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The veterinary perspective of COVID-19

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Abstract

Coronaviridae is a family of RNA viruses responsible for two previous epidemics of viral pneumonia and related illnesses: Severe Acute Respiratory Syndrome in 2002 and Middle East Respiratory Syndrome in 2012. The current COVID-19 pandemic is caused by a new member of the family *Coronaviridae*, named SARS-CoV-2 which emerged in December, 2019 in Wuhan, China. Infected persons present with severe respiratory illness including pneumonia. There have been reports of confirmed cases in different animal species that became infected with SARS-CoV-2, suggesting possible reverse zoonosis. In this review, we discussed the origin, biology, genome organization, replication and virus entry into host cells, immune mechanisms, epidemiological trends, prevention and control strategies employed in combating the threat posed by the COVID-19 pandemic.

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History of Coronaviruses

Viruses that were classified under the family *Coronaviridae* first emerged in the 1960s and of all the members of the order *Nidovirales*, it is the largest family (Ashour *et al*., 2020). The family consists of two subfamilies: *Orthocoronavirinae* having four genera (Alphacoronavirus, Betacoronavirus, Gammacoronavirus and deltacoronavirus) and *Torovirinae* (Woo *et al*., 2010). Alphacoronaviruses and betacoronaviruses are found in bats and other mammals, while deltacoronaviruses are isolated from both mammals and birds unlike gammacoronaviruses which are mostly avian pathogens with few affecting mammalian species (Woo *et al*., 2012). The subfamily *Torovirinae* has two genera (*Torovirus* and *Bafinivirus*) consisting of pathogens affecting both terrestrial and aquatic animals (Lu *et al*., 2020). The *Torovirus* includes equine torovirus (Berne virus), isolated from diarrheic horses and the Breda virus, isolated from diarrheic neonatal calves, while *Bafinivirus* genus on the other hand consists of White bream virus from fish as the type species (Lu *et al*., 2020).

Since their discovery, coronaviruses are known to cause diseases of high economic importance in animals such as infectious bronchitis (IB), transmissible gastroeneteritis (TGE), swine acute diarhoea syndrome (SADS) and porcine epidemic diarrhea (PED) respectively caused by infectious

bronchitis virus (IBV), transmissible gastroenteritis virus (TGEV), swine acute diarrhea syndrome-coronavirus (SADS-CoV) and porcine epidemic diarrhea virus (PEDV) (Ashour *et al*., 2020). In dogs and cats, the coronaviruses cause mild gastrointestinal infection although feline infectious peritonitis is sporadic but fatal (Markey *et al*., 2013). Occasionally, animal coronaviruses can cause infections in humans with potential to be sustained through human to human transmission (Su *et al.,* 2016; Forni *et al*., 2017). In the 1960s, the first human coronaviruses (HCoVs), those causing common cold, such as human CoV-229E (HCoV-229E) from alpha-CoVs and human CoV-OC43 (HCoV-OC43) from the beta-CoVs were described (Lim *et al*., 2016; Milek & Blicharz-Domanska, 2018). Over the years, several HCoVs emerged causing disease with varying morbidities and mortalities. In 2002, Severe Acute Respiratory Syndrome-CoV (SARS-CoV) (beta-CoVs), while in 2004, 2005 and 2012, HCoV-NL63 (alpha-CoVs), HCoV-HKU1 (beta-CoVs) and Middle East Respiratory Syndrome-CoV (MERS-CoV) (beta-CoVs) emerged respectively (van der Hoek, 2007). SARS-CoV and MERS-CoV are associated with severe respiratory illnesses with pandemic potential in contrast to the other HCoVs which are associated with mild respiratory diseases (Zaki *et al*., 2012; Wang *et al*., 2020d). During the 2002-2003 SARS-CoV outbreak, the virus first emerged in China before it quickly spread to other parts of the world, causing about 8,000 infections globally, with approximately 800 associated mortalities (WHO, 2004). MERS-CoV infection first broke out in the Middle East in 2012 before spreading to other countries (Ksiazek *et al*., 2003; Zaki *et al*., 2012). Globally, a total of 2,494 MERS confirmed cases with 858 associated mortalities were recorded (https://www.who.int/emergencies/mers-cov/en/). Both SARS-CoV and MERS-CoV are zoonotic pathogens originating from animals with civet cats and dromedary camels being their respective sources (Guan *et al*., 2003; Ge *et al*., 2013; Azhar *et al*., 2014).

