# History of Pandemics and COVID-19: What We are Learning from this Pandemic to Be Prepared for the Next One

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**Since the beginning of human history, the pathogens affect the humankind. The emerge of the new outbreak of coronavirus-19 (COVID-19) is not new in the history of plagues. However, this pandemic has a huge difference from the others due to its ability to affect worldwide at the same time, which brings new perspectives to our future. In this review, we listed some of the worst epidemics and pandemics of human civilization and the new outbreak, presenting the pathogens, the spread, and the consequences for mankind. Our search included articles in the main database (PubMed/Medline, Elsevier Science Direct, Scopus, Isi Web of Science, Embase, Exerpta Medica, UptoDate, Lilacs, Novel Coronavirus Resource Directory from Elsevier), in the high-impact international scientific Journals (Scimago Journal and Country Rank - SJR - and Journal Citation Reports - JCR), such as The Lancet, Science, Nature, The New England Journal of Medicine, Physiological Reviews, Journal of the American Medical Association, Plos One, Journal of Clinical Investigation, and in the data from Center for Disease Control (CDC), National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID) and World Health Organization (WHO). We prior selected meta-analysis, systematic reviews, article reviews, and original articles in this order. We reviewed 192 articles and used 94 from March to June 2020, using the terms coronavirus, SARS-CoV-2, novel coronavirus, Wuhan coronavirus, severe acute respiratory syndrome, 2019-nCoV, 2019 novel coronavirus, n-CoV-2, COVID, n-SARS-2, COVID-19, corona virus, coronaviruses, history of pandemics and epidemics, pathogens, plagues, with the tools MeSH (Medical Subject Headings), AND, OR, and the characters [,“,; /., to ensure the best review topics. We concluded that this pandemic will change the social and economic order, as well as it is the first that affects us at the same time. So, the experience of COVID-19 could teach us how to be prepared for other outbreaks in the future.**

**Keywords: COVID-19. SARS-CoV-2. Hystory of Pandemics. Humankind. Future.**

## Introduction

During human history, diseases, and illnesses, especially infectious diseases, have disturbed humanity since the earliest days [1].

The infectious disease outbreaks have been closed the human being. More than 60% of human infectious diseases are caused by pathogens shared with wild or domestic animals [2]. Most emerging viruses come from animals and are zoonotic or vector-borne diseases belonging to the families *Orthomyxoviridae*, *Paramyxoviridae*, *Picornaviridae*, *Coronaviridae*, *Adenoviridae*, and *Herpesviridae*.

Nevertheless, community-acquired respiratory viruses are critical pathogens such as influenza, respiratory syncytial virus, adenovirus, parainfluenza virus, human coronavirus, human metapneumovirus, rhinovirus, enterovirus, because of the potential to cause millions of deaths and hospitalizations all over the world every year [3, 4].

The zoonoses are responsible for a billion cases of illness in people and millions of deaths every year, and the emerging zoonoses such as COVID-19 pandemic are an actual threat to global health.

In general, the zoones are responsible for human acts, such as changes in land use and extractive industry actions, animal production systems, and widespread antimicrobial applications, which affect the zoonotic disease transmission [2].

The emergence of novel human pathogens and reemergence of several diseases is a particular issue in the current century [5, 6].

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Before December 2019, there are 6 strains of coronavirus (CoVs) that can infect humans and cause respiratory diseases: HCoV-229E, HCoV-OC43, HCoV-NL63, and HKU1 with mild upper respiratory disease with rare severe infections occurring in infants, young children, and elderly people [7]. The three exception are SARS-CoV-1 and MERS, that was responsible for two outbreaks in 2003 and 2012, respectively. They infect the lower respiratory tract and could lead to a severe respiratory condition in humans. And also the current COVID-19, that since the beginning (December 2019 in Hubei, China) until now (June 3, 2020) spreads for all over the world with a 6,414,473 confirmed cases, and 380,940 deaths [8-10].

The increase of epidemics and pandemics in the last years is a paradox because as more civilized men became, the more likely pandemics would occur (Ebola in 2014-2016, Zika, Dengue, HIV, H1N1, H2N3, and currently COVID-19) [1, 6].

Sometimes the outbreaks change the course of history or ravage millions of lives or signaling to the end of entire civilizations [11]. The social concentration in urban cities, the ease of traveling, the globalization [5], the contact with different populations, and cultural and social behaviors, as well as the destruction of many ecosystems by the human being, the air and water pollution [1, 11], created new opportunities for human and animal interactions, which sped up to such epidemics. And a bad interaction between people, animals, and ecosystems increases the risk of pandemics, such as COVID-19 [10].

However, ecological and evolutionary perspectives can provide valuable insights into pathogen ecology and can inform zoonotic disease-control programs through a multisectoral collaboration, which includes clinicians, public health scientists, epidemiologists, ecologists, and disease ecologists, veterinarians, economists, and others for effective management of the causes and prevention of zoonotic diseases response to zoonotic diseases and elimination or mitigation the transmission routes to prevent future outbreaks [2]. As well as, the healthcare improvements, the new technologies applied to health, the novel discoveries, and the prophylaxis public health, decrease the death rate. Also, the understanding factors that incubate pandemics have been powerful tools in mitigating their impact, despite the critical social and economic repercussions which a pandemic cause in society [1, 11].

In this review, we summarized some of the worst epidemics and pandemics of human civilization until the new outbreak (COVID-19) listing the pathogens, the spread, and the consequences for mankind with the focus in the COVID-19.

## A Timeline of the Main Historical Pandemics

We resumed the main epidemic and pandemic of human history over time in Table 1 and Figure 1, and show the respiratory viral outbreaks in Table 2.

## The Rage of the Gods

In ancient societies, people believed that gods applied diseases and destruction upon those or communities that deserved their rage [1]. The lack of knowledge about the cause of the epidemic or pandemic leads to millions of deaths. For example, Procopius of Caesarea, a Byzantine historian, determined the origins of the Justinian's plague (*Yersinia pestis*): the disease originated from China and northeast India entered in the Byzantine Empire by Mediterranean ports through land and sea commerce routes to Egypt [1, 11]. Despite Procopius's knowledge about the plague, he accused the Emperor Justinian for the outbreak, invoking God's punishment for his evil actions. Some historians believed that this situation could have destroyed Emperor Justinian's forces to join the Western and Eastern remnants of the Roman Empire, and registered the beginning of the Dark Ages [1, 2, 6, 7, 9, 11].

However, the human knowing of the diseases' causes improved in the course of time, which follows in a radical improvement to recent pandemics [1, 9].

**Table 1.** The worst epidemic and pandemic worldwide yhrough the years with the number of human deahts.

| Name | Time period | Type / Pre-human host | Death toll |
|---|---|---|---|
| Circa | 3000 b.C. | No clue | 30,000 |
| Plague of Athenas | 430 b.C. | Believed to be the smallpox | 100,000 |
| Antonine Plague | 165-180 A.D. | Believed to be either smallpox or measles | 5M |
| Plague of Cyprian | 250-271 A.D. | The scientists have no certain about the cause of the epidemic | 5,000 people a day in Rome alone |
| Japanese smallpox epidemic | 735-737 A.D. | Variola major virus | 1M |
| Plague of Justinian | 541-542 A.D. | *Yersinia pestis* bacteria / Rats, fleas | 30-50M |
| Black Death (Figures 2, 3) | 1347-1351 A.D. | *Yersinia pestis* bacteria / Rats, fleas | 200M |
| New World smallpox outbreak (Figures 4, 5) | 1520 – 1971 (erradicated) | Variola major virus | 56M |
| Cocoliztli epidemic | 1545-1548 A.D. | *Salmonella paratyphi* C | 15M |
| American Plagues | 16th century | Influenza, smallpox (brought to the Americasn by European explorers) | Millions of indigenous people |
| Great Plague of London | 1665 A.D. | *Yersinia pestis* bacteria / Rats, fleas | 100,000 |
| Italian Plague | 1629-1631 A.D. | *Yersinia pestis* bacteria / Rats, fleas | 1M |
| Great Plague of Marseille | 1770-1772 A.D. | *Yersinia pestis* bacteria / Rats, fleas | 1M |
| Philadelphia Yellow Fever | 1793 A.D. | Virus / Mosquitoes | >5,000 |
| Cholera pandemics (Figure 6, 7) | 1817-1923 A.D. | Believed to be H2N2 (avian origin) | 1M+ |
| Third Plague | 1885 A.D. | *Yersinia pestis* bacteria / Rats, fleas | 12M (China-India) |
| Yellow Fever (U.S.) | Late 1800s A.D. | Virus / Mosquitoes | 100,000-150,000 |
| Russian Flu (spread to all Europe) | 1889-1890 A.D. | Believed to be H2N2 (avian origin) | 1M |
| American Polio Epidemic | 1916 | Poliovirus | Millions of deaths and millions of children defects |
| Spanish Flu (Figures 8, 9) | 1918-1919 A.D. | H1N1 virus / Pigs | 40-50M |
| Asian Flu | 1957-1958 A.D. | H2N2 virus | 1.1M |
| Hong Kong Flu | 1968-1970 A.D. | H3N2 virus | 1M |
| HIV/AIDS (Figure 10) | 1981-present | Virus / Chimpanzees | 25-35M |
| Dengue Fever | 1994-present | Mosquitoes *Aedes Aegypti* | Millhions of death |
| Swine Flu | 2009-2010 A.D. | H1N1 virus / Pigs | 200,000 |
| SARS (Figure 11) | 2002-2003 A.D. | Coronavirus / Bats, Civets | 770 |
| Ebola (Figure 12) | 2014-2016 A.D. | Ebolavirus / Wild animals | 1,000 |
| Zika Virus | 2015-present | Mosquitoes of the *Aedes* genus | Millions of birth defects (mycrocephalia) |
| MERS (Figure 13) | 2015-present A.D. | Coronavirus / Bats, camels | 850 |
| SARS-COV-2 (COVID-19) (Figures 14, 15) | 2019-present A.D. | Coronavirus – Unknown (possibly pangolins) | 380,940 [8] |

