REVIEW

A comprehensive review of SARS-CoV-2 genetic mutations and lessons from animal coronavirus recombination in one health perspective

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SARS-CoV-2 was originated from zoonotic coronaviruses and confirmed as a novel beta-coronavirus, which causes serious respiratory illness such as pneumonia and lung failure, COVID-19. In this review, we describe the genetic characteristics of SARS-CoV-2, including types of mutation, and molecular epidemiology, highlighting its key difference from animal coronaviruses. We further summarized the current knowledge on clinical, genetic, and pathological features of several animal coronaviruses and compared them with SARS-CoV-2, as well as recent evidences of interspecies transmission and recombination of animal coronaviruses to provide a better understanding of SARS-CoV-2 infection in One Health perspectives. We also discuss the potential wildlife hosts and zoonotic origin of this emerging virus in detail, that may help mitigate the spread and damages caused by the disease.

Keywords: coronavirus disease 2019, genetic mutations, animal coronavirus, pandemic

Introduction

Trend of coronavirus disease 2019 (COVID-19)

COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is the first pandemic of coronavirus that spread from an outbreak in Wuhan, China. However, cases of infection and mortality associated with COVID-19 vary from country to country. COVID-19 is an unprecedented new virus infecting human beings. Therefore, uncertainties remain in the available information on this virus and several aspects are still unknown. Moreover, the potential alterations in the transmission modes of the virus over the next 1–2 years are unpredictable (Epidemiology Working Group for NCIP Epidemic Response and Chinese Center for Disease Control and Prevention, 2020). There will be several additional epidemics in the future until an effective vaccine is created or people develop herd immunity by infecting the majority (about 60% to 70%) of the world's population (Brett and Rohani, 2020). Till then, millions of people would continue to suffer from "Corona-phobia." Hence, how we predict and prepare for this situation until the availability of safe and effective vaccines or attainment of herd immunity is very important (Guo *et al.*, 2020).

Unlike the SARS epidemic in 2003 and MERS epidemic in 2012 (Lee and Hsueh, 2020), the COVID-19 is a record-breaking epidemic that is very contagious. Considering the large number of asymptotic infections, it is a huge mistake to consider only those individuals exhibiting symptoms of fever and cough as patients, and wearing a mask at all times is very important to prevent transmission from asymptomatic patients. In other words, preparing and defending the invisible aspect is one of the most effective defense methods. Moreover, COVID-19 has a higher pre-symptomatic transmission about 1 to 3 days before the onset of symptoms spreading 2.5 to 3.5 cases per infected individual. The mortality rate of COVID-19, reported worldwide so far, is higher than that of the Spanish flu pandemic, which was 2.5%. The United States is breaking the record for the number of confirmed cases every day, and the number of deaths is increasing rapidly. China has also reported a mortality rate of 3.4% (Abdelrahman *et al.*, 2020).

Generally, the pandemic period is about 18 to 24 months, as herd immunity gradually increases among the population through several epidemics, and as its threshold approaches 60% to 70%, the epidemic subsides (Plans-Rubió, 2012). However, there is still uncertainty in case of COVID-19. Although more than 90% of the antibodies are produced during the COVID-19 infection, more data are needed to confirm whether they prevent re-infection. A number of cases with limited long-term immunity, despite substantial antibody production, have been observed; thus, there is a possibility of re-infection due to a drop in the antibody levels within a few months to a couple of years. The uncertainty in the development and persistence of protective immunity as well as the difficulty in neutralizing antibody production pose a number of challenges to completely eradicate COVID-19.

It is expected that by the end of this pandemic, the virus would become less virulent and contagious owing to herd immunity development, and it is likely to gradually trans-

form into seasonal corona, similar to the seasonal flu. The S and V variant groups of SARS-CoV-2 were prevalent worldwide until early April, 2020 (Gussow *et al.*, 2020), whereas the G, GR, and GH groups are prevalent currently. The GR group is dominant in Africa, India, and Russia, while the GH group is dominant in North America, Europe, and the Middle East. It is postulated that the GH group virus replicates better in cells and has high transmissibility through high affinity to the host cells (Mercatelli and Giorgi, 2020). The Center for Infectious Disease Research and Policy predicted three scenarios for the COVID-19 pandemic. The first scenario involves small pandemics repeating several times over a year or two, that subside by thorough quarantine during the outbreaks, but reemerge when it is slightly mitigated (Xu and Li, 2020). The second scenario is that a big pandemic hits during the fall, which is the most worrisome. Finally, the third scenario is the most promising and one that many experts wish for: Despite severe losses during the first wave of the pandemic, only small-scaled epidemics occur thereafter and do not cause much damages. Thus, the third scenario is the most positive, especially as it is easy to control the epidemic through stringent quarantine measures, even though infectious diseases manifest in each region. Moreover, while continuing with this this pattern for about two years, there is a high probability of development of a vaccine.

