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History of Epizootics, Epidemics and Evolution of Coronaviruses

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Abstract: Coronavirus (CoV), which causes animal diseases, has become a human health concern. Prior to 2003, CoV caused respiratory diseases and enteric disorders, but after 2003, CoV caused three acute respiratory syndromes, resulting in significant human deaths. Since then, research on CoV has multiplied, leading to a deeper knowledge of the species. It is in this context that this article reviews the history, the biological aspect, the evolution and the crossing of the CoV species barrier. This review shows that CoVs are formed by a large genome (27 to 33 kb) and by structural proteins (spike S, hemagglutinin esterase HE and membran protein M). Various coronaviruses have been described in a wide range of species including chickens (*IBV-CoV*), pigs (*PHE-CoV, PED-CoV, TGE-CoV PR-CoV, PD-CoV, SADS-CoV*), cattle (*BCoV*), cats (*FCoV*), dogs (*CCoV*), and humans (*HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, SARS-CoV, MERS-CoV*, and *SARS-CoV2*). Birds and bats are the main reservoirs of CoVs, but due to the low fidelity of the replication complex, CoVs have the ability to adapt to various species. Due to the crossing of the species barrier, CoVs have a wide host range resulting in the emergence of various strains worldwide. This information can help researchers develop intervention strategies to prevent the re-emergence of CoVs in the future.

Keywords: Coronavirus, Bats, tMRCA, Viral Evolution, Animal Host, Intermediate Host

1. Introduction

Zoonotic diseases, animal diseases transmissible to humans, represent between 60% and 80% of emerging diseases (Jones et al., 2008). The exploitation of natural territories for economic development increases the contact between human populations and animal reservoirs, and thus the risk of emergence of zoonotic diseases [1]. Asia is among the high-risk areas for zoonotic disease emergence due to the presence of high biodiversity and many instances of proximity between human populations and animal reservoirs [2]. In the last 20 years, the region has seen the emergence of several zoonotic viruses, such as the coronavirus associated with severe acute respiratory syndrome (SARS). First, *SARS-CoV* emerged in November 2002 in southern China (Guangdong Province) and rapidly spread to 36 countries with an overall mortality rate of 9.6-15% [3, 4]. Second, *MERS-CoV* emerged in the Kingdom of Saudi Arabia in 2012, with a clinical syndrome similar to SARS but apparently less transmissible [5]. The outbreak spread to 27 countries with a case fatality rate of 34.4% [5]. Finally, a new CoV initially named 2019-nCoV and then *SARS-CoV2* [6, 7], was detected in Wuhan (Hubei Province, China) in December 2019, and caused an outbreak called COVID-19 (Coronavirus disease 19) or Wuhan pneumonia that became a pandemic on March 11, 2020 [8].

The continued emergence of highly pathogenic CoVs in animals and humans poses a serious threat to animal and human health and draws attention to the importance of understanding the key factors in host range expansion. This knowledge not only helps to prevent the re-emergence of

CoVs in the future but also to ensure better protection of humanitarian life. In this review, we present some important aspects including the history of diseases caused by CoV, virology, evolution and interspecies transmission of Coronaviruses.

2. Structure Coronavirus

Coronaviruses (CoV) are enveloped riboviruses, grouping many viruses that infect several animal species (avian and mammalian), including humans. The term "coronavirus" appeared only in 1968 after the identification of the first human *CoV* or *HCoV* [9]. The authors compare this type of virus spherical, with rounded excrescences, formed mainly by the spike (S) and protein that resembles a petal with its crowns or "*corona*" in Latin (Figure 1).

Coronavirus genomes (27-33 kb) encode five large open reading frames (ORFs), including one polyprotein (ORF1a/ORF1ab) in the 5' and four structural proteins in the 3', namely spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins (Figure 1), common to all CoVs [10]. Yet, some *CoVs* possess a fifth structural protein called HE or hemagglutinin-esterase [11]. In addition to these structural proteins, CoVs also have accessory proteins that interpose between the structural proteins and vary from each CoV (Figures 2).

