Review Article

Emerging Coronavirus Disease (COVID-19), a pandemic public health emergency with animal linkages: Current status update

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Abstract

After the appearance of first cases of 'pneumonia of unknown origin' in the Wuhan city, China, during late 2019, the disease progressed fast. Its cause was identified as a novel coronavirus, named provisionally 2019-nCoV. Subsequently, an official name was given as SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2) by the International Committee on Taxonomy of Viruses (ICTV) study group. The World Health Organization (WHO) named the Coronavirus disease-2019 as COVID-19. The epidemics of COVID-2019 have been recorded over 113 countries/territories/areas apart from China and filched more than 4292 humans, affecting severely around 1,18,326 cases in a short span. The status of COVID-2019 emergency revised by the WHO within 42 days from Public Health International Emergency (January 30, 2020) to a pandemic (March 11, 2020). Nonetheless, the case fatality rate (CFR) of the current epidemic is on the rise (between 2-4%), relatively is lower than the previous SARS-CoV (2002/2003) and MERS-CoV (2012) outbreaks. Even though investigations are on its way, the researchers across the globe have assumptions of animal-origin of current SARS-CoV-2. A recent case report provides evidence of mild COVID-2019 infection in a pet dog that acquired COVID-2019 infection from his owner in Hong Kong. The news on travellers associated spread across the globe have also put many countries on alert with the cancellation of tourist visa to all affected countries and postponement of events where international visits were required. A few diagnostic approaches, including quantitative and differential real-time polymerase chain reaction assays, have been recommended for the screening of the individuals at risk. In the absence of any selective vaccine against SARS-CoV-2, re-purposed drugs are advocated in many studies. This article discourse the current worldwide situation of COVID-2019 with information on virus, epidemiology, host, the role of animals, effective diagnosis, therapeutics, preventive and control approaches making people aware on the disease outcomes.

Keywords: Coronavirus, 2019-nCoV, SARS-CoV-2, Animal coronaviruses, COVID-19, Bat coronavirus, Zoonoses, Epidemiology, Transmission, Diagnosis, Antivirals, Prevention and Control

Introduction

The commencement of the 21st century has witnessed deadly coronaviruses infection, SARS-CoV and MERS-CoV, during 2002 and 2012. The current decade further ascended with the emergence of the first outbreak of pneumonia of unknown-origin **(Lu et al. 2020)**. Several fatal cases dotted in the Wuhan city, Hubei Province of China during the early weeks of December 2019 **(Gao 2020a; Lu et al. 2020)**. This area was later exclusively identified as the epicentre of the disease and was linked to the spread of the virus across the world. The PUO patients exhibited signs of respiratory illness, coughing, sneezing, chest pain, nausea, vomiting, diarrhoea and a large proportion of affected older people acceded to death. The incubation period varied between 2-24 days. A coronavirus (CoV) was recognized as the cause of PUO and being different from the previous human coronavirus, SARS-CoV, it was named provisionally novel CoV of 2019 (2019-nCoV) by the World Health Organization (WHO) and CoV-associated diseases as "COVID-19" **(Du Toit 2020; Gralinski and Menachery 2020)**. Subsequently, the International Committee on Taxonomy of Viruses (ICTV) proposed its name as Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) **(Gorbalenya 2020)**. The current COVID-19 epidemic has turmoil in the global economy affecting the trade of goods and tourism in the past 30 days **(Ayittey et al. 2020)**.

As on March 11, the COVID-19 has disseminated in more than 114 countries of the world affecting 118,326 persons with 4292 deaths. In China alone, SARS-CoV-2 has affected more than 80955 people and 3162 deaths, where confirmed cases and deaths are maximum from Hubei province, the epicentre of the outbreak (67773 cases and 3046 deaths). The disease spread is rapid and has claimed maximum deaths in Italy (631), Iran (291), and Republic of Korea (60), making Risk Assessment of disease to Very High level by the WHO for all affected regions including China. Furthermore, the WHO on January 30, 2020, declared COVID-2019 as "Public Health Emergency of International Concern" **(Du Toit 2020; Habibzadeh and Stoneman 2020; Liu et al. 2020a; Wood 2020)** and on March 11, 2020, its status was amended to pandemic.
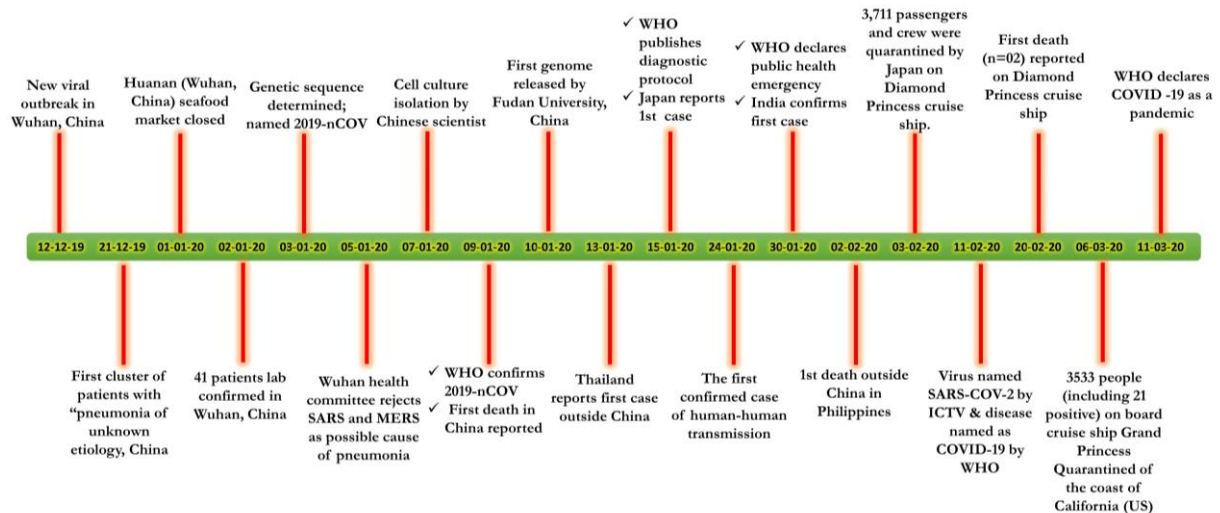
Figure 1: Timeline depicting significant events in due course of the current SARS-CoV-2/COVID-19 outbreak.

As the first cases of the disease occurred near the Wuhan Seafood Market (China), where the consumption of live animals is savoured, the disease spread at the prime-face was linked with animal hosts. Starting from December 2019 wherein new cases of "pneumonia" like disease emerged in Wuhan, China followed by confirmation of Chinese Health committee and WHO that a novel coronavirus is a cause of severe respiratory illness among the patients (Fig 1). In January 2020, several other countries in Europe, Asia, and the Americas reported similar cases of novel coronavirus following which WHO declared it as a public health emergency. Scientists all over the world started unravelling the genome and successively provided data for SARS-CoV-2 outbreaks worldwide. Apart from several countries and regions affected by this outbreak, cases were also reported from cruise ships being quarantined off the coast in Japan (Diamond Princes) and the USA (Grand Princess) (Fig 1). On March 11, 2020, WHO declared the COVID-19 outbreak as a global pandemic with SARS-CoV-2 claiming around 4292 lives in 114 countries worldwide (Fig 1).