During the pandemic influenza in 2009, as the weather became chilly and schools reopened in September, the number of patients increased and peaked by late October and early November. However, antivirals were available at that time and vaccination helped control the outbreak. In contrast, COVID-19 is more damaging because there is no specific treatment or vaccine available to date. In this sense, COVID-19 is still in the first wave of pandemic and would remain there until availability of antivirals and vaccine.

SARS-CoV-2

Origin and evolution of SARS-CoV-2

Genetic analysis of SARS-CoV-2 revealed 96% nucleotide identity with Beta CoV/RaTG13/2013 isolated from bats. According to previous reports, Rhinolophus bats in South China were found to be infected with a number of SARS-CoV-like viruses belonging to the subgenera Sarbecovirus. These viruses exhibit genetic diversity and frequent recombination, which increases the likelihood of cross-species transmission (Wong *et al.*, 2019). Coronavirus from pangolin shows 91.02% and 90.55% identity with SARS-CoV-2 and BatCoV RaTG13, respectively, at the whole genome level. Other than RaTG13, pangolin-CoV is most closely related to SARS-CoV-2. Moreover, the S1 protein of pangolin-CoV is more closely related to SARS-CoV-2 than to RaTG13. The five key amino acid residues involved in the interaction with human ACE2 are perfectly matched between pangolin-CoV and SARS-CoV-2, while there are four amino acid mutations in RaTG13. Neither Pangolin-CoV nor RaTG13 has a putative furin recognition sequence motif at the S1/S2 cleavage site, as observed in SARS-CoV-2. Thus, pangolin may be a natural reservoir of CoVs similar to SARS-CoV-2 (Zhang *et al.*, 2020b).

Based on SNP analysis, L lineage (70%) was found to be more prevalent than S lineage (30%), and evolutionary analysis showed that S was more related to coronavirus in animals (Tang *et al.*, 2020). Comparison of the S protein in SARS-CoV-2 and porcine coronaviruses revealed that PEDV and TGEV share only 42.8% and 43.5%, respectively, genetic similarity with SARS-CoV-2, while PHEV and PDCoV share 49.2–49.3% and 40.3–40.4%, respectively, genome similarity with SARS-CoV-2. Although it is unlikely that SARS-CoV-2 originated from porcine CoVs, the RBD of SARS-CoV-2 has the potential to recognize porcine ACE2 based on the
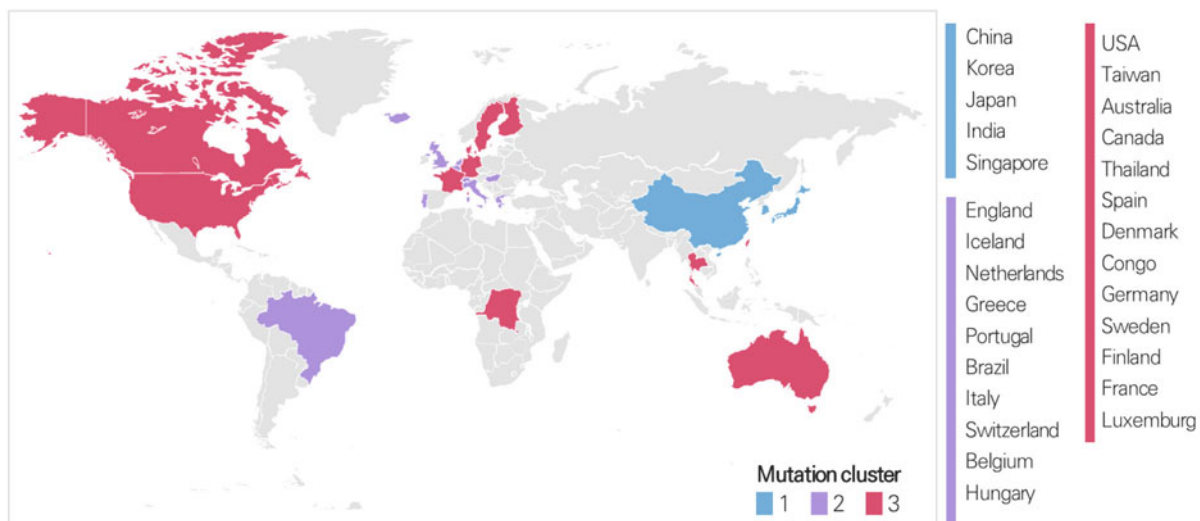

Fig. 1. Clustering analysis of SARS-CoV-2 in 28 countries (modified from Toyoshima *et al.*, 2020). Clustering analysis of SARS-CoV-2 among 28 countries. A global mapping of the three clusters.

high similarity of viral binding residues in human ACE2 (Wen *et al.*, 2020).