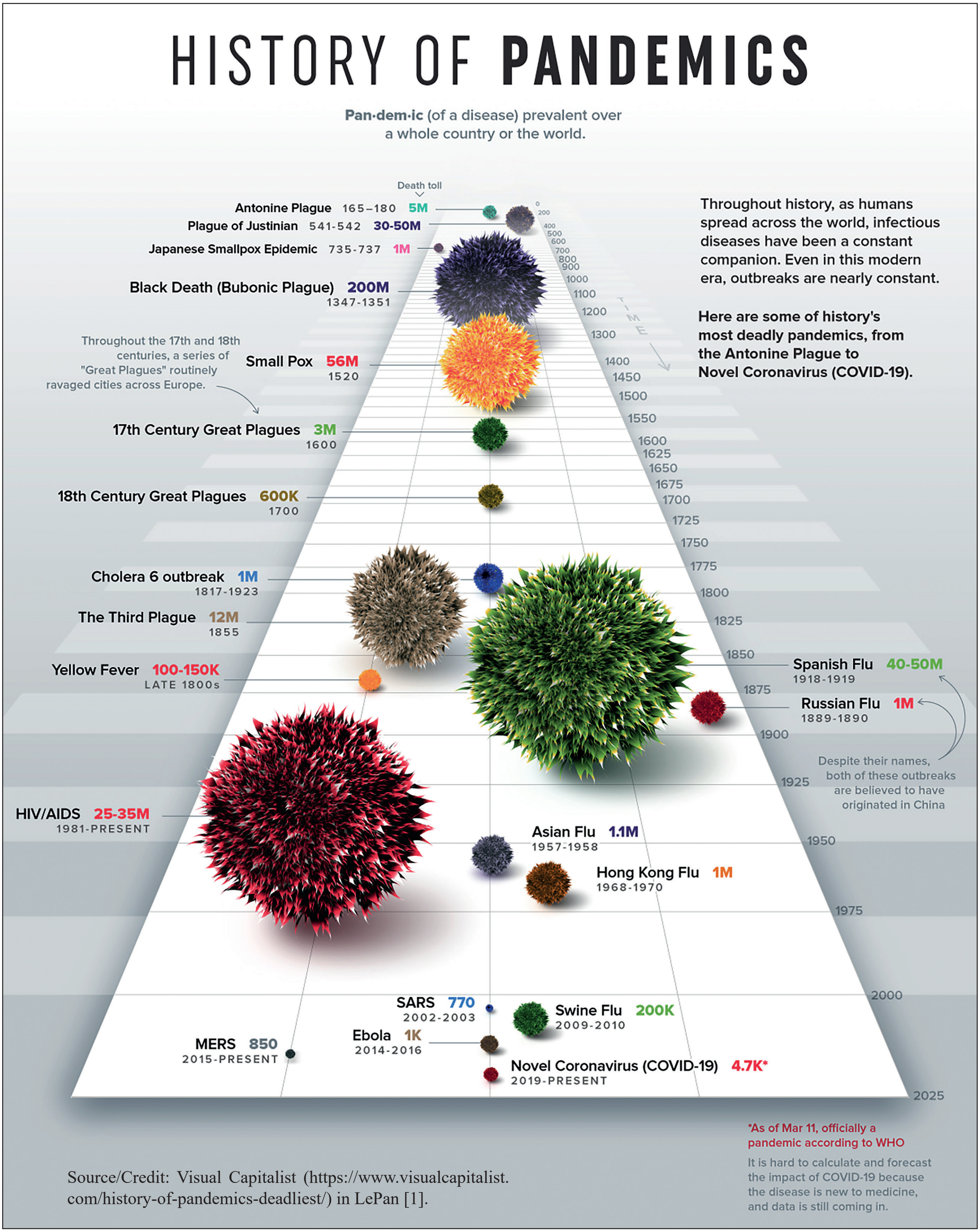
M: million.

## Mitigating the Diseases

During the 14th century, port authorities of Venice, Italy, required the ships that arrived from infected ports to stay at anchor for 40 days before landing. The name quarantine came from Italy of the expression, “quarenta giorni”, which means 40 days [1, 9].

The health surveillance realized that the 40 days in isolation is sufficient to protect coastal cities from plague epidemics. So, this is one of the

**Figure 1.** History of pandemics.



**Pan·dem·ic** (of a disease) prevalent over a whole country or the world.

Throughout history, as humans spread across the world, infectious diseases have been a constant companion. Even in this modern era, outbreaks are nearly constant.

**Here are some of history's most deadly pandemics, from the Antonine Plague to Novel Coronavirus (COVID-19).**

Throughout the 17th and 18th centuries, a series of "Great Plagues" routinely ravaged cities across Europe.

Despite their names, both of these outbreaks are believed to have originated in China

*As of Mar 11, officially a pandemic according to WHO

It is hard to calculate and forecast the impact of COVID-19 because the disease is new to medicine, and data is still coming in.

Source/Credit: Visual Capitalist (https://www.visualcapitalist.com/history-of-pandemics-deadliest/) in LePan [1].

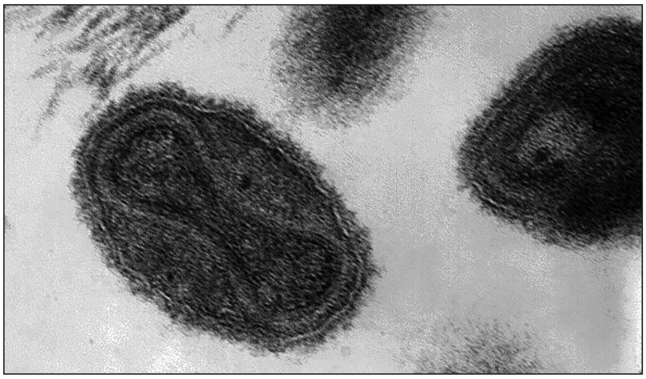
**Figure 2.** A depiction of "Doctor Schnabel" during the plague in Rome.

Source/Credit: Illustration appeared in a 17th Century. First published by Paul Fürst (1608–1666 CE), from Europas Sprung in die Neuzeit, by Johannes Ebert and colleagues [12].

**Figure 3.** The spreading of the plague in Medieval period.

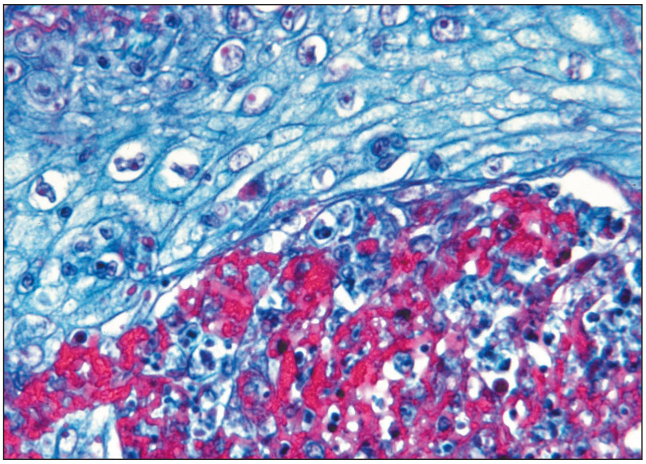
The plague killed a 3/4 from Europe.
Source/Credit: https://nilefm.com/digest/article/5114/7-pandemics-from-human-history-that-make-COVID-19-look-like-a-joke [13].