A controverted report suggesting snake as the source of infection was precluded, as it was based on codon usage studies, but several other reports document bats and pangolins as the primary source of SARS-CoV-2 emergence. The assumption is based primarily on higher genomic sequence similarity of COVID-2019 virus with bat or pangolin origin CoVs. The state-of-art virus detection assays, including qRT-PCR and rapid sequencing-based methods, provided the feasibility of accurate and fast confirmation. As of now, no suitable prophylactic or therapeutics is found effective against the COVID-2019. This review primarily presents the current situation of COVID-2019/SARS-CoV-2 with a focus on the virus, epidemiology,

transmission, details on coronaviruses affecting animals, and prevention and control measures useful in curtailing the spread of disease.

Coronavirus, genome and classification

Coronaviruses (CoV) are a member of a diverse group of RNA viruses comprised of a large genome size varying between 26 to 32 kb. The viral genome is linear and monopartite with a positive sense ssRNA genome. The linear RNA genome of CoVs is capped and polyadenylated. The 5' end of the CoV genome encodes replicase gene which contains two large open reading frames (ORFs), ORF1a and ORF1b. They encompass around two-third or ~20 kb of the genome. Replicase gene translates two large polyproteins, pp1a and pp1ab. The polyprotein pp1ab is expressed as a result of the translational frameshift between ORF1a and ORF1ab. The replicase polyproteins are further cleaved into 16 proteins which include proteins related to enzymatic activities, protease activities, polymerases and helicases which fuses with a zinc finger complex at the N-terminus and a Zn-ribbon-containing papain-like proteinase. The genome further consists of structural proteins spike (S), envelope (E), membrane (M), and nucleocapsid (N), encoded by ORF at 3' end. Apart from the conventional genome replication, the CoV replicase genome complex mediates the synthesis of a subgenomic (Sg) mRNAs to express all ORFs downstream ORF1b. The CoVs also express few proteins which usually encodes accessory non-structural proteins. Few studies suggested their role in virus-host interactions and also performed certain essential functions. They have a unique mechanism of replication which renders with an ability to undergo mutation and recombination, which enables them to evade the host species barrier.

The newly identified 2019-nCoV/SARS-CoV-2 is a member of order *Nidovirales,* family *Coronaviridae* and sub-family *Orthocoronavirinae.* The subfamily *Orthocoronavirinae* is further divided into four genera, namely *Alphacoronavirus, Betacoronavirus, Gammacoronavirus,* and *Deltacoronavirus* (**de Groot et al. 2012**). *Alphacoronavirus*es and *Betacoronavirus*es are responsible for infection in mammals causing respiratory and enteric diseases in humans and animals. A wide variation in the genome size is seen among all the four genera of *Coronaviridae* which ranges from 27 to 29 kb, 26 to 32 kb, 27 to 32 kb, and 26 to 26.5 kb for *Alphacoronavirus, Betacoronavirus, Gammacoronavirus,* and *Deltacoronavirus,* respectively. There are six known strains of coronaviruses, causing mild to severe respiratory illness in humans (**Su et al. 2016**). The strains are from *Alphacoronavirus* (hCoV-229E and hCoVNL63) and *Betacoronaviruses* (hCoV-OC43 and hCoV-HKU1), Severe Acute Respiratory Syndrome (SARS)-CoV in *Betacoronavirus* group B. The Middle East Respiratory Syndrome (MERS-CoV) in

Betacoronavirus group C. *Betacoronaviruses* are further subdivided into five subgenera, namely *Embecovirus, Hibecovirus, Merbecovirus, Nobecovirus and Serbecovirus.* Based on replicase phylogenetic analysis, group 1 CoVs which includes the hCoV-229E also includes other animal infecting viruses like Transmissible Gastroenteritis Virus (TGEV) and Porcine Epidemic Diarrhoea Virus (PEDV). Similarly, the SARS-CoV falls in the group 2 where animal origin mouse hepatitis virus and bovine coronaviruses are found.

The recent 2019-nCoV or SARS-CoV-2 is a member of genus *Betacoronavirus* in the subgenus *Sarbecovirus.* The SARS-CoV and MERS-CoVs are quite distant at genomic levels to current 2019-nCoV but are part of the *Betacoronavirus* genus. The SARS-CoV-2 shows lower similarity (50-51.8%) with MERS-CoV and similarity is near to 79% with SARS-CoV (**Malik et al. 2020**).

SARS-CoV-2/COVID-2019 Epidemiology

A novel coronavirus (2019-nCoV), emerged in Wuhan, China, at the end of 2019. Epidemiologically, the earliest cases were linked to Jianghan, Wuhan and possibly be infected through zoonotic or environmental exposures **(WHO 2003)** and the epicentre of the outbreak was Huanan seafood market. A few reports on 2019-nCoV suggests the possible spread of the virus by Chinese beluga fish or snakes or bats or pangolins. The 2019-nCoV infection in humans is possibly a species jump of the virus. The researchers noticed no epidemiological links between patient zero and later infections. However, the majority of the initial cases had direct exposure to the Wuhan animal market. It is claimed that the patient zero possibly carried the infection to the market, rather than catching the virus at the market. Epidemiologically, the cases outside China initially occurred amongst the travellers from China and those who had contact with travellers from China **(WHO 2003)**.

As on January 20, 2020, only 282 cases restricted to China, Republic of Korea, Japan and Thailand were infected with 2019-nCoV. However, the virus has spread its tentacles rapidly, and as on March 11, 2020, more than 1,10,000 individuals were infected in 113 countries of which >60% of the cases are from mainland China. Other countries from where major confirmed cases were reported to include South Korea, Italy, Iran, and Japan. According to recent reports, the case fatality in China has decreased, and more than 70% of infected people are recovered. The preliminary data suggest that age has an inverse relationship with morbidity and mortality associated with COVID-19 infection.

South-East Asia

In this region, the cases were mainly by foreign travellers. The worst affected countries in this region are Thailand and India, where the local transmission of 2019-nCoV has also seen. India reported its first death due to COVID-19 on March 12, 2020. A Hong Kong person, who travelled for five days on Diamond Princess from Yokohama on January 20, was the source of infection to other persons on Deck and he disembarked in Hong Kong after five days of travel, tested positive for SARS-CoV-2 infection on February 1, six days after leaving the ship. In Diamond Prince's ship, there were 2,666 guests and 1,045 crew members of which 696 were infected, and seven persons have died due to COVID-19.

Europe

In this region, as on March 11, 2020, Italy is the worst affected country with 10149 confirmed positive cases with 631 moralities (Figure 2). According to the reports of WHO, the case fatality rate in Italy is comparatively higher (6.2%) than other parts of the world. The 2019-nCoV after entering into Italy through Chinese tourists spread fast by local transmission. Currently, Italy has the highest number of coronavirus cases in Europe and the second-highest in the world, next to China. In Italy, the local spread is mainly of communal transmission.

Region of the Americas

In this region, the main countries reported COVID-19 positives are United States of America, Canada, Brazil and Ecuador. The Grand Princess Cruise ship off the coast of California, with 3,500 travellers onboard reported 21 confirmed positive cases of COVID-19.

Middle East Region

Iran has the highest number of confirmed positives and moralities in this region. The neighbouring of Iran such as Kuwait, Bahrain, Iraq and the United Arab Emirates also reported higher cases in this region. The Nile Cruise ship docked in Egyptian international waters with over 150 tourists reported 45 positives.

