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

MUDDY WATERS UPDATE: FIRST INSTALLMENT

WRITTEN BY

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Note: The original version of this document was published on September 25, 2024. Several edits have been made to the text to incorporate recent scientific findings, improve the text's clarity, and fix technical errors. Two errors merit a brief explanation. The original draft incorrectly characterized the RGD amino acid sequence on the SARS-CoV-2 spike protein as an integrin "receptor" rather than a motif that can bind to integrins, which are themselves cell-surface receptors. The original draft also incorrectly stated that the central air renovation at the Wuhan Institute of Virology procurement contract was issued for $55.1M USD. The correct number is $550k. The current version, published December 12,2024, is updated and corrects both errors.

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 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 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 receptor, 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 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 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. The sequences did not show evidence of animal adaptation, even though DNA from susceptible animals was found co-mingled with environmental samples. 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, 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, or 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 suggest an interest in the vaccine's protection against SARS-CoV-2 early in the outbreak before

evidence of its neurological effects were 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. 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, point to studies evaluating countermeasures to protect against a novel coronavirus' neurological affects 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 about 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 the focus of a military research program. This is an assessment first raised by a 2022 House Permanent Select Committee on Intelligence (HPSCI) 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.

Part II, which is forthcoming in the second installment, will attempt 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 will also try 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, determination.

This paper's 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 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, published on December 12, 2024, is an updated version of the first installment. Part II will be released in a second installment expected in early January 2025.

Part I

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 the subject. 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 reports 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] 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.[146] Epidemiological investigations later determined that SARS-1 infected palm civets that were held in unhygienic conditions and sold at several animal markets.[147] Conditions described at the Wuhan Huanan market prior to the onset of the COVID-19 pandemic indicated that

susceptible intermediate animal species were 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.[148,149] 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 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.[150] 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.[151] 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.[152]

The 2012 outbreak of the SARS-related Middle East Respiratory Syndrome (MERS) also followed this precedent. The clinical spectrum of MERS is wide ranging from mild to severe fatal disease.[153] For MERS, the presumed intermediate host, dromedary camels (*C. dromedarius*), was quickly identified. Humans became infected by contact with camels or their products.[154] 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.[155] 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.[156]

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 US 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."[157]

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.[158] Eight out of the first 12 cases had no epidemiological link to the market.[159,160]

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.[161] Serological studies detected anti-MERS antibodies in the blood of camel handlers, demonstrating a similar occupational risk of MERS exposure and infection.[162]

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."[163] 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.[164]

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."[165] 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."[166]

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.[167] 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.[168] The study found that several susceptible intermediate species were sold at the market including palm civets, racoon 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.[169] 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. As described, the "government bought them up and had them all killed."[170] 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.[171] As described, killing and disinfecting before testing "made it much harder—perhaps even impossible" to identify an animal origin.[172]

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."[173] They tested the "unsold contents of refrigerators and freezers, swabs from stray animals, and the contents of a fish tank."[174,175]

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 isolate HCoV-19/Wuhan/IVDC-HB-01/2019.[176] 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.[177,178]

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.[179]

SARS-CoV-2 genetic adaptation has been seen in sequences recovered from human infected mink that then spread to other mink in Denmark.[180] 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."[181] 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."[182] 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."[183] 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."[184] 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.[185] 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.[186]