**Figure 4.** Micrography of smallpox virus.



Source/Credit: Wikimedia. https://commons.wikimedia.org/wiki/Category:Variola_virus [14].

**Figure 5.** Smallpox virus attacking a cell.



Source/Credit: Pixnio. https://pixnio.com/?s=smallpox [15].

first sanitary efforts to mitigate diseases spread. Geography and statistical analysis began to be used as a method during the cholera outbreak in London in the 19th century [1, 2].

However, the connections involving urban life play a fundamental role in pandemics [1, 6, 7], notwithstanding the virulent nature of the disease is what will designate the direction of the pandemic [6, 7].

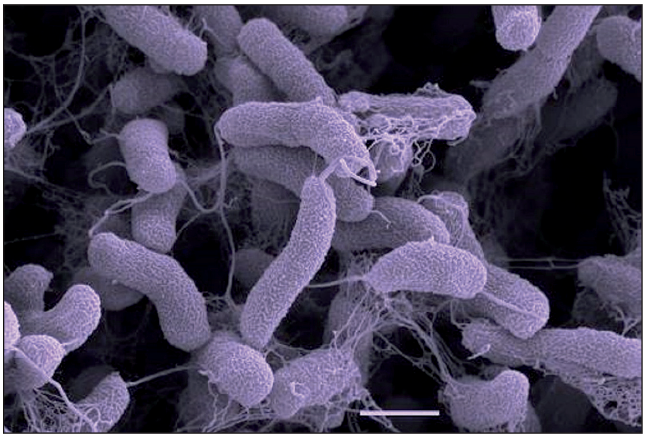
## Tracking Infectiousness

Science measures the track of disease infectiousness with a reproduction number (R0), which predicts on average how many susceptible people getting sick could infect

**Figure 6.** A portrait of transmission of cholera.

"Death's Dispensary": This caricature published during the London cholera epidemic of 1866 was a response to the hypothesis of the English epidemiologist John Snow, who linked the cholera epidemic with sewage seeping into ground water used for drinking (1866)
Source/Credit:http://www.environmentandsociety.org/arcadia/first-cholera-epidemic-st-petersburg [16].

**Figure 7.** Micrography of *Vibrio cholerae*.

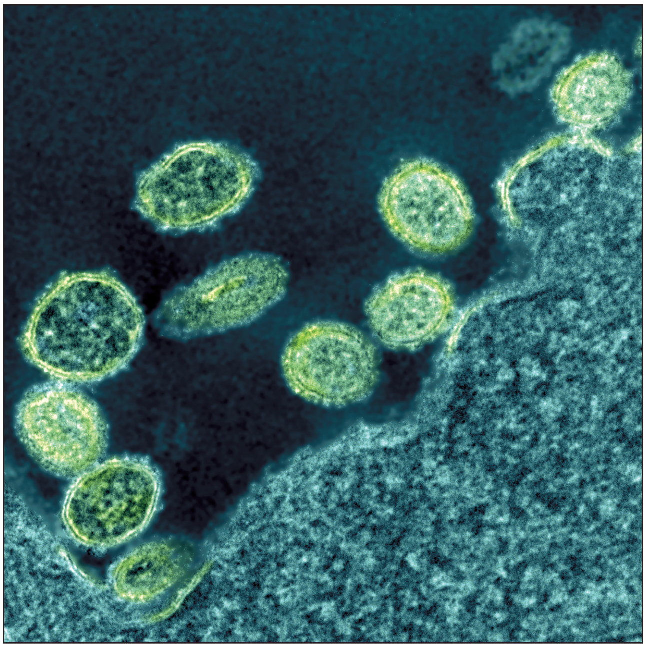


Source/Credit: Luciana Cangussu. https://www.luciacangussu.bio.br/atlas/vibrio-spp/ [17].

**Figure 8.** Spanish flu (measures of contention).

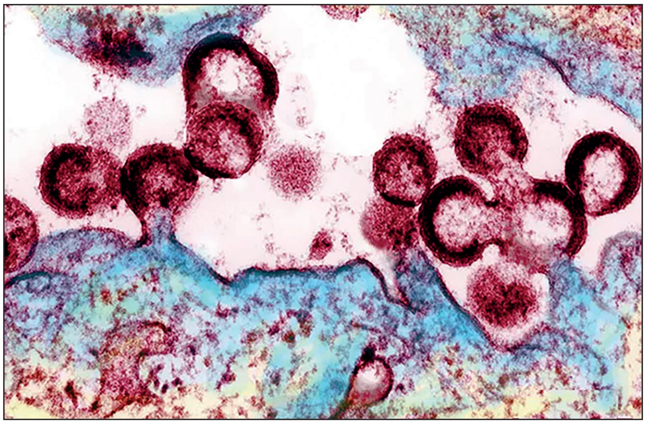
Source/Credit: https://aboutmanchester.co.uk/a-portrait-of-a-pandemic-bbc-marks-the-centenary-of-spanish-flu-revealing-the-untold-stories-of-its-impact-on-people-and-places-across-the-country/. [18, 19].

**Figure 9.** Influenza virus. Virus particles of 1918 H1N1 (Spanish Flu).



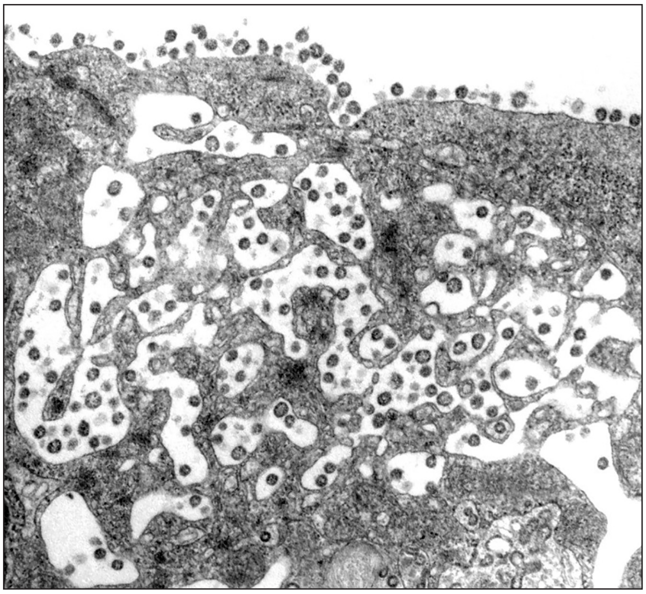
Source/Credit: Electron micrograph of 1918 H1N1 influenza virus particles near a cell. https://www.flickr.com/photos/niaid/30012820867. Credit: NIAID [20].

**Figure 10.** HIV budding from an infected CD4 cell.



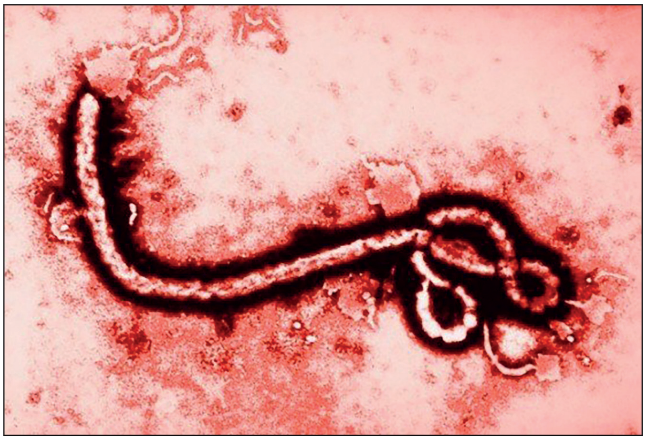
Source/Credit: National Institute of Allergy and Infectious Diseases (NIAID). https://www.niaid.nih.gov/ [21].