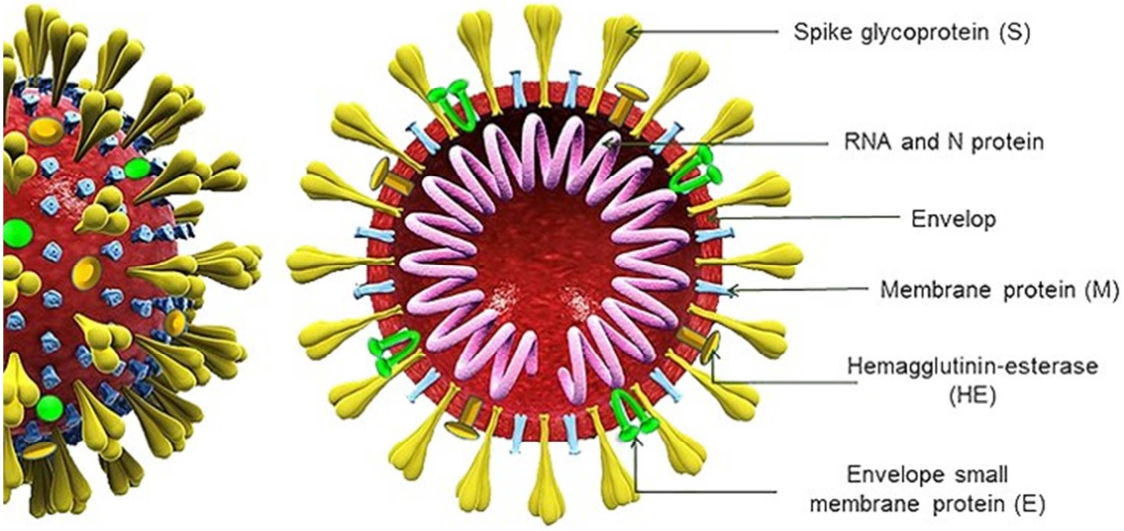

Figure 1. *Schematic structure of coronavirus. The virus is an enveloped, non-segmented, positive-sense single-stranded RNA virus. The virion has a nucleocapsid composed of genomic RNA and phosphorylated nucleocapsid (N) protein, which is buried inside phospholipid bilayers and covered by the spike glycoprotein trimmer (S). The membrane (M) protein hemagglutinin-esterase (HE) and the envelope (E) protein are located among the S proteins in the virus envelope [12].*

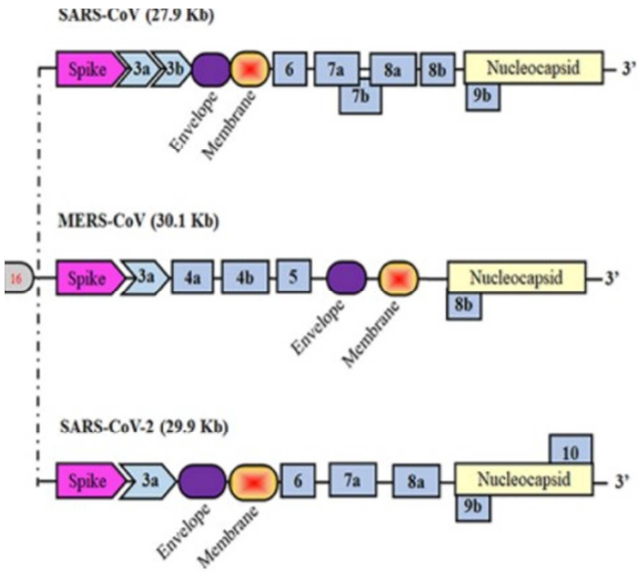

Figure 2. *3' side of the SARS-CoV, MERS-CoV and SARS-CoV2 genomes showing structural and accessory proteins. Adapted according to Shah's team in 2020 [13].*

After the release of the CoV genome into the host cell cytoplasm upon entry marks the beginning of a complex viral gene expression program, which is highly regulated in space and time [14]. Translation of ORF1a and ORF1b from genomic RNA produces two polyproteins, pp1a and pp1ab, respectively [14]. Sixteen nonstructural proteins (nsp) are released upon proteolytic self-cleavage by the two cysteine proteases located in nsp3 for papain-like protease (PLpro) and nsp5 for 3CLpro or chymotrypsin-like protease [14].

3. History of Diseases Caused by Coronaviruses

The first strain of CoV, *IBV* or *Infectious Bronchitis virus* (Figure 3), was isolated and identified from infectious bronchitis in chickens in the 1930s [15]. In human medicine, research on HCoV did not really start until the identification of the SARS-CoV strain in China in 2003 [16], except for a few authors who reported the first human CoVs *HCoV-229E* and *HCoV-O43, which* cause common colds in humans [17, 18]. Prior to 2003, the majority of published articles on CoVs

refer only to epizootics in livestock [19-22], companion animals [23] and mice [24].