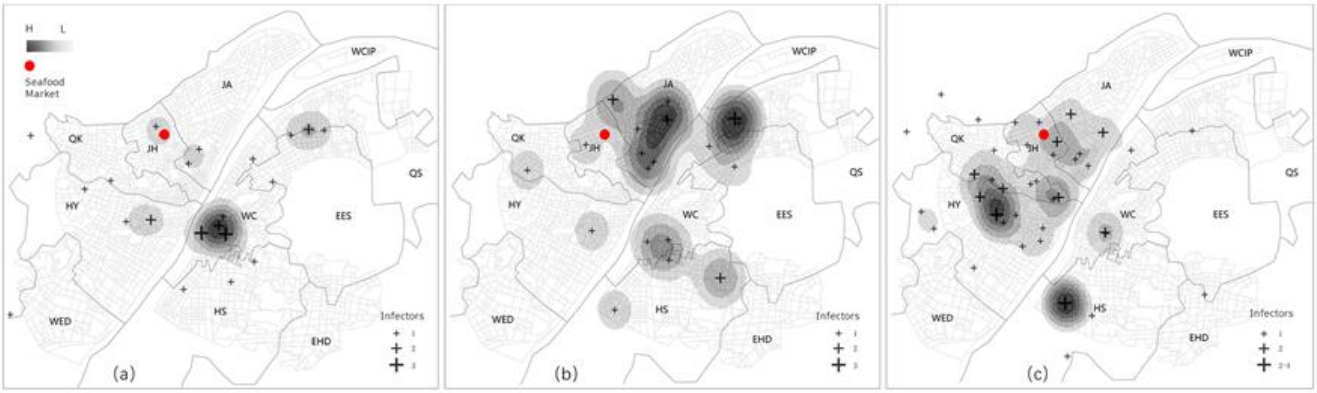
Review of Additional Spatiotemporal Evidence

As Zhengli Shi noted, “the Huanan seafood market may just be a crowded location where a cluster of early novel coronavirus patients were found.”[187] 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.”[188,189,190] 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.[191,192] 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.[193] 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.”[194] Further, neither spatial statistical analysis could support or refute the zoonotic hypothesis.[195]

The authors of the 2022 *Science* article referenced a 2020 study from the Wuhan School of Urban Design.[196] They also analyzed social media geotagged location requests for medical help on China’s microblogging platform Sina Weibo.[197] 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.[198] The early outbreaks occurred in several neighborhoods nearly simultaneously.[199] 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).[200]

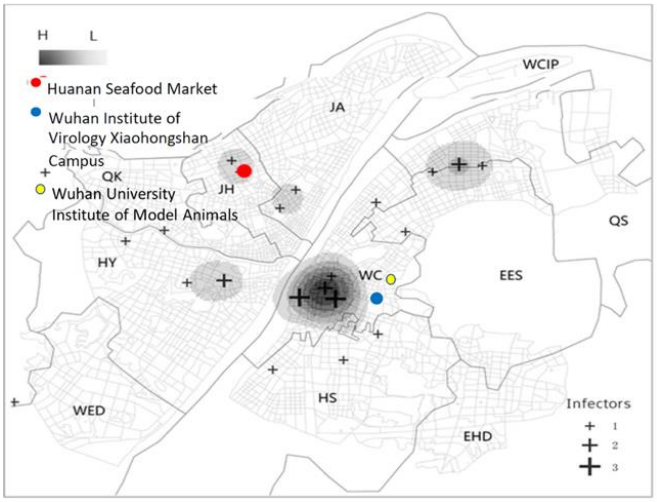


Figure 2. **Chinese social media Begins to See an Increase in Requests for Help for Medical Treatments in Wuchang District, Wuhan December 20, 2019-January 18, 2020.** Density of social media requests and locations of the Huanan Seafood Market, WIV Xiaohongshan Campus and Wuhan University Institute of 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%).[201] The highest new cases occurred in Wuchang (new cases: 4240) and Hongshan (new cases: 3853) during the second period (Jan 23 to Feb 4).

