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.


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 zoonoses 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].
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 through the years with the number of human deaths.

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

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.

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

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)


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


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


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

Figure 10. HIV budding from an infected CD4 cell.

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

Figure 11. SARS-CoV micrography.


Figure 12. Micrography of Ebola virus.

Source/Credit: CDC, USA [23].

Figure 13. Micrography of coronavirus that causes Middle 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].
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.

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

Source/Credit: Çelik and colleagues [6].
**Figure 16.** R0 (basic reproduction number) of diseases.

![R0 diagram](image)


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

![Animal hosts diagram](image)

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].
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].
- 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].
- 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 fell 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

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

<table>
<thead>
<tr>
<th>Virus (Disease)</th>
<th>Origin Virus</th>
<th>Intermediate host</th>
<th>Host</th>
</tr>
</thead>
<tbody>
<tr>
<td>SARS-CoV-1 (SARS 2002)</td>
<td>SARS-like Bat-CoV</td>
<td>Civet Cat</td>
<td>Humans</td>
</tr>
<tr>
<td>MERS-CoV (MERS 2012)</td>
<td>SARS-like Bat-CoV</td>
<td>Camel</td>
<td></td>
</tr>
<tr>
<td>SARS-CoV-2 (COVID 2019)</td>
<td>Bat-CoV RaTG13</td>
<td>Pangolin (could be origin as well [Pangolin-CoV])</td>
<td></td>
</tr>
</tbody>
</table>

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].


