

REVIEW: THE EPIDEMIOLOGY AND ZONOTIC RISKS OF CORONAVIROSES

Ioana BUZDUGAN¹, Mara TRIFAN¹, Gheorghe SAVUȚA¹

Abstract

The following paper includes a synthesis of bibliographical information regarding the main diseases caused by coronaviruses, both in animals (companion and domestic) as well as in humans, observing the imprevisible tendencies of this viral family. These data are completed by an epidemiological analysis of the main events caused by coronaviruses in humans, using the available databases.

Coronaviruses are worldspread entities, producing, in humans and animals, the most diverse diseases, with digestive, respiratory or nervous symptoms in animals, some forms being very serious and with special economic implications and others mild or even clinically unexpressed; in humans, the symptoms are predominantly respiratory, in some cases beginning with digestive signs and the complications that occur may be neurological in nature. Over the years, especially since 2002 (SARS-CoV), continuing with 2012 (MERS) and more recently, from 2019, culminating with SARS-CoV-2, it has been possible to identify the trend of zoonotic transmission (from animal to human), with a particularly high pathogenic potential of these viruses, which have different rates of morbidity and mortality. Another interesting aspect is the fact that cases of anthroozoonotic transmission (from human to animal) have been reported, in the case of pets, but also of fur animals (minks).

Keywords: coronavirus; infectious disease; animals; zoonosis; pandemic.

INTRODUCTION

The first coronavirus, the avian infectious bronchitis virus, was isolated from chicken eggs in 1937. The transmissible swine gastroenteritis virus and the mouse hepatitis virus were subsequently identified from swine and mouse samples in the 1940s. In the following decades, while human coronaviruses were discovered in the 1960s, other animal coronaviruses, such as porcine hemagglutinating encephalomyelitis virus (1962), feline coronavirus (1970), canine coronavirus (1971), bovine coronavirus (1973), turkey coronavirus (1973), porcine epidemic diarrhea virus (1978) and porcine respiratory complex virus (1984) were also discovered. To study coronaviruses, various reverse genetics systems have been established and implemented since 1992 to understand viral replication, elucidate virus-host interaction, and the pathogenesis process, so that the discovery of new coronavirus vaccines is facilitated [1]. Thanks to the next generation high throughput sequencing technology, which was discovered in 2005, its application in virology paved the way for a new era of coronavirus discovery. Thus, several emerging coronaviruses, such as swine

deltacoronavirus, have been identified (2009) and characterized (2014) [2].

In some circumstances, coronaviruses can be transmitted from animals to humans, adapt to the human species and then spread to the human population without the subsequent involvement of animals. Therefore, in humans, infections with the following coronaviruses have been described: Severe acute respiratory syndrome coronavirus, Severe acute respiratory syndrome coronavirus type 2, Middle East respiratory syndrome coronavirus, and Human coronavirus -229E, -NL63, -OC43 and -HKU1. The most recent human Coronavirus infection is COVID-19, produced by SARSCoV-2, declared a pandemic by the World Health Organization on March the 11th, 2020. In animals, the following coronaviruses are more important: Bovine coronavirus (BCV), Equine coronavirus (ECoV), Transmissible gastroenteritis coronavirus of pigs (TGEV), Porcine respiratory coronavirus (PRCV), Porcine epidemic diarrhea virus (PEDV), Porcine hemagglutinating encephalomyelitis virus (PHEV), porcine acute diarrhea syndrome virus (SADS-CoV), Porcine deltacoronavirus (PDCoV), Canine enteric coronavirus (CCoV), Canine respiratory coronavirus (CRCoV), Feline

¹ IULS, Faculty of Veterinary Medicine

coronavirus (FCoV), Infectious bronchitis virus (IBV) and Turkey coronavirus (TCoV) [3].

The world is currently struggling to mitigate the consequences for public health and to survive the socio-economic crisis caused by measures taken around the world to prevent the spread of COVID-19. In addition, SARS-CoV-2 demonstrates the ability to infect and sometimes cause respiratory damage in many species of mammals. Transmission from humans to dogs, cats, lions, tigers and minks took place and, in the latter case, intraspecific transmission from one mink to another has been observed and notified by the OIE in many countries. The involvement of different species of mammals, which are domestic animals, but also wild animals, in the circulation of SARS-CoV-2 indicates the need for surveillance, intervention and management strategies such as "One Health" to mitigate the effects of this potential zoonotic virus [4, 5, 6].

RESULTS

1. Animal coronaviruses

According to current taxonomy, coronaviruses are classified as one of two genera of the Coronavirinae subfamily, the Coronaviridae family of the Nidovirales order. Coronaviruses (CoV) are divided into four genera based on phylogenetic links and genomic structures: Alpha-, Beta-, Gamma- and Delta-CoV. Almost all alpha-CoV and beta-CoV have mammalian hosts, while gamma-CoV and delta-CoV are commonly found in avian hosts, although some of them can also infect mammals. Members of this large family are considered to be the causative agents of respiratory, enteric, hepatic and neurological diseases in birds and mammals [3].

1.1. Avian coronaviruses

Avian coronaviruses belong to the Gammacoronavirus genus which includes three major species: infectious bronchitis virus (IBV), pheasant coronavirus (PhCoV) and turkey coronavirus (TCoV). IBV or IBV-like gammacoronaviruses have been found in other bird species, such as peacocks, partridges, pigeons, guinea fowl and various species of wild birds [7]. Infectious bronchitis virus, the first coronavirus discovered, is by far the most important and best studied gammacoronavirus and is therefore considered the prototype of the genus. This virus is of great economic importance to the poultry industry around the world, affecting both the performance of farmed poultry for meat and eggs. IBV is an extremely contagious disease that affects the respiratory, reproductive and renal systems, with a different degree of severity depending on the viral strain involved [8].

1.2. Domestic carnivores coronaviruses

In dogs, two types of coronaviruses are known: two alpha-coronaviruses, namely CCoV-I and CCoV-II, and betacoronavirus CRCoV. CCoVs are gastrointestinal viruses with fecal-oral transmission, frequently isolated in dogs around the world, but in most cases, they are able to cause a very mild gastrointestinal disease in puppies or are completely asymptomatic [9].

However, a recently characterized strain (CB/05) has led to a fatal evolution due to the systemic spread of the virus [10]. Moreover, CCoV-infected intestinal villi appear to increase the susceptibility of cells to canine parvovirus (CPV) infection. This leads to a synergistic action that ends with a much more serious disease than the one that both viruses can cause separately [11].

