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COVID-19: More on its Possible Origin

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Abstract

The struggle between humans and infectious diseases dates back to the beginning of civilization, where the increase in infectious entities is closely associated with human misconduct and ecosystem management. The objective of this research was to provide more up-to-date information on the possible origin of the new coronavirus officially known as SARS-CoV-2, which causes COVID-19. A series of data/information on the possible origin of the new pandemic is presented, broken down as follows: Where does this virus come from?; bats and pangolins as potential vectors; probable theories about how this virus spread to humans; what do we know?; what we don't know?; and how this virus spread so rapidly until it became a pandemic. It is concluded that this is a highly infectious entity with a high probability of zoonotic transmission, with bats and the mammal known as the pangolin standing out as potential reservoirs, where the joint efforts of all human beings who inhabit, this planet must unite to win the battle against this new coronavirus.

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Introduction

The struggle between humans and infectious diseases dates back to the very beginning of civilization [1]. Throughout history, humanity has suffered the scourge of countless entities of varied etiological diversity (viral, bacterial, fungal and parasitic), which have sown death and disability among millions of the planet's inhabitants [1-4]. The increase in re-emerging and emerging diseases in recent decades has greatly complicated the epidemiological picture worldwide [3, 5, 6], where the occurrence of several epidemic and pandemic outbreaks has been evidenced, with marked repercussions on human and other animal health [7-10]. It is important to note that this increase in infectious diseases has not been, nor is it, a coincidence, but rather the consequence of poor human management of ecosystems [4, 10, 11]. The current situation facing the planet due to the new coronavirus is yet another effect resulting from the poor management of human activity, accumulated over thousands of years [11-13].

The new coronavirus (2019-nCoV) identified on December 31, 2019 in Wuhan, China, currently officially known as SARS-CoV-2, causes COVID-19. Furthermore, this virus is the first of its family to be declared a pandemic by the World Health Organization (WHO) on March 11, 2020 [14] Global epidemiological studies on coronaviruses (CoV) carried out for 15 years have shown that bats in Asia, Europe, Africa, America and Australia are reservoirs for a wide variety of viruses, harboring and spreading these infectious agents quite easily, which increases their transmission capacity [15-17].

The truth is that we still don't know if the virus will become endemic, recurring year after year, or if it will eventually be controlled [20-24]. Nor is it preventing both the disease and the infection. The pace of vaccination is slow, driven by economic interests and uneven distribution, which has led to the emergence of new waves and the development of mutations that could hinder the effectiveness of current vaccines [18, 19, 21, 24].

The objective of the research was to provide more up-to-date information on the possible origin of the new coronavirus officially recognized as SARS-CoV-2, which causes COVID-19.

Where does this virus come from?

There are approximately 6 400 species of mammals on our globe. Bats and fruit bats make up 20% of the mammal population. There are 1, 000 different types of bats and fruit bats, and they are the only mammals that can fly, which explains their wide range of movement. Bats and fruit bats harbor a large number of viruses. Bats and fruit bats in developmental history have probably been the entry point for viruses into the mammalian pedigree [16, 17, 26].

There are numerous dangerous viruses that have spread from "bats" to humans and are responsible for many diseases: measles, mumps, rabies, Marburg fever, Ebola, and other rarer and no less dangerous diseases. In other mammals, viruses derived from "bats" have repeatedly caused massive deaths in pig, chicken or poultry farming [16, 17, 25].

These are biological processes that are millions of years old. The DNA of healthy individuals also contains remnants of viral gene sequences that have been "incorporated" over millennia. SARS and MERS have intensified research on coronaviruses precisely because a new coronavirus epidemic or pandemic was expected soon [16, 25, 26].

Twenty-two of the 38 known and by no means definitively classified coronaviruses have been extensively studied by Chinese researchers (see publications by Peng Zhou [27] on the epidemiology of "bat coronaviruses in China"), and other publications by US authors mentioned above. Zhou *et al.*, 2020 [28] predicted an upcoming new coronavirus epidemic in March 2019 for the following reasons:

1. high biodiversity in China;
2. high number of "bats" in China;
3. high population density in China = close coexistence between animals and humans;
4. high genetic variability of "bats", i.e. a high probability that the genome of individual types of coronaviruses can change spontaneously as a result of random mutations;
5. highly active genetic recombination of coronaviruses means: Coronaviruses of different types exchange genomic sequences with each other, which can make them more aggressive to humans.