Coronavirus Disease 2019 (COVID-19) Outbreak

In the late 2019, an outbreak of pneumonia of unknown etiology began in the city of Wuhan, Hubei Province, China (WHO, 2020a; Lu *et al*., 2020; She *et al*., 2020). By 3rd January, 2020 the World Health Organization (WHO) were notified of 44 cases of pneumonia with no known cause (WHO, 2020a; Lu *et al*., 2020) and by 12th January, 2020 the genetic sequence of the novel coronavirus isolated on 7th January, 2020 was shared with the world and the link between exposures of the patients with Huanan seafood and wild animal market was established (WHO, 2020a; Lu *et al*., 2020). On 11th February, 2020 a name was announced for the new coronavirus disease: (COVID-19) (WHO, 2020b; Lu *et al*., 2020) and the virus causing it was designated as SARS-CoV-2 by the International Committee on Taxonomy of Viruses (ICTV) (Gorbalenya *et al*., 2020). Before long, the outbreak spread to other countries and was declared a public health emergency of international concern by WHO on 30th January, 2020 (WHO, 2020b). This novel virus represents the seventh known coronavirus responsible for human coronavirus diseases (Wang *et al*., 2020b).

Biology of Coronavirus

Structure

In the 1960s, two viruses causing common colds in humans isolated by researchers in the United Kingdom and the United States were shown to have crown-like structures (Cyranoski, 2020). Thereafter, it was observed that the viruses isolated from sick animals had the same coarse structure that is covered with club-shaped glycoprotein peplomers (spikes) protruding outward through the envelope for about 20 nm (Markey *et al*., 2013). Electron microscopic appearance of the viruses resembled the solar corona leading to the coining of the name coronaviruses in 1968 (Cyranoski, 2020). Coronaviruses are large, enveloped and pleomorphic viruses with the largest, linear, single stranded RNA (ssRNA) genome of positive sense polarity (approximately 30 kb). The CoVs peplomers are made up of trimeric viral proteins (Spike/S protein) that mediate attachment of the virus to its specific host cell receptors and the fusion between the host cell membrane and viral envelope. The production of neutralizing antibodies is induced by the S protein due to its interaction with the host receptor and its role in virus attachment to and entry into the host cell (Markey *et al*., 2013). Coronaviruses are spherical in shape, 120–160 nm in diameter with a helical nucleocapsid formed as a result of the complexing of the RNA genome with the basic nucleocapsid (N) protein found within the viral membrane. The viral membrane of all CoVs is made up of at least three viral proteins, namely the spike (S), membrane (M) protein that spans the membrane three times with a short N-terminal ectodomain and a cytoplasmic tail; and a highly hydrophobic small membrane (E) protein (Markey *et al*., 2013).

Genome organization

All CoVs have the same genome organization. The SARS-CoV-2 genome consists of 29,903 nucleotides

encoding several proteins within 14 open reading frames (ORFs) (Markey *et al*., 2013). The replicase gene is encoded at the 5′ end covering approximately 20 to 22 kb and encodes multiple enzymatic activities (Markey *et al*., 2013). Two very large open reading frames, denoted as ORFs 1a and 1b encode the products of replicase gene which when translated give rise to two large polypeptides, pp1a and pp1ab, through frameshifting mechanism involving a pseudoknot structure formed by the genomic RNA (Lee *et al*., 1991; Gorbalenya, 2001). Sixteen nonstructural proteins (nsp) are formed when these two proteins are cleaved by the viral protease (Wang *et al*., 2020c). The structural proteins are encoded by four ORFs in the order of S-E-M-N by the 3′ one-third of the genome, for all CoVs (Markey *et al*., 2013; Wang *et al*., 2020c). Furthermore, each group of CoVs may additionally encode a unique group of small viral proteins located in-between genes coding for structural proteins (ORFs 3a, 3b, 6, 7a, 7b, 8b, 9b and 14) (Wang *et al*., 2020c). These accessory proteins are non-essential and have been speculated to interact or interfere with the host innate immune response (Markey *et al*., 2013; Wang *et al*., 2020c). On both the 5′ and 3′ ends of the genome, there are untranslated regions (UTRs) which may interact with the host proteins and most likely viral proteins to control viral RNA replication, among which is the synthesis of positive and negative strand full length genomic RNA. Similarly, transcriptional regulatory sequences, which are conserved sequences at the beginning of the transcription sites for each of the multiple subgenomic mRNAs (Brian & Baric, 2005) are also present in the genome.

