to isolate a strain (MASCp6) that readily infected BALB/c mice. The purpose of this process was to enable testing SARS-CoV-2 virus in mice that are more readily available and cheaper yet not susceptible to the virus.

As noted in the study, the serial passage of the SARS-CoV-2 virus resulted in several mutations. One mutation on the virus' spike protein was described: "The N501Y substitution in the RBD [receptor binding domain] of SARS-CoV [spike] protein increased the binding affinity of the protein to mouse ACE2."[633] This strain was infectious and mildly pathogenic. This mutation would later emerge during the pandemic, when it was first observed in the Omicron strains that were first detected in November 2021 and later in the B.1.1.710 variant.[634,635,636,637]

The MASCp6 strain was used to infect vaccinated and control (unvaccinated) BALB/c mice that were euthanized and autopsied. The mouse adapted strain "productively



replicated in the respiratory tract and cause[d] interstitial pneumonia in wild-type immunocompetent mice."[638] Additionally, SARS-CoV-2 "viral RNA" was isolated and detected "in heart, liver, spleen, and brain, as well as in feces."[639] Specific data was included in a chart that showed the viral titers in ten different mouse tissues from unimmunized aged and young BALB/c mice (Figure 10). Notably, measurable brain SARS-CoV-2 viral titers (10^4 RNA copies/g) were seen at three days post-infection (dpi) and peaked at five dpi. The titer measured in young mouse brains was higher (~10^6 RNA copies/g) than that in aged mice ones (~10^5 RNA copies/g) on day five, while the level of RNA viral copies in aged mouse brains remained higher longer (seven dpi). The difference, however, was not significant. Notably, and at variance with comparable scientific studies, no similar data from the immunized mice was presented or discussed.

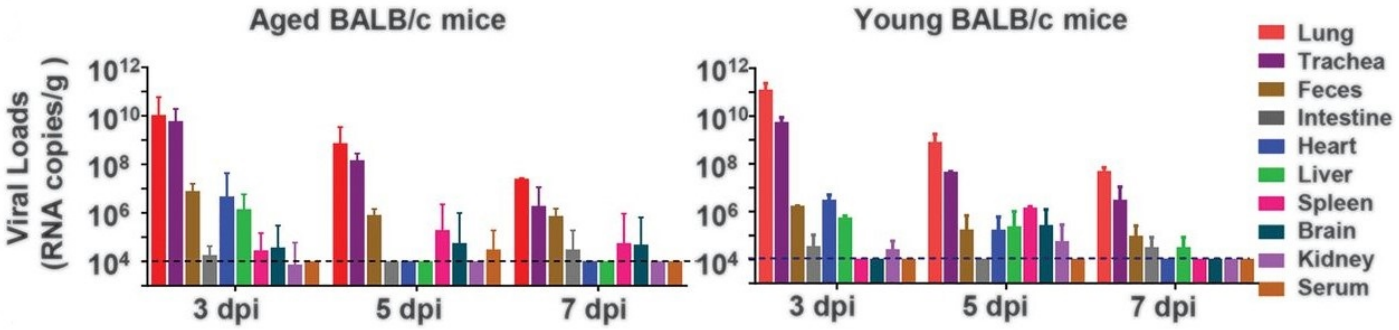


***Figure 10*. Generation and characterization of a mouse-adapted strain of SARS-CoV-2 in BALB/c mice.** Tissue distribution of SARS-CoV-2 viral RNAs in mice infected with MASCp6. Groups of aged and young mice were inoculated with 1.6 Å~ 104 PFU of MASCp6 and sacrificed at 3, 5, or 7 days after inoculation, respectively. Feces, sera, and the indicated tissue samples were collected at the specified times and subjected to viral RNA load analysis by means of quantitative RT-PCR. Dashed lines denote the detection limit. Data is presented as mean ± SEM (n = 3 mice per group). Source: Gu et al. (2020).

This study noted the efficacy of the vaccine only in protecting against the lung disease associated with SARS-CoV-2. As reported, "no apparent pathological damage was observed in the lung of RBD-Fc immunized mice, whereas inflammatory lung injury—with focal perivascular and peribronchiolar inflammation, as well as thickened alveolar septa—were found in the lung of the control mice."[640] There was no mention of or data presented about the vaccine's efficacy to protect the mice's brains.

A recently published study by researchers from Helmholtz Munich and Ludwig-Maximilians-Universität, Germany compared SARS-CoV-2 spike protein levels in vaccinated and unvaccinated wild-type mice. Vaccination, as in the General Zhou study, protected the mice against lung disease and lowered levels of inflammation. Unlike Zhou's study, however, the German study reported that vaccinated mice had lower spike protein levels in lungs, livers, kidneys, hearts, skull marrow and brains. Significantly, it also noted that SARS-CoV-2 spike protein was "significantly decreased in the brain cortex of vaccinated mice."[641]

These findings highlight the absence of similar data in the Zhou study. The researchers from the Institute of Military Cognition and Brain Sciences were acknowledged as having performed experiments and analyzed data though no specific neurological observations or data other than viral titers from unimmunized mice were included.[642]

The N501Y mutation described in General Zhou's study would later be noted by researchers from Northeastern University who found this mutation in the Omicron and other variants.[643,644] The mutation would likely increase the binding affinity of the RGD sequence found in SARS-CoV-2's spike protein receptor binding domain. The RGD sequence is a three amino acid protein that can interact

with human cell-surface receptors and affect cellular functions. They also noted this SARS-CoV-2's spike protein RGD sequence could allow it to interact with cells lining blood vessels (endothelium) and platelets to initiate blood clotting.

University of Texas Medical Branch (Galveston) researchers would also determine that the N501Y mutation increased the binding affinity to human airway epithelial (HAE) cells and the ACE2 receptor.[645] Besides its effect on ACE2 binding, evidence suggests that "an integrin-binding 'RGD motif' near the distal tip of the SARS CoV-2 spike protein may interact with integrins on cell surfaces and lead to extensive dysregulation of [coagulation and angiogenesis] processes."[646] Researchers from the Tulane Brain Center noted that the interaction with SARS-CoV-2's RGD sequence causes significant blood vessel permeability and dysregulation. They observed that in mouse brains, the SARS-CoV-2 virus bound to endothelial cells causing inflammation with white blood cells adhering to the lining of the vessels and the release of inflammatory mediators and coagulation factors.[647]

German researchers also evaluated the spike protein with the N501Y mutation. The spike protein carrying this mutation could bind to wild-type (WT) mouse ACE2 receptors.[648] Following intravenous injection into WT mice, this S1 protein localized near blood vessels in most organs, including the heart, lung, liver, kidney, intestine, thymus, spleen, pancreas, and brain. This mutation expanded the SARS-CoV-2 organ tropism and likely resulted in systemic and neurological inflammation.[649]

The relevance of this increased binding, dysregulation and presence of viral proteins was documented by several research groups. U.K. researchers from the Francis Crick Institute noted that "SARS-CoV-2 affects the normal physiological functions of the [blood brain barrier] and its cellular components and thus contributes to the wide spectrum of neurological manifestations of SARS-CoV-2 that have been observed clinically."[650] They concluded that "the WT [wild-type Wuhan strain] virus and the Omicron variant may have a higher potential for neurological damage" due to their ability to induce CNS cell stress, impact normal brain cell function and damage the blood brain barrier.[651] A later study by researchers from the Second Xiangya Hospital of Central South University in Changsha, China would show the neurological effects caused by the Omicron variant. They reported MRI imagery studies showing that decreased gray matter thickness and subcortical nuclear volume injury were significantly associated with anxiety and cognitive dysfunction.[652] A recent study showed that "detection of viral proteins in the brain following mild Omicron infection suggests it may contribute to long-term memory deficits."[653]

In August 2020, after General Zhou's death, an email exchange between two University of Texas Medical Branch scientists mentioned receiving an email from Dr. Shibo Jiang who was affiliated with Fudan University and the Kimball Blood Center in New York and was one of General Zhou's collaborators on the BALB/c mouse adaptation study.[654] As written, "the first email from Shibo [Jiang] was that the senior guy died [Yusen Zhou] and no one knew anyt[h]ing about the samples or where the virus was. That seemed strange to me."[655] The whereabouts of samples and data from General Zhou's study remain a mystery.

Independently, a 2023 study by the Tulane Brain Institute evaluated the use of BALB/c mice to model SARS-CoV-2's lung and brain pathology.[656,657] Like General Zhou's SARS-CoV-2 adaptation study, the U.S. researchers serially passed the virus in this common experimental mouse.[658] However, unlike General Zhou had done, these researchers did not note the occurrence of the N501Y mutation in their mouse adapted virus.

These Tulane researchers found that infecting BALB/c mice with their mouse adapted strain resulted in similar lung and brain pathology found in human clinical cases including affecting the olfactory nerve. Specifically, they measured increased inflammatory cytokines (IL-6) levels and disruption of the blood brain barrier that resulted in neuroinflammatory effects seen in acute SARS-CoV-2 cerebrovascular disease.[659] As described by these researchers, the mouse adapted strain "could be used as a novel model to study SARS-CoV-2-mediated cerebrovascular pathology."[660] These researchers later used this mouse model to show the neurological effects seen in long COVID.[661]

After General Zhou's unexplained death sometime between May and July 2020, a second study conducted by his colleagues that tested his vaccine in humanized mice and NHPs was submitted in November 2020 and published in March 2021. This subsequent vaccine challenge study used transgenic humanized mice developed by the PRC National Institutes for Food and Drug Control and were likely the same mouse model used in his April 2020 study.[662] The NHPs (Macaca fascicularis macaques) used should have yielded greater relevant pathological and possibly behavioral data to evaluate the neuro-effects of COVID infection and the vaccine's neuroprotection.[663]

This later study demonstrated the vaccine's efficacy against COVID-19 pulmonary disease in these two animal models, but the results did not mention any neuropathology, inflammatory cytokine biomarkers, or brain viral RNA titer data as included in General Zhou's previous transgenic humanized and wild-type mouse studies.[664,665] The curious absence of such data is heightened by the participation of three researchers from the AMMS Institute of Military Cognition and Brain Sciences. One of the three, Ge Li, was recorded as having performed experiments and the other two, Genchen Han and Yan Li, supervised the drafting of the manuscript. Yan Li was noted as one of the two authors who conceived of the project.[666] There was a notable change in the affiliation of these three researchers from the study's pre-print version when they were affiliated with the AMMS Institute of Military Cognition and Brain Sciences to the final published version that listed them as affiliated with the Beijing Institute of Basic Medical Sciences.[667,668]

In 2022, Tulane University researchers conducted SARS-CoV-2 neuropathology studies in two NHP species, including Rhesus macaques. They infected the NHPs by aerosol and mucosal routes (i.e. conjunctival, nasal, pharyngeal, intratracheal). All infected NHPs showed "prominent neuroinflammation, microhemorrhages with and without microthrombi [clots] and neuronal [brain cell] injury and death consistent with hypoxic-ischemic injury but without substantial virus detection in brain."[669] Two of the eight NHPS were euthanized before the planned study endpoints because one became unresponsive and the other became acutely short of breath. Their findings suggested that SARS-CoV-2 neurological effects were caused by infection of brain capillaries that disrupted the blood brain barrier in parts of the NHP's brain (basal ganglia, brainstem and cerebellum).

These effects were likely precipitated by the RGD sequence on SARS-CoV-2's receptor binding domain (RBD) interacting with cells lining the brain capillaries. These findings resembled those observed in the human brains of patients who died from SARS-CoV-2 infections. That the observation in this NHP study occurred "even in the absence of severe disease or overt neurological symptoms" is particularly noteworthy.[670] This suggests that a potentially significant neurological insult may occur without overt symptoms. Another Rhesus macaques study confirmed these neuro-inflammatory findings.[671] The findings from both Tulane studies highlight the likelihood that relevant neurological findings were likely observed in the mice and NHPs but not reported in the studies by General Zhou's research team that included three scientists from an institute devoted to brain science and military cognition.

General Zhou Posthumously Credited in a Study on Treatment of MERS Brain Infection

After General Zhou's death, his research team submitted another relevant study for publication on October 31, 2020, that was published a year later in October 2021. Researchers from the AMMS Institute of Microbiology and Epidemiology and the Department of Basic Medical Sciences of the North China University of Science and Technology showed that a therapeutic antibody could treat the brain infection caused by the MERS virus in mice.[672] Three of the authors were named on General Zhou's patent and participated in the two animal SARS-CoV-2 vaccine challenge studies. Researchers from the AMMS Institute of Military Cognition and Brain Sciences or the Institute of Basic Medical Sciences, however, were not listed as participating.

Infection associated with the MERS virus is mediated by a different cellular receptor than the ACE2 receptor used by SARS-1 or SARS-CoV-2. The MERS receptor, dipeptidyl peptidase 4 (DPP4), is found widely in the brain.[673] In

2018, at the same time as the specialized SARS mouse model used by General Zhou in his April 2020 experiment, researchers at the Beijing National Institutes of Food and Drug Control developed a DPP4 mouse model using the same CRISPR/Cas9 technology.[674,675] These R26-hDPP4 mice, when inoculated with the MERS virus, showed infection in the cerebrum, cerebellum, and cerebral ganglia. This and an earlier 2015 study demonstrated the mechanism by which MERS viral infection leads to brain injury.[676,677]

General Zhou's 2020 study noted that "human coronaviruses are neuroinvasive and neurotropic to the CNS." It also stated that MERS infects "neurons and astrocytes but not microglia" cells. They showed that MERS damaged the blood brain barrier and activated the complement pathway that caused inflammation-mediated neurological damage (Figure 11). They suggested that "microglial activation can initiate neuronal [brain cell] loss, as well as amplify ongoing neuronal damage, and may be crucial to the aetiology and the progressive nature of coronavirus infections and other neurodegenerative diseases." It made only a single mention of SARS-CoV-2, related to its low mortality. The researchers made no mention of SARS-CoV-2 neuropathology even though they made references to SARS-1 brain effects.

The article was dedicated to the memory and contributions of Yusen Zhou. General Zhou likely contributed to and possibly conceived of this experiment before his death. When this study was conducted is not known, but it was possibly performed at the same time as the SARS-CoV-2 vaccine challenge studies. The implication is that General Zhou could assess an antibody to treat MERS's neurological effects in parallel to comparing it to the protection afforded by a vaccine for SARS-CoV-2. As noted earlier this SARS-CoV-2 study was likely performed in the fall of 2019, before the outbreak of a pneumonia of unknown origin was reported on the last day of December 2019, and when it was published in July 2020 there was no mention of or data about the neuroprotection of this vaccine.

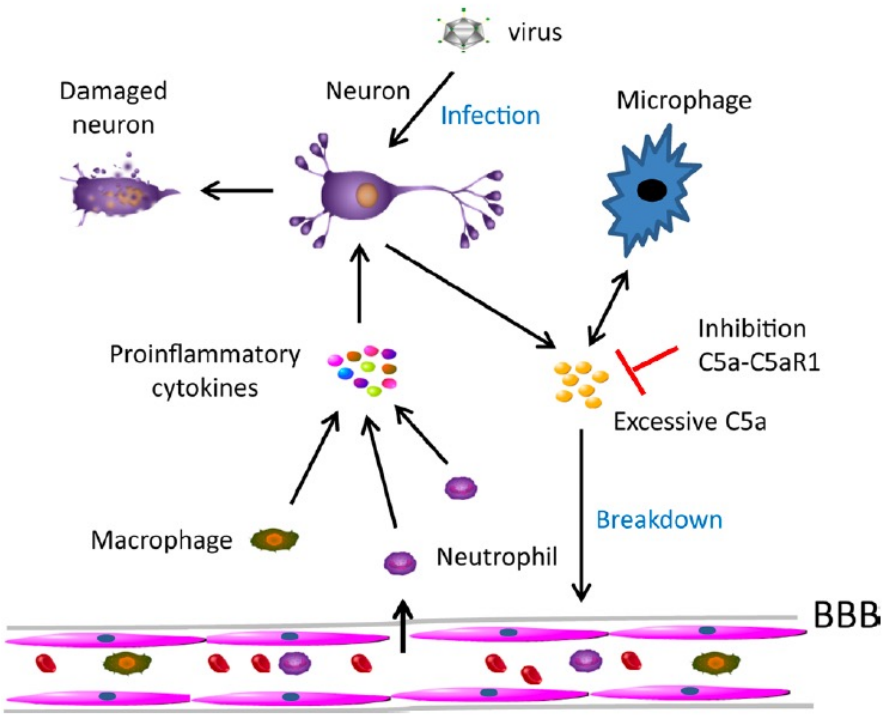


***Figure 11*. Diagram illustrating damage to brain tissues in human DPP4-transgenic mice.** Neurons infected by MERS-CoV secrete complement components which could activate microglia, which, in turn, could also secrete complement components in the brain. Excessive complement activation could activate the endothelial cells of BBB, enhancing the infiltration of inflammatory cells, such as neutrophils and macrophages, into brain parenchyma. The infiltrated inflammatory cells secrete proinflammatory cytokines which could further enhance neuronal damage. However, the inhibition of C5a-C5aR1 interaction could inhibit BBB damage and decrease second damage owing to the excessive inflammatory response. Source: Jiang et al. (2021).

Significantly, work published in early 2023 identified relevant coronavirus research in Wuhan that possibly confirms the presence of General Zhou and his research team in that city and at the WIV at the time of the outbreak. U.S. researchers assembled the complete sequence of a hitherto unpublished coronavirus as a contaminant present in agricultural rice RNA sequencing datasets uploaded to the National Center for Biotechnology Information (NCBI) from the WIV and Huazhong Agricultural University in January 2020.[678]

These U.S. researchers assembled from the contaminating sequence runs the complete sequence of a new, novel coronavirus (HKU4r-HZAU-2020, Genbank accession number OK560913). The new virus is MERS-related (a merbecovirus) with considerable similarity (98.38%) to a bat coronavirus (HKU4, BtTp-GX2012 from *Tylonycteris pachypus*). The U.S. researchers modeled the spike protein of the new virus *in silico* and showed that, like the MERS spike protein, it likely binds to the MERS DPP4/CD26 receptor.

The DNA copy of the new virus genome was carried on a bacterial artificial chromosome (BAC) vector, and flanked by sequence elements (upstream, animal virus and T7 RNA polymerase promoters, downstream Hepatitis D virus ribozyme followed by a polyA signal). Contemporary coronavirus researchers commonly use this approach, placing the full viral genome on a BAC plasmid, flanked by these sequences, to recover live virus from animal cells transfected with the construct or from cells transfected with RNA generated *in vitro*. This work thus indicates a functional reverse genetic system for a so-far-unpublished coronavirus in Wuhan in early 2020.

In addition, the U.S. researchers were able to identify from a partial sequence a second spike protein gene, from MERS itself (reference strain HCoV-EMC/2012). Coincidently, this is the same strain that General Zhou's colleagues used to demonstrate the therapeutic effect of an antibody against MERS neurological infection in specialized DPP/CD26 mice. The U.S. researchers noted that the MERS-CoV RBD binds more efficiently to DPP4/CD26 than the RBD from other HKU4r-CoVs, and that MERS uses furin cleavage of the spike protein, like SARS-CoV-2, to enter cells. The partial sequence of the HKU4r-HZAU-2020+S(MERS) chimera establishes the use of an unpublished HKU4 reverse genetics system in apparent gain-of-function research in Wuhan in early 2020.

The authors note that an unrelated rice sequencing project was registered at NCBI on January 17, 2020 by the WIV, followed two days later by registration of a rice project by Huazhong Agricultural University on January 19. It is thus possible that the University was handling rice sequencing for the WIV. The two institutions have a history of research collaboration. Huazhong Agricultural University and the WIV previously teamed up during an alpha coronavirus Porcine Epidemic Diarrheal Syndrome (PEDS) outbreak.[679]

The same university also played an extensive role in responding to the Wuhan COVID-19 outbreak as described by local Chinese media outlet Guangming Daily on May 12, 2020: "Jin Meilin, deputy director of the Bio-safety Level 3 Laboratory in Huazhong Agricultural University, and his team of scientists have been ramping up their efforts in the search for the source of COVID-19 and potential therapeutic options for COVID-19 patients."[680] Jin also briefed the WHO-China Joint Study on the SARS-CoV-2 infection risk in cats, dogs and pigs.[681] Perhaps the university was assisting the WIV early in the outbreak sequencing coronavirus-related samples because of its BSL-3 laboratory. Regardless, contamination of the samples with HKU4r-HZAU-2020 and the gain of function construct HKU4r-HZAU-2020+S(MERS) could have occurred at either site or during sample transport.

Virus Induced Cognitive Decline and Causal Effects of COVID-19 on Childhood Intelligence

Gencheng Han, Yan Li, and Ge Li were researchers affiliated with the AMMS Institute of Military Cognition and Brain Sciences, the Beijing Institute of Basic Medical Sciences and the Institute of Beijing Brain Sciences.[682,683,684] They were the three researchers who worked with General Zhou's team to patent and develop their SARS-CoV-2 vaccine. In 2023, Han and Li published another article titled, "Biosafety and mental health: Virus induced cognitive decline."[685] As noted earlier, these researchers invoked recent "'black swan' incidents in the field of

biosafety," without specifying exactly what they had in mind.[686] The body of their article, however, focused on the relationship between "pathogenic infection and cognitive deterioration in terms of both neurotoxicity and neuroinflammation."[687] Using published data about SARS-CoV-2 as well as research by others on HIV and Zika viruses—although oddly without referring to their own research they suggested that neurocognitive decline was associated with all these infectious conditions. They note that the three infectious agents impact similar portions of the brain, the hippocampus, and that executive function, learning and memory can be affected. As described "a growing number of studies have shown that SARS-CoV-2 infection caused cognitive decline in the central nervous system."[688]

These authors described direct and indirect mechanisms resulting in SARS-CoV-2 neurocognitive decline. They noted direct viral neurotoxicity, where the virus promotes secretion of toxic byproducts from nerve cells and impedes clearance of factors such as amyloid beta, which is central to the pathology of Alzheimer's dementia. They also identify several indirect immune modulated pathways that result from local or systemic inflammation which can affect the blood brain barrier. Local or systemic inflammation in the brain also impacts microglial cells. These cells represent 10% of the cells in the adult central nervous system and play "physiological roles in learning and memory" and are a "critical immune regulator" in the brain.[689] Their immune function helps to clear cellular debris, such as amyloid beta, that results from trauma, ischemia or infection.

Han and Li's study noted that systemic inflammation was "an important trigger for the local inflammation within the brain."[690] Peripheral inflammatory chemical messengers (cytokines) caused by SARS-CoV-2 infection activated brain microglial cells which in turn resulted in the release of inflammatory cytokines, such as interleukin (IL) 6, which are directly injurious to brain cells.[691] As they noted, "unfortunately, uncontrolled activation of microglia lead[s] to neuroinflammation" (Figure 12).[692] They also noted that "SARS-CoV-2 activates microglial [cells] in the hippocampus promoting the expression of [cytokines] IL-1β and IL-6, which… inhibits neurogenesis [development of new nerve cells], and we all know the hippocampus is responsible for learning, memory and executive function…. In addition, SARS-CoV-2 can activate microglia through activation of NLRP3 inflammasome, causing a sustained inflammatory response in the central nervous system, which will deteriorate cognition by impairing neuronal activity."[693,694,695] They also noted the viral activation of the complement pathway that can result in "long-term memory impairment and cognitive

dysfunction in patients with encephalitis." Significantly, however, this study makes no mention of the 2021 study by General Zhou's research team demonstrating a similar molecular mechanism involving the complement pathway in MERS infection.[696] Han and Li conclude by noting that the cumulative consequences of these direct and indirect effects result in MRI-documented decreases in brain volume, microbleeds and changes in brain microstructure, which all contribute to cognitive decline.[697]

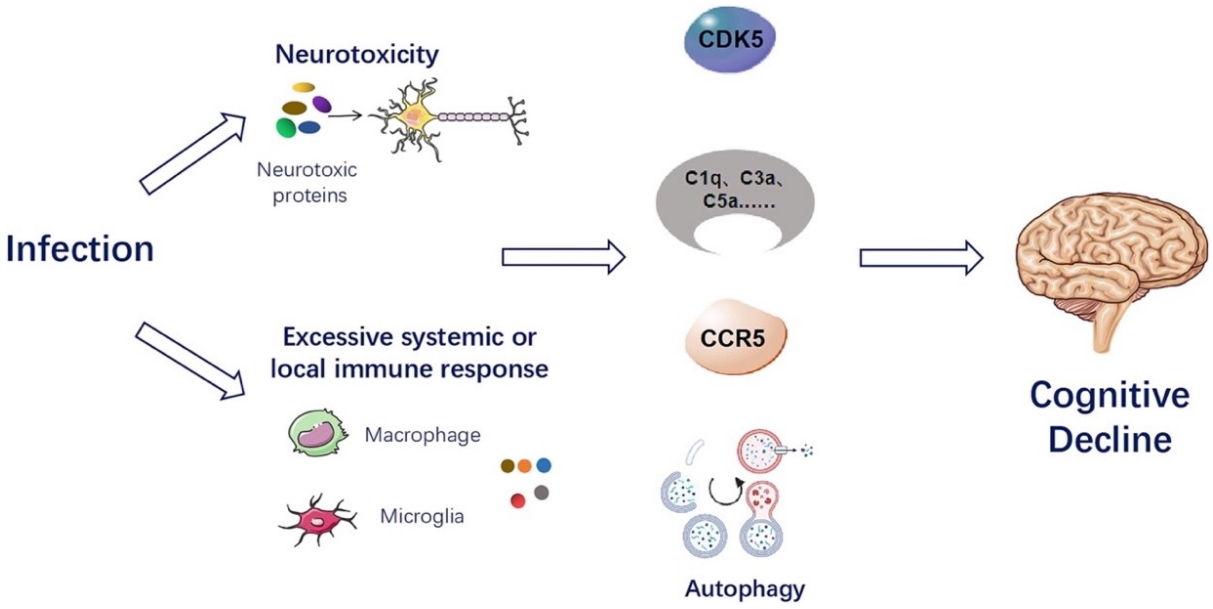


***Figure 12*. Infection-caused cognitive impairment and the molecular mechanisms involved.** Neurotoxic proteins produced during the infection can cause neurotoxicity to neuronal cells and affect neuronal function. Meanwhile, excessive systemic or local immune responses caused by infection can produce a variety of cytokines that can disrupt the blood-brain barrier or directly affect neuronal activity. Aberrant neuronal function ultimately leads to cognitive deterioration. There are various molecular mechanisms involved in the disruption of neuronal function, such as CDK5, CCR5, autophagy, complement pathways and others. Source: Du, Ge, et al. (2023).

U.S. researchers developed a mouse model to evaluate the neuropathology in mild SARS-CoV-2 respiratory illness.[698] When infected with SARS-CoV-2, these mice did not lose weight, showed no discernible sickness, had no evidence of viral infection of the brain and resolved the respiratory symptoms in about a week. The immune response induced by the mild illness, however, resulted "in persistently elevated" inflammatory cytokines that lasted "at least seven weeks."[699] An important contributor to the pronounced systemic inflammation caused by SARS-CoV-2 seems to be related to the presence of the furin cleavage site (FCS) and the S1 segment of the spike protein.

Researchers from the University of Alabama showed that the FCS in SARS-CoV-2 had at least two significant effects: efficiently cleaving the virus's spike protein into two segments S1 and S2 and efficiently secreting free S1 segments from infected cells.[700] Their research showed that the S1 segments were produced independent of replication of the whole SARS-CoV-2 virus. When free S1 was released from infected cells, it activated immune cells (macrophages) and "induce[d] a proinflammatory response… that may be an important contributor to SARS-CoV-2 pathogenesis."[701] Other researchers from Japan showed that the S1 segment contributed to the excessive inflammation observed in COVID-19 patients.[702]

Early in the pandemic, researchers from China noted the similarity of SARS-CoV-2 to murine hepatitis coronavirus (MHC) that possessed a similar FCS that was responsible for the expression of non-fused S1

and S2 fragments.[703] Certain MHC variants (e.g. JHM) have significant neurovirulence. The neurovirulence in the JHM variant is attributed to the spike protein that is proinflammatory and contributes to brain pathology seen in mice.[704] In 2005, University of Pennsylvania researchers demonstrated that a single amino acid substitution in the hypervariable region of the spike protein's S1 segment was responsible for persistent virus and neurovirulence seen in the JHM variant.[705,706] A similar amino acid substitution is seen in the S1 spike protein of SARS-CoV-2 resulting in the integrin binding sequence. As documented by others, "[t]he spike glycoprotein of coronavirus is a major determinant of neurovirulence."[707]

The significance of SARS-CoV-2's free spike (S1) protein effects on the brain was recently published by German researchers. They observed that S1 protein accumulated during acute human and mouse COVID-19 infections in the skull-meninges-brain axis and persisted long after the virus itself had been cleared from the body. The SARS-CoV-2 S1 protein appeared to have a broad range of effects. When administered peripherally to mice, it crossed the blood-brain barrier and induced brain inflammation, neuronal injury, and anxiety-like behavior. It also "exacerbated the effects" of traumatic brain injury and cerebral ischemia. Lingering S1 protein after an acute infection also appeared to potentially contribute to long COVID.[708]

Their published study also reported elevated markers of neurodegeneration in the cerebrospinal fluid of acute and long COVID patients suggesting that neurodegeneration occurred in both conditions. They compared dysregulated proteins found after SARS-CoV-2 infection and onset of Alzheimer's disease. They identified 76 proteins in common and two that are key in Alzheimer's development.[709]

The second article that Han contributed to was titled, "Mendelian randomization study on the causal effects of COVID-19 on childhood intelligence" published in 2022. The team that Han was part of conducted statistical analysis using data from the largest genome-wide association study (GWAS) for COVID-19 in the U.K. They used this statistical analysis to assess the causal association between exposure and outcome. The association they sought was the link between COVID-19 infection and childhood intelligence. Using the largest database for children of European ancestry, they "found that as COVID-19 genetically increased, childhood intelligence had decreased." They asserted that the decrease in childhood intelligence is "not related to the lack of stimulation environment during the pandemic but to COVID-19 infection."[710] They noted that "brain development of infants and children may be impaired by COVID-19 infection" and that "COVID-19 prevention in children is essential."[711]

While Han's second article was heavily referenced, they likely reflected awareness and insights that Han and Li drew from observations in the animal experiments they had conducted with General Yusen Zhou. These studies, however, were not cited in either paper Han and Li or Han published. The COVID-19 pandemic provided an accidental global exposure to this novel virus that permitted assimilating data to evaluate the range of effects seen in multiple ethnic populations. The notion that these researchers were developing a vaccine for a viral agent prior to the pandemic with suspected or known neurotropism and neurovirulence directed at cognitive functions raises the possibility that this research was part of a deliberate effort supporting political and/or military objectives.

Precedent for Developing Non-Lethal Neuro-Incapacitating Agents as Military Weapons

The concept of neuro-incapacitation in war has historical precedents. Between the early 1950s and 1970s, U.S. military researchers studied chemical and biological agents that could affect the central nervous system. Before ending its chemical and biological offensive programs, the United States had developed both types of agents with demonstrated non-lethal incapacitating neurological effects. In 1961, the U.S. military weaponized BZ, an anticholinergic chemical that acted on the brain. Individuals exposed to it fell into a stupor, struggled to speak, showed poor muscular coordination and had difficulty processing thoughts.[712] The United States destroyed its BZ stocks by 1990, several years before the Chemical Weapons Convention entered into force in 1997 and outlawed such chemical agents.

Biological agents could also inflict neuro-incapacitating effects. The United States and the former Soviet Union developed Venezuelan equine encephalitis (VEE) virus for this purpose. In nature, VEE is contracted by the bite of an infected mosquito and is not considered a contagious agent. Individuals who became infected either naturally or through a laboratory-acquired infection developed the illness after an average of 6.4 days incubation. The onset of clinical symptoms would be abrupt with fever and frontal headache and muscle pain that would not be relieved with usual medications. The case fatality rate was estimated at approximately 1%. Symptoms usually lasted 3 to 23 days, though convalescence could last up to 3 ½ months. Relapses occurred in about 30% of cases.

As part of the U.S. bioweapons effort, candidate VEE vaccines were developed to protect the researchers working on these agents, and U.S. military or allies who may be potentially exposed to its effects during its aerosol employment.[713] Research, development and production of all biological agents ended in November 1969 when then-President Richard Nixon unilaterally terminated the U.S. offensive program.

The SARS-CoV-2 virus possesses certain common features with these neuro-incapacitating agents. SARS-COV-2 has a similar incubation period and mortality rate as VEE. The constellation of SARS-CoV-2 symptoms, however, includes significant incidence of asymptomatic and mild infection, a prominent pulmonary component in severe cases in a small percentage of overall infections and a range of neurological effects that are much broader. The reported incidence of neurological symptoms in both severe and mild SARS-CoV-2 disease occurred in 42.2% at onset, 62.7% at hospitalization and in 82.3% at any time during the disease course. The most frequent manifestations were myalgias [muscle aches] (44.8%), headaches (37.7%), cognitive impairment [brain fog] (31.8%), dizziness (29.7%), altered taste (15.9%), and altered smell (11.4%).[714]

PLA Conducted Relevant Research in the Early Phase of the Pandemic

Researchers from the PLA AMMS Institutes of Microbiology and Epidemiology and Biotechnology including two AMMS researchers named in General Yusen Zhou's vaccine patent as well as scientists from several centers, departments and the School of Basic Medicine of the Fourth Military Medical University would later suggest that the CD147 protein played a role in SARS-CoV-2 infection.[715] The article was submitted and published in November 2020. As described, "our study reveals a novel virus entry route, CD147-spike protein.... These findings demonstrate that CD147 provides more entries for SARS-CoV-2 infection and plays a potential role in mediating virus infection, especially in ACE2-deficient cell types." They proposed that an antibody against CD147 could be a potential therapeutic for COVID-19 infection.

This same study noted that in addition to ACE2 receptors, the CD147 protein provides an alternative mechanism to infect host cells. As described, "hCD147 mice were constructed to investigate the infection efficiency of SARS-CoV-2." These specialized transgenic mice with human CD147 receptors showed how SARS-CoV-2 could infect the mice lungs resulting in typical COVID-19 pulmonary effects.[716] This same collaborative research team would publish in 2021 the benefits of a human CD147 antibody that inhibited pulmonary infection by several SARS-CoV-2 variants and prevent the onset of cytokine storm in transgenic CD147 mice.[717] Neither study mentioned any neurological effects observed in these specialized mice. Later, in 2021, researchers from the National Translational Science Center for Molecular Medicine, Fourth Military Medical University, showed the important role CD147 plays in maintaining the blood brain barrier and its pivotal role in the pathology of neurodegenerative illnesses such as Alzheimer's disease.[718]

What is curious about the finding that suggested the CD147 receptor played a role in SARS-CoV-2 infection is that other researchers refuted it. A collaboration between U.S. and U.K. researchers evaluated in vitro whether the CD147 receptor was part of the receptor binding domain of SARS-CoV-2's spike protein. Their study showed "that neither RBD nor full-length spike glycoprotein bind to recombinant human [CD147 receptor]. Further, [anti-CD147 antibody] did not block SARS-CoV-2 infection."[719] This study did not replicate the role of CD147 described by the PLA researchers.

In earlier studies, PLA researchers identified the CD147 protein receptor on the nucleocapsid protein of SARS-

1.[720] This protein is not exposed like the spike protein nor available to bind to a host cell. How this receptor becomes "available" to interact with susceptible human cells was not described by PLA researchers in 2005.[721] As they described in 2020, in vivo studies in mice CD147 enabled SARS-CoV-2 cellular entry by endocytosis rather than receptor binding. Whether this reference was deliberately misleading or suggestive of the role of the integrin-binding RGD sequence found on SARS-CoV-2 spike protein is not known. The SARS-CoV-2 RGD sequence interacts with brain capillary endothelial cells, platelet cells and promotes formation of clots which in turn may activate expression of the CD147 protein.

The significance of CD147 was shown even before the pandemic, by researchers from Penn State Medical College and Louisiana State University Health Sciences Center in 2017. They showed that CD147 played an integral role in strokes by using a CD147 antibody to block its effects. When blood flow to the brain was restricted (ischemic), the CD147 protein would be expressed by the lining (endothelium) of the brain's small blood capillaries. CD147 would promote further clot formation and the expression of inflammatory cytokines increasing the extent and severity of a stroke.[722] The CD147 antibody prevented these effects. The mechanism that promoted CD147's pathological effects was linked to the ischemia caused by blood clots in brain capillaries.

Researchers from the Wuhan Institute of Biomedical Sciences, School of Medicine, and the School of Life Sciences at the Jianghan University in Wuhan demonstrated that brain tissues and cells tested showed significantly higher CD147 and lower ACE2 receptor levels than in the lung.[723] An analysis of 45 different human tissues by Swedish researchers from Uppsala University reported that ACE2 receptors did not have significant expression in the brain.[724] The expression of the CD147 protein was more likely to affect the cerebral nervous system. Canadian researchers from the Hotchkiss Brain Institute, University of Calgary, showed that CD147 was highly expressed in the endothelium of brain capillaries and various sub-regions of the brain including the thalamus, hypothalamus and basal ganglia as well as neuronal layers within the cortex and the cerebellum.[725] Affecting the brain's cortex and cerebellum could result in damage inducing dizziness, ataxia, impaired consciousness and other neurological diseases. As observed by Jianghan University researchers, the susceptibility of these brain regions to SARS-CoV-2 may be one of the reasons for the cognitive and neurological impairment in patients.[72t6]

A 2021 analysis by U.K. researchers showed that the SARS-CoV-2 spike protein, in addition to the RGD integrin-binding sequence, contained sequences of other proteins that could potentially bind to multiple cell receptors or interfere normal cell functioning.[727] Among the specific integrin proteins the SARS-CoV-2 spike protein can bind to are *alpha5beta1* and *alphaVbeta3*.[728] These integrins are found in brain (neuron & glial) and cardiovascular (heart & blood vessel) cells.[729] The integrin alpha5beta1 seems to play a significant role in SARS-CoV-2 infection by increasing the expression of inflammatory mediators (cytokines), causing vascular leakage and adhesion of white blood cells to blood vessels.[730]

The SARS-CoV-2 spike protein's binding to integrins seems to promote "pathologic clotting" in other organs.[731] The reported interaction between the SARS-CoV-2 spike protein and integrins "suggests that virion–integrin interactions may contribute to viral entry, coagulopathy and dangerous tissue damage during the acute phase of disease."[732] "An increasing amount of evidence highlights the crucial role of [brain] endothelial damage in the pathophysiology of long COVID."[733]

The presence of the integrin sequence on SARS-CoV2, found in no other SARS-related or coronavirus, permits it to bind to brain capillary cells and platelets causing clots and impeding blood flow and oxygen transfer. This in turn leads to expression of CD-147 which promotes further clot formation and release of inflammatory mediators disrupting the BBB. The cumulative effect is impacting normal brain function.

The Frontal Lobe as the Possible Primary Target of SARS-CoV-2

In 2021, international neuroscientists and neurologists postulated that the frontal lobe could be the primary target of SARS-CoV-2 because of the significant neurological consequences produced by the virus.

The spectrum of signs and symptoms run the gamut of delirium, amnesia, behavioral and dysexecutive symptoms, anosmia (altered smell), dysgeusia (altered taste), muscle clonus and rigidity. Abnormalities found on magnetic resonance imaging (MRI), electroencephalography (EEG) and positron emission tomography (PET) scans were also noted in these patients.[734] The functional consequences manifest themselves with individuals struggling to organize materials, regulate emotions, set schedules and complete tasks. The relative lack of consistent characteristic pathological findings such as neuropathology, biochemistry and imagery resulted in a variety of clinical characterizations such as encephalopathy and encephalitis, for example.[735] These experts "suggest that an inflammatory para-infectious process preferentially targeting the frontal lobes cause…these shared clinical, neurophysiological and imaging findings."[736]

This constellation of SARS-CoV-2 neuropsychiatric findings has not been seen in other viral infections, such as influenza A (H1N1), where encephalopathy is a rare complication, mostly affecting children, and does not show similar symptoms and imaging features related to frontal lobe dysfunction.[737] Both MERS and SARS-CoV-1 could present with neuropsychiatric symptoms, but the limited data available on neuroimaging and biomarkers do not support similar syndromic changes as SARS-CoV-2.[738] Neurological complications are comparatively rare in both MERS and SARS, though their mortality rates of 35% and 10% respectively are significantly higher than SARS-CoV-2's mortality rate of 1% to 2%.

Reported cases of neurological disease suggest a minimum incidence of ~1:200 cases in MERS and ~1:1,000 cases in SARS.[739] While past studies relating to SARS and MERS have involved small patient samples, evidence on COVID-19 suggests that neurological events occur in a significantly higher proportion of patients.[740] SARS-CoV-2 virus, like SARS and MERS, appears to be both neurotropic and neurovirulent.[741] In both acute and chronic stages, SARS-CoV-2 caused more neurological abnormalities—such as encephalopathy, encephalitis, stroke, peripheral neuropathy, altered smell/taste, amnesia, confusion, stroke and delirium—than the earlier coronavirus outbreaks.[742,743] By some estimates one in three individuals infected with SARS-CoV-2 were diagnosed with a neurological or psychiatric condition and 12.9% developed a serious neurological symptom.[744]

A Disease "Hidden in Plain Sight:" Neurological Consequences Associated with Acute and Long COVID

Several different mechanisms may contribute to the neuro-pathogenesis of SARS-CoV-2 including hypoxia, immune-mediated damage, coagulation problems, and viral invasion into the CNS.[745] As a likely consequence, a constellation of neurological findings has been noted in both patients with severe (hospitalized) and mild (non-hospitalized) disease. Even young people with mild initial illness have experienced neuro-psychiatric symptoms.[746] In acute illness, loss of smell and taste has reportedly affected 68% and 44% of cases respectively.[747] Headaches, confusion, impaired concentration, strokes, depression and effects on peripheral nerves have also been reported. Commonly described as "brain fog," it is the association with difficulty concentrating or thinking during or following COVID-19 infection.[748] The cognitive consequences of COVID-19 include impairment in multiple domains, such as attention, concentration, memory, speed of information processing and executive function.[749] U.S. researchers noted the occurrence of cognitive effects in cases of mild COVID-19 illness.[750] Even a "transient respiratory infection with SARS-CoV-2 induce[d] prolonged neuroinflammatory responses."[751]

Neurologic manifestations of varying severity that affect their cognition and quality of life have been reported in 36.4–82.3% of hospitalized COVID-19 patients worldwide.[752,753] Northwestern University Feinberg School of Medicine conducted a prospective study of one hundred consecutive non-hospitalized patients presenting to their Neuro-COVID-19 clinic between May and November 2020. The main neurologic manifestations at presentation were "brain fog" (81%), headache (68%), numbness and tingling (60%), altered taste (59%), altered smell (55%), and myalgias (55%). Moreover, 85% of the cases also experienced fatigue. Approximately half of the patients in this study had an abnormal neurologic exam, with abnormalities in short-term memory and attention functions being prominent.[754]

Neuropsychological tests, brain FDG-positron-emission tomography (PET) and MRI scans in those who experienced brain fog and cognitive symptoms point to the dysfunction of several brain regions.[755] Significantly, SARS-CoV-2-positive patients performed worse on attention and working memory cognitive tasks compared to a demographic-matched U.S. population ($p < 0.01$).[756] As suggested in other studies published by the Feinberg School, brain fog, with or without fatigue, might represent a mild form of post-COVID-19 encephalopathy. While advanced age and more severe COVID-related disease were associated with these neurological sequelae, another notable finding of this study was that "any neurologic manifestations as a whole were more likely to occur in younger people [which was] surprising."[757]

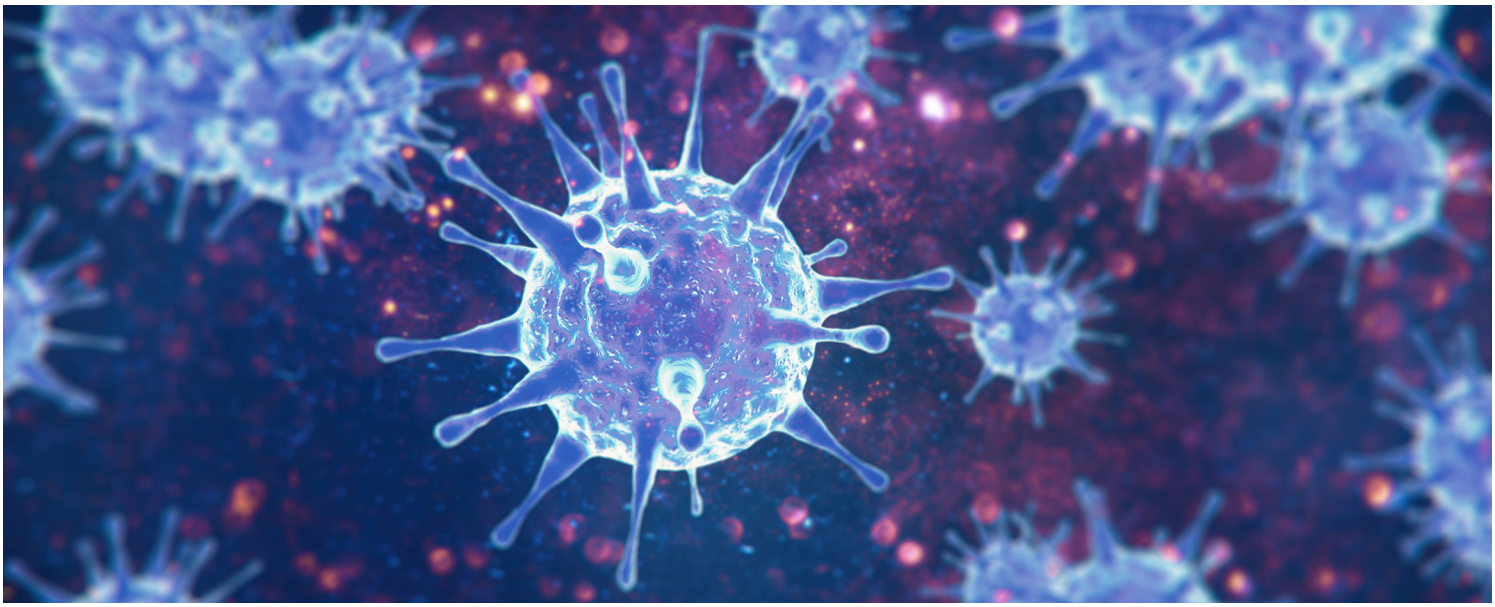
Younger patients tended to have less severe COVID-related illness yet have neurological findings. A November 2024 study published by the Feinberg School, noted that "younger and middle-aged patients with [long COVID] are more severely affected than older patients, regardless of the severity of their acute COVID-19 and hospitalization status." They showed that younger and middle-aged patients suffered from a higher burden of neurologic symptoms, fatigue, sleep disturbance, and cognitive dysfunction… compared to older patients with [long COVID]."[758]

In a review of common clinical neurological imaging studies used during acute SARS-CoV-2 illness and for long COVID, several identifiable findings were noted. PET scans showed hypometabolism in both symptomatic and asymptomatic SARS-CoV-2 cases. A variety of types of PET scans showed amyloid lesions in frontal and anterior cingulate cortex areas, brain hypometabolism and hypoperfusion of blood in the frontal cerebral lobes.[759] Other researchers have shown how such scans can show evidence of effects in several brain areas, such as the prefrontal cortex, prior to symptom onset, during active illness, and six months after infection, mimicking patterns seen in several neurodegenerative disorders.[760] These localized radiological findings comport with the neurological symptoms seen in patients undergoing such studies.[761]

Researchers from John Hopkins University showed that the hypometabolism effects (PET Scan) could be seen in both symptomatic and asymptomatic SARS-CoV-2 cases. They also showed that the effects while persistent may be reversible over time: "At 6–12 months, patients showed a near-complete recovery of brain abnormalities, with residual limited hypometabolic clusters in the anterior cingulate cortex" among other frontal brain regions.[762] MRIs noted structural brain changes showing the effects of clots (infarcts), white matter atrophy, and changes in gray matter volumes. In adults, these images showed disruption of micro-structures and functional brain integrity in the recovery stages of COVID-19, suggesting long-term consequences of SARS-CoV-2.[763] Changes in specific areas of the brain correlated with COVID-19-related neurological symptoms.