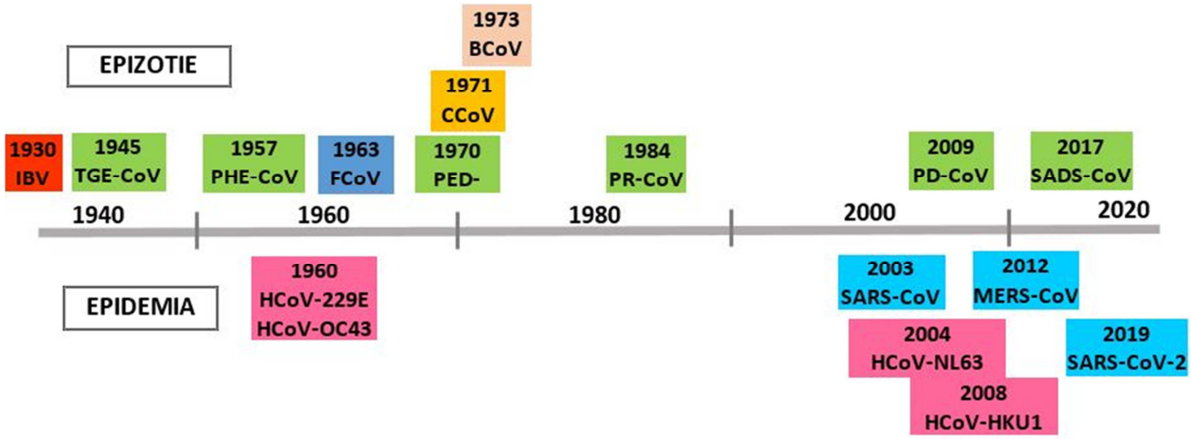

Figure 3. *Chronological representation of CoV epizootics and epidemics [25].*

3.1. CoV Diseases in Animals

3.1.1. Avian Infectious Bronchitis with Coronavirus or CoV-IBV

The first strain of *CoV-IBV,* is the agent of avian infectious bronchitis of the genera *Gallus gallus domesticus* (chickens) and *Anser anser* (geese) [15, 26, 27]. Infection is characterized by acute respiratory distress, rales, coughing, nephritis, severe clutch drop, deterioration of egg quality, and high mortality in young chicks [28].

3.1.2. Porcine Hemagglutinating Encephalomyelitis or PHE

PHE-CoV, the causative agent of neurological and/or digestive diseases in pigs [29], was one of the first porcine CoVs identified in 1957 and the only neurotropic CoV affecting pigs [29, 30]. Clinical manifestations, including vomiting and emaciation and/or neurological signs, are age-related and are typically reported only in piglets less than 4 weeks of age. Subclinical circulation of *PHE-CoV* has been reported worldwide [29].

PHE-CoV and some other *BetaCoV* have a second, shorter spicule, the hemagglutinin-esterase or HE protein [31].

3.1.3. Porcine Epidemic Diarrhea or PED

PED-CoV was determined to be the etiologic agent of porcine epidemic diarrhea in the late 1970s [32, 33]. Since then, the disease has been reported in Europe and Asia [34-37]. *PED-CoV* causes acute diarrhea, vomiting, dehydration, high mortality in suckling piglets and severe gastroenteritis in young piglets [34]. *PED-CoV* presents a similar clinical picture with *TGE-CoV* and *PD-CoV* [38]. In addition, coinfection can occur [39].

3.1.4. Transmissible Swine Gastroenteritis or TGE

TGE-CoV, which causes *porcine transmissible gastroenteritis, was* identified in the United States in 1945 [21]. Subsequently, the disease has been reported in many countries in Europe, Asia, Latin America and Africa [40-46]. *TGE* manifests as an epidemic of watery diarrhea with vomiting, rapidly spreading affecting virtually all pigs in contact within days [47, 48]. This *enteropathogenic TGE-CoV*, affects pigs of all ages [43].

3.1.5. Porcine Respiratory CoV or PR-CoV

PR-CoV was first identified in Belgium in 1984 [49] and subsequently in several countries including China, Japan, Uganda, and the United States [50-52]. This CoV has a close antigenic relationship with enteropathogenic *PEG-CoV* [53].

PR-CoV, derived from *TGE-CoV* by deletion of part of the S gene, has lost its tropism for enterocytes and increased its tropism for the respiratory tract. It can cause mild respiratory disease in pigs, although most infections are subclinical [38]. These two CoVs are cross-reactive, but serological tests are available to distinguish between them [38].

3.1.6. Porcine Deltacoronavirus or PD

Initially, *PD-CoV* was detected in 2009 in porcine fecal samples in Asia and then pigs in Hong Kong in 2012 [54]. This *CoV was* not identified until 2014, when it caused diarrhea in pigs in the United States [32, 55, 56]. Of unknown origin, genomic analyses suspect that *PD-CoV* may originate from an ancestral avian *DeltaCoV* (*DCoV*) [54]. *PD-CoV* has caused diarrhea and intestinal lesions in infected piglets [57, 58]. *PD-CoV* continues to circulate and cause disease in swine herds worldwide [59].

3.1.7. Swine Acute Diarrhea Syndrome or SADS

In 2017, a fatal piglet diarrhea occurred in Guangdong Province, China [60]. This is Swine Acute Diarrhea Syndrome due to *Swine Acute Diarrhea Syndrome-CoV* or *SADS-CoV* [61, 62]. *SADS-CoV* is related to HKU2 virus found in bats of the genus *Rhinolophus* which is also shown to be the source of *SARS-CoV* from 2002-2003 [63]. Since then, the disease has been controlled by immunizing sows from the intestines of infected piglets, but re-emerged on a pig farm two years later [60]. Apart from diarrhea, the disease also causes vomiting and weight loss in piglets which results in considerable economic loss in pig industry [56, 61, 62]. The mortality rate reaches 90% [56].