Replication

The SARS-CoV-2 genomic RNA contains a 5′ cap and a 3′ poly(A) tail that allow recognition and immediate translation after viral uncoating to produce two co-terminal replicase polyproteins pp1a and pp1ab, through ribosomal frameshifting mechanism. Cleavage of the polyproteins by the two viral proteases: papain-like proteases (nsp3-PLpros) and main proteases (nsp5-Mpro) yields the individual non-structural proteins (nsps), 1 to 11 (nsp1-11) and 1 to 16 (nsp1-16), respectively (Fehr & Perlman, 2015). These nsps are assembled into the replicase–transcriptase complex which begins to generate the negative-sense (-) genomic and sub-genomic RNAs that will serve as templates for synthesis of positive-sense genome (+) and sub-genomic mRNA, respectively. These sub-genomic mRNAs are 3′ co-terminal with the viral genome to form a nested set of RNAs because of the stoppage in the extension of the anti-sense RNA. The nsps also promote rearrangement of the membrane of the rough endoplasmic reticulum (ER) to form double-membrane vesicles where the genome replication and transcription processes occur (Zhou *et al*., 2020). The structural proteins are translated from sub-genomic mRNAs and become inserted into the ER secretory pathway up to the ER-Golgi intermediate compartment (ERGIC) (Fehr & Perlman, 2015). Along this pathway, the spike protein is cleaved into its S1 and S2 subunits, by furin-like proteases (Hoffmann *et al*., 2020). The newly synthesized genome forms a complex with N protein and buds into the ERGIC to generate new viral particles (virions). After assembly, the virions are then transported to the cell surface in vesicles for egress through exocytosis (Fehr & Perlman, 2015). Accessory proteins, also translated from sub-genomic mRNAs, carry out accessory functions that are likely important for pathogenesis and innate immune evasion (Fehr & Perlman, 2015).

Virus entry protein (spike protein)

Successful virus infections begin with the recognition and subsequent binding of viral particles to the surface cellular receptors of a permissive host, which is an essential determinant for cell and tissue tropism. Additionally, the ability of a virus to bind to the receptor-analogues in other species is also an important prerequisite for any virus to successfully cross over species (Lu *et al*., 2015a). Among the previously known HCoVs, HCoV-OC43 and HKU1 are shown to bind sugars for cell attachment (Li *et al*., 2005), the other four HCoVs all recognize and bind aminopeptidases as receptors. HCoV-229E binds to human aminopeptidase N (hAPN) (Li *et al*., 2019), and MERS-CoV interacts with human dipeptidyl peptidase 4 (hDPP4 or hCD26) (Lu *et al*., 2013; Raj *et al*., 2013). On the other hand, SARS-CoV and hCoV-NL63 interact with human angiotensin converting enzyme 2 (hACE2) for virus entry (Li *et al*., 2003; Hofmann *et al*., 2005; Wu *et al*., 2009). Studies indicated that newly emerged SARS-CoV-2 responsible for the current outbreak that began in December 2019, also utilizes the hACE2 receptor for attachment and entry into the cell (Zhou *et al*., 2020).

The spike protein that is anchored to the viral envelope mediates coronavirus entry into the host cell achieved first by binding to a specific host receptor followed by fusion between the viral and host membranes (Li, 2016). Initially, the host proteases will cleave the S protein into its two subunits S1 and S2 that mediate receptor recognition

