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Review Article

Why Wuhan? What the Circumstantial Evidence Says About the Origins of COVID-19

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Abstract

In the absence of direct evidence on the immediate origins of the novel coronavirus, COVID-19, the theories of the case are based on circumstantial evidence. The identification of the first cluster of cases in a wet market in Wuhan naturally focused attention on the leap from animal to human having taken place there. The proximity to the wet market of a biological lab naturally prompted a theory of a lab leak. After it was determined that there were earlier cases than those associated with the wet market, the circumstantial evidence for both these theories was undermined. Meanwhile, irrefutable evidence emerged that the virus mutates readily and gains function on its own. There were no wet markets or biological labs associated with the emergence of the European strain that devastated Italy and Spain and later New York. Nor was there a wet market or biological lab in Kent where the UK strain that devastated that country later emerged. The same is true for Manaus in Brazil whence P1 emerged in a population in which three-quarters of the people had antibodies against previous strains, not to mention South Africa, or India where later and more virulent versions emerged. In this context, the key piece of circumstantial evidence becomes timing. Epidemiological modeling dates the start of the outbreak in Wuhan to the window between mid-October and mid-November. The 7th World Military Games held from 18 to 27 October 2019 in Wuhan, which brought together nearly 10,000 athletes from over 100 countries, took place in this window. Importantly, this period witnessed elevated numbers of hospital visits in Wuhan and web searches for symptoms also associated with COVID-19. The games thus provided a unique opportunity for a mutation, possibly through recombination, a well-established property of coronaviruses, which then launched the COVID-19 pandemic proper. The departing athletic teams then carried the virus to Europe, explaining the parallel timing: even as the first identification of a novel disease in Wuhan was made on 27 December when three connected cases of unknown pneumonia were reported, retrospective forensic analysis identified a patient in France with COVID-19, also on 27 December 2019. A number of other studies suggest the virus had already spread internationally prior to its identification in Wuhan. The WHO mission investigating the origins of COVID-19 left open this avenue as a possibility. The circumstantial evidence powerfully supports the hypothesis that the Wuhan virus was in fact the first variant.

Keywords: COVID-19; Coronavirus; Pandemic; Recombination; Wuhan; lab leak; World Military Games.

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Introduction

The first outbreak that attracted attention to the novel coronavirus, COVID-19, was in Wuhan on 27 December when three connected cases of unknown pneumonia were reported by Dr. Zhang Jixian [1, 2]. Even as this connection of cases was being established, retrospective forensic analysis shows that a patient in France had COVID-19, based on samples taken also on 27 December 2019 [3]. That patient had no connection with China; hence it was community spread in France, meaning an infection likely weeks earlier and the original infection in France at least weeks before that.

Retrospective forensic analysis in China has pushed back the first identified case in Wuhan to as far back as 17 November [4, 2]. The WHO 2021 Authoritative Chronology states only that "Analysis of genomic diversity over time found that all sequences share a common ancestor towards the end of 2019, suggesting this as the period when SARS-CoV-2 spilled over to a human host." [5] Studies using genome data collected from the early cases, molecular clock inference and epidemiological simulations are a little more specific:, they estimate that "the most successful variant gained a foothold in humans … [with] human-to-human transmission" in the window of "mid-October to mid-November of 2019 in Hubei Province, China"; they add that there was "a likely short interval before epidemic transmission was initiated" [5].

Meanwhile in France, retrospective analysis identified a patient in Colmar in Alsace with lung damage typical of COVID-19 based on scans taken on 16 November 2019 [6]. The linkage of this case to COVID-19 is supported by anecdotal evidence from a local doctor:

"We had all been struck … this fall by somewhat bizarre flu episodes, which lasted longer than usual, with more pain, more temperature, more fatigue … We had one or two patients per week, at the very beginning. Then came the Christmas celebrations and the Christmas markets and there was a little more contagion. And everything really started with us, in Colmar, on the 6th of March" [6].