Birds can serve as a genetic source of gamma coronavirus and delta-coronavirus, leading to the constant evolution and transmission of CoVs. IBV typically binds to cellular receptors through sialic acid for attachment and entry. Notably a 43.0–43.2% genomic similarity between SARS-CoV-2 and IBV is observed (Zhang *et al.*, 2020c).

Bovine CoVs belong to the genus beta coronavirus. Bovine CoV is similar to a human CoV, alf44/US/94 that was isolated from children and causes public health problems. In addition, human beta coronavirus OC43, which causes common cold in humans, is related to BCoV, and studies suggest that either BCoV is an ancestor of human CoV, or the tow share a common ancestor (Hasoksuz *et al.*, 2007). BCoV also has a wide host range, including dogs, poultry, and giraffes. Genomic analysis revealed that BCoV shows only 49.2–49.3% gene similarity to SARS-CoV-2 (Zhang *et al.*, 2020a).

Genotypes of SARS-CoV-2

A recent study identified 1,234 mutations by analyzing the sequence of 12,343 SARS-CoV-2 genes isolated from patients in six regions. Through hierarchical clustering based on mutation frequency, the COVID-19 fatality rate of 28 countries were classified into 3 clusters (Toyoshima *et al.*, 2020) (Fig. 1). Notably, nucleotide mutations in 11,083 genes encoding Nsps are reportedly related to the severity of COVID-19. The 11083G mutation was commonly observed in symptomatic patients, while asymptomatic infection was found to be associated with the 11083T mutation.

Gene mutations in SARS-CoV-2: Analysis of 30,366 SARS-CoV-2 isolate genomes revealed 11 gene mutations with an incidence rate of over 10%. Eight out of 11 mutations resulted in amino acid changes: C1059T, G11083T, C14408T, A23403G, G25563T, G28881A, G28882A, and G28883C, while the remaining 3 mutations did not result in amino acid changes, causing "synonymous mutation." The most prevalent mutations were C14408T and A23403G in Nsp12 and S protein,

respectively, occurring simultaneously; whereas G25563T of ORF3a has little locational relevance. The most frequent mutations were observed in C241T of the 5′-UTR, which can affect activity, replication, gene assembly, immune regulation, and expression, with the frequency reaching 70.99% (Ugurel *et al.*, 2020). The remaining 10 mutations were observed in nonstructural, structural, and accessory proteins. Specifically, ORF1ab region included 4 variations in more than 10% of SARS-CoV-2 isolate genomes: C3037T, C1059T, G11083T, and C14408T. The C3037T occurs in Nsp3-encoding region with 29.3% frequency. The other three mutations appear in Nsp2-, Nsp6-, and Nsp12-encoding regions, respectively, with more than 10% incidence, inducing amino acid substitutions. The C1059T mutation in Nsp2 induces T266I amino acid substitution, albeit the effect on protein function has not been elucidated yet (Chen *et al.*, 2020). G11083T mutation in Nsp6 causes L36F mutation, which induces vesicles around the microtubule regulation center and influences membrane proliferation. C14408T and C14805T occur in Nsp12, which is essential for protein replication and pathogenicity. The C14408T mutation affects the missense mutation of P232L, and is considered important for virus dissemination because the mutation incidence rate has increased rapidly.

Mutations in accessory and structural proteins: Continuous mutations occur most frequently in G25563T of the accessory protein, A23403G of the S protein, and G28881A, G28882A, and G28883C of the N protein (from GGG to AAC). G25563T is located in the ORF3a, encoding a unique membrane protein with a 3-membrane structure and is essential for pathogenicity. Among the four structural proteins, S, E, M, and N, amino acid substitutions occur at a rate of over 10% in S and N proteins. In S protein, A23403G mutation induces D614G substitution, which is suggested as one of the most important mutations reported so far. Similar to C14408T mutation in Nsp12, the incidence of the A23403G mutation in the S protein is 70.46% (Ugurel *et al.*, 2020).