Unlike CCoV, CRCoV beta-coronavirus, also known as group II canine coronavirus, causes mild respiratory signs in dogs and is considered the etiological agent of canine infectious respiratory disease (CIRD) along with other viral and bacterial agents. This beta-CoV is genetically related to one of the human coronaviruses responsible for the common cold, namely HCoV-OC43, and the bovine coronavirus BCoV [12, 13].

FCoV type I and FCoV type II feline coronaviruses belong to the genus Alphacoronavirus. Both genotypes cause a mild enteric disease that, in most infected cats, shows no signs of disease. However, enteric coronaviruses can undergo a mutation in the host and acquire the ability to infect monocytes and macrophages, causing systemic disease. In this form, called feline infectious peritonitis (FIP), the virus causes a serious disease related to an intense immune response, with a fatal result in most cases [14].

1.3. Porcine coronaviruses

Six coronaviruses can cause infections in pigs. These include four alphacoronaviruses, namely porcine transmissible gastroenteritis virus (TGEV), porcine respiratory coronavirus (PRCoV), porcine epidemic diarrhea virus (PEDV) and SADS-CoV, a betacoronavirus, namely porcine viral hemagglutinitis virus, and porcine deltacoronavirus (PDCoV). TGEV, PEDV, SADS-CoV and PDCoV are responsible for acute gastroenteritis in pigs. PRCoV causes a mild respiratory disease, and PHEV is the causative agent of neurological and/or digestive diseases in pigs [15].

1.4. Bovine coronaviruses

The most common bovine coronavirus is BCoV. This virus is capable of causing many clinical forms, including severe enteric disease in

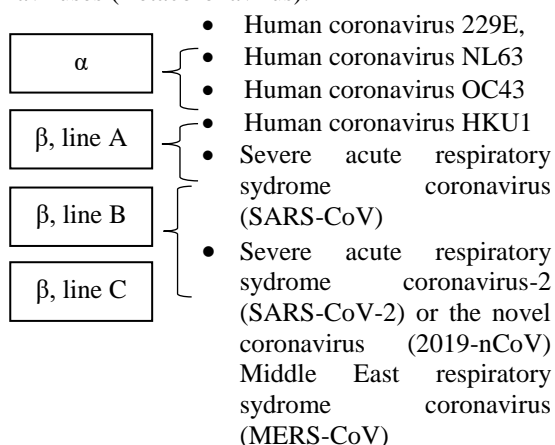
newborn calves, disease with severe enteric evolution in adult dairy cattle, and respiratory disease in cattle of all ages [16]. Interestingly, HCoV-OC43 probably evolved from ancestral BCoV strains that crossed the interspecies barrier and established an infection in humans around 1890, following a 290-length nucleotide deletion downstream of the spike gene [17].

1.5. Equine coronaviruses

The only CoV that has been discovered so far in horses is ECoV, which belongs to the Betacoronavirus genus. ECoV is a newly recognized enteric virus of adult horses that has been associated with fever, lethargy and anorexia, as well as colic and diarrhea. Outbreaks have been reported in Japan, Europe and the USA since 2010 [18].

2. Human coronaviruses

Human coronaviruses fall into the first two categories of the most widely used classification, namely α -coronaviruses (Alphacoronavirus) and β -coronaviruses (Betacoronavirus).



Hosts, reservoirs and infected animals: Bats are the carriers of most viral genotypes. [19]

2.1. Human alphacoronaviruses (HCoV-229E și HCoV-NL63)

These cause acute rhinitis, acute pharyngitis, acute laryngitis, rarely bronchiolitis, acute bronchitis, viral pneumonia. Gastrointestinal symptoms (nausea, diarrhea, vomiting) were encountered, but it was not possible to specify exactly whether these clinical signs were caused by the virus itself, or by another opportunistic pathogen. Severe manifestations occur only in immunosuppressed patients. However, most of the time, the disease goes unnoticed because it has no clinically obvious manifestations [20, 21].

History: The first human coronaviruses were discovered in the 1960s (the first The viral strain was named B814, however, because very few cases were reported at the time and some of them were found to be actually HCoV-229E, it was

concluded that B814 strain is actually HCoV-229E) by researchers at the Common Cold Unit in Salisbury, UK, who showed that common colds can be caused not only by rhinoviruses but also by a coronavirus. In 2003, in a laboratory in the Netherlands, a new coronavirus was discovered, namely HCoV-NL63, a virus that is second to the global spread, being one of the most common viruses. It is considered that some animals, such as bats, are a real reservoir of these viruses, the disease being considered a zoonosis. A new alpaca virus, ACoV, was discovered in 2007, which in 2012 was shown to be 92.2% identical to HCoV-229E after sequencing the viral genome [22, 23, 24, 25, 26].

Epidemiology: Transmission is aerogenic and by direct contact and rarely indirectly, through objects newly contaminated with virus (handkerchiefs). They are ubiquitous viruses and have the phenomenon of "seasonal viruses", being more common at certain times of the year.

Clinical signs: Unpleasant sensation of stuffy and dry nose, followed by repeated sneezing and profuse rhinorrhea (initially watery, then yellowish). Tickling and burning sensation of the nasal mucosa. Smell, taste and appetite are diminished, and digestive signs such as diarrhea, nausea may occur [9]. A hoarse, dry, irritating cough also occurs frequently. fever rarely exceeds 38.2°C in the first 2-3 days. After 5-7 days, all symptoms gradually go away. Sometimes, in more severe cases, nervous signs may appear [20, 27, 28, 29].

Prophylaxis and control: There is no specific vaccine yet. Routine prophylactic measures (isolation, disinfection). A good measure of hygiene is to use cellulose handkerchiefs, then throw them in special closed boxes or on fire [30].

2.2. Human betacoronaviruses

2.2.1. Line A Betacoronaviruses HCoV-OC43

Discovered in 1967 in a laboratory in Maryland, USA, this virus is the most common strain of coronavirus worldwide and is associated with some of the most severe pathological manifestations of HCoV. In 2005, following the sequencing of its entire genome, a link was discovered between OC43 and BCoV (of bovine origin), which proves its zoonotic origin, finding a link with the viral epidemic of 1890, when "Russian/Asian Fever" killed 1 million people [29, 31].

