Iranian Journal of Virology 2022;16 (2):90-106.

Review Article

COVID-19 and Novel Coronaviruses: From Old Problems in Veterinary Medicine To New Challenges For Human Beings

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Abstract

The emergence of the novel human coronavirus (SARS-CoV-2) has been one of the most overwhelming human challenges of recent decades. Despite global efforts to stop or slow down the spread of the disease, it has infected millions of people across the world within a short period of time. Research on human coronaviruses has not been received adequate attention and there is currently no specific treatment or vaccine available for coronaviruses in humans. Interestingly, evolution, pathogenesis, and immunogenicity of coronaviruses in livestock and poultry have been described for many years and they are controlled by mass vaccination programs. Moreover, elevating immune responses to coronaviruses, a major hurdle in virulent human-coronaviruses, has been studied by several investigators in cat populations. Indeed, cross-species transmission and tropism of animal coronaviruses have been investigated by several research groups. It is estimated that three out of every four new emerging infectious diseases are zoonotic. Preliminary reports indicate that like other human coronaviruses, SARS-CoV-2 has been transmitted from bats to humans by an intermediate animal host. Hence, interdisciplinary collaborations among veterinary and medical researchers and clinicians, biologists, and environmental scientists are essential for identifying the possible animal reservoir of the viruses in general and discovering the evolutionary pathway of SARS-CoV-2 in particular. This can also result in the designing of effective prevention and control measures against SARS-CoV-2. In this review, advances in the understanding of different features of animal coronaviruses that can facilitate effective measures in dealing with the SARS-CoV-2 pandemic have been discussed.

Keywords: Animal, Coronavirus, COVID-19, Human, Pandemic

Introduction

The history of human evolution has been affected by three main processes: 1. human conflicts; 2. environmental challenges; 3. infectious diseases (1).

Infectious agents have been always a major threat to human existence. The host-pathogen interactions have directed the human developmental trajectories. The host immune system has been evolved to minimize the pathogenicity of foreign invaders. These selective pressures on the microorganism lead to a full-scale "arms race" (2) between the host and pathogen resulting in the emergence of new diseases. The quality of host immune responses and the genetic capacity of the organism to overcome the immune system determine the winner of this competition. Generally, it is unlikely that new evolving pathogens cause the host extinction without the synergistic effects of predisposing factors (3).

It is clearer about viruses because their life cycle depends on the host. Hence, it is reasonable that they find a way to maintain a balance between their virulence and host existence. However, the long-term effects of infectious diseases, especially viruses, on human polymorphism are not negligible. Genetic variations increase the resistance of

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the host to diseases and subsequently decrease the transmission of viruses. The delta32 mutation in the CC chemokine receptor-5 gene (CCR-5) in European populations (4) and MHC heterozygosity in descendants of Dutch colonists (5) are examples of the effects of pathogens on human evolution. It seems the epidemics of plague, typhoid, and yellow fever in the 14th and 19th centuries in Europe and Surinam have generated more resistance populations to multiple parasites .

Some scientists believe that the emergence of infectious disease epidemics dates back to 11000 years ago simultaneously with the beginning of the agricultural revolution and animal domestication (6, 7). This turning point in history accompanied by the significant growth in population size and elevated the contact rate between humans and livestock. This situation was the keystone of infectious agents spillover across species .

According to Wolf et al (2007) (8), five phases are defined for the transition and confining of a specified animal pathogen to humans: Phase 1. The pathogen is exclusive to a certain animal species that are closely related together. Phase 2. The pathogen has a primary transmission (from animals to humans) but it cannot transmit among humans (secondary infections) under natural conditions. Examples: Anthrax, Nipah, and Rabies. Phase 3. The pathogenicity of the infectious agent is restricted to a few secondary cycles between humans. Examples: Ebola. Phase 4. Direct human-to-human transmission occurs for unlimited times. Examples: Influenza A and COVID-19. Phase 5. The pathogen is confined to humans. Examples: measles, mumps, and smallpox.

Zoonotic diseases, which depend on animals as their primary hosts, have afflicted large numbers of humans throughout history. Various pathogens bring humans into contact with different health disasters from Plague of Justinian (PJ) in 541 CE to the current coronavirus pandemic known as COVID-19. The bacterium Yersinia pestis is responsible for many outbreaks and three deadly pandemics of plague in human history. The first, Plague of Justinian, the earliest documented pandemic of infectious diseases in the world, spread across Europe, Asia, and North Africa killing about 30 to 50 million people (9). Black Death, the second and one of the most devastating recorded plague pandemic, occurred 800 years later (10). It originated from China and dramatically claimed 200 million lives in Eurasia. Furthermore, About 40 recrudescence of plague subjected London in 300 years, and in each epidemic, 20% of the native population were killed by the disease. Smallpox, with a 30% mortality rate, was the first virus infection eradicated by vaccination in the late 20th century. Since the first documented influenza pandemic in 1580, it has happened every 10 to 50 years (11). Cholera which killed tens of thousands in the last centuries is still a public health concern in developing countries.

