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Covid-19: natural or anthropic origin?

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Abstract

Viruses similar to the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) have been discovered in bats of the genus *Rhinolophus* and in the Sunda pangolin, *Manis javanica*, suggesting that these animals have played a key role in the emergence of the Covid-19 outbreak in the city of Wuhan, China. In this paper, we review the available data for sarbecoviruses (viruses related to SARS-CoV [2002-2003 outbreak] and SARS-CoV-2) to propose all possible hypotheses on the origin of Covid-19, i.e., involving direct transmission from horseshoe bats to humans, indirect transmission via the pangolin or another animal, with interspecies contamination between either wild animals or animals kept in cage. Present evidence indicates that *Rhinolophus* bats are the natural reservoir of all sarbecoviruses, and that two divergent SARS-CoV-2-like viruses have circulated in southern China (at least in Guangxi and Guangdong provinces) between August 2017 and March 2019 in captive pangolins destined for sale in wildlife markets. We performed a genetic analysis of seven seized pangolins found to be positive for SARS-CoV-2-like virus using mitochondrial DNA sequences extracted from SRA data. The results reveal that the same SARS-CoV-2-like virus can be found in animals with distinct haplotypes, which means that they were probably captured in different Southeast Asian regions. Our interpretation is that some pangolins were contaminated in captivity (by other pangolins or by another species to be determined), suggesting that illegal trade of living wild mammals is at the origin of the Covid-19 outbreak. To definitely validate this hypothesis, it is however necessary to discover a virus almost identical to SARS CoV-2 (at least 99% of identity) in animals sold in wet markets. Although pangolins are good candidates, other mammals, such as small carnivores, should not be overlooked.

Keywords: Covid-19, SARS-CoV-2, pangolin, carnivores, bat, traffic, wet market.

The number of both emerging infectious diseases and epidemic events has been increasing by ten since 1940 (Jones et al. 2008; Smith et al. 2014). Covid-19 is the last zoonotic disease linking animal reservoirs and human beings that turned epidemic and even uniquely pandemic.

Understanding the origin of this disease is crucial not only to understand the way the SARS-CoV-2 has been selected to provoke infection in human beings but also to prevent further emergence. Hereafter, we critically review recent data published on Covid-19 and analyse new genetic data on pangolins to better understand how the SARS-CoV-2 virus was transmitted to humans.

The two thirds of the first Covid-19 patients were associated with the Huanan Seafood Wholesale Market in Wuhan City, Hubei Province, China (Huang et al. 2020) (**Figure 1**). This market is specialized in seafood products, but a vast array of live animals was also proposed before it was closed by the authorities. Even though the first patient was not reported to have attended this market, it would appear that this person has been in contact with people involved in the trade of living animals. This recalls the SARS epidemic of 2002-2003 which emerged in Guangdong province and then spread to thirty countries, with a total of 8098 cases and 774 deaths (https://www.who.int/csr/sars/country/table2004_04_21/en/). The coronavirus identified then, the SARS-CoV, belongs to the subgenus *Sarbecovirus*, which also contains the new SARS-CoV-2. Since they share only 82% of nucleotide identity, the two sarbecoviruses represent two distinct lineages that split several decades ago. To better understand the origin of the SARS-CoV-2, it is therefore crucial to review the scientific knowledge about the SARS-CoV, studied in the past years, as the two sarbecoviruses have many features in common.