**Figure 11.** SARS-CoV micrography.



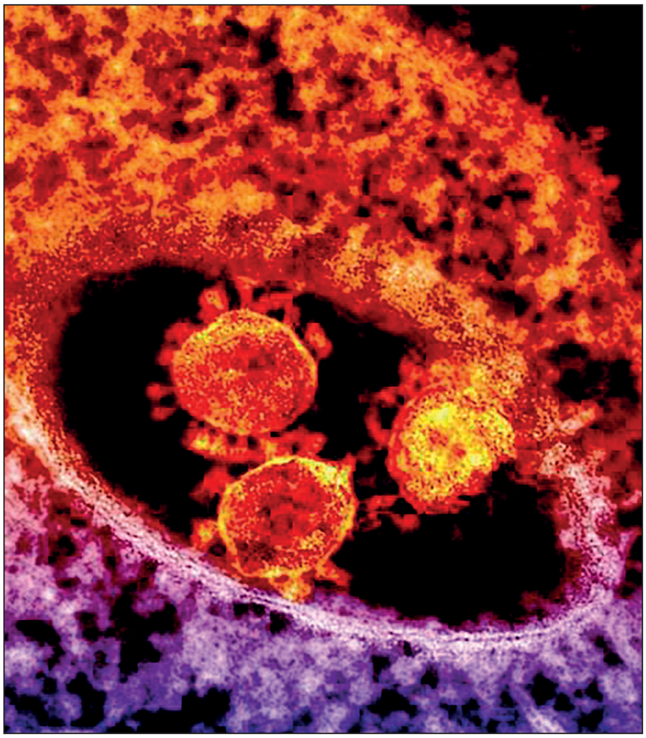
Source/Credit: A SARS-CoV-infected cell with virus particles in vesicles. [22].

**Figure 12.** Micrography of Ebola virus.



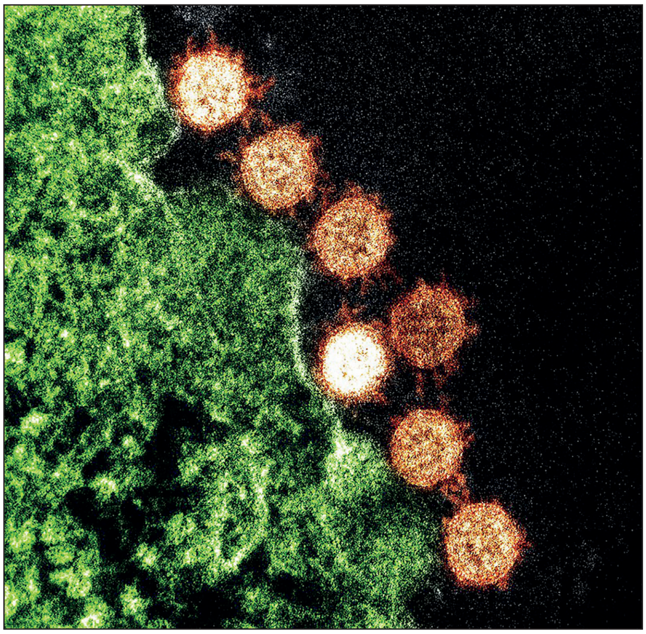
Source/Credit: CDC, USA [23].

**Figure 13.** Micrography of coronavirus that causes Midle East Respiratory Syndrome (MERS).



Source/Credit: CDC, USA [21, 23].

**Figure 14.** Electron micrograph of Severe Acute Respiratory Syndrome (SARS-CoV-2) virus particles.



Colorized transmission electron micrograph of Severe Acute Respiratory Syndrome (SARS-Cov-2) virus particles (orange) found near the periphery of an infected cell (green). Image captured and color-enhanced at the NIAID Integrated Research Facility in Fort Detrick, Maryland.
Source/Credit: NIAID, USA [21].

**Figure 15.** Collecting a sample of SARS-CoV-2 from bat.

Source/Credit: https://edition.cnn.com/2020/03/19/health/coronavirus-human-actions-intl/index.html [24].

others. For example, measles in on the top of the list with R0 range 12-18, which means that one person can infect 12-18 people (Figure 16) [1, 11].

### Urbanization and Disease's Spread

From small hunting and gathering tribes to the metropolis, the development connections, the increasing the populations in urban cities, passenger air traffic doubled in the past decade, and the rise of the contact of people with a globalization world created a good environment for the diseases to spreading and provoking a pandemic [1, 7, 11].

## The COVID-19 Pandemic

### Animals and Coronaviruses

The coronaviruses caused a wide range of animal diseases [10]. In the second half of the 20th century, many research proceeded with these viruses due to their capability to cause severe disease in cattle and pets such as pigs, cows, chickens, dogs, and cats (Figure 17) [10, 37, 38].

### The History of Coronaviruses

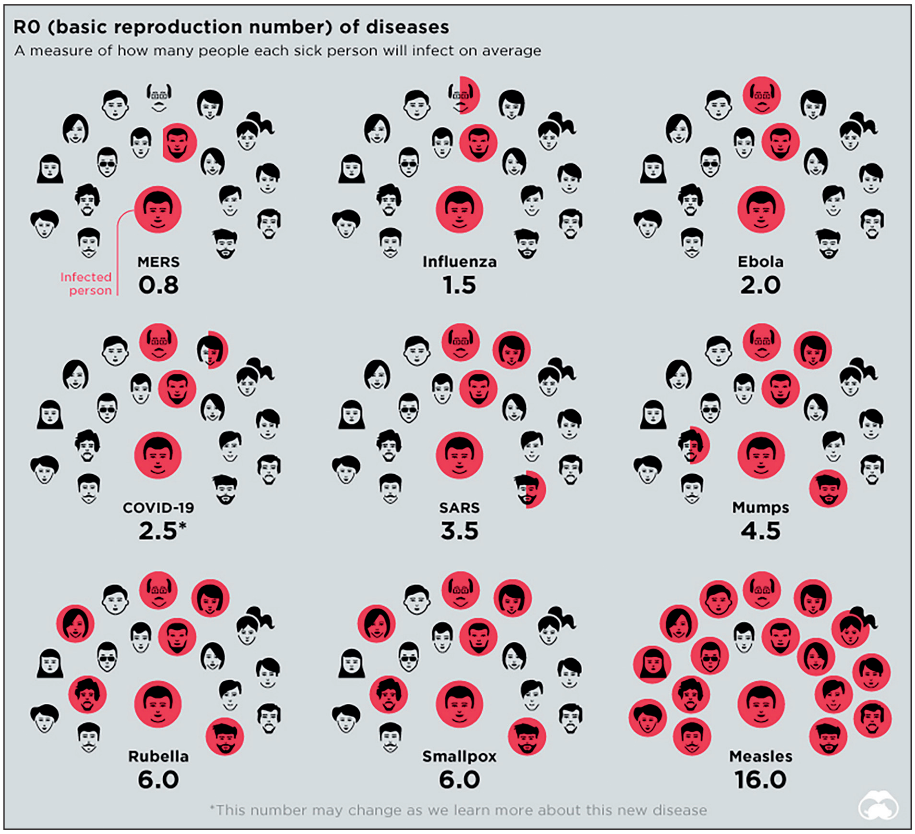
We sumarized in Table 3 a brief history of coronavirus, except to COVID-19.

**Table 2.** Outbreaks of emerging and reemerging respiratory viral infections.

| Virus | Year | Region |
|---|---|---|
| Spanish Flu H1N1 | 1918 | Spain [25] |
| Asian flu H2N2 | 1956 | East Asia [26] |
| HCoV-229E HCoV-OC43 | 1960 | The different part of the World [27] |
| Hong Kong Flu H3N2 | 1968 | Hong Kong [26] |
| Hantavirus pulmonary syndrome | 1993 | USA [28] |
| Influenza A H5N1 | 1997 | Hong Kong [26] |
| Influenza A H9N2 | 1999 | Hong Kong [26] |
| Human metapneumovirus | 2001 | Netherlands [29] |
| SARS CoV | 2002–2003 | Guangdong, China [30] |
| Human CoV NL63 | 2004 | Netherlands [31] |
| Influenza A H7N7 | 2004 | Netherlands [26] |
| Human CoV HKU1 | 2005 | China [31] |
| Triple reassortant H3N2 Influenza A | 2005 | Canada [26] |
| Bocavirus | 2005 | Sweden [32] |
| Influenza A H1N1 pmd09 | 2009 | Mexico [26] |
| Adenovirus 14 | 2010 | USA [33] |
| Influenza (H3N2) | 2011 | USA [34] |
| MERS-CoV | 2012 | Saudi Arabia [35] |
| Influenza A H7N9 | 2013 | China [26] |
| Influenza A H10N7 | 2014 | China [26] |
| SARS-CoV-2 | 2019 | China [36] |

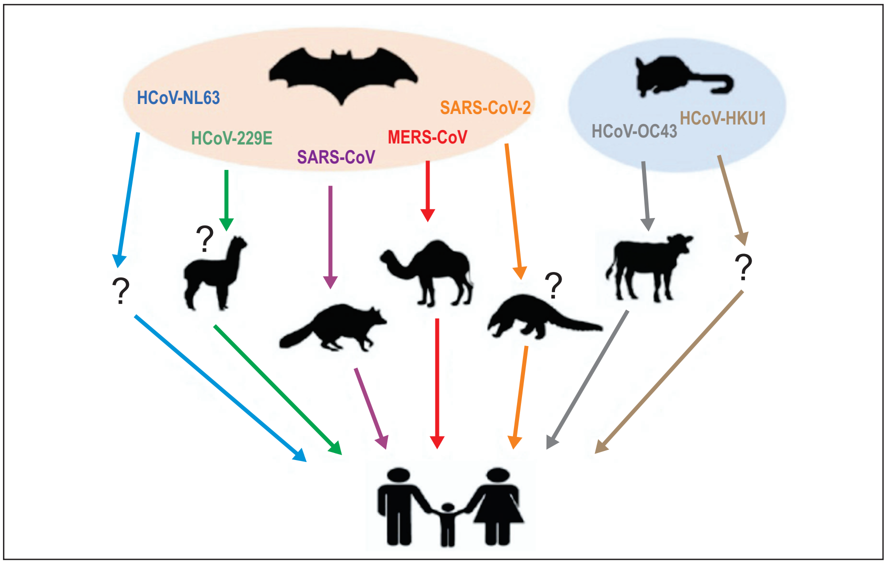
Source/Credit: Çelik and colleagues [6].