The fact is that many of these viruses - coronaviruses, but also Ebola or Marburg viruses - live together in these "bats" and can accidentally exchange genetic material. Although unproven, Peng Zhou also addressed Chinese eating habits, which increase the likelihood of these viruses being transmitted from animals to humans. Peng Zhou warned of a corona pandemic in his March 2019 article. And he wrote, that he could not say exactly when and where this pandemic would break out, but that China would likely be a "hot spot." So much for scientific freedom. Peng Zhou and his Wuhan group continued research, and it was they who identified the COVID-19 genome, on January 7 and shared it with the world [25, 26].

Bats and their Relationship with SARS

There are approximately 6, 400 species of mammals on our planet. Bats are placental mammals of the order Chiroptera (from the Greek, "wings in the hands"), with around 1, 400 species. They represent the largest group of mammals, after rodents, which account for more than 20%. They are the only ones that fly, even over long distances during migration (genera *Pteropus* and *Rousettus*). They are nocturnal, feeding and mating, and live in large colonies in caves, mines, abandoned buildings, bridges, or some types of forests, resting on perches. Their age is estimated at 52 million years, and they are found at all latitudes except the Arctic, Antarctica, and some islands [29]. There are more than 1, 000 different types of bats and fruit bats; Being the only mammals that can fly, this explains their wide range of movements. Fruit bats host a large number of viruses. Throughout their developmental history, fruit bats have likely been the entry point for viruses into the mammalian lineage [16, 17, 26].

There are numerous dangerous viruses that have spread from bats to humans and are responsible for many diseases: measles, mumps, rabies, Marburg fever, Ebola, and other rarer and no less dangerous diseases. In other mammals, viruses derived from bats have repeatedly caused mass deaths in pig, chicken, or poultry farming [16, 17, 25].

The association of bats with infectious processes was traditionally limited to cases of rabies [30, 31]. Since the last third of the last century, they have been associated with emerging viral processes, such as encephalitis caused by the Nipah and Hendra viruses, Ebola hemorrhagic fever or Reovirus [32, 33], but their relationship with infectious diseases changed radically when they were linked to SARS in 2005 [34], revealing their majority association with the origin of coronaviruses, posing as a cause of future epidemic-pandemic events [35] in which some factors such as ecosystem alteration due to the climate emergency, urban pressure, wildlife trade or exotic animal markets would be key.

In practice, bats host more zoonotic viruses than any other mammal or bird species and, in general, although when they are infected with most they do so without clinical signs, there are also some exceptions, such as the Tacaribe virus (which in high titers causes mortality [36], some species of Lyssavirus (depending on the infection route) or species of Filovirus [37]. Other non-viral agents also cause disease and death, such as Pseudogymnoascus destructans, the fungus that causes “white-nose syndrome” [38, 39], a cause of death and danger of extinction in some species in North America.

As we have already seen, the relationship with bats arose following the emergence of SARS, with a coronavirus isolated from bats being identified as the cause [40-42]. Since then, a long road of study and research has been undertaken, reaching extremely important conclusions. Currently, 30 genomes of these viruses have been completed [41], six of them reference and high-quality [42], and coronaviruses have been detected or isolated in specimens from all continents, with high detection rates of the two genera of which they are considered reservoirs (*AlphaCoV* and *BetaCoV*), especially the former, postulated as ancestors of most mammalian CoV, with a great diversity of host species, always related to a particular geographical area.

The Sarbecovirus subgenus includes the SARS-CoV and SARS-CoV-2 viruses. The former was initially associated with the palm civet, but further research identified coronaviruses in *Rhinolophus* bats that showed 87 to 92% nucleotide identities with those isolated from humans [43], indicating these bats as natural reservoirs. It is proposed that SARS-CoV emerged by evolution, through recombination of bat CoVs [38, 43, 44]. The WIV1 strain, the closest to SARS-CoV (95% nucleotide identity) capable of binding to the ACE-2 receptor, may have arisen from the recombination of two prevalent SARS-CoV strains from bats [38, 43, 45].

