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Research article

QUESTIONING THE EARLY EVENTS LEADING TO THE COVID-19 PANDEMIC

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Sixteen months after the January 30, 2020 declaration by the World Health Organization of a Public Health Emergency of International Concern regarding the spread of COVID-19, SARS-CoV-2 had infected ~ 170 million humans worldwide of which > 3.5 million had died. We critically examine information on the virus origin, when and where the first human cases occurred, and point to differences between Chinese and later clinical presentations. The official patient Zero was hospitalized in Wuhan, Hubei province, China, on December 8, 2019, but retrospective analyses demonstrate prior viral circulation. Coronaviruses are present in mammals and birds, but whether a wild animal (e.g. bat, pangolin) was the source of the human pandemic remains disputed. We present two contamination models, the spillover versus the circulation model; the latter brings some interesting hypotheses about previous SARS-CoV-2 virus circulation in the human population. The age distribution of hospitalized COVID-19 patients at the start of the epidemic differed between China and the USA–EU; Chinese hospitalized patients were notably younger. The first Chinese publications did not describe anosmia-dysgeusia, a cardinal symptom of COVID-19 in Europe and USA. The prominent endothelial involvement linked with thrombotic complications was discovered later. These clinical discrepancies might suggest an evolution of the virus.

Key words: *SARS-CoV-2 diagnostics, patient zero, zoonotic disease, autopsies, clinical presentation, dysgeusia / anosmia.*

Sixteen months after the World Health Organization (WHO) declared a Public Health Emergency of International Concern (PHEIC) on January 30, 2020, the novel SARS-CoV-2 betacoronavirus had infected approximately 170 million people worldwide of which > 3.5 million had died. The scientific community's response has been prolific,

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with more than 147,000 articles referenced in PubMed as of May-end, 2021, but several scientific issues remain unresolved.

We critically examine available information on the origin of the virus, when and where the first human cases occurred, and point to differences between Chinese and later clinical presentations of COVID-19 that affected choice of treatment. Our objective is to present the current state of knowledge regarding three major questions: What triggered this pandemic? When did the patient/cluster zero occur? How to explain differences in age of onset and clinical presentation of COVID-19 patients in China and, subsequently, those in Europe and the USA? This first part of our research considers and is based on facts established by the World Health Organization (WHO) reports and extracted (in-extenso citations) from selected published papers, mostly Chinese, but without any pretension of completeness.

The quest for patient zero and the pandemic's early Chinese phase. Biomedical scientists faced with emerging zoonoses and infectious diseases search for the first to fall ill on the assumption this will reveal or illuminate disease acquisition and perhaps even aetiology. The search for Patient Zero and for index cases is a priority for epidemiologists and infectologists. Obviously, the primary case, "*the person who first brings a disease into a group of people*" must be distinguished from the index case which *"is the patient in an outbreak who is first noticed by the health authorities, and who makes them aware that an outbreak might be emerging*". Giesecke [1] cautions that "*For many outbreaks, the primary case will never be known*" adding "*for all outbreaks that are discovered, there will always be one (or more) index cases*". Patient Zero, or more precisely the first, primary case, is almost impossible to find as other cases probably existed concurrently at the beginning of the disease and either sought no medical assistance (asymptomatic or only with mild symptoms) or were diagnosed incorrectly. The official story of the COVID-19 pandemic based on declarations of Chinese national health authorities transmitted to the WHO [2, 3]. Key dates and content of those transmissions are:

♦ December 31, 2019: Declaration of a pneumonia cluster by the Wuhan Municipal Health Commission, Hubei, China;

♦ January 7, 2020: Chinese authorities issue the identification of the causative agent, a novel coronavirus;

♦ January 10, 2020: WHO issues comprehensive technical guidance on how to detect, test and manage cases;

♦ January 12, 2020: Chinese publication of the RNA sequence of the coronavirus genome;

♦ January 30, 2020: WHO publishes evidence of 7,818 confirmed cases of COVID-19 worldwide, of which 82 were present in 18 countries other than China;

♦ February 24, 2020: Report of the WHO–China Joint Mission on Coronavirus Disease 2019;

♦ March 11, 2020: WHO declares COVID-19 to be a pandemic.