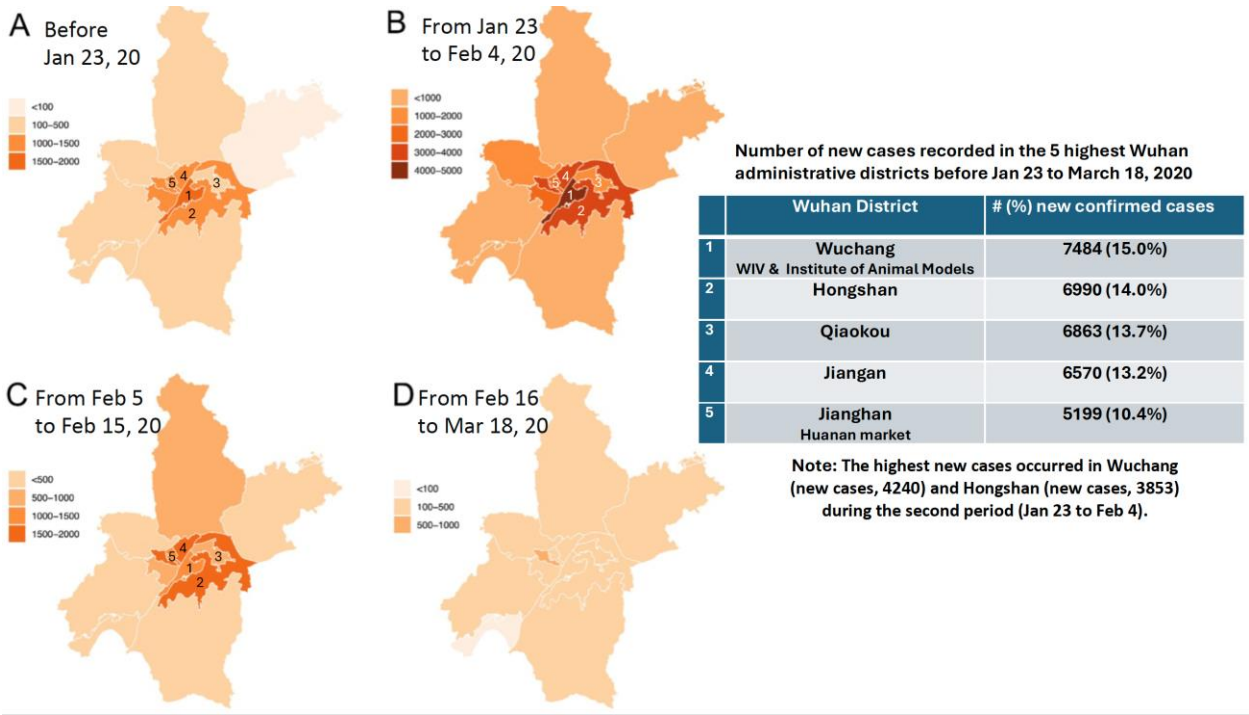


***Figure 3*. The number of new confirmed cases of COVID-19 in Wuhan by administrative district:** A, before Jan 23, 2020; B, from Jan 23 to Feb 4, 2020; C, from Feb 5 to Feb 15, 2020; D, from Feb 16 to Mar 18, 2020. Source: Wang et al. (2020).

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.[202] 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.[203] 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.[204] SARS-CoV-2's incubation period is estimated to be 6.5 to 14 days.[205,206] 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.”[207]

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.[208] 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.[209]

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.[210] In January 2021, the US State Department published declassified intelligence reporting WIV researchers became ill with flu symptoms in the fall of 2019. [211] 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.[212]

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.[213,214,215,216] 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 December 2019 (Figure 4).[217]