**Figure 16.** R0 (basic reproduction number) of diseases.



Source/Credit: Visual Capitalist in https://www.weforum.org/agenda/2020/03/a-visual-history-of-pandemics [1].

**Figure 17.** Animal hosts of HCoVs.



Blue, green, purple, red, orange, grey, brown arrows represent the transmission of HCoV-NL63, HCoV-229E, SARS-CoV, MERS-CoV, SARS-CoV-2, HCoV-OC43 and HCoV-HKU1 from their natural hosts (bats or rodents) to the intermediate hosts (camelids, civets, dromedary camels, pangolins or bovines), and eventually to the human population. No concrete evidence exists on the intermediated host(s) of HCoV-NL63 and HCoV-HKU1, which was shown as a question mark (?). Source/Credit: Ye and colleagues [39].

**Table 3.** Summary of animal coronavirus origins.

| Discovery | Year/Description | Virus Name | Animal hosts | Intermediate hosts | References |
|---|---|---|---|---|---|
| Beaudette & Hudson | 1937 | IBV | Bats | Chickens with respiratory disease | 40 |
| Cheever and colleagues | 1949 | MHV | Rats | Murine and hepatitis viruses | 7 |
| Discovery that the three coronavirus genus described were related | 1946 / 1960 | HCoVs | Bats<br>Rodents | Transmissible gastroenteritis in swine | 7 |
| Tyrrell & Bynoe /<br>Hamre & Procknow | 1965 (The first human coronavirus, and resemble avian IBV) | B814 | Bats<br>Rodents | Chickens | 41, 42 |
| Almeida & Tyrrell | 1967<br>The morphology of the virus is identical to B814 and IBV | HCoV 229E | Bats | Camelids (?) | 43-46 |
| [1] HCoV OC43 / OC43 or 229E | 1967 | HCoV OC43 | Rodents | Bovines | 7, 47 |
| [2] SARS Pandemic | 2002/2003 | SARS-CoV | Bats | Palm civets | 47-59 |
| HCoV-NL63 | 2004 | HCoV-NL63 | Bats | Unidentified | 60, 61 |
| HCoV-HKU1 | 2005 | HCoV-HKU1 | Rodents | Unidentified | 47 |
| MERS-CoV (Camels serve as the bona fide reservoir host of the virus) | 2012 | MERS-CoV | Bats | Dromedary camels | 48, 62-72 |
| SARS-Cov-2 | 2019 | SARS-Cov-2 | Bats | Pangolins (?) | 73 |

[1] Six further strains were recovered using the organ culture technique, including the prototype strains HCoV OC43 as well as three strains considered antigenically unrelated to either OC43 or 229E. [2] The appearence of SARS-Cov was in the Guangdong province, China. In 2002 to 2003, an unusual and often deadly form of pneumonia that lead to a severe acute respiratory syndrome (SARS). It spreads to moere than 29 countries. The SARS-CoV began in Guangdong exotic markets where live animal are held, traded and sold to restaurants in response to the demand for exotic food. Small mammals, such as civet cats, sold in these markets were found to harbour viruses closely related to SARS-CoV, and the initial interspecies transmission to humans probably came from these markets.

### *The History of COVID-19*

The first reported patient with COVID-19 was admitted to the Central Hospital of Wuhan on 26 December 2019, 6 days after the start of the disease, with fever, chest tightness, dry cough, dyspnea, body-pain, and weakness for one week of the symptom's presentation. The radiological findings revealed bilateral lung glassy opacities. Hasöksuz and colleagues [37] reported that the Wuhan Centre for Disease Control and Prevention led an epidemiological investigation and found that the patient worked at a seafood market where a variety of live wild animals (including hedgehogs, badgers, snakes, and birds) were available for sale. However, no bats were available for sale, and the patient reported no exposure to live poultry but possible contact with wild animals [37, 74]. In a sequence of quick events, what the first patient brought with him spread worldwide.

We summarized the dates and events below:

- 31 December 2019 – WHO China Country Office informed that cases of pneumonia with an unknown etiology had been identified in Wuhan City, in the Hubei province of China [37, 75].
- The authorities of China communicated to WHO a total of 44 patients with pneumonia of unknown etiology from 31 December 2019

through 3 January 2020. No causal agent had been identified during this period.

- 7 January 2020 – The Chinese researchers isolated and identified a new type of coronavirus 2019 (2019-nCoV), which received the name “Wuhan Coronavirus”. WHO renamed it to SARS-CoV-2 [76.]
- 11 and 12 January 2020 – WHO received more details from the National Health Commission in China, indicating that the outbreak was directly associated with the seafood markets in Wuhan City [37].
- 12 January 2020 – China globally shared the genetic sequence of the novel coronavirus [77].
- 13 January 2020 – The Ministry of Public Health of Thailand reported the first imported case of lab-confirmed novel coronavirus (2019-nCoV) from Wuhan, Hubei Province, China [77].
- 15 January 2020 – The Ministry of Health, Labour, and Welfare of Japan (MHLW) also recorded an imported case of the novel coronavirus (2019-nCoV) from Hubei Province, China [78].
- 20 January 2020 – The National IHR Focal Point (NFP) for the Republic of Korea communicated the first case of a novel coronavirus, also from Wuhan, China [79].
- 30 January 2020 – WHO declared a global public health emergency.
- By the end of March 2020, the virus spread all over the world, which leads to a large global outbreak [80].
- 3 June 2020 – 6,414,473 confirmed cases, 380,940 deaths and 2,753,935 recovered [8].

### *Origin and Evolution of SARS-CoV-2*

The association of SARS-CoV-2’s first cases with the Hubei (China) seafood market implied that the place represented a role in the early spreading [81, 82]. However, whether the outbreak began and what is the original host(s) of SARS-CoV-2 remain unclear [82]. The first genome sequence analysis of SARS-CoV-2 was performed from six patients [83]. First of all, SARS-CoV-1 and MERS-CoV were compared with SARS-CoV-2, and this analysis presented a high homology of nucleotides with SARS-CoV-1, and poor association with MERS-CoV [83], which suggests that SARS-CoV-1 and SARS-CoV-2 might relate to the same species. Nevertheless, profound research showed that coronaviruses with high similarity to the human SARS-CoV-1 or civet/pangolin (?) SARS-CoV-like virus were isolated from horseshoe bats, which leads to the conclusion that the bats were the potential natural reservoir of SARS-CoV whereas masked palm civets/pangolin (?) are the intermediate hosts [57, 59, 84-87]. The phylogenetic analysis of SARS-CoV-2 showed that the virus is a Betacoronavirus genus, subgenus Sarbecovirus and is related to two bat-derived SARS-like coronaviruses [74, 77, 83, 84, 88-90].

Xu and colleagues determined that the genome sequence of SARS-CoV-2 had a 96.2% identity throughout the genome of BatCoV RaTG13, a bat coronavirus detected n Yunnan province [83]. Moreover, the phylogenetic analysis of the full-length genome of RaTG13 demonstrated that the receptor-binding protein spike (S) gene and RNA-dependent RNA polymerase (RdRp) gene were the closest relatives with the SARS-CoV-2 [83]. But, despite the similarities from the viruses, the SARS-CoV-2 changed topological position in the phylogenetic analysis: SARS-CoV-2 was closer to bat-SL-CoVZC45 in the S gene phylogeny but felled in a basal position within the subgenus Sarbecovirus in the ORF1b tree [74]. This discovery suggests a probable recombination results in this group of viruses. Despite current evidence pointed the origin of SARS-CoV-2 from bats virus [74, 77], an intermediate host between humans and bats might exist. Lu and colleagues [77] suggested four reasons for such consideration:

1. Most bat species hibernates in the period that the outbreak began (December) in the Wuhan city (China);
2. No bats in the Huanan seafood market were sold or found;
3. The sequence identity between SARS-CoV-2 and bat-SL-CoVZC45 or bat-SL-

CoVZXC21 - the closest relatives - is lower than 90%, suggesting an intermediate host;

4. There is an intermediate host between bats and humans. For example, masked palm civet and dromedary camels are the intermediate hosts for SARS-CoV-1 [54] and MERS-CoV, respectively (Figure 18) [91].