3.1.8. Diarrhea, Dysentery and Respiratory Infections in Cattle

Bovine CoV or *BCoV* causes three different diseases in cattle, as well as goats and sheep: calf diarrhea, winter dysentery, and respiratory infections such as bovine respiratory disease complex known as "*shipping fever*" in fattening [64-67] and dairy producing animals [68]. The virus causes heavy economic impact in beef industry [64]. The form and severity of *BCoV* disease is related to season, age of animals, and secondary infections [64].

In calves, *BCoV* diarrhea is often associated with other pathogens, *Rotavirus* and *Cryptosporidium*. A severe form is observed in case of co-infection with *Bovine Viral Diarrhea Virus* (*BVDV*), a *Pestivirus* of the family *Flaviviridae* [69].

In winter, dysentery occurs in adult animals with a sporadic pattern [64]. Signs appear 20-36 hours after infection [67].

In addition to the two digestive diseases, *BCoV* also causes mild respiratory signs such as cough and rhinitis or severe signs such as pneumonia in calves 2-6 months of age [64]. Healthy or diseased carrier cattle then excrete *BCoV* either through the respiratory or digestive tract [64].

3.1.9. Feline CoV Complex

Feline CoV or FCoV causes a mild or asymptomatic infection in domestic cats [70]. But, persistent infection can cause the virus to mutate into a highly virulent strain called *Feline Infectious Peritonitis CoV* or *FIP-CoV.* This virulent strain, *FIP-CoV* is the cause of feline infectious peritonitis. *FIP-CoV* was discovered in 1963 in the United States [71] but *FCoV* was discovered only a few years later [72]. Based on their variability, antigenicity, and *in vitro* growth pattern, *FCoV* can be divided into two serotypes: *FCoV* types-I and II [73, 74]. The *FCoV type-II* variant is the result of heterologous recombination between the canine CoV variant *CCoV type II* and the feline *FCoV type-I* variant [75].

3.1.10. Canine CoV Complex

The first *canine CoV* or *CCoV* infection was reported in 1971 [76]. Through molecular biology and pathobiology, much has been learned about *CCoV*. Like *FCoV*, *CCoV* is subdivided into two serotypes: *CCoV type-I* and *CCoV type-II* [77]. *CCoV type-I* is genetically more similar to *FCoV type-I* than to *CCoV type-II* [78]. Indeed, they evolved from a common ancestral virus [79]. *CCoV type I* infection in dogs is restricted to the enteric tract [75] and produces only mild or asymptomatic forms [80]. Whereas *CCoV type-II* is a *pantropic* variant that is highly pathogenic to dogs [75].

3.2. CoV Diseases in Humans

After the discovery of the first strain of *human CoV* or *HCoV*, epidemiological studies have shown that CoV are generally associated with mild respiratory infections. *HCoV-associated* pathologies were not considered sufficiently moderate and did not arouse a clear interest in researchers. Thus, complete genomic studies of *HCoV* were not performed until 2003, following the identification of *SARS-CoV*, the infectious agent responsible for Severe Acute Respiratory Syndrome in China. Since then, three fatal *HCoV* outbreaks have been reported in 2002, 2012, and recently in 2019 (Figure 4). The severity of the infections varies from outbreak to outbreak although their clinical features are similar to themselves and other respiratory infections, making diagnosis difficult [81].