Chinese preparedness. As a consequence of the 2002–2003 Severe Acute Respiratory Syndrome (SARS) outbreak in Guangdong Province (south of Hubei Province), Chinese authorities had built a medical detection system for new viruses associated with respiratory infections. This surveillance system of influenza-like illness (ILI) and severe acute respiratory infection (SARI) is detailed in the 2021 WHO report [4]. This system gave excellent results for the 2013–2017 Asian-lineage avian H7N9 Influenza epidemics and led to an article co-authored with a U.S. Centers for Disease Control & Prevention (CDC) CDC scientist [5]. The close cooperation between the Chinese CDC and American CDC must be underlined; it started in the nineteen eighties and "*played a crucial role in China's responses to emerging infectious diseases, such as SARS-CoV, avian influenza, and COVID-19"* [6].

The backdrop for the outbreak of COVID-19 in Wuhan, Hubei Province, was

Chinese expertise and experience with zoonotic coronaviruses, not only in regard to human Severe Acute Respiratory Syndrome (SARS) in 2002–2004 but also to Swine Acute Diarrheal Syndrome (SADS), a fatal disease of piglets in 2017, both of which originated in Guangdong Province. Given the apparent rise of bat coronaviruses (CoVs) in China, with potential to induce severe diseases in humans and animals, the Chinese Academy of Sciences Key Laboratory of Special Pathogens and Biosafety of the Wuhan Institute of Virology (WIV) warned of the threat in a paper submitted on January 29, 2019 to the journal *Viruses*, which published the article on March 2, 2019; this was approximately one year before the WHO declared the SARS-CoV-2-related COVID-19 pandemic. In their 2019 paper, Yi Fan and colleagues stated: "*It is generally believed that bat-borne CoVs will re-emerge to cause the next disease outbreak. In this regard, China is a likely hotspot. The challenge is to predict when and where, so that we can try our best to prevent such outbreaks". "These studies, revealed that various SARS-CoVs capable of using human ACE2 [angiotensin converting enzyme-2] are still circulating among bats in China, highlighting the possibility of another SARS-like disease outbreak"* [7]. No doubt, the Chinese medico-scientific community was aware of the hazards and well prepared.

The outbreak management. What happened in China when the SARS-CoV-2-related disease outbreak occurred and when patients came to Wuhan's hospitals diagnosed as "*pneumonia of unknown cause*" or "*atypical pneumonia*"? Standardized medical diagnosis procedures were used in accord with proper medical practice anywhere in the world. "*Since the cause was unknown at the onset of these emerging infections, the diagnosis of pneumonia of unknown cause in Wuhan was based on clinical characteristics, chest imaging, and the ruling out of common bacterial and viral pathogens that cause pneumonia*" [8]. At first, the atypical pneumonia might have been attributed to the usual winter seasonal flu, both by medical teams and by patients. In this regard, it is noteworthy to highlight the statement of Mrs. Wei Guixian, considered to be one of the first index cases: "*Every winter, I always suffer from the flu. So, I thought it was the flu.*"[1]. This impression is underlined by a team from the Wuhan Center for Disease Prevention and Control that stated: *"The time period in concern coincided with the winter peak of influenza and other respiratory illnesses. The number of ILI (influenza-like illness) cases in all age groups increased dramatically starting in early December 2019 and reached the peak by the New Year"* [9]. Assessment of the etiologic diagnosis proved to be challenging: "*Notably, in the early stage, nucleic acid detection kits for SARS-CoV and other coronaviruses were used for COVID-19 diagnosis, with varying specificity and sensitivity. Meanwhile, when detection kits were not available, imaging examinations, especially chest computed tomography (CT), played an important role in the diagnosis of COVID-19, although these examinations are not specific to COVID-19*" [10].