A large longitudinal study using data from the U.K. Biobank compared individuals' baseline pre-COVID-19 MRI scans with their post-COVID-19 infection scans. Analyses of paired MRI scans revealed a "significant, deleterious impact associated with SARS-CoV-2."[764] Changes in grey matter thickness showed bilateral longitudinal differences in several areas of the brain including the parahippocampal gyrus, anterior cingulate cortex and temporal pole. Significantly, greater cognitive decline occurred in all SARS-CoV-2-positive patients. This decline was associated with atrophy of the cognitive lobule of the cerebellum.[765] Neuroimaging of patients "recovered" from mild-to-moderate SARS-CoV-2 infection showed significant brain alterations "commensurate with 7 'years of healthy' aging."[766]

Coincidently, a recent study by the University of Washington associated COVID-19-related lockdowns with premature aging in teenage brains.[767] This study involved MRI imaging of teenagers subject to lockdowns that showed "accelerated cortical thinning in the post-COVID brain, which was more widespread throughout the brain and greater in magnitude in females than in males."[768] The conclusions made by the authors suggested that potential lifestyle changes that induce stress may be the cause for these findings. Notably, however, this study did not control for or identify which adolescents were infected by SARS-CoV-2. Besides accelerated brain aging, recent studies support the possible association of SARS-CoV-2 infection with Parkinson's disease and other neurodegenerative disorders such as Alzheimer's disease.[769]



The risk of cognitive decline following SARS-CoV-2 acute infection was assessed in a longitudinal study of severe and non-severe hospitalized COVID-19 survivors of the initial outbreak in Wuhan, China. The study evaluated the risk in unvaccinated study participants within 12 months of their illness. The participants were assessed using the Chinese version of the Telephone Interview of Cognitive Status-40.[770] It is comprised of eight items that results in a maximum score of 30 points, and includes the following data fields and point values: date (5 points), home address (3 points), counting backward (2 points), word list learning (10 points), subtractions (5 points), responsive naming (2 points), repetition (1 point), and President/Vice President's last name (2 points). This assessment can be used to remotely evaluate different cognitive disorders and can identify the degree of cognitive impairment. The Wuhan study observed, "severe COVID-19 was associated with an increase in risk of early-onset, late-onset, and progressive cognitive decline.... 21% of individuals with severe cases in this cohort experienced progressive cognitive decline, suggesting that COVID-19 may cause long-lasting damage to cognition. These findings imply that the pandemic may substantially contribute to the world dementia burden in the future."[771]

In addition to the acute effects, the chronic consequences of SARS-CoV-2 infection have emerged as a significant legacy of the COVID-19 pandemic. In 2024, over 400 million people globally were experiencing "long COVID" (Figure 13).[772] Symptoms of extreme fatigue that persist over 30 days following acute infection form the diagnosis of long COVID. According to German researchers, "the most common, persistent, and disabling symptoms of long COVID are neurological."[773] After fatigue, difficulty concentrating was the second most common symptom, appearing in 51% of U.K. long COVID patients.[774] Researchers have shown that cognitive impairment can persist after two years.

A study involving 154,068 U.S. veterans who had COVID-19 showed an increased risk of "an array of neurologic disorders spanning several disease categories including stroke, cognition [and] mental health disorders.... The risks were evident even in people who did not need hospitalization during the acute phase of the disease of the infection."[775] Many of those suffering from long COVID were less than 50 years old, were not hospitalized, experienced mild illness and had been previously healthy and active.[776] A 2023 published review noted that "long COVID is associated with all ages and acute phase disease severities, with the highest percentage of diagnoses between the ages of 36 and 50 years, and most long COVID cases are in non-hospitalized patients with a mild acute illness."[777] A more recent review estimated the point prevalence of long COVID in the general population to be between 6 and 7% in adults and approximately 1% in children.[778]

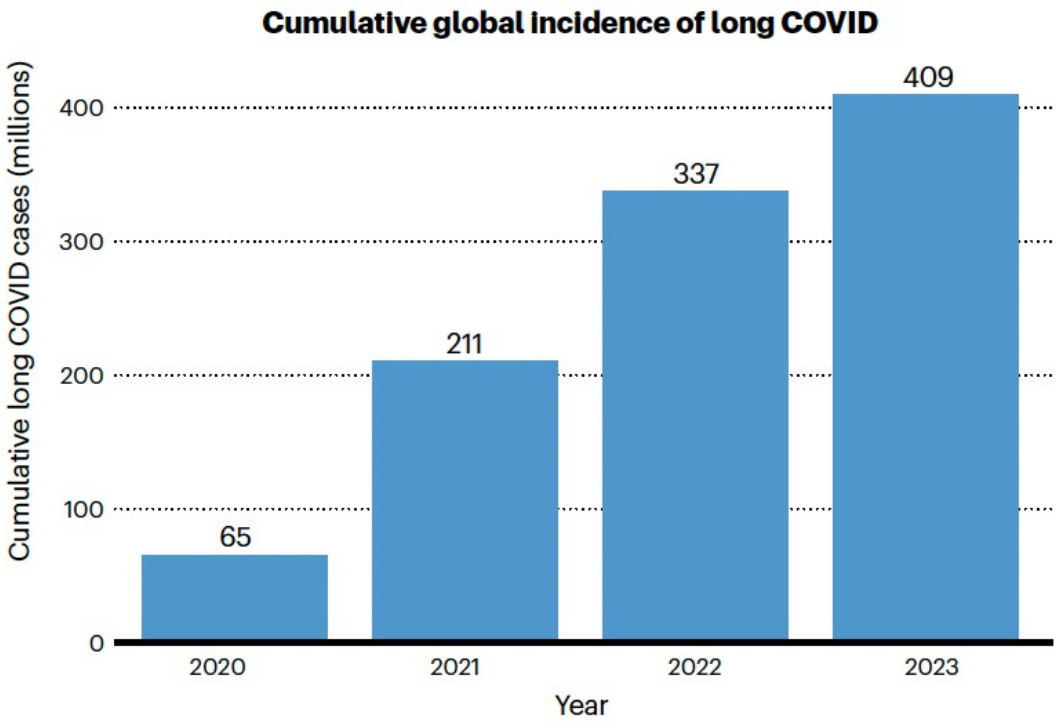


***Figure 13*. Estimated global cumulative incidence of long COVID.** The global incidence of long COVID was estimated on the basis of meta-regression estimates that pool together all the available evidence. Considering the Institute for Health Metrics and Evaluation's annual estimates of SARS-CoV-2 infections and assuming the lower risk estimate of 6.2% for long COVID at 3 months after infection, a proportion symptomatic cases among infections of 65% (ref. 31), and a reduction in the risk of long COVID for 2022 and 2023 (to account for then combination of the putative lower severity of the Omicron variant and the mildly protective effect of vaccination)60, the estimated cumulative global incidence of long COVID was 65 million, 211 million, 337 million and 409 million in 2020, 2021,2022 and 2023, respectively. Source: Al-Aly et. al. (2024).

Long COVID in Children: Limited Data and Uncertain Prognosis

Long COVID and neuro-cognitive problems have been reported in children. Symptoms in children observed after SARS-CoV-2 infection include short-term memory problems, lack of concentration, difficulty understanding instruction and difficulty processing information.[779] According to a review conducted by an international group of researchers, COVID-19 infection among children is a growing problem:

> During the early stages of the COVID-19 pandemic, neonates, children, and adolescents aged less than 19 years occupied a small proportion (1% to 10%) of the total reported COVID-19 cases. They were also more likely to present with a milder clinical course and more favorable short-term outcomes compared with adults. However, with the subsequent surge of cases caused by the [Delta] and [Omicron] variants, and the fact that a large proportion of children under 12 years old still remain unvaccinated globally, the number of neonates, children, and adolescents infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been increasing significantly.[780]

The American Academy of Pediatrics estimates that six million children might be experiencing long COVID. Children with long COVID reported "brain fog in 2 to 44%" of reported cases.[781] In adults, long COVID is estimated to occur in approximately 30% of patients after SARS-CoV-2 infection and is associated with those having more severe

acute illness symptoms and loss of smell and taste.[782] The likelihood of long COVID in children is thought to be the same though some studies challenge this notion. One study aptly noted that "our understanding of the range of neurological issues linked to SARS-CoV-2 infection in children is limited."[783] This limitation is likely a consequence of underreporting: "Children generally have mild acute illness which can result in a lack of testing for SAR-CoV-2. The lack of confirmed COVID-19 diagnosis combined with developmental limitations of children to recognize and describe nonspecific, and indolent [long COVID] symptoms may result in under-recognition or a delay in diagnosis."[784]

Abnormal neuroimaging in children highlights the issue. Pediatric patients having lower initial severity of COVID-19 infection have demonstrated, on average five months later, a significant brain hypometabolic pattern on PET scan similar to that seen in adults.[785] Younger subjects had mild to moderate evidence of hypometabolism of their bilateral medial temporal lobes, brainstem and the cerebellum similar to long COVID adults.[786] Meta-analysis of several pediatric neuroimaging studies noted, "a substantial proportion of pediatric COVID-19 patients with neurological symptoms have abnormal neuroimaging findings, underscoring the need for vigilant monitoring of neurological complications in this vulnerable population."[787] In one study, "patients with memory/cognitive impairment and more numerous complaints were younger."[788] These findings show a common functional brain involvement among subjects regardless of age, and initial severity at the acute stage and support the possibility of long COVID in children similar to adults.[789]

A retrospective cohort study evaluated the increased risks of neurological and psychiatric sequelae following COVID-19 infection in adults and children. Both groups showed elevated risks for several neuro-psychiatric conditions at the end of the two-year follow-up period.[790] Children seemed at lower risk of mood disorders than adults. Children, however, had an "increased risk of cognitive deficit, insomnia, intracranial hemorrhage, ischaemic stroke, nerve, nerve root, and plexus disorders, psychotic disorders, and epilepsy or seizures."[791] This study suggested that the pathogenesis of COVID-19 sequelae in children might be different from that of adults in some respects.[792] Researchers from Johns Hopkins University published a limited case study showing that "approximately a third of children with long COVID demonstrate objective weaknesses on sustained and divided attention tasks but were largely intact in other domains of neuropsychological functioning.... Parents reported high rates of mood, anxiety, and executive functioning difficulties which likely impact daily functioning."[793]

The prospective risk of further neurological injuries to children because of initial or repetitive SARS-CoV-2 infection is currently not well defined. A single prospective study of long COVID in children in Italy found that a significant impact was found in some children and adolescents for up to 36 months after the initial infection. COVID-19 vaccines were associated with a lower risk of developing long COVID, particularly in adolescents. There seemed, however, to be an increased risk of reinfection in children who experienced long COVID.[794]

A large population study conducted by the South Korean Disease Control and Prevention Agency showed that the risk of reinfection of SARS-CoV-2 is elevated in unvaccinated individuals and in children. This study did not detail any risks of sequelae with reinfection. It also noted that while there are breakthrough infections among vaccinated persons, vaccination further decreased the risk of reinfection compared to unvaccinated persons.[795]

A 2024 meta-analysis of COVID vaccine efficacy studies by researchers from Hong Kong, China analyzed data from 25 observational studies (n=14,128,260) with no randomized controlled studies. Their findings suggest that two-dose pre-COVID vaccination and one-dose post-COVID vaccination are associated with a 24% and 15% lower risk respectively of long COVID. They concluded that "since long COVID reduces quality of life substantially, vaccination could be a possible measure to maintain quality of life by partially protecting against long COVID."[796]

A 2023 study by the U.S. National Academies of Science estimated that only approximately seven percent of U.S. children younger than five have received COVID-19

vaccinations.[797] The U.S. CDC reports that as of May 2024 only 14.4% of U.S. children are up to date and effectively immunized against SARS-CoV-2.[798]

As reported by the Harvard Magazine: "Math, reading, and history scores from the past three years show that students experienced a significant decline in learning during the pandemic. The team's calculations indicate that by the spring of 2022, the average student was lagging by approximately one-half year in math and one-third of a year in reading."[799]

The *New York Times* recently reported that "pandemic babies, toddlers and preschoolers are now school-age, and the impact on them is becoming increasingly clear: Many are showing signs of being academically and developmentally behind."[800] The article suggested there are several potential reasons for the developmental delay seen in pandemic born children: parental stress, lack of socialization, excessive screen time, etc. As written, "it's too early to know whether young children will experience long-term effects from the pandemic," but on a positive note, "if the kids come to school, they do learn."[801]

On July 24, 2024, *The Washington Post* reported that "test scores between today's students and their pre-pandemic counterparts are growing wider… and are worse."[802] The data for this assessment was provided by the nation's three largest test providers to school districts. These tests are given periodically to assess students' progress during the academic year. The growing gap appeared more pronounced for older children, though both young and old were affected. As noted in one study, "it's as if the pandemic or some other factor is continuing to result in lower and lower performance."[803] In another report issued in June 2024, analysis of test scores in reading and math showed a pattern of improvement in higher elementary grade students but lower scores persisted in lower elementary grades. Observational studies of U.S. children and their school performance show younger children and students are developmentally delayed and "are either falling behind or consistently hovering below historical [testing scores] trends" in reading and math.[804,805]

Given the known neurocognitive effects of COVID-19 infection, these declines may not be entirely attributable to the "lack of stimulation environment during the pandemic but to COVID-19 infection."[806] As noted by Gencheng Han from the AMMS Institute of Military Cognition and Brain Sciences, who participated in General Zhou's early vaccine trials, "brain development of infants and children may be impaired by COVID-19 infection" and "COVID-19 prevention in children is essential."[807]

Animal Model Findings and Variant Dependence of SARS-CoV-2's Neurological Impact

The cognitive effects of SARS-CoV-2 infection also seem to be variant dependent. Less cognitive impairment was documented with the Delta variant compared to the original (wild-type/Wuhan), Alpha or Omicron strains.[808] This finding seems to fit with the significant incidence of cerebral microhemorrhages noted in autopsies of individuals who died from the initial Wuhan strain compared to later variants.[809]

In published autopsy studies from Switzerland and Italy, significant differences were noted between the initial Wuhan strain and the later strains. In the Swiss study, cerebral microhemorrhages of the cerebral were significantly more frequent in patients of the first (Wuhan strain) wave (p = 0.0003). The Italian study reported autopsy results performed over the first three waves of SARS-CoV-2 (Wuhan, Alpha and Beta). One hundred percent of the first pandemic wave autopsies showed microthrombi (small clots) in the small brain blood vessels. In later pandemic waves, small infarcts caused by small clots were less frequent, occurring in eight out of 22 cases (38%).[810]

Despite the suggestion that the SARS-CoV-2's neurological effects seem to attenuate, Australian and U.K. researchers noted that later omicron subvariants (BA.5 and XBB) had increased neurotropism and neurovirulence comparable with the original Wuhan strain.[811,812] The incidence and persistence of the neurological effects of subsequent circulating SARS-CoV-2 strains is not widely acknowledged or reported.

In non-human primate (NHP) studies, SARS-CoV-2 brain infection appeared to be restricted to brain blood vessel (endothelial) cells. Multiple microhemorrhages and

microinfarcts resulting in ischemia (lack of sufficient blood flow) and hypoxemia (inadequate oxygenation) appear to play a role in nerve cell injury and death observed in the animals. The neuroinflammation, microhemorrhages, brain hypoxia, and nerve cell degeneration and death observed in NHPs is consistent with autopsy findings in SARS-CoV-2 infected patients.[813]

Additionally, pathological investigation suggests a significant role for brain hypoxia in the neuropathogenesis of COVID-19, even in animals without severe disease.[814] Widespread neuroinflammatory response was noted on brain scans of NHPs following a mild infection.[815] These NHP studies suggest that brain damage can be present even in the absence of specific neurological symptoms. Therefore, it is possible that brain involvement could be an underestimated feature in SARS-CoV-2 infected patients.[816] These findings may provide insight into neurological symptoms associated with long COVID. SARS-CoV-2's effects on the brain's astrocytes and microglial cells resulting in potential chronic inflammation could play a role in the later development of chronic neurological disorders.[817]

Underreporting of Neurological Findings in COVID-19 Autopsies

During the first SARS outbreak, the PLA performed early pivotal studies including publishing full autopsy findings noting the brain involvement of SARS-1. Full autopsies involve external and internal examination of the deceased and include removal and examination of the brain. Early in the COVID pandemic, the Fifth Medical Center of the PLA General Hospital published one of the first SARS-CoV-2 case reports on February 17, 2020. They described the clinical progression, management and treatment of a 50-year-old man who had died. The patient's clinical signs and symptoms and pathological findings of an autopsy from "biopsy samples… taken from lung, liver and heart tissue" but made no mention of any neurological symptoms or findings.[818] For reasons that are likely associated with efforts to obscure SARS-CoV-2's neurological effects, limited autopsies were performed, or more likely brain findings were not reported.

In May 2020, the First and Third Army Military Medical Universities published findings from three minimally invasive autopsies of COVID-19 cases. Samples were taken from the lung, heart, kidney, spleen, bone marrow, liver, pancreas, stomach, thyroid and skin of these patients. As described, SARS-CoV-2 is "mainly distributed in the lung, the infection also involves in the damages of heart, [cardiovascular] vessels, liver, kidney and other organs."[819] Any clinical neurological findings in these hospitalized cases were not reported nor were any brain or nerve tissue samples taken.

The concept of minimally invasive tissue sampling (MITS) is an accepted practice in human autopsies during infectious disease outbreaks. In developing, low resource countries, access to such capabilities may be limited, although this does not apply in China. Variations of MITS, such as targeted postmortem biopsies of a few key organs such as the brain, liver, or lungs, have also been proposed and used in the past for the investigation of specific infectious diseases occurring in outbreaks, including Nipah virus infections in Bangladesh, yellow fever in Brazil, malaria deaths in Malawi, or even Ebola deaths in Africa.[820]

The potential aerosol risk of recovering brain tissue following sawing the skull likely required enhanced BSL-3 respiratory precautions including enhanced positive pressure respiratory protection (Figure 14). Other investigators have noted that China's National Health Commission issued a second edition of laboratory biosafety guidance for SARS-CoV-2 on January 23, 2020, that is silent on autopsy sample collection.[821,822] There is no publicly available copy of the first edition of this biosafety guidance, so it is not possible to determine when that was first issued nor what its guidance was.

In 2024, published studies by researchers from Helmholtz Munich and Ludwig-Maximilians-Universität, Germany and University of Helsinki, Finland may have provided further rationale for the aversion to invasive brain autopsies in China. German researchers noted the presence and persistence of the SARS-CoV-2 virus in the skull-meninges-brain axis. The SARS-CoV-2 virus spike and nucleocapsid proteins were identified adjacent to blood vessels in the brain and in the marrow of the skull.[823] Sawing through the bone including the skull is considered a risk for potential aerosol transmission.[824]

Finnish researchers assessed this risk and evaluated skull sawdust generated during COVID-19 autopsies. They found PCR and culture evidence of SARS-CoV-2 in post-mortem samples.[825] In China, the apparent use of MITS may have been driven by both policy and safety considerations rather than resource limitations.

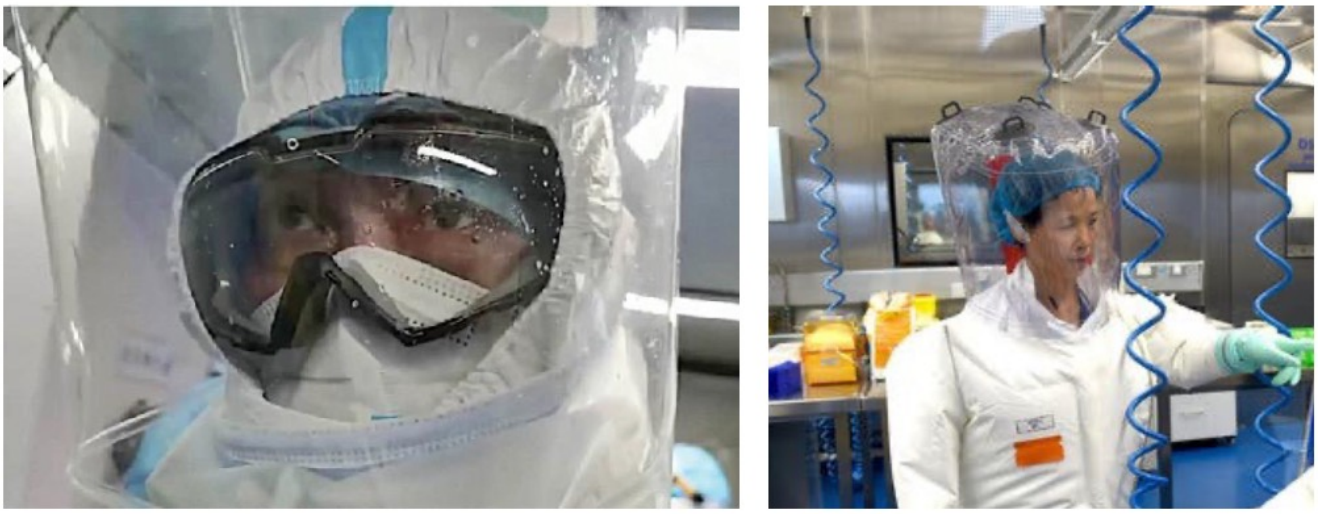


***Figure 14*. Left: A Chinese pathologist performing a COVID-19 autopsy in enhanced BSL3 PPE.** Courtesy of Hongyan Zhang, Southwest Hospital, Chongqing, China. Source: Bian, X. W., & COVID-19 Pathology Team. (2020). Right: A BSL4 researcher at the Wuhan Institute of Virology. Source: Qin, A., Buckley, C. (2021).[826]

In June 2020, one of the largest early published autopsy series was performed by several academic and military hospitals and research institutions in China. They conducted 91 autopsies, 37 systematic and 54 MITS percutaneous multiple-organ biopsies.[827] The author provided extensive descriptions of the histo-pathologic and immunochemical effects of SARS-CoV-2 in the respiratory (trachea and lung), hematopoietic (lymph node, spleen, and bone marrow), cardiovascular (heart and blood vessels), gastrointestinal (esophagus, stomach, small and large intestine), endocrine (thyroid and adrenal) and nervous systems (cerebrum and cerebellum). The neurological findings were described as "brain hyperemia and edema, partial neuron degeneration and ischemic changes were detected. Some cases showed neuronophagia [immune process of removing dead or damaged nerve cells], inflammatory-cell infiltration in perivascular [around blood vessel] regions and focal cerebral infarction [stroke]. A few cases manifested brain herniation."[828] The major cause of death cited in this study was "multiple organ dysfunction syndrome, especially acute respiratory distress syndrome."[829]

The prevalence of the effects on the brain or any other organ system finding in the 37 systematic autopsies was not included. As a result, it is not possible to assess whether the findings occurred in only a few or in most cases. The study reported that "qRT-PCR-based virus nuclear acid detection, electron microscopy and immunohistochemical staining, SARS-CoV-2 was detected in the hilar lymph nodes, spleen, heart, liver, gallbladder, kidneys, stomach, breast, testes, skin, and nasopharyngeal and oral mucosa."[830] In a table accompanying the report, the PCR and immunochemistry test results of brain tissues were listed as "+/- positive result to be confirmed."[831]

The early autopsy findings from China stand in sharp contrast to those published from other countries. A published study of the first 100 consecutive COVID-19-related autopsies performed at Mount Sinai Hospital in New York City detailed the neuropathological examination of 63 brains, with histologic evaluation of 58. The study identified a range of abnormal pathology. The most frequent pathological findings were evidence of brain infarction (stroke), observed in 19 of 58 cases

(32.7%), and the widespread associated presence of microthrombi (clots), noted in 17 of 58 cases (29.3%). Their observations support that clotting disorders and increased clots are a significant component of COVID-19-related neurological morbidity and mortality.[832]

A study by Columbia University Irving Medical Center/New York Presbyterian Hospital published neuropathological and molecular findings from 41 consecutive patients who underwent autopsy after they died of SARS-CoV-2 infection.[833] Of the 41 patients, seven (17%) had a neurology consult during their hospital admission, and one was admitted to the stroke service prior to their death. Eighteen (44%) brains contained infarcts (strokes), acute, subacute, or chronic in several areas of the brain (thalamus, hippocampus, corpus callosum and brainstem) with 10 (24%) containing one or multiple small infarcts. Eight (19%) brains contained hemorrhages. Significantly, diffuse microglial activation was observed in 81% (34 of 41) of the brains.[834] Microglial cells are the brain's immune cells and those of the central nervous system. When they are activated, they release neurochemicals (cytokines) that cause inflammation. Their activation is a hallmark of brain pathology.[835]

Underreporting and Possible Censorship of Neurological Effects in Early Chinese Studies

In addition to the specific animal vaccine studies conducted by the AMMS's General Yusen Zhou that did not report significant neuropathological findings, early Chinese publications seemed to underreport neurological findings in clinical cases. The initial observational case studies that were published in late January and early February 2020 provided important insights for global medical and public health communities preparing for an imminent pandemic. One of the first such observational reports came from clinicians at the Wuhan Jinyintan Infectious Disease Hospital. They provided an initial clinical and epidemiological characterization of 99 patients with the novel coronavirus. The principal clinical manifestations were fever (83%), cough (82%), shortness of breath (31%), muscle ache (11%), confusion (9%), headache (8%), sore throat (5%), runny nose (4%), chest pain (2%), diarrhea (2%), and nausea and vomiting (1%).[836]

A follow up study using National Health Commission data from 1099 hospitalized patients with laboratory-confirmed COVID-19 from 552 hospitals in 30 provinces, autonomous regions, and municipalities in mainland China through January 29, 2020, was published in the New England Journal of Medicine. Symptoms consistent with neurological involvement included headache (13.7%), fatigue (38.1%) and muscle aches (14.9%).[837] An early review paper published in March 2020 by researchers from Peking Union Medical College, the Chinese Academy of Sciences and the PLA General Hospital in Beijing citing data from the National Health Commission and five Wuhan and Hubei provincial hospitals noted the symptoms of pulmonary disease and did not highlight any specific neurological findings except headache and muscle aches (myalgia).[838]

An outlier to studies reporting few neurological findings is an April 2020 retrospective, observational study conducted by the Union Hospital, Tongji Medical College of the Wuhan Huazhong University of Science and Technology and published in the Journal of the American Medical Association (JAMA). Accepted for publication on March 26, 2020, it was the first to identify the range of neurological effects associated with SARS-CoV-2 infection. This hospital system of three centers was designated by the government to treat COVID-19 patients. More than a third (36.4%) of the 214 non-severe and severe clinical cases treated between January 16, 2020, and February 19, 2020, had nervous system manifestations.[839] Almost a quarter (24.8%) had central nervous system (CNS), 8.9% had peripheral nervous system (PNS), and 10.7% had skeletal muscle signs and symptoms. In patients with CNS manifestations, the most common reported symptoms were dizziness (16.8%) and headache (13.1%). The most common reported PNS symptoms were taste (5.6%) and smell impairment (5.1%). The more severe COVID-19 cases were associated with more significant CNS effects such as impaired consciousness, stroke, ataxia and seizure.[840]

In August 2020, an epidemiological and clinical characteristics study published by the Tongji Hospital, also affiliated with the Tongji Medical College, noted a lower incidence of neurological findings. In a review of 1663 hospital patients who were PCR positive for

SARS-CoV-2 between January 14, 2020, and February 28, 2020, only 1.7% reported any nervous system symptom (dizziness or headache).[841] Also in August 2020, PLA Third Military Hospital researchers in Wuhan published a retrospective observational study of 405 PCR positive SARS-CoV-2 patients admitted between January 12 and March 8, 2020. Their study reported headaches and dizziness in only 1.2% of patients treated.[842] Furthermore, a 2021 review article by the WIV's Ben Hu and Zhengli Shi summarized "current knowledge of clinical, epidemiological and pathological features of COVID-19" that focused principally on COVID-19 pulmonary findings. Headaches were mentioned as a "less common symptom" and altered taste and smell as a self-reported symptom in cases reported in Italy.[843] These studies did not reference the April 2020 JAMA article and stand in sharp contrast to the results in that study reporting neurological sequelae in more than a third of patients admitted during nearly the same timeframe.

Comparatively, a U.S. study in a single Chicago hospital network in 509 consecutive hospitalized patients admitted with confirmed COVID-19 between March 5 and April 6, 2020, reported neurologic manifestations present at COVID-19 onset in 215 patients (42.2%), at hospitalization in 319 patients (62.7%), and at any time during the disease course in 419 patients (82.3%).[844] The most frequent neurologic manifestations were myalgias (44.8%), headaches (37.7%), encephalopathy (31.8%), dizziness (29.7%), loss of taste (15.9%), and loss of smell (11.4%). Independent risk factors for developing any neurologic manifestation were severe COVID-19 ($P < 0.001$) and younger age ($P = 0.014$).[845]

A study in Spain found a similar pattern of neurological findings in 841 hospitalized COVID-19 patients. In that cohort, 57.4% developed some form of neurologic symptom. Nonspecific symptoms such as myalgias (17.2%), headache (14.1%) and dizziness (6.1%) were recorded. These symptoms were present mostly in the early stages of infection. Loss of smell (4.9%) and taste (6.2%) occurred early and was the first clinical manifestation in 60% of cases and more frequently in less severe cases. Disorders of consciousness occurred commonly in older patients and in severe COVID-19 cases.[846]

The notion that PRC authorities subjected scientific data to control or manipulation was first raised by CNN News in April 2020:

> China has imposed restrictions on the publication of academic research on the origins of the novel coronavirus, according to a central government directive and online notices published by two Chinese universities, that have since been removed from the web. Under the published order, all COVID-19 academic papers would be subject to extra vetting before being submitted for publication. Studies on the SARS-CoV-2 origin would receive extra scrutiny and must be approved by central government officials, according to the now-deleted posts. A medical expert in Hong Kong who collaborated with mainland researchers to publish a clinical analysis of COVID-19 cases in an international medical journal said his work did not undergo such vetting in February.[847]

An analysis of Chinese documents obtained and translated by a Japanese magazine reported that Chinese Communist Party officials were intent to conceal information about the SARS-CoV-2 outbreak as early as January 3, 2020. The documents were instructions issued by China's National Health Commission to destroy samples of the virus and indicated they "were well aware that they were dealing with a virus that could be passed from person to person."[848] In May 2020, the U.S. Secretary of State Mike Pompeo accused the Chinese Communist Party of trying to "suppress information about this virus, about where it began, about how it started, about how it was being transmitted from human to human."[849]

A more comprehensive investigation performed by the Associated Press (AP) documented that the orders to restrict publication of any data or research related to the SARS-CoV-2 origins were "direct orders from President Xi Jinping." As described, China's government was "strictly controlling all research into its origins, clamping down on some while actively promoting fringe theories that it could have come from outside China."[850] The AP report also noted that China "delayed warnings about the pandemic, blocked sharing of information with the World Health Organization and hampered early testing."

Continued PLA Attenuated Coronavirus Vaccine Research Under Uncertain Biosafety Conditions that Resulted in Potentially Highly Lethal Strains

In 2022, researchers at WIV and at the Beijing University of Chemical Technology (BUCT) studied the risks of pangolin coronavirus spillover. WIV researchers compared coronaviruses collected from Malayan pangolins confiscated in Guangdong (GD) and Guangxi (GX) provinces in March 2019.[851] As mentioned, the spike protein from a Guangdong Pangolin (GD) coronavirus and SARS-CoV-2 are overall 89.6% identical in sequence with 96.9% amino acid identity in the RBD and a difference of one amino acid in the RBM.

The Guanxi pangolin virus (PCoV_GX) is less similar to SARS-CoV-2, sharing 92.3% sequence identity in the spike protein and 86.7% amino acid identity in the RBD.[852] Both pangolin strains had higher affinity for human cells. The GX (P1E) strain infected seven different animal species, including wild-type mice, two different human ACE2 transgenic mice and hamsters. The GX strain caused lung infection but not severe disease in these humanized mice. The WIV and BUCT researchers concluded that while the GX strain could "pose a risk of interspecies infection to humans and other animals... it may not be a highly pathogenic strain."[853]

In an earlier 2022 study, researchers at the BUCT had evaluated the effect of a similar GX (P2V) pangolin coronavirus strain in hamsters. The strain "produced moderate pathogenicity in hamsters and [was] less virulent than SARS-CoV-2." The neutralizing antibodies induced by the GX coronavirus provided protective immunity against SARS-CoV-2.[854] This finding prompted the researchers to note that "after proper modification, [GX] Pangolin-CoV [coronavirus] might have the potential to be developed as a live attenuated SARS-CoV-2 vaccine or could be incorporated into other vaccines."[855] Those published studies performed by the WIV and BUCT were performed under BSL-3 conditions.[856,857]

Researchers in Beijing at the BUCT and the Fifth Medical Center of the PLA General Hospital performed additional studies on the GX(P2V) strain. One of the BUCT researchers, Yigang Tong, had previously been affiliated with the AMMS Fifth Institute (Institute of Microbiology and Epidemiology). Tong and General Yusen Zhou first published together in 2007 and as recently as 2016.[858,859] In 2009 while assigned together at the AMMS, they published a study that showed how to use a designed restriction enzyme assisted technique to perform rapid site-directed mutagenesis on double-stranded plasmid DNA.[860] This technique is relevant to RNA mutagenesis and was recently suggested as being used to recombine sequences of different bat and pangolin coronaviruses seen in SARS-CoV-2.[861]

In Tong's 2024 published study, the researchers carried out directed evolution of the virus by passaging it serially eight times in monkey kidney (Vero) cells. This work resulted in a strain they called GX(P2V) short_3UTR. This strain carried a point mutation and a 104-nucleotide deletion in the hypervariable region of the viral 3'-UTR. The resultant strain was highly attenuated when grown in cell cultures (two monkey and one human lung cell lines) and inoculated in live animals (golden hamsters and wild-type (BALB/c) mice). Notably, the antibody elicited in hamsters infected by this strain inhibited the ability of a pseudovirus (VSV SARS-CoV-2 spike protein) to infect cells that expressed the human ACE2 receptor.

This observation prompted these researchers to suggest that GX(P2V) short_3UTR might be developed into an attenuated live virus vaccine for SARS-CoV-2 itself. Evaluation of this attenuated virus as a vaccine candidate progressed to testing in human cells and ACE2 receptor humanized mice.[862] The humanized mouse line used in this experiment was the same used by General Zhou in his April 2020 study.[863] The mouse strain was developed in 2018.[864] It was different from the two strains of humanized ACE2 mice used earlier by the WIV to evaluate the GX strain. One reported characteristic of the new mouse strain was that the course of infection by SARS-CoV-2 closely mimicked human COVID-19 clinical illness and showed brain infection.[865]

The effect of GX(P2V) short_3UTR on this type of humanized ACE2 mice was unexpected: "Surprisingly, all the mice that were infected with the live virus succumbed to the infection within 7-8 days post-inoculation, rendering a mortality rate of 100%."[866] The "attenuated"

GX(P2V) short_3UTR strain resulted in brain infection and death of the mice. The biosafety level at which these experiments were conducted was not described; however, neither the BUCT nor the Fifth Medical Center of the PLA General Hospital have known BSL-3 labs. The outcome of this experiment highlights the potential unpredictability and risk that accompanies SARS-related research. In this case, vaccine research resulted in a highly lethal neurological pathogen.

The BUCT and the AMMS Institute of Microbiology and Epidemiology previously collaborated with others in submitting for publication the earliest study associating SARS-CoV-2 with Malayan pangolins on February 7, 2020.[867] Their analysis showed that "even though [SARS-CoV-2] was most closely related to bat coronavirus RaTG13," the "Guangdong pangolin coronaviruses and SARS-CoV-2 possess identical amino acids at the five critical residues of the RBD, whereas RaTG13 only shares one amino acid with SARS-CoV-2."[868] This is also the first scientific article from China to acknowledge the presence of the furin cleavage site. French researchers first published the existence of SARS-CoV-2's furin cleavage site on February 8, 2020.[869]

As the BUCT and AMMS authors noted, "all of the pangolin coronaviruses identified to date lack the insertion of a polybasic (furin-like) S1/S2 cleavage site in the spike protein that distinguishes human SARS-CoV-2 from related betacoronaviruses (including RaTG13)."[870] The senior AMMS author of this study, Wu-Chun Cao had previously collaborated with the BUCT's Yigang Tong and Yan Li of the Institute of Military Cognition and Brain Sciences in a 2016 study of a fatal adenovirus pneumonia outbreak in 55 immunocompetent individuals.[871] Wu-Chun Cao also collaborated with the WIV and served on the WIV's Scientific Advisory Committee for its Center for Emerging Infectious Diseases.

CONCLUSION AND FINDINGS:

The COVID-19 pandemic has resulted in political trench warfare. Partisan arguments have prevented an objective discussion of facts related to the pandemic's origins and the implications of its current and future effects. The intent of this study was to distill and discern the relevant facts as they relate to the origins of the pandemic, the virus and the role of China's military (PLA) in relevant coronavirus research. As an additional outcome, however, this study identified the neurological sequalae of past COVID-19 infections and the potential risk of current and future COVID-19 illness. The consequences are particularly concerning in children. The risk of further neurological injury as the result of subsequent reinfection is unclear and should be an urgent research priority. All means at hand—screening, testing, antiviral therapies and vaccines—should be used to prevent and mitigate the neurological consequences of COVID-19 infections, particularly in children.

The SARS-CoV-2 outbreak is an anomaly compared to earlier zoonotic spillover events

The Fall 2019 emergence of COVID-19 in Wuhan was an anomaly. Longitudinal surveillance of Wuhan's animal markets prior to the outbreak confirmed the presence of susceptible intermediate animal species that were held in unhygienic conditions. None, however, harbored a SARS-related coronavirus or SARS-CoV-2. No evidence to date has shown that any animal from any of the seven live animal markets or farms supplying such animals tested positive for either the SARS-CoV-2 virus or antibodies indicating previous SARS-CoV-2 exposure or infection. This same pre-pandemic surveillance did not document the presence or sale of bats or pangolins at the Huanan or any other Wuhan live animal market. At or prior to the recognized outbreak, no live animal vendor had documented COVID-19 illness or tested positive for SARS-CoV-2 antibodies. These epidemiological traits were found in previous zoonotic SARS and MERS outbreaks but have been notably absent in the SARS-CoV-2 outbreak.

Environmental samples later collected at the Huanan market that tested positive for the virus are identical to samples obtained from sequenced human clinical cases, indicating they were deposited in the market by infected people and not animals. None of the early sequenced human or environmental samples show evidence of animal adaptation. Bats collected in Wuhan and Hubei province have not been found with SARS-related progenitor viruses similar to SARS-CoV-2 other than those that were subject to active coronavirus research at the WIV and possibly other Wuhan academic institutes and public health labs. The head of China's CDC and the WIV's lead coronavirus researcher both published and publicly stated that the market may have served as the site of a "super spreader event" and that the virus emerged earlier and somewhere else. Geospatial statistical analyses by researchers outside of China citing the seafood market as the outbreak's epicenter are considered "flawed" and could not differentiate where the outbreak started.

Elements of SARS-CoV-2 were natural in origin and likely manipulated in a lab

Even though it seems unlikely that SARS-CoV-2 emerged at the market, the origin of the SARS-CoV-2 virus, including the recombination event(s) that gave rise to its spike protein, could still be "natural." In that view, its emergence in Wuhan might have come about as a consequence of the numerous active research efforts in that city to collect, identify and characterize coronaviruses capable of causing a pandemic.

SARS-CoV-2 may have arisen, however, after field collection of progenitor viruses and subsequent lab manipulation via genetic engineering and directed evolution. Consistent with that view, the genome of the SARS-CoV-2 virus bears genetic contributions from at least three viruses recovered during field surveillance by researchers in China. The geographic origin of these viruses are hundreds of miles away from each other, distances greater than those flown by migrating bats. Additionally, one of the contributing viruses reportedly came from a pangolin several hundred miles from the range of bats harboring other related viruses.

The SARS-CoV-2 spike protein also bears a furin cleavage

site (FCS) and an RGD integrin-binding sequence not previously seen in SARS-related viruses or coronaviruses, respectively prior to the pandemic. The observation that SARS-CoV-2 contains specific restriction enzyme sites that would have facilitated its assembly from smaller fragments further suggests that SARS-CoV-2 may have resulted from more elaborate laboratory manipulation. So does identification of a hitherto unpublished coronavirus genome carried on a reverse genetics vector used to recover live virus in sequencing samples from an agricultural reverse genetic virus recovery.[872,873]

A recently published study also seems to argue against a natural recombination event. Researchers at the Mount Sinai Icahn School of Medicine in New York recently performed a comprehensive analysis of recombination events among coronaviruses to understand how genetic exchange occurs and contributes to viral evolution. Their findings show that recombination is a common occurrence when two conditions are met. First, recombination occurs among coronaviruses within the same species (e.g., among species of sarbecoviruses). This form of genetic exchange commonly affects specific regions such as the spike protein. Recombination, however, is rare between distant species, genera, or subgenera.[874] The second condition is recombination can occur when the same species co-exist in overlapping geographic regions, enabling a physical exchange of genetic material (e.g. bats roosting in the same cave).

The unique features found on the SARS-CoV-2 spike protein, the FCS and integrin-binding sequence have not been previously observed in other sarbecoviruses prior to the pandemic. This analysis determined they were likely acquired from closely related SARS viruses circulating in geographically overlapping regions in parts of southern Yunnan Province or northern Laos.[875] The closest SARS-related virus with a similar spike protein to SARS-CoV-2 that includes the integrin-binding but not the FCS sequence was found in a pangolin strain in Guangdong province more than 600 miles away.[876] Despite extensive sampling, SARS-related viruses with both the FCS and integrin-binding sequences identified in SARS-CoV-2 have not yet been found in nature. The only SARS-related virus with these exact features emerged in Wuhan, where research on such viruses was being conducted.

The presence of an FCS in SARS-CoV-2 increases the virus's affinity for human lung cells, its transmissibility and its ability to cause systemic inflammation that likely directly contributes to the observed neurocognitive effects.[877] The intent to insert this genetic sequence in SARS-related coronaviruses was described in the 2018 EcoHealth Alliance DEFUSE proposal, which involved WIV researchers, and similar work had been performed by Wuhan researchers prior to the pandemic.

The presence of the RGD sequence and other potential integrin-binding sequences represent a genetic gain of function that had not been previously reported in any SARS-related coronaviruses, though they were identified in the Guangdong pangolin viral strain published in April 2020, after the pandemic started.[878] The pangolin receptor binding domain (RBD) is nearly identical to that found in SARS-CoV-2, including the RGD integrin-binding sequence. Like the FCS, the integrin sequence seems to play an integral contributing role in the neurocognitive effects seen in acute and chronic COVID-19 disease.

WIV activities in the fall of 2019 highlight preexisting biosafety concerns and coincide with SARS-CoV-2's emergence

Whether the recombination events that produced the virus were "natural" or the result of human engineering, some evidence is consistent with the idea that SARS-CoV-2 might have entered the population via an accidental laboratory-related release. In 2019, biosafety of high containment infectious disease research was a matter of serious concern at the WIV and the highest levels of government in China. Prior to the fall of 2019, there was little formal national oversight of high containment research including recombinant (genetic) manipulation of pathogens, such as coronaviruses. Specific concerns cited the risks of performing such infectious disease research at inappropriate biosafety (BSL-2 instead of BSL-3) levels. Research hazards that could lead to lab infections such as the risk from "hidden dangers"—likely unrecognized aerosols—were specifically noted. The WIV attempted to correct biosafety deficiencies by implementing specific improvements with innovation (patents) and procurements. According to WIV researchers and managers, improving WIV biosafety was likely impacted by limited access to international

biosafety equipment due to mandates imposed by PRC authorities seeking to develop indigenous technologies.

The exact timing of SARS-CoV-2 emergence is still not known. The chronological alignment of molecular modeling, epidemiological data and media reporting, however, supports a late October to early November 2019 timeframe. At least two, possibly more, potential biosafety incidents correlate with this period. The first is a short-suspense procurement notice on November 19, 2019, for an air incinerator to augment a biosafety autoclave at the WIV's original Xiaohongshan campus in Wuhan's Wuchang district. This action suggests a potential biocontainment problem. The procurement request coincides with reporting of a surge of influenza-negative influenza-like-illnesses (ILI) in Wuhan in November. U.S. diplomats, Nanjing and Wuhan epidemiologists, and WHO Scientific Advisory Group on the Origins of Novel Pathogens (SAGO) experts all identified a surge in non-influenza ILI and suspected COVID-19 cases in early to mid-November. It also corresponds with a CCDC confirmed SARS-CoV-2 case on November 17, 2019. Declassified U.S. intelligence released by the U.S. State Department described WIV researchers becoming ill with symptoms consistent with COVID-19 in that same timeframe. This surge in ILI cases also coincides with an out of cycle biosafety lecture and training session at the WIV by a senior Chinese Academy of Science security and safety official sent from Beijing on November 19 to 21, 2019.

The second possible biosafety incident that corresponds with this timeframe is a WIV patent filed on December 11, 2019. The patent described correcting a faulty animal cabinet HEPA filter unit that transported infected experimental animals. It likely failed because of corrosion. Early social media requests for medical assistance for COVID-19 symptoms in the Wuchang district could have resulted from transporting SARS-CoV-2 infected animals in a leaky cabinet between the WIV and the Wuhan University's Institute of Animal Models. This lab is where SARS vaccine primate testing had previously occurred.

There are, however, other possible incidents.
Two PLA researchers from the Academy of Military Medical Sciences (AMMS) Institute of Military Cognition and Brain Sciences published an article in 2023 alluding to the failure of a common lab analytical device (flow cytometer) and sample handling incidents as "black swan" biosafety events. These were the same researchers who were named on General Zhou's vaccine patent and involved in some of the earliest SARS-CoV-2 vaccine studies, which likely occurred at or before the time of the outbreak. The possibility that some other unrecognized leak occurred because of corrosion of biocontainment equipment or structure failures due to the inappropriate use of liquid disinfectants cannot be excluded. These risks were cited in a corrective patent submitted in November 2020 by WIV safety officials and researchers.

Finally, the published SARS-CoV-2 research of AMMS Brigadier General Yusen Zhou, who was likely conducting coronavirus vaccine research at the WIV prior to the pandemic, suggests that the hazard of these experiments may have resulted in researchers becoming infected. Animal challenge vaccine studies pose a significant risk of lab-acquired infections. Historical data shows that the source and cause of the majority of lab-acquired infections are never determined. The specific events that may have contributed to SARS-CoV-2 emergence in Wuhan remain speculative. Whether General Zhou's vaccine research caused or contributed to the pandemic's emergence remains a key unanswered question.

The likelihood that SARS-CoV-2 emerged as the result of a lab accident underscores the importance of biosafety and oversight of highly pathogenic viral research. China's government sought to improve recognized biosafety and biosecurity deficiencies in the spring of 2019. Legislation was drafted that required provincial authorities to review and approve high pathogen agent research and required governmental security elements to monitor and enforce both biosecurity and biosafety. China's government had approved but not fully implemented such legislation before the pandemic.

China's initial response to the outbreak was likely impaired by asymptomatic and mild clinical cases and a lack of widespread diagnostic testing

Even if SARS-CoV-2 was discovered or being assessed as a potential novel pathogen, its effects on individuals

or on a population, were likely not known. SARS-CoV-2's proclivity to cause asymptomatic and mild infections that mimicked seasonal illnesses may have delayed immediate recognition of the outbreak. Any delays in the response or efforts to mitigate SARS-CoV-2's spread, such as the absence of diagnostic tests, would have impaired China's ability to contain it.

The response to the emerging outbreak in Wuhan is noteworthy. The "extreme quarantine measures, including sealing off large cities, closing borders and confining people to their homes, [that] were instituted in late January 2020, to prevent spread of the virus" suggest the government's realization that a pathogen with significant potential population effects had been accidentally released.[879] As further described, "but by that time [such measures were instituted] much of the damage had been done, as human-human transmission became evident."[880] On February 21, 2020, China's Center for Disease Control reported that by January 30, 2020, a week after Wuhan was placed on lockdown, SARS-CoV-2 had spread to all of China's 31 provincial level administrative divisions (states).[881] China did not escape SARS-CoV-2 effects. In fact, it likely bore the brunt of them. The number that died in China is not known. Over a million died in the United States and tens of millions in the rest of the world. Hundreds of millions globally have suffered a variety of potentially enduring ill effects.

The PLA outlined a strategy and intention to pursue cognitive warfare and pursued development of a SARS-CoV-2 vaccine likely prior to or coincident with the pandemic's onset

PLA military writings advocated for the development of biological and mental capabilities to achieve military advantages. These theories would later converge with the related concept of achieving cognitive dominance over adversaries. They highlight the aspiration to achieve superiority in a "new combat space" where the human brain is the battlefield.[882] By 2017, China's Science of Military Strategy described the opportunities afforded by advances in biotechnology. The Central Military Commission launched research projects in military brain science.[883] The PLA also created a medical specialty focused on military-related research that included injuring the brain and "causing brain dysfunction."[884] These actions represent more than mere aspiration and suggest a transition and commitment to develop specific military relevant capabilities.

The existence of PLA military strategy, doctrine and relevant neuroscience research into cognitive warfare years prior to the pandemic suggests the research effort may have not been entirely defensive. The collaboration between several institutes of the PLA AMMS and the Wuhan Institute of Virology likely as part of the Military Civil Fusion initiative further demonstrates that specific facilities were involved in such dual-use military research.

The participation of researchers from the AMMS Institute of Military Cognition and Brain Sciences in the earliest stages of development and animal testing for a novel coronavirus vaccine suggests a likely *a priori* awareness of SARS-CoV-2's neurological effects before the acknowledged emergence of SARS-CoV-2 in late December 2019. The design of General Zhou's vaccine to include the RGD integrin-binding sequence indicates an intent to promote immunity against a feature not seen before in SARS-related viruses that appears to play a central role in SARS-CoV-2's neuropathology.

The two subsequent animal (mouse and non-human primate) vaccine challenge studies published by General Zhou with the participation of researchers from the AMMS Institute of Military Cognition and Brain Science is silent on SARS-CoV-2's effects on the brain and the vaccine's neuroprotection. Comparable experiments by Western researchers showed that neurological findings would be a prominent outcome of such studies.[885,886,887] The absence of that data amplifies concerns about the nature of General Zhou's research and the virus they were trying to protect against. This absence is only made more prominent by his earlier April 2020 study noting SARS-CoV-2 brain infection in humanized mice. When published, this study required a cohort of experimental mice that had to be produced in the summer of 2019. This observation supports estimates that place the start of General Zhou's COVID-19 vaccine development work in the fall of 2019, at or before the pandemic's onset.