The N protein plays an important role in regulating the metabolism of infected cells and in the process of viral assembly required for viral replication and transcription. Three

Table 1. Tissue tropism of coronaviruses

| Host | Virus | | Tissue tropism |
	Genus	Species (Scientific name)	
Swine	*Alphacoronavirus*	PEDV	Intestine, Lung
		TGEV	Intestine
		PRCV	Lung
		SeCoV	Intestine
		SADS-CoV	Intestine
	Betacoronavirus	HEV	Central nerve system, lung
	Deltacoronavirus	PDCoV	Intestine
Bovine	*Betacoronavirus*	BCoV	Intestine
Canine	*Alphacoronavirus*	CCoV	Intestine
			Various tissues
	Betacoronavirus	CRCoV	Lung
Feline	*Alphacoronavirus*	FCoV	Intestine, Macrophage
Equine	*Betacoronavirus*	ECoV	Intestine
Chicken	*Gammacoronavirus*	IBV	Trachea and Various tissues

mutations in the N protein (G2881A, G28882A, G28883C) have been reported that occur simultaneously. G28881A and G28882A cause R204K, while G28883C causes G205R substitutions (Kang *et al.*, 2020).

Animal coronaviruses and their dynamic genetic characteristics

SARS-CoV-2, is of zoonotic origin and our knowledge on the unprecedented new virus in humans is limited. However, coronaviruses have been major pathogens in veterinary medicine and countermeasures in various species are available. Coronaviruses cause enteric, respiratory, and systemic diseases in live stocks and companion animals (Domańska-Blicharz *et al.*, 2020). Table 1 summarizes the swine, bovine, canine, feline, equine, and poultry coronaviruses. The animal coronaviruses have evolved and mutated, and can provide insights so as to prepare for potential SARS-CoV-2 mutations.

Coronaviruses in dogs

Canine coronavirus (CCoV) were first reported in 1974 (Ward *et al.*, 1968; Binn *et al.*, 1974). Coronavirus in dogs causes mild to moderate enteric disease when pups are infected with only CCoV. However, CCoV can be fatal in case of co-infection with canine parvovirus 2 (Decaro and Buonavoglia, 2008). Although CCoV naturally infects enterocytes, it can infect other organs, such as the lungs, liver, and tonsils, as observed through animal experiments (Tennant *et al.*, 1991). Since 2009, fatal coronavirus infections have been reported (Buonavoglia *et al.*, 2006). CCoV was detected in dogs with systemic diseases, presenting fever, lethargies, neurological signs, and diarrhea. This virus has been called pantropic CCoV (Buonavoglia *et al.*, 2006; Alfano *et al.*, 2020). As a result of the pantropic CCoV, CCoV infection was no longer confined to enteric disease.

CCoV has two distinct serotypes, type I and type II; type II is further subdivided into type IIa and IIb (Pratelli *et al.*, 2003; Decaro and Buonavoglia, 2008). CCoV type I is recombination product of CCoV and FCoV. An FCoV-like CCoV strain (Elmo/02) presented 81.76% sequence homology with FCoV type I (UCD1) and 54.31% with another CCoV strain (K378) in the S protein (Pratelli *et al.*, 2003). This FCoV-like CCoV designated to CCoV type I and reference CCoV was classified CCoV type II (Decaro and Buonavoglia, 2008). Recombination between CCoV type II and TGEV resulted in TGEV-like CCoV, classified as CCoV type IIb, which has partial recombination of TGEV S1 partial region in CCoV type II back bone (Decaro *et al.*, 2010). Although recombination events in CCoV presented no significant effects on pathology, genetic mutation or divergence might be responsible for virulence in CCoV type II strains (Decaro and Buonavoglia, 2008). CCoV type II BGF strain has long ORF3b sequences compared to other CCoV type II strains and CCoV type II CB/05 strain, which presented deletion in ORF3b (Decaro and Buonavoglia, 2008). These genetic changes result in the abnormal virulence of these two strains severe gastrointestinal symptoms of BGF strain (Sanchez-Morgado *et al.*, 2004), and multiple organ tropism of CB/05 strain (Buonavoglia *et al.*, 2006). In particular, CB/05 strain

exhibits varied tissue tropism, owing to which this strain was designated "pantropic CCoV". Although, the exact mechanism of multi-organ tropism had not been identified, this virus presented continuous circulation in Europe, China, and Brazil (Alfano *et al.*, 2020).