HCoV-HKU1

Discovered in 2005 in a laboratory in Hong Kong, China, this virus is associated with seizures caused by febrile conditions, predominantly among children. Line A betacoronaviruses are found worldwide and have the phenomenon of "seasonal viruses", being more common at certain times of the year.

Epidemiology: Transmission is aerogenous and by direct contact and rarely indirectly, through objects newly contaminated with virus (handkerchiefs). They are ubiquitous viruses.

Clinical signs: Unpleasant sensation of stuffy and dry nose, followed by repeated sneezing and profuse rhinorrhea (initially watery, then yellowish). Tickling and burning sensation of the nasal mucosa. Smell, taste and appetite are diminished. A hoarse, dry, irritating cough also occurs frequently. fever rarely exceeds 38.2 ° C in the first 2-3 days. After 5-7 days, all symptoms gradually go away.

Prophylaxis and control: There is no vaccine yet. Routine prophylactic measures (isolation, disinfection). A good measure of hygiene is to use cellulose handkerchiefs, then throw them in special closed boxes or on fire [28].

2.2.2. Line B Betacoronaviruses

SARS-CoV

(Severe Acute Respiratory Syndrome - Coronavirus)

History: The first case was reported on November the 16th, 2002 in China, in Guandong Province. In the following months, the disease was reported in more than 8,000 people (including 1,706 medical staff). Of these cases, 774 died, the lethality reaching 9.6%. The epidemic has spread to 29 countries on 5 continents (**Figure 1**). No other cases were reported after this epidemic in 2002-2003, the last case being treated in July 2003. The disease was considered to be an extremely fatal infection.

Epidemiology: The natural reservoir is probably bats, from which it is believed that the virus reached civets, then humans, and also, patient 0. The general source of infection is the human with symptomatic infection, a sick person being able to infect an average of up to 3 other people (*Basic reproduction number*). The disease is transmitted directly through nasopharyngeal droplets in the air and indirectly from infected people, through direct contact with them or through objects contaminated with infectious nasopharyngeal secretions [32].

Clinical signs: Severe acute respiratory syndrome: fever (>38°C), chills, myalgia, dry cough, dyspnea and severe impairment of respiratory function (respiratory distress) [33].

Prophylaxis and control: There is no specific or preventive antiviral treatment (vaccine), the treatment being only symptomatic. In the absence of a vaccine, the prevention of SARS transmission involves: epidemiological triage, early detection and isolation of cases, surveillance and quarantine of contacts, sanitary border surveillance [34].

SARS-CoV-2

(Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2) or the novel coronavirus 2019 (2019-nCoV))

History: The first case of nCoV was detected on November the 17th, 2019 in Wuhan, China, from where it spread to most Chinese provinces and several countries around the world, including Europe.

Epidemiology: The primary source of infection is not yet known (probably contact with bat-infected animals; it was previously assumed that the source of infection could be snakes). Transmission is thought to be similar to that of respiratory MERS-CoV and SARS through nasopharyngeal secretions (Flügge drops), produced when an infected person coughs, sneezes or speaks and through direct or indirect contact with nasopharyngeal secretions from an infected person laid on their hands or surfaces (tables, desks, clothing, etc.) in case they touch their eyes, nose or mouth. Initially, a sick person can infect on average up to 3 other people (*Basic reproduction number*), but, against the background of the widespread transmission among the human population, more aggressive variants have appeared and with a higher degree of contagion. Transmission is also possible when there is direct contact with fluids (blood, feces, urine, saliva, semen) from an infected person. The virus is easily transmitted from one person to another. The disease occurs in people who have had close contact with a confirmed or probable case of COVID-19 or have had a history of travel to the affected areas (China, Italy, France, etc.) within 14 days prior to the onset of symptoms. The degree of danger is represented by the carrying of the virus by asymptomatic people, who can spread the virus if they do not respect the imposed hygiene norms, infecting the people around [35, 36].

SARS-CoV-2 uses surface-localized glycoprotein (S) to interact with cells that express the angiotensin 2 conversion enzyme receptor (ACE2) [19]. Glycoprotein S comprises two distinct functional subunits, namely S1 and S2, which are involved in receptor recognition and membrane fusion, respectively [20]. The

interaction between the ACE2 protein and SARS-CoV-2 S involves a C-terminal domain of the S1 subunit, also called the receptor binding domain (RBD), which is a determinant of viral infectivity and host specificity [37]. The sensitivity of different animal species to SARS-CoV-2 is worrying given its potential for transmission, and its understanding is crucial for controlling the spread of the virus. Indeed, coronaviruses have a strong potential for cross-transmission, caused by their ability to genetically adapt (**Figure 2**), especially when they involve RBD [38].

The range of hosts for SARS-CoV-2 can be extremely wide due to ACE2 expression in a wide spectrum of vertebrates. However, the variation of ACE2 residues involved in the RBD-receptor interaction may influence the susceptibility of different species to this CoV. Thus, a comparative analysis of ACE2 protein sequences can be used to predict their affinity for SARS-CoV-2 S-glycoprotein binding and, consequently, the species that can serve as a host for this virus [19].

Li et al. [37] first aligned the amino acid sequence of ACE2 from different species, including humans, five non-human primates, eight domestic animals (cats, dogs, cattle, sheep, goats, pigs, horses and chickens), three wild animals (ferret, civet and Chinese bat) and two species of rodents (mice and rats). The authors found that human and non-human primates share identical sequences in some regional residues. The high degree of sequence similarity observed in most domestic and wild animals implies that ACE2 from these animals can recognize SARS-CoV-2. Thus, these animals may be susceptible to infection. On the other hand, rodents and chickens probably cannot meet the conditions of susceptible hosts.

More recently, Damas et al. [38] used comparative genomic combinations and structural analyzes of proteins to study the conservation of ACE2 in 410 vertebrate species and its potential to be used as a SARS-CoV-2 receptor. This study confirmed the high susceptibility of primates to SARS-CoV-2 infection. On the other hand, this study predicted a wider group of species that could serve as a reservoir or intermediate host for this virus, with mammals having a medium to high score in terms of their tendency to ACE2 to bind to SARS-CoV-2 protein S.

Based on the results of molecular studies, the ACE2 proteins of non-human primates and most domestic and wild animals closely resemble the human ACE2 receptor. However, the results may differ between susceptibility to natural infection and that observed experimentally. Indeed, these studies are based exclusively on in silico analyzes and focus on a small number of amino acid

residues, i.e. 25 amino acids corresponding to known SARS-CoV-2 S protein binding sites [38]. Cross-species transmission is based not only on the presence of the receptor, but also on the levels of ACE2 expression in the respiratory mucosa and on the presence of other cellular factors necessary for viral replication. Therefore, these studies need validation by experimental infection on animal models or examples of natural infections.