Published neuroscience research by the Fourth Military

Medical University and more recent 2024 pangolin coronavirus research and vaccine studies by the Beijing University of Chemical Technology, the Fifth Medical Center of the PLA General Hospital and the AMMS Institute of Microbiology and Epidemiology reveal continued interest in dual-use coronavirus research of concern. How this research relates to China's "active defense" approach to deterrence, biodefense or offensive BW is not known. PRC leadership reveals little about its military biological, chemical and nuclear weapons programs in open-source literature.

The implication that AMMS institutes and likely other PLA-affiliated entities were developing vaccines to protect against novel coronaviruses that have high infectivity, affect the human brain and may alter human cognition raises concerns about the objective of such military research. There is historic precedent for developing neuro-incapacitating biological weapons and the parallel development of vaccines to protect against them. Determining the intent of Beijing's military coronavirus research and whether it supports the development of a weapon remains a difficult question to assess.

The U.S. Government's assessment of China's military research is contradictory and ambiguous

In December 2021, the U.S. Department of Commerce sanctioned the AMMS and all its institutes, including General Zhou's Institute of Epidemiology and Microbiology. This action shows that the U.S. Government assessed research conducted by the AMMS to be a threat to U.S. national security. Whether the Department of Commerce's determination considered any specific coronavirus research or vaccine-related activities is not known.

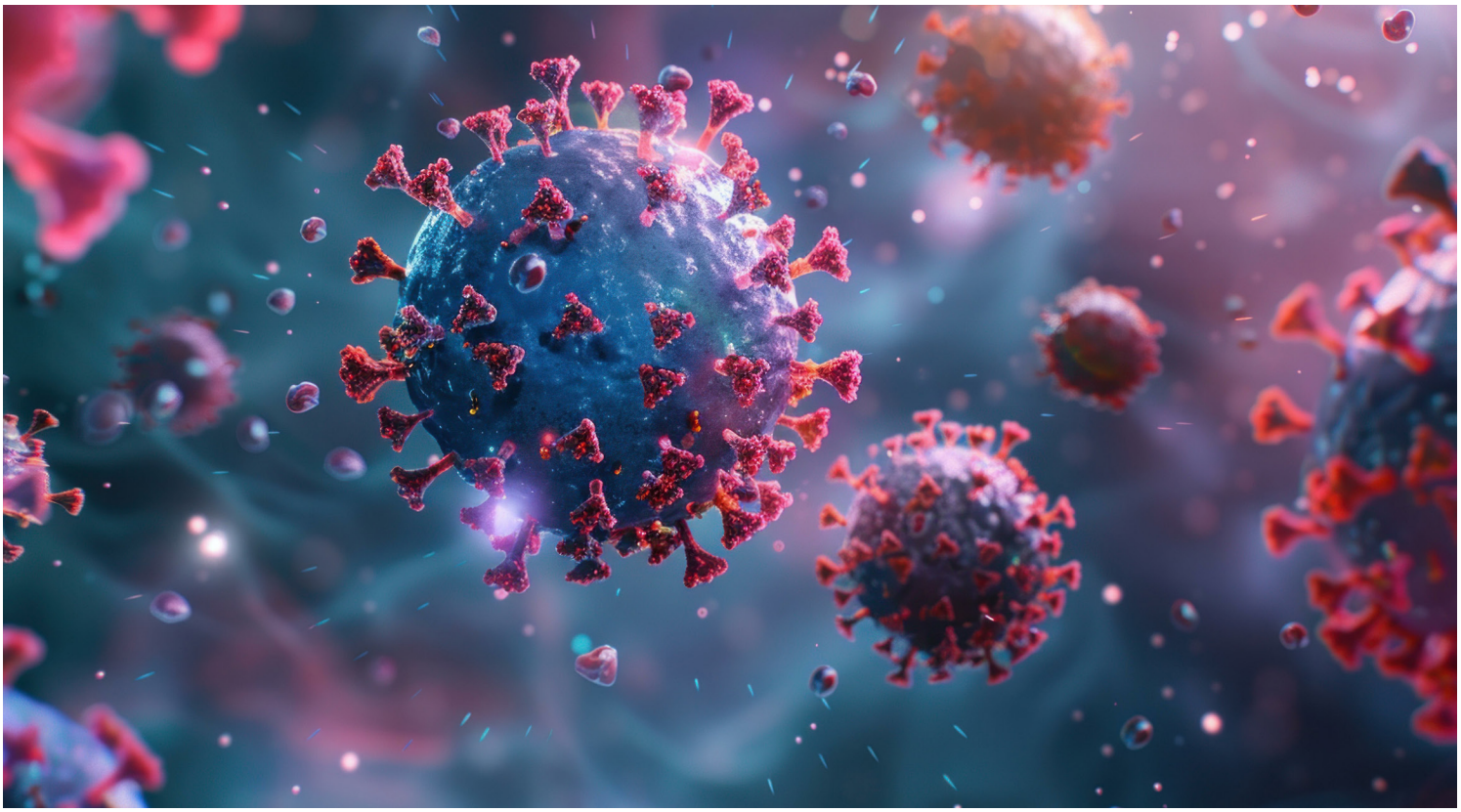
The Office of the Director of National Intelligence's June 2023 assessment of the origins of SARS-CoV-2 notes the ambiguity and lack of sufficient evidence required for a firm assessment on the origin of the virus and pandemic. The 2023 assessment was unambiguous in one area: "All IC agencies assess that SARS-CoV-2 was not developed as a biological weapon." Historical and recent U.S. State and Defense Department annual treaty compliance and threat assessments continue to raise questions about China's adherence to with the Biological Weapons and Toxins Convention (BWC). The House Intelligence Committee's report suggested that "there are indications that SARS-CoV-2 may have been tied to China's biological weapons research program." Based on the U.S. State Department's criteria and available open-source evidence, there may be further reason to question whether China's military coronavirus-related research should be revisited for BWC compliance and subject to further investigation.

The recognition that SARS-CoV-2 can cause acute and chronic residual neurological effects was likely obscured or concealed early in the outbreak and the implication that children may be subject to COVID-19's neurological effects demands urgent study and mitigation

Once the pandemic started, the limited reporting of neurological findings in the earliest cases and deaths likely reflects Beijing's efforts to censor and obscure SARS-CoV-2's true effects. Beyond its acute sequelae, there is now recognition that some of its effects are chronic and neurological. Lingering chronic effects are described as long COVID, and the "most common, persistent, and disabling symptoms of long COVID are neurological… and many people experience cognitive dysfunction."[888] SARS-CoV-2 affects the brain directly and indirectly, impacting both the central and peripheral nerve functions. SARS-CoV-2's initially unrecognized neurological effects are a major emerging legacy of the COVID-19 pandemic.

Long COVID represents a not fully understood spectrum of sequelae that affects tens of millions of adults including six million children in the United States. Neuroimaging examinations (PET and MRI scans) have demonstrated objective evidence of altered brain function and anatomy in regions that are directly linked to patient symptoms.[889]

Recent studies showed that young and middle-aged long COVID patients are "disproportionately" and more severely affected than older patients.[890] Limited but clinically significant neurological effects in children have also been documented. Recent media reporting on observational studies of U.S. children and their school performance shows younger children and students



are developmentally delayed.[891,892] The impact of SARS-CoV-2 infection on childhood learning and intelligence is potentially significant but has not been validated. As noted in one study, "it's as if the pandemic or some other factor is continuing to result in lower and lower performance."[893]

Whether these observations in children are a consequence of social isolation or SARS-CoV-2 infection, reinfection some combination of both or other factors deserve urgent attention and study. Whether repeated COVID-19 infections represent a particular risk to children is not known. Pre- and post-COVID vaccination and antiviral therapies to prevent and treat acute SARS-CoV-2 illness appear to lessen but not eliminate the risk of subsequent long COVID.[894,895] A recent study, however, calls into question the current vaccines' efficacy to prevent the neuro-psychiatric effects of long COVID.[896] While these interventions may lessen the risk and burden of the neurocognitive effects of infection, their ability to mitigate the risk of potential neurocognitive decline has not been well studied. The long-term prognosis for those suffering from this syndrome and whether this condition is treatable, reversible, or progressive will only be learned with time and dedicated study.

Regardless of these observations, there should be focused efforts in the United States to screen and test children for COVID-19 illness, increase current low vaccination rates (14.4%) and use antiviral therapies to mitigate the risk of neurological effects from acute infection. There is likely much more to be learned about the origins of SARS-CoV-2 and the pandemic. However, the most pressing need by far is to address the current and potential risks of continued SARS-CoV-2 infections and the associated neurocognitive sequelae, particularly in children in the United States and around the world.

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From 1993 through 2023, his key national leadership roles in the public sector included Special Assistant to the President & Senior Director for Biodefense Policy in the Homeland Security Council; Director for Biodefense Preparedness & Response, Homeland Security Council; Special Advisor and Senior Assistant roles to the Secretary and Assistant Secretary of Defense for International Security Policy; Deputy Staff Director for the U.S. Senate Select Intelligence Committee; Staff Director for the U.S. Senate Subcommittee on Bioterrorism & Public Health Preparedness; and most recently Senior Pandemic Policy Minority Advisor to the U.S. Senate Health, Education & Labor Committee. In the private sector he has undertaken ongoing advisory roles to the Secretary of Defense as well as the National Academy of Sciences and the Intelligence Community.

As a 26-year military veteran, Kadlec served in operational roles with the 1st Special Operations Wing, Hurlburt Field, the 24th Special Tactics Squadron at Fort Bragg and as a U.S. Special Operations Command detailee to the U.S. Intelligence Community. Kadlec was named the 1986 U.S. Air Force Flight Surgeon of the Year. He has had combat deployments in support of counterproliferation operations during DESERT STORM and IRAQI FREEDOM.

Kadlec was a Distinguished Graduate from the U.S. Air Force Academy. He earned his M.D. and a masters in tropical medicine & hygiene at the Uniformed Services University of the Health Sciences. He received his masters in national security studies from Georgetown University and an honorary Doctor of Science degree from the University of Nebraska. He is a member of the Council on Foreign Relations.

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REFERENCES:

1. Saxena, A., & Mautner, J. (2024). A disease hidden in plain sight: pathways and mechanisms of neurological complications of post-acute sequelae of COVID-19 (NC-PASC). *Molecular Neurobiology*, 10.1007/s12035-024-04421-z. Advance online publication. https://doi.org/10.1007/s12035-024-04421-z

2. Gaudet, L. A., Pillay, J., Saba, S., Zakaria, D., Cheta, N., Gardiner, H., Shaver, L., Middleton, J., Tan, M., Vandermeer, B., & Hartling, L. (2023). Associations between SARS-CoV-2 infection and incidence of new chronic condition diagnoses: a systematic review. *Emerging Microbes & Infections*, 12(1), 2204166. https://doi.org/10.1080/22221751.2023.2204166

3. Al-Aly, Z., Davis, H., McCorkell, L., Soares, L., Wulf-Hanson, S., Iwasaki, A., & Topol, E. J. (2024). Long COVID science, research and policy. *Nature Medicine, 30*(8), 2148–2164. https://doi.org/10.1038/s41591-024-03173-6

4. Soucheray, S. (2023). Survey: 18 million Americans say they have long COVID. *The Center for Infectious Disease Research and Policy*, University of Minnesota. https://www.cidrap.umn.edu/covid-19/survey-18-million-americans-say-they-have-long-covid

5. Harris, E. (2024). Millions of US children experience range of long COVID effects. *JAMA, 331*(9), 726. https://doi.org/10.1001/jama.2024.0356

6. Delorme, C., Paccoud, O., Kas, A., Hesters, A., Bombois, S., Shambrook, P., Boullet, A., Doukhi, D., Le Guennec, L., Godefroy, N., Maatoug, R., Fossati, P., Millet, B., Navarro, V., Bruneteau, G., Demeret, S., Pourcher, V., CoCo-Neurosciences study group, & COVID SMIT PSL study group. (2020). COVID-19-related encephalopathy: a case series with brain FDG-positron-emission tomography/computed tomography findings. *European Journal of Neurology, 27*(12), 2651–2657. https://doi.org/10.1111/ene.14478

7. Spudich, S., & Nath, A. (2022). Nervous system consequences of COVID-19. *Science, 375*(6578), 267–269. https://doi.org/10.1126/science.abm2052

8. Debs, P., Khalili, N., Solnes, L., Al-Zaghal, A., Sair, H. I., Yedavalli, V., & Luna, L. P. (2023). Post-COVID-19 brain [^{18}F] FDG-PET findings: A retrospective single-center study in the United States. AJNR: *American Journal of Neuroradiology, 44*(5), 517–522. https://doi.org/10.3174/ajnr.A7863

9. Al-Aly, Z., Davis, H., McCorkell, L., Soares, L., Wulf-Hanson, S., Iwasaki, A., & Topol, E. J. (2024). Long COVID science, research and policy. *Nature Medicine, 30*(8), 2148–2164. https://doi.org/10.1038/s41591-024-03173-6

10. U.S. Senate Health, Education, Labor and Pension Subcommittee on Oversight and Investigations, Minority Staff. (2022). *Muddy waters: Origins of COVID-19 report*. https://www.marshall.senate.gov/wp-content/uploads/MWG-FDR-Document-04-11-23-EMBARGOED.pdf

11. Senator Marco Rubio's Office. (2022). *"A complex and grave situation": A political chronology of the SARS-CoV-2 outbreak*. https://www.rubio.senate.gov/wp-content/uploads/_cache/files/790b6d70-7150-4f0f-a8b9-01ea45d3b1d1/EAB44A6CA6190D31041C0037E9C5E589.05.01.23-origin-report-clean-v1-11.pdf

12. U.S. House Committee on Foreign Affairs, Minority Staff. (2021). *The origins of COVID-19. An investigation of the Wuhan Institute of Virology* (117th Congress). https://foreignaffairs.house.gov/wp-content/uploads/2021/08/ORIGINS-OF-COVID-19-REPORT.pdf

13. U.S. House Permanent Select Committee on Intelligence, Minority Staff. (2022). *Unclassified summary of the second interim report on the origins of the COVID-19 pandemic*. https://intelligence.house.gov/uploadedfiles/final_unclass_summary_-_covid_origins_report_.pdf

14. Id.

15. Beaudoin, C. A., Hamaia, S. W., Huang, C. L., Blundell, T. L., & Jackson, A. P. (2021). Can the SARS-CoV-2 spike protein bind integrins independent of the RGD sequence?. *Frontiers in Cellular and Infection Microbiology, 11*, 765300. https://doi.org/10.3389/fcimb.2021.765300

16. Makowski, L., Olson-Sidford, W., & W-Weisel, J. (2021). Biological and clinical consequences of integrin binding via a rogue RGD motif in the SARS CoV-2 spike protein. *Viruses, 13*(2), 146. https://doi.org/10.3390/v13020146

17. Patino-Galindo, J., Garcia-Sastre, A., Kuhn J.H., Rabadan, R., Palacios, G. (2024). Recombination across distant coronaviradid species and genera is a rare event with distinct genomic features. Journal of Virology. https://doi.org/10.1128/jvi.01100-24

18. Bruttel, V., Washburn, A., & VanDongen, A. (2022) Endonuclease fingerprint indicates a synthetic origin of SARS-CoV-2. bioRxiv, 10.18.512756. https://doi.org/10.1101/2022.10.18.512756

19. Wu, F. (2023). Updated analysis to reject the laboratory-engineering hypothesis of SARS-CoV-2. *Environmental Research, 224*, 115481. https://doi.org/10.1016/j.envres.2023.115481

20. Barclay, E. (2020, April 29). Why these scientists still doubt the coronavirus leaked from a Chinese lab. *Vox*. https://www.vox.com/2020/4/23/21226484/wuhan-lab-coronavirus-china

21. Lau, S. K., Li, K. S., Huang, Y., Shek, C. T., Tse, H., Wang, M., Choi, G. K., Xu, H., Lam, C. S., Guo, R., Chan, K. H., Zheng, B. J., Woo, P. C., & Yuen, K. Y. (2010). Ecoepidemiology and complete genome comparison of different strains of severe acute respiratory syndrome-related Rhinolophus bat coronavirus in China reveal bats as a reservoir for acute, self-limiting infection that allows recombination events. *Journal of Virology, 84*(6), 2808–2819. https://doi.org/10.1128/JVI.02219-09

22. Stoyan, D., & Chui, S. N. (2024). Statistics did not prove that the Huanan Seafood Wholesale Market was the early epicentre of the COVID-19 pandemic. *Journal of the Royal Statistical Society Series A: Statistics in Society, 187*(3), 710–719. https://doi.org/10.1093/jrsssa/qnad139 (a) The assumption that a centroid of early case locations or another simply constructed point is the origin of an epidemic is unproven. (b) A Monte Carlo test used to conclude that no other location than the seafood market can be the origin is flawed.

23. Liu, W. J., Liu, P., Lei, W., Jia, Z., He, X., Shi, W., Tan, Y., Zou, S., Wong, G., Wang, J., Wang, F., Wang, G., Qin, K., Gao, R., Zhang, J., Li, M., Xiao, W., Guo, Y., Xu, Z., Zhao, Y., ... Wu, G. (2023). Surveillance of SARS-CoV-2 at the Huanan Seafood Market. *Nature*, 10.1038/s41586-023-06043-2. Advance online publication. https://doi.org/10.1038/s41586-023-06043-2

24. Cohen, J. (2020). Wuhan Coronavirus Hunter Shi Zhengli Speaks Out. *Science Magazine*. https://www.science.org/pb-assets/PDF/News%20PDFs/Shi%20Zhengli%20Q&A-1630433861.pdf

25. Twenty-second meeting of the Standing Committee of the 13th National People's Congress. (2020). *Article 1. Biosafety Law of the Peoples Republic of China*. https://www.chinalawtranslate.com/en/biosecurity-law/

26. Id.

27. The Wuhan Institute of Virology of the Chinese Academy of Sciences plans to use a single-source procurement method to publicize the procurement of air incineration devices and test service projects. (2019, December 3) *China Government Procurement Network*. https://archive.is/Jifqr#selection-229.0-229.197

28. Westergard, R. (2020). Surviving the outbreak: Reflections on ConGen Wuhan's evacuation and life in quarantine. *State Magazine*. https://statemag.state.gov/2020/04/0420feat05

29. Sexton, J. (2021, August 23). Josh Rogin: The sick researchers from the Wuhan Institute of Virology lost their sense of smell. *Hot Air*. https://hotair.com/john-s-2/2021/08/23/josh-rogin-the-sick-researchers-from-the-wuhan-institute-of-virology-lost-their-sense-of-smell-n411008; see also Weiss, B. (2021, August 23). You're already living in China's world Pt 1: The lab leak lies. *Honestly with Bari Weiss*. Apple Podcasts. https://podcasts.apple.com/us/podcast/youre-already-living-in-chinas-world-pt-1-the-lab-leak-lies/id1570872415?i=1000532793045

30. Dai, Y., & Wang, J. (2020). Identifying the outbreak signal of COVID-19 before the response of the traditional disease monitoring system. *PLOS Neglected Tropical Diseases, 14*(10), e0008758. https://doi.org/10.1371/journal.pntd.0008758

31. Experts study the source of the new crown [coronavirus]: December 8 last year [2019] may not be the earliest time of onset [专家研判新冠源头:去年 12 月 8 日或许不是最早发病时间. (2020, February 27). *Guancha*. https://www.guancha.cn/politics/2020_02_27_538822.shtml

32. World Health Organization. (2022). Scientific Advisory Group for the Origins of Novel Pathogens (SAGO) *preliminary report of the SAGO*. https://cdn.who.int/media/docs/default-source/scientific-advisory-group-on-the-origins-of-novel-pathogens/sago-report-09062022.pdf?sfvrsn=42b55bbc_1&download=true

33. Office of the Spokesperson, U.S. Department of State. (2021, January 15). *Fact Sheet: Activity at the Wuhan Institute of Virology: Fact Sheet*. U.S. Department of State. https://2017-2021.state.gov/fact-sheet-activity-at-the-wuhan-institute-of-virology/

34. Ma, J. (2020). Coronavirus: China's first confirmed COVID-19 case traced back to November 17. *South China Morning Post*. https://www.scmp.com/news/china/society/article/3074991/coronavirus-chinas-first-confirmed-covid-19-case-traced-back

35. Senator Marco Rubio's Office. (2022). *"A complex and grave situation": A political chronology of the SARS-CoV-2 outbreak*. https://www.rubio.senate.gov/wp-content/uploads/_cache/files/790b6d70-7150-4f0f-a8b9-01ea45d3b1d1/EAB44A6CA6190D31041C0037E9C5E589.05.01.23-origin-report-clean-v1-11.pdf

36. Gao, D., Zhang, Q., Han, K., Qian, Q., & Wenbo, A. (2019). *Integrated biological sensor* (CN 201922213832.2). Google Patents. https://patents.google.com/patent/CN211375358U/en?assignee=Wuhan+Institute+of+Virology+of+CAS&sort=new&page=8

37. Id.

38. Luo, F., Liao, F. L., Wang, H., Tang, H. B., Yang, Z. Q., & Hou, W. (2018). Evaluation of antibody-dependent enhancement of SARS-CoV infection in rhesus macaques immunized with an inactivated SARS-CoV Vaccine. *Virologica Sinica, 33*(2), 201–204. https://doi.org/10.1007/s12250-018-0009-2

39. Partnership & Custom Media unit of Nature Research for Institute of Model Animal of Wuhan University. (2019). Advertisement Feature: Institute of Animal Models of Wuhan University. *Nature*. https://www.nature.com/collections/heihdahdbe

40. Luo, F., Liao, F. L., Wang, H., Tang, H. B., Yang, Z. Q., & Hou, W. (2018). Evaluation of antibody-dependent enhancement of SARS-CoV infection in rhesus macaques immunized with an inactivated SARS-CoV Vaccine. *Virologica Sinica, 33*(2), 201–204. https://doi.org/10.1007/s12250-018-0009-2

41. Peng, Z., Wang, R., Liu, L., & Wu, H. (2020). Exploring urban spatial features of COVID-19 transmission in Wuhan based on social media data. *ISPRS International Journal of Geo-Information 9*(6), 402. https://doi.org/10.3390/ijgi9060402

42. Sewell, D. L. (1995). Laboratory-associated infections and biosafety. *Clinical Microbiology Reviews, 8*(3), 389–405. https://doi.org/10.1128/CMR.8.3.389

43. Du, C., Li, G., & Han, G. (2023). Biosafety and mental health: Virus induced cognitive decline. *Biosafety and Public Health*, 159–167. https://www.sciencedirect.com/science/article/pii/S2590053623000460

44. Aspland, A., Chew, C., Douagi, I., Galland, T., Marvin, J., Monts, J., Nance, D., Smith, A. L., & Solga, M. (2021). Risk awareness during operation of analytical flow cytometers and implications throughout the COVID-19 pandemic. *Cytometry Part A: Journal of Quantitative Cell Science, 99*(1), 81–89. https://doi.org/10.1002/cyto.a.24282

45. Liua, A., Zhanga, C., Hub, C., Ronga,R., Shia, Y., Lia,C. (November 2024).Biological Aerosol Transmission Characteristics and Exposure Risk Assessment in a Typical Biosafety Laboratory. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=5014812

46. Jia, W., Zhiming, Y., Hao, T., Jun, L., Hao, Q., Yi, L., & Lin, W. (2020). *Object surface disinfectant for high-grade biosafety laboratory and preparation method thereof* (CN 112262846B). Google Patents. https://patents.google.com/patent/CN112262846B/en?assignee=Wuhan+Institute+of+Virology+ofCAS&sort=new&page=5

47. Id.

48. Harding, A. L., & Byers, K. B. (2016). Laboratory-associated infections. In D. P. Wooley & K. B. Byers (Eds.), Biological safety: *Principles and practices* (5th ed., Chapter 4). ASM Press. https://www.ehs.ucsb.edu/sites/default/files/docs/bs/Laboratory%E2%80%90Associated%20Infections%20K%20Byers%20and%20A%20Harding%202016.pdf

49. Pedrosa, P. B., & Cardoso, T. A. (2011). Viral infections in workers in hospital and research laboratory settings: a comparative review of infection modes and respective biosafety aspects. *International Journal Of Infectious Diseases, 15*(6), e366–e376. https://doi.org/10.1016/j.ijid.2011.03.005

50. Na, L., Hu, L., Jin, A., & Li, J. (2019) Biosafety laboratory risk assessment. *Journal of Biosafety and Biosecurity, 1*, 90–92. http://creativecommons.org/licenses/by-nc-nd/4.0/

51. Pike, R. M. (1976). Laboratory-associated infections: Summary and analysis of 3921 cases. *Health Lab Sci, 13*(2), 105–114. https://pubmed.ncbi.nlm.nih.gov/946794/

52. Blacksell, S. D., Dhawan, S., Kusumoto, M., Le, K. K., Summermatter, K., O'Keefe, J., Kozlovac, J. P., Almuhairi, S. S., Sendow, I., Scheel, C. M., Ahumibe, A., Masuku, Z. M., Bennett, A. M., Kojima, K., Harper, D. R., & Hamilton, K. (2024). Laboratory-acquired infections and pathogen escapes worldwide between 2000 and 2021: a scoping review. *The Lancet Microbe, 5*(2), e194–e202. https://doi.org/10.1016/S2666-5247(23)00319-1

53. Harding, A. L., & Byers, K. B. (2016). Laboratory-associated infections. In D. P. Wooley & K. B. Byers (Eds.), *Biological safety: Principles and practices* (5th ed., Chapter 4). ASM Press. https://www.ehs.ucsb.edu/sites/default/files/docs/bs/Laboratory%E2%80%90Associated%20Infections%20K%20Byers%20and%20A%20Harding%202016.pdf

54. Zhou, Y., Zhao, G., Gu,. H., Sun, S., He, L., Li, Y., Han, G., Lang, X., Liu, J., Geng, S., & Sheng, X. (2020). *Novel coronavirus COVID-19 vaccine, preparation method and application thereof* (CN 111333704A). Beijing Preliminary Intellectual Property Agency Co. https://patentscope.wipo.int/search/en/detail.jsf?docId=CN298978866

55. Du, L., Zhao, G., Kou, Z., Ma, C., Sun, S., Poon, V. K., Lu, L., Wang, L., Debnath, A. K., Zheng, B. J., Zhou, Y., & Jiang, S. (2013). Identification of a receptor-binding domain in the S protein of the novel human coronavirus Middle East respiratory syndrome coronavirus as an essential target for vaccine development. *Journal of Virology, 87*(17), 9939–9942. https://doi.org/10.1128/JVI.01048-13

56. Manheim, D., & Lewis, G. (2022). High-risk human-caused pathogen exposure events from 1975-2016. *F1000Research, 10*, 752. https://doi.org/10.12688/f1000research.55114.2

57. Gu, H., Chen, Q., Yang, G., He, L., Fan, H., Deng, Y. Q., Wang, Y., Teng, Y., Zhao, Z., Cui, Y., Li, Y., Li, X. F., Li, J., Zhang, N. N., Yang, X., Chen, S., Guo, Y., Zhao, G., Wang, X., Luo, D. Y., … Zhou, Y. (2020). Adaptation of SARS-CoV-2 in BALB/c mice for testing vaccine efficacy. Science (New York, N.Y.), 369(6511), 1603–1607. https://doi.org/10.1126/science.abc4730

58. Sun, S., He, L., Zhao, Z., Gu, H., Fang, X., Wang, T., Yang, X., Chen, S., Deng, Y., Li, J., Zhao, J., Li, L., Li, X., He, P., Li, G., Li, H., Zhao, Y., Gao, C., Lang, X., Wang, X., … Sun, Y. (2021). Recombinant vaccine containing an RBD-Fc fusion induced protection against SARS-CoV-2 in nonhuman primates and mice. *Cellular & Molecular Immunology, 18*(4), 1070–1073. https://doi.org/10.1038/s41423-021-00658-z

59. Raimondo, G. (2021). Commerce acts to deter misuse of biotechnology, other U.S. technologies by the People's Republic of China to support surveillance and military modernization that threaten national security. U.S. Department of Commerce. https://www.bis.gov/press-release/commerce-acts-deter-misuse-biotechnology-other-us-technologies-peoples-republic-china

60. Id.

61. Guo, J-W. (2006) The command of biotechnology and merciful conquest in military opposition. *Military Medicine, 171*(11), 1150–1154. https://doi.org/10.7205/MILMED.171.11.1150

62. Id.

63. Kania, E. B. (2020). *Minds at war: China's pursuit of military advantage through cognitive science and biotechnology*. National Defense University Press. https://ndupress.ndu.edu/Portals/68/Documents/prism/prism_8-3/prism_8-3_Kania_82-101.pdf

64. Id.

65. Id.

66. Jin, H., Hou, L. J., & Wang, Z. G. (2018). Military brain science: How to influence future wars. *Zhonghua Chuang Shang Za Zhi [Chinese Journal of Traumatology], 21*(5), 277–280. https://doi.org/10.1016/j.cjtee.2018.01.006

67. Id.

68. Guo, B., Chen, J., Chen, Q., Ren, K., Feng, D., Mao, H., Yao, H., Yang, J., Liu, H., Liu, Y., Jia, F., Qi, C., Lynn-Jones, T., Hu, H., Fu, Z., Feng, G., Wang, W., & Wu, S. (2019). Anterior cingulate cortex dysfunction underlies social deficits in Shank3 mutant mice. *Nature Neuroscience, 22*(8), 1223–1234. https://doi.org/10.1038/s41593-019-0445-9

69. Hearns, H. J. (1966). *Agent summary status report on Venezuelan equine encephalitis*. U.S. Army Biological Laboratories, Fort Detrick, MD. U.S. National Archives.

70. Leitenberg, M., & Zilinskas, R. A. (2012). *The Soviet biological weapons program: A history*. Harvard University Press.

71. Eisenhower, D. D., (1960, February 18). *Technological developments in non-lethal weapons and doctrine for possible use*. Discussion at the 435th Meeting of the National Security Council. [Eisenhower: Paper, 153-61. Ann Whitman file].

72. Damiano, R. F., Guedes, B. F., de Rocca, C. C., de Pádua Serafim, A., Castro, L. H. M., Munhoz, C. D., Nitrini, R., Filho, G. B., Miguel, E. C., Lucchetti, G., & Forlenza, O. (2022). Cognitive decline following acute viral infections: Literature review and projections for post-COVID-19. *European Archives of Psychiatry and Clinical Neuroscience, 272*(1), 139–154. https://doi.org/10.1007/s00406-021-01286-4

73. Koralnik, I. J., & Tyler, K. L. (2020). COVID-19: A global threat to the nervous system. *Annals of Neurology, 88*(1), 1–11. https://doi.org/10.1002/ana.25807

74. O'Connor, T. (2020). China acknowledges destroying early coronavirus samples, confirming US accusation. *Newsweek*. https://www.newsweek.com/china-acknowledges-destroying-early-coronavirus-samples-confirming-us-accusation-1504484

75. Kang, D., Cheng, M., & McNeil, S. (2020). China clamps down in hidden hunt for coronavirus. *Associated Press*. https://apnews.com/article/united-nations-coronavirus-pandemic-china-only-on-ap-bats-24fbadc58cee3a40bca2ddf7a14d2955

76. National Academies of Sciences, Engineering, and Medicine. (2024). *Long-term health effects of COVID-19: disability and function following SARS-CoV-2 infection*. The National Academies Press. https://doi.org/10.17226/27756

77. Id.

78. Id.

79. Id.

80. Choudhury, N. A., Mukherjee, S., Singer, T., Venkatesh, A., Perez Giraldo, G. S., Jimenez, M., Miller, J., Lopez, M., Hanson, B. A., Bawa, A. P., Batra, A., Liotta, E. M., & Koralnik, I. J. (2024). Neurologic Manifestations of Long COVID Disproportionately Affect Young and Middle-Age Adults. *Annals of neurology*, 10.1002/ana.27128. Advance online publication. https://doi.org/10.1002/ana.27128

81. Frolova, E. I., Palchevska, O., Lukash, T., Dominguez, F., Britt, W., & Frolov, I. (2022). Acquisition of Furin Cleavage Site and Further SARS-CoV-2 Evolution Change the Mechanisms of Viral Entry, Infection Spread, and Cell Signaling. *Journal of virology, 96*(15), e0075322. https://doi.org/10.1128/jvi.00753-22

82. Shirato, K., & Kizaki, T. (2021). SARS-CoV-2 spike protein S1 subunit induces pro-inflammatory responses via toll-like receptor 4 signaling in murine and human macrophages. Heliyon, 7(2), e06187. https://doi.org/10.1016/j.heliyon.2021.e06187

83. Rong, Z., Mai, H., Ebert, G., Kapoor, S., Puelles, V.G., et al. (2024). Persistence of spike protein at the skull-meninges-brain axis may contribute to the neurological sequelae of COVID-19. Cell Host & Microbe. 32, 1-19. https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(24)00438-4

84. Id.

85. Bugatti, A., Filippini, F., Bardelli, M., Zani, A., Chiodelli, P., Messali, S., Caruso, A., & Caccuri, F. (2022). SARS-CoV-2 Infects Human ACE2-Negative Endothelial Cells through an $\alpha_v\beta_3$Integrin-Mediated Endocytosis Even in the Presence of Vaccine-Elicited Neutralizing Antibodies. *Viruses, 14*(4), 705. https://doi.org/10.3390/v14040705

86. Kuhn, C. C., Basnet, N., Bodakuntla, S., Alvarez-Brecht, P., Nichols, S., Martinez-Sanchez, A., Agostini, L., Soh, Y. M., Takagi, J., Biertümpfel, C., & Mizuno, N. (2023). Direct Cryo-ET observation of platelet deformation induced by SARS-CoV-2 spike protein. *Nature communications, 14*(1), 620. https://doi.org/10.1038/s41467-023-36279-5

87. Makowski, L., Olson-Sidford, W., & W-Weisel, J. (2021). Biological and Clinical Consequences of Integrin Binding via a Rogue RGD Motif in the SARS CoV-2 Spike Protein. *Viruses, 13*(2), 146. https://doi.org/10.3390/v13020146

88. Wu, X., & Reddy, D. S. (2012). Integrins as receptor targets for neurological disorders. *Pharmacology & Therapeutics, 134*(1), 68–81. https://doi.org/10.1016/j.pharmthera.2011.12.008

89. Gressett, T. E., Nader, D., Robles, J. P., Buranda, T., Kerrigan, S. W., & Bix, G. (2022). Integrins as Therapeutic Targets for SARS-CoV-2. *Frontiers in cellular and infection microbiology, 12*, 892323. https://doi.org/10.3389/fcimb.2022.892323

90. Du., C, Ge. L., & Han, G. (2023). Biosafety and mental health. *Biosafety and Health, 5*(3), 159–167. https://doi.org/10.1016/j.bsheal.2023.04.002

91. Liu, Y. H., Chen, Y., Wang, Q. H., Wang, L. R., Jiang, L., Yang, Y., Chen, X., Li, Y., Cen, Y., Xu, C., Zhu, J., Li, W., Wang, Y. R., Zhang, L. L., Liu, J., Xu, Z. Q., & Wang, Y. J. (2022). One-Year Trajectory of Cognitive Changes in Older Survivors of COVID-19 in Wuhan, China: A Longitudinal Cohort Study. *JAMA neurology, 79*(5), 509–517. https://doi.org/10.1001/jamaneurol.2022.0461

92. Zhu, G., Zhou, S., Xu, Y., Gao, R., Li, H., Su, W., Han, G., & Wang, R. (2022). Mendelian randomization study on the causal effects of COVID-19 on childhood intelligence. *Journal of Medical Virology, 94*(7), 3233–3239. https://doi.org/10.1002/jmv.27736

93. Harris, E. (2024). Millions of US children experience range of long COVID effects. *JAMA, 331*(9), 726. https://doi.org/10.1001/jama.2024.0356

94. Iversen, A., Blomberg, B., Haug, K., Kittang, B., Özgümüs, T., Cox, R. J., & Langeland, N. (2024). Symptom trajectories of post-COVID sequelae in patients with acute Delta or Omicron infection in Bergen, Norway. *Frontiers in Public Health, 12*, 1320059. https://doi.org/10.3389/fpubh.2024.1320059

95. National Academies of Sciences, Engineering, and Medicine. (2024). *Long-term health effects of COVID-19: disability and function following SARS-CoV-2 infection*. The National Academies Press. https://doi.org/10.17226/27756

96. Id.

97. Bowe, B., Xie, Y., & Al-Aly, Z. (2023). Postacute sequelae of COVID-19 at 2 years. *Nature Medicine, 29*(9), 2347–2357. https://doi.org/10.1038/s41591-023-02521-2

98. Debs, P., Khalili, N., Solnes, L., Al-Zaghal, A., Sair, H. I., Yedavalli, V., & Luna, L. P. (2023). Post-COVID-19 brain [^{18}F] FDG-PET findings: A retrospective single-center study in the United States. *AJNR: American Journal of Neuroradiology, 44*(5), 517–522. https://doi.org/10.3174/ajnr.A7863

99. Martini, A. L., Carli, G., Kiferle, L., Piersanti, P., Palumbo, P., Morbelli, S., Calcagni, M. L., Perani, D., & Sestini, S. (2022). Time-dependent recovery of brain hypometabolism in neuro-COVID-19 patients. *European Journal of Nuclear Medicine and Molecular Imaging, 50*(1), 90–102. https://doi.org/10.1007/s00259-022-05942-2

100. Lu, Y., Li, X., Geng, D., Mei, N., Wu, P. Y., Huang, C. C., Jia, T., Zhao, Y., Wang, D., Xiao, A., & Yin, B. (2020). Cerebral micro-structural changes in COVID-19 patients: An MRI-based 3-month follow-up study. *EClinicalMedicine, 25*, 100484. https://doi.org/10.1016/j.eclinm.2020.100484

101. Al-Aly, Z., Davis, H., McCorkell, L., Soares, L., Wulf-Hanson, S., Iwasaki, A., & Topol, E. J. (2024). Long COVID science, research and policy. *Nature Medicine, 30*(8), 2148–2164. https://doi.org/10.1038/s41591-024-03173-6

102. Douaud, G., Lee, S., Alfaro-Almagro, F., Arthofer, C., Wang, C., McCarthy, P., Lange, F., Andersson, J. L. R., Griffanti, L., Duff, E., Jbabdi, S., Taschler, B., Keating, P., Winkler, A. M., Collins, R., Matthews, P. M., Allen, N., Miller, K. L., Nichols, T. E., & Smith, S. M. (2022). SARS-CoV-2 is associated with changes in brain structure in UK Biobank. *Nature, 604*(7907), 697–707. https://doi.org/10.1038/s41586-022-04569-5

103. Id.

104. Corrigan, N. M., Rokem, A., & Kuhl, P. K. (2024). COVID-19 lockdown effects on adolescent brain structure suggest accelerated maturation that is more pronounced in females than in males. *Proceedings of the National Academy of Sciences of the United States of America, 121*(38), e2403200121. https://doi.org/10.1073/pnas.2403200121

105. Doan-Ngyuen, D. (2023) Post-COVID learning losses: Children face potentially permanent setbacks. *Harvard Magazine*. https://www.harvardmagazine.com/2023/07/kane-covid-learning-losses

106. Meckler, L., & Lumpkin, L. (2024, July 24). Years after the pandemic upheaval, students are still losing ground. *The Washington Post*. https://www.washingtonpost.com/education/2024/07/23/covid-test-scores-learning-loss-absenteeism/

107. Cain-Miller, C., & Mervosh, S. (2024, July 1). Pandemic-era babies are behind in basic skills. *The New York Times*. https://www.nytimes.com/interactive/2024/07/01/upshot/pandemic-children-school-performance.html

108. Id.

109. Meckler, L., & Lumpkin, L. (2024, July 24). Years after the pandemic upheaval, students are still losing ground. *The Washington Post*. https://www.washingtonpost.com/education/2024/07/23/covid-test-scores-learning-loss-absenteeism/

110. Id.

111. Xie, Y., Choi, T., & Al-Aly, Z. (2024). Postacute sequelae of SARS-CoV-2 infection in the pre-Delta, Delta, and Omicron eras. *The New England Journal of Medicine*, 10.1056/NEJMoa2403211. Advance online publication. https://doi.org/10.1056/NEJMoa2403211

112. Chow, K. N., Tsang, Y. W., Chan, Y. H., Telaga, S. A., Ng, L. Y. A., Chung, C. M., Yip, Y. M., & Cheung, P. P. H. (2024). The effect of pre-COVID and post-COVID vaccination on long COVID: a systematic review and meta-analysis. *The Journal of infection*, 106358. Advance online publication. https://doi.org/10.1016/j.jinf.2024.106358

113. U.S. National Academies of Science. (2023). *Applying lessons learned from COVID-19 research and development to future epidemics*. National Academies Press. https://doi.org/10.17226/27194

114. U.S. Centers for Disease Control and Prevention. (2024). *Child coverage and parental intent for vaccination*. https://www.cdc.gov/vaccines/imz-managers/coverage/covidvaxview/interactive/children-coverage-vaccination.html

115. Al-Aly, Z., Davis, H., McCorkell, L., Soares, L., Wulf-Hanson, S., Iwasaki, A., & Topol, E. J. (2024). Long COVID science, research and policy. Nature Medicine, 30(8), 2148–2164. https://doi.org/10.1038/s41591-024-03173-6

116. An, X., Lu, J., Huang, J. D., Zhang, B., Liu, D., Zhang, X., Chen, J., Zhou, Y., & Tong, Y. (2007). Rapid assembly of multiple-exon cDNA directly from genomic DNA. *PLOS ONE, 2*(11), e1179. https://doi.org/10.1371/journal.pone.0001179

117. Li, H., Sheng, C., Liu, H., Liu, G., Du, X., Du, J., Zhan, L., Li, P., Yang, C., Qi, L., Wang, J., Yang, X., Jia, L., Xie, J., Wang, L., Hao, R., Xu, D., Tong, Y., Zhou, Y., Zhou, J., ... Song, H. (2016). An effective molecular target site in Hepatitis B virus S gene for Cas9 cleavage and mutational inactivation. *International Journal of Biological Sciences, 12*(9), 1104–1113. https://doi.org/10.7150/ijbs.16064

118. Sun, S.-H., Chen, Q., Gu, H.-J., Yang, G., Wang, Y.-X., Huang, X.-Y., Liu, S.-S., Zhang, N.-N., Li, X.-F., Xiong, R., Guo, Y., Deng, Y.-Q., Huang, W.-J., Liu, Q., Liu, Q.-M., Shen, Y.-L., Zhou, Y., Yang, X., Zhao, T.-Y., Fan, C.-F., Zhou, Y.-S., Qin, C.-F., Wang, Y.-C. (2020). A mouse model of SARS-CoV-2 infection and pathogenesis. *Cell Host & Microbe*. 28, 124-133. https://doi.org/10.1016/j.chom.2020.05.020

119. Wei, L., Liu S., Lu S., Luo, S., An, X., Fan, H., Chen W-W., Li, E, Tong, Y., Song, L. (2024). *An infection and pathogenesis mouse model of SARS-CoV-2-related pangolin coronavirus GX_P2V(short_3UTR)*. bioRxiv. https://www.biorxiv.org/content/10.1101/2024.01.03.574008v2

120. Al-Aly, Z., Davis, H., McCorkell, L., Soares, L., Wulf-Hanson, S., Iwasaki, A., & Topol, E. J. (2024). Long COVID science, research and policy. *Nature Medicine, 30*(8), 2148–2164. https://doi.org/10.1038/s41591-024-03173-6

121. Id.

122. U.S. Centers for Disease Control and Prevention. (2024). *Child coverage and parental intent for vaccination*. https://www.cdc.gov/vaccines/imz-managers/coverage/covidvaxview/interactive/children-coverage-vaccination.html

123. World Health Organization. (2021). WHO-convened Global Study of Origins of SARS-CoV-2: China Part | Joint WHO-China Study, 14 January-10 February 2021. https://reliefweb.int/report/world/who-convened-global-study-origins-sars-cov-2-china-part-joint-who-china-study-14

124. World Health Organization. (2022). Scientific Advisory Group for the Origins of Novel Pathogens (SAGO) Preliminary Report of the SAGO. https://cdn.who.int/media/docs/default-source/scientific-advisory-group-on-the-origins-of-novel-pathogens/sago-report-09062022.pdf?sfvrsn=42b55bbc_1&download=true

125. US Senate Health, Education, Labor and Pension Subcommittee on Oversight and Investigations Minority Staff Report. (2022). Muddy Waters: Origins of COVID 19 Report. https://www.marshall.senate.gov/wp-content/uploads/MWG-FDR-Document-04-11-23-EMBARGOED.pdf

126. Reid, T., et al. (2022). Senator Rubio COVID-19 Origins Report: "A Complex and Grave Situation": A Political Chronology of the SARS_CoV-2 Outbreak. https://www.rubio.senate.gov/wp-content/uploads/_cache/files/790b6d70-7150-4f0f-a8b9-01ea45d3b1d1/EAB44A6CA6190D31041C0037E9C5E589.05.01.23-origin-report-clean-v1-11.pdf

127. Saxena, A., & Mautner, J. (2024). A disease hidden in plain sight: pathways and mechanisms of neurological complications of post-acute sequelae of COVID-19 (NC-PASC). *Molecular Neurobiology*, 10.1007/s12035-024-04421-z. Advance online publication. https://doi.org/10.1007/s12035-024-04421-z

128. US House Permanent Select Committee on Intelligence Minority. (2022). Unclassified Summary of the Second Interim Report on the Origins of the COVID-19 Pandemic. https://intelligence.house.gov/uploadedfiles/final_unclass_summary_-_COVID_origins_report_.pdf

129. Rutkai, I., Mayer, M. G., Hellmers, L. M., Ning, B., Huang, Z., Monjure, C. J., Coyne, C., Silvestri, R., Golden, N., Hensley, K., Chandler, K., Lehmicke, G., Bix, G. J., Maness, N. J., Russell-Lodrigue, K., Hu, T. Y., Roy, C. J., Blair, R. V., Bohm, R., Doyle-Meyers, L. A., … Fischer, T. (2022). Neuropathology and virus in brain of SARS-CoV-2 infected non-human primates. *Nature communications, 13*(1), 1745. https://doi.org/10.1038/s41467-022-29440-z

130. Gaudet, L. A., Pillay, J., Saba, S., Zakaria, D., Cheta, N., Gardiner, H., Shaver, L., Middleton, J., Tan, M., Vandermeer, B., & Hartling, L. (2023). Associations between SARS-CoV-2 infection and incidence of new chronic condition diagnoses: a systematic review. *Emerging Microbes & Infections, 12*(1), 2204166. https://doi.org/10.1080/22221751.2023.2204166

131. Al-Aly, Z., Davis, H., McCorkell, L., Soares, L., Wulf-Hanson, S., Iwasaki, A., & Topol, E. J. (2024). Long COVID science, research and policy. *Nature Medicine, 30*(8), 2148–2164. https://doi.org/10.1038/s41591-024-03173-6

132. Soucheray, S. (2023). Survey: 18 million Americans say they have long COVID. *The Center for Infectious Disease Research and Policy*, University of Minnesota. https://www.cidrap.umn.edu/covid-19/survey-18-million-americans-say-they-have-long-covid

133. Harris, E. (2024). Millions of US children experience range of long COVID effects. *JAMA, 331*(9), 726. https://doi.org/10.1001/jama.2024.0356

134. Al-Aly, Z., Davis, H., McCorkell, L., Soares, L., Wulf-Hanson, S., Iwasaki, A., & Topol, E. J. (2024). Long COVID science, research and policy. *Nature Medicine, 30*(8), 2148–2164. https://doi.org/10.1038/s41591-024-03173-6

135. Saxena, A., & Mautner, J. (2024). A disease hidden in plain sight: pathways and mechanisms of neurological complications of post-acute sequelae of COVID-19 (NC-PASC). *Molecular Neurobiology*, 10.1007/s12035-024-04421-z. Advance online publication. https://doi.org/10.1007/s12035-024-04421-z

136. Xie, Y., Choi, T., & Al-Aly, Z. (2024). Postacute sequelae of SARS-CoV-2 infection in the pre-Delta, Delta, and Omicron eras. *The New England Journal of Medicine*, 10.1056/NEJMoa2403211. Advance online publication. https://doi.org/10.1056/NEJMoa2403211

137. U.S. Centers for Disease Control and Prevention. (2024). *Child coverage and parental intent for vaccination*. https://www.cdc.gov/vaccines/imz-managers/coverage/covidvaxview/interactive/children-coverage-vaccination.html

138. National Intelligence Council, Office of the Director of National Intelligence. (2023). *Updated assessment on COVID-19 origins*. Office of the Director of National Intelligence. https://www.intelligence.gov/assets/documents/702%20Documents/declassified/Declassified-Assessment-on-COVID-19-Origins.pdf

139. Cohen, J. (2023). CIA bribed its own COVID-19 origin team to reject lab-leak theory, anonymous whistleblower claims. *Science Magazine*. https://www.science.org/content/article/cia-bribed-its-own-covid-19-origin-team-reject-lab-leak-theory-anonymous-whistleblower

140. Pezenik, S. (2023). CIA 'looking into' allegations connected to COVID-19 origins. *ABC News*. https://abcnews.go.com/US/cia-allegations-connected-covid-19-origins/story?id=103162133