and membrane fusion respectively (Lai *et al*., 2007). he S1 subunit consists of a C-terminal and an N-terminal domain, both of which can recognize host receptor. The C-terminal domain (CTD) is the receptor-binding domain (RBD) for SARS-CoV and MERS-CoV that specifically recognizes its host receptor, the angiotensin-converting enzyme 2 (ACE2) (Li *et al*., 2003; Li, 2015), unlike other mammalian coronaviruses such as the mouse hepatitis coronavirus which binds host receptor with the N-terminal domain of its S1 subunit (Taguchi & Hirai-Yuki, 2012). Studies have shown that host susceptibility to SARS-CoV infection is primarily determined by the affinity between the viral RBD and host ACE2 in the initial viral attachment step (Li *et al*., 2004; More *et al*., 2004; Li *et al*., 2005; Qu *et al*., 2005; McCray *et al*., 2007). Similarly, In SARS-CoV-2, the CTD of the S1 subunit has been identified as the domain that interacts with the hACE2 receptor with higher affinity than that observed in SARS-CoV (Wrapp *et al*., 2020). This is supported by the differences in antigenicity observed between SARS-CoV and SARS-CoV-2 when monoclonal and polyclonal antibodies raised against the SARS-CoV S1-RBD failed to bind to the SARS-CoV-2 S protein. The SARS-CoV-2 S protein is activated by enzymatic degradation at two cleavage sites: S1/S2 and S2. The S1/S2 cleavage site contains four peptides RRAR (Coutard *et al*., 2020) that are cleaved by furin, which is an important step necessary for S activation by the human serine protease TMPRSS2 (Park *et al*., 2016; Hoffmann *et al*., 2020). The RRAR peptides found in the S1/S2 cleavage site of SARS-CoV-2 are absent in SARS-CoV, instead, an arginine moiety is present at the cleavage site (Yao *et al.*, 2004). Because ACE2 receptor is expressed by a wide range of animal species with the exception of mouse and rat, the observed cross-species transmission and human-to-human transmission of the virus can be easily explained (Prompetchara *et al*., 2020).

Physicochemical properties of coronaviruses

Generally, coronaviruses are sensitive to heat, lipid solvents, formaldehyde, oxidizing agents and non-ionic detergents. The stability of the virions at low pH values is variable with some species being stable at values as low as pH 3.0. Coronaviruses tend to be difficult to grow in cell culture, a notable exception being infectious bronchitis virus. The isoelectric point (p*I*) of the SARS-CoV-2 S, E and M ptoteins were predicted to be 6.25, 8.57 nd 9.5, respectively using ProtParam tool by ExPASy. The p*I* value provides information on the surface charges of the virus particles in specific environment depending on the electrolyte conditions to which the viruses are exposed. SARS-CoV-2 was found to be extremely stable over a wide range of pH from 3 to 10 (Chin *et al*., 2020). Since SARS-CoV-2 is an enveloped virus, its susceptibility to lipid compounds can be estimated according to the grouping of Klein and Deforest (1983). According to them, all enveloped viruses are lipophilic and will therefore be susceptible to liphopilic antimicrobial agents such as alcohols, halogens, aldehydes, phenolics, quaternary ammonium compounds, peroxides, detergents and proteases (Kapil *et al*., 2004). The usefulness of this was found in the use of lipophilic antimalarial drugs to inhibit the replication of SARS-CoV-2 (Block, 2001). Furthermore, the surface stability and the environmental conditions such as aerosols, plastic, stainless steel, copper, and cardboard and other substance capable of inactivating SARS-CoV-2 and SARS-CoV-1 was investigated by van Doremalen *et al*. (2020). They found that both viruses remained viable for 3 hours in aerosol, and the fall in virus titer was the same ($10^{3.5}$ to $10^{2.7}$ tissue culture infective dose 50($TCID_{50}$) for SARS-CoV-2 against $10^{4.3}$ to $10^{3.5}$ $TCID_{50}$ for SARS-CoV-1). Moreover, the stability of SARS-CoV-2 on stainless steel and plastic was found to be longest (with 6.8 and 5.6 hours half-lives, respectively) compared to SARS-CoV-1 and viable virus was still detectable up to 72 h (van Doremalen *et al*., 2020). The SARS-CoV-2 viral particle was also found to be relatively stable when exposed to heat, UV and or gamma radiation. Exposure to UVA for 15 minutes had no significant effect on the viability of SARS-CoV, while exposure to UVB and UVC radiation for 15 minutes lead to the complete loss of viability. However, presence of bovine serum albumin (BSA) at 10%, 16% or 25% inhibit virus inactivation even after 60 minutes exposure (Darnell & Taylor, 2006).