Horseshoe bats are the reservoir of all sarbecoviruses

After the 2002-2003 SARS epidemic, several teams of virologists have searched over the world to find new coronaviruses. These studies have revealed a great diversity of sarbecoviruses in bats of the genus *Rhinolophus* (Rhinolophidae, commonly known as horseshoe bats), especially in China (Li et al. 2005; Ge et al. 2016), but also in Europe (Bulgaria; Drexler et al. 2010) and in East Africa (Kenya; Tao & Tong 2019). Therefore, there is no doubt that one or several species of *Rhinolophus* constitute the natural reservoir of sarbecoviruses. The SARS-CoV lineage is represented by dozens of genomes in the international nucleotide sequence databases (EMBL, GenBank, etc), which were isolated from several cave-dwelling bat species, including different species of *Rhinolophus*, such as *Rhinolophus affinis*, *Rhinolophus ferrumequinum*, *Rhinolophus macrotis*, *Rhinolophus monoceros*, *Rhinolophus pearsoni*, *Rhinolophus pusillus*, *Rhinolophus sinicus*, as well as *Chaerephon plicatus* (Molossidae) (Yang et al. 2013; Ge et al. 2016; Hu et al. 2018). The SARS-CoV-2 lineage is only represented by three bat viruses, all isolated from *Rhinolophus* species collected in China. Two similar genomes (97% identical) have been isolated from specimens of *Rhinolophus sinicus* collected in 2015 and 2017 in a cave in the city of Zhoushan (Zhejiang province) (Hu et al., 2018) (**Figure 1**); their similarity to the SARS-CoV-2 is 89%. The third genome is much closer to SARS-CoV-2, with a nucleotide sequence identity of 96% (Zhou et al., 2020). It has been discovered in a bat belonging to the species *R. affinis* (intermediate horseshoe bat), collected in 2013 in an abandoned mineshaft in Mojiang, Yunnan province (Ge et al. 2016) (**Figure 1**). Due to the Covid-19 epidemic, many field surveys will be probably conducted on bats in the coming years, and we can expect that more viruses of the SARS-CoV-2 lineage will be discovered. The current data clearly indicates that many sarbecoviruses circulate and diversify in cave bat colonies in China, and likely also in nearby countries (Laos, Myanmar, Thailand, Vietnam). Many scientists suggest that bats are not sensitive to these viruses, but this *ad hoc* hypothesis has never really been tested. Even though

bats can fight well against virus proliferation, it is likely that bats are affected, and that a part of the populations vanishes every year due to these viruses. This has been shown in the African fruit bat *Rousettus aegyptiacus* (family Pteropodidae), which has been identified as the reservoir of Marburg virus (Amman et al. 2012).

Are bats the source of human contaminations?

All the three epidemic outbreaks related to sarbecoviruses have emerged in China at the start of the winter: in November 2002 and in December 2003 in Guangdong province, and in November 2019 in Hubei province. Despite having a different climate (subtropical in Guangdong province and temperate in Hubei province), both regions have minimal temperatures below 10°C from December to February in Guangdong province and November to February in Hubei province. At those temperatures, bats which feed on insects have to hibernate because insect populations become significantly less abundant. This adaptation occurred many times during the evolution of bats and it is highly dependent on the latitudinal distribution of the species. Most of the time, several species of bats, in particular *Rhinolophus* species, occur in the same caves. Some caves can host hundreds or even thousands of bats. Promiscuity and intense flight activity during the pre-hibernation period in swarming sites (where bats mate during the autumn) may favour the transmission of viruses between bat individuals and between bat species. Such a concentration of wild animals attracts hunters who know well the natural history of these bats. However, they are usually interested in tropical large frugivorous bats (body length: 8 to 30 cm) which are frequently consumed, although small bats, such as *Rhinolophus* species (body length: 4 to 8 cm), may be taken as well when food is scarce for the local populations. Bat hunting could therefore be a source of human contaminations. However, this would imply that sarbecoviruses could jump species barrier and infect humans. This hypothesis is possible as bat viruses close to the SARS-

CoV have been shown to be capable of infecting human cells in the laboratory (Ge et al., 2013). Direct transmission to humans or other mammals can be done through contact with body parts, saliva, urine, or faeces of bats, or alternatively through inhalation of liquid droplets and aerosol particles in cave housing thousands of bats and their guano (Li et al. 2010) (**Figure 2**).

Experiments on ferrets have shown that airborne transmission is likely but is considerably less robust than direct contact transmission (Kim et al. 2020). So, if we admit that transmission from bats to humans is possible, direct contact between bats and hunters would be the best scenario. However, no epidemiological data support that direct transmission can happen in real life, and an intermediate host species between bats and humans was found in all previous outbreaks caused by closely related coronavirus: the masked palm civet (*Paguma larvata*, Viverridae) in the SARS-CoV outbreak in 2002-2003 (see below for more details) (Guan et al. 2003) and the Arabian camel (*Camelus dromedarius*, Camelidae) in the Middle East Respiratory Syndrome CoV (MERS-CoV) outbreak that emerged in 2012 in the Arabian Peninsula (Azhar et al. 2014).

An indirect contamination, via an intermediate host, is therefore a very likely explanation for the origin of the Covid-19 outbreak (**Figure 2**). But how can be possible a virus transmission from a bat to another species? First, hunters usually catch not only bats but a large diversity of species, and some are more valuable if kept alive as they will be then sold a higher price on wildlife markets. This is the case for small carnivores and pangolins (**Figure 2**). If live or recently killed bats are placed in close proximity to live carnivores or pangolins, virus transmission will be theoretically possible. Alternatively, transmission may have occurred in the wild (**Figure 2**).