SARS-CoV-2, the COVID-19 coronavirus, belongs to the group of SARS-related coronaviruses. It utilizes the ACE-2 receptor by binding to the S protein RBD (Hoffman *et al*., 2020) and is likely also of bat origin. To date, the most closely related virus, with 96.2% identity, is the BatCoVRaTG13 strain, identified from *Rhinolophus affinis* (Malaiyan *et al*., 2020; Tang *et al*., 2020). The SARS-CoV-2 S protein is highly divergent from other CoVs, with less than 75% identity to all described SARS-CoVs except for RaTG13, with which it is 93.1% similar. Although SARS-CoV-2 uses ACE-2, five of the six critical amino acid residues in the RBD are different from those of SARS-CoV but identical to those of pangolin SARS-CoV, leading to speculation that the SARS-CoV-2 RBD may have arisen through recent recombination events in pangolins or that SARS-CoV-2 and pangolin SARS-CoVs represent the result of coevolution [45].

In reality, bats are rarely consumed in Central China, where market photos usually show Indonesia. The pangolin trade remains a major problem in other Chinese cities and shopping centers, but not in Wuhan. However, there were 47, 381 individuals of 38 species, including 31 protected species, all kept in appalling conditions and riddled with all sorts of infectious diseases, ready to be slaughtered on demand, or even sold as pets. While pork retails for the equivalent of about $5.75 per kilo in Wuhan, a marmot would cost $25. Slightly cheaper were badgers and raccoon dogs, at $15-20, or a hedgehog for $2-3. Among birds, peacocks were popular at $56, or if reptiles were the order of the day, a sharp-nosed viper could be had for $70 per kilo. The pets included everything from squirrels ($25) to mynas ($300). It's clear, then, that this isn't subsistence bushmeat, but an expensive delicacy [41, 42, 45].

Until the emergence of SARS, the relationship between bats and coronaviruses had not aroused interest, although their association with some diseases, such as rabies, had been known for a long time. In the second half of the 20th century, their association with Ebola and Nipah and Hendra encephalitis became evident, thus organizing a body of knowledge that increasingly attracted attention to the relationship between bats and a large group of emerging viruses, among which coronaviruses are a major component [42, 45, 46].

Although bats and rodents are considered the natural reservoir of *AlphaCoV* and *BetaCoV*, and birds are considered the natural reservoir of *DeltaCoV* and *GammaCoV*, the truth is that the host spectrum is actually broader, covering other terrestrial and aquatic mammals, as well as birds and, of course, the case of humans, in which these viruses are related to low-pathogenicity respiratory processes alongside other more serious and pandemic-like ones, such as SARS-CoV-2, the cause of the current COVID-19 pandemic [27, 35, 42].

Characteristic of these viruses is their promiscuity, which, combined with a rapid evolutionary capacity with prone genetic resources (mutation and recombination), facilitates, in coincidence of favourable factors, the overflow or jump of the species barrier, producing infection in other animals directly or, at least in some human coronaviruses, with the intervention of intermediaries [28, 46, 47].

It's not surprising, then, that the wildlife trade in the wet markets of Wuhan, Hubei, China, where this COVID-19 outbreak appears to have originated, has been blamed. Candidate species include bats, which are definitive hosts for generating coronaviruses, and both pangolins and palm civets as possible intermediaries; although the most recent genetic data suggests that the variant found in these latter species is not similar enough to the human variant to be an entirely convincing source [41, 42, 45]. Nevertheless, from January 14 to February 10 of this year, the World Health Organization (WHO) sent an investigative team to Wuhan, where part of its remit was to try to determine, ex post, what animals were being sold in the markets before the lockdowns. Their report was inconclusive, but it drew attention to the particular need to monitor the trade in bats and pangolins.

With these huge concentrations of diverse species under one roof, while we find no evidence to support the original spread of bats or pangolins in Wuhan, it seems only a matter of time before some other undesirable disease spreads to the human population. In fact, it is estimated that around 70% of all diseases affecting humans originate in animals, such as avian flu, HIV, Ebola, and so on [41, 43, 46].