141. U.S. Department of State. (2024). *Adherence to and compliance with arms control, nonproliferation, and disarmament agreements and commitments*. https://www.state.gov/wp-content/uploads/2024/04/2024-Arms-Control-Treaty-Compliance-Report.pdf

142. U.S. Department of Defense. (2023). *2023 Department of Defense strategy for countering weapons of mass destruction*. https://media.defense.gov/2023/Sep/28/2003310413/-1/-1/1/2023_STRATEGY_FOR_COUNTERING_WEAPONS_OF_MASS_DESTRUCTION.PDF

143. U.S. Department of Defense. (2023). *Annual report to Congress: Military and security developments involving the People's Republic of China*. https://media.defense.gov/2023/Oct/19/2003323409/-1/-1/1/2023-MILITARY-AND-SECURITY-DEVELOPMENTS-INVOLVING-THE-PEOPLES-REPUBLIC-OF-CHINA.PDF

144. Pekar, J. E., Magee, A., Parker, E., Moshiri, N., Izhikevich, K., Havens, J. L., Gangavarapu, K., Malpica Serrano, L. M., Crits-Christoph, A., Matteson, N. L., Zeller, M., Levy, J. I., Wang, J. C., Hughes, S., Lee, J., Park, H., Park, M. S., Ching Zi Yan, K., Lin, R. T. P., Mat Isa, M. N., … Wertheim, J. O. (2022). The molecular epidemiology of multiple zoonotic origins of SARS-CoV-2. *Science, 377*(6609), 960–966. https://doi.org/10.1126/science.abp8337

145. Worobey, M., Levy, J. I., Malpica Serrano, L., Crits-Christoph, A., Pekar, J. E., Goldstein, S. A., Rasmussen, A. L., Kraemer, M. U. G., Newman, C., Koopmans, M. P. G., Suchard, M. A., Wertheim, J. O., Lemey, P., Robertson, D. L., Garry, R. F., Holmes, E. C., Rambaut, A., & Andersen, K. G. (2022). The Huanan Seafood Wholesale Market in Wuhan was the early epicenter of the COVID-19 pandemic. *Science, 377*(6609), 951–959. https://doi.org/10.1126/science.abp8715

146. Parrish, C. R., Holmes, E. C., Morens, D. M., Park, E. C., Burke, D. S., Calisher, C. H., Laughlin, C. A., Saif, L. J., & Daszak, P. (2008). Cross-species virus transmission and the emergence of new epidemic diseases. *Microbiology and Molecular Biology Reviews, 72*(3), 457–470. https://doi.org/10.1128/MMBR.00004-08

147. Wells, K. & Clark, N.J. (2019). Host Specificity in Variable Environments. *Trends in Parasitology, 35*(6), 452–465. https://doi.org/10.1016/j.pt.2019.04.001

148. Xu, R. H., He, J. F., Evans, M. R., Peng, G. W., Field, H. E., Yu, D. W., Lee, C. K., Luo, H. M., Lin, W. S., Lin, P., Li, L. H., Liang, W. J., Lin, J. Y., & Schnur, A. (2004). Epidemiologic clues to SARS origin in China. *Emerging Infectious Diseases, 10*(6), 1030–1037. https://doi.org/10.3201/eid1006.030852

149. Guan, Y., Zheng, B. J., He, Y. Q., Liu, X. L., Zhuang, Z. X., Cheung, C. L., Luo, S. W., Li, P. H., Zhang, L. J., Guan, Y. J., Butt, K. M., Wong, K. L., Chan, K. W., Lim, W., Shortridge, K. F., Yuen, K. Y., Peiris, J. S., & Poon, L. L. (2003). Isolation and characterization of viruses related to the SARS coronavirus from animals in southern China. *Science, 302*(5643), 276–278. https://doi.org/10.1126/science.1087139

150. Ziwei, F. (2020). Wild animals sold at seafood market blamed for viral outbreak in China. *Taiwain News*. https://www.taiwannews.com.tw/en/news/3863041

151. Worobey, M., Levy, J. I., Malpica Serrano, L., Crits-Christoph, A., Pekar, J. E., Goldstein, S. A., Rasmussen, A. L., Kraemer, M. U. G., Newman, C., Koopmans, M. P. G., Suchard, M. A., Wertheim, J. O., Lemey, P., Robertson, D. L., Garry, R. F., Holmes, E. C., Rambaut, A., & Andersen, K. G. (2022). The Huanan Seafood Wholesale Market in Wuhan was the early epicenter of the COVID-19 pandemic. *Science, 377*(6609), 951–959. https://doi.org/10.1126/science.abp8715

152. Cui, J., Li, F., & Shi, Z. L. (2019). Origin and evolution of pathogenic coronaviruses. *Nature Reviews Microbiology, 17*(3), 181–192. https://doi.org/10.1038/s41579-018-0118-9

153. Lau, S. K., Li, K. S., Huang, Y., Shek, C. T., Tse, H., Wang, M., Choi, G. K., Xu, H., Lam, C. S., Guo, R., Chan, K. H., Zheng, B. J., Woo, P. C., & Yuen, K. Y. (2010). Ecoepidemiology and complete genome comparison of different strains of severe acute respiratory syndrome-related Rhinolophus bat coronavirus in China reveal bats as a reservoir for acute, self-limiting infection that allows recombination events. *Journal of Virology, 84*(6), 2808–2819. https://doi.org/10.1128/JVI.02219-09

154. Yang, X. L., Hu, B., Wang, B., Wang, M. N., Zhang, Q., Zhang, W., Wu, L. J., Ge, X. Y., Zhang, Y. Z., Daszak, P., Wang, L. F., & Shi, Z. L. (2015). Isolation and characterization of a novel bat coronavirus closely related to the direct progenitor of severe acute respiratory syndrome coronavirus. *Journal of Virology, 90*(6), 3253–3256. https://doi.org/10.1128/JVI.02582-15

155. Memish, Z. A., Perlman, S., Van Kerkhove, M. D., & Zumla, A. (2020). Middle East respiratory syndrome. *Lancet, 395*(10229), 1063–1077. https://doi.org/10.1016/S0140-6736(19)33221-0

156. Omrani, A. S., Al-Tawfiq, J. A., & Memish, Z. A. (2015). Middle East respiratory syndrome coronavirus (MERS-CoV): Animal to human interaction. *Pathogens and Global Health, 109*(8), 354–362. https://doi.org/10.1080/20477724.2015.1122852

157. Cui, J., Li, F., & Shi, Z. L. (2019). Origin and evolution of pathogenic coronaviruses. *Nature Reviews Microbiology, 17*(3), 181–192. https://doi.org/10.1038/s41579-018-0118-9

158. Id.

159. Rand, P. (2023). *Deception: The great COVID cover-up*. Regnery Publishing. Page 5.

160. The 2019-nCoV Outbreak Joint Field Epidemiology Investigation Team, & Li, Q. (2020). An Outbreak of NCIP (2019-nCoV) Infection in China — Wuhan, Hubei Province, 2019−2020[J]. *China CDC Weekly, 2*(5), 79-80. http://dx.doi.org/10.46234/ccdcw2020.022

161. Hu, B., Guo, H., Zhou, P., & Shi, Z.-L. (2021). Characteristics of SARS-CoV-2 and COVID-19. *Nature Reviews Microbiology, 19*, 141–154. https://doi.org/10.1038/s41579-020-00459-7

162. Li, Q., Guan, X., Wu, P., Wang, X., Zhou, L., Tong, Y., Ren, R., Leung, K. S. M., Lau, E. H. Y., Wong, J. Y., Xing, X., Xiang, N., Wu, Y., Li, C., Chen, Q., Li, D., Liu, T., Zhao, J., Liu, M., Tu, W., … Feng, Z. (2020). Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *The New England Journal of Medicine, 382*(13), 1199–1207. https://doi.org/10.1056/NEJMoa2001316

163. Xu, R. H., He, J. F., Evans, M. R., Peng, G. W., Field, H. E., Yu, D. W., Lee, C. K., Luo, H. M., Lin, W. S., Lin, P., Li, L. H., Liang, W. J., Lin, J. Y., & Schnur, A. (2004). Epidemiologic clues to SARS origin in China. *Emerging Infectious Diseases, 10*(6), 1030–1037. https://doi.org/10.3201/eid1006.030852

164. Reusken, C. B., Farag, E. A., Haagmans, B. L., Mohran, K. A., Godeke, G. J., 5th, Raj, S., Alhajri, F., Al-Marri, S. A., Al-Romaihi, H. E., Al-Thani, M., Bosch, B. J., van der Eijk, A. A., El-Sayed, A. M., Ibrahim, A. K., Al-Molawi, N., Müller, M. A., Pasha, S. K., Drosten, C., AlHajri, M. M., & Koopmans, M. P. (2015). Occupational Exposure to dromedaries and risk for MERS-CoV infection, Qatar, 2013-2014. *Emerging Infectious Diseases, 21*(8), 1422–1425. https://doi.org/10.3201/eid2108.150481

165. The 2019-nCoV Outbreak Joint Field Epidemiology Investigation Team, & Li, Q. (2020). An Outbreak of NCIP (2019-nCoV) Infection in China — Wuhan, Hubei Province, 2019−2020[J]. *China CDC Weekly, 2*(5), 79-80. http://dx.doi.org/10.46234/ccdcw2020.022

166. Id.

167. World Health Organization. (2021). *WHO-convened global study of origins of SARS-CoV-2: China part | joint WHO-China Study, 14 January-10 February 2021*. https://reliefweb.int/report/world/who-convened-global-study-origins-sars-cov-2-china-part-joint-who-china-study-14

168. Id.

169. Xiao, X., Newman, C., Buesching, C. D., Macdonald, D. W., & Zhou, Z. M. (2021). Animal sales from Wuhan wet markets immediately prior to the COVID-19 pandemic. *Scientific Reports, 11*(1), 11898. https://doi.org/10.1038/s41598-021-91470-2

170. Id.

171. Id.

172. Page, J., McKay, B., & Hinshaw, D. (2021). Search for Covid's origins leads to China's wild animal farms-and a big problem. *The Wall Street Journal*. https://www.wsj.com/articles/covid-origins-china-wild-animal-farms-pandemic-source-11625060088

173. Watts, J. (2004). China culls wild animals to prevent new SARS threat. *Lancet, 363*(9403), 134. https://doi.org/10.1016/S0140-6736(03)15313-5

174. Page, J., McKay, B., & Hinshaw, D. (2021). Search for Covid's origins leads to China's wild animal farms-and a big problem. *The Wall Street Journal*. https://www.wsj.com/articles/covid-origins-china-wild-animal-farms-pandemic-source-11625060088

175. Liu, W. J., Liu, P., Lei, W., Jia, Z., He, X., Shi, W., Tan, Y., Zou, S., Wong, G., Wang, J., Wang, F., Wang, G., Qin, K., Gao, R., Zhang, J., Li, M., Xiao, W., Guo, Y., Xu, Z., Zhao, Y., … Wu, G. (2023). Surveillance of SARS-CoV-2 at the Huanan Seafood Market. *Nature, 10*.1038/s41586-023-06043-2. Advance online publication. https://doi.org/10.1038/s41586-023-06043-2

176. Observer Network. (May 25, 2020). Gao Fu: Wuhan South China Seafood Market may be a victim unit. No virus has been extracted from animal samples. *Sina News*. https://news.sina.cn/2020-05-26/detail-iircuyvi5002958.d.html

177. Liu, W. J., Liu, P., Lei, W., Jia, Z., He, X., Shi, W., Tan, Y., Zou, S., Wong, G., Wang, J., Wang, F., Wang, G., Qin, K., Gao, R., Zhang, J., Li, M., Xiao, W., Guo, Y., Xu, Z., Zhao, Y., … Wu, G. (2023). Surveillance of SARS-CoV-2 at the Huanan Seafood Market. Nature, 10.1038/s41586-023-06043-2. Advance online publication. https://doi.org/10.1038/s41586-023-06043-2

178. Id.

179. Id.

180. Pekar, J. E., Magee, A., Parker, E., Moshiri, N., Izhikevich, K., Havens, J. L., Gangavarapu, K., Malpica Serrano, L. M., Crits-Christoph, A., Matteson, N. L., Zeller, M., Levy, J. I., Wang, J. C., Hughes, S., Lee, J., Park, H., Park, M. S., Ching Zi Yan, K., Lin, R. T. P., Mat Isa, M. N., … Wertheim, J. O. (2022). The molecular epidemiology of multiple zoonotic origins of SARS-CoV-2. *Science, 377*(6609), 960–966. https://doi.org/10.1126/science.abp8337

181. Wang, L. F., Shi, Z., Zhang, S., Field, H., Daszak, P., & Eaton, B. T. (2006). Review of bats and SARS. *Emerging Infectious Diseases, 12*(12), 1834–1840. https://doi.org/10.3201/eid1212.060401

182. Oreshkova, N., Molenaar, R. J., Vreman, S., Harders, F., Oude Munnink, B. B., Hakze-van der Honing, R. W., Gerhards, N., Tolsma, P., Bouwstra, R., Sikkema, R. S., Tacken, M. G., de Rooij, M. M., Weesendorp, E., Engelsma, M. Y., Bruschke, C. J., Smit, L. A., Koopmans, M., van der Poel, W. H., & Stegeman, A. (2020). SARS-CoV-2 infection in farmed minks, the Netherlands, April and May 2020. *European Communicable Disease Bulletin [Bulletin Europeen sur les Maladies Transmissibles], 25*(23), 2001005. https://doi.org/10.2807/1560-7917.ES.2020.25.23.2001005

183. World Health Organization. (2020). *SARS-CoV-2 mink-associated variant strain – Denmark*. https://www.who.int/emergencies/disease-outbreak-news/item/2020-DON301

184. Frutos, R., & Devaux, C. A. (2020). Mass culling of minks to protect the COVID-19 vaccines: is it rational?. *New Microbes and New Infections, 38*, 100816. https://doi.org/10.1016/j.nmni.2020.100816

185. Cohen, J. (2020). Wuhan Coronavirus Hunter Shi Zhengli Speaks Out. *Science Magazine*. https://www.science.org/pb-assets/PDF/News%20PDFs/Shi%20Zhengli%20Q&A-1630433861.pdf

186. Id.

187. Wrobel, A. G., Benton, D. J., Xu, P., Calder, L. J., Borg, A., Roustan, C., Martin, S. R., Rosenthal, P. B., Skehel, J. J., & Gamblin, S. J. (2021). Structure and binding properties of Pangolin-CoV spike glycoprotein inform the evolution of SARS-CoV-2. *Nature Communications*, *12*(1), 837. https://doi.org/10.1038/s41467-021-21006-9

188. Chen, X., Wu, T., Liang, J., & Zhou, L. (2020). Urban mosquito management administration: Mosquito (Diptera: Culicidae) habitat surveillance and questionnaire survey in Wuhan, Central China. *PlOS ONE*, *15*(5), e0232286. https://doi.org/10.1371/journal.pone.0232286

189. Cohen, J. (2020). Wuhan Coronavirus Hunter Shi Zhengli Speaks Out. *Science Magazine*. https://www.science.org/pb-assets/PDF/News%20PDFs/Shi%20Zhengli%20Q&A-1630433861.pdf

190. Observer Network. (May 25, 2020). Gao Fu: Wuhan South China Seafood Market may be a victim unit. No virus has been extracted from animal samples. *Sina News*. https://news.sina.cn/2020-05-26/detail-iircuyvi5002958.d.html

191. Liu, W. J., Liu, P., Lei, W., Jia, Z., He, X., Shi, W., Tan, Y., Zou, S., Wong, G., Wang, J., Wang, F., Wang, G., Qin, K., Gao, R., Zhang, J., Li, M., Xiao, W., Guo, Y., Xu, Z., Zhao, Y., ... Wu, G. (2023). Surveillance of SARS-CoV-2 at the Huanan Seafood Market. *Nature*, 10.1038/s41586-023-06043-2. Advance online publication. https://doi.org/10.1038/s41586-023-06043-2

192. World Health Organization. (2021). *WHO-convened global study of origins of SARS-CoV-2: China part | joint WHO-China Study, 14 January-10 February 2021*. https://reliefweb.int/report/world/who-convened-global-study-origins-sars-cov-2-china-part-joint-who-china-study-14

193. Worobey, M., Levy, J. I., Malpica Serrano, L., Crits-Christoph, A., Pekar, J. E., Goldstein, S. A., Rasmussen, A. L., Kraemer, M. U. G., Newman, C., Koopmans, M. P. G., Suchard, M. A., Wertheim, J. O., Lemey, P., Robertson, D. L., Garry, R. F., Holmes, E. C., Rambaut, A., & Andersen, K. G. (2022). The Huanan Seafood Wholesale Market in Wuhan was the early epicenter of the COVID-19 pandemic. *Science, 377*(6609), 951–959. https://doi.org/10.1126/science.abp8715

194. Feldwisch-Drentrup, H. (2024). Criticism of statistical analysis on the origin of Corona. *Frankfurter Allgemeine Sonntagzeitung*. https://www.faz.net/aktuell/wissen/medizin-ernaehrung/wo-der-corona-ursprung-wirklich-lag-fruehere-analyse

195. Stoyan, D., & Chui, S. N. (2024). Statistics did not prove that the Huanan Seafood Wholesale Market was the early epicentre of the COVID-19 pandemic. *Journal of the Royal Statistical Society Series A: Statistics in Society, 187*(3), 710–719. https://doi.org/10.1093/jrsssa/qnad139

196. Feldwisch-Drentrup, H. (2024). Criticism of statistical analysis on the origin of Corona. *Frankfurter Allgemeine Sonntagzeitung*. https://www.faz.net/aktuell/wissen/medizin-ernaehrung/wo-der-corona-ursprung-wirklich-lag-fruehere-analyse

197. Stoyan, D., & Chui, S. N. (2024). Statistics did not prove that the Huanan Seafood Wholesale Market was the early epicentre of the COVID-19 pandemic. *Journal of the Royal Statistical Society Series A: Statistics in Society, 187*(3), 710–719. https://doi.org/10.1093/jrsssa/qnad139

198. Peng, Z., Wang, R., Liu, L., & Wu, H. (2020). Exploring urban spatial features of COVID-19 transmission in Wuhan based on social media data. *ISPRS International Journal of Geo-Information*, *9*(6), 402.

199. Id.

200. Id.

201. Id.

202. U.S. Senate Health, Education, Labor and Pension Subcommittee on Oversight and Investigations, Minority Staff. (2022). *Muddy waters: Origins of COVID-19 report*. https://www.marshall.senate.gov/wp-content/uploads/MWG-FDR-Document-04-11-23-EMBARGOED.pdf.

203. Wang, D., Cai, J., Shi, T., Xiao, Y., Feng, X., Yang, M., Li, W., Liu, W., Yu, L., Ye, Z., Xu, T., Ma, J., Li, M., & Chen, W. (2020). Epidemiological characteristics and the entire evolution of coronavirus disease 2019 in Wuhan, China. *Respiratory Research*, *21*(1), 257. https://doi.org/10.1186/s12931-020-01525-7

204. Zhong, N. S., Zheng, B. J., Li, Y. M., Poon, Xie, Z. H., Chan, K. H., Li, P. H., Tan, S. Y., Chang, Q., Xie, J. P., Liu, X. Q., Xu, J., Li, D. X., Yuen, K. Y., Peiris, & Guan, Y. (2003). Epidemiology and cause of severe acute respiratory syndrome (SARS) in Guangdong, People's Republic of China, in February, 2003. *Lancet*, *362*(9393), 1353–1358. https://doi.org/10.1016/s0140-6736(03)14630-2

205. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. (2020). the epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) — China, 2020[J]. *China CDC Weekly, 2*(8), 113-122. https://doi:/10.46234/ccdcw2020.032

206. Dai, Y., & Wang, J. (2020). Identifying the outbreak signal of COVID-19 before the response of the traditional disease monitoring system. *PLOS Neglected Tropical Diseases*, *14*(10). https://doi.org/10.1371/journal.pntd.0008758

207. Centers for Disease Control and Prevention. (2024). *CDC yellow book 2024: COVID-19 travel-associated infections & diseases.* https://wwwnc.cdc.gov/travel/yellowbook/2024/infections-diseases/covid-19

208. Alene, M., Yismaw, L., Assemie, M. A., Ketema, D. B., Gietaneh, W., Birhan, T. Y. (2021). Serial interval and incubation period of COVID-19: A systematic review and meta-analysis. *BMC Infectious Diseases, 21*(1), 257. https://doi.org/10.1186/s12879-021-05950-x

209. Experts study the source of the new crown [coronavirus]: December 8 last year [2019] may not be the earliest time of onset [专家研判新冠源头:去年 12 月 8 日或许不是最早发病时间. (2020, February 27). *Guancha*. https://www.guancha.cn/politics/2020_02_27_538822.shtml

210. Ma, J. (2020). Coronavirus: China's first confirmed COVID-19 case traced back to November 17. *South China Morning Post*. https://www.scmp.com/news/china/society/article/3074991/coronavirus-chinas-first-confirmed-covid-19-case-traced-back

211. Reed, C. (2020, March 4). What it's REALLY like to catch coronavirus: First British victim, 25, describes how 'worst disease he ever had' left him sweating, shivering, and struggling to breathe as his eyes burned and bones ached. *The Daily Mail*. https://www.dailymail.co.uk/news/article-8075633/First-British-victim-25-describes- coronavirus.html

212. Westergard, R. (2020). Surviving the outbreak: Reflections on ConGen Wuhan's evacuation and life in quarantine. *State Magazine*. https://statemag.state.gov/2020/04/0420feat05 /

213. Office of the Spokesperson, U.S. Department of State. (2021, January 15). *Fact Sheet: Activity at the Wuhan Institute of Virology: Fact Sheet*. U.S. Department of State. https://2017-2021.state.gov/fact-sheet-activity-at-the-wuhan-institute-of-virology/

214. Sexton, J. (2021, August 23). Josh Rogin: The sick researchers from the Wuhan Institute of Virology lost their sense of smell. *Hot Air.* https://hotair.com/john-s-2/2021/08/23/josh-rogin-the-sick-researchers-from-the-wuhan-institute-of-virology-lost-their-sense-of-smell-n411008; *see also* Weiss, B. (2021, August 23). You're already living in China's world Pt 1: The lab leak lies. *Honestly with Bari Weiss.* Apple Podcasts. https://podcasts.apple.com/us/podcast/youre-already-living-in-chinas-world-pt-1-the-lab-leak-lies/id1570872415?i=1000532793045

215. Okanyene Nsoesie, E., Rader, B., Barnoon, Y. L., Goodwin, L., Brownstein, J. S. (2020). *Analysis of hospital traffic and search engine data in Wuhan China indicates early disease activity in the fall of 2019.* https://dash.harvard.edu/bitstream/handle/1/42669767/Satellite_Images_Baidu_COVID19_manuscript_DASH.pdf?sequence=3&isAllowed=y

216. Ma, V. L. & Nair, M. S.. (2020, June 12). Coronavirus may have spread in China last August, preliminary Harvard study suggests. *The Harvard Crimson*. https://www.thecrimson.com/article/2020/6/12/coronavirus-satellite-research/. *See also*: Brownstein, J. S. et al. (2020). *Analysis of hospital traffic and search engine data in Wuhan China indicates early disease activity in the fall of 2019.* https://dash.harvard.edu/bitstream/handle/1/42669767/Satellite_Images_Baidu_COVID19_manuscript_DASH.pdf?sequence=3&isAllowed=y

217. An, P., Chen, H., Ren, H., Su, J., Ji, M., Kang, J., Jiang, X., Yang, Y., Li, J., Lv, X., Yin, A., Chen, D., Chen, M., Zhou, Z., Dong, W., Ding, Y., & Yu, H. (2021). Gastrointestinal symptoms onset in COVID-19 patients in Wuhan, China. *Digestive Diseases and Sciences*, *66*(10), 3578–3587. https://doi.org/10.1007/s10620-020-06693-6

218. Luo, S., Deng, Z., Zhang, X., Pan, Z., & Xu, H. (2021). Clinical characteristics and outcomes of 2019 novel coronavirus disease patients presenting with initial gastrointestinal symptoms in Wuhan, China: A retrospective cohort study. *Journal of Gastroenterology and Hepatology*, *36*(3), 694–699. https://doi.org/10.1111/jgh.15199

219. Dai, Y., & Wang, J. (2020). Identifying the outbreak signal of COVID-19 before the response of the traditional disease monitoring system. *PLOS Neglected Tropical Diseases*, *14*(10), e0008758. https://doi.org/10.1371/journal.pntd.0008758

220. You, M., Wu, Z., Yang, Y., Liu, J., & Liu, D. (2020). Spread of Coronavirus 2019 from Wuhan to rural villages in the Hubei Province. *Open Forum Infectious Diseases*, *7*(7), ofaa228. https://doi.org/10.1093/ofid/ofaa228

221. Guan, W. J., Ni, Z. Y., Hu, Y., Liang, W. H., Ou, C. Q., He, J. X., Liu, L., Shan, H., Lei, C. L., Hui, D. S. C., Du, B., Li, L. J., Zeng, G., Yuen, K. Y., Chen, R. C., Tang, C. L., Wang, T., Chen, P. Y., Xiang, J., Li, S. Y., … China Medical Treatment Expert Group for Covid-19 (2020). Clinical characteristics of Coronavirus Disease 2019 in China. *The New England Journal of Medicine*, *382*(18), 1708–1720. https://doi.org/10.1056/NEJMoa2002032

222. Id.

223. Pekar, J. E., Magee, A., Parker, E., Moshiri, N., Izhikevich, K., Havens, J. L., Gangavarapu, K., Malpica Serrano, L. M., Crits-Christoph, A., Matteson, N. L., Zeller, M., Levy, J. I., Wang, J. C., Hughes, S., Lee, J., Park, H., Park, M. S., Ching Zi Yan, K., Lin, R. T. P., Mat Isa, M. N., … Wertheim, J. O. (2022). The molecular epidemiology of multiple zoonotic origins of SARS-CoV-2. *Science, 377*(6609), 960–966. https://doi.org/10.1126/science.abp8337

224. Kumar, S., Tao, Q., Weaver, S., Sanderford, M., Caraballo-Ortiz, M. A., Sharma, S., Pond, S. L. K., & Miura, S. (2021). An evolutionary portrait of the progenitor SARS-CoV-2 and its dominant offshoots in COVID-19 pandemic. *Molecular Biology and Evolution*, *38*(8), 3046–3059. https://doi.org/10.1093/molbev/msab118

225. Holmes, E. C., Goldstein, S. A., Rasmussen, A. L., Robertson, D. L., Crits-Christoph, A., Wertheim, J. O., Anthony, S. J., Barclay, W. S., Boni, M. F., Doherty, P. C., Farrar, J., Geoghegan, J. L., Jiang, X., Leibowitz, J. L., Neil, S. J. D., Skern, T., Weiss, S. R., Worobey, M., Andersen, K. G., Garry, R. F., … Rambaut, A. (2021). The origins of SARS-CoV-2: A critical review. *Cell*, *184*(19), 4848–4856. https://doi.org/10.1016/j.cell.2021.08.017

226. Pekar, J. E., Magee, A., Parker, E., Moshiri, N., Izhikevich, K., Havens, J. L., Gangavarapu, K., Malpica Serrano, L. M., Crits-Christoph, A., Matteson, N. L., Zeller, M., Levy, J. I., Wang, J. C., Hughes, S., Lee, J., Park, H., Park, M. S., Ching Zi Yan, K., Lin, R. T. P., Mat Isa, M. N., … Wertheim, J. O. (2022). The molecular epidemiology of multiple zoonotic origins of SARS-CoV-2. *Science*, *377*(6609), 960–966. https://doi.org/10.1126/science.abp8337

227. Id.

228. Yu, W.-B., Tang, G.-D., Zhang, L., & Corlett, R. T., (2020). Decoding the evolution and transmissions of the novel pneumonia coronavirus (SARS-CoV-2) using whole genomic data**.** ChinaXiv. http://chinaxiv.org/abs/202002.00033

229. World Health Organization. (2022). Scientific Advisory Group for the Origins of Novel Pathogens (SAGO) *preliminary report of the SAGO*. https://cdn.who.int/media/docs/default-source/scientific-advisory-group-on-the-origins-of-novel-pathogens/sago-report-09062022.pdf?sfvrsn=42b55bbc_1&download=true

230. Cobb, N. L., Collier, S., Attia, E. F., Augusto O., West T. E., & Wagenaar, B. H. (2022). Global influenza surveillance systems to detect the spread of influenza-negative influenza-like illness during the COVID-19 pandemic: Time series outlier analyses from 2015–2020. *PLOS Medicine, 19*(7), e1004035. https://doi.org/10.1371/journal.pmed.1004035

231. Id.

232. Liu, P., Jiang, J. Z., Wan, X. F., Hua, Y., Li, L., Zhou, J., Wang, X., Hou, F., Chen, J., Zou, J., & Chen, J. (2020). Are pangolins the intermediate host of the 2019 novel coronavirus (SARS-CoV-2)?. *PLOS Pathogens*, *16*(5), e1008421. https://doi.org/10.1371/journal.ppat.1008421

233. Lu, R., Zhao, X., Li, J., Niu, P., Yang, B., Wu, H., Wang, W., Song, H., Huang, B., Zhu, N., Bi, Y., Ma, X., Zhan, F., Wang, L., Hu, T., Zhou, H., Hu, Z., Zhou, W., Zhao, L., Chen, J., … Tan, W. (2020). Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet, 395*(10224), 565–574. https://doi.org/10.1016/S0140-6736(20)30251-8

234. Wu, F., Zhao, S., Yu, B., Chen, Y. M., Wang, W., Song, Z. G., Hu, Y., Tao, Z. W., Tian, J. H., Pei, Y. Y., Yuan, M. L., Zhang, Y. L., Dai, F. H., Liu, Y., Wang, Q. M., Zheng, J. J., Xu, L., Holmes, E. C., & Zhang, Y. Z. (2020). A new coronavirus associated with human respiratory disease in China. *Nature*, *579*(7798), 265–269. https://doi.org/10.1038/s41586-020-2008-3

235. Bai, C., Zhong, Q., & Gao, G. F. (2022). Overview of SARS-CoV-2 genome-encoded proteins. *Science China Life Sciences*, *65*(2), 280–294. https://doi.org/10.1007/s11427-021-1964-4

236. Nassar, A., Ibrahim, I. M., Amin, F. G., Magdy, M., Elgharib, A. M., Azzam, E. B., Nasser, F., Yousry, K., Shamkh, I. M., Mahdy, S. M., & Elfiky, A. A. (2021). A review of human coronaviruses' receptors: The host-cell targets for the crown bearing viruses. *Molecules (Basel, Switzerland)*, *26*(21), 6455. https://doi.org/10.3390/molecules26216455

237. Xiong, Q., Cao, L., Ma, C., Tortorici, M. A., Liu, C., Si, J., Liu, P., Gu, M., Walls, A. C., Wang, C., Shi, L., Tong, F., Huang, M., Li, J., Zhao, C., Shen, C., Chen, Y., Zhao, H., Lan, K., Corti, D., … Yan, H. (2022). Close relatives of MERS-CoV in bats use ACE2 as their functional receptors. *Nature*, *612*(7941), 748–757. https://doi.org/10.1038/s41586-022-05513-3

238. Peng, Q., Fang, L., Ding, Z., Wang, D., Peng, G., & Xiao, S. (2020). Rapid manipulation of the porcine epidemic diarrhea virus genome by CRISPR/Cas9 technology. *Journal of Virological Methods*, *276*, 113772. https://doi.org/10.1016/j.jviromet.2019.113772

239. Id.

240. Hu, D., Zhu, C., Ai, L., He, T., Wang, Y., Ye, F., Yang, L., Ding, C., Zhu, X., Lv, R., Zhu, J., Hassan, B., Feng, Y., Tan, W., & Wang, C. (2018). Genomic characterization and infectivity of a novel SARS-like coronavirus in Chinese bats. *Emerging Microbes & Infections*, *7*(1), 154. https://doi.org/10.1038/s41426-018-0155-5

241. Temmam, S., Vongphayloth, K., Baquero, E., Munier, S., Bonomi, M., Regnault, B., Douangboubpha, B., Karami, Y., Chrétien, D., Sanamxay, D., Xayaphet, V., Paphaphanh, P., Lacoste, V., Somlor, S., Lakeomany, K., Phommavanh, N., Pérot, P., Dehan, O., Amara, F., Donati, F., … Eloit, M. (2022). Bat coronaviruses related to SARS-CoV-2 and infectious for human cells. *Nature*, *604*(7905), 330–336. https://doi.org/10.1038/s41586-022-04532-4

242. Id.

243. Makarenkov, V., Mazoure, B., Rabusseau, G., & Legendre, P. (2021). Horizontal gene transfer and recombination analysis of SARS-CoV-2 genes helps discover its close relatives and shed light on its origin. *BMC Ecology and Evolution*, *21*(1), 5. https://doi.org/10.1186/s12862-020-01732-2

244. Lan, J., Ge, J., Yu, J., Shan, S., Zhou, H., Fan, S., Zhang, Q., Shi, X., Wang, Q., Zhang, L., & Wang, X. (2020). Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. *Nature*, *581*(7807), 215–220. https://doi.org/10.1038/s41586-020-2180-5

245. Lam, T. T., Jia, N., Zhang, Y. W., Shum, M. H., Jiang, J. F., Zhu, H. C., Tong, Y. G., Shi, Y. X., Ni, X. B., Liao, Y. S., Li, W. J., Jiang, B. G., Wei, W., Yuan, T. T., Zheng, K., Cui, X. M., Li, J., Pei, G. Q., Qiang, X., Cheung, W. Y., … Cao, W. C. (2020). Identifying SARS-CoV-2-related coronaviruses in Malayan pangolins. *Nature*, *583*(7815), 282–285. https://doi.org/10.1038/s41586-020-2169-0

246. Lan, J., Ge, J., Yu, J., Shan, S., Zhou, H., Fan, S., Zhang, Q., Shi, X., Wang, Q., Zhang, L., & Wang, X. (2020). Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. *Nature*, *581*(7807), 215–220. https://doi.org/10.1038/s41586-020-2180-5

247. Beaudoin, C. A., Hamaia, S. W., Huang, C. L., Blundell, T. L., & Jackson, A. P. (2021). Can the SARS-CoV-2 spike protein bind integrins independent of the RGD sequence?. *Frontiers in Cellular and Infection Microbiology*, *11*, 765300. https://doi.org/10.3389/fcimb.2021.765300

248. Chan, J. F., Kok, K. H., Zhu, Z., Chu, H., To, K. K., Yuan, S., & Yuen, K. Y. (2020). Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerging Microbes & Infections*, *9*(1), 221–236. https://doi.org/10.1080/22221751.2020.1719902

249. Hu, D., Zhu, C., Ai, L., He, T., Wang, Y., Ye, F., Yang, L., Ding, C., Zhu, X., Lv, R., Zhu, J., Hassan, B., Feng, Y., Tan, W., & Wang, C. (2018). Genomic characterization and infectivity of a novel SARS-like coronavirus in Chinese bats. *Emerging Microbes & Infections*, *7*(1), 154. https://doi.org/10.1038/s41426-018-0155-5

250. Xiao, K., Zhai, J., Feng, Y., Zhou, N., Zhang, X., Zou, J. J., Li, N., Guo, Y., Li, X., Shen, X., Zhang, Z., Shu, F., Huang, W., Li, Y., Zhang, Z., Chen, R. A., Wu, Y. J., Peng, S. M., Huang, M., Xie, W. J., … Shen, Y. (2020). Isolation of SARS-CoV-2-related coronavirus from Malayan pangolins. *Nature*, *583*(7815), 286–289. https://doi.org/10.1038/s41586-020-2313-x

251. Wrobel, A. G., Benton, D. J., Xu, P., Calder, L. J., Borg, A., Roustan, C., Martin, S. R., Rosenthal, P. B., Skehel, J. J., & Gamblin, S. J. (2021). Structure and binding properties of Pangolin-CoV spike glycoprotein inform the evolution of SARS-CoV-2. *Nature Communications*, *12*(1), 837. https://doi.org/10.1038/s41467-021-21006-9

252. Xiao, K., Zhai, J., Feng, Y., Zhou, N., Zhang, X., Zou, J. J., Li, N., Guo, Y., Li, X., Shen, X., Zhang, Z., Shu, F., Huang, W., Li, Y., Zhang, Z., Chen, R. A., Wu, Y. J., Peng, S. M., Huang, M., Xie, W. J., … Shen, Y. (2020). Isolation of SARS-CoV-2-related coronavirus from Malayan pangolins. *Nature*, *583*(7815), 286–289. https://doi.org/10.1038/s41586-020-2313-x

253. Liu, P., Jiang, J. Z., Wan, X. F., Hua, Y., Li, L., Zhou, J., Wang, X., Hou, F., Chen, J., Zou, J., & Chen, J. (2020). Are pangolins the intermediate host of the 2019 novel coronavirus (SARS-CoV-2)?. *PLOS Pathogens*, *16*(5), e1008421. https://doi.org/10.1371/journal.ppat.1008421

254. Lytras, S., Xia, W., Hughes, J., Jiang, X., & Robertson, D. L. (2021). The animal origin of SARS-CoV-2. *Science, 373*(6558), 968–970. https://doi.org/10.1126/science.abh0117

255. Lau, S. K., Li, K. S., Huang, Y., Shek, C. T., Tse, H., Wang, M., Choi, G. K., Xu, H., Lam, C. S., Guo, R., Chan, K. H., Zheng, B. J., Woo, P. C., & Yuen, K. Y. (2010). Ecoepidemiology and complete genome comparison of different strains of severe acute respiratory syndrome-related Rhinolophus bat coronavirus in China reveal bats as a reservoir for acute, self-limiting infection that allows recombination events. *Journal of Virology*, *84*(6), 2808–2819. https://doi.org/10.1128/JVI.02219-09

256. Wang, N., Li, S. Y., Yang, X. L., Huang, H. M., Zhang, Y. J., Guo, H., Luo, C. M., Miller, M., Zhu, G., Chmura, A. A., Hagan, E., Zhou, J. H., Zhang, Y. Z., Wang, L. F., Daszak, P., & Shi, Z. L. (2018). Serological evidence of bat SARS-related coronavirus infection in humans, China. *Virologica Sinica*, *33*(1), 104–107. https://doi.org/10.1007/s12250-018-0012-7

257. Id.

258. Lau, S. K., Li, K. S., Huang, Y., Shek, C. T., Tse, H., Wang, M., Choi, G. K., Xu, H., Lam, C. S., Guo, R., Chan, K. H., Zheng, B. J., Woo, P. C., & Yuen, K. Y. (2010). Ecoepidemiology and complete genome comparison of different strains of severe acute respiratory syndrome-related Rhinolophus bat coronavirus in China reveal bats as a reservoir for acute, self-limiting infection that allows recombination events. *Journal of Virology*, *84*(6), 2808–2819. https://doi.org/10.1128/JVI.02219-09

259. Hu, D., Zhu, C., Ai, L., He, T., Wang, Y., Ye, F., Yang, L., Ding, C., Zhu, X., Lv, R., Zhu, J., Hassan, B., Feng, Y., Tan, W., & Wang, C. (2018). Genomic characterization and infectivity of a novel SARS-like coronavirus in Chinese bats. *Emerging Microbes & Infections*, *7*(1), 154. https://doi.org/10.1038/s41426-018-0155-5

260. Wu, F., Zhao, S., Yu, B., Chen, Y. M., Wang, W., Song, Z. G., Hu, Y., Tao, Z. W., Tian, J. H., Pei, Y. Y., Yuan, M. L., Zhang, Y. L., Dai, F. H., Liu, Y., Wang, Q. M., Zheng, J. J., Xu, L., Holmes, E. C., & Zhang, Y. Z. (2020). A new coronavirus associated with human respiratory disease in China. *Nature*, *579*(7798), 265–269. https://doi.org/10.1038/s41586-020-2008-3

261. Chan, J. F., Kok, K. H., Zhu, Z., Chu, H., To, K. K., Yuan, S., & Yuen, K. Y. (2020). Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerging Microbes & Infections*, *9*(1), 221–236. https://doi.org/10.1080/22221751.2020.1719902

262. Hu, D., Zhu, C., Ai, L., He, T., Wang, Y., Ye, F., Yang, L., Ding, C., Zhu, X., Lv, R., Zhu, J., Hassan, B., Feng, Y., Tan, W., & Wang, C. (2018). Genomic characterization and infectivity of a novel SARS-like coronavirus in Chinese bats. *Emerging Microbes & Infections*, *7*(1), 154. https://doi.org/10.1038/s41426-018-0155-5

263. Zhou, P., Yang, X.-L., Wang, X.-G., Hu, B., Zhang, L., Zhang, W., Si, H.-R., Zhu, Y., Li, B., Huang, C.-L., Chen, H.-D., Chen, J., Luo, Y., Guo, H., Jiang, R.-D., Liu, M.-Q., Chen, Y., Shen, X.-R., Wang, X., … Shi, Z.-L. (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature, 579*, 270–273. https://doi.org/10.1038/s41586-020-2012-7

264. Stone, R. (2014). A new killer virus in China? Novel pathogen found in cave may solve medical mystery. *Science*. https://doi:/10.1126/article.23370

265. Stanway, D. (2021). Explainer: China's Mojiang mine and its role in the origins of COVID-19. *Reuters*. https://www.reuters.com/business/healthcare-pharmaceuticals/chinas-mojiang-mine-its-role-origins-covid-19-2021-06-09/

266. Li, X. (2013). *Master's Thesis: The analysis of six patients with severe pneumonia caused by unknown viruses. School of Clinical Medicine*, Kunming Medical University. https://www.documentcloud.org/documents/6981198-Analysis-of-Six-Patients-With-Unknown-Viruses.html

267. Rahalkar, M. C., & Bahulikar, R. A. (2020). Lethal pneumonia cases in Mojiang Miners (2012) and the mineshaft could provide important clues to the origin of SARS-CoV-2. *Frontiers in Public Health*, *8*, 581569. https://doi.org/10.3389/fpubh.2020.581569

268. Li, X. (2013). *Master's Thesis: The analysis of six patients with severe pneumonia caused by unknown viruses. School of Clinical Medicine*, Kunming Medical University. https://www.documentcloud.org/documents/6981198-Analysis-of-Six-Patients-With-Unknown-Viruses.html

269. Id.

270. Zhou, P., Yang, X. L., Wang, X. G., Hu, B., Zhang, L., Zhang, W., Si, H. R., Zhu, Y., Li, B., Huang, C. L., Chen, H. D., Chen, J., Luo, Y., Guo, H., Jiang, R. D., Liu, M. Q., Chen, Y., Shen, X. R., Wang, X., Zheng, X. S., ... Shi, Z. L. (2020). Addendum: A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*, *588*(7836), E6. https://doi.org/10.1038/s41586-020-2951-z

271. Calvert, J., & Arbuthnott, G. (2023, June 10). What really went on inside the Wuhan lab weeks before Covid erupted. *The Sunday Times*. https://www.thetimes.co.uk/article/inside-wuhan-lab-covid-pandemic-china-america-qhjwwwvm0

272. Cohen, J. (2020). Wuhan Coronavirus Hunter Shi Zhengli Speaks Out. *Science Magazine*. https://www.science.org/pb-assets/PDF/News%20PDFs/Shi%20Zhengli%20Q&A-1630433861.pdf

273. Bobay, L. M., O'Donnell, A. C., & Ochman, H. (2020). Recombination events are concentrated in the spike protein region of Betacoronaviruses. *PLOS Genetics*, *16*(12), e1009272. https://doi.org/10.1371/journal.pgen.1009272

274. de Klerk, A., Swanepoel, P., Lourens, R., Zondo, M., Abodunran, I., Lytras, S., MacLean, O. A., Robertson, D., Kosakovsky Pond, S. L., Zehr, J. D., Kumar, V., Stanhope, M. J., Harkins, G., Murrell, B., & Martin, D. P. (2022). Conserved recombination patterns across coronavirus subgenera. *Virus Evolution*, *8*(2), veac054. https://doi.org/10.1093/ve/veac054

275. Plowright, R. K., Eby, P., Hudson, P. J., Smith, I. L., Westcott, D., Bryden, W. L., Middleton, D., Reid, P. A., McFarlane, R. A., Martin, G., Tabor, G. M., Skerratt, L. F., Anderson, D. L., Crameri, G., Quammen, D., Jordan, D., Freeman, P., Wang, L. F., Epstein, J. H., Marsh, G. A., ... McCallum, H. (2015). Ecological dynamics of emerging bat virus spillover. *Proceedings of the Royal Society B: Biological Sciences*, *282*(1798), 20142124. https://doi.org/10.1098/rspb.2014.2124

276. Cohen, L. E., Fagre, A. C., Chen, B., Carlson, C. J., & Becker, D. J. (2023). Coronavirus sampling and surveillance in bats from 1996-2019: a systematic review and meta-analysis. Nature microbiology, 8(6), 1176–1186. https://doi.org/10.1038/s41564-023-01375-1

277. Id.

278. EcoHealth Alliance. (2018). *Project DEFUSE: Defusing the threat of bat-borne coronaviruses*. Draft Defense Advanced Research Projects Agency proposal. (HR001118S0017-PREEMPT-PA 001). https://s3.documentcloud.org/documents/21066966/defuse-proposal.pdf

279. Id.

280. Baric, R. S. (2018, February 8). *RE: Email First (rough) Draft of the DARPA abstract – Project DEFUSE*. https://usrtk.org/wp-content/uploads/2023/12/2021-006245-Combined-Records_Redacted-1-235.pdf

281. Menachery, V. D., Yount, B. L., Jr, Debbink, K., Agnihothram, S., Gralinski, L. E., Plante, J. A., Graham, R. L., Scobey, T., Ge, X. Y., Donaldson, E. F., Randell, S. H., Lanzavecchia, A., Marasco, W. A., Shi, Z. L., & Baric, R. S. (2015). A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence. *Nature Medicine*, *21*(12), 1508–1513. https://doi.org/10.1038/nm.3985

282. Menachery, V., Yount, B., Debbink, K. et al. (2016) Correction: Corrigendum: A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence. *Nature Medicine, 22*, 446. https://doi.org/10.1038/nm0416-446d

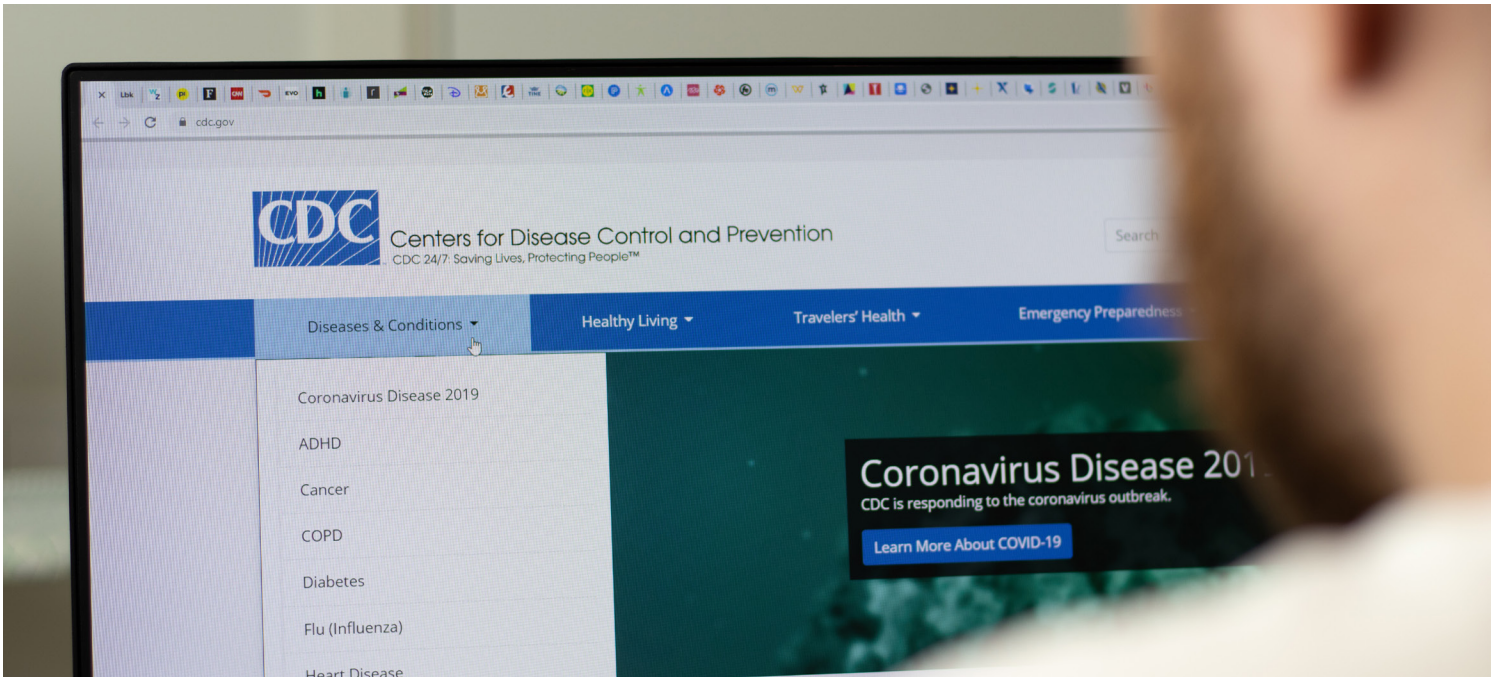
283. Menachery, V. D., Yount, B. L., Jr, Debbink, K., Agnihothram, S., Gralinski, L. E., Plante, J. A., Graham, R. L., Scobey, T., Ge, X. Y., Donaldson, E. F., Randell, S. H., Lanzavecchia, A., Marasco, W. A., Shi, Z. L., & Baric, R. S. (2015). A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence. *Nature Medicine*, *21*(12), 1508–1513. https://doi.org/10.1038/nm.3985