In addition, humans met many other different pandemics as Spanish flu, yellow fever, H1N1, HIV, Ebola, SARS, and MERS which have strongly affected the world.

Coronaviruses- An Overview

Coronavirus (COVs) is the common name of the enveloped, single-stranded, non-segmented, positive-sense RNA viruses belonging to the large family of Coronaviridae and order Nidovirales infecting a wide range of birds and mammals around the world (12). The Latin name corona refers to the crown-like or solar corona appearance of the virus surface projections captured by electron microscopy. With a length of 27-32 Kb, coronaviruses have the largest genome size among RNA viruses. The single-stranded RNA nature of the genome increases the risk of mutation and genetic recombination in these viruses and enhances the virus's ability to adapt to new circumstances within new hosts .

The coronaviruses are further divided into four genera α, β, γ, and δ (13). The first identified human COVs, OC43, and 299E were discovered in the 1960s. Almost 15% of cases of the common colds are developed by α and β human COVs. Despite the mild respiratory diseases caused by 229E, OC43, NL63, and HKU1, the three outbreaks related to SARS-CoV, MERS-CoV and SARS-CoV-2 develop more serious diseases. SARS was first reported

from China in 2002 and spread to 26 countries of Asia, Europe, Africa, and North America (14).

Ten years later, in 2012, the MERS outbreak originated from Saudi Arabia, disseminated through 27 countries around the world (15). The COVID-19 as a highly pathogenic viral infection caused by severe acute respiratory syndrome corona virus-2 (SARS-COV-2) was first reported from Wuhan, Hubei province, China in late December 2019 (16). The wave of this highly contagious disease swept across the world so that it is now accounted for as a new pandemic by WHO (17). Although the fatality rates of SARS and MERS are more (two percent against 10 % in SARS and 34% in MERS), infectious rate and human-to-human transmission of the COVID-19 virus is higher. Scientists suggest that, like many other COVs, bats are the most possible origins of SARS-CoV-2 (18). However, it is believed that the infection of humans with these viruses is associated with close contact with the mammalian intermediate hosts (19). Civet cats, camels, and maybe pangolin bred for human consumptions are supposed to act as intermediate recipients of SARS, MERS, and COVID-19, respectively .

The genome of SARS-CoV-2 encodes four structural and 16 nonstructural proteins (nsps) that are synthesized during discontinuous transcription and frameshift process. ORF 1a and 1b at 5′end of the genome are responsible for synthesizing functional proteins of SARS-COV-2.

The programmed -1 ribosomal frameshifting (-1 PRF) is stimulated by slippery site and three-stemmed RNA pseudoknot secondary structures at downstream of 1a RNA sequence (20). Subsequent translation of polyprotein 1a/1ab from the genomic RNA forms the replication-transcription complex (RTC) (21). A third of the virus genome, near the 3′ terminus, allocated for the four M, S, N, and E structural proteins (22). The RTC synthesizes the structural proteins from a nested set of subgenomic RNAs (sgRNAs) by discontinues transcription. These proteins are essential for the infection and virion assembly (23).

The cell surface angiotensin-converting enzyme (ACE2) receptor and the virus S protein mediates SARS-CoV and SARS-CoV-2 entry into cells (24). A cleavage process by cellular Serine protease TMPRSS2 at S2′site of the virus genome is required for cell membrane-virus fusion. However, while the Blockade of ACE2 receptors and TMPRSS2 significantly suppress SARS-CoV entry into cells, it fails to completely inhibit the SARS-COV-2 infection (25). In this regard, it is assumed that the acquisition of a furin cleavage site at the S1–S2 junction improves cell-cell fusion (26). Consequently, as many some other virulent viruses (26-30), forming a polybasic furin cleavage site (RRAR) following the insertion of 12-nucleotides between S1 and S2 subunits may relate to high transmissibility and pathogenesis of the virus.

Coronavirus Classification

Approximately 3 out of every 4 emerging infectious diseases (75%) are zoonosis that means originated from animals (31). Although the emergence of highly pathogen human COVs has recently attracted the attention of scientists, the veterinary communities have faced with many animal COV challenges, so far. Since the study of the coronaviruses in their natural animal hosts is easier than humans, it is a good idea to take a look back at these documented data for more information about the coronavirus pathogenesis, shedding, cross-reactivity, and prevention strategies.