Ji and colleagues [92] found that SARS-CoV-2, bat-SL-CoVZC45, and snakes had similar synonymous codon usage bias, and speculated that snake might be the intermediate host [92]. Nevertheless, no SARS-CoV-2 has been isolated from the snake yet.

Hence, another suspicious about the host of SARS-CoV-2 fell on the pangolins as a natural reservoir, since an analysis of the genome from Malytan pangolins showed two sub-lineages related to SARS-CoV-2 [93]. This Pangolin-CoV's whole genome had 91.02% similarity with SARS-CoV-2 and 90.55% similarity with Bat-CoV RaTG13 [94]. Proteomic analysis exhibited that the S1 subunit of Spike glycoprotein (S) was more nearly related to that of SARS-CoV-2 compared to BaT-CoV RaTG13. Moreover, five amino acid residues of the S protein of SARS-CoV-2 combining with the ACE2 receptor are equal in Pangolin-CoV [94]. Interestingly, the furin identification motif, necessary to the S1/S2 cleavage, is absent in both Pangolin-CoV and BaT-CoV RaTG13 [94]. This furin identification sequence is intact within the SARS-CoV-2. The discovery of coronavirus close to SARS-CoV-2 from pangolin insinuates that pangolin is the possible intermediate host [76] (Figure 19). However, the roles of bat and pangolin as the natural reservoir and intermediate host still need further researches.

The timeline of the origin of SARS-CoV-2 is represented in Figure 20.

## Conclusion

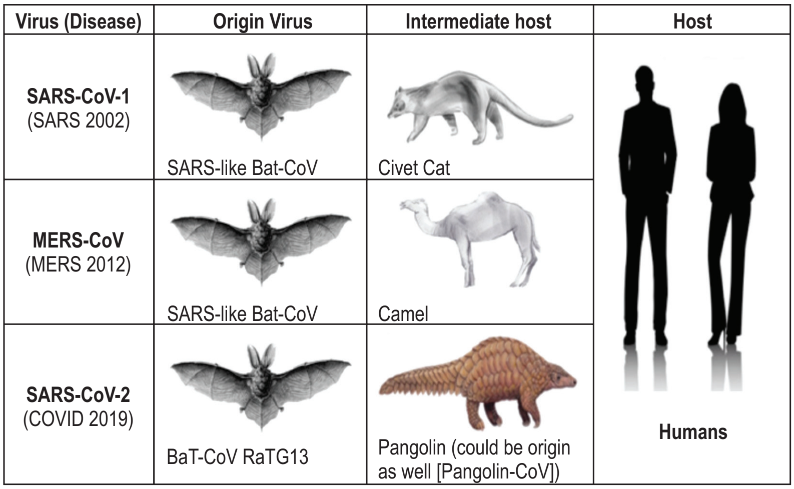
The COVID-19 pandemic continues. Huge efforts and progress have been done since the beginning of the outbreak in pathogen monitoring, mitigating process, identifying sources, basic etiology, clinical treatment, drug testing, and vaccine development. Future research on viral replication, pathogenesis, antiviral drugs, and other aspects of SARS-CoV-2 will contribute to the treatment and prevention of the virus.

However, given the emergence of COVID-19 pneumonia as a new infectious disease with interspecies transmission from animals, we should reflect on the origin of the human pathogen and learn from our experience because the globalization put worldwide together, and a pandemic could devastate the human civilization. The high lethality viruses such as SARS-CoV-1, MERS-CoV, H5N1, H7N9, Ebola, and emerging 2019-nCoV is as an alarm to the world.

## References

1. LePan. Visualizing the history of pandemics. Visual Capitalist 2020; March 14. https://www.visualcapitalist.com/history-of-pandemics-deadliest/.
2. Karesh WB, Dobson A, Lloyd-Smith JO, Lubroth J, Dixon MA, et al. Ecology of zoonoses: natural and unnatural histories. Lancet 2012; Dec 1;380(9857):1936-45. Doi: 10.1016/S0140-6736(12)61678-X.
3. World Health Organization. Influenza (Avian and other zoonotic). Geneva, Switzerland: WHO; 2019.
4. Karron RA, Black RE. Determining the burden of respiratory syncytial virus disease: The known and the unknown. Lancet 2017;390:917-918. Doi: 10.1016/s0140-6736(17)31476-9.
5. Dikid T, Jain SK, Sharma A, Kumar A, Narain JP. Emerging & re-emerging infections in India: an overview. The Indian Journal of Medical Research 2013;138(1):19-31.
6. Çelik I, Saatçi E, Tyüboglu FO. Emerging and reemerging respiratory viral infections up to COVID-19. Turk J Med Sci 2020;50:557-562. Doi:10.3906/sag-2004-126.
7. McIntosh K, Peiris J. Coronaviruses. In: Richman D, Whitley R, Hayden F (editos). Clinical Virology, 3rd Edition. Washington, DC, USA: ASM Press; 2009. Pp. 1155-1171.
8. John Hopkins, Coronavirus Research Center. 2020. https://coronavirus.jhu.edu/map.html.
9. Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. Methods in Molecular Biology 2015;1282:1-23. Doi: 10.1007/978-1-4939-2438-7_1. 10.
11. Jarus O. Twenty of the worst epidemics and pandemics in history. Live Science 2020; March 20. https://www.livescience.com/worst-epidemics-and-pandemics-in-history.html.
12. Ebert et al. Europas Sprung in die Neuzeit, Die große Chronik-Weltgeschichte. Gütersloh: Wissen Media, 2008. p. 197. https://books.google.co.uk/books?id=3DVH8dVGkX0C&pg=PA197.
13. Map of the Black Plague. https://nilefm.com/digest/article/5114/7-pandemics-from-human-history-that-make-COVID-19-look-like-a-joke.

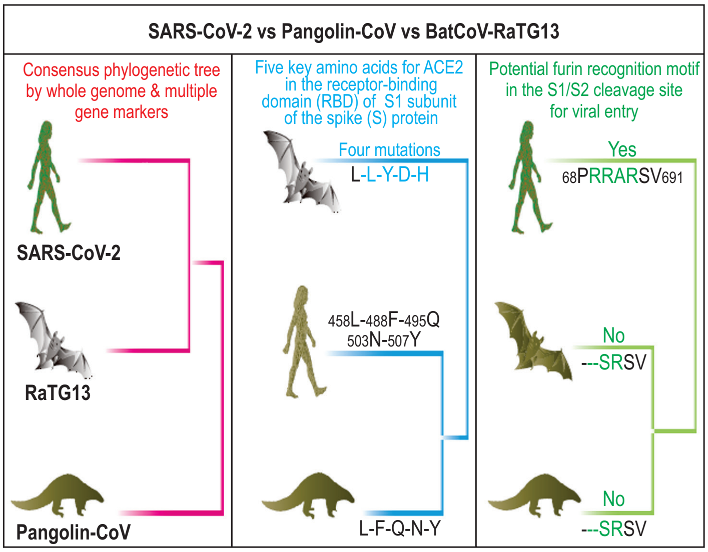
**Figure 18.** Summary of the natural reservoir, intermediate host and target in major coronaviruses.



| Virus (Disease) | Origin Virus | Intermediate host | Host |
|---|---|---|---|
| **SARS-CoV-1** (SARS 2002) | SARS-like Bat-CoV | Civet Cat | Humans |
| **MERS-CoV** (MERS 2012) | SARS-like Bat-CoV | Camel | |
| **SARS-CoV-2** (COVID 2019) | BaT-CoV RaTG13 | Pangolin (could be origin as well [Pangolin-CoV]) | |

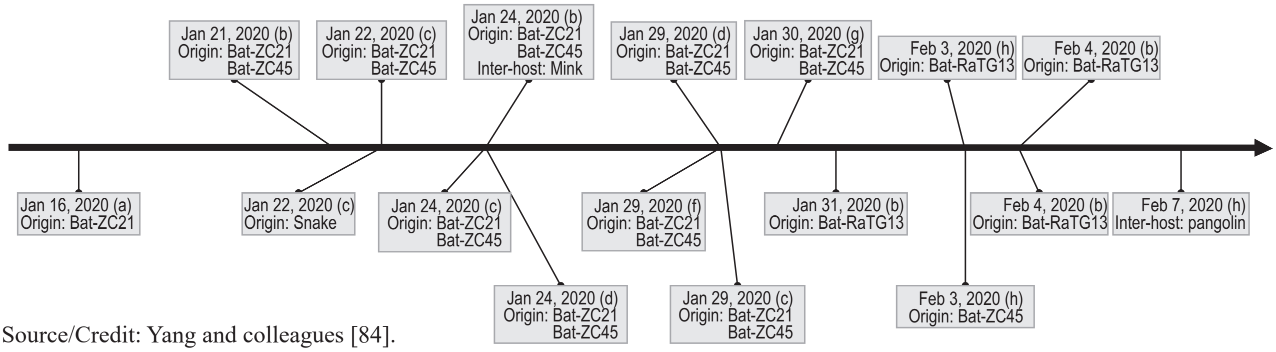
Source/Credit: Kakodkar and colleagues [76].