284. Id.

285. Menachery, V., Yount, B., Debbink, K. et al. (2016) Correction: Corrigendum: A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence. *Nature Medicine, 22*, 446. https://doi.org/10.1038/nm0416-446d

286. Menachery, V. D., Yount, B. L., Jr, Debbink, K., Agnihothram, S., Gralinski, L. E., Plante, J. A., Graham, R. L., Scobey, T., Ge, X. Y., Donaldson, E. F., Randell, S. H., Lanzavecchia, A., Marasco, W. A., Shi, Z. L., & Baric, R. S. (2015). A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence. *Nature Medicine*, *21*(12), 1508–1513. https://doi.org/10.1038/nm.3985

287. U.S. Centers for Disease Control and Prevention. (2021). *Infographic: Biosafety labs levels*. https://www.cdc.gov/orr/infographics/biosafety.htmm



288. Menachery, V. D., Yount, B. L., Jr, Debbink, K., Agnihothram, S., Gralinski, L. E., Plante, J. A., Graham, R. L., Scobey, T., Ge, X. Y., Donaldson, E. F., Randell, S. H., Lanzavecchia, A., Marasco, W. A., Shi, Z. L., & Baric, R. S. (2015). A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence. *Nature Medicine*, *21*(12), 1508–1513. https://doi.org/10.1038/nm.3985

289. EcoHealth Alliance. (2018). *Project DEFUSE: Defusing the threat of bat-borne coronaviruses*. Draft Defense Advanced Research Projects Agency proposal. HR001118S0017-PREEMPT-PA 001 https://s3.documentcloud.org/documents/21066966/defuse-proposal.pdf

290. Bobay, L. M., O'Donnell, A. C., & Ochman, H. (2020). Recombination events are concentrated in the spike protein region of Betacoronaviruses. *PLOS Genetics*, *16*(12), e1009272. https://doi.org/10.1371/journal.pgen.1009272

291. de Klerk, A., Swanepoel, P., Lourens, R., Zondo, M., Abodunran, I., Lytras, S., MacLean, O. A., Robertson, D., Kosakovsky Pond, S. L., Zehr, J. D., Kumar, V., Stanhope, M. J., Harkins, G., Murrell, B., & Martin, D. P. (2022). Conserved recombination patterns across coronavirus subgenera. *Virus Evolution*, *8*(2), veac054. https://doi.org/10.1093/ve/veac054

292. Plowright, R. K., Eby, P., Hudson, P. J., Smith, I. L., Westcott, D., Bryden, W. L., Middleton, D., Reid, P. A., McFarlane, R. A., Martin, G., Tabor, G. M., Skerratt, L. F., Anderson, D. L., Crameri, G., Quammen, D., Jordan, D., Freeman, P., Wang, L. F., Epstein, J. H., Marsh, G. A., … McCallum, H. (2015). Ecological dynamics of emerging bat virus spillover. *Proceedings of the Royal Society B: Biological Sciences*, *282*(1798), 20142124. https://doi.org/10.1098/rspb.2014.2124

293. Schemmel, A. (2022). DOD rejects EcoHealth bid due to concerns over gain-of-function research, report says. *NBC Online News*. https://nbcmontana.com/news/coronavirus/dod-rejects-ecohealth-bid-due-to-concerns-over-gain-of-function-research-report-says

294. Hu, B., Zeng, L. P., Yang, X. L., Ge, X. Y., Zhang, W., Li, B., Xie, J. Z., Shen, X. R., Zhang, Y. Z., Wang, N., Luo, D. S., Zheng, X. S., Wang, M. N., Daszak, P., Wang, L. F., Cui, J., & Shi, Z. L. (2017). Discovery of a rich gene pool of bat SARS-related coronaviruses provides new insights into the origin of SARS coronavirus. *PLOS Pathogens, 13*(11), e1006698. https://doi.org/10.1371/journal.ppat.1006698

295. Abdel-Moneim, A. S., & Abdelwhab, E. M. (2020). Evidence for SARS-CoV-2 infection of animal hosts. *Pathogens (Basel, Switzerland)*, *9*(7), 529. https://doi.org/10.3390/pathogens9070529

296. Hu, B., Zeng, L. P., Yang, X. L., Ge, X. Y., Zhang, W., Li, B., Xie, J. Z., Shen, X. R., Zhang, Y. Z., Wang, N., Luo, D. S., Zheng, X. S., Wang, M. N., Daszak, P., Wang, L. F., Cui, J., & Shi, Z. L. (2017). Discovery of a rich gene pool of bat SARS-related coronaviruses provides new insights into the origin of SARS coronavirus. *PLOS Pathogens, 13*(11), e1006698. https://doi.org/10.1371/journal.ppat.1006698

297. Daszak, P. (2018, February 8) *RE: Email First (rough) Draft of the DARPA abstract – Project DEFUSE*. https://usrtk.org/wp-content/uploads/2023/12/2021-006245-Combined-Records_Redacted-1-235.pdf

298. Id.

299. Zeng L-P. (2017). *Reverse genetic system of bat SARS-like coronavirues and function of ORFX*. Wuhan Institute of Virology, Chinese Academy of Sciences. Available at https://docs.google.com/document/d/1uZrBG5A720aLGtVI4kPp6nJM7FuuolwO/edit

300. Hu, B., Zeng, L. P., Yang, X. L., Ge, X. Y., Zhang, W., Li, B., Xie, J. Z., Shen, X. R., Zhang, Y. Z., Wang, N., Luo, D. S., Zheng, X. S., Wang, M. N., Daszak, P., Wang, L. F., Cui, J., & Shi, Z. L. (2017). Discovery of a rich gene pool of bat SARS-related coronaviruses provides new insights into the origin of SARS coronavirus. *PLOS Pathogens, 13*(11), e1006698. https://doi.org/10.1371/journal.ppat.1006698

301. Daszak, P. (2018). *Understanding the risk of bat coronavirus emergence: Year 4 report.* National Institutes of Allergy and Infectious Disease Grant 5R01AI110964-05. https://s3.documentcloud.org/documents/21055989/understanding-risk-bat-coronavirus-emergence-grant-notice.pdf

302. EcoHealth Alliance. (2018). *Project DEFUSE: Defusing the threat of bat-borne coronaviruses*. Draft Defense Advanced Research Projects Agency proposal. (HR001118S0017-PREEMPT-PA 001). https://s3.documentcloud.org/documents/21066966/defuse-proposal.pdf

303. Id.

304. Becker, G. L., Lu, Y., Hardes, K., Strehlow, B., Levesque, C., Lindberg, I., Sandvig, K., Bakowsky, U., Day, R., Garten, W., & Steinmetzer, T. (2012). Highly potent inhibitors of proprotein convertase furin as potential drugs for treatment of infectious diseases. *Journal of Biochemistry, 287*(26): 21992-22003. https://doi.org/10.11074/jbc.M111.332643

305. Duckert, P., Brunak, S., & Blom, N. (2004). Prediction of proprotein convertase cleavage sites. *Protein Engineering, Design & Selection*, *17*(1), 107–112. https://doi.org/10.1093/protein/gzh013

306. Tian, S., Huajun, W., & Wu, J. (2012). Computational prediction of furin cleavage sites by a hybrid method and understanding mechanism underlying diseases. *Scientific Reports*, *2*, 261. https://doi.org/10.1038/srep00261

307. EcoHealth Alliance. (2018). *Project DEFUSE: Defusing the threat of bat-borne coronaviruses*. Draft Defense Advanced Research Projects Agency proposal. (HR001118S0017-PREEMPT-PA 001). https://s3.documentcloud.org/documents/21066966/defuse-proposal.pdf

308. Id.

309. Li, X., Duan, G., Zhang, W., Jinsong, S., Jiayuan C., Shunmei, C.,Shan G., Jishou R. (2020). A furin cleavage site was discovered in the S protein of the 2019 novel coronavirus. Chinese Journal of Bioinformatics (In Chinese translated into English). 18(2): 103-108. https://doi.org/10.12113/202002001

310. Id.

311. Pohl, M. O., Busnadiego, I., Kufner, V., Glas, I., Karakus, U., Schmutz, S., Zaheri, M., Abela, I., Trkola, A., Huber, M., Stertz, S., & Hale, B. G. (2021). SARS-CoV-2 variants reveal features critical for replication in primary human cells. *PLOS Biology*, *19*(3), e3001006. https://doi.org/10.1371/journal.pbio.3001006

312. Johnson, B. A., Xie, X., Bailey, A. L., Kalveram, B., Lokugamage, K. G., Muruato, A., Zou, J., Zhang, X., Juelich, T., Smith, J. K., Zhang, L., Bopp, N., Schindewolf, C., Vu, M., Vanderheiden, A., Winkler, E. S., Swetnam, D., Plante, J. A., Aguilar, P., Plante, K. S., … Menachery, V. D. (2021). Loss of furin cleavage site attenuates SARS-CoV-2 pathogenesis. *Nature*, *591*(7849), 293–299. https://doi.org/10.1038/s41586-021-03237-4

313. Id.

314. Sasaki, M., Toba, S., Itakura, Y., Chambaro, H. M., Kishimoto, M., Tabata, K., Intaruck, K., Uemura, K., Sanaki, T., Sato, A., Hall, W. W., Orba, Y., & Sawa, H. (2021). SARS-CoV-2 bearing a mutation at the S1/S2 cleavage site exhibits attenuated virulence and confers protective immunity. *mBio*, *12*(4), e0141521. https://doi.org/10.1128/mBio.01415-21

315. Chan, Y. A., & Zhan, S. H. (2022). The emergence of the spike furin cleavage site in SARS-CoV-2. *Molecular Biology and Evolution*, *39*(1), msab327. https://doi.org/10.1093/molbev/msab327

316. Baltimore, D. (2021). Interview of David Baltimore: The debate over origins of SARS-CoV-2. *Caltech Weekly*. https://www.caltech.edu/about/news/the-debate-over-origins-of-sars-cov-2.

317. Romeu, A. R. (2023). Probable human origin of the SARS-CoV-2 polybasic furin cleavage motif. *BMC Genomic Data*, *24*(1), 71. https://doi.org/10.1186/s12863-023-01169-8

318. Chan, Y. A., & Zhan, S. H. (2022). The emergence of the spike furin cleavage site in SARS-CoV-2. *Molecular Biology and Evolution*, *39*(1), msab327. https://doi.org/10.1093/molbev/msab327

319. Kumar, N., Kaushik, R., Tennakoon, C., Uversky, V. N., Mishra, A., Sood, R., Srivastava, P., Tripathi, M., Zhang, K. Y. J., & Bhatia, S. (2021). Evolutionary signatures governing the codon usage bias in coronaviruses and their implications for viruses infecting various bat species. *Viruses*, *13*(9), 1847. https://doi.org/10.3390/v13091847

320. Li, X., Duan, G., Zhang, W., Jinsong, S., Jiayuan C., Shunmei, C.,Shan G., Jishou R. (2020). A furin cleavage site was discovered in the S protein of the 2019 novel coronavirus. Chinese Journal of Bioinformatics (In Chinese translated into English). 18(2): 103-108. https://doi.org/10.12113/202002001

321. Temmam, S., Montagutelli, X., Herate, C., Donati, F., Regnault, B., Attia, M., Baquero Salazar, E., Chretien, D., Conquet, L., Jouvion, G., Pipoli Da Fonseca, J., Cokelaer, T., Amara, F., Relouzat, F., Naninck, T., Lemaitre, J., Derreudre-Bosquet, N., Pascal, Q., Bonomi, M., Bigot, T., … Eloit, M. (2023). SARS-CoV-2-related bat virus behavior in human-relevant models sheds light on the origin of COVID-19. *EMBO Reports*, *24*(4), e56055. https://doi.org/10.15252/embr.202256055

322. Li, W., Wicht, O., van Kuppeveld, F. J., He, Q., Rottier, P. J., & Bosch, B. J. (2015). A single point mutation creating a furin cleavage site in the spike protein renders porcine epidemic diarrhea coronavirus trypsin independent for cell entry and fusion. *Journal of Virology*, *89*(15), 8077–8081. https://doi.org/10.1128/JVI.00356-15

323. Sands, B., & Brent, R. (2016). Overview of post Cohen-Boyer methods for single segment cloning and for multisegment DNA assembly. *Current Protocols in Molecular Biology*, *113*(1), 3.26.1–3.26.20. https://doi.org/10.1002/0471142727.mb0326s113

324. Xia, S., Lan, Q., Su, S., Wang, X., Xu, W., Liu, Z., Zhu, Y., Wang, Q., Lu, L., & Jiang, S. (2020). The role of furin cleavage site in SARS-CoV-2 spike protein-mediated membrane fusion in the presence or absence of trypsin. *Signal Transduction and Targeted Therapy*, *5*(1), 92. https://doi.org/10.1038/s41392-020-0184-0

325. Id.

326. Bruttel, V., Washburn, A., & VanDongen, A. (2022) Endonuclease fingerprint indicates a synthetic origin of SARS-CoV-2. bioRxiv, 10.18.512756. https://doi.org/10.1101/2022.10.18.512756

327. Id.

328. Id.

329. Kopp, E. (2024). US scientists proposed to make viruses with unique features of SARS-CoV-2 in Wuhan. *U.S. Right to Know*. https://usrtk.org/covid-19-origins/scientists-proposed-making-viruses-with-unique-features-of-sars-cov-2-in-wuhan/

330. Wade, N. (2024). The story of the decade**:** New documents strengthen—perhaps conclusively—the lab-leak hypothesis of Covid-19's origins. *City Journal*. https://www.city-journal.org/article/new-documents-bolster-lab-leak-hypothesis

331. Wrobel, A. G., Benton, D. J., Xu, P., Calder, L. J., Borg, A., Roustan, C., Martin, S. R., Rosenthal, P. B., Skehel, J. J., & Gamblin, S. J. (2021). Structure and binding properties of Pangolin-CoV spike glycoprotein inform the evolution of SARS-CoV-2. *Nature communications*, *12*(1), 837. https://doi.org/10.1038/s41467-021-21006-9

332. Li, X., Giorgi, E. E., Marichannegowda, M. H., Foley, B., Xiao, C., Kong, X. P., Chen, Y., Gnanakaran, S., Korber, B., & Gao, F. (2020). Emergence of SARS-CoV-2 through recombination and strong purifying selection. *Science advances*, *6*(27), eabb9153. https://doi.org/10.1126/sciadv.abb9153

333. Yan, L-M., Kang, S., Hu, S. (2020). Unusual Features of the SARS-CoV-2 Genome Suggesting Sophisticated Laboratory Modification Rather Than Natural Evolution and Delineation of Its Probable Synthetic Rout. Yan Research – An Independent Research Team. https://www.researchgate.net/figure/Two-restriction-sites-are-present-at-either-end-of-the-RBM-of-SARS-CoV-2-providing_fig3_344240007

334. Lan, J., Ge, J., Yu, J. et al. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. Nature 581, 215–220 (2020). https://doi.org/10.1038/s41586-020-2180-5

335. Fowler DM, Fields S. Deep mutational scanning: a new style of protein science. Nat Methods. 2014 Aug;11(8):801-7. https://doi/10.1038/nmeth.3027

336. Hussein, H. A., Walker, L. R., Abdel-Raouf, U. M., Desouky, S. A., Montasser, A. K., & Akula, S. M. (2015). Beyond RGD: virus interactions with integrins. *Archives of virology, 160*(11), 2669–2681. https://doi.org/10.1007/s00705-015-2579-8

337. Sigrist, C. J., Bridge, A., & Le Mercier, P. (2020). A potential role for integrins in host cell entry by SARS-CoV-2. *Antiviral research*, *177*, 104759. https://doi.org/10.1016/j.antiviral.2020.104759

338. Makowski, L., Olson-Sidford, W., & W-Weisel, J. (2021). Biological and Clinical Consequences of Integrin Binding via a Rogue RGD Motif in the SARS CoV-2 Spike Protein. *Viruses, 13*(2), 146. https://doi.org/10.3390/v13020146

339. Mezu-Ndubuisi, O.J., Maheshwari, A. The role of integrins in inflammation and angiogenesis. *Pediatr Res* **89**, 1619–1626 (2021). https://doi.org/10.1038/s41390-020-01177-9

340. Makowski, L., Olson-Sidford, W., & W-Weisel, J. (2021). Biological and Clinical Consequences of Integrin Binding via a Rogue RGD Motif in the SARS CoV-2 Spike Protein. *Viruses, 13*(2), 146. https://doi.org/10.3390/v13020146

341. Beaudoin, C. A., Hamaia, S. W., Huang, C. L., Blundell, T. L., & Jackson, A. P. (2021). Can the SARS-CoV-2 spike protein bind integrins independent of the RGD sequence?. *Frontiers in Cellular and Infection Microbiology*, *11*, 765300. https://doi.org/10.3389/fcimb.2021.765300

342. Id.

343. Id.

344. Wu, X., & Reddy, D. S. (2012). Integrins as receptor targets for neurological disorders. *Pharmacology & Therapeutics*, *134*(1), 68–81. https://doi.org/10.1016/j.pharmthera.2011.12.008

345. Beaudoin, C. A., Hamaia, S. W., Huang, C. L., Blundell, T. L., & Jackson, A. P. (2021). Can the SARS-CoV-2 spike protein bind integrins independent of the RGD sequence?. *Frontiers in Cellular and Infection Microbiology*, *11*, 765300. https://doi.org/10.3389/fcimb.2021.765300

346. Ryu, J. K., Yan, Z., Montano, M., Sozmen, E. G., Dixit, K., Suryawanshi, R. K., Matsui, Y., Helmy, E., Kaushal, P., Makanani, S. K., Deerinck, T. J., Meyer-Franke, A., Rios Coronado, P. E., Trevino, T. N., Shin, M. G., Tognatta, R., Liu, Y., Schuck, R., Le, L., Miyajima, H., … Akassoglou, K. (2024). Fibrin drives thromboinflammation and neuropathology in COVID-19. *Nature*, 10.1038/s41586-024-07873-4. Advance online publication. https://doi.org/10.1038/s41586-024-07873-4

347. Liu, P., Jiang, J. Z., Wan, X. F., Hua, Y., Li, L., Zhou, J., Wang, X., Hou, F., Chen, J., Zou, J., & Chen, J. (2020). Are pangolins the intermediate host of the 2019 novel coronavirus (SARS-CoV-2)?. *PLOS Pathogens*, *16*(5), e1008421. https://doi.org/10.1371/journal.ppat.1008421

348. Id.

349. Li, X., Giorgi, E. E., Marichannegowda, M. H., Foley, B., Xiao, C., Kong, X. P., Chen, Y., Gnanakaran, S., Korber, B., & Gao, F. (2020). Emergence of SARS-CoV-2 through recombination and strong purifying selection. *Science Advances*, *6*(27), eabb9153. https://doi.org/10.1126/sciadv.abb9153

350. Moffit, R. E., & McCloskey, M. (2023). COVID-19 origins: Experts consulted by Fauci suddenly changed their minds. *The Daily Signal*. https://www.dailysignal.com/2023/09/01/covid-19-origins-a-steady-drip-of-intriguing-revelations/

351. U.S. House Oversight Committee Select Subcommittee on the Coronavirus Pandemic, Majority Staff. (2023). *The proximal origin of a cover-up: Did the "Bethesda Boys" downplay a lab leak?.* https://oversight.house.gov/wp-content/uploads/2023/07/Final-Report-6.pdf

352. NIH Email to Senior HHS Officials. (2020, February 1). Subject: Follow up. https://www.heritage.org/public-health/commentary/covid-19-origins-experts-consulted-fauci-suddenly-changed-their-minds

353. Office of the Spokesperson, U.S. Department of State. (2021, January 15). *Fact Sheet: Activity at the Wuhan Institute of Virology: Fact Sheet*. U.S. Department of State. https://2017-2021.state.gov/fact-sheet-activity-at-the-wuhan-institute-of-virology/

354. Calvert, J., & Arbuthnott G. (2023, June 10). What really went on inside the Wuhan lab weeks before Covid erupted. *The Sunday Times*. https://www.thetimes.co.uk/article/inside-wuhan-lab-covid-pandemic-china-america-qhjwwwvm0

355. Chan, Y. A., & Zhan, S. H. (2022). The emergence of the spike furin cleavage site in SARS-CoV-2. *Molecular Biology and Evolution*, *39*(1), msab327. https://doi.org/10.1093/molbev/msab327

356. Chan, J. F., Kok, K. H., Zhu, Z., Chu, H., To, K. K., Yuan, S., & Yuen, K. Y. (2020). Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerging Microbes & Infections*, *9*(1), 221–236. https://doi.org/10.1080/22221751.2020.1719902

357. Baltimore, D. (2021). Interview of David Baltimore: The debate over origins of SARS-CoV-2. *Caltech Weekly*. https://www.caltech.edu/about/news/the-debate-over-origins-of-sars-cov-2.

358. Rogin, J. (2020, April 14). State Department cables warned of safety issues at wuhan lab studying bat coronaviruses. *The Washington Post*. https://www.washingtonpost.com/opinions/2020/04/14/state-department-cables-warned-safety-issues-wuhan-lab-studying-bat-coronaviruses/

359. Zhiming, Y. (2019). Current status and future challenges of high-level biosafety laboratories in China. *Journal of Biosafety and Biosecurity*, *1*(2), 123–127. https://doi.org/10.1016/j.jobb.2019.09.005

360. Id.

361. Eban, K. (2023, November 21). Secret warnings about Wuhan research predated the pandemic. *Vanity Fair*. https://www.vanityfair.com/news/2023/11/covid-origins-warnings-nih-department-of-energy

362. Id.

363. Baric, R. S. (2018, February 8). *RE: Email First (rough) Draft of the DARPA abstract – Project DEFUSE*. https://usrtk.org/wp-content/uploads/2023/12/2021-006245-Combined-Records_Redacted-1-235.pdf

364. Zeng, L. P., Gao, Y. T., Ge, X. Y., Zhang, Q., Peng, C., Yang, X. L., Tan, B., Chen, J., Chmura, A. A., Daszak, P., & Shi, Z. L. (2016). Bat severe acute respiratory syndrome-like coronavirus WIV1 encodes an extra accessory protein, ORFX, involved in modulation of the host immune response. *Journal of Virology*, *90*(14), 6573–6582. https://doi.org/10.1128/JVI.03079-15

365. Baric, R. S. (2018, February 8). *RE: Email First (rough) Draft of the DARPA abstract – Project DEFUSE*. https://usrtk.org/wp-content/uploads/2023/12/2021-006245-Combined-Records_Redacted-1-235.pdf

366. Zhou, D., Song, H., Wang, J., Li, Z., Ji, X., Hou, X., & Xu, J. (2019). Biosafety and biosecurity. *Journal of Biosafety and Biosecurity, 1*, 15-18. https://doi.org/10.1016/j.jobb.2019.01.001

367. Id.

368. Wuhan Institute of Virology, Chinese Academy of Sciences. (2019, March 1). Announcement of competitive consultation on the maintenance project of P3 laboratory and experimental animal center in Zhengdian Park. Wuhan Institute of Virology, Chinese Academy of Sciences. http://www.ccgp.gov.cn/cggg/dfgg/jzxcs/201903/t20190301_11699621.htm

369. Dou, E., Wu, P.L., Aries, Q., & Tan, R. (2021). Inside the Wuhan lab: French engineering, deadly viruses and a big mystery. *The Washington Post.* https://www.washingtonpost.com/world/asia_pacific/wuhan-lab-covid-china/2021/09/07/f293325c-fb11-11eb-911c-524bc8b68f17_story.html

370. Gao, G. F. (2019). For a better world: Biosafety strategies to protect global health. *Biosafety and Health*, *1*(1), 1–3. https://doi.org/10.1016/j.bsheal.2019.03.001

371. Wuhan Institute of Virology. (2019, April 8). *Wuhan Institute of Virology convenes 2019 security work conference [*武汉病毒所召　*2019*年度安全工作会议*]*. The quoted text is "他强调，要严格落实'党政同责，一岗双责，齐抓共管，失职追责'的安全管理责任制要求，坚持'管业务必须管安全，管生产必须管安全'，必须使・方面工作齐头并进." The quoted text is "要严格遵守国家，中科院和研究所各项安全管理法律，法规及法章制度，加强日常安全管理，不定期　展安全自查与隐患整改..."

372. Announcement of deal reached for project to renovate the hazardous waste management system at the Zhengdian Campus of the Chinese Academy of Sciences Wuhan Institute of Virology. (2019, July 31). *Chinese Government Procurement Network.*

373. Senator Marco Rubio's Office. (2022). *"A complex and grave situation": A political chronology of the SARS-CoV-2 outbreak*. https://www.rubio.senate.gov/wp-content/uploads/_cache/files/790b6d70-7150-4f0f-a8b9-01ea45d3b1d1/EAB44A6CA6190D31041C0037E9C5E589.05.01.23-origin-report-clean-v1-11.pdf. *See also:* Dou, E. (2021, June 22). Wuhan lab's classified work complicates search for pandemic's origins. *The Washington Post*. *See also:* Peng Er, L., & Clarke. (2021, May 20). *Coronavirus research in China: Origins, international networks, and consequences*. Non-Traditional Security (NTS)-Asia Consortium, Nanyang Technological University Singapore. Page 14.

374. Wuhan Branch, Chinese Academy of Sciences. (2019, May 13). *Wuhan Institute of Virology held a special training on national security in 2019.* https://web.archive.org/web/20200504162244/http:/www.whb.cas.cn/xw/gzdt/201905/t20190521_5298484.html

375. Eban, K. (2023, November 21). Secret warnings about Wuhan research predated the pandemic. *Vanity Fair*. https://www.vanityfair.com/news/2023/11/covid-origins-warnings-nih-department-of-energy https://www.vanityfair.com/news/2023/11/covid-origins-warnings-nih-department-of-energy

376. Office of the Spokesperson, U.S. Department of State. (2021, January 15). *Fact Sheet: Activity at the Wuhan Institute of Virology: Fact Sheet*. U.S. Department of State. https://2017-2021.state.gov/fact-sheet-activity-at-the-wuhan-institute-of-virology/

377. Dou, E. (2021, June 22). Wuhan lab's classified work complicates search for pandemic's origins. *The Washington Post*. https://www.washingtonpost.com/world/asia_pacific/wuhan-lab-leak-secret-coronavirus/2021/06/22/b9c45940-cf08-11eb-a224-bd59bd22197c_story.html

378. Zhiming, Y. (2019). Current status and future challenges of high-level biosafety laboratories in China. *Journal of Biosafety and Biosecurity*, *1*(2), 123–127. https://doi.org/10.1016/j.jobb.2019.09.005

379. Id.

380. Wu, G. (2019). Laboratory biosafety in China: Past, present and future. *Journal of Biosafety and Health, 1*, 56-58. http://dx.doi.org/10.1016/j.bsheal.2019.10.003

381. Senator Marco Rubio's Office. (2022). *"A complex and grave situation": A political chronology of the SARS-CoV-2 outbreak*. https://www.rubio.senate.gov/wp-content/uploads/_cache/files/790b6d70-7150-4f0f-a8b9-01ea45d3b1d1/EAB44A6CA6190D31041C0037E9C5E589.05.01.23-origin-report-clean-v1-11.pdf. The quoted text is "聚焦生物安全领域'▪▪子'问题, 提出解决方案, 通过攻坚克难, 切实 推进生物安全大科学中心的建设与发展, 助力国家科技发展." *See also:* Wuhan Institute of Virology. (2019, June 21). *Wuhan Institute of Virology convenes promotion meeting for work on the educational theme of 'staying true to our original aspiration, keeping firmly in mind our mission'* and a study session of the Expanded Party Committee Central Group *[武汉病毒所召 "不忘初心，牢记使命"主题教育工作推进会暨党委中心组(扩大)学习会议].*

382. Id. See also: Wuhan Institute of Virology. (2019, July 09). Wuhan Institute of Virology organizes centralized study on the educational theme of 'staying true to our original aspiration, keeping firmly in mind our mission' [武汉病毒所组织"不忘初心，牢记使命"主题教育 集中学习]. The quoted text is "党员领导班子成员通过深入调研和广泛征求意见，充分了解和认识到限制研究所 发展的短板和底板 并提出有针对性和可操作性的解决措施."

383. Senator Marco Rubio's Office. (2022). *"A complex and grave situation": A political chronology of the SARS-CoV-2 outbreak*. https://www.rubio.senate.gov/wp-content/uploads/_cache/files/790b6d70-7150-4f0f-a8b9-01ea45d3b1d1/EAB44A6CA6190D31041C0037E9C5E589.05.01.23-origin-report-clean-v1-11.pdf. The quoted text is "参会党员针对生物安全理论和技术培训，安全隐患的筛查和管理制度的完善，高精端 仪器的共享及郑店实验室整体搬 等方面提出了意见和建议." *See also:* Wuhan Institute of Virology. (2019, July 22). *Party branch of the Wuhan Institute of Virology Microbiological Resources and Bioinformatics Research Center organizes monthly party day activities and specialized investigation and study of 'staying true to our original aspiration, keeping firmly in mind our mission' [武汉病毒所微生物资源与生物信息研究中心党支部组织"不忘初心，牢记使命"主题党日活动暨主 题教育专题调研会].*

384. Senator Marco Rubio's Office. (2022). *"A complex and grave situation": A political chronology of the SARS-CoV-2 outbreak*. https://www.rubio.senate.gov/wp-content/uploads/_cache/files/790b6d70-7150-4f0f-a8b9-01ea45d3b1d1/EAB44A6CA6190D31041C0037E9C5E589.05.01.23-origin-report-clean-v1-11.pdf

385. Id.

386. Zhang, Z., Wu, J., Hao, L., Yi, Y., & Qi, J. (2020). Development of biosafety equipment for high-containment laboratory and for person protection in China. *Biosafety and Health, 2,* 12-17. http://dx.doi.org/10.1016/j.bsheal.2019.12.008

387. Id.

388. Id.

389. Cohen, J. (2020). Wuhan Coronavirus Hunter Shi Zhengli Speaks Out. *Science Magazine*. https://www.science.org/pb-assets/PDF/News%20PDFs/Shi%20Zhengli%20Q&A-1630433861.pdf

390. National Intelligence Council, Office of the Director of National Intelligence. (2023). *Updated assessment on COVID-19 origins*. Office of the Director of National Intelligence. https://www.intelligence.gov/assets/documents/702%20Documents/declassified/Declassified-Assessment-on-COVID-19-Origins.pdf

391. Zeng, L,-P. (2017) *Dissertation: Reverse genetic system of bat SARS-like coronaviruses and function of ORFX*. Wuhan Institute of Virology, Chinese Academy of Sciences. https://twitter.com/TheSeeker268/status/1392575246843080704/photo/1

392. Zeng, L. P., Gao, Y. T., Ge, X. Y., Zhang, Q., Peng, C., Yang, X. L., Tan, B., Chen, J., Chmura, A. A., Daszak, P., & Shi, Z. L. (2016). Bat severe acute respiratory syndrome-like coronavirus WIV1 encodes an extra accessory protein, ORFX, involved in modulation of the host immune response. *Journal of Virology*, *90*(14), 6573–6582. https://doi.org/10.1128/JVI.03079-15

393. Hu, B., Zeng, L. P., Yang, X. L., Ge, X. Y., Zhang, W., Li, B., Xie, J. Z., Shen, X. R., Zhang, Y. Z., Wang, N., Luo, D. S., Zheng, X. S., Wang, M. N., Daszak, P., Wang, L. F., Cui, J., & Shi, Z. L. (2017). Discovery of a rich gene pool of bat SARS-related coronaviruses provides new insights into the origin of SARS coronavirus. *PLOS Pathogens, 13*(11), e1006698. https://doi.org/10.1371/journal.ppat.1006698

394. U.S. Centers for Disease Control and Prevention & U.S. National Institutes of Health. (2020). *Biosafety in Microbiological and Biomedical Laboratories (BMBL) 6th Edition.* https://www.cdc.gov/labs/pdf/SF__19_308133-A_BMBL6_00-BOOK-WEB-final-3.pdf

395. Pike, R. M. (1976). Laboratory-acquired infections: summary and analysis of 3921 cases. *Health Lab Sci*. 13(2):105-114. https://pubmed.ncbi.nlm.nih.gov/946794/

396. Phillips, G. B. (1965). *Causal factors of microbiological laboratory accidents*. US Army Biological Laboratories, Fort Detrick.

397. Aspland, A., Chew, C., Douagi, I., Galland, T., Marvin, J., Monts, J., Nance, D., Smith, A. L., & Solga, M. (2021). Risk awareness during operation of analytical flow cytometers and implications throughout the COVID-19 pandemic. *Cytometry Part A: Journal of Quantitative Cell Science*, *99*(1), 81–89. https://doi.org/10.1002/cyto.a.24282

398. Liua, A., Zhanga, C., Hub, C., Ronga,R., Shia, Y., Lia,C. (November 2024).Biological Aerosol Transmission Characteristics and Exposure Risk Assessment in a Typical Biosafety Laboratory. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=5014812

399. Id.

400. Du, C., Li, G., & Han, G. (2023). Biosafety and mental health: Virus induced cognitive decline. *Biosafety and Public Health,* 159–167. https://www.sciencedirect.com/science/article/pii/S2590053623000460

401. Id.

402. McKinnon, K. M. (2018). Flow cytometry: An overview. *Current Protocols in Immunology*, *120*, 5.1.1–5.1.11. https://doi.org/10.1002/cpim.40

403. Aspland, A., Chew, C., Douagi, I., Galland, T., Marvin, J., Monts, J., Nance, D., Smith, A. L., & Solga, M. (2021). Risk awareness during operation of analytical flow cytometers and implications throughout the COVID-19 pandemic. *Cytometry Part A: Journal of Quantitative Cell Science*, *99*(1), 81–89. https://doi.org/10.1002/cyto.a.24282

404. Id.

405. Id.

406. Na, L., Hu, L., Jin, A., & Li, J. (2019). Biosafety laboratory risk assessment. *Journal of Biosafety and Biosecurity, 1*, 90-92. http://creativecommons.org/licenses/by-nc-nd/4.0/

407. Pike, R. M. (1976). Laboratory-associated infections: Summary and analysis of 3921 cases. *Health Lab Sci*, *13*(2), 105–114. https://pubmed.ncbi.nlm.nih.gov/946794/

408. Sewell, D. L. (1995). Laboratory-associated infections and biosafety. *Clinical Microbiology Reviews*, *8*(3), 389–405. https://doi.org/10.1128/CMR.8.3.389

409. Harding, A.L., & Byers, K.B. (2006). Epidemiology of laboratory-associated infections. In D. O. Fleming & D. L. Hunt (Eds.), *Biological safety: Principles and practices* (4th ed., Chapter 4). ASM Press. https://doi.org/10.1128/9781555815899.ch4

410. Id.

411. Martin, J. C. (1980). Behavior factors in laboratory safety: personnel characteristics and modifications of unsafe act. In *Laboratory Safety: Theory and Practice*. Academic Press.

412. Cohen, J. (2020). Wuhan Coronavirus Hunter Shi Zhengli Speaks Out. *Science Magazine*. https://www.science.org/pb-assets/PDF/News%20PDFs/Shi%20Zhengli%20Q&A-1630433861.pdf

413. Senator Marco Rubio's Office. (2022). *"A complex and grave situation": A political chronology of the SARS-CoV-2 outbreak*. https://www.rubio.senate.gov/wp-content/uploads/_cache/files/790b6d70-7150-4f0f-a8b9-01ea45d3b1d1/EAB44A6CA6190D31041C0037E9C5E589.05.01.23-origin-report-clean-v1-11.pdf

414. Demaneuf, G. (2020). A count of BSL-3 Labs in China. *DRASTIC Report*. https://gillesdemaneuf.medium.com/a-count-of-bsl-3-labs-in-china-664f2b354276#:~:text=We%20were%20able%20to%20determine%20that%20at%20least,August%202020%2C%20across%2062%20lab-complexes%20%28excluding%20mobile%20laboratories%29.

415. Doshi, R. (2021). The long game: China's grand strategy to displace American order. Oxford University Press. Pages 286-287.

416. Senator Marco Rubio's Office. (2022). *"A complex and grave situation": A political chronology of the SARS-CoV-2 outbreak*. https://www.rubio.senate.gov/wp-content/uploads/_cache/files/790b6d70-7150-4f0f-a8b9-01ea45d3b1d1/EAB44A6CA6190D31041C0037E9C5E589.05.01.23-origin-report-clean-v1-11.pdf. The quoted text is "习近平强调, 科技领域安全是国家安全的重要组成部分. 要加强体系建 设和能力建设, 完善国家创新体系, 解决资源配置重 , 科研力量分散, 创新主体功能定位不清晰等突出问题, 提高创新体系整体效能. 要加快补短板, 建立自主创新的制度机制 优势. 要加强重大创新领域战略研判和前 瞻部署, 抓紧布局国家实验室, 重组国家重点实验室体系, 建设重大创新基地和创新平台, 完善产学研协同创 新机制. 要强化事 国家安全和经济社会发展全局的重大科技任务的统 • 组织, 强化国家战略科技力量建设. 要加快科技安全预警监测体系建设, 围绕人工智能, 基因编辑, 医疗诊断, 自动驾驶, 无人机, 服务机器人等领 域, 加快推进相 立法工作." *See also:* Xi Jinping: Be on guard against 'black swan' incidents, prevent 'grey rhinos' [习近平:警惕"黑天鹅" 防范"灰犀牛"]. (2019, January). *People's Daily*.

417. Senator Marco Rubio's Office. (2022). *"A complex and grave situation": A political chronology of the SARS-CoV-2 outbreak*. https://www.rubio.senate.gov/wp-content/uploads/_cache/files/790b6d70-7150-4f0f-a8b9-01ea45d3b1d1/EAB44A6CA6190D31041C0037E9C5E589.05.01.23-origin-report-clean-v1-11.pdf. The quoted text is "要以立法高质量发展保障和促进经济持续健康发展." *See also:* Xi Jinping chairs the opening of the second meeting of the Central Committee's Commission on the Comprehensive Use of the Law to Rule the Country [习近平主持召开中央全面依法治国委员会第二次会议]. (2019, February 25). *Xinhua News Agency* re-posted on the *PLA Daily*.

418. 13th National People's Congress Standing Committee. (2018). *13th National People's Congress Standing Committee Legislative Plan*. https://zh.wikisource.org/user:NPCObserver/13thNPCSCLegislativePlan

419. Zhu, N. N. [朱]. (2019, April 2). Six legislative items will complete interim goals this year [6 个立法项目将于今年完成阶段性目标]. *The Legal Daily* reprinted on the *National People's Congress.*

420. Huigang, L., Xiaowei X., Haixia, M., & Zhiming, Y. (2019). History of and suggestions for China's biosafety legislation. *Journal of Biosafety and Biosecurity*. https://www.sciencedirect.com/science/article/pii/S2588933819300342

421. Senator Marco Rubio's Office. (2022). *"A complex and grave situation": A political chronology of the SARS-CoV-2 outbreak*. https://www.rubio.senate.gov/wp-content/uploads/_cache/files/790b6d70-7150-4f0f-a8b9-01ea45d3b1d1/EAB44A6CA6190D31041C0037E9C5E589.05.01.23-origin-report-clean-v1-11.pdf. *See also:* Li Zhanshu: use the law to delimit the boundaries of the development of biotechnology, ensure and accelerate the healthy development of biotechnology [栗战书:用法律 定生物技术发展边界 保障和促进生物技术健康 发展]. (2019, July 11). *Xinhua* reprinted on the *PRC National People's Congress*. The quoted text is "以习近平同志为核心的党中央高度重视生物安全问题, 习近平总 书记多次作出重要指示, 为生物安全立法工作指明了方向, 提供了遵循. 要深入贯彻习近平总书记重要指示要 求, 坚持从总体国家安全观的高度充分认识生物安全立法的必要性和紧迫性, 通过立法确立生物安全领域的基础性制度原则, 突出风险防范, 用法律武器保卫国家生物安全, 保障人民生命健康."

422. World Health Organization. (2019, July 17). *Ebola outbreak in the Democratic Republic of the Congo declared a public health emergency of international concern*. World Health Organization. https://www.who.int/news/item/17-07-2019-ebola-outbreak-in-the-democratic-republic-of-the-congo-declared-a-public-health-emergency-of-international-concern

423. Eban, K. (2021, June 3). The lab leak theory: Inside the fight to uncover COVID-19's origins. *Vanity Fair*. https://www.vanityfair.com/news/2021/06/the-lab-leak-theory-inside-the-fight-to-uncover-covid-19s-origins

424. Demaneuf, G., Bostickson, B., & Small, C. (2021). *An investigation into the databases taken offline at the Wuhan Institute of Virology.* http://dx.doi.org/10.13140/RG.2.2.28029.08160

425. U.S. Senate Health, Education, Labor and Pension Subcommittee on Oversight and Investigations, Minority Staff. (2022). *Muddy waters: Origins of COVID-19 report*. https://www.marshall.senate.gov/wp-content/uploads/MWG-FDR-Document-04-11-23-EMBARGOED.pdf

426. Announcement of Contract Award for Central Air Conditioning Renovation Project at Wuhan Institute of Virology, Chinese Academy of Sciences. (2019, September 30). *Hubei Guohua Project Management Co., Ltd*. https://www.gianuzzimarino.com/wanboguanwangmanbetx/bidding/zbgs/zhengfucaigou/093012530.html

427. Office of Research Facilities, Division of Technical Resources. (2014). *BSL-3 and ABSL-3 HVAC system requirements-Part 1*. National Institutes of Health. https://orf.od.nih.gov/TechnicalResources/Documents/News%20to%20Use%20PDF%20Files/2014%20NTU/BSL-3%20ABSL-3%20HVAC%20System%20Requirements%20-%20Part%20I%20ll%20June%202014%20News%20to%20Use%20_508.pdf

428. U.S. Centers for Disease Control and Prevention & U.S. National Institutes of Health. (2020). *Biosafety in Microbiological and Biomedical Laboratories (BMBL) 6th Edition.* https://www.cdc.gov/labs/pdf/SF__19_308133-A_BMBL6_00-BOOK-WEB-final-3.pdf

429. Ai, H. X. [艾红霞]. (2019, September 16). Testing begins for special passage through airport for military world games [军运会航空 口岸专用通道开通测试]. *Hebei Daily* reprinted by *Xinhua News Agency*.

430. Yang, J. [杨均]. (2019, September 18). Wuhan customs hold emergency response drill for sudden incidents at the port of entry as [enter] 30-day countdown to military world games [武汉海　举办军　会倒计时 30 天暨口岸突发事件应急处 置演练]. *Chutian Transportation Broadcasting* reprinted on *Sina.com*, Since this report has been removed from the Sina website, we include the relevant paragraph from which the quote was extracted here: "　据武汉机场海　副　长李真涵介绍，该　前期做了大量工作全力保障军　会口岸安全，制定了口岸核与 辐射安全事件、化学类突发事件、生物类突发事件、口岸食源性疾病突发事件、口岸突发公共卫生事件、 口岸动植物检疫突发事件等 8 个应急预案;建立了覆盖全面、快速反应、高效　转、处置得当的应急处置 体系;成立了处置专家组和联络组;▪ 用了门户式核辐射监测系统，形成了初探报警、定量定性分析和个 人防护一体化的辐射探测工作机制;加强了与省卫健委、中科院武汉病毒所合作，建立疫情通报、病例转 送和重点传染病研究合作机制;实时　展专项实战化培训、▪ 面推演和大型实战化演练，强化应急协调处 置能力;建全口岸快筛室，增派护士驻点提高采样送样质量."

431. Senator Marco Rubio's Office. (2022). *"A complex and grave situation": A political chronology of the SARS-CoV-2 outbreak*. https://www.rubio.senate.gov/wp-content/uploads/_cache/files/790b6d70-7150-4f0f-a8b9-01ea45d3b1d1/EAB44A6CA6190D31041C0037E9C5E589.05.01.23-origin-report-clean-v1-11.pdf. *See also:* Explanation regarding the draft biosecurity law of the People's Republic of China [　于中华人民共和国 生物安全法草案的说明]. (2020, October 19). *The National People's Congress*. The quote is "防范和禁止 利用生物及生物技术侵害国家安全为重点." For an English source, see Tse, D., & Ong, L. (2020). Coronavirus pushes CCP factional struggle to inflection point. *SinoInsider*.

432. Id. The quote is "防范和禁止 利用生物及生物技术侵害国家安全为重点."

433. Id. The quote is "生物技 术在带给人类进 和益处的同时，也带来生物安全问题和威胁。当前我国生物安全形势严峻，生物战和以 非典、埃博拉病毒、非洲猪瘟等为代表的重大新发突发传染病及动植物疫情等传统生物威胁依然多发，生 物恐怖袭击、生物技术误用谬用、实验室生物泄漏等非传统生物威胁凸显."

434. Twenty-second meeting of the Standing Committee of the 13th National People's Congress. (2020). *Article 1. Biosafety Law of the Peoples Republic of China.* https://www.chinalawtranslate.com/en/biosecurity-law/

435. Id.

436. Huang, Y. (2020). U.S.-Chinese distrust is inviting dangerous coronavirus conspiracy theories: And undermining efforts to contain the epidemic. *Foreign Affairs.* https://www.foreignaffairs.com/articles/united-states/2020-03-05/us-chinese-distrust-inviting-dangerous-coronavirus-conspiracy?utm_medium=promo_email&utm_source=lo_flows&utm_campaign=registered_user_welcome&utm_term=email_1&utm_content=20240228

437. Markson, S. (2021). What really happened in Wuhan: A virus like no other, countless infections, millions of deaths. Harper Collins Publishers. Pages: 369- 372.