There are four genetic and antigenic groups of coronaviruses including I, II, III, and IV causing respiratory and enteric diseases in poultry, livestock, and human populations (32). Three swine COVs (TGEV, PRCV, and PEDV), besides canine and feline COVs, have been assigned to group I. Group II constitutes various COVs including bovine, rat and mouse COVs. These viruses are distinguished from other CoVs by a specific surface haemagg-lutinin (HE) protein. Bird species COVs are distinctively classified as group III. Infectious bronchitis virus (IBV) affecting poultry was the first coronavirus discovered in the 1930s (33). This virus with a more than 40%

mortality rate in chickens is one of the most devastating diseases leading to major economic losses worldwide. Based on the phylogenetic analyses, SARS-CoV and other SARS-related CoVs are genetically far from other coronaviruses and may be a result of recombination between avian COVs of group III and mammalian COVs of group II (34). Consequently, they can be placed in a new group (group IV) of coronaviruses.

The Challenges to Developing a COVID-19 Vaccine

Targets for Vaccine Development

Despite antigenic divergence, cross-reactivity has been observed between these groups. For example, Nucleocapsid (N) protein is responsible for cross-reactivity between SARS-CoV and group I coronaviruses such as human COV 229E, feline infectious peritonitis virus (FIPV), canine coronavirus (CCoV), porcine respiratory coronavirus (PRCV) and porcine transmissible gastroenteritis virus (TGEV) (35-37). Exploring similar cross-reactions between animal coronaviruses and SARS-CoV-2 could help to find a conserved target for immunization or treatment individuals exposed to SARS-CoV-2.

Conversely, using the same epitopes in different coronaviruses is not a good idea for developing diagnostic tests. It may increase the number of false-positive rates. Moreover, these epitopes can interfere with the process of finding reservoir hosts .

Due to its major role in pathogenesis and immunogenicity of the virus, spike (S) protein epitopes have focused the interests of researchers rather than other proteins of coronaviruses (33). In this regard, different aspects of IBV vaccination including route and type of immunization, have been investigated, so far (38). These studies could promote our insight for future experiments on SARS-CoV-2. The IBV S protein is commonly used for vaccine development in poultries (38). indeed, Seo et al. suggested that N protein efficiently induces protective immunity against IBV (39).

However, the main argument against this statement is that this protein could only prime cellular immunity and it is not solely sufficient to induce strong protective immunity (40, 41).

The efficient vaccine should trigger more conserve and stable epitopes and cover different mutants of the virus The S and N epitopes are highly immunogenic and induce the most humoral and cellular immune responses (42-44). Furthermore, stable and long-lasting cell-mediated responses of these proteins (up to 11 years post-infection) are of absorbing interest to researchers for vaccine propagation (45-47). Several research has tended to focus on epitopes at the receptor-binding domain (RBD) domain of S1 subunit and epitopes of S2 subunit for designing vaccines against COVID-19 (33). Despite SARS-CoV (48), the RBD domain epitopes in other coronaviruses are highly variable and species-dependent. Hence, protective immunity elicited against the SARS-CoV RBD region may not provide cross-protection against COVID-19. In contrast, epitopes found at the S2 subunit of SARS-CoV are more map identical to SARS-CoV-2 (49). Therefore, it is more reliable for inducing immune responses against SARS-CoV-2 compared to the S1 subunit.

It seems that more identical S1epitopes that have fewer mutations and sequences that do not overlap with ACE2 receptor binding motif (50) may be promising options for designing COVID-19 vaccine.

New Mutants and Vaccination

Animal COVs are recognized as viruses with high mutation and genetic recombination rates. These changes often result in the emergence of new strains of coronaviruses with different virulence and new host range or tissue tropism. The propensity for genetic modifications is due to the replication strategy, long size of the genome, and lack of proofreading mechanism of the virus during replication (32).

For example, PRCV and TGEV are both closely corresponding with canine and feline coronaviruses. It is supposed that TGEV has derived from Canine coronavirus type II (CCoV-II). Moreover, less virulent PRCV is evolved from the virulent TGEV as a result of the deletion ≈ of 600 nucleotides at the 5' end of the S gene (51). This mutation not only

changed the virulence but also alter the tissue tropism of the virus from a gastrointestinal tract (GI) to the respiratory system .

Feline coronaviruses are another example of mutation-dependent changes. In this case, FIPV as a highly virulent pathogen is responsible for systemic infection. in response to persistent infection, this virus is evolved from feline enteric coronavirus (FECV) following the virus spontaneous mutations (52). Of note, this may happen about SARS-CoV-2 if it could stay in the human body for a long time.

Vaccination and Immune Enhancement

Vaccine development against coronaviruses encompasses formidable challenges including short-lived protection and immune enhancement interfering with the immunization process (53).

To date, several vaccine candidates to tackle SARS-CoV and MERS-CoV are provided. However, considering the undesirable immune reactions against them, no vaccine has been licensed as yet (89). Furthermore, cat immunization against FIPV with available live-attenuated or killed vaccines, not only fail to induce strong protection against the disease but also worsen the peritonitis following the secondary infection with the pathogen (54). In contrast, vaccination is widely used for curbing different livestock and poultry COVs worldwide (38). Therefore, vaccination not only should eliminate infectious virions but also need to contain excess inflammation.