Coronaviruses in cats

FCoV was first reported in 1968 (Ward *et al.*, 1968; Binn *et al.*, 1974). FCoV has two serotypes, type I and type II (Fiscus and Teramoto, 1987; Shiba *et al.*, 2007). It is divided into two biotypes according to clinical manifestation (Jaimes and Whittaker, 2018): feline enteric coronavirus (FECV), and feline infectious peritonitis virus (FIPV). FCoV type II is a result of recombination between FCoV and CCoV (Fiscus and Teramoto, 1987; Herrewegh *et al.*, 1998). Several studies have reported that ORF1, S, and M genes presented the recombination between CCoV and FCoV (Herrewegh *et al.*, 1998; Terada *et al.*, 2014). The S protein is the most common region for recombination. This recombination results in differences in neutralization and cellular receptor for infection between FCoV type I and type II strains. As coronaviruses originally used aminopeptidase N (APN) as receptor, FCoV was considered to use feline APN (fAPN). However, only FCoV type II uses fAPN, whereas FCoV type I does not (Dye *et al.*, 2007; Terada *et al.*, 2014; Jaimes and Whittaker, 2018; Jaimes *et al.*, 2020). Although, feline C-type lectin dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (fDC-SIGN) had been suggested as a co-receptor for FCoV type I and II, the specific cellular receptor (Regan and Whittaker, 2008) of the FCoV type I needs to be identified (Jaimes *et al.*, 2020). The characteristics of the cellular receptor may facilitate cell adaptation of the FCoV type II rather than type I, leading to the cell culture property of the FCoV type II (Jaimes and Whittaker, 2018; Jaimes *et al.*, 2020).

In cats, coronavirus causes the most fatal disease, feline infectious peritonitis (FIP) (Jaimes and Whittaker, 2018). Moreover, the clinical significance of FCoV is its relation with FIP, which is the one of the most fatal diseases in cats. Although the origin of FIP is controversial, its pathogenesis can be explained by a genetic mutation, the "internal mutation" hypothesis (Pedersen *et al.*, 2012), which proposes mutation of the S, ORF7, and ORF3 region in FECV, regardless of types. The most critical mutation is the amino acid substitution in the S protein that is known responsible for tissue tropism from enterocytes to macrophages or monocytes (Meli *et al.*, 2004; Tekes and Thiel, 2016; Jaimes and Whittaker, 2018). As per the recently accepted hypothesis for FIP, FCoV infects the intestine of kittens and changes the host cell from enterocytes to macrophages; this change in tissue tropism converts a mild to moderate enteric disease into a fatal systemic disease.

Coronaviruses in pigs

Five representative porcine coronavirus are known: transmissible gastroenteritis virus (TGEV), porcine respiratory coronavirus (PRCV), porcine epidemic diarrhea virus (PEDV), porcine hemagglutinating encephalomyelitis virus (PHEV), and porcine delta-coronavirus (PDCoV). Among these,
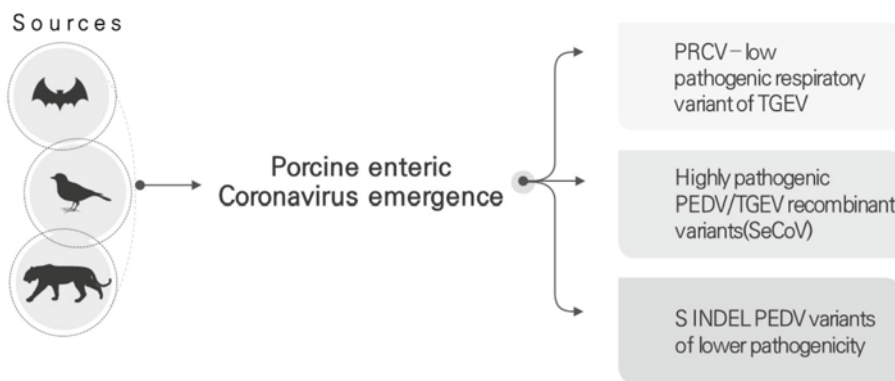
Fig. 2. Different stages of evolution of swine enteric coronaviruses (modified from Vlasova *et al.*, 2020). Swine enteric CoVs (TGEV, PEDV, and PDCoV) are highly contagious and are associated with severe disease forms such as diarrhea and vomiting, causing sporadic outbreaks (endemic) or large-scale epidemics in swine-producing countries.

TGEV, PRCV, and PHEV have been infecting pigs for decades, while PEDV and PDCoV have begun to appear relatively recently. Most recently, swine acute diarrhea syndrome coronavirus (SADS-CoV), another highly pathogenic intestinal coronavirus, appeared in China in 2016 with a high mortality rate among piglets (Vlasova *et al.*, 2020).