438. Wan, Y., Shang, J., Sun, S., Tai, W., Chen, J., Geng, Q., He, L., Chen, Y., Su, J., Shi, Z-L., Zhou, Y., Du, L., & Li, F. (2019). Molecular mechanism for antibody-dependent enhancement of coronavirus entry. *Journal of Virology*. *94*(5), https://doi.org/10.1128/jvi.02015-19

439. Zhou, Y., Zhao, G., Gu,. H., Sun, S., He, L., Li, Y., Han, G., Lang, X., Liu, J., Geng, S., & Sheng, X. (2020). *Novel coronavirus COVID-19 vaccine, preparation method and application thereof* (CN 111333704A). Beijing Preliminary Intellectual Property Agency Co. https://patentscope.wipo.int/search/en/detail.jsf?docId=CN298978866

440. Makowski, L., Olson-Sidford, W., & W-Weisel, J. (2021). Biological and clinical consequences of integrin binding via a rogue RGD motif in the SARS CoV-2 spike protein. *Viruses*, *13*(2), 146. https://doi.org/10.3390/v13020146

441. Beaudoin, C. A., Hamaia, S. W., Huang, C. L., Blundell, T. L., & Jackson, A. P. (2021). Can the SARS-CoV-2 spike protein bind integrins independent of the RGD sequence?. *Frontiers in Cellular and Infection Microbiology*, *11*, 765300. https://doi.org/10.3389/fcimb.2021.765300

442. Du, L., Zhao, G., Kou, Z., Ma, C., Sun, S., Poon, V. K., Lu, L., Wang, L., Debnath, A. K., Zheng, B. J., Zhou, Y., & Jiang, S. (2013). Identification of a receptor-binding domain in the S protein of the novel human coronavirus Middle East respiratory syndrome coronavirus as an essential target for vaccine development. *Journal of Virology*, *87*(17), 9939–9942. https://doi.org/10.1128/JVI.01048-13

443. Id.

444. Gu, H., Chen, Q., Yang, G., He, L., Fan, H., Deng, Y. Q., Wang, Y., Teng, Y., Zhao, Z., Cui, Y., Li, Y., Li, X. F., Li, J., Zhang, N. N., Yang, X., Chen, S., Guo, Y., Zhao, G., Wang, X., Luo, D. Y., ... Zhou, Y. (2020). Adaptation of SARS-CoV-2 in BALB/c mice for testing vaccine efficacy. *Science*, *369*(6511), 1603–1607. https://doi.org/10.1126/science.abc4730

445. Id.

446. Xu, A., Hong, B., Lou, F., Wang, S., Li, W., Shafqat, A., An, X., Zhao, Y., Song, L., Tong, Y., & Fan, H. (2022). Sub-lineages of the SARS-CoV-2 Omicron variants: Characteristics and prevention. *MedComm*, *3*(3), e172. https://doi.org/10.1002/mco2.172

447. Liu, Y., Liu, J., Plante, K. S., Plante, J. A., Xie, X., Zhang, X., Ku, Z., An, Z., Scharton, D., Schindewolf, C., Widen, S. G., Menachery, V. D., Shi, P. Y., & Weaver, S. C. (2022). The N501Y spike substitution enhances SARS-CoV-2 infection and transmission. *Nature*, *602*(7896), 294–299. https://doi.org/10.1038/s41586-021-04245-0

448. Wang, Y., Tai, W., Yang, J., Zhao, G., Sun, S., Tseng, C. K., Jiang, S., Zhou, Y., Du, L., & Gao, J. (2017). Receptor-binding domain of MERS-CoV with optimal immunogen dosage and immunization interval protects human transgenic mice from MERS-CoV infection. *Human Vaccines & Immunotherapeutics*, *13*(7), 1615–1624. https://doi.org/10.1080/21645515.2017.1296994

449. van Boheemen, S., de Graaf, M., Lauber, C., Bestebroer, T. M., Raj, V. S., Zaki, A. M., Osterhaus, A. D., Haagmans, B. L., Gorbalenya, A. E., Snijder, E. J., & Fouchier, R. A. (2012). Genomic characterization of a newly discovered coronavirus associated with acute respiratory distress syndrome in humans. *mBio*, *3*(6), e00473-12. https://doi.org/10.1128/mBio.00473-12

450. Du, L., Zhao, G., Kou, Z., Ma, C., Sun, S., Poon, V. K., Lu, L., Wang, L., Debnath, A. K., Zheng, B. J., Zhou, Y., & Jiang, S. (2013). Identification of a receptor-binding domain in the S protein of the novel human coronavirus Middle East respiratory syndrome coronavirus as an essential target for vaccine development. *Journal of Virology*, *87*(17), 9939–9942. https://doi.org/10.1128/JVI.01048-13

451. Sun, S., He, L., Zhao, Z., Gu, H., Fang, X., Wang, T., Yang, X., Chen, S., Deng, Y., Li, J., Zhao, J., Li, L., Li, X., He, P., Li, G., Li, H., Zhao, Y., Gao, C., Lang, X., … Sun, Y. (2021). Recombinant vaccine containing an RBD-Fc fusion induced protection against SARS-CoV-2 in nonhuman primates and mice. *Cellular & Molecular Immunology, 18*(4), 1070–1073. https://doi.org/10.1038/s41423-021-00658-z

452. Gu, H., Chen, Q., Yang, G., He, L., Fan, H., Deng, Y. Q., Wang, Y., Teng, Y., Zhao, Z., Cui, Y., Li, Y., Li, X. F., Li, J., Zhang, N. N., Yang, X., Chen, S., Guo, Y., Zhao, G., Wang, X., Luo, D. Y., … Zhou, Y. (2020). Adaptation of SARS-CoV-2 in BALB/c mice for testing vaccine efficacy. *Science, 369*(6511), 1603–1607. https://doi.org/10.1126/science.abc4730

453. Sun, S., He, L., Zhao, Z., Gu, H., Fang, X., Wang, T., Yang, X., Chen, S., Deng, Y., Li, J., Zhao, J., Li, L., Li, X., He, P., Li, G., Li, H., Zhao, Y., Gao, C., Lang, X., … Sun, Y. (2021). Recombinant vaccine containing an RBD-Fc fusion induced protection against SARS-CoV-2 in nonhuman primates and mice. *Cellular & Molecular Immunology, 18*(4), 1070–1073. https://doi.org/10.1038/s41423-021-00658-z

454. Id.

455. Jiang, Y., Chen, Y., Sun, H., Zhang, X., He, L., Li, J., Zhao, G., & Sun, S. (2021). MERS-CoV infection causes brain damage in human DPP4-transgenic mice through complement-mediated inflammation. *The Journal of General Virology*, *102*(10), 001667. https://doi.org/10.1099/jgv.0.001667

456. Frieman, M., & Menachery, V. (2020, August 2). Email (SLACK) exchange University of Texas Medical Branch scientists. U.S. Right to Know Freedom of Information Request. https://usrtk.org/wp-content/uploads/2024/03/UTMB-11-partial-production-combined.pdf

457. Sun, S., He, L., Zhao, Z., Gu, H., Fang, X., Wang, T., Yang, X., Chen, S., Deng, Y., Li, J., Zhao, J., Li, L., Li, X., He, P., Li, G., Li, H., Zhao, Y., Gao, C., Lang, X., … Sun, Y. (2021). Recombinant vaccine containing an RBD-Fc fusion induced protection against SARS-CoV-2 in nonhuman primates and mice. *Cellular & Molecular Immunology, 18*(4), 1070–1073. https://doi.org/10.1038/s41423-021-00658-z

458. Li, Y. D., Chi, W. Y., Su, J. H., Ferrall, L., Hung, C. F., & Wu, T. C. (2020). Coronavirus vaccine development: from SARS and MERS to COVID-19. *Journal of Biomedical Science*, *27*(1), 104. https://doi.org/10.1186/s12929-020-00695-2

459. Dong, Y., Dai, T., Wang, B., Zhang, L., Zeng, L. H., Huang, J., Yan, H., Zhang, L., & Zhou, F. (2021). The way of SARS-CoV-2 vaccine development: success and challenges. *Signal Transduction and Targeted Therapy*, *6*(1), 387. https://doi.org/10.1038/s41392-021-00796-w

460. Yan, Z., Yang, M., & Lai, C. L. (2021). COVID-19 Vaccinations: A Comprehensive Review of Their Safety and Efficacy in Special Populations. *Vaccines*, *9*(10), 1097. https://doi.org/10.3390/vaccines9101097

461. Li, D. D., & Li, Q. H. (2021). SARS-CoV-2: vaccines in the pandemic era. *Military Medical Research*, *8*(1), 1. https://doi.org/10.1186/s40779-020-00296-y

462. Deng, Y.-Q., Zhang, N.-N., Zhang, Y.-F., Zhong, X., Xu, S., Qiu, H.-Y., Wang, T.-C., Zhao, H., Zhou, C., Zu, S.-L., Chen, Q., Cao, T.-S., Ye, Q., Chi, H., Duan, X.-H., Lin, D.-D., Zhang, X.-J., Xie, L.-Z., Gao, Y.-W., … Qin, C.-F. (2022). Lipid nanoparticle-encapsulated mRNA antibody provides long-term protection against SARS-CoV-2 in mice and hamsters. *Cell Research, 32*(4), 375–382. https://doi.org/10.1038/s41422-022-00630-0

463. Wu, S., Zhong, G., Zhang, J., Shuai, L., Zhang, Z., Wen, Z., Wang, B., Zhao, Z., Song, X., Chen, Y., Liu, R., Fu, L., Zhang, J., Guo, Q., Wang, C., Yang, Y., Fang, T., Lv, P., Wang, J., Xu, J., … Chen, W. (2020). A single dose of an adenovirus-vectored vaccine provides protection against SARS-CoV-2 challenge. *Nature Communications*, *11*(1), 4081. https://doi.org/10.1038/s41467-020-17972-1

464. An, Y., Li, S., Jin, X., Han, J. B., Xu, K., Xu, S., Han, Y., Liu, C., Zheng, T., Liu, M., Yang, M., Song, T. Z., Huang, B., Zhao, L., Wang, W., A, R., Cheng, Y., Wu, C., Huang, E., Yang, S., … Gao, G. F. (2022). A tandem-repeat dimeric RBD protein-based covid-19 vaccine zf2001 protects mice and nonhuman primates. *Emerging Microbes & Infections*, *11*(1), 1058–1071. https://doi.org/10.1080/22221751.2022.2056524

465. Pan, X., Shi, J., Hu, X., Wu, Y., Zeng, L., Yao, Y., Shang, W., Liu, K., Gao, G., Guo, W., Peng, Y., Chen, S., Gao, X., Peng, C., Rao, J., Zhao, J., Gong, C., Zhou, H., Lu, Y., Wang, Z., … Xiao, G. (2021). RBD-homodimer, a COVID-19 subunit vaccine candidate, elicits immunogenicity and protection in rodents and nonhuman primates. *Cell Discovery*, *7*(1), 82. https://doi.org/10.1038/s41421-021-00320-y

466. Zhang, Z., Wu, J., Zhang, E., Zhao, S., Wang, D., Yi, Y., & Qi, J. (2019). Research and development of airtight biosafety containment facility for stainless steel structures. *Journal of Biosafety and Biosecurity, 1*(1), 56–62. https://doi.org/10.1016/j.jobb.2019.01.010

467. Wuhan Institute of Virology, Chinese Academy of Sciences. (2019, March 1). Announcement of competitive consultation on the maintenance project of P3 laboratory and experimental animal center in Zhengdian Park. Wuhan Institute of Virology, Chinese Academy of Sciences. http://www.ccgp.gov.cn/cggg/dfgg/jzxcs/201903/t20190301_11699621.htm

468. Zhou, J., Wang, W., Zhong, Q., Hou, W., Yang, Z., Xiao, S. Y., Zhu, R., Tang, Z., Wang, Y., Xian, Q., Tang, H., & Wen, L. (2005). Immunogenicity, safety, and protective efficacy of an inactivated SARS-associated coronavirus vaccine in rhesus monkeys. *Vaccine*, *23*(24), 3202–3209. https://doi.org/10.1016/j.vaccine.2004.11.075

469. U.S. House Committee on Foreign Affairs, Minority Staff. (2021). *The origins of COVID-19. An investigation of the Wuhan Institute of Virology* (117th Congress). https://foreignaffairs.house.gov/wp-content/uploads/2021/08/ORIGINS-OF-COVID-19-REPORT.pdf. The Committee Staff credits the House report for its discovery of the original Chinese source, but after examining that source, we note that the House report miscalculated the sum of the tender when it converted from Chinese RMB to U.S. dollars. The correct amount is roughly US $1.3 million, not US$132 million.

470. Henneman, J. R., McQuade, E. A., Sullivan, R. R., Downard, J., Thackrah, A., & Hislop, M. (2022). Analysis of range and use of a hybrid hydrogen peroxide system for biosafety level 3 and animal biosafety level 3 agriculture laboratory decontamination. *Applied Biosafety, 27*(1), 7–14. https://doi.org/10.1089/apb.2021.0012

471. Linsen, L., Van Landuyt, K., Ectors, N. (2020). Automated sample storage in biobanking to enhance translational research: The bumpy road to implementation. *Front Med (Lausanne), 6*(309). https://doi.org/10.3389/fmed.2019.00309

472. Google. (n.d.). Retrieved September 10, 2024 from https://www.google.com/maps/@30.5516757,114.3556817,7767m/data=!3m1!1e3?entry=ttu&g_ep=EgoyMDI0MDkxMS4wIKXMDSoASAFQAw%3D%3D

473. Chen, Y., Wei, Q., Li, R., Gao, H., Zhu, H., Deng, W., Bao, L., Tong, W., Cong, Z., Jiang, H., & Qin, C. (2020). Protection of Rhesus Macaque from SARS-Coronavirus challenge by recombinant adenovirus vaccine. bioRxiv, 2020.02.17.951939. https://doi.org/10.1101/2020.02.17.951939

474. Wu, S., Zhong, G., Zhang, J., Shuai, L., Zhang, Z., Wen, Z., Wang, B., Zhao, Z., Song, X., Chen, Y., Liu, R., Fu, L., Zhang, J., Guo, Q., Wang, C., Yang, Y., Fang, T., Lv, P., Wang, J., Xu, J., … Chen, W. (2020). A single dose of an adenovirus-vectored vaccine provides protection against SARS-CoV-2 challenge. *Nature Communications*, *11*(1), 4081. https://doi.org/10.1038/s41467-020-17972-1

475. Zhu, F. C., Li, Y. H., Guan, X. H., Hou, L. H., Wang, W. J., Li, J. X., Wu, S. P., Wang, B. S., Wang, Z., Wang, L., Jia, S. Y., Jiang, H. D., Wang, L., Jiang, T., Hu, Y., Gou, J. B., Xu, S. B., Xu, J. J., Wang, X. W., Wang, W., … Chen, W. (2020). Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial. *Lancet*, *395*(10240), 1845–1854. https://doi.org/10.1016/S0140-6736(20)31208-3

476. Zhu, F. C., Guan, X. H., Li, Y. H., Huang, J. Y., Jiang, T., Hou, L. H., Li, J. X., Yang, B. F., Wang, L., Wang, W. J., Wu, S. P., Wang, Z., Wu, X. H., Xu, J. J., Zhang, Z., Jia, S. Y., Wang, B. S., Hu, Y., Liu, J. J., Zhang, J., … Chen, W. (2020). Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet, 396*(10249), 479–488. https://doi.org/10.1016/S0140-6736(20)31605-6

477. Wu, S., Huang, J., Zhang, Z., Wu, J., Zhang, J., Hu, H., Zhu, T., Zhang, J., Luo, L., Fan, P., Wang, B., Chen, C., Chen, Y., Song, X., Wang, Y., Si, W., Sun, T., Wang, X., Hou, L., & Chen, W. (2021). Safety, tolerability, and immunogenicity of an aerosolised adenovirus type-5 vector-based COVID-19 vaccine (Ad5-nCoV) in adults: preliminary report of an open-label and randomised phase 1 clinical trial. *The Lancet Infectious Diseases*, *21*(12), 1654–1664. https://doi.org/10.1016/S1473-3099(21)00396-0

478. Liu, A. (2020, March 18). China's CanSino pushes coronavirus vaccine into clinical testing as Moderna kicks off trial. *Fierce Pharma.* https://www.fiercepharma.com/vaccines/china-s-cansino-pushes-coronavirus-vaccine-into-clinical-testing-as-moderna-doses-1st

479. Wu, S., Zhong, G., Zhang, J., Shuai, L., Zhang, Z., Wen, Z., Wang, B., Zhao, Z., Song, X., Chen, Y., Liu, R., Fu, L., Zhang, J., Guo, Q., Wang, C., Yang, Y., Fang, T., Lv, P., Wang, J., Xu, J., … Chen, W. (2020). A single dose of an adenovirus-vectored vaccine provides protection against SARS-CoV-2 challenge. *Nature Communications*, *11*(1), 4081. https://doi.org/10.1038/s41467-020-17972-1

480. Liu, A. (2020, March 18). China's CanSino pushes coronavirus vaccine into clinical testing as Moderna kicks off trial. *Fierce Pharma*. https://www.fiercepharma.com/vaccines/china-s-cansino-pushes-coronavirus-vaccine-into-clinical-testing-as-moderna-doses-1st

481. A phase I clinical trial for recombinant novel coronavirus (2019-COV) vaccine (adenoviral vector). (2020, March 17). Chinese Clinical Trial Registry. https://www.chictr.org.cn/showproj.html?proj=51154

482. Chen, W. Shipo, W. Hou, S., Zhang, Z. et al. (2020, March 18). *A recombinant novel coronavirus vaccine using human replication-deficient adenovirus as a vector* (CN 111218459 A). Google Patents. https://patents.google.com/patent/CN111218459A/en

483. U.S. House Committee on Energy and Commerce, Subcommittee on Investigations. (2024). *E&C investigation uncovers earliest known SARS-CoV-2 sequence released outside of China*. U.S. House of Representatives. https://energycommerce.house.gov/posts/e-and-c-investigation-uncovers-earliest-known-sars-co-v-2-sequence-released-outside-of-china

484. U.S. House Committee on Energy and Commerce, Subcommittee on Investigations. (2024). *E&C investigation uncovers earliest known SARS-CoV-2 sequence released outside of China*. U.S. House of Representatives. https://energycommerce.house.gov/posts/e-and-c-investigation-uncovers-earliest-known-sars-co-v-2-sequence-released-outside-of-china

485. U.S. Senate Health, Education, Labor and Pension Subcommittee on Oversight and Investigations, Minority Staff. (2022). *Muddy waters: Origins of COVID-19 report*. https://www.marshall.senate.gov/wp-content/uploads/MWG-FDR-Document-04-11-23-EMBARGOED.pdf

486. Office of the Spokesperson, U.S. Department of State. (2021, January 15). *Fact Sheet: Activity at the Wuhan Institute of Virology: Fact Sheet*. U.S. Department of State. https://2017-2021.state.gov/fact-sheet-activity-at-the-wuhan-institute-of-virology/

487. Gordon, J., Strobel W.P., & Hinshaw, D. (2021, May 23). U.S.-funded scientist among three Chinese Researchers who fell ill amid early COVID-19 outbreak. *The Wall Street Journal.* https://www.wsj.com/articles/u-s-funded-scientist-among-three-chinese-researchers-who-fell-ill-amid-early-covid-19-outbreak-3f919567

488. Shellenberger, M., Taibbi, M., & Gutentag, A. (2023, June 13). First people sickened by COVID-19 were Chinese scientists at Wuhan Institute of Virology, say U.S. government sources. *Public*. https://public.substack.com/p/first-people-sickened-by-covid-19

489. Party [CCP] Committee of the Wuhan Institute of Virology. (August 30, 2019). Deeds of the Party Branch of the Zhengdian Laboratory, Wuhan Institute of Virology, Chinese Academy of Sciences. https://kydj.sciencenet.cn/content.aspx?id=3844

490. U.S. Senate Health, Education, Labor and Pension Subcommittee on Oversight and Investigations, Minority Staff. (2022). *Muddy waters: Origins of COVID-19 report*. https://www.marshall.senate.gov/wp-content/uploads/MWG-FDR-Document-04-11-23-EMBARGOED.pdf. *See also:* Wuhan Institute of Virology. (2019, November 12). *Keep firmly in mind your responsibilities, hold fast to the mission, be a pioneer for our nation in the realm of high-level biosafety – the achievements of the Zhengdian Lab Party Branch of the Chinese Academy of Sciences Wuhan Institute of Virology*.

491. Senator Marco Rubio's Office. (2022). *"A complex and grave situation": A political chronology of the SARS-CoV-2 outbreak*. https://www.rubio.senate.gov/wp-content/uploads/_cache/files/790b6d70-7150-4f0f-a8b9-01ea45d3b1d1/EAB44A6CA6190D31041C0037E9C5E589.05.01.23-origin-report-clean-v1-11.pdf.The quoted text is "由于 P4 实验室的研究对象是高致病性病原微生物, 在实验室里, 一旦打　了保存病毒的试管, 犹如打　了潘多拉魔盒, 这些病毒来无影去无踪, 虽有各 ▪ 防护措施, 但仍然需要实验 人员小心翼翼的操作, 避免由于操作失误而造成危险.　当这时, 郑店实验室党支部党员总是冲在第一线, 他 们用实际行动带动和感染着实验室其他人员." *See also:* Wuhan Institute of Virology. (2019, November 12). *Keep firmly in mind your responsibilities, hold fast to the mission, be a pioneer for our nation in the realm of high-level biosafety – the achievements of the Zhengdian Lab Party Branch of the Chinese Academy of Sciences Wuhan Institute of Virology [*牢记责任，坚守使命 做我国高等 级生物安全领域的　拓者—中科院武汉病毒所郑店实验室党支部事迹*].*

492. Dou, E., Wu, P.L., Aries, Q., & Tan, R. (2021). Inside the Wuhan lab: French engineering, deadly viruses and a big mystery. *The Washington Post.* https://www.washingtonpost.com/world/asia_pacific/wuhan-lab-covid-china/2021/09/07/f293325c-fb11-11eb-911c-524bc8b68f17_story.html

493. Li W., & Zhen W. J. (2019, November 15). Explore the Institute of Model Animals of Wuhan University, which used to be one of the battlefields against SARS. *Chutian Metropolis Daily*.

494. Luo, F., Liao, F. L., Wang, H., Tang, H. B., Yang, Z. Q., & Hou, W. (2018). Evaluation of Antibody-Dependent Enhancement of SARS-CoV Infection in Rhesus Macaques Immunized with an Inactivated SARS-CoV Vaccine. *Virologica Sinica*, *33*(2), 201–204. https://doi.org/10.1007/s12250-018-0009-2

495. Partnership & Custom Media unit of Nature Research for Institute of Model Animal of Wuhan University. (2019). Advertisement Feature: Institute of Animal Models of Wuhan University. *Nature*. https://www.nature.com/collections/heihdahdbe

496. U.S. Senate Health, Education, Labor and Pension Subcommittee on Oversight and Investigations, Minority Staff. (2022). *Muddy waters: Origins of COVID-19 report*. https://www.marshall.senate.gov/wp-content/uploads/MWG-FDR-Document-04-11-23-EMBARGOED.pdf

497. Ann [ann@ann95657173]. (2021). [Tweet]. Twitter. https://twitter.com/torontofarmen/status/1396961056212365316

498. Senator Marco Rubio's Office. (2022). *"A complex and grave situation": A political chronology of the SARS-CoV-2 outbreak*. https://www.rubio.senate.gov/wp-content/uploads/_cache/files/790b6d70-7150-4f0f-a8b9-01ea45d3b1d1/EAB44A6CA6190D31041C0037E9C5E589.05.01.23-origin-report-clean-v1-11.pdf. Party Committee of the Wuhan Institute of Virology. (2019). Keep in mind the responsibility and stick to the mission to be a pioneer in the field of high-level biosecurity in my country. *Kejuan Dangjian, 4*. https://kydj.sciencenet.cn/content.aspx?id=3844 The quoted text is "在实验室里，他们常常需要连续工作4个小时，甚至长　6小时，期间不能饮食，排泄，这对人的意志和体力是·大的考验。这不仅要求实验人员要具备熟练的操作技能，还要具备应对各·意外情况的能力." Note that the word translated here as "unexpected" (意外) can also when used as a noun, refer to an "accident" or "mishap." Emphasis added. The quoted text is "由于P4实验室的研究对象是高致病性病原微生物, 在实验室里, 一旦打　了保存病毒的试管 Id. The quoted text is "不要将工作任务看作压力，　一个任务都是·不断提升自我的机遇和阶梯. 我们这个团队的理念是吃亏是福..."

499. Id. See also: Wuhan Institute of Virology. (2019, November 21). Wuhan Institute of Virology launches training on safety work [武汉病毒所　展安全工作培训]..

500. For more information on the pishi system, see Tsai W-H, & Liu X. (2016). Concentrating power to accomplish big things: The CCP's Pishi system and operation in contemporary China. *Journal of Contemporary China, 26*(104), 1-14. https://www.tandfonline.com/doi/abs/10.1080/10670564.2016.1223109#:~:text=https%3A//doi.org/10.1080/10670564.2016.1223109

501. Tsai-H. (2015). A unique pattern of policymaking in China's authoritarian regime: The CCP's Neican/Pishi model. *Asian Survey, 55*(6), 1093-1115. https://online.ucpress.edu/as/article-abstract/55/6/1093/24827/A-Unique-Pattern-of-Policymaking-in-China-s?redirectedFrom=fulltext

502. Senator Marco Rubio's Office. (2022). *"A complex and grave situation": A political chronology of the SARS-CoV-2 outbreak*. https://www.rubio.senate.gov/wp-content/uploads/_cache/files/790b6d70-7150-4f0f-a8b9-01ea45d3b1d1/EAB44A6CA6190D31041C0037E9C5E589.05.01.23-origin-report-clean-v1-11.pdf. Emphasis added. The quoted text is "培训会上，武汉病毒所安保办副主任胡谦总结了过去一年安全检查过程中发现的若干共性问题，指出安全隐患可能引发的严重后果，强调隐患整改要彻底，规范管理要保持."

503. Id. See also: Wuhan Institute of Virology. (2019, November 28). Wuhan Institute of Virology holds 2019 training class on biosafety laboratory management and techniques for conducting experiments [武汉病毒所举办2019年生物安全实验室管理与实验技术培训班].

504. Id. The quoted text is "课程内容涵盖了国家生物安全法律法规及标准，高等级生物安全实验室管理体系，实验室生物安全风险评估方法，菌毒·保藏，动物实验以及实验室废弃物处理等内容."

505. Id. *See also:* Wen, J. [文俊]. (2019, December 7). Xiao Juhua stresses all-out support for construction of center for biosafety mega-science [肖菊华强调全力支持建设生物安全大科学中心]. *Hebei Daily* reprinted on *Hubei Provincial People's Government*. The quoted text is "肖菊华考察了武汉国家生物安全实验室 (P4 实验室)，详细了解其建设历程，研究现状与发展方向等，就有关支持事项进行现场办公."

506. Senator Marco Rubio's Office. (2022). *"A complex and grave situation": A political chronology of the SARS-CoV-2 outbreak*. https://www.rubio.senate.gov/wp-content/uploads/_cache/files/790b6d70-7150-4f0f-a8b9-01ea45d3b1d1/EAB44A6CA6190D31041C0037E9C5E589.05.01.23-origin-report-clean-v1-11.pdf

507. Markson, S. (2021). What really happened in Wuhan: A virus like no other, countless infections, millions of deaths. Harper Collins Publishers.

508. The Wuhan Institute of Virology of the Chinese Academy of Sciences plans to use a single-source procurement method to publicize the procurement of air incineration devices and test service projects. (2019, December 3). *China Government Procurement Network.* https://archive.is/Jifqr#selection-229.0-229.197

509. Id.

510. Wuhan Institute of Virology. (2019). *Biosafety autoclave and sterilization method* (CN 201910325059.0). Google Patents. https://patents.google.com/patent/CN210078382U/en?assignee=Wuhan+Institute+of+Virology+of+CAS&sort=new &page=12

511. U.S. Senate Health, Education, Labor and Pension Subcommittee on Oversight and Investigations, Minority Staff. (2022). *Muddy waters: Origins of COVID-19 report*. https://www.marshall.senate.gov/wp-content/uploads/MWG-FDR-Document-04-11-23-EMBARGOED.pdf

512. Gao, D., Zhang, Q., Han, K., Qian, Q., & Wenbo, A. (2019). *Integrated biological sensor* (CN 201922213832.2). Google Patents. https://patents.google.com/patent/CN211375358U/en?assignee=Wuhan+Institute+of+Virology+of+CAS&sort=new&page=8

513. Guo, M., Yong, M., Liu, J., Huang, X., & Li, X. (2019). Biosafety and data quality considerations for animal experiments with highly infectious agents at ABSL-3 facilities. *Journal of Biosafety and Biosecurity, 1,* 50-55. https://doi.org/10.1016/j.jobb.2018.12.011

514. Carpenter, C. B. (2018). Safety considerations for working with animal models involving human health hazards. *Animal Models and Experimental Medicine*, *1*(2), 91–99. https://doi.org/10.1002/ame2.12019

515. Gao, D., Zhang, Q., Han, K., Qian, Q., & Wenbo, A. (2019). *Integrated biological sensor* (CN 201922213832.2). Google Patents. https://patents.google.com/patent/CN211375358U/en?assignee=Wuhan+Institute+of+Virology+of+CAS&sort=new&page=8

516. Id.

517. Zhang, Z., Wu, J., Zhang, E., Zhao, S., Wang, D., Yi, Y., & Qi, J. (2019). Research and development of airtight biosafety containment facility for stainless steel structures. *Journal of Biosafety and Biosecurity, 1*(1), 56–62. https://doi.org/10.1016/j.jobb.2019.01.010 National Chemical Laboratories Safety Data Sheet. May 2022. https://www.nclonline.com/products/view/micro_chem_plus_#tab-safety

518. Arthur J. (2009). Know the causes of stainless-steel corrosion in reports and take practical steps to prevent corrosion, 2019. Food Engineering. https://www.foodengineeringmag.com/articles/98614-know-the-causes-of-stainless-steel-corrosion-in-retorts-and-take-practical-steps-to-prevent-corrosion;

519. Mathiesen, Troels & Frantsen. Corrosion aspects for stainless steel surfaces in the brewery, dairy and pharmaceutical sectors. NACE - International Corrosion Conference Series. https://www.researchgate.net/publication/242584517_Corrosion_aspects_for_stainless_steel_surfaces_in_the_brewery_dairy_and_pharmaceutical_sectors

520. Zhang, H., Peng C, Liu B, Liu J, Zhiming Y, Shi, Z. (2018). Evaluation of MICRO-CHEM PLUS as a disinfectant for biosafety level 4 laboratory in China. Applied Biosafety Journal of ABSA International. 23(1): 32-38. https://doi.org/10.1177/1535676018758891

521. U.S. Senate Health, Education, Labor and Pension Subcommittee on Oversight and Investigations, Minority Staff. (2022). *Muddy waters: Origins of COVID-19 report*. https://www.marshall.senate.gov/wp-content/uploads/MWG-FDR-Document-04-11-23-EMBARGOED.pdf. Email communication U.S. Senate Health, Education, Labor and Pension with Technical Representative National Chemical Laboratories. (2022, May 11). https://www.marshall.senate.gov/wp-content/uploads/MWG-FDR-Document-04-11-23-EMBARGOED.pdf.

522. Jia W, Zhiming Y, Hao T, Jun L, Hao Q, Yi L, Lin W. (2020). Google Patents. Object surface disinfectant for high-grade biosafety laboratory and preparation method thereof. https://patents.google.com/patent/CN112262846B/en?assignee=Wuhan+Institute+of+Virology+ofCAS&sort=new&page=5

523. Zhang, Z., Wu, J., Zhang, E., Zhao, S., Wang, D., Yi, Y., & Qi, J. (2019). Research and development of airtight biosafety containment facility for stainless steel structures. *Journal of Biosafety and Biosecurity, 1*(1), 56–62. https://doi.org/10.1016/j.jobb.2019.01.010

524. Zhang, Z., Wu, J., Hao, L., Yi, Y., & Qi, J. (2020) Development of biosafety equipment for high-containment laboratory and for person protection in China. *Biosafety and Health, 2,* 12-17. http://dx.doi.org/10.1016/j.bsheal.2019.12.008

525. Zhang, Z., Wu, J., Zhang, E., Zhao, S., Wang, D., Yi, Y., & Qi, J. (2019). Research and development of airtight biosafety containment facility for stainless steel structures. *Journal of Biosafety and Biosecurity, 1*(1), 56–62. https://doi.org/10.1016/j.jobb.2019.01.010

526. Id.

527. Id.

528. He, Y., Zhou, Y., Siddiqui, P., & Jiang, S. (2004). Inactivated SARS-CoV vaccine elicits high titers of spike protein-specific antibodies that block receptor binding and virus entry. *Biochemical and biophysical research communications*, *325*(2), 445–452. https://doi.org/10.1016/j.bbrc.2004.10.052

529. He, Y., Li, J., Du, L., Yan, X., Hu, G., Zhou, Y., & Jiang, S. (2006). Identification and characterization of novel neutralizing epitopes in the receptor-binding domain of SARS-CoV spike protein: revealing the critical antigenic determinants in inactivated SARS-CoV vaccine. *Vaccine*, *24*(26), 5498–5508. https://doi.org/10.1016/j.vaccine.2006.04.054

530. Du, L., Zhao, G., Chan, C. C., Sun, S., Chen, M., Liu, Z., Guo, H., He, Y., Zhou, Y., Zheng, B. J., & Jiang, S. (2009). Recombinant receptor-binding domain of SARS-CoV spike protein expressed in mammalian, insect and E. coli cells elicits potent neutralizing antibody and protective immunity. *Virology*, *393*(1), 144–150. https://doi.org/10.1016/j.virol.2009.07.018

531. Du, L., He, Y., Zhou, Y., Liu, S., Zheng, B. J., & Jiang, S. (2009). The spike protein of SARS-CoV--a target for vaccine and therapeutic development. *Nature reviews. Microbiology*, *7*(3), 226–236. https://doi.org/10.1038/nrmicro2090

532. Ma, C., Wang, L., Tao, X., Zhang, N., Yang, Y., Tseng, C. K., Li, F., Zhou, Y., Jiang, S., & Du, L. (2014). Searching for an ideal vaccine candidate among different MERS coronavirus receptor-binding fragments--the importance of immunofocusing in subunit vaccine design. *Vaccine*, *32*(46), 6170–6176. https://doi.org/10.1016/j.vaccine.2014.08.086

533. Du, L., Kou, Z., Ma, C., Tao, X., Wang, L., Zhao, G., Chen, Y., Yu, F., Tseng, C. T., Zhou, Y., & Jiang, S. (2013). A truncated receptor-binding domain of MERS-CoV spike protein potently inhibits MERS-CoV infection and induces strong neutralizing antibody responses: implication for developing therapeutics and vaccines. *PloS one*, *8*(12), e81587. https://doi.org/10.1371/journal.pone.0081587

534. Tai, W., Wang, Y., Fett, C. A., Zhao, G., Li, F., Perlman, S., Jiang, S., Zhou, Y., & Du, L. (2016). Recombinant Receptor-Binding Domains of Multiple Middle East Respiratory Syndrome Coronaviruses (MERS-CoVs) Induce Cross-Neutralizing Antibodies against Divergent Human and Camel MERS-CoVs and Antibody Escape Mutants. *Journal of virology*, *91*(1), e01651-16. https://doi.org/10.1128/JVI.01651-16

535. Wang, Y., Tai, W., Yang, J., Zhao, G., Sun, S., Tseng, C. K., Jiang, S., Zhou, Y., Du, L., & Gao, J. (2017). Receptor-binding domain of MERS-CoV with optimal immunogen dosage and immunization interval protects human transgenic mice from MERS-CoV infection. *Human vaccines & immunotherapeutics*, *13*(7), 1615–1624. https://doi.org/10.1080/21645515.2017.1296994

536. Zhou, Y., Yang, Y., Huang, J., Jiang, S., & Du, L. (2019). Advances in MERS-CoV Vaccines and Therapeutics Based on the Receptor-Binding Domain. *Viruses*, *11*(1), 60. https://doi.org/10.3390/v11010060

537. House Permanent Select Committee on Intelligence. (2022). House Permanent Select Committee on Intelligence Staff Report on COVID-19 Origins-Unclassified Summary. https://intelligence.house.gov/uploadedfiles/COVID_origins_hpsci_handout_final.pdf

538. House Permanent Select Committee on Intelligence. (2022). House Permanent Select Committee on Intelligence Staff Report on COVID-19 Origins-Unclassified Summary. https://intelligence.house.gov/uploadedfiles/COVID_origins_hpsci_handout_final.pdf

539. Fritz, A. (2019). China's Evolving Conception of Civil-Military Collaboration. Center for Strategic International Studies. https://www.csis.org/blogs/trustee-china-hand/chinas-evolving-conception-civil-military-collaboration

540. International Security Advisory Board. (October 2024). Report on Biotechnology in the People's Republic of China's Military-Civil Fusion Strategy. US Department of State. https://www.state.gov/wp-content/uploads/2024/11/ISAB-Report-on-Biotechnology-in-the-PRC-MCF-Strategy_Final.pdf

541. Guo, J.-W., Xue-sen, Y. (2005) Ultramicro, Nonlethal, and Reversible: Looking Ahead to Military Biotechnology. Military Review. Army University Press. https://www.armyupress.army.mil/Journals/Military-Review/Directors-Select-Articles/Nanatechnology/

542. Guo J. W. (2006). The command of biotechnology and merciful conquest in military opposition. *Military medicine*, *171*(11), 1150–1154. https://doi.org/10.7205/milmed.171.11.1150

543. Guo J. W. (2009). The command of biotechnology and merciful conquest in military opposition. *Journal of special operations medicine : a peer reviewed journal for SOF medical professionals*, *9*(1), 69–73. https://doi.org/10.55460/PWZR-55N0

544. Kania, E. Vorndick,W. (2019). "Weaponizing Biotech: How China's Military Is Preparing for a 'New Domain of Warfare." https://www.defenseone.com/ideas/2019/08/chinas-military-pursuing-biotech/159167/?oref=DefenseOneTCO Defense One.

545. Kania, E.B. (2020). Minds at War China's Pursuit of Military Advantage through Cognitive Science and Biotechnology. National Defense University Press. https://ndupress.ndu.edu/Portals/68/Documents/prism/prism_8-3/prism_8-3_Kania_82-101.pdf

546. Kania, E. Vorndick,W. (2019). "Weaponizing Biotech: How China's Military Is Preparing for a 'New Domain of Warfare." https://www.defenseone.com/ideas/2019/08/chinas-military-pursuing-biotech/159167/?oref=DefenseOneTCO Defense One.

547. Kania, E. Vorndick,W. (2019). "Weaponizing Biotech: How China's Military Is Preparing for a 'New Domain of Warfare." https://www.defenseone.com/ideas/2019/08/chinas-military-pursuing-biotech/159167/?oref=DefenseOneTCO Defense One.

548. Id.

549. Wortzel, L. (2022). Chinese Expectations for Biotechnology and Cognitive Enhancement in Future Warfare. Modern Warfare Institute at West Point. https://mwi.westpoint.edu/wp-content/uploads/2022/10/2022-10-05-MWI_Chinese_Biotechnology_Wortzel.pdf

550. Id.

551. Id.

552. Xiao, T. (2022). In Their own Words: Science of Military Strategy (2020). China Aerospace Studies Institute. https://www.airuniversity.af.edu/Portals/10/CASI/documents/Translations/2022-01-26%202020%20Science%20of%20Military%20Strategy.pdf

553. Wortzel, L. (2022). Chinese Expectations for Biotechnology and Cognitive Enhancement in Future Warfare. Modern Warfare Institute at West Point. https://mwi.westpoint.edu/wp-content/uploads/2022/10/2022-10-05-MWI_Chinese_Biotechnology_Wortzel.pdf

554. Id.

555. Id.

556. Id.

557. Defense Intelligence Agency. (2019). China Military Power: Modernizing a Forces to Fight to Win. https://www.dia.mil/Portals/110/Images/News/Military_Powers_Publications/China_Military_Power_FINAL_5MB_20190103.pdf

558. US Department of Defense. (2023). Biodefense Posture Review. https://media.defense.gov/2023/Aug/17/2003282337/-1/-1/1/2023_BIODEFENSE_POSTURE_REVIEW.PDF

559. Wortzel, L. (2022). Chinese Expectations for Biotechnology and Cognitive Enhancement in Future Warfare. Modern Warfare Institute at West Point. https://mwi.westpoint.edu/wp-content/uploads/2022/10/2022-10-05-MWI_Chinese_Biotechnology_Wortzel.pdf

560. Jin, H., Hou, L. J., & Wang, Z. G. (2018). Military Brain Science - How to influence future wars. *Chinese journal of traumatology = Zhonghua chuang shang za zhi*, *21*(5), 277–280. https://doi.org/10.1016/j.cjtee.2018.01.006

561. Id.

562. Id.

563. Kania, E.B. (2020). Minds at War China's Pursuit of Military Advantage through Cognitive Science and Biotechnology. National Defense University Press. https://ndupress.ndu.edu/Portals/68/Documents/prism/prism_8-3/prism_8-3_Kania_82-101.pdf

564. Id.

565. Id.

566. Id.

567. Guo, B., Chen, J., Chen, Q., Ren, K., Feng, D., Mao, H., Yao, H., Yang, J., Liu, H., Liu, Y., Jia, F., Qi, C., Lynn-Jones, T., Hu, H., Fu, Z., Feng, G., Wang, W., & Wu, S. (2019). Anterior cingulate cortex dysfunction underlies social deficits in Shank3 mutant mice. *Nature neuroscience*, *22*(8), 1223–1234. https://doi.org/10.1038/s41593-019-0445-9

568. Brockett, A. T., & Roesch, M. R. (2021). Anterior cingulate cortex and adaptive control of brain and behavior. *International review of neurobiology*, *158*, 283–309. https://doi.org/10.1016/bs.irn.2020.11.013

569. Bliss-Moreau, E., Santistevan, A. C., Bennett, J., Moadab, G., & Amaral, D. G. (2021). Anterior Cingulate Cortex Ablation Disrupts Affective Vigor and Vigilance. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *41*(38), 8075–8087. https://doi.org/10.1523/JNEUROSCI.0673-21.2021

570. Wortzel, L. (2022). Chinese Expectations for Biotechnology and Cognitive Enhancement in Future Warfare. Modern Warfare Institute at West Point. https://mwi.westpoint.edu/wp-content/uploads/2022/10/2022-10-05-MWI_Chinese_Biotechnology_Wortzel.pdf

571. Kania, E.B. (2020). Minds at War China's Pursuit of Military Advantage through Cognitive Science and Biotechnology. National Defense University Press. https://ndupress.ndu.edu/Portals/68/Documents/prism/prism_8-3/prism_8-3_Kania_82-101.pdf

572. Wortzel, L. (2022). Chinese Expectations for Biotechnology and Cognitive Enhancement in Future Warfare. Modern Warfare Institute at West Point. https://mwi.westpoint.edu/wp-content/uploads/2022/10/2022-10-05-MWI_Chinese_Biotechnology_Wortzel.pdf

573. Kania, E. Vorndick,W. (2019). "Weaponizing Biotech: How China's Military Is Preparing for a 'New Domain of Warfare." https://www.defenseone.com/ideas/2019/08/chinas-military-pursuing-biotech/159167/?oref=DefenseOneTCO

574. Id.

575. Raimondo, G. (2021). Commerce Acts to Deter Misuse of Biotechnology, Other US Technologies by the People's Republic of China to Support Surveillance and Military Modernization that Threaten National Security. https://www.bis.gov/press-release/commerce-acts-deter-misuse-biotechnology-other-us-technologies-peoples-republic-china

576. Nakashima, E., Schaffer, A. (December 16, 2021). Biden administration places top Chinese military institute on export blacklist over its use of surveillance, 'brain-control' technology. The Washington Post. https://www.washingtonpost.com/business/2021/12/16/china-entity-list-military-institute-added/

577. Industry and Security Bureau. (December 17, 2021). Addition of Certain Entities to the Entity List and Revision of an Entry on the Entity List. US Department of Commerce. https://www.federalregister.gov/documents/2021/12/17/2021-27406/addition-of-certain-entities-to-the-entity-list-and-revision-of-an-entry-on-the-entity-list

578. Sun, S., He, L., Zhao, Z., Gu, H., Fang, X., Wang, T., Yang, X., Chen, S., Deng, Y., Li, J., Zhao, J., Li, L., Li, X., He, P., Li, G., Li, H., Zhao, Y., Gao, C., Lang, X., Wang, X., … Sun, Y. (2021). Recombinant vaccine containing an RBD-Fc fusion induced protection against SARS-CoV-2 in nonhuman primates and mice. *Cellular & molecular immunology*, *18*(4), 1070–1073. https://doi.org/10.1038/s41423-021-00658-z

579. Id.

580. United Nations. (1975). The Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction. https://disarmament.unoda.org/biological-weapons/

581. US Department of State. (April 2023). Adherence to and Compliance with Arms Control, Nonproliferation, and Disarmament Agreements and Commitments. https://www.state.gov/wp-content/uploads/2024/04/2024-Arms-Control-Treaty-Compliance-Report.pdf

582. US Department of State. (April 2024). Adherence to and Compliance with Arms Control, Nonproliferation, and Disarmament Agreements and Commitments. https://www.state.gov/wp-content/uploads/2024/04/2024-Arms-Control-Treaty-Compliance-Report.pdf

583. US Department of State Cable. (August 2020). Analysts Probe PLA Links to Biotech Labs and Companies in Wuhan. US Right to Know FOIA request. https://usrtk.org/wp-content/uploads/2023/06/FL-2022-00075-April-2023-Production-cable-1.pdf

584. Id.

585. US Department of State. (April 2024). Adherence to and Compliance with Arms Control, Nonproliferation, and Disarmament Agreements and Commitments. https://www.state.gov/wp-content/uploads/2024/04/2024-Arms-Control-Treaty-Compliance-Report.pdf

586. Arbour, N., Day, R., Newcombe, J., & Talbot, P. J. (2000). Neuroinvasion by human respiratory coronaviruses. *Journal of virology*, *74*(19), 8913–8921. https://doi.org/10.1128/jvi.74.19.8913-8921.2000

587. Desforges, M., Le Coupanec, A., Dubeau, P., Bourgouin, A., Lajoie, L., Dubé, M., & Talbot, P. J. (2019). Human Coronaviruses and Other Respiratory Viruses: Underestimated Opportunistic Pathogens of the Central Nervous System?. Viruses, 12(1), 14. https://doi.org/10.3390/v12010014

588. Duan, Q., Zhu, H., Yang, Y., Li, W., Zhou, Y., He, J., He, K., Zhang, H., Zhou, T., Song, L., Gan, Y., Tan, H., Jin, B., Li, H., Zuo, T., Chen, D., & Zhang, X. (2003). Reovirus, isolated from SARS patients. *Chinese science bulletin = Kexue tongbao*, *48*(13), 1293–1296. https://doi.org/10.1007/BF03184165

589. Liang, L., He, C., Lei, M., Li, S., Hao, Y., Zhu, H., & Duan, Q. (2005). Pathology of guinea pigs experimentally infected with a novel reovirus and coronavirus isolated from SARS patients. *DNA and cell biology*, *24*(8), 485–490. https://doi.org/10.1089/dna.2005.24.485

590. Xu, J., Zhong, S., Liu, J., Li, L., Li, Y., Wu, X., Li, Z., Deng, P., Zhang, J., Zhong, N., Ding, Y., & Jiang, Y. (2005). Detection of severe acute respiratory syndrome coronavirus in the brain: potential role of the chemokine mig in pathogenesis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, *41*(8), 1089–1096. https://doi.org/10.1086/444461

591. McCray, P. B., Jr, Pewe, L., Wohlford-Lenane, C., Hickey, M., Manzel, L., Shi, L., Netland, J., Jia, H. P., Halabi, C., Sigmund, C. D., Meyerholz, D. K., Kirby, P., Look, D. C., & Perlman, S. (2007). Lethal infection of K18-hACE2 mice infected with severe acute respiratory syndrome coronavirus. *Journal of virology*, *81*(2), 813–821. https://doi.org/10.1128/JVI.02012-06

592. Ding, Y., Wang, H., Shen, H., Li, Z., Geng, J., Han, H., Cai, J., Li, X., Kang, W., Weng, D., Lu, Y., Wu, D., He, L., & Yao, K. (2003). The clinical pathology of severe acute respiratory syndrome (SARS): a report from China. *The Journal of pathology*, *200*(3), 282–289. https://doi.org/10.1002/path.1440

593. Gu, J., Gong, E., Zhang, B., Zheng, J., Gao, Z., Zhong, Y., Zou, W., Zhan, J., Wang, S., Xie, Z., Zhuang, H., Wu, B., Zhong, H., Shao, H., Fang, W., Gao, D., Pei, F., Li, X., He, Z., Xu, D., … Leong, A. S. (2005). Multiple organ infection and the pathogenesis of SARS. *The Journal of experimental medicine*, *202*(3), 415–424. https://doi.org/10.1084/jem.20050828

594. Id.

595. Xiang-Hua, Y., Le-Min, W., Ai-Bin, L., Zhu, G., Riquan, L., Xu-You, Z., Wei-Wei, R., & Ye-Nan, W. (2010). Severe acute respiratory syndrome and venous thromboembolism in multiple organs. *American journal of respiratory and critical care medicine*, *182*(3), 436–437. https://doi.org/10.1164/ajrccm.182.3.436

596. Lau, K. K., Yu, W. C., Chu, C. M., Lau, S. T., Sheng, B., & Yuen, K. Y. (2004). Possible central nervous system infection by SARS coronavirus. *Emerging infectious diseases*, *10*(2), 342–344. https://doi.org/10.3201/eid1002.030638

597. Kenna, H. A., Poon, A. W., de los Angeles, C. P., & Koran, L. M. (2011). Psychiatric complications of treatment with corticosteroids: review with case report. Psychiatry and clinical neurosciences, 65(6), 549–560. https://doi.org/10.1111/j.1440-1819.2011.02260.x

598. Lotan, I., Fireman, L., Benninger, F., Weizman, A., & Steiner, I. (2016). Psychiatric side effects of acute high-dose corticosteroid therapy in neurological conditions. *International clinical psychopharmacology*, *31*(4), 224–231. https://doi.org/10.1097/YIC.0000000000000122

599. Lee, D. T., Wing, Y. K., Leung, H. C., Sung, J. J., Ng, Y. K., Yiu, G. C., Chen, R. Y., & Chiu, H. F. (2004). Factors associated with psychosis among patients with severe acute respiratory syndrome: a case-control study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, *39*(8), 1247–1249. https://doi.org/10.1086/424016

600. Zubair, A. S., McAlpine, L. S., Gardin, T., Farhadian, S., Kuruvilla, D. E., & Spudich, S. (2020). Neuropathogenesis and Neurologic Manifestations of the Coronaviruses in the Age of Coronavirus Disease 2019: A Review. *JAMA neurology*, *77*(8), 1018–1027. https://doi.org/10.1001/jamaneurol.2020.2065

601. Russo, M., Calisi, D., De Rosa, M. A., Evangelista, G., Consoli, S., Dono, F., Santilli, M., Gambi, F., Onofrj, M., Di Giannantonio, M., Parruti, G., & Sensi, S. L. (2022). COVID-19 and first manic episodes: a systematic review. *Psychiatry research*, *314*, 114677. https://doi.org/10.1016/j.psychres.2022.114677

602. Tsai, L. K., Hsieh, S. T., Chao, C. C., Chen, Y. C., Lin, Y. H., Chang, S. C., & Chang, Y. C. (2004). Neuromuscular disorders in severe acute respiratory syndrome. *Archives of neurology*, *61*(11), 1669–1673. https://doi.org/10.1001/archneur.61.11.1669

603. Tsai, L. K., Hsieh, S. T., & Chang, Y. C. (2005). Neurological manifestations in severe acute respiratory syndrome. *Acta neurologica Taiwanica*, *14*(3), 113–119.

604. Hwang C. S. (2006). Olfactory neuropathy in severe acute respiratory syndrome: report of A case. *Acta neurologica Taiwanica*, *15*(1), 26–28.