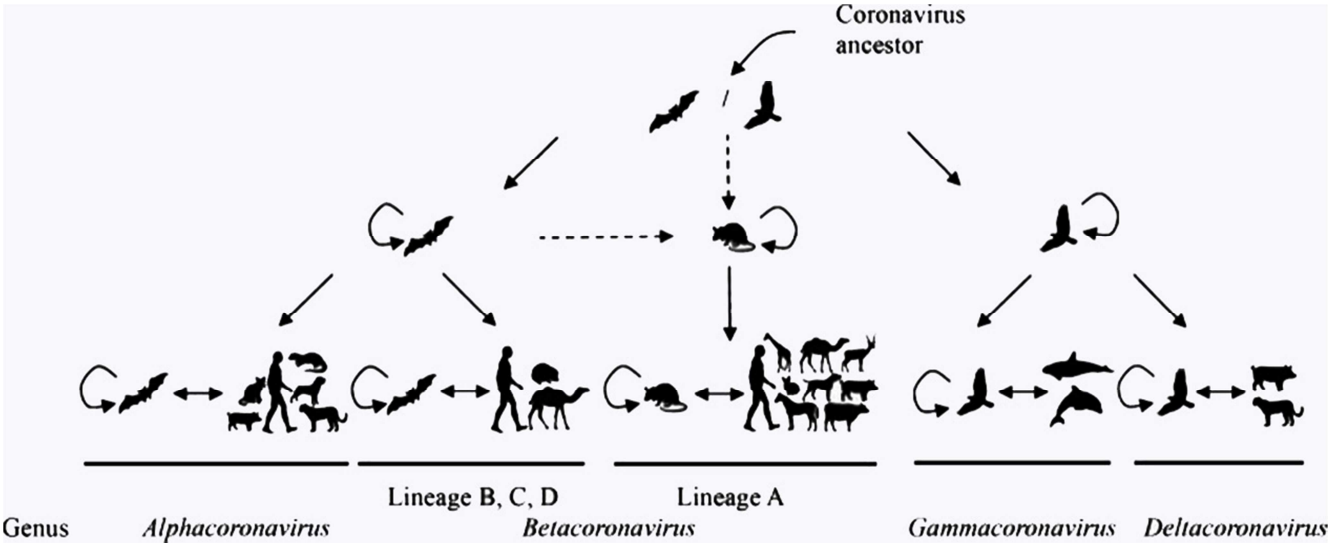

Figure 4. *Evolution of CoVs from their ancestors in bats, birds and rodents to virus species that infect other animals. Dashed arrows, possible transmission routes from bats or birds to rodents before the establishment of the A lineage. Betacoronavirus [54].*

3.2.1. Cold Flu

CoVs are among the infectious agents that cause the common cold in humans during the winter months [82-86]. The first two strains of *HCoV* (*HCoV-229E* and *HCoV-OC43*) were isolated in 1962 and 1967, respectively [18, 87-89]. After the SARS event in China, two other *HCoV* strains (*HCoV-NL63 in 2004* and *HCoV-HKU1 in 2008*) were isolated from patients with bronchiolitis and viral pneumonia

[86, 89-91].

These four *HCoVs* are endemic and cause 15-30% of upper respiratory tract infections each year [11, 92, 93]. In addition, these *HCoVs* are adapted, spread and co-circulated in the human population [94].

3.2.2. Severe Acute Respiratory Syndrome (SARS-2002)

In 2002-2003, severe acute respiratory syndrome (SARS) emerged in Guangdong Province, China [95, 96]. The disease clinically manifests as fever, headache, rhinorrhea, dry cough, difficulty breathing [97, 98] and can progress to fatal pneumonia [98]. *SARS-CoV* infection has resulted in 8,096 cases and 774 deaths with 66% of cases in China and has spread to 36 countries [98, 99]. The overall mortality rate is 9.6-15% while the reproduction rate is greater than 2 [99]. *SARS-CoV* is considered extinct within two years of its occurrence [3].

3.2.3. Middle East Respiratory Syndrome (MERS)

In June 2012, a new respiratory syndrome was detected in Saudi Arabia [3, 97]. The outbreak spread to 27 other countries [3, 97]. After incubation, the most common symptoms are influenza-like illness [100]. The disease can be accompanied by acute respiratory distress syndrome, severe pneumonia, and multiple organ dysfunction resulting in death of the patient [100-103]. To date, the majority of cases have been reported from Saudi Arabia [3].

3.2.4. Wuhan Pneumonia or COVID-19

In late 2019, a new, unknown *human CoV* was identified in the city of Wuhan, China [104]. In 2018, WHO already predicted a future deadly respiratory "*disease X*" [105]. This disease is the third human *CoV* epidemic called COVID-19 or *CoV Disease 2019* whose causative agent is *SARS-CoV2* [106], formerly known as *2019-nCov* [81, 107, 108]. Since its discovery, the number of reported cases of COVID-19 has been steadily increasing in several countries and WHO has classified it as an epidemic and then a pandemic of COVID-19 [8].

4. Origin and Evolution of *CoV*

4.1. Evolution and Plasticity of CoV

The significant plasticity of their genome makes CoVs agents with high evolutionary potential [109]. The two major modes of CoV evolution are mutations and recombination [110]. Indeed, recombination was concluded by Forni's team in 2017 to explain the origin of ORF8 of *SARS-CoV*, which has high sequence identity with that of civet *CoV* [111]. The acquisition of an ORF8 (accessory protein) closely related to that of civet/human *SARS-CoV* was the results of recombination between CoVs within *SARSr-Rs-CoV* (*Rs*: *Rhinolophus sinicus*) or between *SARSr-Rs-CoV* and *SARSr-Rf-CoV* (*Rf*: *Rhinolophus ferrumequinum*) from bats [112, 113].

In CoV, despite the presence of nsp14 proofreading function [114], the replication complex generates many variants [115, 116]. As with all RNA viruses, CoV is heterogeneous and has a quasi-species distribution [117]. This distribution can be seen as an optimization strategy to cope with environmental changes [118]. It has been described for several CoVs not only in persistent infections, but also in acute infections [117, 119, 120].

In bats, various CoVs are zoonotic potentials. Indeed, there are many opportunities for these zoonotic CoVs to evolve and recombine, leading to the emergence of new CoVs that are in the future more transmissible and/or lethal, in domestic animals as well as in humans [121].