Western Pacific Western Pacific

The Republic of Korea, which is a neighbouring country to hotspot China, has been affected severely with COVID-19. In this region, the infection spreads by local transmission. As on March 11, 2020, the total number of confirmed positive cases was 7755 with 60 deaths (Figure 2).

Transmission, case fatality rate and risk groups

The human-to-human transmission of SARS-CoV-2 mainly occurs through large droplets, where the risk confines up to ~6 feet from the COVID-19 affected patient. For curtailing such virus transmission (large droplets) use of a standard surgical-style mask is advised. As of now, airborne transmission of SARS-CoV-2, where for a more extended period the smaller droplets remain aloft in the air, is under investigation. Moreover, the transmission of SARS-CoV-2 from the asymptomatic patients remains a more critical area of consideration as the virus transmission could occur even in the absence of any clinical symptoms. In another situation, the patient in a carrier stage (after clinical recovery) may also shed virus and as reported the recovered patients usually may carry a low viral load with a comparatively lower risk of virus transmission. There is a further need to investigate the role of these convalesced patients in maintaining or transmitting the virus. The fomite-to-face (contact transmission) mode sometimes goes unnoticed, though is enormously significant. The virus could be expelled during coughing and sputum, nasal secretions, stool, saliva, urine, and blood. Thus, in several ways, the infected patient could shed virus into the environment. The virus could persist on fomites in the environment for weeks together. Therefore from this spool of infected material, one can pick up the virus and initiate the event of the next virus infection cycle. It is also hypothesised that the faecal-oral route may also play a role. The first human-to-animal transmission of SARS-CoV-2 is reported in a pet dog of a COVID-19 infected patient in Hong Kong.

The global case fatality rate of COVID-19 is 3.4%. The attack and case fatality rate in an age of fewer than 18 years are relatively low. However, people aged over 50 years and with chronic conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease and cancer have a higher risk. The highest risk group is in above 80 years of people with a case fatality rate of 21.9% **(WHO 2003; Chen 2020; Munster et al. 2020)**. The sex-wise case fatality rate of COVID-19 of China showed that males are more prone to infection than females because of the smoking habits of a Chinese male.

(Li et al. 2020b) estimated that the mean incubation period of infection with SARS-CoV-2 was 5.2 days (95% CI, 4.1–7.0), with the majority of the cases showing symptoms within 12.5 days of exposure, justify 14 days of quarantine. However, recent reports suggest that more than 14 days incubation period was observed in exposed persons recommending a double quarantine period of 28 days. Recent epidemiological analysis, indicate that the exposed person may act as a source of infection to others during the incubation period. According to the WHO the estimated reproductive number (R_0) to be 2.2 (95% CI, 1.4–3.9); however, have determined an R_0 between 3.6 and 4.0, and between 2.24 to 3.58 and 7.4 days (95% CI, 4.2–14), respectively **(Zhao et al. 2020)**.
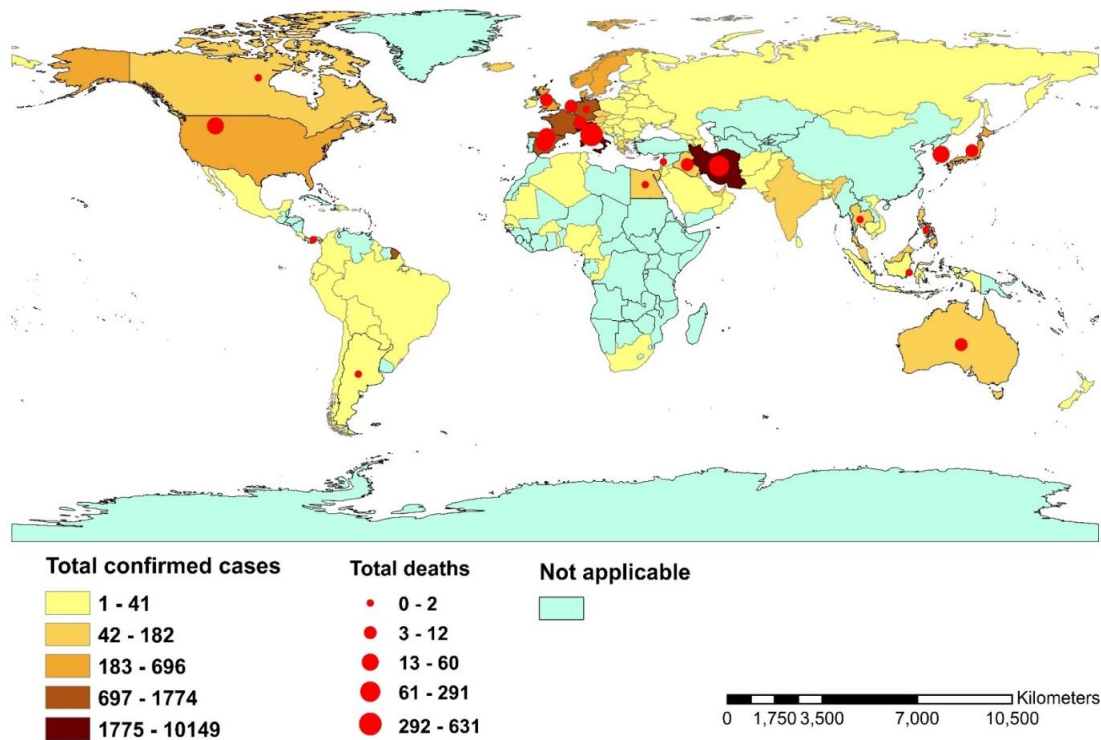
Figure 2: Countries, territories or areas outside China with reported laboratory-confirmed COVID-19 cases and deaths. Data as of 11 March 2020.

Indian Scenario

On account of emerging cases, India prepared an evacuation plan for the Indian nationals stranded in the hotspot Wuhan. It airlifted 767 people, including people from Nepal, Sri Lanka and the Maldives in two phases. India has also evacuated Indian nationals from Iran. The virus spread in the country has primarily occurred due to foreign travellers or travel. The first positive cases were reported during February 2020 in Kerala from the students travelled from Wuhan city, China. However, there were no secondary cases reported from the Kerala positive persons. Later, the positive cases in India included a Delhi dweller who returned from Italy and a man from Telangana who returned from Dubai. The other positive cases are Italian tourists and their tour guide who was detected positive in Rajasthan. As on March 11, 2020, India reported 76 confirmed positive cases, with one mortality of an older adult in Karnataka who has a recent history of travel to Saudi Arabia. The COVID-19 cases in India comprise both foreign national (n=17) as well as Indian nationals (n=59) having travel history to affected countries after that locally transmitting the virus to other people in contact (Fig 3).
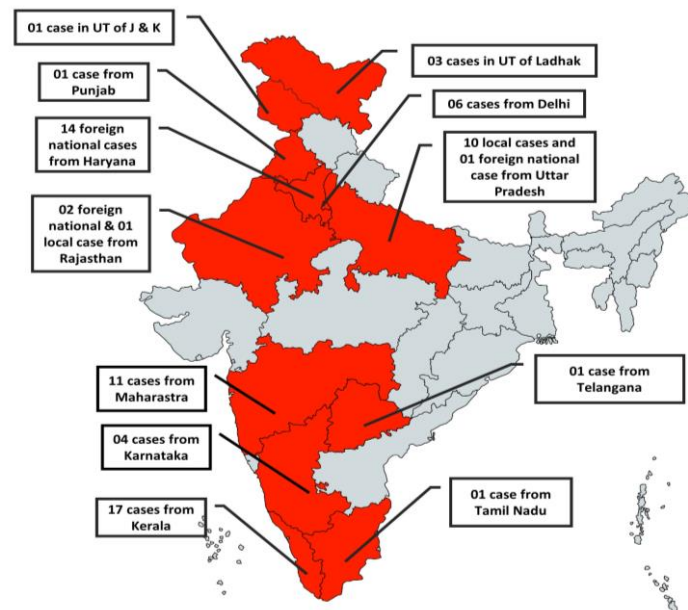
Figure 3: State & union territories with COVID-19 confirmed cases in India as on March 12, 2020. The first case of SARS-CoV-2/COVID-19 reported in India on January 30, 2020. The list includes ten states and two union territories having 56 Indian national and 17 foreign national confirmed cases.