605. Subbarao, K., McAuliffe, J., Vogel, L., Fahle, G., Fischer, S., Tatti, K., Packard, M., Shieh, W. J., Zaki, S., & Murphy, B. (2004). Prior infection and passive transfer of neutralizing antibody prevent replication of severe acute respiratory syndrome coronavirus in the respiratory tract of mice. *Journal of virology*, *78*(7), 3572–3577. https://doi.org/10.1128/jvi.78.7.3572-3577.2004

606. Glass, W. G., Subbarao, K., Murphy, B., & Murphy, P. M. (2004). Mechanisms of host defense following severe acute respiratory syndrome-coronavirus (SARS-CoV) pulmonary infection of mice. *Journal of immunology (Baltimore, Md. : 1950)*, *173*(6), 4030–4039. https://doi.org/10.4049/jimmunol.173.6.4030

607. McCray, P. B., Jr, Pewe, L., Wohlford-Lenane, C., Hickey, M., Manzel, L., Shi, L., Netland, J., Jia, H. P., Halabi, C., Sigmund, C. D., Meyerholz, D. K., Kirby, P., Look, D. C., & Perlman, S. (2007). Lethal infection of K18-hACE2 mice infected with severe acute respiratory syndrome coronavirus. *Journal of virology*, *81*(2), 813–821. https://doi.org/10.1128/JVI.02012-06

608. Netland, J., Meyerholz, D. K., Moore, S., Cassell, M., & Perlman, S. (2008). Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. *Journal of virology*, *82*(15), 7264–7275. https://doi.org/10.1128/JVI.00737-08

609. Id.

610. Xu, J., Zhong, S., Liu, J., Li, L., Li, Y., Wu, X., Li, Z., Deng, P., Zhang, J., Zhong, N., Ding, Y., & Jiang, Y. (2005). Detection of severe acute respiratory syndrome coronavirus in the brain: potential role of the chemokine mig in pathogenesis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, *41*(8), 1089–1096. https://doi.org/10.1086/444461

611. Chen, Z., Mi, L., Xu, J., Yu, J., Wang, X., Jiang, J., Xing, J., Shang, P., Qian, A., Li, Y., Shaw, P. X., Wang, J., Duan, S., Ding, J., Fan, C., Zhang, Y., Yang, Y., Yu, X., Feng, Q., Li, B., ... Zhu, P. (2005). Function of HAb18G/CD147 in invasion of host cells by severe acute respiratory syndrome coronavirus. *The Journal of infectious diseases*, *191*(5), 755–760. https://doi.org/10.1086/427811

612. Fenizia, C., Galbiati, S., Vanetti, C., Vago, R., Clerici, M., Tacchetti, C., & Daniele, T. (2021). SARS-CoV-2 Entry: At the Crossroads of CD147 and ACE2. *Cells*, *10*(6), 1434. https://doi.org/10.3390/cells10061434

613. Pallarés-Moratalla, C., & Bergers, G. (2024). The ins and outs of microglial cells in brain health and disease. Frontiers in immunology, 15, 1305087. https://doi.org/10.3389/fimmu.2024.1305087

614. Gao, C., Jiang, J., Tan, Y., & Chen, S. (2023). Microglia in neurodegenerative diseases: mechanism and potential therapeutic targets. *Signal transduction and targeted therapy*, *8*(1), 359. https://doi.org/10.1038/s41392-023-01588-0

615. Wei, M., Li, H., Shang, Y., Zhou, Z., & Zhang, J. (2014). Increased CD147 (EMMPRIN) expression in the rat brain following traumatic brain injury. *Brain research*, *1585*, 150–158. https://doi.org/10.1016/j.brainres.2014.06.018

616. Patrizz, A., Doran, S. J., Chauhan, A., Ahnstedt, H., Roy-O'Reilly, M., Lai, Y. J., Weston, G., Tarabishy, S., Patel, A. R., Verma, R., Staff, I., Kofler, J. K., Li, J., Liu, F., Ritzel, R. M., & McCullough, L. D. (2020). EMMPRIN/CD147 plays a detrimental role in clinical and experimental ischemic stroke. *Aging*, *12*(6), 5121–5139. https://doi.org/10.18632/aging.102935

617. Sun S-H, Chen Q, Gu H-J, Yang G, Wang Y-X, X-Y H, Liu S-S, Zhang N-N, Li X-F, Xiong R, Guo Y, Deng Y-Q, Huang W-J, Liu Q, Liu Q-M, Shen Y-L, Zhou Y, Yang X, Zhao T-Y, Fan C-F, Zhou Y-S, Qin C-F, Wang Y-C. (2020). A mouse model of SARS-CoV-2 infection and pathogenesis. Cell Host and Microbe. 28, 124-133. https://doi.org/10.1016/j.chom.2020.05.020

618. Jiang, Y., Li, J., Teng, Y., Sun, H., Tian, G., He, L., Li, P., Chen, Y., Guo, Y., Li, J., Zhao, G., Zhou, Y., & Sun, S. (2019). Complement Receptor C5aR1 Inhibition Reduces Pyroptosis in hDPP4-Transgenic Mice Infected with MERS-CoV. *Viruses*, *11*(1), 39. https://doi.org/10.3390/v11010039

619. Xiong, R., Lu, J-J., Nie, J-H., Liu, Q-M., Fan, C-A. (February 29, 2020) Advances in coronavirus animal models and potential small animal models susceptible for 2019-nCoV. Infect Dis Info, Vol. 33, No. 1

620. Bao, L., Deng, W., Huang, B., Gao, H., Liu, J., Ren, L., Wei, Q., Yu, P., Xu, Y., Qi, F., Qu, Y., Li, F., Lv, Q., Wang, W., Xue, J., Gong, S., Liu, M., Wang, G., Wang, S., Song, Z., … Qin, C. (2020). The pathogenicity of SARS-CoV-2 in hACE2 transgenic mice. *Nature*, *583*(7818), 830–833. https://doi.org/10.1038/s41586-020-2312-y

621. Sun S-H, Chen Q, Gu H-J, Yang G, Wang Y-X, X-Y H, Liu S-S, Zhang N-N, Li X-F, Xiong R, Guo Y, Deng Y-Q, Huang W-J, Liu Q, Liu Q-M, Shen Y-L, Zhou Y, Yang X, Zhao T-Y, Fan C-F, Zhou Y-S, Qin C-F, Wang Y-C. (2020). A mouse model of SARS-CoV-2 infection and pathogenesis. Cell Host and Microbe. 28, 124-133. https://doi.org/10.1016/j.chom.2020.05.020

622. Id.

623. Qi, F., Qian, S., Zhang, S., & Zhang, Z. (2020). Single cell RNA sequencing of 13 human tissues identify cell types and receptors of human coronaviruses. *Biochemical and biophysical research communications*, *526*(1), 135–140. https://doi.org/10.1016/j.bbrc.2020.03.044

624. Zou, X., Chen, K., Zou, J., Han, P., Hao, J., & Han, Z. (2020). Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. *Frontiers of medicine*, *14*(2), 185–192. https://doi.org/10.1007/s11684-020-0754-0

625. Murray, S. A., Morgan, J. L., Kane, C., Sharma, Y., Heffner, C. S., Lake, J., & Donahue, L. R. (2010). Mouse gestation length is genetically determined. *PloS one*, *5*(8), e12418. https://doi.org/10.1371/journal.pone.0012418

626. Sewell, D. L. (1995). Laboratory-associated infections and biosafety. *Clinical Microbiology Reviews*, *8*(3), 389–405. https://doi.org/10.1128/CMR.8.3.389

627. Zhou, D., Song, H., Wang, J., Li, Z., Ji, X., Hou, X., & Xu, J. (2019). Biosafety and biosecurity. *Journal of Biosafety and Biosecurity, 1, 15-18.* https://doi.org/10.1016/j.jobb.2019.01.001

628. Gao, G. F. (2019). For a better world: Biosafety strategies to protect global health. *Biosafety and Health*, *1*(1), 1–3. https://doi.org/10.1016/j.bsheal.2019.03.001

629. Kadlec, R. (2024) Origins of COVID-19 a critical review: Hidden in plain sight. Pg 43. https://bush.tamu.edu/wp-content/uploads/2024/09/MUDDY-WATERS-First-Installment-PUBLISHED-09-20-24.pdf

630. Zhu, N. N. [朱宁宁]. (2019, April 2). Six legislative items will complete interim goals this year [6 个立法项目将于今年_完成阶段性目标]. *The Legal Daily* reprinted on the *National People's Congress.*

631. Gu, H., Chen, Q., Yang, G., He, L., Fan, H., Deng, Y. Q., Wang, Y., Teng, Y., Zhao, Z., Cui, Y., Li, Y., Li, X. F., Li, J., Zhang, N. N., Yang, X., Chen, S., Guo, Y., Zhao, G., Wang, X., Luo, D. Y., ... Zhou, Y. Rapid adaptation of SARS-CoV-2 in BALB/c mice: Novel mouse model for vaccine efficacy bioRxiv 2020.05.02.073411; doi: https://doi.org/10.1101/2020.05.02.073411

632. Gu, H., Chen, Q., Yang, G., He, L., Fan, H., Deng, Y. Q., Wang, Y., Teng, Y., Zhao, Z., Cui, Y., Li, Y., Li, X. F., Li, J., Zhang, N. N., Yang, X., Chen, S., Guo, Y., Zhao, G., Wang, X., Luo, D. Y., ... Zhou, Y. (2020). Adaptation of SARS-CoV-2 in BALB/c mice for testing vaccine efficacy. *Science (New York, N.Y.)*, *369*(6511), Supplementary Information. abc4730-gu-sm.pdf . https://doi.org/10.1126/science.abc4730

633. Gu, H., Chen, Q., Yang, G., He, L., Fan, H., Deng, Y. Q., Wang, Y., Teng, Y., Zhao, Z., Cui, Y., Li, Y., Li, X. F., Li, J., Zhang, N. N., Yang, X., Chen, S., Guo, Y., Zhao, G., Wang, X., Luo, D. Y., ... Zhou, Y. (2020). Adaptation of SARS-CoV-2 in BALB/c mice for testing vaccine efficacy. *Science (New York, N.Y.)*, *369*(6511), 1603–1607. https://doi.org/10.1126/science.abc4730

634. Id.

635. Xu, A., Hong, B., Lou, F., Wang, S., Li, W., Shafqat, A., An, X., Zhao, Y., Song, L., Tong, Y., & Fan, H. (2022). Sub-lineages of the SARS-CoV-2 Omicron variants: Characteristics and prevention. *MedComm*, *3*(3), e172. https://doi.org/10.1002/mco2.172

636. Liu, Y., Liu, J., Plante, K. S., Plante, J. A., Xie, X., Zhang, X., Ku, Z., An, Z., Scharton, D., Schindewolf, C., Widen, S. G., Menachery, V. D., Shi, P. Y., & Weaver, S. C. (2022). The N501Y spike substitution enhances SARS-CoV-2 infection and transmission. *Nature*, *602*(7896), 294–299. https://doi.org/10.1038/s41586-021-04245-0

637. World Health organization. (2021). Classification of Omicron (B.1.1.529): SARS-CoV-2 Variant of Concern. https://www.who.int/news/item/26-11-2021-classification-of-omicron-(b.1.1.529)-sars-cov-2-variant-of-concern

638. Gu, H., Chen, Q., Yang, G., He, L., Fan, H., Deng, Y. Q., Wang, Y., Teng, Y., Zhao, Z., Cui, Y., Li, Y., Li, X. F., Li, J., Zhang, N. N., Yang, X., Chen, S., Guo, Y., Zhao, G., Wang, X., Luo, D. Y., ... Zhou, Y. (2020). Adaptation of SARS-CoV-2 in BALB/c mice for testing vaccine efficacy. Science (New York, N.Y.), 369(6511), 1603–1607. https://doi.org/10.1126/science.abc4730

639. Id.

640. Id.

641. Rong, Z., Mai, H., Ebert, G., Kapoor, S., Puelles, V.G., et al. (2024). Persistence of spike protein at the skull-meninges-brain axis may contribute to the neurological sequelae of COVID-19. Cell Host & Microbe. 32, 1-19. https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(24)00438-4

642. Gu, H., Chen, Q., Yang, G., He, L., Fan, H., Deng, Y. Q., Wang, Y., Teng, Y., Zhao, Z., Cui, Y., Li, Y., Li, X. F., Li, J., Zhang, N. N., Yang, X., Chen, S., Guo, Y., Zhao, G., Wang, X., Luo, D. Y., … Zhou, Y. (2020). Adaptation of SARS-CoV-2 in BALB/c mice for testing vaccine efficacy. Science (New York, N.Y.), 369(6511), 1603–1607. https://doi.org/10.1126/science.abc4730

643. Shuai, H., Chan, J. F., Yuen, T. T., Yoon, C., Hu, J. C., Wen, L., Hu, B., Yang, D., Wang, Y., Hou, Y., Huang, X., Chai, Y., Chan, C. C., Poon, V. K., Lu, L., Zhang, R. Q., Chan, W. M., Ip, J. D., Chu, A. W., Hu, Y. F., … Chu, H. (2021). Emerging SARS-CoV-2 variants expand species tropism to murines. *EBioMedicine*, *73*, 103643. https://doi.org/10.1016/j.ebiom.2021.103643

644. Niu, Z., Zhang, Z., Gao, X., Du, P., Lu, J., Yan, B., Wang, C., Zheng, Y., Huang, H., & Sun, Q. (2021). N501Y mutation imparts cross-species transmission of SARS-CoV-2 to mice by enhancing receptor binding. *Signal transduction and targeted therapy*, *6*(1), 284. https://doi.org/10.1038/s41392-021-00704-2

645. Liu, Y., Liu, J., Plante, K. S., Plante, J. A., Xie, X., Zhang, X., Ku, Z., An, Z., Scharton, D., Schindewolf, C., Menachery, V. D., Shi, P. Y., & Weaver, S. C. (2022). The N501Y spike substitution enhances SARS-CoV-2 infection and transmission. *Nature* **602**, 294–299. https://doi.org/10.1038/s41586-021-04245-0

646. Makowski, L., Olson-Sidford, W., & W-Weisel, J. (2021). Biological and Clinical Consequences of Integrin Binding via a Rogue RGD Motif in the SARS CoV-2 Spike Protein. *Viruses*, *13*(2), 146. https://doi.org/10.3390/v13020146

647. Gressett, T. E., Nader, D., Robles, J. P., Buranda, T., Kerrigan, S. W., & Bix, G. (2022). Integrins as Therapeutic Targets for SARS-CoV-2. *Frontiers in cellular and infection microbiology*, *12*, 892323. https://doi.org/10.3389/fcimb.2022.892323

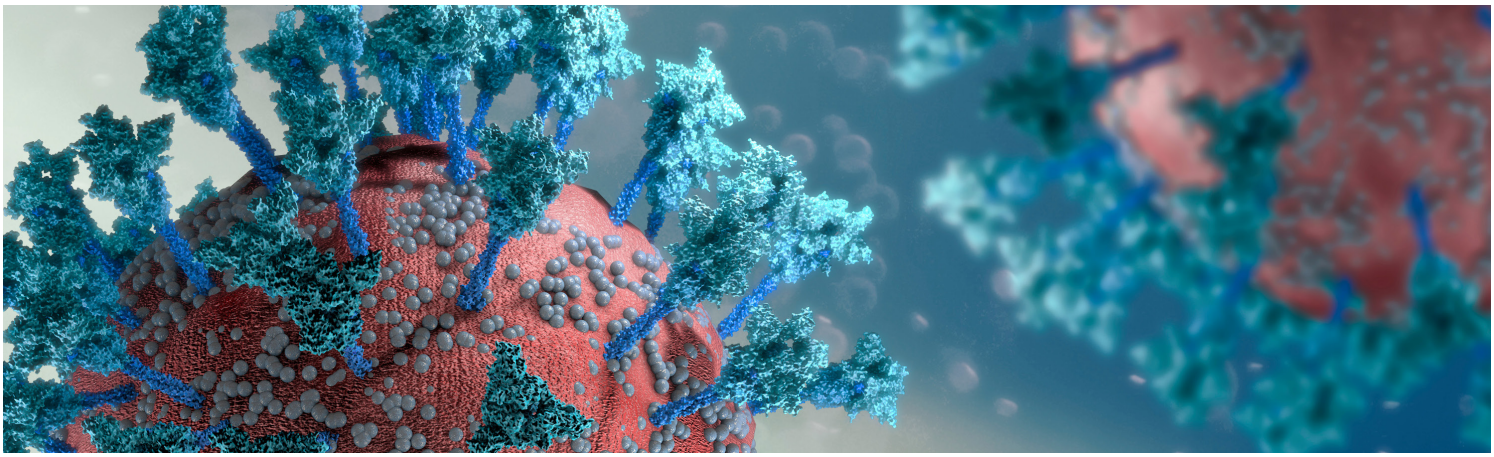
648. Gu, H., Chen, Q., Yang, G., He, L., Fan, H., Deng, Y. Q., Wang, Y., Teng, Y., Zhao, Z., Cui, Y., Li, Y., Li, X. F., Li, J., Zhang, N. N., Yang, X., Chen, S., Guo, Y., Zhao, G., Wang, X., Luo, D. Y., … Zhou, Y. (2020). Adaptation of SARS-CoV-2 in BALB/c mice for testing vaccine efficacy. Science (New York, N.Y.), 369(6511), 1603–1607. https://doi.org/10.1126/science.abc4730

649. Rong, Z., Mai, H., Ebert, G., Kapoor, S., Puelles, V.G., et al. (2024). Persistence of spike protein at the skull-meninges-brain axis may contribute to the neurological sequelae of COVID-19. CellPress. https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(24)00438-4

650. Proust, A., Queval, C. J., Harvey, R., Adams, L., Bennett, M., & Wilkinson, R. J. (2023). Differential effects of SARS-CoV-2 variants on central nervous system cells and blood-brain barrier functions. *Journal of neuroinflammation*, *20*(1), 184. https://doi.org/10.1186/s12974-023-02861-3

651. Id.

652. Du, Y., Zhao, W., Huang, S. (2023). et al. Gray Matter Thickness and Subcortical Nuclear Volume in Men After SARS-CoV-2 Omicron Infection. *JAMA Netw Open.* 6(11):e2345626. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10690469/



653. Rong, Z., Mai, H., Ebert, G., Kapoor, S., Puelles, V.G., et al. (2024). Persistence of spike protein at the skull-meninges-brain axis may contribute to the neurological sequelae of COVID-19. CellPress. https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(24)00438-4

654. Id.

655. Frieman, M., Menachery, V. (August 2,2020). Email (SLACK) exchange University of Texas Medical Branch scientists. US Right to Know Freedom of Information Request. https://usrtk.org/wp-content/uploads/2024/03/UTMB-11-partial-production-combined.pdf

656. Leist, S. R., Dinnon, K. H., 3rd, Schäfer, A., Tse, L. V., Okuda, K., Hou, Y. J., West, A., Edwards, C. E., Sanders, W., Fritch, E. J., Gully, K. L., Scobey, T., Brown, A. J., Sheahan, T. P., Moorman, N. J., Boucher, R. C., Gralinski, L. E., Montgomery, S. A., & Baric, R. S. (2020). A Mouse-Adapted SARS-CoV-2 Induces Acute Lung Injury and Mortality in Standard Laboratory Mice. *Cell*, *183*(4), 1070–1085.e12. https://doi.org/10.1016/j.cell.2020.09.050

657. Amruta, N., Ismael, S., Leist, S. R., Gressett, T. E., Srivastava, A., Dinnon, K. H., 3rd, Engler-Chiurazzi, E. B., Maness, N. J., Qin, X., Kolls, J. K., Baric, R. S., & Bix, G. (2022). Mouse Adapted SARS-CoV-2 (MA10) Viral Infection Induces Neuroinflammation in Standard Laboratory Mice. *Viruses*, *15*(1), 114. https://doi.org/10.3390/v15010114

658. Leist, S. R., Dinnon, K. H., 3rd, Schäfer, A., Tse, L. V., Okuda, K., Hou, Y. J., West, A., Edwards, C. E., Sanders, W., Fritch, E. J., Gully, K. L., Scobey, T., Brown, A. J., Sheahan, T. P., Moorman, N. J., Boucher, R. C., Gralinski, L. E., Montgomery, S. A., & Baric, R. S. (2020). A Mouse-Adapted SARS-CoV-2 Induces Acute Lung Injury and Mortality in Standard Laboratory Mice. *Cell*, *183*(4), 1070–1085.e12. https://doi.org/10.1016/j.cell.2020.09.050

659. Amruta, N., Ismael, S., Leist, S. R., Gressett, T. E., Srivastava, A., Dinnon, K. H., 3rd, Engler-Chiurazzi, E. B., Maness, N. J., Qin, X., Kolls, J. K., Baric, R. S., & Bix, G. (2022). Mouse Adapted SARS-CoV-2 (MA10) Viral Infection Induces Neuroinflammation in Standard Laboratory Mice. *Viruses*, *15*(1), 114. https://doi.org/10.3390/v15010114

660. Id.

661. Gressett, T. E., Leist, S. R., Ismael, S., Talkington, G., Dinnon, K. H., Baric, R. S., & Bix, G. (2023). Mouse Adapted SARS-CoV-2 Model Induces "Long-COVID" Neuropathology in BALB/c Mice. *bioRxiv : the preprint server for biology*, 2023.03.18.533204. https://doi.org/10.1101/2023.03.18.533204

662. Sun S-H, Chen Q, Gu H-J, Yang G, Wang Y-X, X-Y H, Liu S-S, Zhang N-N, Li X-F, Xiong R, Guo Y, Deng Y-Q, Huang W-J, Liu Q, Liu Q-M, Shen Y-L, Zhou Y, Yang X, Zhao T-Y, Fan C-F, Zhou Y-S, Qin C-F, Wang Y-C. (2020). A mouse model of SARS-CoV-2 infection and pathogenesis. Cell Host and Microbe. 28, 124-133. https://doi.org/10.1016/j.chom.2020.05.020

663. Sun, S., He, L., Zhao, Z., Gu, H., Fang, X., Wang, T., Yang, X., Chen, S., Deng, Y., Li, J., Zhao, J., Li, L., Li, X., He, P., Li, G., Li, H., Zhao, Y., Gao, C., Lang, X., Wang, X., ... Sun, Y. (2021). Recombinant vaccine containing an RBD-Fc fusion induced protection against SARS-CoV-2 in nonhuman primates and mice. *Cellular & molecular immunology*, *18*(4), 1070–1073. https://doi.org/10.1038/s41423-021-00658-z

664. Sun S-H, Chen Q, Gu H-J, Yang G, Wang Y-X, X-Y H, Liu S-S, Zhang N-N, Li X-F, Xiong R, Guo Y, Deng Y-Q, Huang W-J, Liu Q, Liu Q-M, Shen Y-L, Zhou Y, Yang X, Zhao T-Y, Fan C-F, Zhou Y-S, Qin C-F, Wang Y-C. (2020). A mouse model of SARS-CoV-2 infection and pathogenesis. Cell Host and Microbe. 28, 124-133. https://doi.org/10.1016/j.chom.2020.05.020

665. Gu, H., Chen, Q., Yang, G., He, L., Fan, H., Deng, Y. Q., Wang, Y., Teng, Y., Zhao, Z., Cui, Y., Li, Y., Li, X. F., Li, J., Zhang, N. N., Yang, X., Chen, S., Guo, Y., Zhao, G., Wang, X., Luo, D. Y., ... Zhou, Y. (2020). Adaptation of SARS-CoV-2 in BALB/c mice for testing vaccine efficacy. Science (New York, N.Y.), 369(6511), 1603–1607. https://doi.org/10.1126/science.abc4730

666. Id.

667. Sun, S., He, L., Zhao, Z., Gu, H., Fang, X., Wang, T., Yang, X., Chen, S., Deng, Y., Li, J., Zhao, J., Li, L., Li, X., He, P., Li, G., Li, H., Zhao, Y., Gao, C., Lang, X., Wang, X., ... Sun, Y. (2020). Recombinant Fc-fusion vaccine of RBD induced protection against SARS-CoV-2 in non- human primate and mice. BioRx. https://www.biorxiv.org/content/10.1101/2020.11.29.402339v1

668. Sun, S., He, L., Zhao, Z., Gu, H., Fang, X., Wang, T., Yang, X., Chen, S., Deng, Y., Li, J., Zhao, J., Li, L., Li, X., He, P., Li, G., Li, H., Zhao, Y., Gao, C., Lang, X., Wang, X., ... Sun, Y. (2021). Recombinant vaccine containing an RBD-Fc fusion induced protection against SARS-CoV-2 in nonhuman primates and mice. *Cellular & molecular immunology*, *18*(4), 1070–1073. https://doi.org/10.1038/s41423-021-00658-z

669. Rutkai, I., Mayer, M. G., Hellmers, L. M., Ning, B., Huang, Z., Monjure, C. J., Coyne, C., Silvestri, R., Golden, N., Hensley, K., Chandler, K., Lehmicke, G., Bix, G. J., Maness, N. J., Russell-Lodrigue, K., Hu, T. Y., Roy, C. J., Blair, R. V., Bohm, R., Doyle-Meyers, L. A., ... Fischer, T. (2022). Neuropathology and virus in brain of SARS-CoV-2 infected non-human primates. *Nature communications*, *13*(1), 1745. https://doi.org/10.1038/s41467-022-29440-z

670. Id.

671. Beckman, D., Bonillas, A., Diniz, G. B., Ott, S., Roh, J. W., Elizaldi, S. R., Schmidt, B. A., Sammak, R. L., Van Rompay, K. K. A., Iyer, S. S., & Morrison, J. H. (2022). SARS-CoV-2 infects neurons and induces neuroinflammation in a non-human primate model of COVID-19. *Cell reports*, *41*(5), 111573. https://doi.org/10.1016/j.celrep.2022.111573

672. Jiang, Y., Chen, Y., Sun, H., Zhang, X., He, L., Li, J., Zhao, G., & Sun, S. (2021). MERS-CoV infection causes brain damage in human DPP4-transgenic mice through complement-mediated inflammation. *The Journal of general virology*, *102*(10), 001667. https://doi.org/10.1099/jgv.0.001667

673. Toniolo, S., Di Lorenzo, F., Scarioni, M., Frederiksen, K. S., & Nobili, F. (2021). Is the Frontal Lobe the Primary Target of SARS-CoV-2?. Journal of Alzheimer's disease : JAD, 81(1), 75–81. https://doi.org/10.3233/JAD-210008

674. Fan, C., Wu, X., Liu, Q., Li, Q., Liu, S., Lu, J., Yang, Y., Cao, Y., Huang, W., Liang, C., Ying, T., Jiang, S., & Wang, Y. (2018). A Human DPP4-Knockin Mouse's Susceptibility to Infection by Authentic and Pseudotyped MERS-CoV. *Viruses*, *10*(9), 448. https://doi.org/10.3390/v10090448

675. Sun S-H, Chen Q, Gu H-J, Yang G, Wang Y-X, X-Y H, Liu S-S, Zhang N-N, Li X-F, Xiong R, Guo Y, Deng Y-Q, Huang W-J, Liu Q, Liu Q-M, Shen Y-L, Zhou Y, Yang X, Zhao T-Y, Fan C-F, Zhou Y-S, Qin C-F, Wang Y-C. (2020). A mouse model of SARS-CoV-2 infection and pathogenesis. Cell Host and Microbe. 28, 124-133. https://doi.org/10.1016/j.chom.2020.05.020

676. Tao, X., Garron, T., Agrawal, A. S., Algaissi, A., Peng, B. H., Wakamiya, M., Chan, T. S., Lu, L., Du, L., Jiang, S., Couch, R. B., & Tseng, C. T. (2015). Characterization and Demonstration of the Value of a Lethal Mouse Model of Middle East Respiratory Syndrome Coronavirus Infection and Disease. *Journal of virology*, *90*(1), 57–67. https://doi.org/10.1128/JVI.02009-15

677. Li, K., Wohlford-Lenane, C., Perlman, S., Zhao, J., Jewell, A. K., Reznikov, L. R., Gibson-Corley, K. N., Meyerholz, D. K., & McCray, P. B., Jr (2016). Middle East Respiratory Syndrome Coronavirus Causes Multiple Organ Damage and Lethal Disease in Mice Transgenic for Human Dipeptidyl Peptidase 4. *The Journal of infectious diseases*, *213*(5), 712–722. https://doi.org/10.1093/infdis/jiv499

678. Jones, A., Zhang, D., Massey, S. E., Deigin, Y., Nemzer, L. R., & Quay, S. C. (2023). Discovery of a novel merbecovirus DNA clone contaminating agricultural rice sequencing datasets from Wuhan, China. *bioRxiv : the preprint server for biology*, 2023.02.12.528210. https://doi.org/10.1101/2023.02.12.528210

679. Guo, X., Hu, H., Chen, F., Li, Z., Ye, S., Cheng, S., Zhang, M., & He, Q. (2016). iTRAQ-based comparative proteomic analysis of Vero cells infected with virulent and CV777 vaccine strain-like strains of porcine epidemic diarrhea virus. *Journal of proteomics*, *130*, 65–75. https://doi.org/10.1016/j.jprot.2015.09.002

680. Guangming Daily. (2020). The spirit of the university exemplified in Wuhan's fight against COVID-19. http://en.moe.gov.cn/features/EducationAntiEpidemic/Stronger/202005/t20200513_453826.html

681. World Health Organization. (2021). WHO-convened Global Study of Origins of SARS-CoV-2: China Part | Joint WHO-China Study, 14 January-10 February 2021. https://reliefweb.int/report/world/who-convened-global-study-origins-sars-cov-2-china-part-joint-who-china-study-14

682. Li, G., Hou, C., Dou, S., Zhang, J., Zhang, Y., Liu, Y., Wang, Z., Xiao, H., Wang, R., Chen, G., Li, Y., Feng, J., Shen, B., & Han, G. (2019). Monoclonal antibody against human Tim-3 enhances antiviral immune response. *Scandinavian journal of immunology*, *89*(2), e12738. https://doi.org/10.1111/sji.12738

683. Gu, H., Chen, Q., Yang, G., He, L., Fan, H., Deng, Y. Q., Wang, Y., Teng, Y., Zhao, Z., Cui, Y., Li, Y., Li, X. F., Li, J., Zhang, N. N., Yang, X., Chen, S., Guo, Y., Zhao, G., Wang, X., Luo, D. Y., ... Zhou, Y. (2020). Adaptation of SARS-CoV-2 in BALB/c mice for testing vaccine efficacy. *Science (New York, N.Y.)*, *369*(6511), 1603–1607. https://doi.org/10.1126/science.abc4730

684. Wang, X., Wei, Y., Xiao, H., Liu, X., Zhang, Y., Han, G., Chen, G., Hou, C., Ma, N., Shen, B., Li, Y., Egwuagu, C. E., & Wang, R. (2016). A novel IL-23p19/Ebi3 (IL-39) cytokine mediates inflammation in Lupus-like mice. *European journal of immunology*, *46*(6), 1343–1350. https://doi.org/10.1002/eji.201546095

685. Du., C, Ge. L., Han, G. (2023). Biosafety and Mental Health. Biosafety and Health Vol 5: 3. Pp. 159-167. https://doi.org/10.1016/j.bsheal.2023.04.002

686. Id.

687. Id.

688. Id.

689. Id.

690. Id.

691. Monje, M., & Iwasaki, A. (2022). The neurobiology of long COVID. Neuron, 110(21), 3484–3496. https://doi.org/10.1016/j.neuron.2022.10.006

692. Du., C, Ge. L., Han, G. (2023). Biosafety and Mental Health. Biosafety and Health Vol 5: 3. Pp. 159-167. https://doi.org/10.1016/j.bsheal.2023.04.002

693. Id.

694. Ferrari-Souza, J. P., Ferreira, P. C. L., Bellaver, B., Tissot, C., Wang, Y. T., Leffa, D. T., Brum, W. S., Benedet, A. L., Ashton, N. J., De Bastiani, M. A., Rocha, A., Therriault, J., Lussier, F. Z., Chamoun, M., Servaes, S., Bezgin, G., Kang, M. S., Stevenson, J., Rahmouni, N., Pallen, V., ... Pascoal, T. A. (2022). Astrocyte biomarker signatures of amyloid-β and tau pathologies in Alzheimer's disease. *Molecular psychiatry*, *27*(11), 4781–4789. https://doi.org/10.1038/s41380-022-01716-2

695. Soung, A. L., Vanderheiden, A., Nordvig, A. S., Sissoko, C. A., Canoll, P., Mariani, M. B., Jiang, X., Bricker, T., Rosoklija, G. B., Arango, V., Underwood, M., Mann, J. J., Dwork, A. J., Goldman, J. E., Boon, A. C. M., Boldrini, M., & Klein, R. S. (2022). COVID-19 induces CNS cytokine expression and loss of hippocampal neurogenesis. *Brain : a journal of neurology*, *145*(12), 4193–4201. https://doi.org/10.1093/brain/awac270

696. Jiang, Y., Chen, Y., Sun, H., Zhang, X., He, L., Li, J., Zhao, G., & Sun, S. (2021). MERS-CoV infection causes brain damage in human DPP4-transgenic mice through complement-mediated inflammation. *The Journal of general virology*, *102*(10), 001667. https://doi.org/10.1099/jgv.0.001667

697. Id.

698. Israelow, B., Song, E., Mao, T., Lu, P., Meir, A., Liu, F., Alfajaro, M. M., Wei, J., Dong, H., Homer, R. J., Ring, A., Wilen, C. B., & Iwasaki, A. (2020). Mouse model of SARS-CoV-2 reveals inflammatory role of type I interferon signaling. The Journal of experimental medicine, 217(12), e20201241. https://doi.org/10.1084/jem.20201241

699. Monje, M., & Iwasaki, A. (2022). The neurobiology of long COVID. Neuron, 110(21), 3484–3496. https://doi.org/10.1016/j.neuron.2022.10.006

700. Frolova, E. I., Palchevska, O., Lukash, T., Dominguez, F., Britt, W., & Frolov, I. (2022). Acquisition of Furin Cleavage Site and Further SARS-CoV-2 Evolution Change the Mechanisms of Viral Entry, Infection Spread, and Cell Signaling. Journal of virology, 96(15), e0075322. https://doi.org/10.1128/jvi.00753-22

701. Id.

702. Shirato, K., & Kizaki, T. (2021). SARS-CoV-2 spike protein S1 subunit induces pro-inflammatory responses via toll-like receptor 4 signaling in murine and human macrophages. Heliyon, 7(2), e06187. https://doi.org/10.1016/j.heliyon.2021.e06187

703. Li, X., Duan, G., Zhang, W., Jinsong, S., Jiayuan C., Shunmei, C.,Shan G., Jishou R. (2020). A furin cleavage site was discovered in the S protein of the 2019 novel coronavirus. Chinese Journal of Bioinformatics (In Chinese translated into English). 18(2): 103-108. https://doi.org/10.12113/202002001

704. Iacono, K. T., Kazi, L., & Weiss, S. R. (2006). Both spike and background genes contribute to murine coronavirus neurovirulence. *Journal of virology, 80*(14), 6834–6843. https://doi.org/10.1128/JVI.00432-06

705. MacNamara, K. C., Chua, M. M., Phillips, J. J., & Weiss, S. R. (2005). Contributions of the viral genetic background and a single amino acid substitution in an immunodominant CD8+ T-cell epitope to murine coronavirus neurovirulence. *Journal of virology, 79*(14), 9108–9118. https://doi.org/10.1128/JVI.79.14.9108-9118.2005

706. Chan, Y. A., & Zhan, S. H. (2022). The emergence of the spike furin cleavage site in SARS-CoV-2. *Molecular Biology and Evolution, 39*(1), msab327. https://doi.org/10.1093/molbev/msab327

707. Gao, W., He, W., Zhao, K., Lu, H., Ren, W., Du, C., Chen, K., Lan, Y., Song, D., & Gao, F. (2010). Identification of NCAM that interacts with the PHE-CoV spike protein. *Virology journal, 7,* 254. https://doi.org/10.1186/1743-422X-7-254

708. Rong, Z., Mai, H., Ebert, G., Kapoor, S., Puelles, V.G., et al. (2024). Persistence of spike protein at the skull-meninges-brain axis may contribute to the neurological sequelae of COVID-19. Cell Host & Microbe. 32, 1-19. https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(24)00438-4

709. Rong, Z., Mai, H., Ebert, G., Kapoor, S., Puelles, V.G., et al. (2024). Persistence of spike protein at the skull-meninges-brain axis may contribute to the neurological sequelae of COVID-19. Cell Host & Microbe. 32, 1-19. https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(24)00438-4

710. Zhu, G., Zhou, S., Xu, Y., Gao, R., Li, H., Su, W., Han, G., & Wang, R. (2022). Mendelian randomization study on the causal effects of COVID-19 on childhood intelligence. *Journal of medical virology*, *94*(7), 3233–3239. https://doi.org/10.1002/jmv.27736

711. Zhu, G., Zhou, S., Xu, Y., Gao, R., Li, H., Su, W., Han, G., & Wang, R. (2022). Mendelian randomization study on the causal effects of COVID-19 on childhood intelligence. *Journal of medical virology*, *94*(7), 3233–3239. https://doi.org/10.1002/jmv.27736

712. Dando, M. (2003). Biologists napping while work militarized. *Nature.* Vol 460.950-951. https://www.nature.com/articles/460950a.pdf

713. Hearn, H.J., (1966). Agent Summary Status Report on Venezuelan Equine Encephalitis. Fort Detrick MD, Biological Sciences Laboratories.

714. Liotta, E. M., Batra, A., Clark, J. R., Shlobin, N. A., Hoffman, S. C., Orban, Z. S., & Koralnik, I. J. (2020). Frequent neurologic manifestations and encephalopathy-associated morbidity in COVID-19 patients. *Annals of clinical and translational neurology*, *7*(11), 2221–2230. https://doi.orgworobey10.1002/acn3.51210

715. Wang, K., Chen, W., Zhang, Z., Deng, Y., Lian, J. Q., Du, P., Wei, D., Zhang, Y., Sun, X. X., Gong, L., Yang, X., He, L., Zhang, L., Yang, Z., Geng, J. J., Chen, R., Zhang, H., Wang, B., Zhu, Y. M., Nan, G., ... Chen, Z. N. (2020). CD147-spike protein is a novel route for SARS-CoV-2 infection to host cells. *Signal transduction and targeted therapy*, *5*(1), 283. https://doi.org/10.1038/s41392-020-00426-x

716. Id.

717. Geng, J., Chen, L., Yuan, Y., Wang, K., Wang, Y., Qin, C., Wu, G., Chen, R., Zhang, Z., Wei, D., Du, P., Zhang, J., Lin, P., Zhang, K., Deng, Y., Xu, K., Liu, J., Sun, X., Guo, T., Yang, X., ... Chen, Z. N. (2021). CD147 antibody specifically and effectively inhibits infection and cytokine storm of SARS-CoV-2 and its variants delta, alpha, beta, and gamma. Signal transduction and targeted therapy, 6(1), 347. https://doi.org/10.1038/s41392-021-00760-8

718. Wang, H., Lv, J. J., Zhao, Y., Wei, H. L., Zhang, T. J., Yang, H. J., Chen, Z. N., & Jiang, J. L. (2021). Endothelial genetic deletion of CD147 induces changes in the dual function of the blood-brain barrier and is implicated in Alzheimer's disease. *CNS neuroscience & therapeutics*, *27*(9), 1048–1063. Advance online publication. https://doi.org/10.1111/cns.13659

719. Ragotte, R. J., Pulido, D., Donnellan, F. R., Hill, M. L., Gorini, G., Davies, H., Brun, J., McHugh, K., King, L. D. W., Skinner, K., Miura, K., Long, C. A., Zitzmann, N., & Draper, S. J. (2021). Human Basigin (CD147) Does Not Directly Interact with SARS-CoV-2 Spike Glycoprotein. *mSphere*, *6*(4), e0064721. https://doi.org/10.1128/mSphere.00647-21

720. Chen, Z., Mi, L., Xu, J., Yu, J., Wang, X., Jiang, J., Xing, J., Shang, P., Qian, A., Li, Y., Shaw, P. X., Wang, J., Duan, S., Ding, J., Fan, C., Zhang, Y., Yang, Y., Yu, X., Feng, Q., Li, B., ... Zhu, P. (2005). Function of HAb18G/CD147 in invasion of host cells by severe acute respiratory syndrome coronavirus. *The Journal of infectious diseases*, *191*(5), 755–760. https://doi.org/10.1086/427811

721. Li, X., Duan, G., Zhang, W., Jinsong, S., Jiayuan, C., Shunmei, C., Shan, G., & Jishou, R. (2020). A furin cleavage site was discovered in the S protein of the 2019 novel coronavirus. *Chinese Journal of Bioinformatics* (In Chinese translated into English). 18(2): 103-108. https://doi.org/10.12113/202002001

722. Iacono, K. T., Kazi, L., & Weiss, S. R. (2006). Both spike and background genes contribute to murine coronavirus neurovirulence. *Journal of Virology, 80*(14), 6834–6843. https://doi.org/10.1128/JVI.00432-06

723. Gao, W., He, W., Zhao, K., Lu, H., Ren, W., Du, C., Chen, K., Lan, Y., Song, D., & Gao, F. (2010). Identification of NCAM that interacts with the PHE-CoV spike protein. *Virology Journal, 7*, 254. https://doi.org/10.1186/1743-422X-7-254

724. Hikmet, F., Méar, L., Edvinsson, Å., Micke, P., Uhlén, M., & Lindskog, C. (2020). The protein expression profile of ACE2 in human tissues. *Molecular systems biology*, *16*(7), e9610. https://doi.org/10.15252/msb.20209610

725. Kaushik, D. K., Hahn, J. N., & Yong, V. W. (2015). EMMPRIN, an upstream regulator of MMPs, in CNS biology. *Matrix biology : journal of the International Society for Matrix Biology*, *44-46*, 138–146. https://doi.org/10.1016/j.matbio.2015.01.018

726. Qiao, J., Li, W., Bao, J., Peng, Q., Wen, D., Wang, J., & Sun, B. (2020). The expression of SARS-CoV-2 receptor ACE2 and CD147, and protease TMPRSS2 in human and mouse brain cells and mouse brain tissues. *Biochemical and biophysical research communications*, *533*(4), 867–871. https://doi.org/10.1016/j.bbrc.2020.09.042

727. Id.

728. Id.

729. Wu, X., & Reddy, D. S. (2012). Integrins as receptor targets for neurological disorders. *Pharmacology & therapeutics*, *134*(1), 68–81. https://doi.org/10.1016/j.pharmthera.2011.12.008

730. Robles, J. P., Zamora, M., Adan-Castro, E., Siqueiros-Marquez, L., Martinez de la Escalera, G., & Clapp, C. (2022). The spike protein of SARS-CoV-2 induces endothelial inflammation through integrin α5β1 and NF-κB signaling. The Journal of biological chemistry, 298(3), 101695. https://doi.org/10.1016/j.jbc.2022.101695

731. Makowski, L., Olson-Sidford, W., & W-Weisel, J. (2021). Biological and Clinical Consequences of Integrin Binding via a Rogue RGD Motif in the SARS CoV-2 Spike Protein. *Viruses*, *13*(2), 146. https://doi.org/10.3390/v13020146

732. Id.

733. Saxena, A., & Mautner, J. (2024). A Disease Hidden in Plain Sight: Pathways and Mechanisms of Neurological Complications of Post-acute Sequelae of COVID-19 (NC-PASC). *Molecular neurobiology*, 10.1007/s12035-024-04421-z. Advance online publication. https://doi.org/10.1007/s12035-024-04421-z

734. Toniolo, S., Di Lorenzo, F., Scarioni, M., Frederiksen, K. S., & Nobili, F. (2021). Is the Frontal Lobe the Primary Target of SARS-CoV-2?. *Journal of Alzheimer's disease : JAD*, *81*(1), 75–81. https://doi.org/10.3233/JAD-210008 Morgello S. (2020). Coronaviruses and the central nervous system. *Journal of neurovirology*, *26*(4), 459–473. https://doi.org/10.1007/s13365-020-00868-7

735. Toniolo, S., Di Lorenzo, F., Scarioni, M., Frederiksen, K. S., & Nobili, F. (2021). Is the Frontal Lobe the Primary Target of SARS-CoV-2?. *Journal of Alzheimer's disease : JAD, 81*(1), 75–81. https://doi.org/10.3233/JAD-210008

736. Id.

737. Damiano, R. F., Guedes, B. F., de Rocca, C. C., de Pádua Serafim, A., Castro, L. H. M., Munhoz, C. D., Nitrini, R., Filho, G. B., Miguel, E. C., Lucchetti, G., & Forlenza, O. (2022). Cognitive decline following acute viral infections: literature review and projections for post-COVID-19. *European archives of psychiatry and clinical neuroscience*, *272*(1), 139–154. https://doi.org/10.1007/s00406-021-01286-4

738. Id.

739. Koralnik, I. J., & Tyler, K. L. (2020). COVID-19: A Global Threat to the Nervous System. *Annals of neurology*, *88*(1), 1–11. https://doi.org/10.1002/ana.25807

740. Ng Kee Kwong, K. C., Mehta, P. R., Shukla, G., & Mehta, A. R. (2020). COVID-19, SARS and MERS: A neurological perspective. *Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia*, *77*, 13–16. https://doi.org/10.1016/j.jocn.2020.04.124

741. Graham, E. L., Clark, J. R., Orban, Z. S., Lim, P. H., Szymanski, A. L., Taylor, C., DiBiase, R. M., Jia, D. T., Balabanov, R., Ho, S. U., Batra, A., Liotta, E. M., & Koralnik, I. J. (2021). Persistent neurologic symptoms and cognitive dysfunction in non-hospitalized COVID-19 "long haulers". *Annals of clinical and translational neurology*, *8*(5), 1073–1085. https://doi.org/10.1002/acn3.51350

742. Tian, T., Wu, J., Chen, T., Li, J., Yan, S., Zhou, Y., Peng, X., Li, Y., Zheng, N., Cai, A., Ning, Q., Xiang, H., Xu, F., Qin, Y., Zhu, W., & Wang, J. (2022). Long-term follow-up of dynamic brain changes in patients recovered from COVID-19 without neurological manifestations. *JCI insight*, *7*(4), e155827. https://doi.org/10.1172/jci.insight.155827

743. Prakash, A., Singh, H., Sarma, P., Bhattacharyya, A., Dhibar, D. P., Balaini, N., Shree, R., Goyal, M., Modi, M., & Medhi, B. (2021). nCoV-2019 infection induced neurological outcome and manifestation, linking its historical ancestor SARS-CoV and MERS-CoV: a systematic review and meta-analysis. *Scientific reports*, *11*(1), 12888. https://doi.org/10.1038/s41598-021-92188-x

744. News Insight. (February 3, 2023). How COVID-19 affects the brain, New Scientist. https://www.newscientist.com/article/2356287-the-COVID-19-virus-gets-into-the-brain-what-does-it-do-there/

745. Bauer, L., Laksono, B. M., de Vrij, F. M. S., Kushner, S. A., Harschnitz, O., & van Riel, D. (2022). The neuroinvasiveness, neurotropism, and neurovirulence of SARS-CoV-2. *Trends in neurosciences, 45*(5), 358–368. https://doi.org/10.1016/j.tins.2022.02.006

746. Spudich, S., & Nath, A. (2022). Nervous system consequences of COVID-19. *Science (New York, N.Y.)*, *375*(6578), 267–269. https://doi.org/10.1126/science.abm2052

747. Lang, K. (2024). What do we know about COVID-19's effects on the brain? British Medical Journal. 385. https://doi.org/10.1136/bmj.q897

748. Hampshire A. (2024). Cognition and Memory after COVID-19 in a large Community Samples. NEJM. https://www.nejm.org/doi/full/10.1056/NEJMoa2311330i

749. Monje, M., & Iwasaki, A. (2022). The neurobiology of long COVIBID. *Neuron*, *110*(21), 3484–3496. https://doi.org/10.1016/j.neuron.2022.10.006

750. Fernández-Castañeda, A., Lu, P., Geraghty, A. C., Song, E., Lee, M. H., Wood, J., O'Dea, M. R., Dutton, S., Shamardani, K., Nwangwu, K., Mancusi, R., Yalçın, B., Taylor, K. R., Acosta-Alvarez, L., Malacon, K., Keough, M. B., Ni, L., Woo, P. J., Contreras-Esquivel, D., Toland, A. M. S., … Monje, M. (2022). Mild respiratory COVID can cause multi-lineage neural cell and myelin dysregulation. Cell, 185(14), 2452–2468.e16. https://doi.org/10.1016/j.cell.2022.06.008

751. Al-Aly, Z., Davis, H., McCorkell, L., Soares, L., Wulf-Hanson, S., Iwasaki, A., & Topol, E. J. (2024). Long COVID science, research and policy. Nature medicine, 30(8), 2148–2164. https://doi.org/10.1038/s41591-024-03173-6

752. Mao, L., Jin, H., Wang, M., Hu, Y., Chen, S., He, Q., Chang, J., Hong, C., Zhou, Y., Wang, D., Miao, X., Li, Y., & Hu, B. (2020). Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA neurology*, *77*(6), 683–690. https://doi.org/10.1001/jamaneurol.2020.1127

753. Romero-Sánchez, C. M., Díaz-Maroto, I., Fernández-Díaz, E., Sánchez-Larsen, Á., Layos-Romero, A., García-García, J., González, E., Redondo-Peñas, I., Perona-Moratalla, A. B., Del Valle-Pérez, J. A., Gracia-Gil, J., Rojas-Bartolomé, L., Feria-Vilar, I., Monteagudo, M., Palao, M., Palazón-García, E., Alcahut-Rodríguez, C., Sopelana-Garay, D., Moreno, Y., Ahmad, J., … Segura, T. (2020). Neurologic manifestations in hospitalized patients with COVID-19: The ALBACOVID registry. *Neurology*, *95*(8), e1060–e1070. https://doi.org/10.1212/WNL.0000000000009937

754. Graham, E. L., Clark, J. R., Orban, Z. S., Lim, P. H., Szymanski, A. L., Taylor, C., DiBiase, R. M., Jia, D. T., Balabanov, R., Ho, S. U., Batra, A., Liotta, E. M., & Koralnik, I. J. (2021). Persistent neurologic symptoms and cognitive dysfunction in non-hospitalized COVID-19 "long haulers". *Annals of clinical and translational neurology*, *8*(5), 1073–1085. https://doi.org/10.1002/acn3.51350

755. Delorme, C., Paccoud, O., Kas, A., Hesters, A., Bombois, S., Shambrook, P., Boullet, A., Doukhi, D., Le Guennec, L., Godefroy, N., Maatoug, R., Fossati, P., Millet, B., Navarro, V., Bruneteau, G., Demeret, S., Pourcher, V., & CoCo-Neurosciences study group and COVID SMIT PSL study group (2020). COVID-19-related encephalopathy: a case series with brain FDG-positron-emission tomography/computed tomography findings. *European journal of neurology*, *27*(12), 2651–2657. https://doi.org/10.1111/ene.14478

756. Graham, E. L., Clark, J. R., Orban, Z. S., Lim, P. H., Szymanski, A. L., Taylor, C., DiBiase, R. M., Jia, D. T., Balabanov, R., Ho, S. U., Batra, A., Liotta, E. M., & Koralnik, I. J. (2021). Persistent neurologic symptoms and cognitive dysfunction in non-hospitalized COVID-19 "long haulers". *Annals of clinical and translational neurology*, *8*(5), 1073–1085. https://doi.org/10.1002/acn3.51350

757. Liotta, E. M., Batra, A., Clark, J. R., Shlobin, N. A., Hoffman, S. C., Orban, Z. S., & Koralnik, I. J. (2020). Frequent neurologic manifestations and encephalopathy-associated morbidity in COVID-19 patients. *Annals of clinical and translational neurology*, *7*(11), 2221–2230. https://doi.org/10.1002/acn3.51210

758. Choudhury, N. A., Mukherjee, S., Singer, T., Venkatesh, A., Perez Giraldo, G. S., Jimenez, M., Miller, J., Lopez, M., Hanson, B. A., Bawa, A. P., Batra, A., Liotta, E. M., & Koralnik, I. J. (2024). Neurologic Manifestations of Long COVID Disproportionately Affect Young and Middle-Age Adults. *Annals of neurology*, 10.1002/ana.27128. Advance online publication. https://doi.org/10.1002/ana.27128

759. Bauer, L., Laksono, B. M., de Vrij, F. M. S., Kushner, S. A., Harschnitz, O., & van Riel, D. (2022). The neuroinvasiveness, neurotropism, and neurovirulence of SARS-CoV-2. *Trends in Neurosciences, 45*(5), 358–368. https://doi.org/10.1016/j.tins.2022.02.006

760. Eibschutz, L. S., Rabiee, B., Asadollahi, S., Gupta, A., Assadi, M., Alavi, A., & Gholamrezanezhad, A. (2022). FDG-PET/CT of COVID-19 and Other Lung Infections. *Seminars in nuclear medicine*, *52*(1), 61–70. https://doi.org/10.1053/j.semnuclmed.2021.06.017

761. Cull, O., Al Qadi, L., Stadler, J., Martin, M., El Helou, A., Wagner, J., Maillet, D., & Chamard-Witkowski, L. (2023). Radiological markers of neurological manifestations of post-acute sequelae of SARS-CoV-2 infection: a mini-review. *Frontiers in neurology*, *14*, 1233079. https://doi.org/10.3389/fneur.2023.1233079

762. Debs, P., Khalili, N., Solnes, L., Al-Zaghal, A., Sair, H. I., Yedavalli, V., & Luna, L. P. (2023). Post-COVID-19 Brain [^{18}F] FDG-PET Findings: A Retrospective Single-Center Study in the United States. *AJNR. American journal of neuroradiology*, *44*(5), 517–522. https://doi.org/10.3174/ajnr.A7863

763. Lu, Y., Li, X., Geng, D., Mei, N., Wu, P. Y., Huang, C. C., Jia, T., Zhao, Y., Wang, D., Xiao, A., & Yin, B. (2020). Cerebral Micro-Structural Changes in COVID-19 Patients - An MRI-based 3-month Follow-up Study. *EClinicalMedicine*, *25*, 100484. https://doi.org/10.1016/j.eclinm.2020.100484

764. Douaud, G., Lee, S., Alfaro-Almagro, F., Arthofer, C., Wang, C., McCarthy, P., Lange, F., Andersson, J. L. R., Griffanti, L., Duff, E., Jbabdi, S., Taschler, B., Keating, P., Winkler, A. M., Collins, R., Matthews, P. M., Allen, N., Miller, K. L., Nichols, T. E., & Smith, S. M. (2022). SARS-CoV-2 is associated with changes in brain structure in UK Biobank. *Nature*, *604*(7907), 697–707. https://doi.org/10.1038/s41586-022-04569-5

765. Id.

766. Al-Aly, Z., Davis, H., McCorkell, L., Soares, L., Wulf-Hanson, S., Iwasaki, A., & Topol, E. J. (2024). Long COVID science, research and policy. Nature medicine, 30(8), 2148–2164. https://doi.org/10.1038/s41591-024-03173-6

767. Corrigan, N. M., Rokem, A., & Kuhl, P. K. (2024). COVID-19 lockdown effects on adolescent brain structure suggest accelerated maturation that is more pronounced in females than in males. Proceedings of the National Academy of Sciences of the United States of America, 121(38), e2403200121. https://doi.org/10.1073/pnas.2403200121

768. Id.

769. Saxena, A., & Mautner, J. (2024). A Disease Hidden in Plain Sight: Pathways and Mechanisms of Neurological Complications of Post-acute Sequelae of COVID-19 (NC-PASC). *Molecular neurobiology*, 10.1007/s12035-024-04421-z. Advance online publication. https://doi.org/10.1007/s12035-024-04421-z

770. Fong, T. G., Fearing, M. A., Jones, R. N., Shi, P., Marcantonio, E. R., Rudolph, J. L., Yang, F. M., Kiely, D. K., & Inouye, S. K. (2009). Telephone interview for cognitive status: Creating a crosswalk with the Mini-Mental State Examination. Alzheimer's & dementia : the journal of the Alzheimer's Association, 5(6), 492–497. https://doi.org/10.1016/j.jalz.2009.02.007

771. Liu, Y. H., Chen, Y., Wang, Q. H., Wang, L. R., Jiang, L., Yang, Y., Chen, X., Li, Y., Cen, Y., Xu, C., Zhu, J., Li, W., Wang, Y. R., Zhang, L. L., Liu, J., Xu, Z. Q., & Wang, Y. J. (2022). One-Year Trajectory of Cognitive Changes in Older Survivors of COVID-19 in Wuhan, China: A Longitudinal Cohort Study. *JAMA neurology*, *79*(5), 509–517. https://doi.org/10.1001/jamaneurol.2022.0461

772. Al-Aly, Z., Davis, H., McCorkell, L., Soares, L., Wulf-Hanson, S., Iwasaki, A., & Topol, E. J. (2024). Long COVID science, research and policy. Nature medicine, 30(8), 2148–2164. https://doi.org/10.1038/s41591-024-03173-6

773. Saxena, A., & Mautner, J. (2024). A Disease Hidden in Plain Sight: Pathways and Mechanisms of Neurological Complications of Post-acute Sequelae of COVID-19 (NC-PASC). *Molecular neurobiology*, 10.1007/s12035-024-04421-z. Advance online publication. https://doi.org/10.1007/s12035-024-04421-z.