Injured or dying bats which fell on the cave floor can attract scavengers, which could be infected by consuming these bats. Several species of small carnivores are known to scavenge occasionally, such as civets (Viverridae) and raccoon dog (*Nyctereutes procyonoides*, Canidae) (IUCN 2020), in which the SARS-CoV has been isolated in the past (Kan et al., 2005); other small carnivores, such as badgers and ferret badgers (Mustelidae) may also feed on carcasses of

small mammals (IUCN 2020). All these small carnivores may also prey on bats roosting too close to the ground or in parts of the caves that are accessible by climbing. Although pangolins (*Pholidota*, *Manidae*) feed mainly on ants and termites, they can also come into contact with bats. Since many ant species are known to feed on carrion, pangolins can lick dead or dying bats on a cave floor, and may be then contaminated by sarbecoviruses.

How wildlife illegal trade and consumption is involved in the epidemic?

The index case of the two SARS-CoV epidemic events was not contaminated by bats. In the 2002-2003 SARS-CoV outbreak, the first patients were identified as clients of a restaurant in Shenzhen (Guangdong province) where meat of wild animals was proposed to consumers. The southern regions of China have a dietary tradition favouring freshly slaughtered game meat, which implies a huge trafficking industry dedicated to live animal trading in specialized markets, called wet markets (Shi & Wang 2011). Various wild animals of Shenzhen market were tested, and a virus identical at 99.8 % to the SARS-CoV was isolated in the masked palm civet (*Paguma larvata*, *Viverridae*) (Guan et al. 2003). This small carnivore is nocturnal and arboreal; it is kept in farms in China and sold alive in markets. This species was also identified as the source of the second SARS-Cov epidemic event in 2003-2004 in the city of Guangzhou, also in Guangdong province, only a few months after the end of the ban of civet consumption by Chinese authorities. Among the four people infected, two had a link with a restaurant where six civets were held in cages. All the civets were found to be positive to a virus which was 99.8% similar to the SARS-CoV (Song et al. 2005; Wang et al. 2005). The patients in this case had a mild form of the disease and were not the source of further contaminations. Surprisingly, no virus was detected in 1107 masked palm civets sampled in 25 farms of 12 provinces in China (Kan et al. 2005). This suggests that civets of Shenzhen and Guangzhou restaurants, source of the two SARS outbreaks,

were infected not in the farms, but when kept in cages in markets or in restaurants. The SARS-CoV and/or neutralizing antibodies were also detected in raccoon dogs (*Nyctereutes procyonoides*) and Chinese ferret-badger (*Melogale moschata*) (Guan et al. 2003), suggesting that another species may have been used as intermediate host between bats and civets.

In the case of Covid-19, a link was established between the first patients and the wildlife market of Wuhan. Two viruses of the SARS-CoV-2 lineage have been isolated in Sunda pangolins (*Manis javanica*) obtained from wildlife traffic (so their exact geographic origin is unknown) in Guangdong and Guangxi provinces (Lam et al. 2020). The Sunda pangolin does not occur naturally in China, except in the south of Yunnan province (**Figure 1**; IUCN 2020). Therefore, it is assumed that all the animals tested came from illegal trade from Southeast Asia (Cheng et al. 2017) (**Figure 2**). The sequences of virus obtained from these pangolins are divergent from the SARS-CoV-2 (between 86 and 92%), indicating that these viruses are not the source of the Covid-19 outbreak. However, the virus isolated from pangolins seized in Guangdong province is similar at 97.4% with SARS-CoV-2 in the amino acid sequence of the receptor binding domain (RBD) of the S protein. If the RBD sequence is recognized by the receptor of Angiotensin Converting Enzyme 2 (ACE2) of human cells, the virus is allowed to enter and infect them. In other words, this means that some virus detected in pangolins were capable of infecting humans. More important is the fact that several pangolins, seized in anti-smuggling operations in southern China between August 2017 and March 2019 and studied by three different Chinese teams (Liu et al., 2019; Lam et al. 2020; Xiao et al. submitted), were found positive for SARS-Cov-2-like viruses. Liu et al. (2019) wrote: “The Guangdong Wildlife Rescue Center received 21 live Malayan pangolins from the Anti-smuggling Customs Bureau on 24 March 2019; most individuals, including adults and subadults, were in poor health, and their bodies were covered with skin eruptions. All these Malayan pangolins were rescued by the Guangdong Wildlife

Rescue Center, however, 16 died after extensive rescue efforts. Most of the dead pangolins had a swollen lung which contained a frothy liquid, as well as the symptom of pulmonary fibrosis.”