Immune Mechanisms for COVID-19

Innate immunity

There is paucity of information available on the host innate immune response of SARS-CoV-2 infected patients. The few available data generated from COVID-19 patients showed 38%, 35%, 52% and 84% increased total neutrophils, reduced total lymphocytes, increased serum IL-6 and increased c-reactive protein respectively (Zhou *et al*., 2020). A correlation was observed between disease severity and death with increased neutrophils and decreased lymphocytes (Wu *et al*., 2020a). In addition, patients in critical conditions had higher plasma concentrations of cytokines such as IP-10, MCP-1,

MIP-1A and TNFα (Huang *et al*., 2020) suggesting association between disease severity and cytokine storm; a feature that was also observed in SARS-CoV and MERS-CoV infections (Mahallawi *et al*., 2018; Wong *et al*., 2018). Effective virus mediated innate immune response relies heavily on type I interferon (IFN) responses and its downstream cascade that culminates in controlling viral replication and induction of effective adaptive immune response (Prompetchara *et al*., 2020). The putative receptor of SARS-CoV-2, ACE2, is mainly expressed in type 2 alveolar cells within the lungs, with minimal percentages of the alveolar monocytes/macrophages in the lung expressing the ACE2 receptor (Zhu *et al*., 2020). Possibly, the virus utilizes other receptors or other non-ACE2 dependent entry mechanisms such as antibody-dependent enhancement of infection to infect immune cells (Prompetchara *et al*., 2020).

Genomic viral RNAs serve as the pathogen-associated molecular patterns that aid the recognition of coronavirus by the endosomal RNA receptors; TLR3 and TLR7 and the cytosolic RNA sensor: RIG-I/ MDA5. This recognition leads to activation of the downstream signaling cascade, i.e. NF-κB and IRF3, accompanied by their nuclear translocation. In the nuclei, these transcription factors induce expression of type I IFN and other pro-inflammatory cytokines as the first line of defense against viral infection at the entry site (de Wit *et al*., 2016). Type I IFN via IFNAR, in turn, activates the JAK-STAT pathway, where JAK1 and TYK2 kinases phosphorylate STAT1 and STAT2. STAT1/2 forms a complex with IRF9, and together they move into the nucleus to initiate the transcription of IFN-stimulated genes (ISGs) under the control of IFN-stimulated response element (ISRE) containing promoters (de Wit *et al*., 2016). A successful mounting of this type I IFN response should be able to suppress viral replication and dissemination at an early stage as observed for SARS-CoV and MERS-CoV infection. Both coronaviruses employ multiple strategies to interfere with the signaling leading to type I IFN production and/or the signaling downstream of IFNAR, a strategy that modulates disease severity (Channappanavar & Perlman, 2017). At the step of type I IFN induction, the SARS-CoV virus particle interferes directly or indirectly with the downstream signaling of RNA sensors via ubiquitination for example and the degradation of RNA sensor adaptor molecules MAVS and TRAF3/6 as well as inhibiting IRF3 nuclear translocation (Kindler *et al*., 2016). MERS-CoV also utilizes some of these strategies in addition to other mechanisms such as repressive histone modification (Kindler *et al*., 2016). Once type I IFN is secreted, SARS-CoV and MERS-CoV inhibit IFN signaling by using mechanisms that decrease the phosphorylation of STAT1 molecules (de Wit *et al*., 2016) which is controlled by M and N structural proteins as well as non-structural proteins (ORF proteins) (Prompetchara *et al*., 2020).

Acquired immunity

There are two types of helper T cells that modulate adaptive immune responses: Th1 and Th2 cells. For viral infections, the Th1 cells dominate the mediation of the adaptive immune responses. The cytokine microenvironment generated by antigen presenting cells dictates the direction of T cell responses. Helper T cells coordinate the overall direction of the adaptive response, with the cytotoxic T cells being responsible for the elimination of virus infected cells. The production of specific neutralizing antibodies by B cells is controlled by Th2 cells and plays a protective role by limiting infection at later phase and preventing re- infection in the future. Due to the limited amount of information on the SARS-CoV-2 immunology at the moment, the immunology of SARS-CoV and MERS-CoV whose T and B cell epitopes were extensively mapped for the structural proteins (S, N, M and E) (Liu *et al*., 2017), will be the basis upon which the SARS-CoV-2 immunology will be studied. In SARS-CoV infected individuals, seroconversion becomes evident in few cases 4 days after onset of disease and by 14 days post infection (pi), most patients become seroconverted and may last up to 2 years (Liu *et al*., 2006). A delay in seroconversion for MERS-CoV infection has been observed, where antibodies are seen at about the second or third week post infection (pi). For both types of coronavirus infections, delayed and weak antibody response are associated with severe outcome (Liu *et al*., 2017). A limited serologic response to SARS-CoV-2 infection was reported in which peak specific IgM was observed in a patient after 9 days of disease onset with immunoglobulin switching to IgG occurring at 14 days pi (Zhou *et al*., 2020). Interestingly, convalescent sera from COVID-19 confirmed patients showed some degree of cross-reactivity with SARS-CoV, but not other coronaviruses (Zhou *et al*., 2020). Again, all tested sera from COVID-19 patients neutralized SARS-CoV-2 viral particles via plaque assay, suggesting the effective mounting of humoral immune responses (Zhou *et al*., 2020). Studies investigating T cell response dynamics in SARS-CoV infection using convalescent samples, reported higher CD8+ T cell responses than CD4+ T cell responses, and higher