TGEV, an alpha coronavirus, was first discovered in the United States in 1946 as an outbreak of acute diarrhea with a high piglet mortality. However, the clinical impact of TGEV was mitigated by the emergence and extensive spread of PRCV, wherein a mutation in the S protein of TGEV was naturally deleted. Currently, severe diarrhea symptoms occur sporadically in piglets due to TGEV in ranches that are negative for TGEV and PRCV in North America, Europe, and Asia. Previous studies of the genetic structure of PRCV and TGEV have revealed two unique properties. First, PRCV S gene encodes a smaller S glycoprotein in PRCV than TGEV owing to the elimination of nt 621–681. Second, TGEV and PRCV are different for each ORF3 part. Leader RNA-binding site (CTAAAC) preceding the ORF3a gene in PRCV is altered or partially eliminated (Zhang *et al.*, 2017).

In the past few years, chimeric viruses in which TGEV backbone and the S protein of PEDV are recombined have been identified in several European countries, and suggested the possibility of emergence of such chimeric viruses in the United States. Six TGEV mutants in the United States, showed 8 dropouts that could have a major biological biologically and 119 distinct amino acid changes that formed a mutated genotype. The mutated genotype shared dropouts and amino acid changes with a recently identified PRCV variant, suggesting recombination between TGEV and PRCV. Further, this mutated genotype is the dominant TGEV genotype prevalent in the United States (Chen *et al.*, 2019).

In 2016, another recombinant virus, designated SeCoV, had been reported in Italy (Boniotti *et al.*, 2016). However, the recombinant virus was isolated in 2009, and other studies revealed that that the SeCoV existed in Spain at least since 2003, as well as in Germany and Central Europe (Boniotti *et al*., 2016; de Nova *et al.*, 2020). The clinical symptoms of SeCoV infection are also related to gastrointestinal system, similar to TGEV and PEDV infections; however, there are no reports on changes to tissue tropisms resulting from recombination causing changes in the S protein, such as amino acid substitution or deletion (Belsham *et al.*, 2016; Boniotti *et al*., 2016).

Since the 2000s, classic PEDV, clinically similar to TGEV, has been rarely reported. In 2014, non-insertion and deletion (INDEL) mutations in S gene, altering S1 protein, in PEDV was reported in Ukraine and the United States; S INDEL mutations were confirmed in other European countries as well. In the case of the non-S INDEL mutation, the mortality rate of newborn pigs with non-S INDEL mutation reached 50–100%. In addition, PEDV transmission through direct or aerosol contact was significantly higher in the case of non-S INDEL mutation- than S INDEL mutation-harboring viruses, while S INDEL mutation causes mild disease leading a large number of infected piglets in farms with low herd immunity. Although classic PEDV, emerging non-S INDEL, and non-S INDEL PEDV strains exist in Asia and Europe, new non-S INDEL and S INDEL PEDV strains are currently circulating in the United States. Up to date, PEDV infection has not been reported in the African and the Australian continent. Infections associated with the Classic PEDV mutation were reported in China in the late 1970s. Since then, despite the use of the vaccine, it has spread among pig farms, becoming the leading cause of viral diarrhea (Fig. 2).

Recombination of RNA viruses occurs mainly in 7 major regions of the gene, including the S1 region, Nsp2, Nsp3, and Nsp14–16 of the nuclear capsid genes. The recombination pattern is largely divided into two: The first pattern occurs when other coronaviruses are recombined with PEDV. This is seen in case of recombinant TGEV and PEDV chimeric viruses such as SeCoV/GER/L00930/2012, Italy/213306/2009, and PEDV/Belgorod/dom/2008. The second pattern results from recombination with other PEDV strains, such as XM1-2, GYJ130330, and HNQX-3 strain, which belong to the GII-a subtype. Recombination of pathogenic strains belonging to different subtypes enriches the genetic diversity. Therefore, further attention should be paid to the prevention and treatment of PEDV.

PDCoV was first reported in China's livestock market in 2005–2006, while DCoVs were identified in pigs and wild birds in 2007–2011 in a China and Hong Kong surveillance study. It has been suggested that other DCoVs can be transmitted between carnivores, pigs, and birds because their helicase and S genes are closely related to PDCoV. Although the origin of PDCoV is still unclear, recent outbreak suggests that its adaptation to pigs may be incomplete. PDCoV was also reported in Canada in March 2014, Korea in April 2014, Mainland China in 2015, Thailand in 2015. Genetic analysis

revealed that the S gene harbors the most genetic variations in mutant strains. The ORF1a is also a highly variable region, including the Nsp2 and Nsp3, exhibiting dropout, insertion, and replacement (Sun *et al.*, 2020).