According to available data (Liu et al. 2019; Lam et al. 2020; Xiao et al. submitted), we estimate that 42% of seized pangolins (28 positive individuals / 67 tested) were infected by at least one SARS-Cov-2-like virus. Such a high level of viral prevalence and the symptoms of acute interstitial pneumonia detected in most dead pangolins indicate that pangolins are highly permissive to infection by SARS-Cov-2-like viruses. But how contamination occurred? The first hypothesis is that they were contaminated by bats in the wild in their native Southeast Asian forests. This seems unlikely as the sensitivity of the pangolins to these viruses would limit the spread of the viruses in their populations. In addition, pangolins seem rare in their natural habitat and they live a solitary life (IUCN 2020), which implies that direct contacts with their congeners are rare. As a consequence, even if a viral infection from bats to pangolins is theoretically possible in the wild, the chains of transmission among pangolins should break very quickly under natural conditions. The second hypothesis involves an anthropic origin, in which pangolins were contaminated because of their captivity. Cross contamination between bats (or an intermediate host) and pangolins may have occurred during the transport from Southeast Asia, or during the storage in China, or in the wildlife markets in China. This is very likely as the pangolins are kept in very poor living conditions, with large numbers of individuals from different species in close proximity, which can facilitate the diffusion of the virus. Moreover, the contamination can be increased by the fact that ill animals (pangolins and possibly small carnivores) can multiply and better transmit the virus to their congeners or to other species, including humans (**Figure 2**). If pangolins were contaminated by bats in the wild, we would expect to discover a large diversity of viruses in Chinese markets, because pangolins can be illegally imported from different regions of Southeast Asia. Current data show the existence of two different SARS-CoV-2-like viruses in pangolins: one from Guangxi (sequenced in at least six individuals) and another one from

Guangdong (sequenced in two individuals). By analysing mitochondrial reads of pangolins from SRA (Sequence Reads Archive) data recently published (Liu et al. 2019; Lam et al. 2020), we identified five mtDNA haplotypes among the pangolins seized in Guangxi (GX) and Guangdong (GD) (GX1: SRR11093268, SRR11093266, SRR11093267; GX3: SRR11093269; GX3: SRR11093270; GD1: SRR10168377, GD1: SRR10168378), suggesting that the animals were collected in different geographic localities in Southeast Asia. Although pangolins need to be further sequenced (including, for instance, full mitogenomes and microsatellites), these preliminary data provide some evidence that inter-animal transmission of SARS-CoV-2-like viruses occurred during their captivity. One question remains to be solved: from which animal in captivity these viruses initially come from? Bats? Some pangolins naturally infected by bats in the wild and illegally imported into China? Another species kept in cage with pangolins? (**Figure 2**) Regarding this last point, it is important to mention that several species of carnivores, in particular ferrets and cats, are permissive to SARS-CoV-2 infection (Shi et al., 2020), as was the masked palm civet to SARS-CoV. Wild carnivores, which are commonly sold in Chinese wet market, should be therefore also targeted with pangolins for the search of coronaviruses. All this indicates a strong suspicion that the Covid-19 outbreak is a consequence of illegal trade and consumption of wild animals.

What we need to do for a better future?

If this scenario is validated by future researches, it would indicate once more that illegal trade of live wild animals and land degradation can select together for the development of viral human infectious diseases (Guéguan 2019). Land change and especially deforestation ease the capture of pangolins by giving access to new and still game-rich areas for poachers. Indeed, human population growth and expansion into remote areas, and the availability of better hunting tools have increase harvesting pressure on wildlife, and rare species became prestige foods for the

urban elite in China (Lau et al. 2010). While the capture of wild animals has sometimes been replaced by farming for small carnivore species (Lau et al. 2010), this is not the case for pangolins, which are taken from the wild (Shepherd 2009), the species being very difficult to keep and to breed in captivity (Yang et al. 2007). The decline in Chinese pangolins (*Manis pentadactyla*) has driven an increase of illegal trade for other species of pangolins from other neighbouring Southeast Asian countries (whole animals), and also from Africa (body parts, such as scales). The harvest of pangolins is unsustainable and is driving pangolin species to extinction, with for instance, the Sunda pangolin and the Chinese pangolin both classified as Critically Endangered (IUCN 2020). Almost a million pangolins have been trafficked in the past decade, and pangolins are nowadays the most heavily trafficked wild mammals, with 33 countries and territories involved in international pangolin trafficking (Heinrich et al. 2017). Long-lasting environmental degradation in China may have also favoured the roosting of bats in abandoned mines rather than caves. In addition, communal roosting in larger groups than in hollowed trees or other natural habitats in forests harbouring a few individuals only forces for virus prevalence in bats populations and for stronger hunting pressures.