A number of other studies now suggest there may have been early spread in several other jurisdictions in late 2019 as well, including Italy, Spain and the United States, based on blood samples and wastewater samples, backed up in some cases by anecdotal information describing patients with COVID-19-like symptoms[1]. Ex post laboratory tests are not necessarily conclusive in and of themselves given the possibility of false positives, questions about the validity of the specific tests used, and/or potential cross reactivity with other common coronavirus infections. Low rates of positives may be called into question on grounds of statistical significance; high rates on grounds of lacking corroborating evidence of a full-fledged outbreak. Circumstantial evidence is therefore important. Several questions arise in this regard:

- Why Wuhan?
- Why did the first outbreak that drew attention to the virus occur in late December 2019?
- And crucially, why the parallel evolution of the pandemic in several different countries on a similar timeline?

This note focuses on these questions based on the circumstantial evidence.

Why Wuhan? Why December 2019?

The fact that Wuhan was the first location for the pandemic has naturally focussed global attention on this city. A World Health Organization (WHO) delegation conducted a field visit to Wuhan on 20-21 January 2020 to learn about the response to the pandemic [14]. A follow-up WHO mission was conducted 14 January to 10 February 2021 [15]. To date, several theories of the pandemic's origins have focussed on things specific to Wuhan:

- The Wuhan wet market, which was linked to the first cluster of cases identified by local health authorities, and which was suggested as possibly being ground zero for the source of the pandemic in terms of the leap of the virus from animals to humans;
- The proximity to the wet market of a biological lab studying bat-related viruses collected from the China-Thai border where the bat virus with the closest genetic resemblance to COVID-19 was identified, which led to speculation of a possible accidental release of the virus; and
- The world military games, which happened prior to the outbreak and were suggested as possibly having introduced the virus to Wuhan.

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[1] A retrospective analysis by a team involved in the Measles and Rubella Network, which explored the possibility of COVID-19 being the agent for a number of measles-like cases that tested negative for measles, identified one early positive case based on a swab sample. This involved a child in the Milan area who developed cough and rhinitis symptoms as of 21 November, was taken to the emergency department with respiratory symptoms and vomiting on 30 November, and developed a measles-like rash on 1 December, a pattern observed in younger COVID patients [7]. Another Italian study tested for COVID-19 antibodies in blood samples of asymptomatic individuals enrolled in a prospective lung cancer screening trial; it found an unexpected very early (and very high) presence of the virus with 14% of those tested in September 2019 found to be positive [8]. Similarly, retrospective research on sewage water samples has identified a suspected early COVID-19 presence in Turin and Milan in mid-December 2019 [9]. The US Centers for Disease Control and Prevention have identified COVID-19 in blood donations in December 2019 [10, 11]; these results lend support to the suspicion that COVID-19 was the cause of the spike in patients with coughs and acute respiratory failure at UCLA Health hospitals and clinics beginning in late December 2019 [12], Only one finding of the presence of a COVID-like virus comes from an earlier period and that is in Barcelona in wastewater sampled on 12 March 2019 [13] – a period that followed immediately upon the 2019 Mobile World Congress held on 25-28 February 2019.

Introduction of the virus to Wuhan via the cold chain in food distribution system has also been speculated; this would lead to an origin search elsewhere. In this note, I look at the three main theories of the case linked to Wuhan, based on the circumstantial evidence surrounding them.

The Wet Market as Ground Zero

The initial leap to conclusion regarding the source of the pandemic was that it came from the Huanan Seafood Wholesale Market, also known as the Huanan Seafood Market, and described as a "wet market", in Jianghan District, Wuhan. This is the market that was connected to the first cluster of COVID-19 infections identified. It traded in live animals that are known to be possible hosts to coronaviruses. The idea was that the leap from animal to human was made in this market.

The theory of the immediate zoonotic leap from infected animals to humans has had to be revised to take into account two key facts. First, it has since been established through retrospective forensic analysis that the virus was circulating in Wuhan prior to the identification of the first cluster associated with the Huanan wet market in individuals without any connection to that market. Second, the splitting of the A and B lineages had already occurred prior to the breakout at the Huanan market, with a smaller number of infections with the A lineage associated with other wet markets, and some with no wet markets [16]. The investigation by Gao Fu, Director of China's CDC, who collected samples from the Huanan market in early January, found no viruses in the animal samples, only in environmental samples, including sewage. This provides supporting evidence that the wet market was downstream from the original source of infection [17, 18], although the WHO investigation in 2021 identifies a pattern of spread within that market from the areas where wildlife was sold to other areas.