The Government of India has issued travel restrictions and suspended visa of Iranian, Italian, Japanese and South Korean nationals. Lately, tourist visa for all citizens kept on hold until 15th April 2020. The travel advisory is issued not to travel the worst gaffed countries. In all airports and ports, screening has been in place. The health ministry has also advised observing good personal hygiene, regular monitoring of health, frequent handwashing with soap and water or use of alcohol-based hand sanitizer. Advisory has been issued to follow respiratory etiquettes, to avoid touching your eyes, nose and mouth to avoid close contact with people who are unwell or showing symptoms of illness, to wear a mask if you have symptoms such as cough, fever or difficulty in breathing and to contact a doctor immediately if cough, fever or problem in breathing arises. For information dissemination and help regarding COVID-19 infection, the helpline has been launched. The India based company Serum Institute of India and Codagenix, a US-based firm have entered in a collaboration to develop a viral deoptimized live-attenuated vaccine against the SARS-CoV-2. The vaccine is proposed to provide many advantages, including provoking the host immune response to multiple antigens of the virus **(SerumInstitute 2020)**.

Coronaviruses Host Range

The CoVs have breached host-species restriction twice in the past. The first incident was for SARS seen in 2002/2003 in humans and virus-origin was linked with bats, and later the second time it occurred in the form of MERS, where it had been linked with dromedary

camels in the Middle-east countries. The SARS-CoV-2 also appears to have crossed the host-species barrier, making CoVs species jumping phenomenon a standard feature. The virus genomic configuration, stability of several replication-associated genes/enzymes, higher mutation rates being RNA virus lacking proofreading features are assumed as the reason behind the emergence of novel CoVs that infects and maintain in several host species (**Su et al. 2016**). The significant role in the host-range expansion is plated by the outer surface glycoprotein spike gene where a mutation in the Receptor Binding Domain region helps to adapt virus to host species including animals or humans (**Chen 2020; Patel and Jernigan 2020**).

Coronaviruses infecting animals

The CoVs are associated with respiratory and enteric illness and usually of mild infections with marginal mortality (**Salata et al. 2019; Ji et al. 2020; Li et al. 2020b**). Infections due to CoVs have been observed in humans and several farm animals, companion animals, laboratory animals, bats, marine whales, and wild animals. The viruses under *Alphacoronavirus* and *Betacoronavirus* genera usually infect bats and other mammals, while viruses under *Gammacoronavirus* and *Deltacoronavirus* infects poultry, pigs, fish, and mammals (**Woo et al. 2012b; Hu et al. 2017; Cui et al. 2019**). Several reports confirm that several avian and mammalian animal species like bovine, equine, porcine, canine, lapine, camelids, avian, rodents, ferrets, mink, bats, snake, frogs, marmots, hedgehogs (*Erinaceus europaeus*), Malayan or Javan or Sunda pangolin (*Manis javanica*) serve as carrier/ reservoirs (**WHO 2003; Dhama et al. 2014a; Dhama et al. 2015; Monchatre-Leroy et al. 2017; Ji et al. 2020; Xu 2020**). Coronaviruses affect several animal hosts and belong to a different genus in *Coronavirudae* family (Figure 4). Species-wise coronaviruses are detailed.
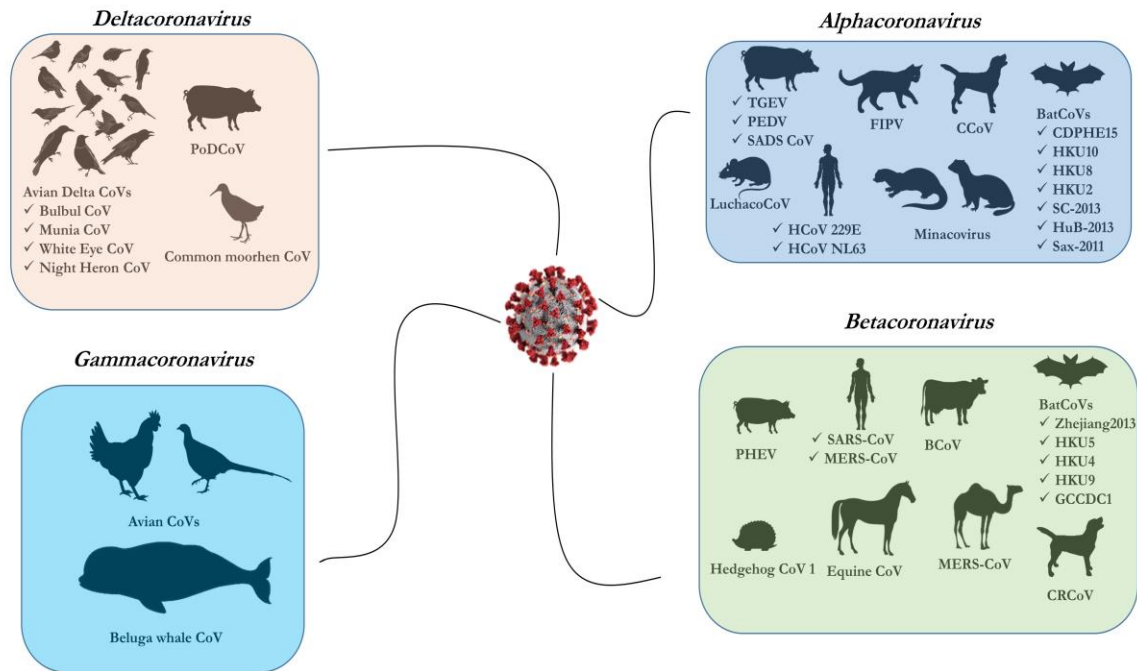
Figure 4: Depiction of different coronaviruses under four genuses (Alphaco*ronavirus, Betacoronavirus, Gammacoronavirus,* and *Deltacoronavirus*) found in a diverse group of mammalian and avian species.