774. Lang, K. (2024). What do we know about COVID-19's effects on the brain? British Medical Journal. 385. https://doi.org/10.1136/bmj.q897

775. Bowe, B., Xie, Y., & Al-Aly, Z. (2023). Postacute sequelae of COVID-19 at 2 years. *Nature medicine*, *29*(9), 2347–2357. https://doi.org/10.1038/s41591-023-02521-2

776. Spudich, S., & Nath, A. (2022). Nervous system consequences of COVID-19. *Science (New York, N.Y.)*, *375*(6578), 267–269. https://doi.org/10.1126/science.abm2052

777. Davis, H. E., McCorkell, L., Vogel, J. M., & Topol, E. J. (2023). Long COVID: major findings, mechanisms and recommendations. Nature reviews. Microbiology, 21(3), 133–146. https://doi.org/10.1038/s41579-022-00846-2

778. Al-Aly, Z., Davis, H., McCorkell, L., Soares, L., Wulf-Hanson, S., Iwasaki, A., & Topol, E. J. (2024). Long COVID science, research and policy. Nature medicine, 30(8), 2148–2164. https://doi.org/10.1038/s41591-024-03173-6

779. Ding, Q., & Zhao, H. (2023). Long-term effects of SARS-CoV-2 infection on human brain and memory. *Cell death discovery*, *9*(1), 196. https://doi.org/10.1038/s41420-023-01512-z

780. Jiang, L., Li, X., Nie, J., Tang, K., & Bhutta, Z. A. (2023). A Systematic Review of Persistent Clinical Features After SARS-CoV-2 in the Pediatric Population. *Pediatrics*, *152*(2), e2022060351. https://doi.org/10.1542/peds.2022-060351

781. Harris E. (2024). Millions of US Children Experience Range of Long COVID Effects. *JAMA*, *331*(9), 726. https://doi.org/10.1001/jama.2024.0356

782. Chen, E. Y., Burton, J. M., Johnston, A., Morrow, A. K., Yonts, A. B., & Malone, L. A. (2023). Considerations in Children and Adolescents Related to Coronavirus Disease 2019 (COVID-19). *Physical medicine and rehabilitation clinics of North America*, *34*(3), 643–655. https://doi.org/10.1016/j.pmr.2023.03.004

783. Safadieh, G. H., El Majzoub, R., & Abou Abbas, L. (2024). Neuroimaging findings in children with COVID-19 infection: a systematic review and meta-analysis. *Scientific reports*, *14*(1), 4790. https://doi.org/10.1038/s41598-024-55597-2

784. Chen, E. Y., Burton, J. M., Johnston, A., Morrow, A. K., Yonts, A. B., & Malone, L. A. (2023). Considerations in Children and Adolescents Related to Coronavirus Disease 2019 (COVID-19). Physical medicine and rehabilitation clinics of North America, 34(3), 643–655. https://doi.org/10.1016/j.pmr.2023.03.004

785. Martini, A. L., Carli, G., Kiferle, L., Piersanti, P., Palumbo, P., Morbelli, S., Calcagni, M. L., Perani, D., & Sestini, S. (2022). Time-dependent recovery of brain hypometabolism in neuro-COVID-19 patients. *European journal of nuclear medicine and molecular imaging*, *50*(1), 90–102. https://doi.org/10.1007/s00259-022-05942-2

786. Martini, A. L., Carli, G., Kiferle, L., Piersanti, P., Palumbo, P., Morbelli, S., Calcagni, M. L., Perani, D., & Sestini, S. (2022). Time-dependent recovery of brain hypometabolism in neuro-COVID-19 patients. *European journal of nuclear medicine and molecular imaging*, *50*(1), 90–102. https://doi.org/10.1007/s00259-022-05942-2

787. Safadieh, G. H., El Majzoub, R., & Abou Abbas, L. (2024). Neuroimaging findings in children with COVID-19 infection: a systematic review and meta-analysis. *Scientific reports*, *14*(1), 4790. https://doi.org/10.1038/s41598-024-55597-2

788. Martini, A. L., Carli, G., Kiferle, L., Piersanti, P., Palumbo, P., Morbelli, S., Calcagni, M. L., Perani, D., & Sestini, S. (2022). Time-dependent recovery of brain hypometabolism in neuro-COVID-19 patients. *European journal of nuclear medicine and molecular imaging*, *50*(1), 90–102. https://doi.org/10.1007/s00259-022-05942-2

789. Morand, A., Campion, J. Y., Lepine, A., Bosdure, E., Luciani, L., Cammilleri, S., Chabrol, B., & Guedj, E. (2022). Similar patterns of [^{18}F]-FDG brain PET hypometabolism in paediatric and adult patients with long COVID: a paediatric case series. *European journal of nuclear medicine and molecular imaging*, *49*(3), 913–920. https://doi.org/10.1007/s00259-021-05528-4

790. Taquet, M., Sillett, R., Zhu, L., Mendel, J., Camplisson, I., Dercon, Q., & Harrison, P. J. (2022). Neurological and psychiatric risk trajectories after SARS-CoV-2 infection: an analysis of 2-year retrospective cohort studies including 1 284 437 patients. *The lancet. Psychiatry*, *9*(10), 815–827. https://doi.org/10.1016/S2215-0366(22)00260-7

791. Id.

792. Id.

793. Luedke, J. C., Vargas, G., Jashar, D. T., Malone, L. A., Morrow, A., & Ng, R. (2024). Neuropsychological functioning of pediatric patients with long COVID. The Clinical neuropsychologist, 38(8), 1855–1872. https://doi.org/10.1080/13854046.2024.2344455

794. Camporesi, A., Morello, R., La Rocca, A., Zampino, G., Vezzulli, F., Munblit, D., Raffaelli, F., Valentini, P., & Buonsenso, D. (2024). Characteristics and predictors of Long Covid in children: a 3-year prospective cohort study. EClinicalMedicine, 76, 102815. https://doi.org/10.1016/j.eclinm.2024.102815

795. Jang, E. J., Choe, Y. J., Yun, G. W., Kim, R. K., Park, S. K., Lee, J. H., Lee, K. H., Yi, S., Lee, S., & Park, Y. J. (2023). Age-specific Risk of SARS-CoV-2 Reinfection During Omicron Outbreaks, South Korea. *The Pediatric infectious disease journal*, *42*(8), e296–e297. https://doi.org/10.1097/INF.0000000000003960

796. Chow, K. N., Tsang, Y. W., Chan, Y. H., Telaga, S. A., Ng, L. Y. A., Chung, C. M., Yip, Y. M., & Cheung, P. P. H. (2024). The effect of pre-COVID and post-COVID vaccination on long COVID: a systematic review and meta-analysis. *The Journal of infection*, 106358. Advance online publication. https://doi.org/10.1016/j.jinf.2024.106358

797. US National Academies of Science (2023). Applying Lessons Learned from COVID-19 Research and Development to Future Epidemics. National Academies Press. https://doi.org/10.17226/27194

798. US Centers for Disease Control and Prevention. (2024). Child Coverage and Parental Intent for Vaccination. https://www.cdc.gov/vaccines/imz-managers/coverage/COVIDvaxview/interactive/children-coverage-vaccination.html

799. Doan-Ngyuen, D. (2023) Post-COVID Learning Losses: Children face potentially permanent setbacks. Harvard Magazine. https://www.harvardmagazine.com/2023/07/kane-COVID-learning-losses

800. Cain-Miller, C. Mervosh, S. (July 1, 2024). Pandemic-Era Babies are Behind in Basic Skills. *The New York Times.* *https://www.nytimes.com/interactive/2024/07/01/upshot/pandemic-children-school-performance.html*

801. Id.

802. Meckler, L., Lumpkin L. (July 24, 2024). Years after the pandemic upheaval, students are still losing ground. *The Washington Post.* Print version pg. A13. https://www.washingtonpost.com/education/2024/07/23/COVID-test-scores-learning-loss-absenteeism/

803. Id.

804. Cain-Miller, C. Mervosh, S. (July 1, 2024). Pandemic-Era Babies are Behind in Basic Skills. *The New York Times.* *https://www.nytimes.com/interactive/2024/07/01/upshot/pandemic-children-school-performance.html*

805. Young, E., Young K. (2024). Student Growth in the Post-COVID Era. Curriculum Associates: Research Report June 2024. https://cdn.bfldr.com/LS6J0F7/at/4rqc5wtpxqf85mk4pxj6rm7/ca-2024-summer-research-student-growth-technical-report.pdf

806. Zhu, G., Zhou, S., Xu, Y., Gao, R., Li, H., Su, W., Han, G., & Wang, R. (2022). Mendelian randomization study on the causal effects of COVID-19 on childhood intelligence. *Journal of medical virology*, *94*(7), 3233–3239. https://doi.org/10.1002/jmv.27736

807. Zhu, G., Zhou, S., Xu, Y., Gao, R., Li, H., Su, W., Han, G., & Wang, R. (2022). Mendelian randomization study on the causal effects of COVID-19 on childhood intelligence. *Journal of medical virology*, *94*(7), 3233–3239. https://doi.org/10.1002/jmv.27736

808. Hampshire, A., Azor, A., Atchison, C., Trender, W., Hellyer, P. J., Giunchiglia, V., Husain, M., Cooke, G. S., Cooper, E., Lound, A., Donnelly, C. A., Chadeau-Hyam, M., Ward, H., & Elliott, P. (2024). Cognition and Memory after COVID-19 in a Large Community Sample. *The New England journal of medicine*, *390*(9), 806–818. https://doi.org/10.1056/NEJMoa2311330

809. Maccio, U., Zinkernagel, A. S., Schuepbach, R., Probst-Mueller, E., Frontzek, K., Brugger, S. D., Hofmaenner, D. A., Moch, H., & Varga, Z. (2022). Long-Term Persisting SARS-CoV-2 RNA and Pathological Findings: Lessons Learnt From a Series of 35 COVID-19 Autopsies. *Frontiers in medicine*, *9*, 778489. https://doi.org/10.3389/fmed.2022.778489

810. Fabbri, V. P., Riefolo, M., Lazzarotto, T., Gabrielli, L., Cenacchi, G., Gallo, C., Aspide, R., Frascaroli, G., Liguori, R., Lodi, R., Tonon, C., D'Errico, A., & Foschini, M. P. (2022). COVID-19 and the Brain: The Neuropathological Italian Experience on 33 Adult Autopsies. *Biomolecules*, *12*(5), 629. https://doi.org/10.3390/biom12050629

811. Stewart, R., Yan, K., Ellis, S. A., Bishop, C. R., Dumenil, T., Tang, B., Nguyen, W., Larcher, T., Parry, R., Sng, J. J., Khromykh, A. A., Sullivan, R. K. P., Lor, M., Meunier, F. A., Rawle, D. J., & Suhrbier, A. (2023). SARS-CoV-2 omicron BA.5 and XBB variants have increased neurotropic potential over BA.1 in K18-hACE2 mice and human brain organoids. *Frontiers in microbiology*, *14*, 1320856. https://doi.org/10.3389/fmicb.2023.1320856

812. Proust, A., Queval, C. J., Harvey, R., Adams, L., Bennett, M., & Wilkinson, R. J. (2023). Differential effects of SARS-CoV-2 variants on central nervous system cells and blood-brain barrier functions. *Journal of neuroinflammation*, *20*(1), 184. https://doi.org/10.1186/s12974-023-02861-3

813. Rutkai, I., Mayer, M. G., Hellmers, L. M., Ning, B., Huang, Z., Monjure, C. J., Coyne, C., Silvestri, R., Golden, N., Hensley, K., Chandler, K., Lehmicke, G., Bix, G. J., Maness, N. J., Russell-Lodrigue, K., Hu, T. Y., Roy, C. J., Blair, R. V., Bohm, R., Doyle-Meyers, L. A., … Fischer, T. (2022). Neuropathology and virus in brain of SARS-CoV-2 infected non-human primates. *Nature communications*, *13*(1), 1745. https://doi.org/10.1038/s41467-022-29440-z

814. Id.

815. Nieuwland, J. M., Nutma, E., Philippens, I. H. C. H. M., Böszörményi, K. P., Remarque, E. J., Bakker, J., Meijer, L., Woerdman, N., Fagrouch, Z. C., Verstrepen, B. E., Langermans, J. A. M., Verschoor, E. J., Windhorst, A. D., Bontrop, R. E., de Vries, H. E., Stammes, M. A., & Middeldorp, J. (2023). Longitudinal positron emission tomography and postmortem analysis reveals widespread neuroinflammation in SARS-CoV-2 infected rhesus macaques. *Journal of neuroinflammation*, *20*(1), 179. https://doi.org/10.1186/s12974-023-02857-z

816. Romoli, M., Jelcic, I., Bernard-Valnet, R., García Azorín, D., Mancinelli, L., Akhvlediani, T., Monaco, S., Taba, P., Sellner, J., & Infectious Disease Panel of the European Academy of Neurology (2020). A systematic review of neurological manifestations of SARS-CoV-2 infection: the devil is hidden in the details. *European journal of neurology*, *27*(9), 1712–1726. https://doi.org/10.1111/ene.14382

817. Fabbri, V. P., Riefolo, M., Lazzarotto, T., Gabrielli, L., Cenacchi, G., Gallo, C., Aspide, R., Frascaroli, G., Liguori, R., Lodi, R., Tonon, C., D'Errico, A., & Foschini, M. P. (2022). COVID-19 and the Brain: The Neuropathological Italian Experience on 33 Adult Autopsies. *Biomolecules*, *12*(5), 629. https://doi.org/10.3390/biom12050629

818. Xu, Z., Shi, L., Wang, Y., Zhang, J., Huang, L., Zhang, C., Liu, S., Zhao, P., Liu, H., Zhu, L., Tai, Y., Bai, C., Gao, T., Song, J., Xia, P., Dong, J., Zhao, J., & Wang, F. S. (2020). Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *The Lancet. Respiratory medicine*, *8*(4), 420–422. https://doi.org/10.1016/S2213-2600(20)30076-X

819. Yao, X. H., Li, T. Y., He, Z. C., Ping, Y. F., Liu, H. W., Yu, S. C., Mou, H. M., Wang, L. H., Zhang, H. R., Fu, W. J., Luo, T., Liu, F., Guo, Q. N., Chen, C., Xiao, H. L., Guo, H. T., Lin, S., Xiang, D. F., Shi, Y., Pan, G. Q., … Bian, X. W. (2020). *Zhonghua bing li xue za zhi = Chinese journal of pathology*, *49*(5), 411–417. https://doi.org/10.3760/cma.j.cn112151-20200312-00193

820. Bassat, Q., Varo, R., Hurtado, J. C., Marimon, L., Ferrando, M., Ismail, M. R., Carrilho, C., Fernandes, F., Castro, P., Maixenchs, M., Rodrigo-Calvo, M. T., Guerrero, J., Martínez, A., Lacerda, M. V. G., Mandomando, I., Menéndez, C., Martinez, M. J., Ordi, J., & Rakislova, N. (2021). Minimally Invasive Tissue Sampling as an Alternative to Complete Diagnostic Autopsies in the Context of Epidemic Outbreaks and Pandemics: The Example of Coronavirus Disease 2019 (COVID-19). *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, *73*(Suppl_5), S472–S479. https://doi.org/10.1093/cid/ciab760

821. Reid, T., et al. (2022). Senator Rubio COVID-19 Origins Report: "A Complex and Grave Situation": A Political Chronology of the SARS_CoV-2 Outbreak. https://www.rubio.senate.gov/wp-content/uploads/_cache/files/790b6d70-7150-4f0f-a8b9-01ea45d3b1d1/EAB44A6CA6190D31041C0037E9C5E589.05.01.23-origin-report-clean-v1-11.pdf

822. National Health Commission ff The People's Republic Of China (2020). Laboratory biosafety guide for 2019-nCoV (Second Edition). *Biosafety and health*, *2*(1), 1–2. https://doi.org/10.1016/j.bsheal.2020.01.001

823. Rong, Z., Mai, H., Ebert, G., Kapoor, S., Puelles, V.G., et al. (2024). Persistence of spike protein at the skull-meninges-brain axis may contribute to the neurological sequelae of COVID-19. Cell Host & Microbe. 32, 1-19. https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(24)00438-4

824. Pluim, J. M. E., Jimenez-Bou, L., Gerretsen, R. R. R., & Loeve, A. J. (2018). Aerosol production during autopsies: The risk of sawing in bone. *Forensic science international*, *289*, 260–267. https://doi.org/10.1016/j.forsciint.2018.05.046

825. Kantonen, J. N., Kuivanen, S., Smura, T., Puttonen, H., Kekäläinen, E., Sajantila, A....Carpén, O. (2024). Infective SARS-CoV-2 in Skull Sawdust at Autopsy, Finland. *Emerging Infectious Diseases*, *30*(8), 1735-1737. https://doi.org/10.3201/eid3008.240145.

826. Qin, A., & Buckley, C. (2021). A top virologist in China, at center of a pandemic storm, speaks out. *New York Times.* https://www.nytimes.com/2021/06/14/world/asia/china-COVID-wuhan-lab-leak.html

827. Bian, X. W., & COVID-19 Pathology Team (2020). Autopsy of COVID-19 patients in China. *National science review*, *7*(9), 1414–1418. https://doi.org/10.1093/nsr/nwaa123

828. Id.

829. Id.

830. Id.

831. Id.

832. Bryce, C., Grimes, Z., Pujadas, E., Ahuja, S., Beasley, M. B., Albrecht, R., Hernandez, T., Stock, A., Zhao, Z., AlRasheed, M. R., Chen, J., Li, L., Wang, D., Corben, A., Haines, G. K., 3rd, Westra, W. H., Umphlett, M., Gordon, R. E., Reidy, J., Petersen, B., ... Fowkes, M. E. (2021). Pathophysiology of SARS-CoV-2: the Mount Sinai COVID-19 autopsy experience. *Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc*, *34*(8), 1456–1467. https://doi.org/10.1038/s41379-021-00793-y

833. Thakur, K. T., Miller, E. H., Glendinning, M. D., Al-Dalahmah, O., Banu, M. A., Boehme, A. K., Boubour, A. L., Bruce, S. S., Chong, A. M., Claassen, J., Faust, P. L., Hargus, G., Hickman, R. A., Jambawalikar, S., Khandji, A. G., Kim, C. Y., Klein, R. S., Lignelli-Dipple, A., Lin, C. C., Liu, Y., ... Canoll, P. (2021). COVID-19 neuropathology at Columbia University Irving Medical Center/New York Presbyterian Hospital. *Brain : a journal of neurology*, *144*(9), 2696–2708. https://doi.org/10.1093/brain/awab148

834. Id.

835. Dheen, S. T., Kaur, C., & Ling, E. A. (2007). Microglial activation and its implications in the brain diseases. *Current medicinal chemistry*, *14*(11), 1189–1197. https://doi.org/10.2174/092986707780597961

836. Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., Qiu, Y., Wang, J., Liu, Y., Wei, Y., Xia, J., Yu, T., Zhang, X., & Zhang, L. (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet (London, England)*, *395*(10223), 507–513. https://doi.org/10.1016/S0140-6736(20)30211-7

837. Guan, W. J., Ni, Z. Y., Hu, Y., Liang, W. H., Ou, C. Q., He, J. X., Liu, L., Shan, H., Lei, C. L., Hui, D. S. C., Du, B., Li, L. J., Zeng, G., Yuen, K. Y., Chen, R. C., Tang, C. L., Wang, T., Chen, P. Y., Xiang, J., Li, S. Y., … China Medical Treatment Expert Group for COVID-19 (2020). Clinical Characteristics of Coronavirus Disease 2019 in China. *The New England journal of medicine*, *382*(18), 1708–1720. https://doi.org/10.1056/NEJMoa2002032

838. Yang, Y., Peng, F., Wang, R., Yange, M., Guan, K., Jiang, T., Xu, G., Sun, J., & Chang, C. (2020). The deadly coronaviruses: The 2003 SARS pandemic and the 2020 novel coronavirus epidemic in China. *Journal of autoimmunity*, *109*, 102434. https://doi.org/10.1016/j.jaut.2020.102434

839. Mao, L., Jin, H., Wang, M., Hu, Y., Chen, S., He, Q., Chang, J., Hong, C., Zhou, Y., Wang, D., Miao, X., Li, Y., & Hu, B. (2020). Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA neurology*, *77*(6), 683–690. https://doi.org/10.1001/jamaneurol.2020.1127

840. Id.

841. Yu, C., Lei, Q., Li, W., Wang, X., Li, W., & Liu, W. (2020). Epidemiological and clinical characteristics of 1663 hospitalized patients infected with COVID-19 in Wuhan, China: a single-center experience. *Journal of infection and public health*, *13*(9), 1202–1209. https://doi.org/10.1016/j.jiph.2020.07.002

842. Zhan, T., Liu, M., Tang, Y., Han, Z., Cheng, X., Deng, J., Chen, X., Tian, X., & Huang, X. (2020). Retrospective analysis of clinical characteristics of 405 patients with COVID-19. *The Journal of international medical research*, *48*(8), 300060520949039. https://doi.org/10.1177/0300060520949039

843. Hu, B., Guo, H., Zhou, P., & Shi, Z. L. (2021). Characteristics of SARS-CoV-2 and COVID-19. *Nature reviews. Microbiology*, *19*(3), 141–154. https://doi.org/10.1038/s41579-020-00459-7

844. Liotta, E. M., Batra, A., Clark, J. R., Shlobin, N. A., Hoffman, S. C., Orban, Z. S., & Koralnik, I. J. (2020). Frequent neurologic manifestations and encephalopathy-associated morbidity in COVID-19 patients. *Annals of clinical and translational neurology*, *7*(11), 2221–2230. https://doi.org/10.1002/acn3.51210

845. Id.

846. Romero-Sánchez, C. M., Díaz-Maroto, I., Fernández-Díaz, E., Sánchez-Larsen, Á., Layos-Romero, A., García-García, J., González, E., Redondo-Peñas, I., Perona-Moratalla, A. B., Del Valle-Pérez, J. A., Gracia-Gil, J., Rojas-Bartolomé, L., Feria-Vilar, I., Monteagudo, M., Palao, M., Palazón-García, E., Alcahut-Rodríguez, C., Sopelana-Garay, D., Moreno, Y., Ahmad, J., … Segura, T. (2020). Neurologic manifestations in hospitalized patients with COVID-19: The ALBACOVID registry. *Neurology*, *95*(8), e1060–e1070. https://doi.org/10.1212/WNL.0000000000009937

847. Gan, N., Hu, C., Watson I. (April 16, 2020). Beijing tightens grip over coronavirus research, amid US-China row on virus origin. https://www.cnn.com/2020/04/12/asia/china-coronavirus-research-restrictions-intl-hnk/index.html#

848. Japan Forward. (2021). China Destroyed Incriminating Documents on Gross Mishandling of Wuhan Virus. https://japan-forward.com/china-destroyed-incriminating-documents-on-gross-mishandling-of-wuhan-virus/

849. O'Connor, T., (2020). China acknowledges destroying early coronavirus samples, confirming US accusation. Newsweek. https://www.newsweek.com/china-acknowledges-destroying-early-coronavirus-samples-confirming-us-accusation-1504484

850. Kang, D., Cheng, M. McNeil S. (2020). "China clamps down in hidden hunt for coronavirus." Associated Press. https://apnews.com/article/united-nations-coronavirus-pandemic-china-only-on-ap-bats-24fbadc58cee3a40bca2ddf7a14d2955

851. Liu, P., Chen, W., & Chen, J. P. (2019). Viral Metagenomics Revealed Sendai Virus and Coronavirus Infection of Malayan Pangolins (*Manis javanica*). *Viruses*, *11*(11), 979. https://doi.org/10.3390/v11110979

852. Zhang, S., Qiao, S., Yu, J., Zeng, J., Shan, S., Tian, L., Lan, J., Zhang, L., & Wang, X. (2021). Bat and pangolin coronavirus spike glycoprotein structures provide insights into SARS-CoV-2 evolution. *Nature communications*, *12*(1), 1607. https://doi.org/10.1038/s41467-021-21767-3

853. Liu, M. Q., Lin, H. F., Li, J., Chen, Y., Luo, Y., Zhang, W., Hu, B., Tian, F. J., Hu, Y. J., Liu, Y. J., Jiang, R. D., Gong, Q. C., Li, A., Guo, Z. S., Li, B., Yang, X. L., Tong, Y. G., & Shi, Z. L. (2023). A SARS-CoV-2-Related Virus from Malayan Pangolin Causes Lung Infection without Severe Disease in Human ACE2-Transgenic Mice. *Journal of virology*, *97*(2), e0171922. https://doi.org/10.1128/jvi.01719-22

854. Guo, Z., Zhang, C., Zhang, C., Cui, H., Chen, Z., Jiang, X., Wang, T., Li, Y., Liu, J., Wan, Z., Meng, K., Li, J., Tong, Y., & Gao, Y. (2022). SARS-CoV-2-related pangolin coronavirus exhibits similar infection characteristics to SARS-CoV-2 and direct contact transmissibility in hamsters. *iScience*, *25*(6), 104350. https://doi.org/10.1016/j.isci.2022.104350

855. Id.

856. Liu, M. Q., Lin, H. F., Li, J., Chen, Y., Luo, Y., Zhang, W., Hu, B., Tian, F. J., Hu, Y. J., Liu, Y. J., Jiang, R. D., Gong, Q. C., Li, A., Guo, Z. S., Li, B., Yang, X. L., Tong, Y. G., & Shi, Z. L. (2023). A SARS-CoV-2-Related Virus from Malayan Pangolin Causes Lung Infection without Severe Disease in Human ACE2-Transgenic Mice. *Journal of virology*, *97*(2), e0171922. https://doi.org/10.1128/jvi.01719-22

857. Guo, Z., Zhang, C., Zhang, C., Cui, H., Chen, Z., Jiang, X., Wang, T., Li, Y., Liu, J., Wan, Z., Meng, K., Li, J., Tong, Y., & Gao, Y. (2022). SARS-CoV-2-related pangolin coronavirus exhibits similar infection characteristics to SARS-CoV-2 and direct contact transmissibility in hamsters. *iScience*, *25*(6), 104350. https://doi.org/10.1016/j.isci.2022.104350

858. An, X., Lu, J., Huang, J. D., Zhang, B., Liu, D., Zhang, X., Chen, J., Zhou, Y., & Tong, Y. (2007). Rapid assembly of multiple-exon cDNA directly from genomic DNA. *PloS one*, *2*(11), e1179. https://doi.org/10.1371/journal.pone.0001179

859. Li, H., Sheng, C., Liu, H., Liu, G., Du, X., Du, J., Zhan, L., Li, P., Yang, C., Qi, L., Wang, J., Yang, X., Jia, L., Xie, J., Wang, L., Hao, R., Xu, D., Tong, Y., Zhou, Y., Zhou, J., ... Song, H. (2016). An Effective Molecular Target Site in Hepatitis B Virus S Gene for Cas9 Cleavage and Mutational Inactivation. *International journal of biological sciences*, *12*(9), 1104–1113. https://doi.org/10.7150/ijbs.16064

860. Zhang, B., Ran, D., Zhang, X., An, X., Shan, Y., Zhou, Y., & Tong, Y. (2009). *Sheng wu gong cheng xue bao = Chinese journal of biotechnology*, *25*(2), 306–312.

861. Bruttel, V., Washburne, A., VanDongen, A. (2022).Endonuclease fingerprint indicates a synthetic origin of SARS-CoV-2 bioRxiv10.18.512756; doi: https://doi.org/10.1101/2022.10.18.512756

862. Lu, S., Luo, S., Liu, C., Li, M., An, X., Li, M., Hou, J., Fan, H., Mao, P., Tong, Y., & Song, L. (2023). Induction of significant neutralizing antibodies against SARS-CoV-2 by a highly attenuated pangolin coronavirus variant with a 104nt deletion at the 3'-UTR. *Emerging microbes & infections*, *12*(1), 2151383. https://doi.org/10.1080/22221751.2022.2151383

863. Sun S-H, Chen Q, Gu H-J, Yang G, Wang Y-X, X-Y H, Liu S-S, Zhang N-N, Li X-F, Xiong R, Guo Y, Deng Y-Q, Huang W-J, Liu Q, Liu Q-M, Shen Y-L, Zhou Y, Yang X, Zhao T-Y, Fan C-F, Zhou Y-S, Qin C-F, Wang Y-C. (2020). A mouse model of SARS-CoV-2 infection and pathogenesis. Cell Host and Microbe. 28, 124-133. https://doi.org/10.1016/j.chom.2020.05.020

864. Xiong, R., Lu, J-J., Nie, J-H., Liu, Q-M., Fan, C-A. (February 29, 2020) Advances in coronavirus animal models and potential small animal models susceptible for 2019-nCoV. Infect Dis Info, Vol. 33, No. 1

865. Sun S-H, Chen Q, Gu H-J, Yang G, Wang Y-X, X-Y H, Liu S-S, Zhang N-N, Li X-F, Xiong R, Guo Y, Deng Y-Q, Huang W-J, Liu Q, Liu Q-M, Shen Y-L, Zhou Y, Yang X, Zhao T-Y, Fan C-F, Zhou Y-S, Qin C-F, Wang Y-C. (2020). A mouse model of SARS-CoV-2 infection and pathogenesis. Cell Host and Microbe. 28, 124-133. https://doi.org/10.1016/j.chom.2020.05.020

866. Wei, L., Liu S., Lu S., Luo, S., An, X., Fan, H., Chen W-W., Li, E, Tong, Y., Song, L. (2024). An infection and pathogenesis mouse model of SARS-CoV-2-related pangolin coronavirus GX_P2V(short_3UTR). bioRxiv 2024.01.03.574008; https://www.biorxiv.org/content/10.1101/2024.01.03.574008v2

867. Lam, T.TY., Jia, N., Zhang, YW. *et al.* Identifying SARS-CoV-2-related coronaviruses in Malayan pangolins. *Nature* **583**, 282–285 (2020). https://doi.org/10.1038/s41586-020-2169-0

868. Id.

869. Coutard, B., Valle, C., de Lamballerie, X., Canard, B., Seidah, N. G., & Decroly, E. (2020). The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. *Antiviral research*, *176*, 104742. https://doi.org/10.1016/j.antiviral.2020.104742

870. Lam, T.TY., Jia, N., Zhang, YW. *et al.* Identifying SARS-CoV-2-related coronaviruses in Malayan pangolins. *Nature* **583**, 282–285 (2020). https://doi.org/10.1038/s41586-020-2169-0

871. Zhang, S. Y., Luo, Y. P., Huang, D. D., Fan, H., Lu, Q. B., Wo, Y., Chen, G., Zhang, X. A., Li, Y., Tong, Y. G., Cao, W. C., & Liu, W. (2016). Fatal pneumonia cases caused by human adenovirus 55 in immunocompetent adults. *Infectious diseases (London, England)*, *48*(1), 40–47. https://doi.org/10.3109/23744235.2015.1055585

872. Bruttel, V., Washburne, A., VanDongen, A. (2022).Endonuclease fingerprint indicates a synthetic origin of SARS-CoV-2 bioRxiv10.18.512756; doi: https://doi.org/10.1101/2022.10.18.512756

873. Wu F. (2023). Updated analysis to reject the laboratory-engineering hypothesis of SARS-CoV-2. Environmental research, 224, 115481. https://doi.org/10.1016/j.envres.2023.115481

874. Patino-Galindo, J., Garcia-Sastre, A., Kuhn J.H., Rabadan, R., Palacios, G. (2024). Recombination across distant coronaviradid species and genera is a rare event with distinct genomic features. Journal of Virology. https://doi.org/10.1128/jvi.01100-24

875. Id.

876. Lam, T.TY., Jia, N., Zhang, YW. *et al.* Identifying SARS-CoV-2-related coronaviruses in Malayan pangolins. *Nature* **583**, 282–285 (2020). https://doi.org/10.1038/s41586-020-2169-0

877. Frolova, E. I., Palchevska, O., Lukash, T., Dominguez, F., Britt, W., & Frolov, I. (2022). Acquisition of Furin Cleavage Site and Further SARS-CoV-2 Evolution Change the Mechanisms of Viral Entry, Infection Spread, and Cell Signaling. *Journal of virology*, *96*(15), e0075322. https://doi.org/10.1128/jvi.00753-22

878. Beaudoin, C. A., Hamaia, S. W., Huang, C. L., Blundell, T. L., & Jackson, A. P. (2021). Can the SARS-CoV-2 Spike Protein Bind Integrins Independent of the RGD Sequence?. Frontiers in cellular and infection microbiology, 11, 765300. https://doi.org/10.3389/fcimb.2021.765300

879. Yang, Y., Peng, F., Wang, R., Yange, M., Guan, K., Jiang, T., Xu, G., Sun, J., & Chang, C. (2020). The deadly coronaviruses: The 2003 SARS pandemic and the 2020 novel coronavirus epidemic in China. *Journal of autoimmunity*, *109*, 102434.

880. Id.

881. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. (2020). Vital Surveillances: The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) — China, 2020. China Center for Disease Control and Prevention. https://weekly.chinacdc.cn/article/id/e53946e2-c6c4-41e9-9a9b-fea8db1a8f51

882. Kania, E.B. (2020). Minds at War China's Pursuit of Military Advantage through Cognitive Science and Biotechnology. National Defense University Press. https://ndupress.ndu.edu/Portals/68/Documents/prism/prism_8-3/prism_8-3_Kania_82-101.pdf

883. Id.

884. Jin, H., Hou, L. J., & Wang, Z. G. (2018). Military Brain Science - How to influence future wars. *Chinese journal of traumatology = Zhonghua chuang shang za zhi*, *21*(5), 277–280. https://doi.org/10.1016/j.cjtee.2018.01.006

885. Leist, S. R., Dinnon, K. H., 3rd, Schäfer, A., Tse, L. V., Okuda, K., Hou, Y. J., West, A., Edwards, C. E., Sanders, W., Fritch, E. J., Gully, K. L., Scobey, T., Brown, A. J., Sheahan, T. P., Moorman, N. J., Boucher, R. C., Gralinski, L. E., Montgomery, S. A., & Baric, R. S. (2020). A Mouse-Adapted SARS-CoV-2 Induces Acute Lung Injury and Mortality in Standard Laboratory Mice. *Cell*, *183*(4), 1070–1085.e12. https://doi.org/10.1016/j.cell.2020.09.050

886. Amruta, N., Ismael, S., Leist, S. R., Gressett, T. E., Srivastava, A., Dinnon, K. H., 3rd, Engler-Chiurazzi, E. B., Maness, N. J., Qin, X., Kolls, J. K., Baric, R. S., & Bix, G. (2022). Mouse Adapted SARS-CoV-2 (MA10) Viral Infection Induces Neuroinflammation in Standard Laboratory Mice. *Viruses*, *15*(1), 114. https://doi.org/10.3390/v15010114

887. Rutkai, I., Mayer, M. G., Hellmers, L. M., Ning, B., Huang, Z., Monjure, C. J., Coyne, C., Silvestri, R., Golden, N., Hensley, K., Chandler, K., Lehmicke, G., Bix, G. J., Maness, N. J., Russell-Lodrigue, K., Hu, T. Y., Roy, C. J., Blair, R. V., Bohm, R., Doyle-Meyers, L. A., ... Fischer, T. (2022). Neuropathology and virus in brain of SARS-CoV-2 infected non-human primates. *Nature communications*, *13*(1), 1745. https://doi.org/10.1038/s41467-022-29440-z

888. Saxena, A., & Mautner, J. (2024). A Disease Hidden in Plain Sight: Pathways and Mechanisms of Neurological Complications of Post-acute Sequelae of COVID-19 (NC-PASC). *Molecular neurobiology*, 10.1007/s12035-024-04421-z. Advance online publication. https://doi.org/10.1007/s12035-024-04421-z

889. Cull, O., Al Qadi, L., Stadler, J., Martin, M., El Helou, A., Wagner, J., Maillet, D., & Chamard-Witkowski, L. (2023). Radiological markers of neurological manifestations of post-acute sequelae of SARS-CoV-2 infection: a mini-review. *Frontiers in neurology*, *14*, 1233079. https://doi.org/10.3389/fneur.2023.1233079

890. Choudhury, N. A., Mukherjee, S., Singer, T., Venkatesh, A., Perez Giraldo, G. S., Jimenez, M., Miller, J., Lopez, M., Hanson, B. A., Bawa, A. P., Batra, A., Liotta, E. M., & Koralnik, I. J. (2024). Neurologic Manifestations of Long COVID Disproportionately Affect Young and Middle-Age Adults. *Annals of neurology*, 10.1002/ana.27128. Advance online publication. https://doi.org/10.1002/ana.27128

891. Cain-Miller, C. Mervosh, S. (July 1, 2024). Pandemic-Era Babies are Behind in Basic Skills. *The New York Times.* https://www.nytimes.com/interactive/2024/07/01/upshot/pandemic-children-school-performance.html

892. Young, E., Young K. (2024). Student Growth in the Post-COVID Era. Curriculum Associates: Research Report June 2024. https://cdn.bfldr.com/LS6J0F7/at/4rqc5wtpxqf85mk4pxj6rm7/ca-2024-summer-research-student-growth-technical-report.pdf

893. Meckler, L., Lumpkin L. (July 24, 2024). Years after the pandemic upheaval, students are still losing ground. *The Washington Post.* Print version pg. A13. https://www.washingtonpost.com/education/2024/07/23/COVID-test-scores-learning-loss-absenteeism/

894. Al-Aly, Z., Davis, H., McCorkell, L., Soares, L., Wulf-Hanson, S., Iwasaki, A., & Topol, E. J. (2024). Long COVID science, research and policy. Nature medicine, 30(8), 2148–2164. https://doi.org/10.1038/s41591-024-03173-6

895. Chow, K. N., Tsang, Y. W., Chan, Y. H., Telaga, S. A., Ng, L. Y. A., Chung, C. M., Yip, Y. M., & Cheung, P. P. H. (2024). The effect of pre-COVID and post-COVID vaccination on long COVID: a systematic review and meta-analysis. *The Journal of infection*, 106358. Advance online publication. https://doi.org/10.1016/j.jinf.2024.106358

896. Kim, S. A., Maeda, M., Murata, F., & Fukuda, H. (2024). Effect of COVID-19 vaccination on the risk of developing post-COVID conditions: The VENUS study. *Vaccine*, *43*(Pt 2), 126497. Advance online publication. https://doi.org/10.1016/j.vaccine.2024.126497

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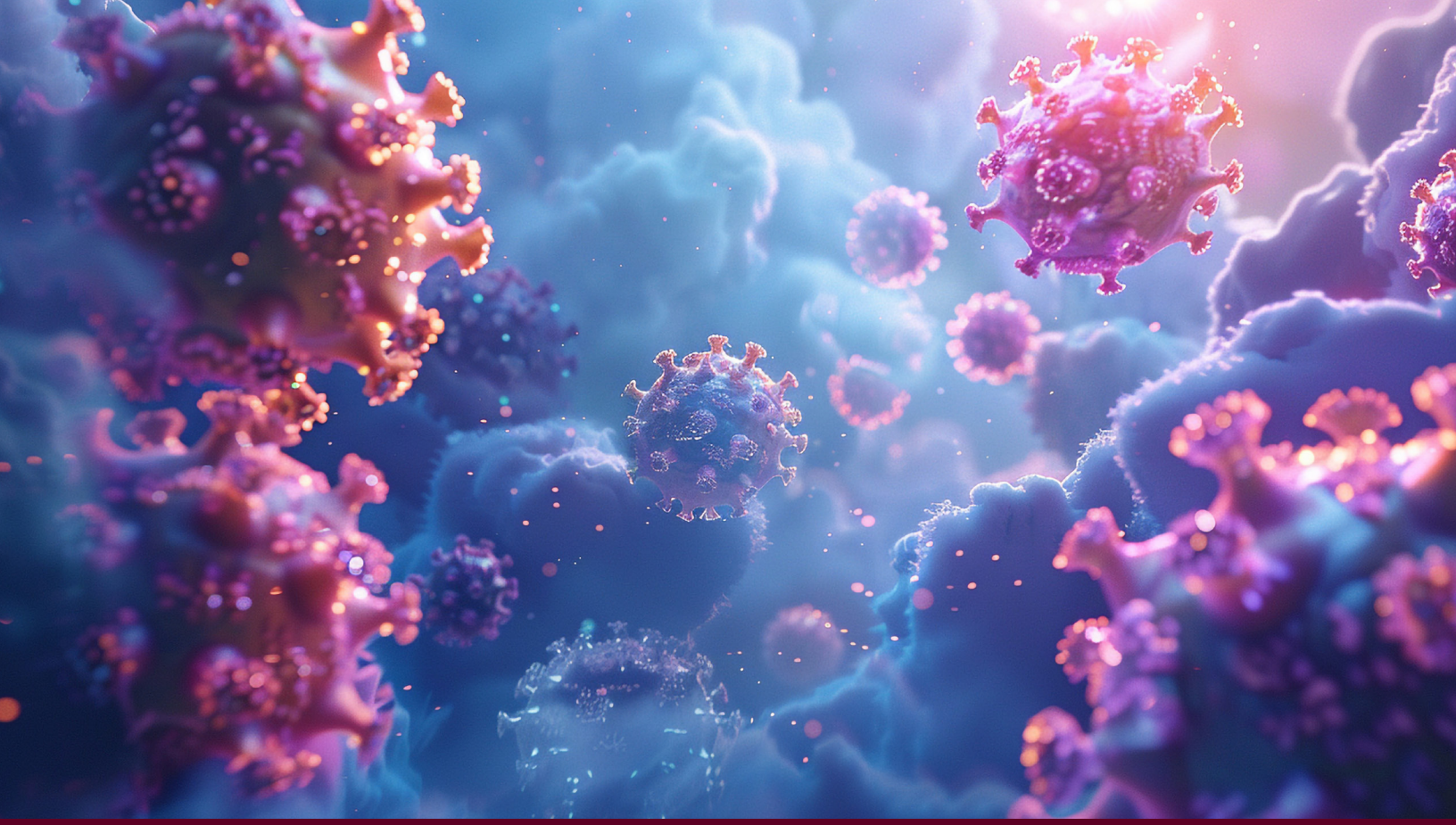

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