Vaccine-mediated immune enhancement has been indicated for many viruses. In this situation, vaccinated humans or animals develop more severe illness after reinfection with the virus. Pathogen priming will introduce by vaccination which then leads to deleterious immune reactions (55).

Antibody-dependent enhancement (ADE) and cell-based enhancement are two identified pathways of immune enhancement (56). In ADE, Ag-Ab immune complexes facilitate the viral entry into Fc receptor-expressing myeloid cells like macrophages (55). Besides, anti-viral activities of the host immune system are blocked by the viruses (57). Conversely, cell-based enhancement is a Th2-type immune response evoked by antibody-dependent cellular cytotoxicity (ADCC) or complement-mediated pathway. Reduction in Th1/Th2 cell ratio and skewing toward Th2 responses consequently leads to the aberrant allergic reactions and subsequent organ dysfunction (58). As mentioned, the available FIPV vaccines designed to protect cats from infection, conversely provide a life-threatening disease (59). This complication occurs even after contact of cats with antigenically similar coronaviruses like TGEV (60), CCoV (61), and FECV (62). Therefore, there is still no stringent vaccination approach for protecting cats against FIPV.

SARS and MERS-mediated ADE were reported in several animal model studies (58, 63-70). In an experiment conducted by Li et al. (65), recruitment of monocytes and MQ cells and accumulation of pro-inflammatory cytokines, such as CCL2, CCL3, IL-8 and IL-6 in response to anti–spike IgG (S-IgG) production were observed in macaques after immunization with vaccinia Ankara (MVA) vectors encoding SARS-CoV S protein. These over-stimulated reactions along with suppression of anti-inflammatory cytokines including TGFβ and IL10 caused further acute lung injury (ALI) .

In a set of studies, N protein, as an immunogenic structure, was used for designing recombinant vaccines against SARS-CoV (71, 72). Similar to the previous investigation, mouse vaccination resulted in myeloid cell recruitment, releasing a large amount of pro-inflammatory cytokines and eosinophilic infiltration in the lung tissue after the SARS-CoV challenge .

Nevertheless, despite disappointing results from SARS vaccination, serum therapy by antibodies obtained from convalescent patients appeared to improve symptoms and survival rates of patients affected by SARS disease (71). Quite the opposite, infection of naïve New Zealand white rabbits with MERS-CoV after passive immunization via previously infected rabbit serum enhanced severe lung inflammation (64).

These perplexing discrepancy outcomes could be explained by the type or quality differences of antibodies induced by infection or vaccination. Likewise, in another study, recovered

patients displayed lower neutralization antibodies rather than anti-N antibodies compared to deceased patients (63). However, blockade of FcγRs, Anti-S antibody modulation (71), or using Toll-like receptor (TLR) agonists as a vaccine adjuvant (58) may alleviate lung injury. The unintended immune enhancement reactions were also reported in other organs. Weingart and colleagues (67) found that immunization of ferrets with a vaccinia virus Ankara (rMVA) expressing the SARS-CoV S protein enhanced hepatitis following SARS-CoV infection.

The immune enhancement following infection or vaccination in other viruses raises concerns about the risk of immune backfiring against SARS-CoV-2. Previous exposure of COVID-19 patients with other coronaviruses likely contributes to more hospitalization periods and higher case fatality rates rate. Therefore, people in geographical areas that are more affected by other coronaviruses, may be at a greater risk of a deadly infection. Previous exposure to other coronaviruses could be asymptomatic or confused with the common cold. If this hypothesis is true, reports about the recurrence of the disease in recovered COVID-19 patients (73) will be extremely concerning. In this regard, the secondary infection will lead to immune-related adverse events in convalescent people. Hence, seroconversion investigation of the human population in different geographical regions will increase the chance of designing an effective and safe vaccine against SARS-CoV-2.

Animal Reservoirs of SARS-CoV-2

Bats are considered as the natural host of SARS-CoV-2. However, the role of intermediate hosts is still debatable. Pangolin has been touted as the most likely intermediate host COVID-19 virus. RBD of pangolin COVs in S protein has the highest level of similarity (97.5%) to that in SARS-CoV-2. Moreover, six major amino acids at positions 455, 486, 493, 494, 501, and 505 in this domain are conserved in both viruses. However, the presence of different wobble bases coding the same amino acids in these two viruses and lack of furin cleavage site in pangolin COVs raises important questions about the definitive host of SARS-CoV-2.