The Pangolin and Its Relationship with SARS

The name pangolin comes from the Malay peng-goling ("the one that curls up"). They are characterized by large, hardened, plate-like scales that cover the entire body except for the snout, face, belly, and inner limbs, making them the only mammals to possess them (Figure 1). The plates are composed of keratin, the same material that makes up human fingernails, animal claws, and rhinoceros' horns. This armor can withstand attacks from hyenas and most felids (Figure 2).

Fig 1: External morphology of a pangolin.

Fig 2: Typical pangolin scales.

When threatened, pangolins curl into a ball, using the plates as a form of armor and hiding their faces under their tails. The defensive function of these scales is reinforced by the fact that they are very sharp and can be controlled by the animal using special muscles. They can use them to injure any animal that tries to push its snout or paw inside the shell (Figure 3).

Fig 3: Pangolin coiled up in the face of a threat to its life.

African species typically have one young per gestation, while Asian species can have between one and three. They are born at a length of approximately 15 centimeters and a weight of approximately 330 grams. At birth, the young already have their eyes open, but their scales are still soft. They depend on their mother until they are three or four months old. During their first outings from the burrow, the young remain very close to the mother (in some cases, even perched on the base of her tail) so that, if she senses danger, the young can quickly hide under the mother when she curls up for protection. African pangolins inhabit southern and central Africa, from Sudan and Senegal in the north to South Africa in the south.

Taxonomic ubication

Class: Mammalia
Order: Pholidota (Weber, 1904)
Family: Manidae (Gray, 1821)
Generas: *Manis* (typical of the Asian continent), *Phataginus* (typical of the African continent)
Species: *Manis crassicaudata*, *M. culionensis* (Philippine pangolin), *M. pentadactyla* (long-tailed pangolin), *M. javanica* (Malay pangolin), *M. gigantea* (giant pangolin-Figure 4), *M. tricuspis* (tree pangolin-Figure 5), *M. temminckii* (The Cape pangolin).

Fig 4: Giant pangolin

Fig 5: Tree pangolin.

In a study by Xiao *et al*. (2020) [48], entitled “Isolation of SARS-CoV-2 related coronavirus from Malayan pangolins, ” and published in the prestigious journal Nature, they demonstrated that a coronavirus, called pangolin-CoV, isolated from a Malayan pangolin, exhibits 100%, 98.6%, 97.8%, and 90.7% amino acid identity with SARS-CoV-2 in the E, M, N, and S proteins, respectively. Notably, the receptor-binding domain of the pangolin-CoV S protein is nearly identical to that of SARS-CoV-2, with one non-critical amino acid difference. This comparative genomic analysis suggests that SARS-CoV-2 may have originated from the recombination of a pangolin-CoV-like virus with a RaTG13-like virus. The pangolin-CoV virus was detected in 17 of the 25 Malayan pangolins analyzed. Infected pangolins showed clinical signs and histological changes, and circulating antibodies against pangolin-CoV virus reacted with the S protein of SARS-CoV-2.

The isolation of a coronavirus in pangolins, closely related to SARS-CoV-2, suggests that these animals have the potential to act as intermediate hosts for SARS-CoV-2. This coronavirus, recently identified in pangolins—the most trafficked mammal in the illegal wildlife trade—could pose a future threat to public health if the wildlife trade is not effectively controlled [45, 47].

All of these sites along Route G56 were investigated, in addition to the Kunming-to-Laos route, which provides a broader view of the wildlife trafficking complex, which added many buildings between 2011 and 2019 en route to Wuhan. Sixty-five of the 66 COVID-19 restriction sites originate from BANAL lineages in these locations and from pangolins. The above placement is justified by the high level of pangolin trafficking, from Laos to China and vice versa (published by: https://www.rage.com.my/pangolin/).