➤ *The zoonotic and anthrozoonic character of SARS-CoV-2*

The current hypothesis that the primary source of infection was a probable contact with infected animals has not yet been confirmed. It is expected the connection between bats and pangolins, which are a genus of tropical mammals of the order of edentates whose body and tail are covered with horn-like scales, which feed on insects; it was previously thought that the source of the infection could be snakes. In any case, it is considered to be a zoonosis. Unfortunately, there are no clear data on the precise origin of this pandemic, and speculation can still be easily elaborated [35, 39].

One noteworthy aspect is the fact that there have been numerous situations in which pets, in particular ferrets and cats, have shown a susceptibility to this virus. Dogs and hamsters were also susceptible, but to a much lesser extent. In most cases, the pets took the virus from the owners who tested positive for COVID, the exposure being long, the owners being quarantined at home with them. The animals usually showed no clinical signs, only through molecular (RT-PCR) and serological tests (especially ELISA) were found, either traces of virus in the animals' blood or anti-SARS-CoV-2 antibodies. Most cases were found in outbreak areas, especially in China and Italy [40,41].

Another situation that should not be overlooked is the situation of outbreaks of SARS-CoV-2 in mink fur farms. More than 50 million minks are raised annually for fur, mainly in China, Denmark, the Netherlands and Poland. Outbreaks have occurred in the Netherlands, Denmark, Spain, Sweden, Italy and the United States, killing millions of animals [42, 43, 44, 45].

A special phenomenon took place on farms in the Netherlands. In 4 of the 16 farms studied (in the SE part of the Netherlands, in April and May, 2020), minks are thought to have become ill from workers, and the virus was transmitted rapidly from animal to animal (minks have had fairly severe respiratory signs, but there were also asymptomatic animals) then other workers, who were healthy at the time, took the virus from minks. Finally, 66/97 (67%) of farm staff tested

positive for SARS-CoV-2 through PCR/or serologically. The same viral strain was isolated from minks and humans. A favorable aspect is that the possible exposure to the virus in the areas adjacent to the farms proved to be negligible, the infected people being represented only by the workers who were repeatedly exposed [43]. The total cases and outbreaks of SARS-CoV-2 recorded in animals can be seen in **Table no. 1**, and the outbreaks worldwide can be seen in **Figure no. 3**.

2.2.3. Line C Betacoronavirus

MERS-CoV

(Middle East Respiratory Syndrome - Coronavirus)

History: The first cases of MERS-CoV virus infections occurred in June 2012 in Saudi Arabia and Qatar. In May 2015, 1180 cases were confirmed and 483 (41%) deaths were reported. The countries of the Middle East - Saudi Arabia, Qatar, Jordan and the United Arab Emirates - were predominantly affected, but cases imported into the United Kingdom, the Netherlands, the USA and Asia were reported. The largest outbreak outside the Middle East occurred in South Korea in 2015, affecting several hospitals and 185 people, causing 36 (19.5%) deaths. From 2012 to January 2020, 2,519 cases of MERS-CoV virus infection and 866 deaths were reported to the World Health Organization (WHO), so we face a rate of approximately 34.3% among fatal cases (**Figure no. 4**).

Epidemiology: The natural reservoir is probably the bats that transmit the virus to the intermediate host - camelids, especially dromedaries, which are the source of infection for humans, the infection being settled after consuming milk or camel meat. Most cases of MERS occurred in health care facilities. The virus is not easily transmitted from one person to another except in close contact, as in the case of caring for a patient without the application of protective measures. Cases of infected but asymptomatic people have also been reported. Transmission between individuals in the general population is limited; a sick person can infect on average up to 0.3-0.8 other people (*Basic reproduction number*), this number <1 is encouraging, as it indicates that although the disease still exists worldwide (it has not been completely eradicated), affects an extremely limited number of people, and its completely descending slope highlights the end character of the disease, the virus will soon disappear on its own [46, 47, 40].

Clinical signs: The symptoms are extremely similar to SARS-CoV-2; these include: fever, dyspnea and cough. Gastrointestinal symptoms with diarrhea, vomiting, and abdominal pain may also be present. Unusual compared to other coronaviruses is the presence of acute kidney problems. Most (90%) develop severe pneumonia or respiratory distress syndrome and require intensive care [46, 47, 48, 40].

Prophylaxis and control: There is no specific or preventive antiviral treatment (vaccine), the treatment being only symptomatic. Washing hands with soap and water, or other disinfectants, especially after coughing, sneezing. Covering the nose and mouth with a paper handkerchief in case of coughing or sneezing and then throwing the handkerchief in the trash for safe disposal. Avoiding touching the eyes, nose and mouth with hands, as this can transmit the virus after contact with contaminated surfaces. Avoiding contact with infected people and applying facial masks in overcrowded places. Avoiding close contact with sick people, such as kissing, exchanging drinks and eating utensils. Frequent cleaning and disinfection of affected surfaces, e.g. of toys and door handle [40].

DISCUSSION

SARS-CoV-2 can infect and sometimes cause disease in many species of animals. Of all, the closest phylogenetically to humans (macaque, orangutan and chimpanzee) and possessing a virus receptor identical to ours are certainly the most susceptible to infections and disease development. Also, cats have certainly been shown in both laboratory studies and reported cases to be susceptible to the virus and sometimes able to transmit it to other animals. Frequently, the virus transmitted between cats has caused visible symptoms, which are mild in most cases (sneezing, loss of appetite, apathy, weakness, and sometimes lacrimal hypersecretion have been observed), while in few cases severe respiratory symptoms have been reported with bilateral pneumonia and shortness of breath [49].

Dogs are the only species of Canidae that has been reported to contact the SARS-CoV-2 infection and, in most cases, no signs of disease have been observed in the affected animals. Only in the USA, passive surveillance has identified nonspecific symptoms in older animals with various comorbidities that do not allow the understanding of the pathogenicity mechanism in dogs. In all documented cases where the virus infected domestic animals, transmission occurred from human to animal. Therefore, pets do not pose a risk to the transmission or maintenance of

the virus in the human population and it is mandatory to avoid what happened in China, where many pets were killed or abandoned, following the public statement of a member of the the team of senior experts from China's National Health Commission that pet owners should take extra care of their animals [50].