**Figure 19.** SARS-CoV-2 *vs* Pangolin-CoV *vs* BatCoV-RaTG13.



Source/Credit: Zhang and colleagues [94].

**Figure 20.** The origin and inter-host timeline of SARS-CoV-2.



Source/Credit: Yang and colleagues [84].

14. Wikimedia.https://commons.wikimedia.org/wiki/Category:Variola_virus.
15. Pixnio.Pixnio. https://pixnio.com/?s=smallpox.
16. Death's Dispensary. http://www.environmentandsociety.org/arcadia/first-cholera-epidemic-st-petersburg.
17. Vibrio cholerae. Luciana Cangussu. https://www.luciacangussu.bio.br/atlas/vibrio-spp/.
18. Spanish Flu. https://aboutmanchester.co.uk/a-portrait-of-a-pandemic-bbc-marks-the-centenary-of-spanish-flu-revealing-the-untold-stories-of-its-impact-on-people-and-places-across-the-country/.
19. Ilness people in Spanich Flu. https://aboutmanchester.co.uk/a-portrait-of-a-pandemic-bbc-marks-the-centenary-of-spanish-flu-revealing-the-untold-stories-of-its-impact-on-people-and-places-across-the-country/.
20. Centers for Disease Control and Prevention's Public Health Image Library (PHIL), with identification number #8160.
21. National Institute of Allergy and Infectious Diseases (NIAID). HIV Photo Gallery. 2020. https://www.niaid.nih.gov/.
22. Goldsmith CD. A SARS-CoV-infected cell with virus particles in vesicles. CDC, USA, 2020. https://www.cdc.gov/sars/lab/images.html.
23. CDC. Centers for Disease Control and Prevention. Atlanta USA. 2020. https://www.cdc.gov/.
24. CNN. Collecting samples in bats for SARS-CoV-2. https://edition.cnn.com/2020/03/19/health/coronavirus-human-actions-intl/index.html.
25. Taubenberger JK, Morens DM. 1918 influenza: the mother of all pandemics. Emerging Infectious Diseases 2006;12(1):15-22. Doi: 10.1093/infdis/jiaa105.
26. Yoshikura H. Spanish flu, Asian flu, Hong Kong flu, and seasonal influenza in Japan under social and demographic influence: review and analysis using the two-population model. Japanese Journal of Infectious Diseases 2014;67:245-257. Doi: 10.7883/yoken.67.245.
27. Vassilara F, Spyridaki A, Pothitos G, Deliveliotou A, Papadopoulos A. A rare case of human coronavirus 229E associated with acute respiratory distress syndrome in a healthy adult. Case Reports in Infectious Diseases 2018:1-4. Doi: 10.1155/2018/6796839.
28. Macneil A, Nichol ST, Spiropoulou CF. Hantavirus pulmonary syndrome. Virus Research 2011;162:138-147. Doi: 10.1016/j.virusres.2011.09.017.
29. Shafagati N, Williams J. Human metapneumovirus-what we know now. F1000 Research 2018;7:1-11. Doi: 10.12688/f1000research.12625.1.
30. World Health Organization. The operational response to SARS. Geneva, Switzerland: WHO; 2019.
31. Burrell C, Howard C, Murphy F. Coronaviruses. Fenner and White's Medical Virology. 5th ed. Cambridge, MA, USA: Academic Press; 2017. pp: 437-446.
32. Körner RW, Söderlund-Venermo M, Van Koningsbruggen-Rietschel S, Kaiser R, Malecki M, et al. Severe human Bocavirus infection, Germany. Emerging Infectious Diseases 2011;17(12):2303-2305. Doi: 10.3201/eid1712.110574.
33. Tawfiq JA, Zumla A, Gautret P, CGray G, SHui D Surveillance for emerging respiratory viruses. Lancet of Infectious Diseases 2014;14:992-1000.
34. Paules C, Subbarao K. Influenza. Lancet 2017;390(10095):697-708. Doi: 10.1016/S0140-6736(17)30129-0.
35. Cowling BJ, Park M, Fang VJ, Wu P, Leung G, et al. Preliminary epidemiological assessment of MERS-CoV outbreak in South Korea, May to June 2015. European Surveillance Bulletin 2015;20:7-13. Doi: 10.2807/15607917.es2015.20.25.21163.
36. Peeri NC, Shrestha N, Rahman S, Zaki R, Tan Z, et al. The SARS, MERS and novel coronavirus (COVID-19) epidemics, the newest and biggest global health threats: what lessons have we learned. International Journal of Epidemiology 2020:1-10. Doi: 10.1093/ije/dyaa033.
37. Hasoksuz M, Vlasova A, Saif LJ. Detection of group 2a coronaviruses with emphasis on bovine and wild ruminant strains. In: Cavanag D (editor). SARS and Other Coronaviruses. Totowa, NJ, USA: Humana Press; 2008. pp. 43-60.
38. Ismail MM, Cho KO, Hasoksuz M, Saif LJ, Saif YM. Antigenic and genomic relatedness of turkey-origin coronaviruses, bovine coronaviruses, and infectious bronchitis virus of chickens. Avian Diseases 2001;45(4):978-984.
39. Ye ZW, Yuan S, Yuen KS, Fung SY, Chan CP, Jin DY. Zoonotic origins of human coronaviruses. International Journal of Biological Sciences 2020;16(10):1686-1697. Doi: 10.7150/ijbs.45472.
40. Fabricant J. The Early History of Infectious Bronchitis. Avian Diseases 1998;42(4):648-650. Doi: 10.2307/1592697.
41. Tyrrell DAJ, Bynoe ML. Cultivation of a novel type of common cold virus in organ culture. British Medical Journal 1965;1:1467-1470. Doi: 10.1136/bmj.1.5448.1467.
42. Hamre D, Procknow JJ. A new virus isolated from the human respiratory tract. Proceedings of the Society for Experimental Biology and Medicine 1966;121(1):190-193. Doi: 10.3181/00379727-121-3073.
43. Almeida JD, Tyrrell DAJ. The morphology of three previously uncharacterized human respiratory viruses that grow in organ culture. The Journal of General Virology 1967;1(2):175-178. Doi:0.1099/0022-1317-1-2-175
44. Corman VM, Baldwin HJ, Tateno AF, Zerbinati RM, Annan A, Owusu M, et al. Evidence for an ancestral association of human coronavirus 229E with bats. J Virol 2015;89:11858-70.
45. Tao Y, Shi M, Chommanard C, Queen K, Zhang J, Markotter W, et al. Surveillance of bat coronaviruses in Kenya identifies relatives of human coronaviruses NL63 and 229E and their recombination history. J Virol 2017;91.
46. Corman VM, Eckerle I, Memish ZA, Liljander AM, Dijkman R, Jonsdottir H, et al. Link of a ubiquitous human coronavirus to dromedary camels. Proc Natl Acad Sci U S A 2016;113:9864-9.
47. Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. Nat Ver Microbiol 2019;17:181-92.
48. Park TRS, Openshaw PJM. COVID-19: Lessons from SARS and MERS. European Journal of Immunology 2020;50:308-316. Doi: 10.1002/eji.202070035.
49. Menachery VD, Yount Jr BL, Debbink K, Agnihothram S, Gralinski LE, Plante JA, et al. A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence. Nature Medicine 2015;21(12):1508. Doi:10.1038/nm.3985.