frequency of memory cells comprising of polyfunctional CD4+ T cells (IFNγ, TNFα, and IL-2) and CD8+ T cells (IFNγ, TNFα and degranulated state) being observed in patients with severe form of the disease as compared with patients with the mild-moderate form. The study further revealed the correlation between disease severity, higher level of neutralizing antibody and strong T cell responses and the higher the fatality, the higher the level of serum Th2 cytokines (IL-4, IL-5, IL-10) (Li *et al*., 2008). Similarly, in MERS-CoV infection, the disease severity was found to be associated with early rise of CD8+ T cells, while at the convalescent phase Th1 cells become dominant (Shin *et al*., 2019). The role of Th17 in hCoVs infections is currently not known, but current evidences indicated that Th1 mediated response is the key for the successful control of SARS-CoV and MERS-CoV infections which may also be the case for SARS-CoV-2 (Prompetchara *et al*., 2020).

Epidemiological Trend of COVID-19

As of May 2, 2020 SARS-CoV-2 has affected persons in more than 210 countries and territories in Asia, Europe, Africa, North America and Latin America (WHO, 2020c). Due to very high transmissibility across the borders, it was declared as public health emergency of international concern by the WHO on January 30, 2020 and later as pandemic situation (WHO, 2020c). The culinary habits of Chinese people involve consumption of wild animals for their meat. The common motivation which informed consumption of wild animal meat in China is their belief that they have medicinal value as well as health promoting effects (Harypursat & Chen, 2020). Circumstantial evidence linked the first case of COVID-19 to the Huanan South Seafood Market where various exotic live animals are sold. Repeated human-animal interactions either in the market or in the animal industry without using proper environmental biosecurity are considered as significant risk factors for the emergence of zoonotic diseases, particularly in the rural communities of southern China (Daszak *et al*., 2020). After these reports, China temporarily banned the sale of wildlife and trading in bats. Furthermore, Wuhan animal food market was also kept closed so that further zoonotic transmission of SARS-CoV-2 and evolution of new viral variants could be prevented.

Coronaviruses are known to infect a number of avian and mammalian species (Holmes & Lai, 2001). The Danish Veterinary and Food Administration detected COVID-19 in minks from samples collected by its officials in a farm in North Jutland (PROMED, 2020). The Office of International Epizootics (OIE) member countries have been keeping the OIE updated on investigations or outcomes in animals. So far, SARS-CoV-2 has been detected in dogs in Hong Kong and cats in Belgium, Spain, Germany, Russia and France; in a tiger, a lion and a dog in the USA. SARS-CoV-2 was also detected in domestic cats in the USA, and on mink farms in the Netherlands and Denmark (PROMED, 2020; CDC, 2020).