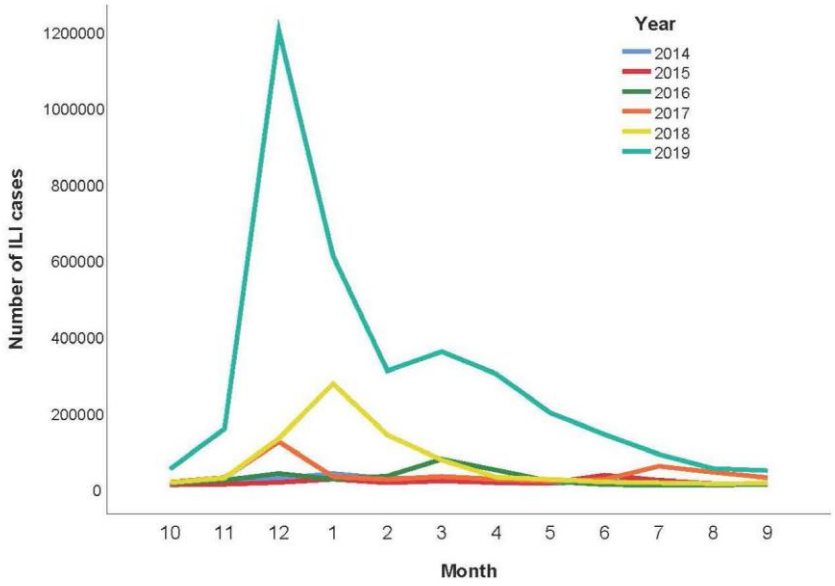


Figure 4. China National Health Commission (NHC) Reported influenza-like illness (ILI) cases during 2014-2019: Comparison of monthly reported ILI cases in different years. Source: Dai and Wang (2020).

Additional research is consistent with the idea that the outbreak centered in Wuhan in Hubei province.[218] 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.[219] 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.[220]

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.[221,222,223] 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.[224] This study specifically calculated that the first emergence likely occurred "around 18 November 2019."[225]

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.”[226]

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).[227]

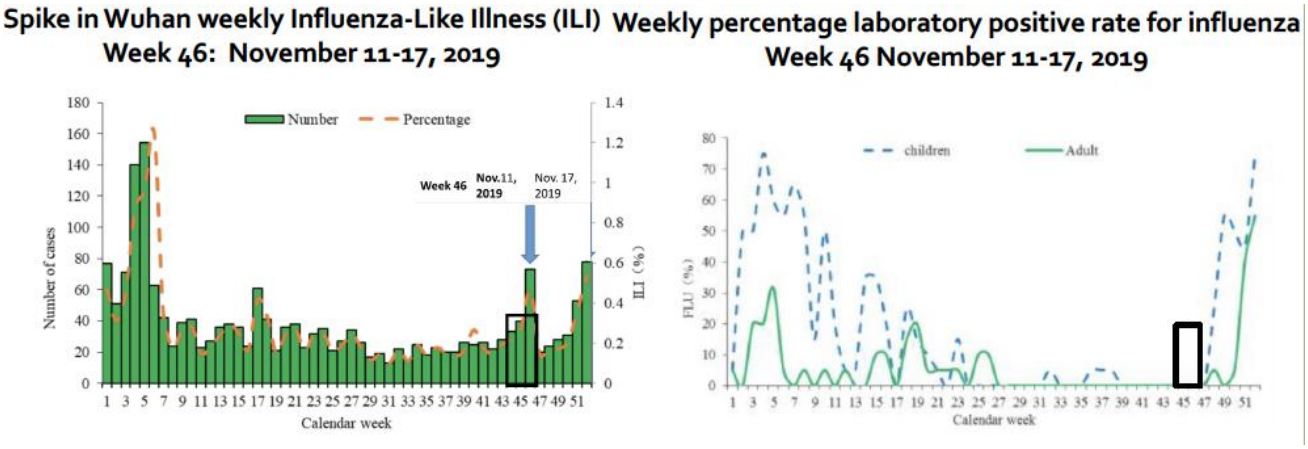


***Figure 5*. (Left) Weekly number of ILI cases in adults in the sentinel surveillance in Wuhan in 2019** (and percentage of outpatient visits categorized as ILI, [ILI %]). **(Right) Weekly percentage of ILI cases with laboratory-confirmed influenza** [FLU %] in the sentinel surveillance in children 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.[228] 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.[229] 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.[230] The SARS-CoV-2 genome consists of 14 functional Open Reading Frames (ORFs) that encode for nonstructural, accessory, and structural proteins.[231,232] There are four structural proteins: nucleocapsid, envelope, membrane and spike proteins.[233] 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).[234,235]

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).[236] 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."[237]