50. Song H-D, Tu C-C, Zhang G-W, Wang S-Y, Zheng K, et al. Cross-host evolution of severe acute respiratory syndrome coronavirus in palm civet and human. Proceedings of the National Academy of Sciences 2005;102(7):2430-2435. Doi:10.1073/pnas.0409608102.
51. Hu B, Ge X, Wang LF, Shi Z. Bat origin of human coronaviruses. Virol J 2015;12: 221.
52. Lau SK, Woo PC, Yip CC, Tse H, Tsoi HW, Cheng VC, et al. Coronavirus HKU1 and other coronavirus infections in Hong Kong. J Clin Microbiol. 2006;44:2063-71.
53. Centers for Disease C, Prevention. Prevalence of IgG antibody to SARS-associated coronavirus in animal traders--Guangdong Province, China, 2003. MMWR Morb Mortal Wkly Rep 2003;52:986-7.
54. Guan Y, Zheng BJ, He YQ, Liu XL, Zhuang ZX, Cheung CL, et al. Isolation and characterization of viruses related to the SARS coronavirus from animals in southern China. Science 2003;302:276-8.
55. Poon LL, Chu DK, Chan KH, Wong OK, Ellis TM, Leung YH, et al. Identification of a novel coronavirus in bats. J Virol 2005;79:2001-9.
56. Tu C, Crameri G, Kong X, Chen J, Sun Y, Yu M, et al. Antibodies to SARS coronavirus in civets. Emerg Infect Dis 2004;10:2244-8.
57. Lau SK, Woo PC, Li KS, Huang Y, Tsoi HW, Wong BH, et al. Severe acute respiratory syndrome coronavirus-like virus in Chinese horseshoe bats. Proc Natl Acad Sci U S A 2005;102:14040-5.
58. Li W, Shi Z, Yu M, Ren W, Smith C, Epstein JH, et al. Bats are natural reservoirs of SARS-like coronaviruses. Science 2005;310:676-9.
59. Ge XY, Li JL, Yang XL, Chmura AA, Zhu G, Epstein JH, et al. Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. Nature 2013; 503: 535-8.
60. Donaldson EF, Haskew AN, Gates JE, Huynh J, Moore CJ, Frieman MB. Metagenomic analysis of the viromes of three North American bat species: viral diversity among different bat species that share a common habitat. J Virol 2010;84:13004-18.
61. Huynh J, Li S, Yount B, Smith A, Sturges L, Olsen JC, et al. Evidence supporting a zoonotic origin of human coronavirus strain NL63. J Virol 2012;86: 12816-25.
62. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020.
63. van Boheemen S, de Graaf M, Lauber C, Bestebroer TM, Raj VS, Zaki AM, et al. Genomic characterization of a newly discovered coronavirus associated with acute respiratory distress syndrome in humans. mBio 2012;3.
64. Cotten M, Lam TT, Watson SJ, Palser AL, Petrova V, Grant P, et al. Full-genome deep sequencing and phylogenetic analysis of novel human betacoronavirus. Emerg Infect Dis 2013;19:736-42B.
65. Annan A, Baldwin HJ, Corman VM, Klose SM, Owusu M, Nkrumah EE, et al. Human betacoronavirus 2c EMC/2012-related viruses in bats, Ghana and Europe. Emerg Infect Dis 2013;19:456-9.
66. Lau SKP, Zhang L, Luk HKH, Xiong L, Peng X, Li KSM, et al. Receptor Usage of a Novel Bat Lineage C Betacoronavirus Reveals Evolution of Middle East Respiratory Syndrome-Related Coronavirus Spike Proteins for Human Dipeptidyl Peptidase 4 Binding. J Infect Dis 2018;218:197-207.
67. Luo CM, Wang N, Yang XL, Liu HZ, Zhang W, Li B, et al. Discovery of novel bat coronaviruses in south China that use the same receptor as Middle East Respiratory Syndrome Coronavirus. J Virol 2018;92.
68. Reusken CB, Haagmans BL, Muller MA, Gutierrez C, Godeke GJ, Meyer B, et al. Middle East respiratory syndrome coronavirus neutralising serum antibodies in dromedary camels: a comparative serological study. Lancet Infect Dis 2013;13:859-66.
69. Chan JF, Lau SK, To KK, Cheng VC, Woo PC, Yuen KY. Middle East respiratory syndrome coronavirus: another zoonotic betacoronavirus causing SARS-like disease. Clin Microbiol Rev 2015;28:465-522.
70. Raj VS, Farag EA, Reusken CB, Lamers MM, Pas SD, Voermans J, et al. Isolation of MERS coronavirus from a dromedary camel, Qatar, 2014. Emerg Infect Dis 2014;20:1339-42.
71. Adney DR, Letko M, Ragan IK, Scott D, van Doremalen N, Bowen RA, et al. Bactrian camels shed large quantities of Middle East respiratory syndrome coronavirus (MERS-CoV) after experimental infection. Emerg Microbes Infect 2019;8:717-23.
72. Samara EM, Abdoun KA. Concerns about misinterpretation of recent scientific data implicating dromedary camels in epidemiology of Middle East respiratory syndrome (MERS). mBio 2014;5:e01430-14.
73. Lam T, Shum M, Zhu H, Tong Y, Ni X, Liao Y, et al. Identification of 2019-nCoV related coronaviruses in Malayan pangolins in southern China. BIORXIV 2020. Doi: 10.1101/2020.02.13.945485.
74. Wu F, Zhao S, Yu B, Chen YM, Wang W, et al. A new coronavirus associated with human respiratory disease in China. Nature 2020; 579, 265-269. Doi:10.1038/s41586-020-2008-3.
75. Wuhan Municipal Health Commission. Wuhan Municipal Health Commission on the current situation of pneumonia in our city Release organization; 2020.
76. Kakodkar P, Kaka N, Baig MN. A Comprehensive literature review on the clinical presentation, and management of the pandemic coronavirus disease 2019 (COVID-19). Cureus 12(4):e7560. Doi: 10.7759/cureus.7560.
77. Lu R, Zhao X, Li J, Niu P, Yang B, et al. Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. The Lancet 2020;395(10224):565-574. Doi: 10.1016/S0140-6736(20)30251-8.
78. World Health Organization. Novel Coronavirus – Japan (ex-China); 2020.
79. Park WB, Kwon NJ, Choi SJ, Kang CK, Choe PG et. al. Virus isolation from the first patient with SARS-CoV-2 in Korea. Journal of Korean Medical Science 2020; 35(7): e84. Doi: 10.3346/jkms.2020.35.e84.
80. Cheng Laia C, Ping Shih T, Chien Ko W, Tang H, Ren Hsueh P. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. International Journal of Antimicrobial Agents 2020;55(3):1-9. Doi: 10.1016/j.ijantimicag.2020.105924.
81. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med 2020;23.

82. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
83. Xu X, Chen P, Wang J, Feng J, Zhou H, Li X, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Sci China Life Sci 2020.
84. Yang Y, Peng F, Wang R, Guana K, Jiang T, et al. The deadly coronaviruses: The 2003 SARS pandemic and the 2020 novel coronavirus epidemic in China. Journal of Autoimmunity 2020. https://doi.org/10.1016/j.jaut.2020.102434.
85. Shi Z, Hu Z. A review of studies on animal reservoirs of the SARS coronavirus. Virus Res. 2008; 133: 74-87
86. Li W, Shi Z, Yu M, Ren W, Smith C, Epstein JH, et al. Bats are natural reservoirs of SARS-like coronaviruses. Science 2005;310:676-9.
87. Hu B, Zeng LP, Yang XL, Ge XY, Zhang W, Li B, et al. Discovery of a rich gene pool of bat SARS-related coronaviruses provides new insights into the origin of SARS coronavirus. PLoS Pathog 2017;13:e1006698.
88. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet 2020; 395:514-23.
89. Jiang S, Du L, Shi Z. An emerging coronavirus causing pneumonia outbreak in Wuhan, China: calling for developing therapeutic and prophylactic strategies. Emerg Microbes Infect 2020;9:275-7.
90. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS. J Virol 2020.
91. Alagaili AN, Briese T, Mishra N, Kapoor V, Sameroff SC, Burbelo PD, et al. Middle East respiratory syndrome coronavirus infection in dromedary camels in Saudi Arabia. mBio 2014;5:e00884-14.
92. Ji W, Wang W, Zhao X, Zai J, Li X. Homologous recombination within the spike glycoprotein of the newly identified coronavirus may boost crossspecies transmission from snake to human. Journal of Medical Virology. 2020.
93. Lam TTY, Shum MHH, Zhu HC, Tong YG, Ni XB, Liao YS, et al. Identification of 2019-nCoV related coronaviruses in Malayan pangolins in southern China. bioRxiv. Doi: https://Doi.org/10.1101/2020.02.13.945485.
94. Zhang T, Wu Q, Zhang Z: Probable pangolin origin of SARS-CoV-2 associated with the COVID-19 outbreak. Curr Biol 2020;30:1-6. Doi: 10.1016/j.cub.2020.03.022.