The focus of the zoonotic leap still focuses on wet markets in Wuhan, just not on the Huanan wet market, and the pathway is less clear (e.g., the source of the infection in the wet markets might have been dealers in wild animals who moved from market to market). The markets themselves thus might all be downstream from the original infection.

In retrospect, that the initial epicentre of the Wuhan outbreak was in a meat market is not surprising in view of the multiple major outbreaks in meat packing plants elsewhere around the world. Such markets provide ideal conditions for the virus to survive. The wet market was thus, in this sense, a red herring – and an unfortunate one in that it focussed attention on the risk of fomite transmission rather than human-to-human transmission, giving health authorities around the world wiggle room to delay in imposing unpopular and expensive countermeasures.

The Lab Leak Hypothesis

The Wuhan Institute of Virology (WIV), which is run by China's "Bat lady", Shi Zhengli, is located in the immediate vicinity of the South China Seafood Market. This Institute collects samples of bat viruses for study; it has the RaTG13 sample whose genome is closest genetically among known bat viruses to COVID-19. This prompted almost immediate speculation that the lab was the source of the outbreak through an accidental release. This theory has been extensively elaborated [e.g., 19, 20], and in May 2021 received a major boost in public attention due to a letter posted in Science signed by 20 scientists [21] that called for a re-investigation of the lab leak theory, and from an initiative mounted by the Biden White House for US intelligence agencies to investigate this hypothesis [22].

Shi Zhengli has strongly – even stridently – rejected the possibility; a large number of epidemiologists have also dismissed it (see, e.g., [20] for details and discussion). Moreover, the WIV staff tested negative for antibodies to the virus, which, as [23] observes should largely have ruled out the lab leak hypothesis[2].

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[2] As a footnote to this discussion of the lab leak hypothesis, the general dynamic has been for (a) scientists to table evidence that militates strongly against the virus emerging from successful "gain of function" experiments designed to anticipate possible future pandemics and to prepare remedies; and (b) for the lab leak hypothesis to develop more complicated pathways. For example, when basic "cut and paste" genetic engineering of the virus for "gain of function" objectives was ruled out as implausible based on the complex pattern of mutations in the virus compared to the original sampled virus, the lab leak hypothesis then shifted to repeated "forcing" of the sampled virus through intermediate hosts or cell cultures [24, 19, 20]. This hypothesis too met with skepticism since viruses tend to lose pathogenicity rather than gaining it in such experiments (see [25]). Moreover, the genetic distance between the bat virus that most closely resembles SARS-CoV2 suggests, in a natural environment, a long history of evolution, measured in decades or even hundreds of years, probably through intermediate species, before the leap into humans in contagious form (see, e.g., [26]). This suggests the probability of success in a short period of time is low (see, e.g., [23]).

Further, serological studies of local populations in areas close to bat caves in China's Yunnan province have identified previous likely human infection by bat-origin SARS-type coronaviruses or related viruses [27]; however, none of these repeated leaps from bat to humans, which presumably have been ongoing, resulted in sustained transmission, although obviously any one of these could have. Indeed, it has been observed that most spillovers do not lead to self-sustaining transmission: "By characterizing the likely dynamics of the virus before it was discovered, we show that more than two-thirds of SARS-CoV-2–like zoonotic events would be self-limited, dying out without igniting a pandemic." [5] Interestingly, in this regard, the history of lab leaks is that many have occurred but none triggered sustained human transmission: for example, from 2009 to 2013, there were some 800 cases in US labs where workers received medical attention because of exposure to "select agent pathogens", and one in which the original SARS virus leaked from a Beijing lab. [28] Simply put, the probability of an individual accident leading to a pandemic is very low.

What does the circumstantial evidence suggest?