i. Avian coronaviruses

The Infectious Bronchitis Virus (IBV), a member of the *Gammacoronavirus,* causes sizeable economic loss in poultry industry through respiratory illness, urinary tract infection, and reproductive disturbances **(Dhama et al. 2014b)**. The Avian Infectious Bronchitis (AIB) is among the most common viral diseases with significant mortality and morbidity, causing substantial economic losses in the poultry industry worldwide **(Cavanagh 2007)**. AIB was first described in 1931 from the United States, North Dakota **(Schalk 1931)**. Nonetheless, IBV infects mainly chickens of all ages; the younger population is more susceptibility where high mortality is recorded. Furthermore, several IBV-like viruses are documented from pheasants, turkeys and guinea fowls **(Weiss and Navas-Martin 2005)**. AIB spreads through mechanical transmission, including faecal-oral and airborne routes (inhalation and ingestion). The virus targets the respiratory tract of its natural host (Chicken), causing severe respiratory symptoms characterized by gasping, tracheal rales, coughing, nasal exudates, sneezing, respiratory distress, wet eyes and occasionally, swollen sinuses **(Weiss and Navas-Martin 2005)**. Additionally, the virus also affects the digestive tract, reproductive tract and urogenital tract, results in proventriculitis, salpingitis, egg-drop syndrome and nephritis **(Fan et al. 2018)**. The virus replicates in high titre in the ciliated epithelial cells of the respiratory tracts. Mucosal thickening of the upper and lower respiratory tract is the main gross pathological

findings. The virus is highly diverse and possesses several serotypes, genotypes and pathotypes. The virus is contained through commercially available inactivated and live vaccines (**Weiss and Navas-Martin 2005; Fan et al. 2018**). Moreover, the continuous emergence of novel strains with low cross-protection from vaccines sometime hampers the prevention and control strategies adopted on poultry farms (**Zhang et al. 2020b**). A few more CoVs from the genus *Deltacoronavirus* found infecting birds including Wigeon coronavirus HKU20, Bulbul coronavirus HKU11, Munia coronavirus HKU13, White-eye coronavirus HKU16, Night-heron coronavirus HKU19 and Common moorhen coronavirus HKU21 (**Paim et al. 2019**).

ii. Porcine coronaviruses

Several CoVs are found infecting pigs including Transmissible Gastroenteritis Virus (TGEV), Porcine respiratory coronavirus virus (PRCoV), Porcine Epidemic Diarrhea Virus (PEDV), Porcine hemagglutinating encephalomyelitis virus (PHEV), Swine acute diarrhoea syndrome coronavirus (SADS-CoV) and Porcine deltacoronavirus (PDCoV).

TGE is a highly contagious and economically significant disease of pigs reported all over the world (**Weiss and Navas-Martin 2005**). TGEV was first described in 1946 as a sporadic disease affecting pigs and characterized clinically by diarrhoea, vomition, rapid weight loss, and high mortality, predominantly in young pigs (**Doyle and Hutchings 1946**). The virus spread occurs through the faecal-oral route (ingestion). The clinical signs of TGE appear after a short incubation period of 18-72 hours. The virus selectively targets, multiplies and destroys the absorptive epithelial cells of the villi causing villous atrophy and impair absorption (malabsorption) (**Wu et al. 2020**). TGE cause severe diarrhoea with a watery, whitish or whitish-green stool. The upper respiratory tract and less often, the lungs also get affected with the disease (**Enjuanes et al. 1995**). Immunization of sows before farrowing is available with both live attenuated and killed vaccines.

Porcine respiratory coronavirus virus (PRCoV) is the attenuated variant of TGEV, originated due to a large 5' region deletion (621-681 nt) in the Spike (S) gene of the virus. The emergence of PRCoV is one of the examples of the evolution of CoVs with altered tropism and virulence (**Saif 2004**).

Another important porcine enteric disease PEDV, recognised in the early 1970s in Europe is growing and fattening pigs (**Oldham 1972**). Since its first report in 1982 in Asian countries, PEDV had a tremendous economic impact on the Asian pork industry (**Lee 2015**). The disease occurred in 2013 in the US, along with Canada and Mexico, causing deaths of more than 8 million piglets (Lee, 2015). Infection caused by oral and nasal route with an

incubation period of 1-4 days. Though there is a similarity in disease symptoms with TGEV, it differs in the spread within the herd, which is comparatively slower and with low mortality **(Lin et al. 2019)**.

Further, in PEDV older population affected more than younger ones **(Tan et al. 2020)**. PEDV and TGEV use the same receptor for entry into the cell. The closest known relatives of PEDV are found in bats and humans (HCoV-NL63) (Saif 2004). Several vaccines are available for the control of disease in swine **(Hsueh et al. 2020)**.

PHEV is known to affect the digestive and nervous system in pigs. It was first isolated in 1962 and classified under coronavirus in 1971 **(Greig et al. 1962; Clarke and McFerran 1971)**. PHEV is one of the first CoVs identified with neurotropic properties in pigs **(Mora-Díaz et al. 2019)**. Due to low clinical prevalence, PHEV is the least explored swine CoV worldwide. PHEV infect pigs of all ages but the clinical manifestation, mortality and morbidity are high in piglets below four weeks of age. Serological survey data describes the worldwide subclinical presence of PHEV **(Mora-Díaz et al. 2019)**.

SADS-CoV is a member of the genus *Alphacoronavirus.* It causes acute enteritis in the piglets. An early report on SADS-CoV had shown mortality of nearly 24,500 piglets in China. The SADS-CoV sequence analysis revealed high similarity (95-96%) to horseshoe bat origin (*Rhinolophus* sp.) and was named as HKU2-CoV **(Zhou et al. 2018)**. The disease outbreak projected the likelihood of host species leaping from bat CoV to pigs **(Zhou et al. 2018)**.

PDCoV was identified in the porcine population for the first time in 2012 in Hong Kong **(Woo et al. 2012a)**. Since then, PDCoV has spread to many countries, including China, Canada, Vietnam, Laos, USA, Thailand, and South Korea **(Koonpaew et al. 2019)**. Clinical severity of PDCoV is mild than other porcine CoVs. The mortality rate during PDCoV outbreaks reaches up to 40% **(Jung et al. 2016)**. As on date, limited information is available regarding the pathogenicity and virus-host interaction of PDCoV.

iii. Lab animals

The CoVs are also detected to infect several laboratory animals, including mice, ferret, guinea pig, rat, and rabbit. CoV-like mouse hepatitis virus (MHV), rat sialodacryoadenitis-CoV, guinea pig-CoV, ferret-CoV, and rabbit-CoVs are some important CoVs found responsible for hepatitis, enteritis, and respiratory infections in the lab animals. MHV is the most important and explored laboratory animal CoV which vary widely in its tissue tropism. The highly contagious enterotropic MHV strains infect digestive tract of infant mice and cause up to 100% mortality **(Compton et al. 2004)**. Whereas, polytropic

MHV primarily affects the upper respiratory tract and secondarily several organs including lymph node, CNS, vascular endothelium, haemopoietic tissue and liver. Rat sialodacryoadenitis-CoV primarily target nasal respiratory epithelium which later spreads to salivary and lacrimal glands **(Funk et al. 2009)**. High mortality rates observed in suckling rats. Ferrets are infected by enterotropic CoVs which cause epizootic catarrhal enteritis or green slime disease **(Doria-Torra et al. 2016)**. Very little is known about the prevalence of CoVs infecting rabbit and guinea pig, which mainly cause enteric disease characterized by villous atrophy, malabsorption and diarrhoea **(Lau et al. 2012)**.