4.2. Reservoirs of CoV

Birds and bats are the primary reservoirs of CoV [54]. Due to their clustering behavior and ability to fly long distances [122, 123], they have the potential to spread emerging viruses among themselves and to other animal species and humans [54]. Indeed, the flight adaptation of bats and birds promotes a rise in their body temperature allowing for an increased efficiency of the immune response [124-126].

Bats harbor a diversity of CoVs including the ancestors of *AlphaCoV* and *BetaCoV* [127], while the CoVs of birds are the ancestors of *GammaCoV* and *DeltaCoV* (Figure 4).

4.3. Origin of the CoV

Phylogenetic dating on RNA-dependent RNA polymerase divergence (nsp12: RdRp) suggests that the time of the most recent common ancestor or tMRCA (*Time of Most Recent Common Ancestor*) of mammalian *AlphaCoV*, *BetaCoV* and avian *GammCoV* appeared around 7,000 - 8,000 BP or Before Present (Figure 5). That of *GammaCoV* and *BetaCoV* with *DeltaCoV* goes back another 2,000 years earlier to around -10,000 BP [122]. These dates coincide with the onset of various human agricultural activities during the Neolithic Revolution (Figure 6) such as forest clearing for agriculture and domestication of wild animals [128, 129]. These activities have led to a significant change in the ecology and population dynamics of CoV, due to the intrusion of wildlife habitat and the intensified mixing of wild or domestic animals, as primary, secondary, or tertiary hosts [122, 130]. Clearly, these human activities increase the potential for transmission of infections between bats, either with domesticated animals or with humans, via these intermediate hosts [54].

This tree was generated by analyzing the RNA-dependent RNA polymerase (RdRp) genes under the relaxed clock model with an uncorrelated logarithmic normal with BEAST software. The values at the branch points represent the estimated time divergence in number of years to the present according to Woo's team [131].

For years prior to the SARS outbreak in 2003, CoVs have been identified to cause various diseases in companion and production animals, often requiring vaccination [133, 134]. For the case of viruses causing infectious bronchitis (*IBV* - *GammaCoV*) in chickens, tMRCA with *Alpha* and *BetaCoV* has been traced back to around 8,000 BP (Figure 6). *IBV* was

first described in 1937 [135] phylogenetically very similar strains have been found in several wild bird species [123]. In Madagascar, 28% (Lac Alaotra - n=357) of individuals tested (17 wild bird species) tested positive for *GammaCoV* and the species *Foudia madagascariensis,* with a rate of 27% (n=11), was the most prevalent [123]. The presence of different *GammaCoV* species in several healthy wild bird species [123, 136, 137], demonstrated the circulation and adaptation as well as evolution of *GammaCoV* in poultry [138]. In other words, the presumed intermediate hosts of this avian *IBV CoV* are wild birds [139]. Since then, this avian disease has resulted in highly contagious and deadly acute respiratory epizootics worldwide [140]. Like other CoVs and *Riboviruses*, *GammaCoVs* are characterized by high genetic diversity induced by mutation and recombination [141, 142]. In addition, the massive vaccination campaign has generated positive selection at the spike or S glycoprotein level of circulating *IBV* strains [141, 143]. These characteristics can lead to the emergence of new *GammaCoV* and new lethal epizootics in avian species at any time [131].