Chinese publications, notably the *China CDC Weekly*, documented subsequent events [11–14]. Usual techniques were used to culture and isolate the virus. Thereafter, extraction and sequencing of the virus's RNA allowed the realization of PCR testing tools and serological detection of SARS-CoV-2 antibodies. RT-PCR methods were then assessed for their sensitivity and specificity. Reports unfolded as shown chronologically below:

♦ December 21, 2019: Cluster of pneumonia cases in Wuhan Jinyintan Hospital (public hospital in Wuhan's Dongxihu District). RNA extraction, sequencing and culture to assess the virus in three cases [11, 13];

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[1] Woods A. Shrimp vendor at Wuhan market may be coronavirus «patient zero». *New York Post*. Available at: https://nypost.com/2020/03/27/shrimp-vendor-at-wuhan-market-may-be-coronavirus-patient-zero/ (June 15, 2021).

♦ December 29, 2019: Report to the Wuhan health authorities of a cluster of cases of viral pneumonia of unknown aetiology (VPUE) (i.e., four individuals working in the Jianghan District Huanan Seafood Wholesale Market (HSWM) hospitalized with pneumonia);

♦ December 30, 2019: Wuhan CDC investigations revealed additional patients linked to the seafood market; health authorities from Hubei Province reported this cluster to China CDC Beijing;

♦ December 31, 2019: China CDC experts sent to Wuhan to support the investigation and to provide samples from patients for laboratory analyses;

♦ January 3, 2020: China National Institute for Viral Disease Control and Prevention (IVDC) sequenced a novel β-genus coronavirus (2019-nCoV, later named SARS-CoV-2) with three distinct strains identified in a patient's sample of bronchoalveolar lavage fluid [11];

♦ January 6, 2020: China National Pathogen Resource Center reported electron microscope findings that the new virus showed the typical morphology of a coronavirus [14];

♦ January 9, 2020: "*Chinese CDC announce that a novel coronavirus (2019-nCoV) had been detected as the causative agent of 15 of the 59 pneumonia cases*" [15];

♦ January 11, 2020: "*A team led by Prof. Yong-Zhen Zhang of Fudan University in Shanghai posts the genetic sequence of the virus on an open-access platform, sharing it with the world. China CDC and two other Chinese teams subsequently also post genetic sequences of the virus on an open-access platform. China shares the virus' genomic sequence with WHO*" [16];

♦ January 11, 2020: PCR tests for 2019-nCoV provided to Wuhan hospitals [11];

♦ January 21, 2020: A German led team publishes an in-silico real-time PCR test for the new coronavirus, research that was "*enabled by the willingness of scientists from China to share genome information before formal publication, as well as the availability of broad sequence knowledge from ca 15 years of investigation of SARS-related viruses in animal reservoirs*" [17]. This test served to diagnose the early cases across Europe.

Early in January 2020, three research teams, each working independently (Shanghai, Wuhan, Beijing), successfully sequenced the new virus and published their results. Metagenomic RNA sequencing of a sample of bronchoalveolar lavage fluid (BALF), obtained from a Wuhan Central Hospital patient hospitalized on 26 December 2019, allowed identification of the complete viral genome of a new RNA virus strain of 29,903 nucleotides, which was designated as "WH-Human 1" [18]. Analysing samples from seven patients with severe pneumonia who had been admitted to Wuhan Jinyintan Hospital, the WIV laboratory found five samples to be PCR-positive for CoVs. Metagenomics analysis using next-generation sequencing identified a 29,891 base-pair CoV genome using one patient's BALF [19]. The third team identified ten genome sequences of 2019-nCoV obtained from nine patients that showed 99.98 % sequence identity, with base pairs ranging from 29,829 to 29,844 [20]. This breakthrough allowed the construction of RT-PCR tests in China [14] and assessment of their sensitivity and specificity.