On the other hand, while pangolin COVs do not include the furin cleavage site presented in SARS-CoV-2, the other coronaviruses with less similarity to SARS-CoV-2 like MERS-CoV, OC43 and HKU1 have this new sequence (74). Whether the novel coronavirus is the result of recombination or convergent evolution is still uncovered. For finding a reliable answer to this question different wild and domestic animals should be tested for infection or immune response against the virus .

Interspecies transmission of viruses is not a novel issue in veterinary medicine (44, 75, 76) and it was predictable for human COVs. Unfortunately, many coronaviruses of wild animals have not been sequenced as yet.

Veterinarians are responsible for examining the reservoir of animals for COVID-19 infection. Ignoring this question unsolved can lead to the next waves of COVID-19 pandemic.

According to a recent study, it is unlikely that dogs, pigs, chickens, and ducks to be reservoirs of SARS-CoV-2. In this study, the infectious viral particles and antibodies against the nCoV were detected in cats.

Furthermore, these infected cats could transmit the virus to uninfected animals. These results are compatible with the animal reservoir definition. Within the context of infectious disease, a population could be considered as the reservoir when the virus replication and transmission of the infectious agent to other populations do not cause severe disease in the reservoir host. Along similar lines, while no serological cross-reactivity was observed between SARS-CoV-2 and FIPV, Zhang et al. (77) showed that neutralizing antibodies against SARS-CoV-2 are produced at infected cats. Since civet cats are recognized as the intermediate host of SARS infection, it is necessary to understand more about the pathogenesis of the novel coronavirus in these animals. Furthermore, regarding the susceptibility of ferrets to SARS-CoV-2, it could be used as a suitable model for the studies on respiratory diseases.

SARS-CoV-2 Pathogenesis

The initial site of the SARS-CoV-2 replication is supposed to be the respiratory system. SARS-CoV-2 enters into human airway epithelia and lung parenchyma cells expressing ACE2 receptors (24). The virus S glycoprotein is a trimeric class I fusion structure which is consists of S1 and S2 subunits.

These sequences are responsible for binding and fusion of the SARS-CoV-2 to the host cell plasma membrane, respectively. However, it is still controversial whether the virus, after initial infection, transmitted to secondary organs by blood circulation during viremia (25) or spreading via peripheral nerves (78).

furthermore, with different levels of expression, ACE2 receptors are distributed to multiple extrapulmonary tissues like vascular endothelia, kidney cells, neurons, and small intestine cells (78). Dissemination through peripheral nerve cell terminals and subsequent controlling the cardiovascular, respiratory and gastrointestinal centers at the central nervous system (CNS) was observed in other beta-coronaviruses such as SARS (79), MERS (80), 229E (81), OC43 (82), mouse hepatitis virus (MHV) (83), porcine hemagglutinating encephalomyelitis coronavirus (HEV) (84) and IBV (85). On the other hand, it is believed that SARS-CoV-2 with the size of 80-100 nm can infect the endothelial cells (25). According to this statement, following the blood vessel infection, the virus migrates to other ACE-2 receptors expressing organs including the kidney and gastrointestinal cells. In this way, the excretion of the virus from urine and feces is a consequence of viremia.

While the mechanism of immune evasion of SARS-CoV and MERS-CoV is suggested by several studies (21, 30, 86-89), it is still unclear that how SARS-CoV-2 can deceive the immune system. However, it is supposed that insertion an additional furin cleavage site between S1 and S2 subunits and some mutations at S1 RBD enhance the pathogenesis of causative agent of COVID-19 (26, 90). Kidney failure, respiratory and gastrointestinal dysfunctions are common pathological symptoms among different coronaviruses.

Consequently, studying the pathogenesis and the replication cycle of other previously identified coronaviruses can be somewhat related to the novel coronavirus.

Swine Coronaviruses

Like SARS-CoV-2, the PRCV strains excreted through both the gastrointestinal and respiratory tracts (91). However, fecal PRCV strains have been found to have lower point mutations in the S gene than nasal strains. Moreover, low fecal shedding may be related to the limited stability of these strains in the GI tract. Therefore, it is considered important that the genetic and pathogenic properties of SARS-CoV-2 strains will be detected not only in different individuals but also in specimens taken from different organs in the same person.

Stimulation of mucosal immunity in tissue does not necessarily induce protective immunity in another tissue. This issue was observed for swine COVs in which PRCV priming does not cause enough protection against diarrhea and virus shedding of TGEV infection (92). On the other hand, there is some evidence about the appearance of GI disorders and fecal shedding of SARS-COV-2 in COVID-19 patients (93). It should be noted that although the intranasal administration of coronavirus vaccines may induce higher titers of mucosal antibodies (94), it can not provide a robust immunity in the GI tract and prevent the virus shedding from the faces (32).