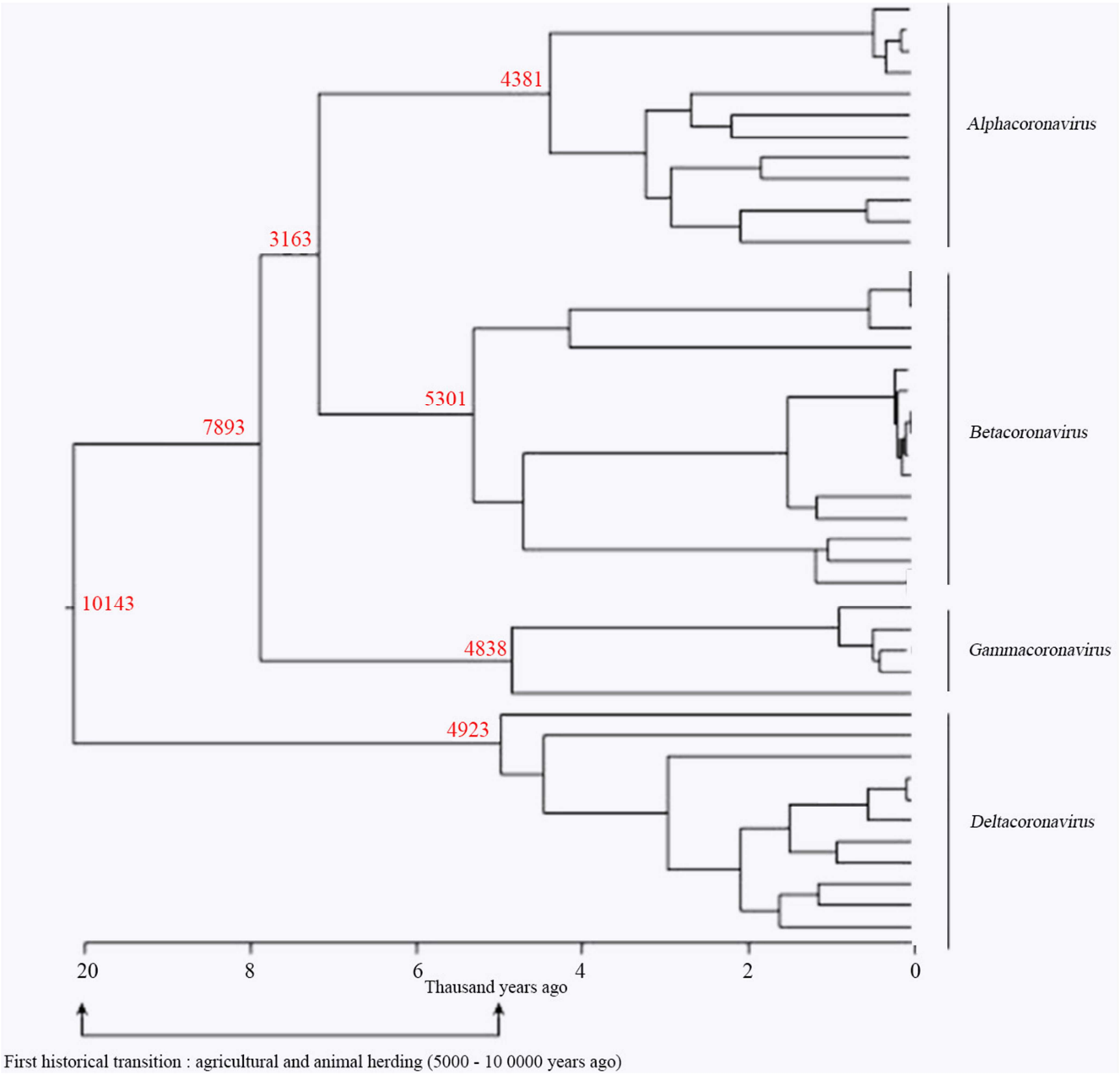

Figure 5. *Molecular dating estimating the divergence of the genera AlphaCoV, BetaCoV, GammaCoV and DeltaCoV according to Chan team in 2013 [122].*