The situation of mustelids requires a different approach. As observed in experimental infection studies, ferrets, once infected with the virus, develop signs of respiratory disease and transmit the virus to other ferrets [49]. Mink farms have been affected in almost all European countries, but also in the USA. In the cases reported by the Dutch authorities, where strict veterinary surveillance was implemented, in 60% of cases, the positivity was observed post-mortem, with no signs of the disease observed in the farm, while in the remaining 40%, the cases were identified after signs of disease in the farm (increased mortality, loss of appetite, etc.). In addition, serological investigation detected up to 70% of animals with antibodies [51].

As described in Spain, the first weak positivity, defined as inconclusive, was observed in the second half of May. The virus circulated on the farm for at least 6 weeks, until July, when the epidemic broke out on the farms, reaching a positive rate of 86.7%. In Italy, a lower spread of the virus was observed in the monitored farms, with only a few samples that gave positive results [52].

CONCLUSIONS

The spread of coronavirus between animals inevitably leads to mutations of the virus. The spike protein of the virus is the most affected by these mutations. The spread of SARS-CoV-2 in mink farms in Denmark has led to the emergence of a new variant of the virus called Y435F, which has also been observed in human populations living in the district. However, the Y435F mutation has already been observed in other countries (Russian Federation, South Africa, Switzerland and the United States). Thus, it can be stated that recombination within viral structural proteins between coronaviruses from different hosts may be responsible for cross-transmission. These characteristics could allow the virus to become endemic in some populations of domestic and wild animals.

Individuals working in contact with animals must be provided with appropriate safety equipment, thus reducing the viral spread from human to animal. Also, worker testing, contact tracking, isolation and quarantine should be initiated

immediately when a human case is related to an animal farm, and this approach should not be limited to highly sensitive farm animals such as minks. Hunting and wildlife farming bring people into contact with wildlife, and these animals often suffer from debilitating and immunosuppressive disorders that encourage zoonotic outbreaks. Therefore, veterinary surveillance of zoonotic diseases should be maintained and implemented where it is not present, in order to detect early the presence of SARS-CoV-2 in animals. Isolated strains of SARS-CoV-2 should be sequenced, and these sequences obtained from infected animals should be made available to the scientific community to monitor the occurrence or spread of virus variants adapted to animals, but still potentially dangerous to humans. Given the availability of vaccination in the human population, veterinary surveillance should be strengthened among susceptible species, but also other animal species, including wild animals, with a particular focus on wild mustelids.

REFERENCES

1. Shi, ZL., Guo, D. & Rottier, P.J.M. Coronavirus: epidemiology, genome replication and the interactions with their hosts. *Virology*. 2016, 31, 1–2 (2016). <https://doi.org/10.1007/s12250-016-3746-0>
2. Sun, J.; He, W.; Wang, L.; Lai, A.; Ji, X.; Zhai, X.; Li, G.; Suchard, M.A.; Tian, J.; Zhou, J.; et al. COVID-19: Epidemiology, Evolution, and Cross-Disciplinary Perspectives. *Trends Mol. Med.* 2020, 26, 483–495. <https://doi.org/10.1016/j.molmed.2020.02.008>
3. Almeida, J.D.; Berry, D.M.; Cunningham, C.H.; Hamre, D.; Hofstad, M.S.; Mallucci, L.; McIntosh, K.; Tyrrell, D.A.J. *Virology: Coronaviruses*. *Nature* 1968, 220, 650.
4. Wang, C.; Horby, P.W.; Hayden, F.G.; Gao, G.F. A novel coronavirus outbreak of global health concern. *Lancet* 2020, 395, 470–473. [https://doi.org/10.1016/S0140-6736\(20\)30185-9](https://doi.org/10.1016/S0140-6736(20)30185-9)
5. Wu, D.; Wu, T.; Liu, Q.; Yang, Z. The SARS-CoV-2 outbreak: What we know. *Int. J. Infect. Dis.* 2020, 94, 44–48. <https://doi.org/10.1016/j.ijid.2020.03.004>
6. Bonilauri, P.; Rugna, G. Animal Coronaviruses and SARS-COV-2 in Animals, What Do We Actually Know? *Life* 2021, 11, 123. <https://doi.org/10.3390/life11020123>
7. Wickramasinghe, I.A.; Van Beurden, S.; Weerts, E.; Verheije, M.H. The avian coronavirus spike protein. *Virus Res.* 2014, 194, 37–48. <https://doi.org/10.1016/j.virusres.2014.10.009>
8. Cook, J.K.A.; Jackwood, M.; Jones, R.C. The long view: 40 years of infectious bronchitis research. *Avian Pathol.* 2012, 41, 239–250. <https://doi.org/10.1080/03079457.2012.680432>
9. Decaro, N.; Buonavoglia, C. *Canine Coronavirus: Not Only an Enteric Pathogen*. *Vet. Clin. Small Anim. Pract.* 2011, 41, 1121–1132. <https://doi.org/10.1016/j.cvsm.2011.07.005>