Bovine Coronaviruses

Bovine coronaviruses (BCoVs) are related to the three diseases in cattle. Neonatal calf diarrhea (NCD) and respiratory complex on calves and winter dysentery (BWD) in adult cattle. While subtle changes occur among isolates, BoCVs comprise of one serotype. However, nucleotide differences in the S gene sequence between enteric and respiratory isolates of BoCV are detectable even in the same animal. BoCVs and SARS-CoV-2 both are excreted in faces and nasal discharges. Prolonged respiratory shedding of BoCVs in both healthy and sick animals and lack of long-term mucosal immunity (95, 96) are consistent with re-infection and high transmission of the virus to other animals. Generally, it is hard to isolate BCV in tissue or cell cultures (97).

However, some types of colon and rectum cancer cells support virus replication (97). On the other hand, the duration of the virus shedding and the effectiveness of the digestive tract for clearance of SARS-CoV-2 throughout COVID-19 infection are not completely understood. While the viral load in faces is lower than of respiratory tract samples, the viral shedding is observed 2-3 days before the onset of clinical symptoms and it persists up to three weeks after the manifestation of the symptoms (98-100). However, it seems the viral shedding pattern of the SARS-CoV-2 is more similar to the influenza virus than of SARS-CoV and MERS-CoV infections.

Accordingly, evaluating viral shedding properties and duration of the virus transmission in asymptomatic and presymptomatic individuals is essential for developing effective clinical countermeasures against SARS-CoV-2.

Poultry Coronaviruses

IBV establishes persistent infection in cecal tonsils and kidneys of poultries. The viruses maintain in these organs and cause serious disease. IBV excreted intermittently 28 days after the onset of infection from respiratory tracts and several weeks after clinical recovery from faces (101). Pro-inflammatory cytokines and viral RNA persist up to 20 days after infection (102, 103). IBV vaccine strains may persist in vaccinated chickens for more than six months. Moreover, shedding theses strains could periodically transmit the IB infection to susceptible chickens and cause a complicated epizootiological situation in the field (104-106).

In a similar fashion to poultry coronavirus (103, 107), SARS-CoV-2 is found in urine, stool, and respiratory secretions for three weeks. Therefore, it has a wide range of tissue distribution for the respiratory, digestive, and urinary systems. The shedding of the virus from SARS-CoV-2 infected or even apparently healthy person will transmit the causative agent to other individuals. Given tissue propensity of vaccines (108, 109), finding and targeting a presumptive reservoir organ may direct future research into designing more effective prophylaxis and treatment programs.

Feline coronaviruses

Two forms of feline COVs affect cats: low virulent FECV that usually causes mild chronic disease and high pathogen FIPV that develops a fatal and incurable disease. Persistence FECV infection in cats may lead to mutations of the virus and generation FIPV (52). These changes alter the tropism of the virus from the intestine to macrophages. Prolonged virus shedding is also described in the affected cats. It is documented that about 10% of cats affected by FCoV excrete the virus for more than one year (110). Like other coronaviruses, FIPV pathogenesis is also along with the host inappropriate humoral responses to the virus (111). A major challenge with the disease, despite many other infections, is that antibody-positive cats develop more severe illnesses than antibody-negative ones.

The preexisting antibody, as a result of vaccination or primary challenges with the disease, enhances uptake of the virus into macrophages. Subsequently, following Ag-Ab-complement immune complex formation and complement fixation, it will deposit in sites of high blood pressure like peritoneum, uvea, and kidney and granulomatous inflammation will damage the multiple tissues. As noted earlier, the available vaccines against FIPV develop immune enhancement reaction.

This complication may be predictable about vaccines that are being currently designed against SARS-CoV-2. This problem will be more complexes if we know that primary infection with some other coronaviruses such as (TGEV) of pigs, the respiratory coronavirus of man (strain 229E), and the enteric coronavirus of dogs have the same consequence in developing a lethal disease (75, 109, 112).

Predisposing Factors

The genetic characteristics of the virus, as discussed earlier, is just one of the three main conditions determining the severity of the disease. Host genetic variation and environmental factors including patient age, co-infection, and immunosuppressive drugs are associated with the systemic complications that may ensue from COVID-19 infection.

Host Genetic

Host genetic diversity influences the quantity and quality of immune responses. Approximately 2-3% changes in the IBV S1 subunit, which induces virus-neutralizing antibodies, could generate a new serotype (113). Many studies have been conducted to evaluate the cross-immunity between the IBV vaccines and field virus strains (114-116). Notwithstanding, the various interpretations, it is clear that chickens, even with the same parental stocks, did not show the same immune responses to the vaccination. Therefore, the effectiveness of vaccination against IBV is not only influenced by the degree of antigenic similarity between the vaccine and prevalent field strains but also is affected by individual differences.