iv. Domestic and wild ruminants

Among large animals, bovine coronaviruses (BoCoVs) have zoonotic potential as having been isolated from children. They may communicate a disease to many domestic and wild ruminants, in which calf diarrhoea in neonates, bloody diarrhoea in adult cattle and respiratory form of shipping fever in all age groups of animals are universal implications **(Suzuki et al. 2020)**. The high mortality rate due to BoCoVs mostly attributed to its high capability of destroying villi of both large and small intestine leading to bloody diarrhoea **(Torres-Medina et al. 1985)**. The presence of carrier animals and route of infection through faecal-oral is the primary cause of its spread **(Carman and Hazlett 1992)**. Carrier animals mainly shed the virus in stress conditions like winter **(Carman and Hazlett 1992)**. Besides affecting the bovine species, several Bovine-like CoVs have been reported from wild and domestic ruminants like Reindeer, Samber deer, White-tailed deer, Water deer, Wood bison, Waterbuck, Sable antelope, Himalayan tahr, Giraffe, Nyala, Sitatunga, Alpaca, Dromedary camel, Water buffalo, sheep, goat etc. **(Amer 2018; Kim et al. 2018)**.

v. Equine coronavirus

Equine coronaviruses (ECoVs) were initially reported in foals of less than two weeks of age, and infect the host with or without overt clinical sign and mostly associated with mild enteritis **(Dhama et al. 2014a)**. ECoVs belongs to the genus *Betacoronavirus*. ECoV was first reported in 1991 in foals from the USA and in an adult horse in 2011 in Japan **(Guy et al. 2000; Pusterla et al. 2013)**. They are responsible for causing self-limiting enteritis in horse population **(Sanz et al. 2019)**.

vi. Companion animals

Canine enteric coronavirus (CCoV) of *Alphacoronavirus* and canine respiratory coronavirus (CRCoV) of *Betaacoronavirus* genera affects the enteric and respiratory tract, respectively **(Licitra et al. 2014)**. CCoVs are present worldwide and infect all ages of animals, though puppies are known to be affected more severely. CCoV was first reported in

1971 in Germany from dogs with acute enteritis **(Binn et al. 1974)**. CCoV also possesses two genotypes known as type I and II. Both the types can infect the same host at a time which favours the chances of recombination between virus strains **(Escutenaire et al. 2007)**. CCoV shows more similarity with TGEV and probably TGEV originated from CCoV-II **(Perlman and Netland 2009)**. As per tissue tropism, there are two types of CCoV known, an enterotropic which cause enteritis primarily and another pantropic which targets several organs including the liver, spleen, central nervous system (CNS), lung, and kidney **(Buonavoglia et al. 2006)**. CCoV-I is not cultivable, but CCoV-II can quickly be grown in cell culture. CRCoV is more related to BoCoVs from *Betacoronavirus* genus and causes mild to a severe respiratory infection known as kennel cough **(Erles et al. 2007; Szczepanski et al. 2019)**.

Feline infectious peritonitis virus (FIPV) and Feline enteric coronavirus (FECV) are two common CoVs affecting the feline population. Feline-CoVs affect the respiratory tract, CNS, abdominal cavity and gastrointestinal tract to produce enteritis and infectious peritonitis **(Tekes and Thiel 2016)**. Feline infectious peritonitis (FIP) was first described in 1963 as a fatal and systemic progressive debilitating febrile disease of both domestic and wild feline **(Holzworth 1963)**. FIPV originated from FECV due to mutation in the S gene, which changes the tropism for macrophages **(Rottier et al. 2005)**. All the feline CoVs belongs to the *Alphacoronavirus* genus, and two distinct serotypes have been identified. Serotype I is a comparatively common cause of infection than serotype II. Serotype II believed to have originated due to recombination with canine CoV **(Herrewegh et al. 1998)**. The incubation period varies from as short as two weeks to as long as two months. The disease symptoms are seen typically in very young and old animals concerning suppressed immunity. The disease has two distinct forms, one is wet (effusive), and another is dry (non-effusive) **(Kipar et al. 2005)**. Host immune response is mainly responsible for the particular disease form. Antigen-antibody complexes are considered responsible for the lesions in the wet way **(Jaimes et al. 2020)**. The CNS dysfunction is most commonly seen during the dry form. Though both the types are fatal, still wet from proceeds more rapidly.

vii. Marine coronavirus

In addition to terrestrial animals, a novel coronavirus named SW1-CoV was recognized using state-of-art panviral microarray technology from the liver tissue specimens of the captive beluga whale (*Delphinapterus leucas*) **(Mihindukulasuriya et al. 2008)**. The name beluga derived from the Russian word "bielo" meaning white. This highly vocal beluga whale is known for its white colour and globular head and counted as a social animal. The

beluga whale belongs to the *Monodontidae* family and lives in the cold waters of the Arctic and some subarctic regions. Marine CoVs also have been reported from novel bottlenose dolphin reveals a distinct species in Gammacoronavirus **(Woo et al. 2014)**.

viii. Bat coronaviruses

Since the identification of many CoVs in bats, these are now considered as ideal reservoirs for CoVs. The bats harbour CoVs persistently for an extended period as an asymptomatic carrier and while flying in search of food might shed the virus in more extensive areas including some animal-human hosts which come in direct or indirect contact **(Fan et al. 2019)**. Notably, in China, bats are used as food as well as used to prepare Traditional Chinese Medicine (TCM). Bats pose a higher risk of transmitting a new zoonotic infection **(Wassenaar and Zou 2020)**.

Origin of SARS-CoV-2 and animal linkages (zoonosis)

The first case of pneumonia of unknown origin appeared in the South China Wet Seafood wholesale market in Wuhan, Hubei Province, China, was further investigated and found to be due to coronavirus. The live animal market with restaurants in this place is known for servings of several types of wild and live animals including bats, snakes, and marmots **(Hu et al. 2015; Hui et al. 2020; Lu et al. 2020)**. A few researcher groups also suggested the role of traditional cooking practices in China accountable for the current CoV infection in humans. Though in China live-slaughtered animals are considered more nutritious, several pathogens including SARS-CoV, Nipah virus, Hepatitis A virus, Hepatitis E virus, Norovirus, Rotavirus, Highly Pathogenic Avian Influenza virus also pass on through this way of food servings **(FAO/WHO 2008).** Looking as the scare situation, the government of China banned the sale of wildlife and trading of bats, Wuhan animal food market was closed to avoid zoonotic transmission of COVID-19 and evolution of any new viral variant **(Benvenuto et al. 2020)**. Later the virus was named 2019-nCoV/SARS-CoV-2. The original link of CoV was suspected to be from animal to human, and subsequently, virus maintained human-to-human transmission **(Hui et al. 2020; Ji et al. 2020; Nishiura et al. 2020)**.