Role of animals as reservoirs for SARS-CoV-2

In the second week of January, 2020 a 61-year-old man died from a mysterious pneumonia causing a spate of illnesses from an unknown virus in Wuhan, China. The man was a regular customer at Wuhan's giant seafood and live animal market, which also sold exotic animals, for meat. Of the first 41 cases of pneumonia tied to the viral infection that first arose in December, 2019, two-thirds had either been workers or customers at the market (Joseph, 2020). According to a widely circulated menu and the reports from vendors and observers, offerings at the market included snakes, dogs, baby crocodiles, arctic foxes, raccoon dogs, bamboo rats and civet cats, sometimes butchered on site (Page & Khan, 2020). At such Asian markets, exotic animals are often stacked in cages on top of animals they might never have encountered in natural settings. Exchanging excretion and saliva under stressful conditions makes animals prone to contagion and creates an enabling environment for viruses to jump from one species to another. There was wide speculation that the Wuhan market was the source of the virus that causes COVID-19, which erupted into a pandemic that has killed hundreds of thousands of people across the globe. But in recent months, scientists have cast doubt on the theory. They instead fear that the virus jumped earlier from an animal to a human, perhaps in the wild, and that the market's crowded conditions simply helped to spread the virus from one infected human to many others (Areddy, 2020). Regardless of what exactly happened, COVID-19 is just the most recent example of a growing threat to human health — zoonotic diseases, which leap from animals to humans and which, if the virus mutates successfully in humans, can also be transmitted from human to human. Researchers believe that COVID-19 spilled over from a horseshoe bat in China, possibly to another intermediate animal, such as an endangered pangolin, considered a culinary luxury in China, and then to humans (Cyranoski, 2020). Bats appear to be the natural reservoirs or sources of origin for SARS-

CoV-2 (Li *et al.,* 2020a) that causes zoonotic infection in humans through an intermediate host yet to be identified. Currently, investigations are centred on pangolin, ferrets and possibly snake to determine their roles. Future explorations might reveal the actual intermediate host of SARS-CoV-2 responsible for zoonotic transmission (Almendros, 2020; Dhama *et al.,* 2020; Shi *et al.,* 2020; Zhang *et al.,* 2020).

Prevention and Control

Enormous efforts are being made to contain and control the spread of SARS-CoV 2 which is haunting the lives of humans and now a serious pandemic. All round the world, significant strides has been made to rapidly diagnose and ensure strict vigilance, appropriate isolation, and quarantine procedures required to halt further spread of the virus. Enhanced surveillance and monitoring, strengthening of medical facilities and intensive care units, networking programs, quick communication of outcomes and providing updates, knowledge awareness of public health risks to the general population alongside legislations, for compliance and non-compliance with established WHO safety procedures will go a long way to safeguard public health.

Vaccines

Several candidate vaccines are being evaluated with few undergoing clinical trials (Shang *et al*., 2020). Moderna Biopharmaceutical Company USA started with the mRNA-1273 vaccine (Flanagan, 2020). An intranasal vaccine against COVID-19 named AdCOVID is being developed by adopting pandemic influenza vaccine strategy and inhalation anthrax vaccine (Hansen *et al*., 2020). In addition, Clover Biopharmaceuticals China is working on SARS-CoV-2 protein-based subunit vaccine (Clover Biopharmaceuticals, 2020) to help fight the pandemic. Generally, WHO has identified about 44 candidate vaccines which include live attenuated, formaldehyde inactivated, DNA, m-RNA, protein subunit, virus-like-particles (VLP), replicating, and non-replicating vector-based SARS-CoV-2 vaccines. Adenovirus type 5 vector vaccine and LNP-encapsulated mRNA vaccine is under phase-1 clinical evaluation. Few of the vaccines that are in pre-clinical stage of clinical evaluation against COVID-19 include DNA plasmid vaccine, formaldehyde inactivated alum vaccine, live attenuated virus vaccine, adenovirus-based NasoVAX expressing SARS-CoV-2 spike protein (named GREVAXTM), Drosophila S2 insect cell expression system using VLPs as protein subunit vaccine, peptide based vaccine, S protein through baculovirus production system, full length S trimers nanoparticle with Matrix M protein, gp-96 backbone based vaccine, S1 or RBD protein base, adjuvanted microsphere peptide vaccine candidate, LNP encapsulated mRNA encoding RBD, and small activating ds-RNA based COVID-19 vaccine.