On the road from Laos to Wuhan

Bus stops allow buses to return in the opposite direction, after stopping to refuel, eat, rest, and, of course, unload "special cargo" from the bus holds. On a highway, this type of departure is typically seen at least every three hours. Imagine a relay race, with buses traveling three to four hours each way and returning the way they came each day. Nearly all bus stops like this one on G56 show evidence of wildlife trade and investment, and most showed construction activity in the fall of 2019. Due to unsynchronized schedules or other unforeseen events, the locations where buses turn around often have low buildings for storing "stuff." However, at two special locations, there are much more extensive wildlife breeding buildings.

The first is Babian city in Yunnan. The road from Boten to Kunming is the G8511, which becomes the G56 in Kunming and continues to Shanghai, passing through Huangshi, two hours south of Wuhan. But more importantly, it passes half an hour from Longgangzhen, Hubei, making Longgangzhen a key city for wildlife breeding and instrumental in the origin of COVID-19. The first turnaround point is just 25 km from Boten. There are huge, compartmentalized, single-story buildings that appear to be designed for wildlife. A white bus was spotted here on this date in 2019 [48].

This location is strategic because it is far enough from the border, yet close enough that Lao bus drivers do not have to drive all the way to Babian Town. It makes more sense for buses to travel regularly from here to the next major return point. This bus stop is located in Babian Town (250 km from Boten, Laos). There are not many people here. It is a remote location, suspected of being controlled by the Triad criminal organization. They are known to be in Kunming, another 250 km away. The buildings in this town betray that it is well-organized, well-funded, and discreet, with the money controlled by a single entity. Just past the toll gate is a convenient bus stop parking lot [48].

Over four hours from Babian Town is Kunming, the main city. There is a long-distance bus station (LDBS) here. There is no wildlife breeding barracks within cities. Below is another long-distance bus station (LDBS) along the G56, with a small red structure added in early 2020. This is most likely for surveillance purposes, as it was built before PCR testing existed. The "main route" seems to be the best option for going to Chongqing or Wuhan. The "secondary route" favors Shanghai, Shenzhen/Guangzhou, and other coastal cities. But other than these, any route would work, depending on surveillance on a given day. Let's first take the main route to Wuhan. The first stop on the G56 is Wangjia, Wuji. The Shengji LDBS is located behind a large market, with some warehouses available behind it. A new white structure, similar to the red one in Kunming, has been in use since 2020, next to the main blue eaves. The grounds are hidden by trees, but extend alongside the market buildings, extending from the blue eaves, where there are shadows in the lower center [48].

This whole framework of conjectures shown in the study carried out by Xiao *et al*. (2020) [48], has a quite plausible logic, but there are still questions to be elucidated, specifically, how did this virus spread to humans?

Probable theories as to how this virus spread to humans

1. The COVID-19 virus has been transmitted directly from a bat to humans. However, the structure of the virus that is in question and that genetically matches 96% of the current "COVID-19" virus cannot bind to the "angiotensin-converting enzyme" (ACE) type 2 in the lungs. However, the virus needs this enzyme in order to penetrate lung cells (and heart, kidney and intestinal cells) and destroy them.
2. A COVID-19 virus jumped to humans from the pangolin, a dan ruffed mammal from Malaysia that was illegally imported into China, and which initially did not cause disease. As part of consecutive human-to-human transmissions, this virus has adapted to general human conditions through mutation or adaptation, and was eventually able to attach to the ACE2 receptor, and penetrate cells, which "started" the pandemic.
3. There is an original strain of these two viruses COVID-19, which unfortunately so far has not been detected.
4. It is a synthetic laboratory virus, because this is exactly what was investigated and the biological mechanism of the excitation, and described in detail in 2016.

The virologists in question denied this possibility, of course, but they also cannot rule it out in the "Nature Medicine" just published: "The proximate origin of SARS-CoV-2" by Kristian Andersen [26].

What is special about these facts is that coronaviruses can live together with the Ebola virus in the same "bat" without the bat getting sick. On the one hand, this is scientifically interesting, because perhaps immune mechanisms can be found that explain why these bats do not get sick. These immune mechanisms against coronaviruses and Ebola virus could provide important information for *Homo sapiens*. On the other hand, these facts are worrisome, because one can imagine that due to high and active genetic recombination, a supervirus can form, which has a longer incubation period than the current COVID-19 virus, but with similar lethality to the Ebola virus [26].