10. Decaro, N.; Campolo, M.; Lorusso, A.; Desario, C.; Mari, V.; Colaianni, M.L.; Elia, G.; Martella, V.; Buonavoglia, C. Experimental infection of dogs with a novel strain of canine coronavirus causing systemic disease and lymphopenia. *Vet. Microbiol.* 2008, 128, 253–260. <https://doi.org/10.1016/j.vetmic.2007.10.008>
11. Decaro, N.; Martella, V.; Desario, C.; Bellacicco, A.L.; Camero, M.; Manna, L.; d'Aloja, D.; Buonavoglia, C. First detection of canine parvovirus type 2c in pups with haemorrhagic enteritis in Spain. *J. Vet. Med. B Infect. Dis. Vet. Public Health* 2006, 53, 468–472. <https://doi.org/10.1111/j.1439-0450.2006.00974.x>
12. Mitchell, J.A.; Brooks, H.W.; Szladovits, B.; Erles, K.; Gibbons, R.; Shields, S.; Brownlie, J. Tropism and pathological findings associated with canine respiratory coronavirus (CRCoV). *Vet. Microbiol.* 2013, 162, 582–594. <https://doi.org/10.1016/j.vetmic.2012.11.025>
13. Erles, K.; Toomey, C.; Brooks, H.W.; Brownlie, J. Detection of a group 2 coronavirus in dogs with canine infectious respiratory disease. *Virology* 2003, 310, 216–223. [https://doi.org/10.1016/S0042-6822\(03\)00160-0](https://doi.org/10.1016/S0042-6822(03)00160-0)
14. Brown, M.A. Genetic determinants of pathogenesis by feline infectious peritonitis virus. *Vet. Immunol. Immunopathol.* 2011, 143, 265–268. <https://doi.org/10.1016/j.vetimm.2011.06.021>
15. Vlasova, A.N.; Wang, Q.; Jung, K.; Langel, S.N.; Malik, Y.S.; Saif, L.J. Porcine coronaviruses. In *Emerging and Transboundary Animal Viruses. Livestock Diseases and Management*; Malik, Y., Singh, R., Yadav, M., Eds.; Springer: Singapore, 2020. https://doi.org/10.1007/978-981-15-0402-0_4
16. Salem, E.; Vijaykrishna, D.; Cassard, H.; Hause, B.M.; Maman, S.; Meyer, G.; Ducatez, M.F. Global Transmission, Spatial Segregation, and Recombination Determine the Long-Term Evolution and Epidemiology of Bovine Coronaviruses. *Viruses* 2020, 12, 534. <https://doi.org/10.3390/v12050534>
17. Vijgen, L.; Keyaerts, E.; Moës, E.; Thoelen, I.; Wollants, E.; Lemey, P.; Vandamme, A.M.; Van Ranst, M. Complete genomic sequence of human coronavirus OC43: Molecular clock analysis suggests a relatively recent zoonotic coronavirus transmission event. *J. Virol.* 2005, 79, 1595–1604. <https://doi.org/10.1128/JVI.79.3.1595-1604.2005>
18. Pusterla, N.; Vin, R.; Leutenegger, C.; Mittel, L.; Divers, T. Enteric coronavirus infection in adult horses. *Vet. J.* 2018, 231, 13–18. <https://doi.org/10.1016/j.tvjl.2017.11.004>
19. Li, F. Structure, Function, and Evolution of Coronavirus Spike Proteins. *Annu. Rev. Virol.* 2016, 3, 237–261. <https://doi.org/10.1146/annurev-virology-110615-042301>
20. Arbour N., Day R., Newcombe J., Talbot P.J., (2000), Neuroinvasion by human respiratory coronaviruses. *J Virol*, 74(19):8913-8921
21. Esper F., Ou Z., Huang Y., (2010), Human coronaviruses are uncommon in patients with gastrointestinal illness. *J Clin Vir*, 48:131-133
22. Corman V.M., Baldwin H.J., Tateno A.F., Zerbini R.M., Annan A., Owusu M., Nkrumah E.E., Maganga G.D., Oppong S., AduSarkodie Y., Vallo P., da Silva Filho L.V., Leroy E.M., Thiel V., van der Hoek L., Poon L.L., Tschapka M., Drosten C., Drexler J.F., (2015), Evidence for an Ancestral Association of Human Coronavirus 229E with Bats. *J Virol*, 89(23):11858-11870
23. Dijkman R., Mulder H.L., Rumping L., Kraaijvanger I., Deijs M., Jebbink M.F., Verschoor E.J., van der Hoek L., (2009), Seroconversion to HCoV-NL63 in Rhesus Macaques. *Viruses*, 1(3):647-656
24. Huynh J., Li S., Yount B., Smith A., Sturges L., Olsen J.C., Nagel J., Johnson J.B., Agnihothram S., Gates J.E., Frieman M.B., Baric R.S., Donaldson E.F., (2012), Evidence supporting a zoonotic origin of human coronavirus strain NL63. *J Virol*, 86(23):12816-12825
25. Walsh E.E., Shin J.H., Falsey A.R., (2013), Clinical impact of human coronaviruses 229E and OC43 infection in diverse adult populations. *J Infect Dis*, 208(10):1634-1642
26. Crossley, Beate & Mock, Richard & Callison, Scott & Hietala, Sharon. (2012). Identification and Characterization of a Novel Alpaca Respiratory Coronavirus Most Closely Related to the Human Coronavirus 229E. *Viruses*. 4. 3689-700. 10.3390/v4123689.
27. Desforges M., Le Coupandec A., Dubeau P., Bourgouin A., Lajoie L., Dubé M., Talbot P.J., (2019), Human Coronaviruses and Other Respiratory Viruses: Underestimated Opportunistic Pathogens of the Central Nervous System? *Viruses*, 12(1)pii:E14
28. Gaunt E.R., Hardie A., Claas E.C., Simmonds P., Templeton K.E., (2010), Epidemiology and clinical presentations of the four human coronaviruses 229E, HKU1, NL63, and OC43 detected over 3 years using a novel multiplex real-time PCR method. *J Clin Microbiol*, 48(8):2940-2947
29. Gerna G., Campanini G., Rovida F., Percivalle E., Sarasini A., Marchi A., Baldanti F., (2006), Genetic variability of human coronavirus OC43-, 229E-, and NL63-like strains and their association with lower respiratory tract infections of hospitalized infants and immunocompromised patients. *J Med Virol*, 78:938-949
30. Greenberg S.B., (2016), Update on human rhinovirus and coronavirus infections. *Semin Respir Crit Care Med*, 37:555-571
31. Vijgen L., Keyaerts E. , Moës E. , Thoelen I. , Wollants E., Lemey P., Vandamme A-M., and Van Ranst M. (2005) - Complete Genomic Sequence of Human Coronavirus OC43: Molecular Clock Analysis Suggests a Relatively Recent Zoonotic Coronavirus Transmission Event *Journal of Virology*, Volume 79, Issue 3, 1 February 2005, Pages 1595-1604 <https://doi.org/10.1128/JVI.79.3.1595-1604.2005>
32. Guan Y., Zheng B.J., He Y.Q., Liu X.L., Zhuang Z.X., Cheung C.L.L.S.W., Li P.H., Zhang L.J., Guan Y.J., Butt K.M., Wong K.L.C.K.W., Lim W., Shortridge K.F., Yuen K.Y., Peiris J.S.M., Poon L.L.M., (2003), Isolation and characterization of viruses related to the SARS coronavirus from animals in China. *Science*, 302(5643): 276-278
33. Kamps B.S., Hoffmann C., (2003), Pediatric SARS, In: SARS Reference, 3rd ed., (Ed.) Flying Publisher, Germany, 49-60
34. Fouchier R.A., Kuiken T., Schutten M., van Amerongen G., van Doornum G.J., van den Hoogen B.G., Peiris M., Lim W., Stohr K.,