A highly pathogenic PDCoV, CHN-GD-2016, shared a 97.3–99.5% nucleotide identity with other 26 PDCoV mutants. Compared with the PDCoV mutation, a 3nt deletion was also observed in S gene of the PDCoV mutation CHN-GD-2016, which was also present in all PDCoV mutations from mainland China. Phylogenetic analysis showed that PDCoV strains in the United States and Korea were largely grouped together, while PDCoV strain CHN-GD-2016 was grouped with other PDCoV strains detected in China since 2014. Thus, the CHN-GD-2016 strain was most closely related to other PDCoV mutants from mainland China (Xu *et al.*, 2018).

A new type of alpha-coronavirus that is genetically distinct, but clinically similar, from other viruses was reported from 2016 to 2017. SADS-CoV is a newly discovered highly pathogenic virus that likely evolved from HKU2 bat coronavirus, which transmits Rhinolophus bat species similar to SARS-CoV in China. SADS-CoV has 98.48% sequence identity with HKU2 bat coronavirus, suggesting that the two may have originated from a common ancestor (Zhou *et al.*, 2018). No cases have been reported on other pig farms since the first outbreak from May 2017 to January 2019; however, a mutant SADS-CoV/CN/GDLX/2019 was found in February 2019. The S gene of SADS-CoV/CN/GDLX/2019 showed a very high identity (99.2–99.9%) with other SADS-CoV mutations detected in Guangdong, and the lowest identity of 97.5% with SADS-CoELFJ. Recombinant rSADS-CoV has been efficiently replicated in a variety of animals, including primate cell lines such as human primary liver and rectal cancer cell lines. Moreover, rSADS-CoV did not use human coronavirus ACE-2, DPP4, or CD13 receptors for docking and entry. Although there are no studies showing that SADS-CoV replication in humans to date, there is a possibility of human transition because of its ability to replicate in primary human cells (Edwards *et al.*, 2020).

Coronaviruses in chicken

Since chicken Coronavirus (IBV) was first isolated and identified in the United States in 1931, a number of mutant strains have been identified worldwide. Many mutant strains occur through recombination with other strains rather than through accumulation of point mutations. Mutation and recombination of IBV can occur in both structural and non-structural proteins. Most mutations and recombination are found in the S gene and can also occur in polyproteins 1a and 1ab. Changes in the IBV S protein, especially the S1 gene, play critical roles in immunogenicity and viral diversity, so mutations and recombination of this gene markedly affect viral phenotype and virulence (Zhang *et al.*, 2020c).

Despite the existence of various vaccines against IBV, mutations have resulted in new genotypes, serotypes, or pathogenic IBV mutants that heave been continuously emerging in recent years. These IBV mutations have been identified in China, Korea, and Egypt. Seven major IBV genotypes (GI–GVII), 35 lineages (1–35) and several other genotypes have been identified. Among these lineages, the distribution of GI-1 (formerly Massachusetts; Mass), GI-13 (793/B, 4/91, or CR88), GI-19 (LX4 or QX), GI-16 (ck/CH/LDL/97I (LDL/97I) or Q1), GI-21 (Italy 02), and GI-23 (Var2) is limited to specific continents, countries, or regions. Moreover, nucleotide replacement or recombination between the field strain and the vaccine occurs frequently. The GI-1 genotype H120 vaccine, which is currently the most widely used commercial vaccine, has very little similarity to the most prevalent GI-19 or other genotypes at present. Therefore, this vaccine reportedly does not provide effective protection against other genotype infections, causing several cases of outbreaks in vaccinated livestock (Ma *et al.*, 2019).

A newly emerged recombinant IBV strain CK/CH/2010/JT-1 was found highly pathogenic and belongs to a new genotype. The serum against H120 and 4/91 did not completely neutralize CK/CH/2010/JT-1, suggesting that this mutant strain has a different serotype than H120 and 4/91. Therefore, H120 and 4/91 vaccines against Mass strains do not effectively protect against CK/CH/2010/JT-1. In addition, isolate strains similar to CK/CH/2010/JT-1 were found to form a new genetic cluster (Zhou *et al.*, 2017).