Moreover, variation in responses to SARS-CoV-2 may relate to genetic heterogeneity in human populations. For example, FcγRs are associated with the quality of immune responses against the pathogen. Individuals with FcγRIIa-R/R131 allelic polymorphism develop more critical disease upon infection compared to those with a FcγRIIa-H/H131 isoform (117). Indeed, the influence of rs12252-C / C SNP in IFN-induced transmembrane protein-3 (IFITM-3) gene on pathogenicity of the SARS-CoV-2 was studied in the Chinese community (118). As other studies on the H7N9 influenza virus (119, 120), patients with this genetic map are more susceptible to both influenza and COVID-19 diseases. However, the impression of the host genetic on the severity and progression of diseases is still unexplored and worth future investigation.

Environmental Factors

In addition to the virus and host genetic interplay, environmental factors contribute to the disease severity and fatality rates. as further explained, similarly to some animal respiratory disease complexes like shipping fever (32), harder illness and higher mortality rate in COVID-19 patients can be related to underlying medical conditions, respiratory co-infection, or immunosuppressive treatments (121).

Co-Infection

Co-infection of COVID-19 patients with other viruses enhances host susceptibility to severe respiratory diseases. Despite the early reports (122), a new investigation suggests that the co-infection rate with SARS-CoV-2 and other respiratory pathogens in patients is significantly higher (123).

While less virulent coronaviruses like OC43 and 229E cause mild respiratory disorders, they can exacerbate the symptoms and prolong the shedding of SARS-CoV-2. Moreover, due to similar clinical symptoms and overlap of the occurrence of COVID-19 and seasonal flu diseases in late autumn and early winter, SARS-CoV-2 and less virulent coronaviruses may have enhanced the inflammation-mediated respiratory damages. Base on a report from Iran (124) the coincidence rate of COVID-19 patients with seasonal flu was more than previous studies.

This mechanism was explained in two other studies on dual infections of pigs with PRCV, as a coronavirus, and Simian Immunodeficiency Virus (SIV) (125) or porcine respiratory reproductive syndrome virus (PRRSV) (126). In this condition, inducing IFN secretion by PRCV suppressed SIV and PRRSV proliferations. Conversely, widespread secretion of pro-inflammatory cytokines causes more tissue destruction in the respiratory tract. Immune-mediated damages and high expression of pro-inflammatory cytokines are observed in chickens affected by poultry coronavirus (102). Co-infection with the influenza virus and IBV increases the severity of disease and mortality rate of chickens (127, 128). Furthermore, even immunization with chicken coronavirus (IBV) vaccines could increase the propagation and shedding of avian influenza virus (AIV) (129-134) which could raise concerns for human COV vaccine development.

In contrast, In a study conducted by Ranjbar et al. (135) replication and shedding of the H9N2 influenza virus was decreased in immunosuppressed chickens infected by IBD. However, it did not attenuate the severity of the disease.

Antibiotic Treatment

The secondary bacterial infection is a leading cause of death in COVID-19 patients (136). Secondary infection is especially common in animals and poultry with an intensive farming system (106). It may increase the intensity of

symptoms of mild respiratory viruses and lead to fatal fibrinous pneumonia (32). This synergistic interaction between respiratory viruses and bacterial LPS is examined in different studies (137-139).

In one trial of an investigation (140), the co-infection of pigs with PRCV and LPS induced the high level of TNF-α and IL-1. These cytokines contribute to leukocyte recruitment during the inflammatory reactions. In this case, antibiotic therapy is the primary strategy for controlling secondary bacterial infections during viral diseases (121). Nevertheless, antibiotic prescribing among patients with severe infectious diseases is still challenging. Pro-inflammatory cytokine secretion mediated by gram-negative bacterial LPS results in more respiratory damages (32, 140). So, route, the dose of administration, and even the type of antibiotics should be determined more carefully for the treatment of patients with COVID-19. Moreover, as well as cytokines, evaluation of the LPS level can also be used as an indicator of the disease severity.

Corticosteroids

Corticosteroids are widely used to attenuate inflammation-associated damages caused by SARS-CoV-2 (141). The recommendation of steroids is a double-edged sword. Decreasing inflammation suppress immune responses, delay clearance of viral RNA, and lead to more viral proliferation and shedding (142, 143). This problem was also investigated in animal coronaviruses. treatment of WD BCoV-infected cows with dexamethasone results in intermittent fecal shedding of BCoV (144).

Moreover, treatment with dexamethasone before the TGEV challenge has the same effect on older pigs (145). Likewise, corticosteroid therapy is a part of SARS (146) and MERS (147) treatment protocol. However, some scientists believe that this strategy delays viral clearance and lead to super-spread of the viruses and more secondary infections (142, 143). In addition, despite the Chinese Thoracic Society recommendation (148) and Shang et al study (149) and based on the interim guidance of the World Health Organization (WHO) released on Jan 28, 2020 (150), using corticosteroids must be used more cautiously in COVID-19 patients.