SARS had a lethality of 10%, MERS lethality was 36%. It was not due to *Homo sapiens* that SARS and MERS did not spread as fast as COVID-19 now. It was just luck. The claim that a virus with a high mortality rate could not spread because it was killing its host too fast was correct at the time when a caravan of "infected" camels had left Xian for the Silk Road and that is why the high mortality did not spread to the next caravan. Today it is very easy. Today everyone is massively networked. A virus that kills in three days still goes around the world.

What do we know? and What don't we know?

We know that it is an aggressive virus;

1. that the average incubation period lasts five days; the maximum incubation period is not yet clear;
2. that asymptomatic carrier of COVID-19 can infect other people, and that this virus is "extremely contagious" and "extremely resistant";
3. we know the populations at risk;
4. that in the last 17 years it has not been possible to develop a vaccine or a monoclonal antibody against coronaviruses;
5. that it has never been possible to develop a vaccine against any coronavirus;
6. that the so-called "flu vaccine" has minimal effect, contrary to popular publicity.

What we do not know

1. Whether or not immunity exists after passing an infection. Some data indicate that humans can develop class G immunoglobulins after day 15, which should prevent re-infection for the same virus. But this has not yet been definitively proven;

2. how long a possible immunity could protect;
3. whether this COVID-19 virus remains stable or whether a slightly different COVID-19 spreads again worldwide in autumn, analogous to the usual flu wave, against which there is no immunity;
4. If higher temperatures in summer help us because the COVID-19 casing is unstable at higher temperatures. It should be mentioned here that the MERS virus spread in the Middle East from May to July, when temperatures were higher than we have ever experienced;
5. How long it takes for a population to become so infected that the R-value is <1:
   If 1 million people in Zurich are tested at a given time, COVID-19 12% to 18% are said to be positive at this time. To deprive the pandemic of its pandemic character, the R-value must be <1, i.e., about 66% of the population must have had contact with the virus and developed immunity. No one knows how long, how many months it will take until the infection, currently assumed to be 12% to 18%, has reached 66%! But it can be assumed that the spread of the virus from 12% to 18% to 66% of the population will continue to generate seriously ill patients.
6. So, we do not know how long we will be dealing with this virus. Two reports, which should not be publicly available (US Government COVID Response Plan and a report from Imperial College London) independently arrive at a "shutdown" phase of up to 18 months;
7. and we do not know if this virus will occupy us epidemically / pandemically or perhaps even endemically;
8. We still do not have a recognized and widely applicable defined therapy, and we have never been able to present one of these therapies in the case of influenza.

Perhaps the authorities and the media should put the facts on the table instead of presenting every other day reports of a seemingly successful vaccine, and that is still a long way off.

How did this virus spread so quickly that it became a pandemic?

This wouldn't be the case with SARS-CoV-2, the virus that causes COVID-19. The phenomenon known as "zoonotic spillover" is when a pathogen/etiological agent passes from a wild/natural reservoir (bats and pangolins) to humans, as happened with the Black Death in the 14th century of our era (a.C.).

Let us keep in mind that these viruses are characterized by their promiscuity, which, combined with a rapid evolutionary capacity with prone genetic resources (mutation and recombination), facilitate, due to the coincidence of favorable factors, the overflow or jump of the species barrier, producing infection in other animals directly or, at least in some human coronaviruses, with the intervention of intermediaries, which is why answers to these questions are still awaited: does the original/mother strain of SARS-CoV-2 come from Wuhan?, how many lineages emerged/were derived for sure from said mother strain?, what is the index case of this pandemic? and will this case precisely originate in Wuhan?

Conclusion

This is a highly infectious entity with a high probability of zoonotic transmission, with bats and pangolins standing out as potential reservoirs. Humans themselves have played a decisive role in the introduction and spread of SARS-CoV-2, the virus that causes COVID-19. Therefore, we do not know if the virus will become endemic, recurring year after year, or will eventually be controlled. What we do know is that we need the joint effort of all human beings who inhabit this planet to win the battle against this new coronavirus.

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