In the first instance, this theory depends heavily on the proximity of the lab to the Huanan wet market. For the same reasons as given above concerning the earlier identification of the disease in individuals with no connection to the market, the lineage split prior to the Huanan market outbreak, not to mention the identification of cases abroad at about the same time as the outbreak in Wuhan, the weight of the circumstantial evidence supporting the lab leak theory is greatly reduced.

Second, the behaviour of the Chinese authorities does not suggest there was any suspicion on their part of a lab leak of a potentially pandemic-inducing virus. The reports from Wuhan to the Beijing WHO office and onward to WHO itself followed the established bureaucratic process and timeline, with the triggering of the WHO Article 10 (International Health Regulations, IHR) process through a formal request on 1 January and a filing of a report by China's National Focal Point under Article 10 of IHR on 3 January (although the formal reporting added no new information to the initial report from Wuhan, which was already generally available).

Third, as regards the analysis of the genome, the initial efforts were by private labs, which received samples for analysis from hospitals in Wuhan. Accounts by anonymous sources of a possible new virus were reported in the Chinese press (Caixin) on 26 December. One private lab shared the sequence data with Wuhan officials and the Chinese Academy of Medical Sciences on 27 December ([2]; the Authoritative Chronology). The virus was isolated and partially sequenced by the Wuhan Institute for Virology on 2 January; the sequencing was completed by the Shanghai Public Health Clinical Center and School of Public Health on 5 January [29], and uploaded to the US National Center for Biotechnology Information (NCBI) on that same day, 5 January, as per the submission date listed on the NCBI's Genbank [30]. The Wuhan Institute for Virology completed the sequencing on 7 January ([2]; the Authoritative Chronology). A member of Zhang's consortium, Australian scientist Eddie Holmes, subsequently posted the genome on Virological.org, with Zhang's permission on 10 January [29].

There are a few specific points that warrant further comment, however. The first concerns the disciplining of Li Wenliang and seven others for social media posts on the outbreak. These disciplinary actions were taken even as China was sending the official notice to WHO headquarters, and after several days of state media coverage of the outbreak and social media commentary thereon [31]. In context, the move to silence Li and the other individuals appears to be a heavy-handed attempt by the government to prevent panic as the messaging mentioned SARS at a time when the first death from COVID-19 had yet to be recorded. The disciplining had no impact on international transmission of the information on the virus: Li was disciplined on 2 January; the report to WHO was sent on 3 January (although the essentials had already gone worldwide by 30 December – and been acted on by governments abroad; [31]); and the first death attributed to COVID-19 was only on 9 January. Notably, the disciplinary measures triggered outrage in China after Li died of COVID-19 in February and were a factor in the political leadership of Wuhan and Hubei losing their jobs.

The second concerns the measures taken by the Chinese government to bar Zhang Yongzhen, whose team decoded the genome, from his Shanghai lab after the genome was shared internationally, where it led to an immediate launch of pharmaceutical research to identify vaccine candidates. This suggests ex post considerations about potentially foregone economic or other benefits from proprietary knowledge of the genome rather than ex ante concerns about a lab leak.

The third concerns the much-criticized delay by China in shutting down Wuhan. The three weeks that lapsed between the 3 January notification by China to WHO and the shutdown of Wuhan witnessed growing numbers of infections, but until 17 January, very few deaths. It was only when the body bags started to fill that the authorities took decisive action. This too suggests primary focus on avoiding economic damage through possibly premature countermeasures (an almost universal public policy reaction) rather than concerns about a leak of an engineered virus [31]. In this regard, one can compare the reaction of Chinese municipal, provincial and national authorities to those in Canada during the earlier SARS outbreak in Toronto [31].

The World Military Games

The third connection is the 7th World Military Games held from 18 to 27 October 2019[3]. This is by far the most intriguing – and not, I hasten to add, because of any conspiracy theory that the virus was deliberately introduced into Wuhan. The Wuhan games drew some 9,308 participants, along with their entourages, from over 100 countries to Wuhan. Athletes would have arrived sooner and departed after those dates.