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).[238] 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.[239] One of the Laotian strains, BANAL-52, bears slightly more similarity to SARS-COV-2 (96.8%) than RaTG13 (96.1%).[240] 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."[241]

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.[242] 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.[243] 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.[244] 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 receptor at the distal end of the RBD. This receptor is novel and was not identified in a previous SARS-related virus 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."[245]

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.[246] 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.[247]

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.[248]

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.[249] Because of substantial sequence differences from SARS-CoV-2, the Pangolin-GD strain is unlikely directly linked to the current outbreak.[250] At least one other study also does not support that SARS-CoV-2 evolved directly from an infected pangolin.[251] 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), or from genetic engineering with recombinant DNA assembly and directed evolution in a laboratory.

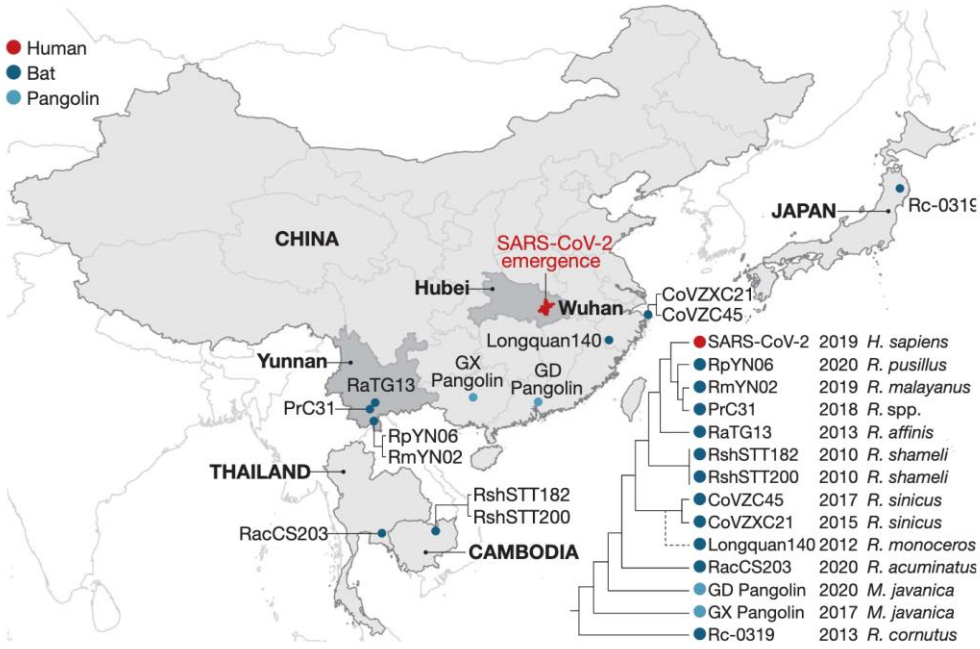


***Figure 6*. Distribution of bats species from which SARS-CoV-2 and SARS-related viruses have been found.** Source: Lytras et al. (2021).[252]

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 genuses (eg. *Rhinophilus*, or horseshoe bats) that carry these viruses.[253] Approximately 2.7% of people living in southern China within six kilometers of caves harboring SARS-related viruses showed possible infection.[254] This study suggests the risk of spillover to people living near bat colonies is a "relatively rare event."[255] 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* bats foraging range.[256]

ZC45 and ZXC21

The earliest reported viral relatives of SARS-CoV-2 were two novel SARS-like viruses (ZXC21 and ZC45) discovered by People's Liberation Army (PLA) researchers during field bat sampling in 2015 and 2017 from bats collected from Zhoushan city in eastern Zhejiang province.[257] In early January 2020, strain ZC45 was initially reported as the closest relative to SARS-CoV-2 with 89.1% genetic similarity.[258] 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 ZC45and ZXC21 strains and SARS-1.[259] 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."[260]

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.[261] 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.[262] 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.[263,264,265] Oral swabs and blood from the mineworkers were initially tested for a panel of possible viral agents, including SARS-1, and were

reportedly negative.[266] 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.[267] 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 detected antibodies against the SARS-CoV-2 nucleocapsid. This report stated that the results of these retests were negative.[268] 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."[269] 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)."[270]

Recombination certainly occurs among highly similar SARS-related coronaviruses within the sarbecovirus subgenus.[271] Dissimilar viruses do not recombine.[272] 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."[273] As described, the reported viruses most like different parts of the SARS-CoV-2 genome come 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.