Bat-like SARS-CoV linkage

The perusal of literature revealed the prospective role of bat origin SARS-CoVs in infecting humans. Since the establishment of bats involvement in the transmission of SARS-CoV in 2002/2003 outbreaks occurred in China, the scientist's conjectured bats association in the current epidemic of SARS-CoV-2/COVID-2019 as well **(Fan et al. 2019; Wong et al. 2019; Zhou et al. 2020a)**. The resemblance of bat CoVs with current SARS-CoV-2 at the genomic level has been evaluated by several research groups world over. The SARS-CoV-2

has shown the similarity of 88-89% with two bat origin SARS-CoVs (bat-SL-CoVZC45 and bat-SL-CoVZXC21 or also named as ZC45 and ZXC21). The similarity of SARS-CoV-2 at genomic level remains lower (82%) with human SARS-CoV Tor2 and human SARS-CoV BJ01 2003 **(Drexler et al. 2014; Hu et al. 2017; Hu et al. 2018; Chan et al. 2020; Malik et al. 2020)**. The genomic level phyloanalysis reveal the greater closeness of SARS-CoV-2 with bat origin SARS-CoVs **(Mohd et al. 2016; Ramadan and Shaib 2019; Malik et al. 2020; Ren et al. 2020).** Now, surveillance strategies and preventive guidelines should be drafted to have an analysis of bat origin *Betacoronavirus* especially in the *Rhinolophus* bat family as in the past SARS, MERS, and now COVID-19 epidemic has become havoc. From epidemic, it is turning to pandemic **(Daszak et al. 2020)**.

Bat coronavirus (BatCoV RaTG13)—which was previously detected in *Rhinolophus affinis* from Yunnan province—showed high sequence identity to SARS-CoV-2. Simplot analysis reveals the highest similarity of SARS-CoV-2 throughout the genome to RaTG13, with an overall genome sequence identity of 96.2%. The receptor-binding spike protein (S) was highly divergent from other previously described SARS-CoVs, except for a 93.1% nucleotide identity to RaTG13. The *S* genes of SARS-CoV-2 and RaTG13 are longer than other SARSr-CoVs. The close phylogenetic relationship to RaTG13 provides evidence that SARS-CoV-2 may have originated in bats **(Zhou et al. 2020b)**.

Malayan pangolin-CoV linkage

In addition to bats, CoV has been isolated from Malayan pangolin (*Manis javanica*) also known as Sunda pangolin or Javan pangolin, a mammalian species under the order *Pholidota* and the critically endangered species under the Red List of International Union for the Conservation of Nature (IUCN) **(Lam et al. 2020)**. Notably, the RBD region in the S protein of SARS-CoV-2/2019-nCoV was found closely related to that of Malayan pangolin-CoV **(Wong et al. 2020)**. This finding suggests the pangolin role as an intermediate host of ongoing CoV-2 epidemic **(Xiao et al. 2020)**. Further studies might be needed to approve this assumption fully. It is found throughout Southeast Asia, including Brunei, Cambodia, Java, Sumatra, Borneo, the Lesser Sunda Islands, Laos, Malaysia, Singapore, Thailand, Myanmar and Vietnam. It prefers forested habitats and plantations. The chances of spread of CoV-2 from pangolins are emphasized as the demand for pangolin's meat is high as well as the overlapping keratinized outer skin scales are having a value in TMC **(Liu et al. 2020b)**. These mammals, due to global demand, are most poached and trafficked mammals.

First-case of SARS-CoV-2 Human to animal transmission (Reverse Zoonoses)

Currently, the knowledge about the origin of this virus, its receptor binding motif in the host and its natural host are not known. Speculations suggest their origin to Bat-SARS-Like coronaviruses is still a point of the question. Few preliminary studies indicate that the recent SARS-CoV-2 is genetically similar to pangolin CoVs and a group of bat CoVs yet phylogenetic analysis failed to prove their ancestor directly from pangolin CoVs. A recent report also confirmed the transmission of SARS-CoV-2 to pet dog where the dog was found with mild respiratory illness symptoms of COVID-19 disease. Dogs are known to harbour Canine Respiratory coronaviruses (CRCoVs) which are responsible for severe respiratory problem dogs, and they fall in a different subgenus called *Embecovirus* (**Szczepanski et al. 2019**). CRCoVs are related to bovine coronavirus (BCoV) and human coronavirus-OC43 which are *Betacoronaviruses* (**Szczepanski et al. 2019**). They are further distinct to canine enteric coronavirus (CECoV), which are *Alphacoronaviruses,* and known for enteric infections in dogs. Phylogenetically, a bat origin isolates Bat-CoV-RaTG13 (Accession no. MN996532) was found closer to SARS-CoV-2 which may play as an intermediate host involved in the origin of this current outbreak strain (**Lv et al. 2020**).

Clinical picture and disease pathology

Because of the severity of COVID-19 infection, four types of infections are seen, including mild, moderate, severe, and critical. The COVID-19 infected patient exhibit clinical symptoms such as fever, dry cough, myalgia, fatigue, and diarrhoea (**Chen 2020; Huang et al. 2020**). A few of the sufferers also exhibit dyspnoea and lymphopenia. The expected incubation period of COVID-19 varies from 2-24 days. In complicated cases, acute cardiac injury and secondary infections also occur (**Huang et al. 2020**). The chest computed tomography (CT) show abnormal bilateral ground-glass opacity in the asymptomatic patients (**Huang et al. 2020**), while in severely ill patients bilateral multiple lobular and sub-segmental areas of consolidation are seen (**Huang et al. 2020**). The virological and clinical picture of the SARS-CoV-2 and COVID-19 is still not clear and under investigation. The COVID-19 pathology prominently is similar to SARS and MERS-CoVs infection (**Tian et al. 2020; Xu et al. 2020b**). The SARS-CoV-2 majority injury the lower respiratory tract and virus hits the epithelial cells leading to alveolar damage. It further affects other organs, including intestinal mucosa, kidney, brain, among others (**Luo et al. 2020; Xu et al. 2020b**). In later stages of COVID-19 infection, death noticed as of substantial alveolar damage and respiratory failure (**Tian et al. 2020**).

Virus Diagnosis

The COVID-19 diagnosis faces difficulty in the absence of apparent clinical symptoms, unusually at early stages of the infection where the laboratory findings and chest radiographic images fail to yield any conclusive idea of COVID-19 infection. However, the new sequence information from virus genome of SARS-CoV-2 aided in developing rapid point-of-care molecular tools such as real-time quantitative reverse transcription-polymerase chain reaction (RT-PCR) diagnostic tests specific for SARS-CoV-2 (2019-nCoV) and differentiates from other SARS-CoV and MERS-CoVs. Now the frequent laboratory confirmation of COVID-19 cases is based on either nucleic acid-based virus genome sequencing, RT-PCR, real-time PCR, real-time RT-PCR (rRT-qPCR), POCT/bedside testing, serological methods including Enzyme-linked immunoassay, and computed tomography technique (CT) imaging and X-Ray **(Corman et al. 2012; Dhama et al. 2020a; Huang et al. 2020; Xu et al. 2020a; Zhang et al. 2020a)**. A reverse transcriptional loop-mediated isothermal amplification (RT-LAMP) diagnostic tool has also been designed for rapid and colourimetric detection of SARS-CoV-2 **(Yu et al. 2020)**. An interactive web-based dashboard to track COVID-19 in real-time has also been developed **(Dong et al. 2020)**. The cumbersomeness and costly applications of genome-based sequencing methods have shown their limited use in identification of the pathogen.

On the other hand, nucleic acid amplification assays such as real-time PCR are targeting the spike (S), and nucleocapsid (N) genes are widely available. Several manufacturers have commercialized in the kit format for early and accurate detection of the SARS-CoV-2. However, the false positivity and cross-contamination amplifications come as a hurdle in these assays result confirmation. Recently, a fluorescence-based quantitative PCR assay was developed based on N and ORF1ab regions on the SARS-CoV-2 genome **(Wang et al. 2020)**. Among serological tests, ELISA is preferred because of higher sensitivity and detection limit for COVID-19 virus and takes a short time in providing results at low costs. Clinical samples suitable for COVID-19 diagnosis comprise of sputum, endotracheal aspirate, bronchoalveolar lavage, blood, serum, nasopharyngeal swabs and oropharyngeal swabs. Countries lacking diagnostic facilities need to follow up with proper laboratory shipping guidelines for transferring to WHO reference laboratories.