- Osterhaus A.D., (2003), Aetiology: Koch's Postulates Fulfilled for Sars Virus. *Nature*, 423(6937):240
35. Huang C., Wang Y., Li X., Ren L., Zhao J., Hu Y., Zhang L., Fan G., Xu J., Gu X., Cheng Z., Yu T., Xia J., Wei Y., Wu W., Xie X., Yin W., Li H., Liu M., Xiao Y., Gao H., Guo L., Xie J., Wang G., Jiang R., Gao Z., Jin Q., Wang J., Cao B., (2020), Clinical features of patients infected with 2019 novel coronavirus in Wuhan. *Lancet*, pii:S0140-6736 (20)30183-5
 36. Wu F., Zhao S., Yu B., Chen Y.M., Wang W., Song Z.G., Hu Y., Tao Z.W., Tian J.H., Pei Y.Y., Yuan M.L., Zhang Y.L., Dai F.H., Liu Y., Wang Q.M., Zheng J.J., Xu L., Holmes EC., Zhang Y.Z., (2020), A new coronavirus associated with human respiratory disease in China. *Nature*, 579(7798):265-269
 37. Li, R.; Qiao, S.; Zhang, G. Analysis of angiotensin-converting enzyme 2 (ACE2) from different species sheds some light on cross-species receptor usage of a novel coronavirus 2019-nCoV. *J. Infect.* 2020, 80, 469–496. <https://doi.org/10.1016/j.jinf.2020.02.013>
 38. Damas, J.; Hughes, G.M.; Keough, K.C.; Painter, C.A.; Persky, N.S.; Corbo, M.; Hiller, M.; Koepfli, K.-P.; Pfenning, A.R.; Zhao, H.; et al. Broad host range of SARS-CoV-2 predicted by comparative and structural analysis of ACE2 in vertebrates. *Proc. Natl. Acad. Sci. USA* 2020, 117, 22311–22322. <https://doi.org/10.1073/pnas.2010146117>
 39. <https://www.eccvid.org/media-33-nbsp-possibilities-of-different-origin-location-of-the-covid-19-pandemic>
 40. https://www.who.int/health-topics/middle-east-respiratory-syndrome-coronavirus-mers#tab=tab_1
 41. <https://www.avma.org/resources-tools/animal-health-and-welfare/covid-19/sars-cov-2-animals-including-pets>
 42. <https://www.thelocal.dk/20201014/why-denmark-is-culling-millions-of-minks-due-to-coronavirus>
 43. <https://www.eccvid.org/media-748-sars-cov-2-zoonosis-or-reverse-zoonosis>
 44. <https://www.eccvid.org/media-543-jumping-back-and-forth-anthropozoonotic-and-zoonotic-transmission-of-sars-cov-2-on-mink-fa>
 45. <https://www.oie.int/en/for-the-media/press-releases/detail/article/oie-statement-on-covid-19-and-mink/>
 46. Assiri A., Al-Tawfiq J.A., Al-Rabeeh A.A., Al-Rabiah F.A., Al-Hajjar S., Al-Barrak A., Flemban H., Al-Nassir W.N., Balkhy H.H., Al-Hakeem R.F., Makhdoom H.Q., Zumla A.I., Memish Z.A., (2013), Epidemiological, demographic and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: A descriptive study. *Lancet Infect Dis*, 13(9): 752-761
 47. MacLachlan N.J., Dubovi E.J., (2017), *Fenner's Veterinary Virology*, 5th Ed., (Ed.) Academic Press, Cambridge, MA, SUA, 435-461
 48. Paden C.R., Yusof M., Al Hammadi Z.M., Queen K., Tao Y., Eltahir Y.M., Elsayed E.A., Marzoug B.A., Bensalah O.K.A., Khalafalla A.I., Al Mulla M., Khudhair A., Elkheir K.A., Issa Z.B., Pradeep K., Elsaleh F.N., Imambaccus H., Sasse J., Weber S., Shi M., Zhang J.I, Li Y., Pham H., Kim L., Hall A.J., Gerber S.I., Al Hosani F.I., Tong S., Al Muhairi S.S.M., (2018), Zoonotic origin and transmission of Middle East respiratory syndrome coronavirus in the UAE. *Zoonoses Public Health*, 65(3):322-333
 49. Shi, J.; Wen, Z.; Zhong, G.; Yang, H.; Wang, C.; Huang, B.; Liu, R.; He, X.; Shuai, L.; Sun, Z.; et al. Susceptibility of ferrets, cats, dogs, and other domesticated animals to SARS–coronavirus 2. *Science* 2020, 368, 1016–1020. <https://doi.org/10.1126/science.abb7015>
 50. Safoora. Virus Panic: Owners Throw Away Pets from Highrise Buildings. 2020.: <https://www.siasat.com/virus-panic-owners-throw-away-pets-highrise-buildings-1812619/>
 51. Woo, P.C.Y.; Lau, S.K.P.; Huang, Y.; Yuen, K.-Y. Coronavirus Diversity, Phylogeny and Interspecies Jumping. *Exp. Biol. Med.* 2009, 234, 1117–1127. <https://doi.org/10.3181/0903-MR-94>
 52. Costagliola, A.; Liguori, G.; d'Angelo, D.; Costa, C.; Ciani, F.; Giordano, A. Do Animals Play a Role in the Transmission of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2)? *Animals* 2021, 11, 16. <https://doi.org/10.3390/ani11010016>
 53. <https://www.oie.int/en/what-we-offer/emergency-and-res>

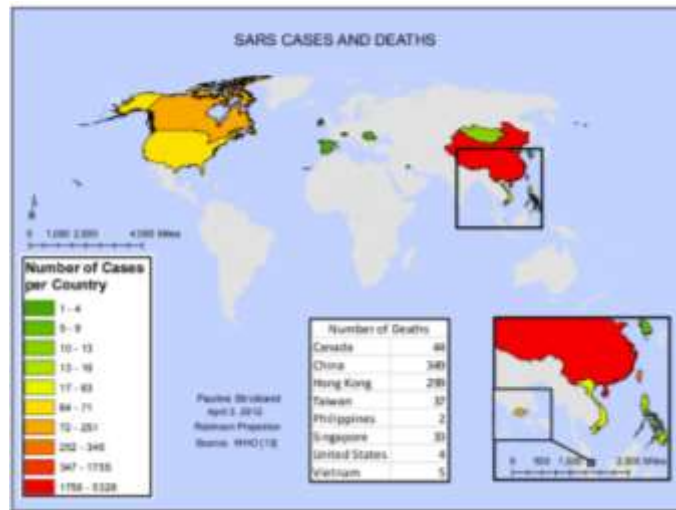


Fig. 1. : SARS-CoV: Number of cases and deaths

Source: https://upload.wikimedia.org/wikipedia/commons/3/33/Sars_Cases_and_Deaths.pdf