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.[274]

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."[275]

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."[276]

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.[277,278] 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.[279] 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).[280,281,282]

Researchers were required to wear Powered Air Purifying Respirators (PAPRs).[283]

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.[284] 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."[285]

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.[286,287] In nature, recombination takes place when related viruses simultaneously infect the same bat(s) in close physical proximity.[288]

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."[289] 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.[290,291] 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.[292] 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.[293] EcoHealth's principle 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."[294] 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.[295,296]

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.[297]

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.[298] 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.[299]

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.[300] 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 furin cleavage sites."[301,302,303] 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.[304]

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

The 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. Its presence 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.[305,306] SARS-CoV-2 strains losing the FCS have significantly less pulmonary pathology.[307,308]

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].[309] 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.[310]

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.[311,312] 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.[313]

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.[314] But in 2015, Wuhan researchers used point mutagenesis to insert a functional FCS in the alphacoronavirus Porcine Epidemic Diarrhea Coronavirus.[315]

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.[316] 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.[317] Researchers in China demonstrated inserting an FCS into SARS-1 and RaTG-13 betacoronaviruses in early 2020.[318]

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.[319] Restriction sites occur naturally and randomly. These researchers noted that the restrictions 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."[320]

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."[321]

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.[322,323] 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).[324] 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."[325] 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.[326]

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.[327] 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."[328] 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, and it is found in several other viruses responsible for human illnesses, including Human Metapneumoviruses, Adenoviruses, Rotaviruses, Epstein-Barr and cytomegaloviruses for example. It plays a role in cell adhesion. Its discovery was notable because this binding protein had not previously been identified in other SARS-related viruses.[329] 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.[330] Integrins provide alternative ways for a virus to infect different cells and interfere with host signaling pathways.[331] 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 normal cell functioning.[332] Among the specific integrins the SARS-CoV-2 spike protein can bind to are *alpha5beta1* and *alphaVbeta3.*[333] These integrins are found in brain (neuron and glial) and cardiovascular (heart and blood vessel) cells.[334] 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."[335]

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."[336]

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.[337] These researchers determined that SARS-CoV-2 did not, however, "directly" evolve from the GD pangolin strain.[338] 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.[339]

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.[340]

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."[341] The participating scientists did not reach consensus on the issue and suggested it be referred to the WHO.[342]

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."[343] 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."[344]

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 receptor, and the acquisition of an FCS on the spike protein between its S1 and S2 segments.[345] However, SARS-COV-2 recombination had to have resulted in an S2 fragment 99% identical to SARS-related strains ZXC21, ZC45 and SARS-1.[346]

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?"[347] This 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."[348] 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.[349] It became fully operational in 2018.[350] 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."[351] 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."[352]

U.S. researchers were also aware that WIV researchers often conducted coronavirus research in BSL-2 labs.[353] A February 2018 draft of Ecohealth Alliance's DEFUSE proposal made explicit mention of this practice.[354] 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."[355]

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.[356] 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.[357]

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.[358] 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."[359] 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.[360]

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."[361] 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 text 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.[362]

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.[363] 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.[364]

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."[365] 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.[366,367]

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.[368] 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."[369]

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."[370]

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."[371,372,373] 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.[374] 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."[375] 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."[376] These authors further noted the that since the 2003 SARS outbreak, China has made steady progress. They note that a variety of biosafety related 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.[377] Though progress was made on biosafety equipment, they also noted challenges remained in the number 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.[378]