Early cohort reviews. In mid-January 2020, the Chinese teams began to publish on the new coronavirus infection in international journals, several weeks before WHO would declare the disease pandemic. The major Chinese publications [8, 21–23], plus the 2021 WHO–China report [24], described the timing of the start of the Wuhan pandemic, yet with certain discrepancies. At the start of the outbreak, all reports distinguished Huanan Seafood Wholesale Market (HSWM) workers or visitors from those with no HSWM contact. All agreed that Patient Zero had been hospitalized in early December 2019 in Wuhan. However, depending on the individual articles, it seems that several index cases were identified, since the hospitalization dates were recorded as December 1, December 8 and December 12. The *South China Morning Post* even reported (from their examination of government data) that "*a 55-year-old from Hubei province could have been the first person to have contracted COVID-19 on November 17*" [10, 25]. An interesting article that tries to detangle the aetiology of influenza-like illness cases in Wuhan by retrospective analysis of 640 throat swabs collected between October 6, 2019 and January 21, 2020 found only 9 swabs in the period January 4 and 20, 2020 to be positive for SARS-CoV-2 RNA by quantitative PCR. The authors suggested that "*COVID-19 was gradually expanding among the ILI cases during January*" [9].

Evidence of human-to-human transmission among close contacts was established in mid-December 2019 [21]. This interhuman contamination was also assessed in a family cluster in Shenzhen, Guangdong, after two members had visited a relative in a Wuhan hospital: *"We report here a familial cluster of unexplained pneumonia due to 2019-nCoV. These findings suggested that person-to-person transmission and intercity spread of 2019-nCoV by air travel are possible, supporting reports of infected Chinese travellers from Wuhan being detected in other geographical regions"* [26].

Limitations have been evoked by the Chinese scientists and mathematical models have provided better estimations of the epidemic. Thus, a Beijing study estimated a total of 3,933 cases of novel coronavirus-infected pneumonia in Wuhan (95 % confidence interval (CI): 3,454–4,450) with onset of symptoms by January 19, 2020 [27]. Li and colleagues pointed to the limitations of their cohort of 425 cases: "*Confirmed cases could more easily be identified after the PCR diagnostic reagents were made available to Wuhan on January 11, which helped us shorten the time for case confirmation", "Early infections with atypical presentations may have been missed, and it is likely that infections of mild clinical severity have been under-ascertained among the confirmed cases" [21].*

Index cases outside China. Examination of peer-reviewed papers published between December 1, 2019 and July 9, 2020 and listed in *PubMed*, the *China National Knowledge Infrastructure*, *Web of Science*, and the WHO database of publications on COVID-1, revealed the identification of index cases in 16 different countries / regions from Asia, Europe, North America and South America. Twelve first cases occurred in January 2020, all from China or in contact with Chinese patients, while four additional cases in February and March reported travel histories in Italy (Bolivian, Brazilian), Iran (Afghan) and UK (American) [28]. Additional information, shown below, has since become available regarding the citizenship and travel origin of the index cases from China:

♦ January 3, 2020: Index case in Nepal [28];

♦ January 13, 2020: Index case in Thailand [29];

♦ January 16, 2020: Index case in Japan [29];

♦ January 16, 2020: Index cases in France, two Chinese tourists and a traveller returning from Wuhan [28, 30];

♦ January 19, 2020: Index cases in Washington State, USA [31] and in South Korea [28, 29];

♦ January 23, 2020: Index cases in Italy: two Chinese tourists [32], Toronto (Canada) and Vietnam [28];

♦ January 24, 2020: Index case in Germany (infected by a Chinese woman on professional travel) [28, 33];

♦ January 26, 2020: Index cases in UK and Finland [28];

♦ January 31, 2020: Index cases in Russia. Chinese tourists in Siberia, who needed medical assistance [34].

Based on this information, it would appear that, by the end of January 2020, WHO would have been justified in declaring a pandemic, which is defined as *"a worldwide spread of a new disease"* [35]. Perhaps WHO waited for the certainty of *"an epidemic over a very wide area, crossing international boundaries and usually affecting a large number of people"* [36], an unequivocal fact by March 11, when the pandemic was declared?

Quickly, the quest for the primary patient native to their respective country interested teams in France, UK, Italy and the USA. This search was also one of the 2021 Joint WHO – China study [4], which concluded that "*studies from different countries suggest SARS-CoV-2 circulation preceded initial detection of cases by several weeks*." This statement was based on the discovery of neutralizing antibodies in a few participants in an Italian cancer screening program (October, 2019), PCR analysis of a throat swab from a child with suspected measles (early December, 2019), and PCR-based sewage sample analysis in northern Italy (mid-December, 2019). Additional data from France included the isolation of neutralizing antibodies in blood samples from mid-December and PCR-based detection of oropharyngeal SARS-CoV-2 in a patient hospitalized at the end of December. In Brazil, RT-PCR testing of sewage detected SARS-CoV-2 (November 27, 2019), and serological testing of 7,389 donated blood samples collected in the USA between December 13, 2019 and January 17, 2020 yielded 106 positive samples.