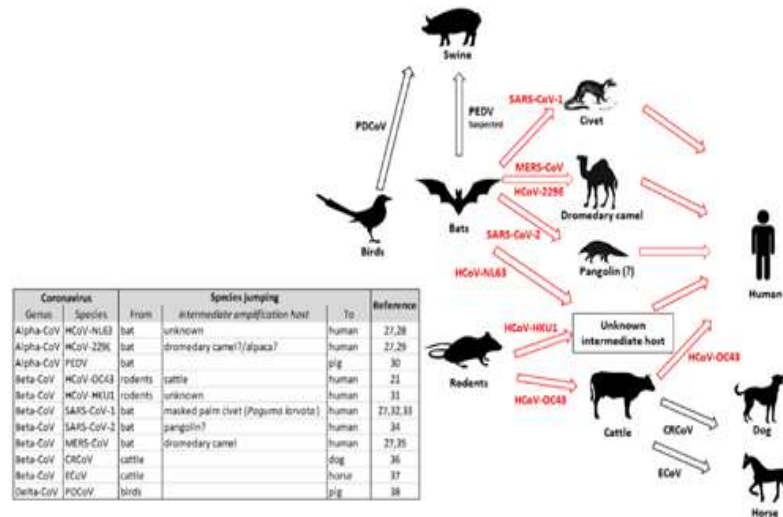


Fig. 2 - Representation of interspecies transmission of coronaviruses. Red arrows indicate cross-transmission involving an intermediate amplifier host (diagnosed, suspected or undetermined). Black arrows indicate a direct transmission between two species [6]

Table no. 1 : Total cases and outbreaks of SARS-CoV-2 in animals

Continent	Species	Outbreaks	Cases	Slaughtered	Deaths
Africa	Lion	1	3	0	0
	Puma	1	1	0	0
The Americas	American Mink	18	4	0	14130
	Lion	10	10	0	0
	Tigers	15	23	0	0
	Gorilla	4	16	0	0
	Dog	106	87	1	5
	Asian Otter	4	11	0	0
	Mustelidae	10	263	10.917	248
	Amur Leopard	2	0	0	0
	Snow Leopard	3	5	0	0
	Cat	94	89	0	9
	White-tailed deer	1	8	0	0
	Puma	3	2	0	0
	Jaguar	2	0	0	0
Rabbit	1	0	0	0	
Pig	1	0	0	0	

Asia	Tiger	3	6	0	0
	Dog	22	21	0	0
	Cat	11	14	0	0
Europe	Mustelidae	43	22.729	0	1.578
	Dog	7	8	0	0
	Cat	12	13	0	0
	American Mink	6	338	0	338
	Ferret	1	1	0	0
	TOTAL	381	23.652	10.918	16.308



Fig. 3.: Outbreaks of SARS-CoV-2 in animals worldwide

Source: <https://www.oie.int/en/scientific-expertise/specific-information-and-recommendations/questions-and-answers-on-2019-novel-coronavirus/events-in-animals/>

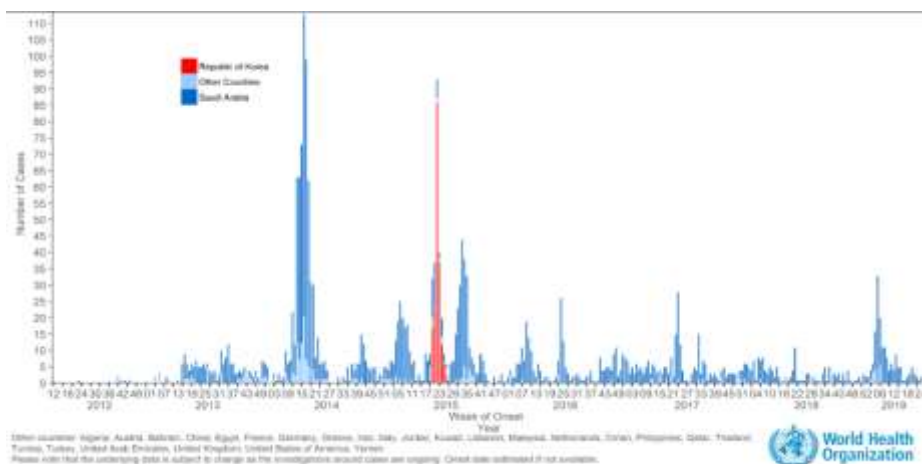
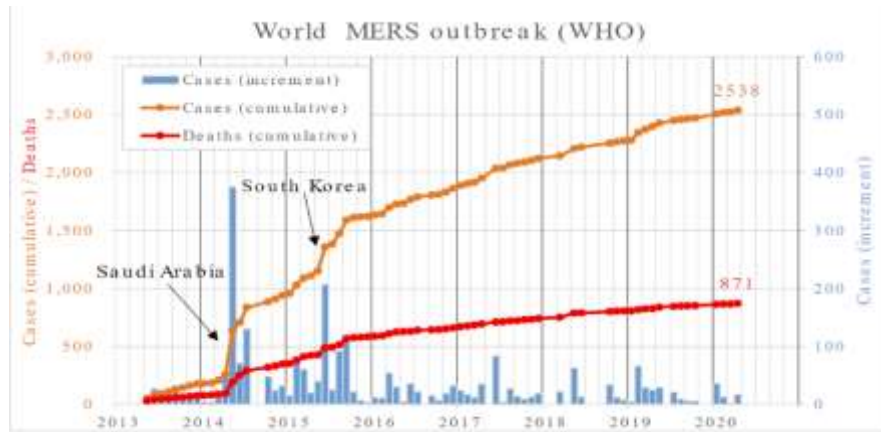


Fig. 4: MERS: Number of cases and deaths reported worldwide in 2012-2020

Source: https://www.who.int/health-topics/middle-east-respiratory-syndrome-coronavirus-mers#tab=tab_1