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.[379]

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."[380] 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.[381,382,383] 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.[384] There are numerous documented occurrences of lab-acquired infections at this containment level resulting from manipulations including viral isolation, viral culture and centrifuging of viral cultures.[385,386,387]

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.[388] According to their data, 70% of all bioaerosols caused by mishandling incidents are deposited on surfaces such as walls, equipment, and humans.[389]

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."[390] 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."[391]

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.[392]

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.[393] 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.[394] 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."[395] 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.[396,397] 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.[398]

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.[399] 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.[400] The common routes of exposure are ingestion, needle-sticks, cuts, animal scratches and bites, and inhalation.[401] 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.[402]

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."[403] 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.[404] 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.[405]

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."[406] 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.[407]

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.[408] 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.[409]

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.[410]

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."[411] 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. [412]

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.[413] 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.[414] 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.[415] The procurement contract award was announced on September 30, 2019. Work for this approximately $550k (USD) renovation project was estimated to take 210 days.[416]

Air handling and conditioning play a "critical role" in the control of infectious hazards in a biocontainment lab.[417] 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.[418] 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.[419] 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]."[420]

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."[421] 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.[422] 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."[423]

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 organs. 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."[424] One curious provision included the explicit prohibition of selling "used laboratory animals into the market."[425] In January 2020, a noted researcher, Li Ning, was sentenced to jail for 12 years for selling a variety of used experimental animals.[426] 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.[427] 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.[428]

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.[429] 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.[430,431] 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 of 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).[432] 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.[433]

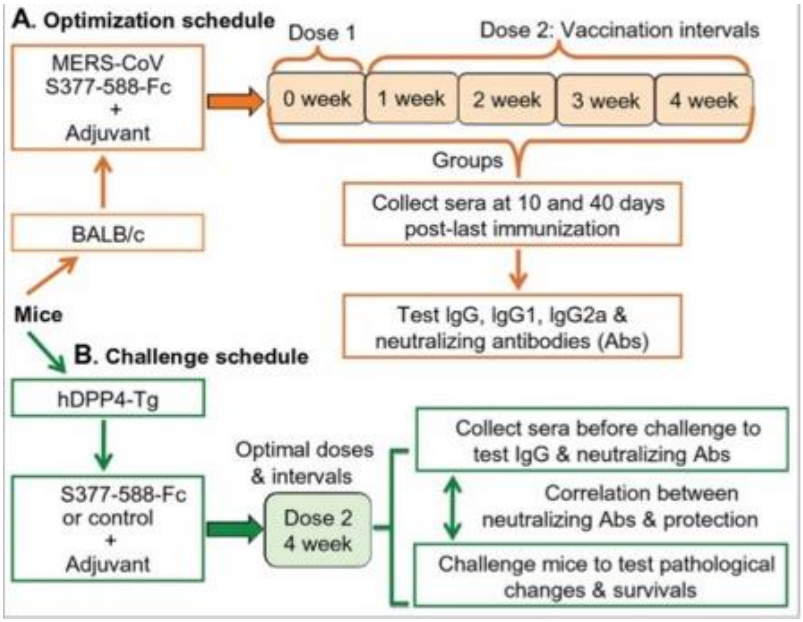


***Figure 7*. Vaccination optimization and challenge schedules for the RBD-Fc MERS vaccine challenge studies**. (A) Optimization schedule BALB/c mice (5 groups) were immunized with S377-588-Fc and either boosted once at 1-,2-,3-, or 4-week intervals, respectively. Sera were collected from the immunized 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.[434] 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.[435,436,437]

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).[438,439,440] He then challenged vaccinated humanized ACE2 mice and controls with human SARS-CoV-2 virus.[441] 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. [442,443] 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. [444] He was also memorialized in a later study evaluating the mechanism of MERS brain infection in specialized humanized DPP4 mice.[445] 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.[446]

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.[447,448,449,450,451]

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.[452]