Unsolved mysteries about the origin of SARS-CoV-2. The origin of SARS-CoV-2 and routes of human infection are subjects of intense debate shadowed by political concerns. Lack of data on index cases, assessment difficulties, other uncertainties and the complexity of interactions, which are taken into account by the scientific community, are the characteristics of such an inquiry. Metagenomics and specific molecular genetic tools such as phylodynamic and phylogeographic analysis, and Bayesian phylogeographic reconstruction, are tools that have been used to clarify these concerns. Since these complex analyses are incomplete and beyond the scope of this article, the following assumes SARS-CoV-2 had a primary zoonotic origin and the outbreak is Wuhan can be explained by one of two lines of hypotheses.

The 2021 WHO – China report. On March 29, 2021, the WHO experts proposed four hypotheses that could account for the emergence of the SARS-CoV-2 in the section of their report entitled "*Zoonotic Origins of SARS-CoV-2"* [4]. These four hypotheses were discussed and rated according to their probability: a direct transmission from bats to humans, transmission via an intermediate host, the consumption of frozen meat infected by the virus, and a laboratory accident. Doubt was expressed that the Wuhan Huanan market represented a major source of contamination, where 38 wild and wild-caught and farmed non-domesticated terrestrial species were sold between May 2017 and November 2019 [37]. The 2021 WHO Report triggered many comments, notably in prestigious journals, e.g. *Science* [38] and *The Lancet* [39]. On April 1, 2021, *Nature* stated: "*A World Health Organization report makes a reasonable start, scientists say, but there are many questions yet to be answered. The report concludes that the chances of COVID-19 having originated in a lab accident are slim. But there is growing pressure, including some from researchers, for a more comprehensive inquiry into this possible route. The question of the pandemic's origins has been politically fraught from the start*" [40]. By June 2021, it was clear that the origin of COVID-19 was under renewed examination beyond WHO.

A novel approach, the "viral circulation model". The current paradigm for the emergence of zoonotic diseases is the "spillover" model. According to this model, a zoonotic virus capable of infecting humans is already present in a reservoir species and transmitted to humans by an intermediate species. However, this was never observed. The spillover model is an intellectual construction that failed to confront reality when it was created. While seemingly sound when first advanced, SARS, MERS and COVID-19 has shown that none of the predictions of the spillover model has been realized. No reservoir, no intermediate species and no human-adapted viruses were found in the wild.

Given the apparent failure of the spillover concept, a new evidence-based model – the "circulation model" – was developed to explain the emergence and transmission of

SARS-CoV-2 infectious diseases [41–43]. Based on field observations, the "circulation model" hypothesizes that viruses circulate among various hosts simply upon contact and compatibility. These viruses evolve differently in each host. The human pandemic viruses exist only in humans, which explains why they are not found in the wild. Only related viruses of the same group can be found.

The virus circulation model describes a process of emergence of naturally occurring viruses in the human population but does not pinpoint the exact origin of SARS-CoV-2. Two different steps must be considered: 1) the original infection of humans with a virus circulating in the wild, and 2) the undetected inter-human transmission of the virus prior to any recognition of the disease. The former is very likely to occur in anthropogenic rural areas. The emergence is directly linked to human behaviour, mobility and societal factors, when the epidemic threshold is overridden. As stated by Frutos and colleagues, "*The danger, i.e., the presence of CoVs potentially capable of emerging as an epidemic or a pandemic is recognized. It requires human activity to amplify the frequency of virus encounters and thus create amplification loops to reach the threshold necessary to trigger an epidemic. This is where the risk lies, in the anthropogenic amplification loop*s" [42]. This model is consistent with early virus circulation in Wuhan: "*However, the virus had probably already been circulating since early October 2019*" [42]. Plato and colleagues [44, 45] support this model and name the early phase "*the pre-Wuhan period*", which they suggest started in the first half of 2019.