SARS-CoV-2/COVID-2019 vaccines and therapeutics

Since the reporting of the first case, several re-purposed medicines, including some traditional Chinese herbal medicines, have been evaluated for their anti-COVID-19 activity **(Dhama et al. 2020a)**. A few of the genetically targeted antiviral therapies, drugs, and

vaccines, including some engineered monoclonal antibodies would prove useful in combating the ongoing global threat **(Liu et al. 2020c; Moderna 2020; NIAID 2020; Shanmugaraj et al. 2020)**. Recent threats of epidemics and pandemics posed by Ebola, Zika, Nipah, and earlier ones of swine flu, avian flu, SARS-CoV-2, MERS-CoV have paved pace for developing an effective and advanced vaccine and therapeutics and drugs, and hopefully, soon we will have suitable vaccines and drugs to counter the present COVID-19 pandemic **(Dhama et al. 2012; Dhama 2013; Munjal et al. 2017; Dhama et al. 2018; Singh et al. 2019; Dhama et al. 2020a; Di Pierro et al. 2020; DST and Health Commission China 2020; Li et al. 2020a; Malik et al. 2020)**. Few of the initiatives to develop COVID vaccines include chimpanzee adenovirus vectored vaccine **(NIAID 2020)**. The vaccine being developed by Moderna Therapeutics is anticipated by the end of April 2020 **(Moderna 2020)**, and Kaiser Permanente Washington, Health Research Institute, intends to build vaccine in coming time **(LiveScience 2020)**.

Gilead Sciences (NASDAQ-GILD) is testing remdesivir against SARS CoV-2; Moderna (NASDAQ: MRNA) manufactured mRNA-based vaccine (mRNA-1273), which is under clinical trials. Inovio Pharmaceuticals (NASDAQ-INO) designing INO-4800 as a vaccine candidate. US President Donald Trump boosted significant pharmaceutical companies such as Johnson & Johnson (NYSE: JNJ), Sanofi (NASDAQ: SNY) and Pfizer (NYSE: PFE) to develop potent vaccines and effective drugs to counter COVID-19 **(Fool 2020)**.

Prevention and control

The past information based on tackling the SARS- and MERS- CoVs epidemics in 2002 and 2012 have been used instantly to combat the spread of the current pandemic due to the SARS-CoV-2/COVID-19. Additionally, the progress made in the field of disease diagnosis and vaccines development proved helpful in developing rapid and accurate diagnostics as well as effective vaccines **(Dhama et al. 2020a; Dhama et al. 2020b; Rodriguez-Morales et al. 2020a)**. The disease diagnostic kits are available in the market which differentiates between different types of the CoVs and the vaccines developed to counter COVID-19 infection is in the final stages of clinical trials. In networking mode, several countries have entered in collaboration making the vaccine on priority to safeguard the public. Like the virus, SARS-CoV-2 has spread across more than 125 countries, efforts have been initiated to control its further spread, and presently high efforts are being made and tackle the pandemic situation **(Gao 2020b; Guo et al. 2020; Wilder-Smith et al. 2020)** Therefore, worldwide countries have emphasised the strict vigilance of entry of travellers at tourism sites as well as their people using correction diagnostics, instant isolation and

quarantine of suspected patients, equipped with best medical facilities for handling any untoward situation **(Hellewell et al. 2020; Khan et al. 2020; Malik et al. 2020; Rodriguez-Morales et al. 2020c; Wilson and Chen 2020)**. Apart from large scale awareness programmes for the public have been initiated to educate the public on the COVID-19 associated disease health risks. Seeing the high socio-economic impacts and implications related to SARS-CoV-2 / COVID-19, various kind of advisories and preventive measures have been advised to avoid infection from this virus such as closing schools and offices for a while, preventing international tours and travels to the affected countries/regions, cancellation of visas, recommendations to public to stay at home in affected areas, along with designing and implementing appropriate strategies during pandemic to be implemented and challenges ahead **(Ayittey et al. 2020; Biscayart et al. 2020; CDC 2020; Cohen and Kupferschmidt 2020; Lai et al. 2020; WHO 2020)**.

Furthermore, there is a need to strengthen the medical infrastructure and human resources development in the medical arena. Strict compliance of the provided guidelines of Centres for Disease Control and Prevention (CDC) is a must. As the COVID-19 cases may lead to nosocomial infections in health-care workers, they must adopt all good hygiene and health practices while dealing with COVID-19 patient. The spread of the virus through contact must be blocked. The environmental surface cleaning with 70% ethanol or 0.5% sodium hypochlorite solutions are advised besides, personnel hygiene including hand hygiene and restricting touch of nose and face **(Dhama et al. 2020b; Rodriguez-Morales et al. 2020a).** With zoonotic links associated with the virus, effective implementation of One health approach may also play a crucial role in controlling the further spread of this pandemic virus **(Dhama et al. 2013; Bonilla-Aldana et al. 2020; OIE 2020; Rodriguez-Morales et al. 2020b)**.

Conclusion and prospects

Even the case fatality rate in the current COVID-19 epidemic is much lower than the previous human coronaviruses (SARS-CoV and MERS-CoV), on March 11, 2020, the SARS-CoV-2 affected 118326 humans and claimed 4292 deaths world over affecting 114 countries. Nevertheless, the latest reports from China shows effective containment of the spread of SARS-CoV-2 in the epicentre, Wuhan area, the COVID-19 cases are on surge globally. Majorly the spread has linked to travellers flying from affected areas. In India, the first case of COVID-19 was reported on January 30, 2020, with the entry of three students from Wuhan city and now within 42 days, the cases have surged to 73 (56 Indian nationals and 17 Foreign nationals) affecting 12 states/regions as on 12th March 2020. The restriction

has been enforced on all international air terminals and seaports with compliance of strict vigilance of persons. The diagnostics are available not only useful in detecting SARS-CoV-2 but also differentiates it from other human-CoVs. Promisingly, good signs have noticed on developments of anti-SARS-CoV-2 vaccine which possess the potential to combat emerging global threat effectively. The availability of SARS-CoV-2 genome sequences from different parts of global in the public domain has helped researchers to dig out important information on virus pathobiology and designing of virus-specific antivirals. However, until we get a practical approach to win over the COVID-19 infection, there is a need to rely on the available re-purposed drugs which are also found useful. The computational biology approaches might also show some right way to design virus-specific therapeutic shortly. The transmission routes play an essential role in the maintenance of the virus in humans. Although a few of the direct transmission routes have been suggested, including aerosol/contact, vertical transmission (mother to foetus) of SARS-CoV-2 needs further investigation. The observation of a mild-infection in the pet dog of a COVID-19 infected patient in Hong Kong has shown Human-to-animal transmission (zooanthroponotic) route but need further research to establish the finding. It is anticipated that near future will see an apparent triumph over the COVID-19 infection under the collective effort of virologists, clinicians, pharmacology and epidemiology researchers working globally in network mode.

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