Accordingly, the low probability of success in engineering a virus must then be multiplied by the low probability of a leak from a lab with the highest-level of biosecurity, and then by the probability that this leak actually took hold in the local population – and not in the locale of the WIV. Thus, it can be stated that the wave of speculation about a lab leak in the press has not been fueled by any new considerations that put wind in the sails of this hypothesis – rather speculation has been fanned in the face of mounting considerations underscoring the implausibility of the hypothesis.

[3] The 44th World Bridge Team Championships were held in Wuhan in September 2019 (WHO, 2021); this event however has not elicited further interest. From the Bridge Championships, one Italian came down with acute gastroenteritis [2].

During this period, circumstantial evidence suggests that an outbreak of a disease that gave rise to some COVID-19-like symptoms was underway in Wuhan. For example, an analysis of satellite data on hospital traffic shows rising hospital visits in Wuhan starting in August:

"…between September and October 2019, 5 of the 6 hospitals show their highest relative daily volume of the analyzed series, coinciding with elevated levels of Baidu search queries for the terms "diarrhea" and "cough" [18].

Notably these types of Internet search queries have been linked to known outbreaks of COVID-19 elsewhere. Also, notably, this finding in the professional literature is consistent with reports that US intelligence had spotted the outbreak in November. In the latter regard, raw intelligence showing increased activity at health facilities in Wuhan had also been reportedly gathered at the time by the United States in the form of communications intercepts and overhead images [32]. This was distributed to a number of federal public health officials in the form of a "situation report" in late November, but was not converted into an "intelligence product" or briefing until January 2020 [36].

A number of athletes reported getting ill during or after the games, including one US citizen who presented with gastroenteritis [2], and several others who had symptoms that in retrospect led them to suspect COVID-19 (see, e.g., [33-35]). Note that the version of the story that the visitors introduced the virus to Wuhan does not fit the time profile – the athletes report getting sick after they arrived in Wuhan, meaning they caught a virus circulating locally.

Of particular interest is the dynamics of the early breakout in Wuhan, which indicate a peak in September and October [18]. Meanwhile, the epidemiological path of COVID-19 suggests a somewhat later start. This raises an intriguing possibility: namely, that the visitors to Wuhan introduced another coronavirus that had been circulating silently elsewhere, which through a process of recombination with the local Wuhan virus, led to the creation of a new and more deadly and infectious version, which then started the pandemic proper. In other words, the games provided the opportunity to mix different viruses that had already made the leap into the human population and were already adapted to humans as host.

This would help explain the surprise voiced by researchers at how well adapted COVID-19 was to humans [36]:

"Our observations suggest that by the time SARS-CoV-2 was first detected in late 2019, it was already pre-adapted to human transmission to an extent similar to late epidemic SARS-CoV. However, no precursors or branches of evolution stemming from a less human-adapted SARS-CoV-2-like virus have been detected."

So, what do we know about recombination? Recombination is known feature of coronaviruses [26]:

"Mutations can have their advantages for viruses. Influenza mutates up to three times more often than coronaviruses do, a pace that enables it to evolve quickly and sidestep vaccines. **But coronaviruses have a special trick that gives them a deadly dynamism: they frequently recombine, swapping chunks of their RNA with other coronaviruses**. Typically, this is a meaningless trading of like parts between like viruses. **But when two distant coronavirus relatives end up in the same cell, recombination can lead to formidable versions that infect new cell types and jump to other species**" [Emphasis added].

Specifically, with regard to the coronavirus reserve in the bat population in Southern China:

"…a high diversity of coronavirus species have been found in Rhinolophus bats collected in several provinces of China. To date, the closest relatives to SARS-CoV-2 were identified from bats sampled in the Yunnan province, southern China … More distant and **highly mosaic recombinant viruses** were also sampled from bats in the Zhejiang province, in eastern China in 2015 and 2017." [37]

Recombination is a pathway for mutation in coronaviruses – indeed, recombination has been proposed as the pathway through which COVID-19 obtained its pathogenicity [38]. The much-discussed furin cleavage site is not found in the viruses most closely related to COVID-19, but is found in many other viruses, including coronaviruses circulating in humans [25]. Thus, 10,000 athletes and their entourages from over 100 countries coming to a region with an ongoing outbreak of a COVID-19 precursor virus may have brought the genetic material for a recombination that created the COVID-19 outbreak in Wuhan that is now thought to have started in late October/early November as the military games were ending.