Drug therapies

Looking at the proposed benefits of hydroxychloroquine, a multicentric randomised study is underway to assess its effectiveness as a prophylactic measure in curbing secondary SARS-CoV-2 infections as well as associated clinical symptoms progression, thereby reducing the overall spread of the virus (Mitja & Clotet, 2020). Other drugs whose efficacies are being evaluated include β-D-N4-hydroxycytidine (NHC) (Shi *et al.,* 2020), Remdesivir (Holshue *et al.,* 2020; Kujawski *et al.,* 2020), Ivermectin (Caly *et al.,* 2020), Lopinavir/Ritonavir (Sanders *et al*., 2020), Arbidol (Wang *et al.,* 2020a), Ribavirin (McCreary & Pogue, 2020), Nizatoxanide (Wang *et al.,* 2020a), Homoharringtonine (Neerukonda & Katneni, 2020), Emetine (Choy *et al.,* 2020; Shen *et al.,* 2019), Corticosteroids (Wu *et al.,* 2020b), Tocilizumab and Sarilumab (Xu *et al.,* 2020) and convalescent plasma (Duan *et al*., 2020). Giving the adverse effects encountered during evaluation, clinicians must weigh the risks and benefits of any of the drugs carefully as they are used on patients to manage COVID-19.

Social distancing

Till the vaccines and therapeutic antiviral agents are developed, prevention and control strategies need to be focused on social distancing and avoiding crowded places, avoiding going out regularly except when highly necessary, and ensuring strict compliance to wearing of nose masks. There is the need for strengthening veterinary laboratory infrastructure and capacity building with trained workforce, hospitals, veterinary public health workers to identify possible SARS-CoV-2 affected animals and by extension infected animal owners or handlers. To effectively prevent COVID-19 spread, the first measure is to diagnose the case with accuracy and speed. While confirming any suspected COVID-19 case, the NCDC guidelines must be strictly followed (NCDC, 2020). As the suspected case is a good source of nosocomial spread, the veterinary and public health workers must follow all precautionary practices while handling the COVID-19 case. Veterinarians are to be vigilant as animals are reportedly being infected. There is need to send

nasopharyngeal samples for testing in NCDC accredited laboratories all over Nigeria including National Veterinary Research Institute and Veterinary Faculties. This will reinforce the efforts of veterinarians in disease monitoring and prevention in both companion animals and livestock.

Strategic partnerships to mitigate and control covid-19 pandemic

Moving toward its first permanent national ban on the trade in wildlife food, China's legislature is considering changes to their wildlife laws to outlaw sale and human consumption of some wild animals. This will replace the temporary wildlife ban issued in January, 2020 in the wake of the coronavirus outbreak in Wuhan, which was to stay in effect until the end of the pandemic (Stanway, 2020). In April, the Chinese government issued a proposed list of animals that could be sold for meat, drastically curtailed from the species that are currently legal. Notably, the approved list left out some of the animals of most concern for zoonotic disease, such as pangolins, civet cats and bamboo rats as well as dogs, which Chinese markets have long sold for food (Westcott, 2020). China's wildlife ban will have limited effect if nearby countries continue the exotic animal trade. In March, Vietnamese Prime Minister Nguyen Xuân Phúc requested draft legislation by April 1, 2020, to restrict the trade in, and consumption of wildlife, but no information about a ban has been made public, raising concerns among conservation groups as to the government's seriousness (Tatarski, 2020).

WHO food safety and animal diseases expert Peter Ben Embarek said live animal markets — which exist in many countries, including in Africa are essential to providing food and livelihoods to millions around the world and that governments should focus on improving the markets' hygiene and food safety standards. No law has been instituted to ban trade in wildlife in Nigeria and many African countries. It is known that apart from rural areas, it is not a common practice to have humans live in close proximity to bats and pangolins. However, bats strategically move all round the country from Ife to Oyo, to Ondo, to Abuja, Niger and beyond. Therefore, hunters continue to encroach into their roosts thereby creating fears of possible infection.

Conclusion

Scientists are still learning about SARS-CoV-2, and as at now, there is no evidence indicating the involvement of pets in the spread of the virus to humans despite evidence of infection. Thus, there is no justification in taking measures that may compromise their welfare. Nevertheless, it is important for the veterinary community to develop surveillance strategies to monitor COVID-19 in animals which could pose a threat to both animal and human health, as the world is raging war to curtail this pandemic. Veterinarians and animal health related workers should ensure strict compliance of the WHO and or NCDC COVID-19 guidelines on personal hygiene, use of personal protective gears when handling sick or apparently healthy pets or livestock to avoid risk of infection (Benvenuto *et al*., 2020). They should be proactive in monitoring animals that had been in contact with COVID-19 suspected and confirmed cases. Strategic partnership with all relevant stakeholders should be encouraged at all levels for effective COVID-19 diagnosis, case management, prevention and control.

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