However, some researchers suggest that using methylprednisolone could reduce the fatality rate of the severe form of COVID-19 (151). Nevertheless, acute lung injury somewhat caused by uncontrolled host immunologic response must be controlled. Therefore, more comprehensive research about the effectiveness of steroid therapy in patients with COVID-19 should be performed.

Age

Despite most animal COVs (32), less than two percent of patients affected by SARS-CoV-2 are children (152). Based upon a recent study, the higher nasal expression of ACE2 receptors, in part, is the cause of the more morbidity of older patients compared to young patients (153). The age-dependent disease severity may contribute to poor immune responses in elderly people.

Accordingly, vaccination in older people may not evoke sufficient immune responses. Therefore, induction of IFN-β, IFN-γ, IL-1β, and tumor necrosis factor (TNF) expression in lung tissue before vaccination can improve the efficacy of vaccination in the aged patients (154). However, based on some reports the median age of newly diagnosed COVID patients has dropped in the past few weeks (155, 156). It is unlikely that doing more testing be the main cause of the surge of the infection in young people. In this situation, we expect that the total number of positive cases increases for all age groups.

Another hypothesis, which is needed to be evaluated, is that young people are not complying with health guidelines. This situation may be worsened in hot weather of summer that social distancing rules are not observed well. Indeed, consumption of ice cream and other cold milk by-products is increased in summer, especially among young people. Although oral-fecal transmission of SARS-CoV-2 is not demonstrated yet, a considerable number of studies have detected the viral RNA and viable virus in the patient stool (157-163). Based on these findings the alkaline microenvironment of the stomach following the consumption of dairy products may increase the stability of the

virus. In this regard, overfeeding milk may predispose the newborn calves to neonatal calf diarrhea caused by BoCVs (164). Bicarbonate may have the same effect on the susceptibility of poultries to IBV. The poultry diet is often supplemented with bicarbonate compounds to diminish the deleterious effects of heat stress in chickens (165).

Although ameliorative roles of bicarbonate on body performance are explained in several studies, the excess amount of this compound has negative effects on poultry function affected by viral diseases like IBV (166, 167). Furthermore, providing an alkaline microenvironment in the GI tract could predispose chicken to avian coronaviruses.

Conclusion

The emergence of new coronaviruses is entirely predictable according to the evolutionary patterns of these viruses. For almost a century, the veterinarians have dealt with numerous challenges caused by poultry and animal COVs. However, the incidence of highly pathogenic human COV outbreaks has attracted researchers' great attention during the last two decades. The history of recurrent pandemics indicates that we are not able to stop the incidence of new outbreaks.

Therefore, more effective responses to future pandemics rely on the information obtained from the previous challenges. Approximately 75% of emerging human diseases are zoonotic (31). Bats and rodents are identified as the natural host of all human COVs (168).

However, the role of intermediate hosts in the transmission of COVs from bats to humans is remarkable. To date, pangolins are the most probable suspect that can carry the coronaviruses closely related to SARS-CoV-2. Indeed, because of the high propensity of SARS-CoV-2 to ACE2 receptors in cats and ferrets, they can efficiently support the replication of the virus (169). Hence, these animals may act as a reservoir and cause the superspreading event of the virus. However, our knowledge about the potential reservoir of wildlife and domesticated livestock and/or susceptibility of these animals to be infected by afflicted individuals is little .

Analyzing animal COVs in their natural hosts provides useful data about the different features of novel human COVs. Multiple mutations and genetic recombination, interspecies transmission, tissue tropism, and host range alteration have been detailed studied in animal COVs. Moreover, the relation between host genetic, environmental factors, and severity of some animal diseases caused by coronaviruses have been described.

Vaccination is a major strategy for controlling bovine, swine, and poultry COVs. However, uncontrolled immune responses, short-lasting immunity, viral immune evasion, and long-term shedding are hurdles to vaccination against some animal COVs like FIPV and IBV. Nevertheless, experiences provided by these studies can help scientists to develop infection-control measures against the novel human COVs as quickly as possible.

A wide variety of research on doses and different immunization approaches against SARS disease have been conducted over the last two decades. Due to the high overall homology of this virus to SARS-CoV-2, the data obtained from these studies are a good source for targeting an appropriate immunogenic region for designing a safe and effective vaccine against COVID-19.

In conclusion, it seems that interdisciplinary cooperation among veterinary and medical researchers and clinicians, biologists, and environmental scientists is necessary to investigate different aspects of novel coronaviruses such as the evolutionary process, pathogenesis, immunogenesis, and risk of reverse zoonotic transmission.

These collaborations accelerate the process of finding animal reservoirs or intermediate hosts. Moreover, this relation makes it easier to select appropriate experimental animal models for further research.

These all result in the development of more effective countermeasures in the face of novel human diseases.

Acknowledgment

None.

Conflict of Interest

No conflict of interest is declared.

Funding

This study was not financially supported by any individual, agency, or institution.

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