The athletes returning to their home countries could then have served as vectors for the disease to establish itself elsewhere in late 2019, on a more or less parallel track with Wuhan. For example, a correlation has been identified between the outbreak of COVID-19 at US domestic military bases as of 31 March 2020 and participation of personnel in the Wuhan games [35].

This conjecture ties together a number of strands of the pandemic story and, importantly, offers an explanation as to why Wuhan was the site of the original COVID-19 outbreak – and does so in a way consistent with the timing of the outbreak: a virus that emerged through recombination/mutation in late October, remained in circulation in Wuhan, building up to the outbreak identified in late December, while at the same time dispersing worldwide with the departing athletes to spawn outbreaks in due course elsewhere.

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The First Variant

Circumstantial evidence can be very powerful in determining "whodunnit" – much more so than eyewitness evidence, which has often been found to be unreliable. In the absence of direct evidence on the immediate origins of the virus, the theories of the case are based entirely on circumstantial evidence. The identification of the first cluster of cases in the Huanan wet market in Wuhan naturally focused attention on the leap from animal to human having taken place there. The proximity to the wet market of a biological lab naturally prompted a theory of a lab leak. However, when it was determined that there were earlier cases than those associated with the Huanan wet market, and that the lineage had split prior to the Huanan market outbreak, the circumstantial evidence for these theories was undermined and the accounts of the pathway from lab to pandemic became a lot more complicated.

Meanwhile, irrefutable evidence has emerged that the virus mutates readily and gains function on its own. There were no wet markets or biological labs associated with the emergence of the European strain that devastated Italy and Spain and later New York. Nor was there a wet market or biological lab in Kent where the UK strain that devastated that country later emerged. The same is true for Manaus in Brazil whence P1 emerged in a population in which three-quarters of the people had antibodies against previous strains, not to mention South Africa, or India where later and more virulent versions emerged.

The most powerful circumstantial evidence currently available is the timing of events. Epidemiological modeling backdates the start of the outbreak in Wuhan to the window between mid-October and mid-November [5]. This is the window in which the world military games, which brought close to 10,000 athletes and their entourage from over 100 countries to Wuhan, took place. Additional circumstantial evidence (satellite data on hospital visits and data on Baidu searches for symptoms also associated with COVID-19) indicates that Wuhan was having an outbreak of a disease prior to and during the Wuhan military games, yet in a way that did not attract attention to itself and whose epidemiological path does not match COVID's.

The fall weather conditions, the heavy exertion of competition, and the celebrations and social mingling of such an event are ideal for transmitting a virus; a number of athletes reported getting sick with COVID-like symptoms during and following the games in Wuhan on their return home.

Accordingly, Wuhan uniquely provides the setting for a mutation/recombination event between viruses previously circulating in humans in different parts of the world, which might be the origin of a virus – COVID-19 – that emerges in a form already well-adapted to its human hosts and with added transmissibility and lethality. In other words, the Wuhan virus might well have been the "first variant".

The scattering of the athletes to their homes following the games would then explain the evidence for COVID-19 showing up in a number of jurisdictions prior to the identification of the disease in Wuhan. The fact that the carriers were world-class athletes would explain the low profile of the disease as it initially took root in other countries. Meanwhile, the larger concentration of the new virus in Wuhan would explain its earlier visible outbreak there.

This issue remains unresolved. The WHO mission investigating the origins of COVID-19 left open this avenue as a possibility. The WHO mission report recommended "Consideration should be given to further joint review of the data on respiratory illness from the on-site clinics at the Military Games in October 2019." The circumstantial evidence supports this hypothesis strongly.

As of this writing, half a decade following the start of the pandemic, the politicized battle over its origins is largely reduced to zoonotic leap vs. lab leak. The circumstantial evidence, however, suggests the third option has a far stronger claim.

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