Inter-species transmission

SARS-CoV in 2002, MERS-CoV in 2013, and SARS-CoV-2 in 2019 presented close genetic relationship with bat coronaviruses and are transmitted by intermediate host masked civet, dromedary, and pangolin, respectively (Song *et al.*, 2005; Zhang *et al.*, 2016; Lam *et al.*, 2020). These inter-species transmission events were most recent in human. Animal coronavirus, especially swine coronaviruses, such as PDCoV and SADS-CoV (also known as SeACoV), also show genetic evidence of inter-species transmissions from birds and bats, respectively; SeACoV (swine) is closely related to bat HKU2-CoV (bat) (Yang *et al.*, 2020). Although the natural hosts of the delta-coronaviruses are wild birds, such as sparrows and bulbuls, they may also infect few mammals, including pigs, Chinese ferret badgers, and Asian leopard cats, through intra-species transmissions (Wille and Holmes, 2020). Another delta-coronavirus, PDCoV, presented inter-species transmission from pigs to chicken in an experimental setup. Comingled chickens presented viral shedding and sero-conversion against PDCoV (Boley *et al.*, 2020). Despite the different genus from SARS-CoV-2, SeACoV, and PDCoV might be models of inter-species transmission for alphacoronaviruses and delta-coronaviruses, respectively. Considering that PDCoV showed successful inter-species transmission in an experiment, studies on animal coronaviruses can provide practical information on their infection dynamics. Further, the recombinant coronaviruses, such as FCoV type II (FCoV + CCoV), CCoV type I (CCoV+FCoV), CCoV type IIb (CCoV type II+TGEV), and SeCoV (TGEV+PEDV), may be considered inter-species recombination models in human betacoronaviruses, which has not has been reported so far.

Alterations in tissue tropism

Altered tissue tropism due to mutation of the S gene in FIPV, pantropic CCoV, PRCV, PEDV large deletion, and genetic diversity in IBV were described in this article. Most of the changes in tissue tropism result from mutations in the S

protein that is crucial for interaction with cellular receptors. Interestingly, SARS-CoV, MERS-CoV, and SARS-CoV-2 presented multiorgan tropism regardless of genetic mutations (Gu *et al.*, 2005; Cha *et al.*, 2016; Puelles *et al.*, 2020). Similar to SARS-CoV and MERS-CoV, SARS-CoV-2 caused renal failure in patients (Krishnamoorthy *et al.*, 2020). These findings may correspond to the role of IBV in renal infections. Thus, IBV and SARS-CoV-2 initiate infection in the respiratory tract and then spread to the kidneys via primary viremia (Najimudeen *et al.*, 2020; Puelles *et al.*, 2020).

Animal coronaviruses and one health perspectives

SARS-CoV-2 is a beta-coronavirus. Similar to SARS-CoV-2, animal beta-coronaviruses, such as BCoV and canine respiratory coronavirus (CRCoV), commonly present respiratory signs and diarrhea (Table 1). Thus, animals exhibiting similar viral pathogenesis of beta-coronavirus can be candidate infection model for SARS-CoV-2.

Ferrets, with physiologic homology, are used as models for respiratory infections, including influenza viruses and coronaviruses. The clinical symptoms and infection dynamics can be simulated in ferret (Belser *et al.*, 2011). The inter-species scenarios of the PDCoV and SADS-CoV may be used for simulation of the SARS-CoV-2 spill over theory. Further, considering the antigenic variation, vaccine development, and infection dynamics, poultry herd may be a useful etiologic and economic model for SARS-CoV-2. IBV has continuously evolved since its identification (Najimudeen *et al.*, 2020), and the accumulation of the genetic diversity and variations in tissue tropism challenged the development of effective vaccines (Decaro *et al.*, 2020). Additionally, the patterns of poultry industry can mimic the human community in in terms of community density.

Since the first description of coronavirus IBV in 1931 (Cook *et al.*, 2012), coronaviruses have been significant pathogens in animals and livestock industry. Despite identification of human coronaviruses in the 1960s, they remained a relatively underestimated pathogen group in the clinic the SARS outbreak in 2002. Today, the coronavirus is not an unfamiliar virus as it was in the 21st century; it had been known for at least 90 years, nearly a century. Extensive research has been carried out to control coronavirus infections in livestock, such as chickens, cattle and pigs, and companion animals. The trials and errors in veterinary fields might be a touchstone for control of the fatal coronavirus infection in present times. Similarly, the state-of-the-art technology developed for controlling COVID-19 and the potential novel vaccine platforms or antivirals can be used for breakthroughs in controlling animal coronavirus infections.

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Conflict of Interest

We have no conflicts of interest to report.

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