Data from COVID-19 clinical presentations and autopsies: comparison between China and Western countries. Comparison of the first Chinese clinical descriptions issued from study of a small series of hospitalized patients with those originating from Western countries reveals discrepancies that merit examination. Below we consider the difference in the age distribution of the first hospitalized patients, the quasi absence of smell and taste alterations in Chinese patients, and the practice of autopsies.

The age distribution of the early cases. Review of 278 hospitalized patients with COVID-19 pneumonia in Wuhan gave insight into the early demographic data of Chinese persons with the disease [46]. Chinese publications of early cases [8, 21–23] reported a predominance of males and a median age at diagnosis under 60 years. *"As of 10 February 2020, only three relatively large-scale case studies have thoroughly demonstrated the clinical features of patients with pneumonia caused by SARS-CoV-2 pneumonia in Wuhan"* [47]. However, significant differences are noticed in reports originating from medical authors in Wuhan. In the Wuhan Jinyintan Hospital, the average age was 55.5 years, and the patients' percentage over 60 years was 37 % [22], while the China CDC data show, respectively, an average age of 49 years, with 13.8 % over 65 [23]. These data differ from those from Western countries (USA, Europe), where older patients were most heavily affected. The U.S. CDC consistently reported throughout the pandemic that hospitalization risk was linked with older age [48]. In Italy, the average age ranged between 60 and 67 years [47] and, in New York City, USA, an average patient age of 63 is found in one cohort of 5,700 hospitalized patients [47]. However, the age group distribution varies markedly among different published series. In Australia, the median age was 58 years [49] while two case series from Iraq showed a very large variability ranging from 12 % to 40 % for COVID-19 patients over 60 [50, 51]. Interpretation of the typical age distribution of the first cases of COVID-19 is challenging because in must consider many variables, including general demographic data, national population age distribution, patient recruitment from urban/rural areas and patient behaviours.

Anosmia and dysgeusia. Posted on February 25, 2020 at medRxiv, Mao and colleagues [52] were the first to describe hyposmia and hypogeusia in the 214-person cohort of Wuhan hospitalized patients. They noted a small percentage of patients with disorders of smell and taste but noted the difficulty of capturing such subjective symptoms in their cohort. *“In patients with PNS symptoms, the most common reported symptoms were taste impairment (12 (5.6 %)) and smell impairment (11 (5.1 %)”* [52]. Smell and taste alterations are now considered as pathognomonic symptoms of COVID-19, occurring early and sometimes as the only symptom in mild and moderate clinical forms of the disease in 65–70 % of patients [53]. In March 2020, several warning calls regarding this phenomenon were issued from different countries, including Korea, Italy, Germany and Iran [54, 55]. This Iranian study [55] used an unusual methodology with self-reporting of anosmia and an online auto-questionnaire available on the social networks that attracted 15,228 persons but all with an unknown COVID-19 status. This study found that 76.2 % (10,069) of presumably COVID-19 patients had reported the sudden onset of anosmia or hyposmia. These alerts prompted Ears, Nose and Throat specialty organizations in France, UK and the USA to inform their members in March 2020 [56–58]. Publications followed on-line from a Belgian-French team on April 2 [59] and from an Italian team [60] on April 15. The latter had observed chemosensory dysfunction in 19.4 % of their 320 cases. This symptom elicited great interest and led to publications in April–May from Korea [61], Italy [62], France [63], and Iran [64]. A European collaborative group started follow-up of a European cohort that increased in size over time [65]. *“A total of 1,754 patients (87 %) reported loss of smell, whereas 1,136 (56 %) reported taste dysfunction”* [66]. Interest in the chemosensory dysfunction of COVID-19 grew rapidly [67], with assessment and therapeutic proposals [68], follow-up and evolution [69–71].