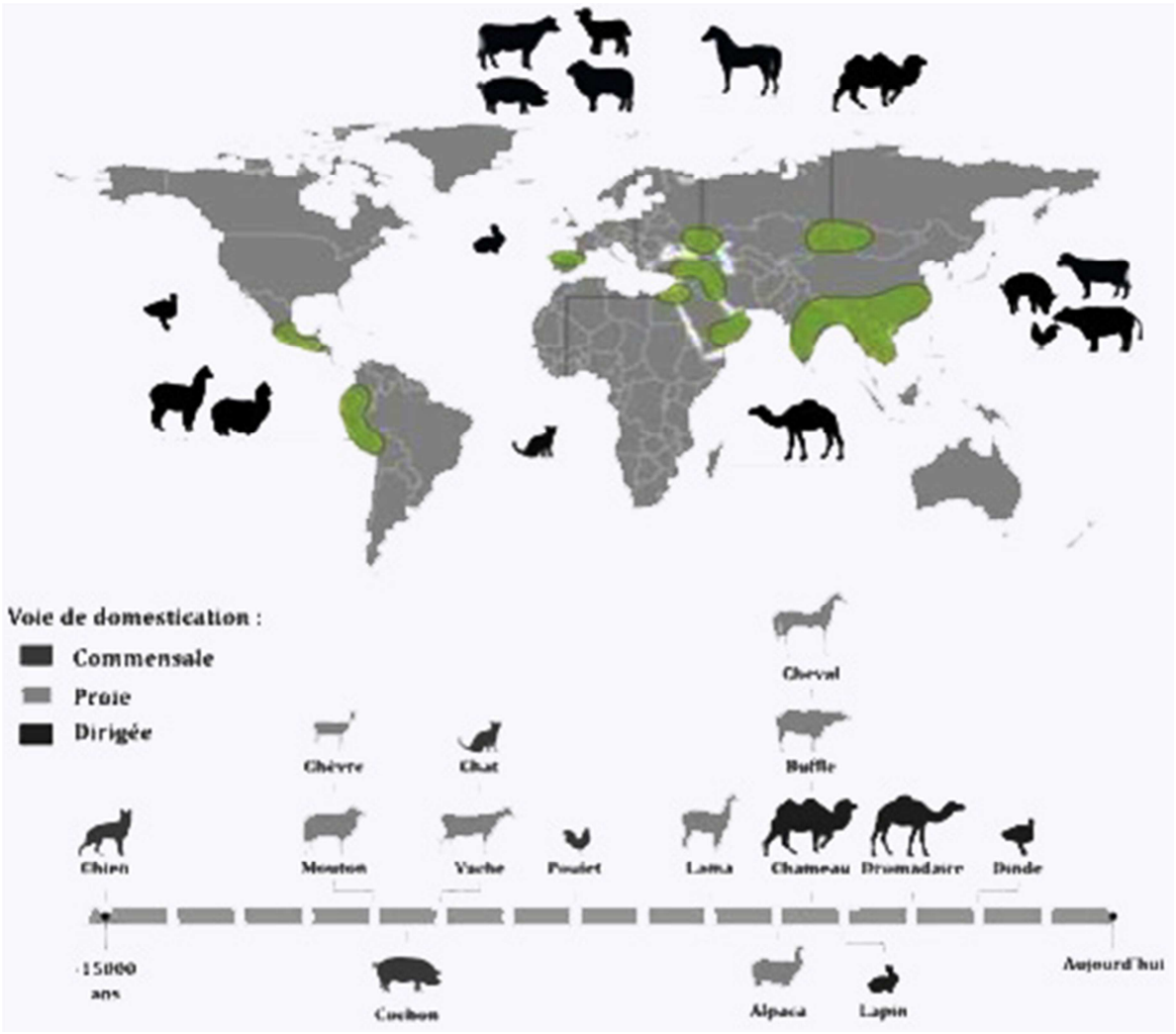

Figure 6. *Neolithic Revolution - locations and dates of domestication of major domestic animals [132].*

In humans, intermediate hosts, such as cattle (Bovidae: *Bos sp*), alpaca (Camelidae: *Vicugna pacos*), dromedary (Camelidae: *Camelus dromedarius*), rodents (*Rattus sp*), and palm civet (Viviveridae: *Paradoxurus hermaphroditus*), have been cited as the origin of viruses, *HCoV-OC43* [144], *HCoV-229E* [145], *MERS-CoV*, *HCoV-HKU1* [146] and *SARS-CoV1* [147].

Indeed, the *HCoVs* responsible for the winter cold *(-229E, -OC43, -NL63, and -HKU1)* are currently well-adapted after hundreds or thousands of years of circulation in the human population. Their evolutionary histories and associations with its hosts provide important information about the history of winter cold epidemics [94, 148]. The probable tMRCAs of these four winter cold-causing *HCoVs are found* in the years 1,200-1,500; 1,800; 1,900 and 1,950 respectively [111, 113, 145]. These dates coincided respectively with European discoveries of new lands such as America in the year 1500 [149, 150], the industrial revolution and new means of transportation such as steamboats leading to the dispersal of rats in the year 1800 [151], as well as the intensification of agriculture especially poultry, pig and cattle farming in the year 1900 [130, 152].

For COVID-19, the molecular divergence study between *SARS-CoV2* and other related bat *SARS-CoVs* (*SARSr-CoV*; *RaTG13*) showed 4% genomic nucleotide variability. The novel functional site variations in the receptor binding domain (RBD) observed in *SARS-CoV2* and pangolin *SARS-CoVs* are likely caused by mutations and natural selection in addition to recombination.

4.4. Source of Zoonotic Diseases and Species Barrier

Currently, based on molecular analyses, bats are the main reservoir of different strains of *SARS-CoV* (2002) and *MERS-CoV* (2012), *SARS-CoV2* in 2019 [110]. These CoVs have crossed the species barrier and enzootically infect their intermediate host palm civet (*Paguma larvata*) and Dromedary or *Camelus dromedarius* respectively [153]. While for *SARS-CoV* and *MERS-CoV* the intermediate hosts are known, questions still remain, whether *SARS-CoV2* would be transmitted directly from bats to humans or indirectly via an intermediate host [110, 154]. A second time, these CoVs will cross the species barrier by infecting humans and have become zoonotic [153]. The explosion of these three CoV into pandemics in humans is due to the fact that

they are mainly spread by human-to-human transmission in society or nosocomial [155].

5. Conclusion

CoVs infect a wide range of hosts causing mainly respiratory or enteric diseases but in some cases neurological diseases or hepatitis. Although bats and birds act as the natural reservoir species for many CoVs, the host range has broadened mainly during their evolutionary history. Thus, CoVs have adapted in animals by causing livestock important diseases. In the course of their evolution, CoVs that circulate freely in their animal reservoirs have crossed the species barrier and adapted in humans, causing diseases ranging from the common cold to Severe Respiratory Syndrome (SARS-CoVs, MERS-CoV). These Severe Respiratory Syndrome have caused fatal and even pandemic disease worldwide with significant loss of life. Given the severity of CoV illnesses, it would be wise to further study the continued emergence of these viruses and their reservoirs to prevent their re-emergence in the future.

Authors Contributions

Designed and conceived: M. O. F; Wrote the manuscript: M. O. F and R. M. S.

Competing Interests

The authors declare that they have no competing interests.

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