Trade of alive wild animals on wet markets offers great opportunities of contact between bats and other animals, allowing exchange of viruses, their recombination and finally the emergence of new human infectious diseases. A general ban of wildlife markets, in particular in China, may be a key action in limiting the possibility of virus transmission, and it will also decrease illegal trade, and therefore favours the conservation of species.

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Figure 1

Geographic distribution of the Sunda pangolin (*Manis javanica*), intermediate horseshoe bat (*Rhinolophus affinis*) and Chinese horseshoe bat (*Rhinolophus sinicus*). Alexandre Hassanin, Author provided.

Google Earth US Dept of State Geographer © 2020 Google - Image Landsat / Copernicus - Data SIO, NOAA, U.S. Navy, NGA, GEBCO

Figure 2

Synthesis on the knowledge and hypotheses on the origin of SARS-CoV-2.

Alexandre Hassanin, Author provided.



Figure 1

183x108mm (300 x 300 DPI)

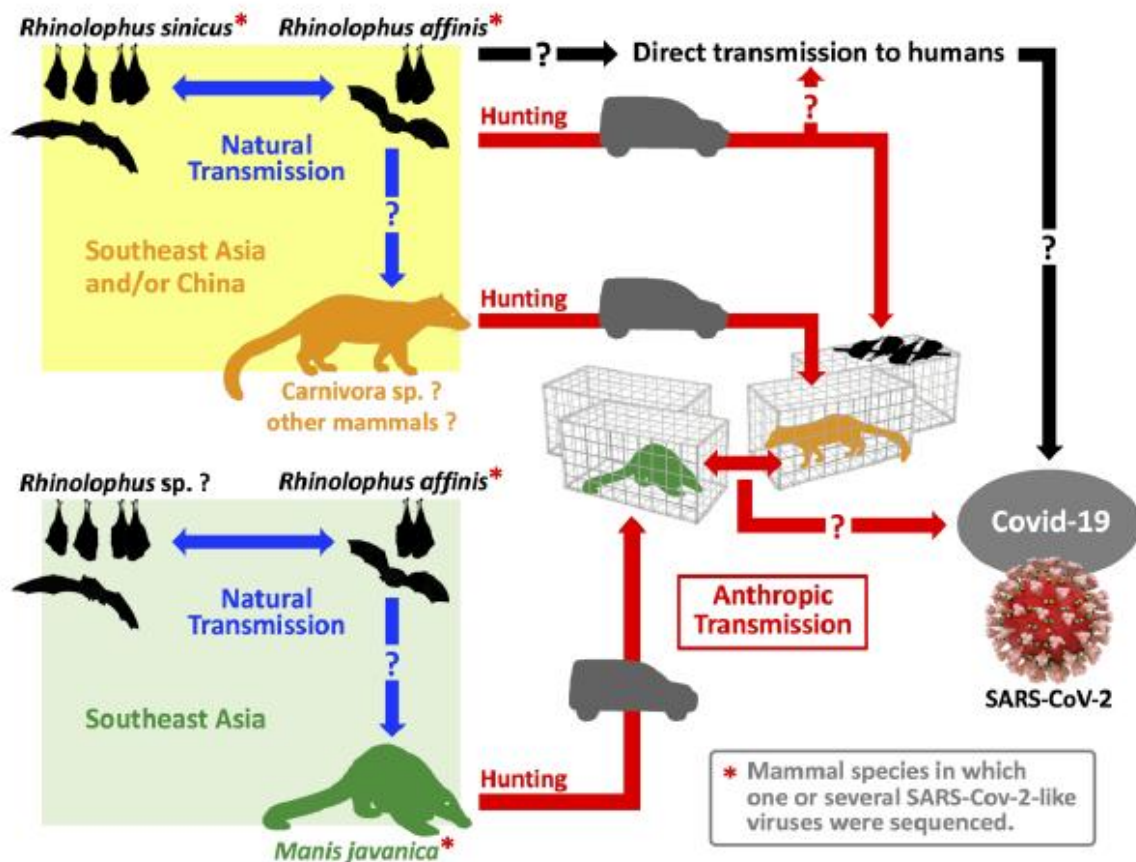


Figure 2