The clinical evolution of hyposmia/anosmia and dysgeusia is an important issue for patients because, for example, reduction or loss of smell perception raises the possibility of early central nervous system SARS-CoV-2 involvement, notably of the olfactory bulb [63, 64, 69, 70]. Complete clinical screening of COVID-19, as with any disease, not only appropriately engages the patient but also provides information critical for accurate diagnosis. Indeed, the strikingly common chemosensory symptoms have helped to differentiate clinically a nose-ears and throat COVID-19 presentation from symptoms associated with influenza. Meng and colleagues [71] have addressed why the apparent prevalence of chemosensory dysfunction was lower in China than elsewhere. Among their hypotheses is their proposal of a differential susceptibility among populations to SARS-CoV-2 mutants, citing Forster and colleagues who found different clades of the virus in Europe compared to China [72]. That SARS-Cov-2 mutated during its spreading phase from China to abroad is legitimate, as the further evolution of the pandemic showed the emergence of multiple variants in several countries across the world.

Autopsies and SARS-CoV-2 targets. To our knowledge and as noted in a review [73], only a few autopsy reports and no series were published by Chinese teams in the early months of the pandemic. Among the first autopsies cited in the WHO–China report [24], is one dedicated to the lung. Another, cited by Mao and colleagues [52], also examined the brain; the report issued in Chinese by the *“National Health Commission of the People's Republic of China. Diagnosis and treatment of the novel coronavirus pneumonia (Trial version 7)”*, *“Autopsy results of patients with COVID-19 showed that the brain tissue was hyperaemic and oedematous and some neurons degenerated”* [52]. Later (in April 2020), a histopathological analysis of 26 autopsies showed endothelium involvement in the kidneys [74]. Autopsies are considered risky since COVID-19 and specific protective equipment was mandatory [75].

Several autopsies were undertaken in the USA [76, 77] and in European laboratories [78–80]. The results of these post-mortem studies explained the multiple tissue targets of

COVID-19 and, as a result, dramatically changed the therapeutic approach in severe cases of COVID-19. A key finding was the suggestion of vascular dysfunction, severe capillary congestion, widespread Endothelitis and microthrombi [78, 79], notably: *"we demonstrate endothelial cell involvement across vascular beds of different organs in a series of patients with COVID-19"* [78]. This explained why COVID-19 could induce, along with an intravascular disseminated coagulopathy, thrombosis of arterial vessels in the brain (ischemic stroke) as well as in the lung (embolism).

Final comments. Despite the tremendous efforts of the medico-scientific community in documenting many aspects of COVID-19, uncertainties and grey zones persist about the origin and early stages of the pandemic. The disease clearly first exploded in Wuhan, but the timing and causes are still unclear. Was it in January 2020 in association with the Chinese New Year holiday period? Retrospective analyses have established early viral circulation beyond China, notably in Brazil, France, Italy and the USA. Answers to these critically important questions will likely assist in anticipating, detecting and monitoring future outbreaks of highly infective viruses, whether of coronavirus pedigree or otherwise.

The COVID-19 pandemic has demonstrated the difficulties of detecting an outbreak of a new disease, whether represented by a unique patient and/or by small clusters of index cases. If these difficulties are to be surmounted, it may be possible to restrict virus spread using public health methods that, in the case of COVID-19, were successfully utilized in countries such as Australia, New Zealand and Taiwan, where testing, tracing, isolation and communication were practiced effectively. However, no matter the effectiveness of public health responses, control of the medical phase caused by a rapidly spreading infectious agent is far too late to detect avert the threat of a looming pandemic from an environmental agent [81]. Consistent with the precautionary principle, as applied to environmental disease, humanity needs a far greater degree of global cooperation for the effective detection and monitoring of circulating viruses that pose a threat to human or animal health. Embracing the "One Health" approach of simultaneous attention to animal and human disease should be helpful in addressing virus detection and transmission. Additionally, timely reporting with complete transparency and universal access to supporting data is mandatory for the prevention and, if necessary, tracking and containment, of future outbreaks of infectious diseases with pandemic potential. Notwithstanding collective human responsibilities, we must find ways to surmount the usual "I" trilogy, ignorance, ideology, inertia, that has been identified in another context [82].

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