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.[453,454,455] 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.[456]

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.[457] 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).[458]

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.[459] A gaseous vaporized hydrogen peroxide system is an effective, less corrosive means to sterilize a laboratory conducting infectious agent research.[460] 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.[461]

***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).[462]

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.[463] 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.[464,465,466,467]

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.[468] This team performed vaccine challenge experiments with humanized mice, ferrets and NHP at the Harbin veterinary BSL-4 research laboratory in northern China.[469] Photos of vials of the CanSinoBIO adenovirus-based vaccine showed that they were filled on February 26, 2020.[470] Human clinical trials began on March 17, 2020.[471] General Wei Chan, the senior PLA officer, submitted a patent

application for this vaccine the next day on March 18, 2020.[472]

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 Chinese Academy of Medical Sciences in Beijing, China.[473] 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.[474]

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.[475] 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."[476] Further details about this information was 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.[477,478]

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.[479] 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.[480,481] 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."[482] 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."[483] This media article contradicts a 2018 *Virologica Sinica* journal study describing the institute's SARS-related vaccine challenge experiment in Rhesus monkeys in 2017.[484] 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 by the institute's Partnership & Custom Media Unit of Nature Research.[485] To place this advertisement in *Nature*, the order would have had to be submitted no later than October 30, 2019.[486] 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.

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.[487]

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.[488] 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.[489] 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.[490,491] 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."[492] 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.[493] 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."[494]

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."[495] 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."[496] 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."[497]

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.[498] 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.[499] 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.[500] 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 effectiveness to filter out infectious particles.[501] 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.[502] Infected animals create a variety of potentially hazardous infectious aerosols from urine, feces, fur and by respiration.[503] 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.[504] 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."[505] 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."[506]

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.[507] Stainless steel corrosion is a well-documented challenge in the food and pharmaceutical industries and biosafety laboratories.[508,509] The liquid disinfectant used in the WIV's high-containment labs was subject of a published study in 2018.[510] 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."[511]

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."[512]

The stainless steel design and construction of China's high containment labs and supporting biosafety equipment put them at a 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.[513,514] 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.[515,516]

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.[517]

Conclusion to the First Installment:

The SARS-CoV-2 outbreak is an anomaly compared to earlier zoonotic 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 a SARS-related virus 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.[518,519]

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.[520] 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.[521] 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.[522] 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.[523] 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.[524] 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.[525] As further described, "but by that time [such measures were instituted] much of the damage had been done, as human-human transmission became evident."[526] 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).[527] 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.

Concluding Note: The Second Installment

While this document does not provide unambiguous proof about the origins of SARS-CoV-2, it presents a preponderance of circumstantial evidence pointing to its origin as a research-related incident. It also raises additional questions. Why would PLA scientists be working on a coronavirus vaccine before the pandemic? What was the nature of this work, and could it be associated with a military research program focused on the neurological consequences of novel coronavirus strains? The Second Installment of this Muddy Waters Update, expected in January 2025, will include a Part II exploring these questions—and questions about COVID-19's neurological impacts—in greater depth.

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Dr. Kadlec has built a distinguished record of service at the highest levels of U.S. biodefense and pandemic preparedness, both in civilian and military roles. From 2017 to 2021 he served as Assistant Secretary for Preparedness and Response (ASPR) at the U.S. Department of Health and Human Services. In this capacity, he played a central role creating and executing Operation Warp Speed which developed COVID-19 vaccines and therapeutics in record time.

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 an 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 he is a member of the Council on Foreign Relations.

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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."

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[481] 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 开了保存病毒的试管, 犹如打开了潘多拉魔盒, 这些病毒来无影去无踪, 虽有各种防护措施, 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. 每当这时, 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 级生物安全领域的开拓者—中科院武汉病毒所郑店实验室党支部事迹]*.

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[494] 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**, **菌毒种保藏**, 动**物**实验**以及**实验**室**废**弃物**处**理等内容**."

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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."

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