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Emergence, Evolution and Economics of Coronaviruses

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ABSTRACT

Viruses are the most abundant biological entities on our planet. On the basis of parameters like capsid structure, morphology, genetic material, etc., they are classified into different families. The *Coronaviridae* family of viruses includes a diverse group of positive strand RNA viruses and a subset of these viruses infects humans. Though some of these human-infecting coronaviruses cause minor respiratory ailments in healthy adults but three of them are responsible for major pandemics of the 21st century. These pandemics claimed thousands to several hundred thousands of human lives and have plunged the regional economies and even the global economy into an abyss. This work highlights the current research on human coronaviruses involving their diversity, evolution, clinical, and zoonotic attributes. An economic impact analysis of major coronaviruses is also presented to point out how these pathogens have claimed billions of dollars.

Keywords: ACE-2 receptor, *Coronaviridae*, Coronaviruses, COVID-19, Evolution, MERS, SARS

INTRODUCTION

Viruses are sub-microscopic, infectious agents which require a living cell as a host for their replication. In most well-studied habitats, they significantly outnumber the cellular forms and infect all known cellular life forms (1). Origin of viruses is nothing less than a biological enigma. Though many hypotheses are proposed but none of them can individually explain the emergence of all viruses. As per the 'virus-first' hypothesis, viruses originated in primordial pool even before the origin of cellular forms (1,2). The two other hypotheses (Escape hypothesis and Reduction hypothesis), generally termed as 'cell-first' hypothesis, believe in the origin of cells prior to viruses (3,4).

Major families of RNA virus families having medical importance are shown in Table 1. Coronaviruses belong to the family *Coronaviridae*. These viruses are enveloped and have a single stranded RNA genome (positive strand). These genomes are made up of around 30,000 nucleotides. Human coronaviruses (HCoVs) can cause a range of health issues from minor complications like common colds to serious diseases like pneumonia, bronchitis, or bronchiolitis (5). Members of coronavirus family are solely responsible for three major pandemics recorded in the 21st century, namely Severe Acute Respiratory syndrome (SARS), Middle East Respiratory syndrome (MERS) (6), and Coronavirus Disease 2019 (COVID-19). Though certain researchers shy away from using the term 'pandemic' for SARS and MERS but as these outbreaks have infected people in multiple countries, it is accurate to term both of them as pandemics (7).

The aim of this review is multi-directional. First, it talks briefly about the diversity and evolution of coronaviruses. Second, it summarizes the information available on

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Table 1. Major families of RNA viruses having a medical impact.

Family (RNA viruses)	Examples
Picornaviridae	Poliovirus, Human Rhino virus, Hepatitis A virus
Caliciviridae	Hepatitis E virus
Flaviviridae	Yellow fever virus, Hepatitis C virus, Zika Virus, Dengue virus
Togaviridae	Rubella virus
Reoviridae	Reovirus, Human Rotavirus
Orthomyxoviridae	Influenza virus A, B, C
Paramyxoviridae	Mumps virus, Measles virus, Nipah Virus
Rhabdoviridae	Rabies virus
Bunyaviridae	Hantavirus
Coronaviridae	Human Coronaviruses
Arenaviridae	Lymphocytic choriomeningitis virus (LCMV)
Retroviridae	Human Immunodeficiency Virus (HIV)
Filoviridae	Marburg virus

HCoVs, especially taking into account the novel coronavirus. Finally, it tries to shed light on the impact that members of *Coronaviridae* have on humans both medically and economically. Though many reviews are available in this field (6,8-10), a broad review highlighting the economic and medical impacts of coronaviruses is not available, especially covering the COVID-19 pandemic and other aspects like CoVs infecting poultry animals.

DIVERSITY AND EVOLUTION

In animals, CoV was first reported in 1931 in chickens (11,12), whereas HCoVs were first reported in 1965 in patients having a common cold (13). Based upon the available genetic sequences, all human-infecting coronaviruses seem to have animal origins (Table 2). This observation highlights the zoonotic attribute of these viruses. *Coronoviridae* family involves a sub-family *Coronavirinae*, which has four major genera, namely *Alphacoronavirus, Betacoronavirus, Gammacoronavirus*, and *Deltacoronavirus*. The former two exclusively infect mammals, especially bats, whereas the latter two mainly infect birds. Yet some can have mammalian hosts as well (14).

Coronaviruses seem to be the viruses of ancient lineage. The time of the most recent common ancestor (tMRCA) for the four above mentioned genera was reported to be 10,100 years (14). However, another study (15) questioned this time estimation of tMRCA as it contradicted with the co-evolution hypothesis of coronaviruses and natural hosts (bats/birds). Using tMRCA extrapolation methodology, they concluded that the last tMR-

Table 2. CoVs which infect humans or have a major impact on agriculture. *possible natural hosts of origin.

HCoVs	Origin	Genus	Reference
HCoV-229E	Bats	*Alphacoronavirus*	(9,23)
HCoV-OC43	Rodents*	*Betacoronavirus*	(9-10)
HCoV-HKU1	Rodents*	*Betacoronavirus*	(9-10)
HCoV-NL63	Bats	*Alphacoronavirus*	(9, 23)
SARS-CoV	Bats	*Betacoronavirus*	(8, 40)
MERS-CoV	Bats	*Betacoronavirus*	(9, 48)
SARS-CoV-2	Bats	*Betacoronavirus*	(18)
Animal CoVs	**Origin**	**Genus**	**Reference**
PEDV	Bats	*Alphacoronavirus*	(16)
PDCoV	Avian*	*Deltacoronavirus*	(100,101)
SADS-CoV	Bats	*Alphacoronavirus*	(102)
IBV	Avian*	*Gammacoronavirus*	(14)

(HCoV: Human Coronavirus, SARS: Severe Acute Respiratory Syndrome, MERS: Middle East Respiratory Syndrome, PEDV: Porcine Epidemic Diarrhoea Virus, PDCoV: Porcine Delta Coronavirus, SADS-CoV: Swine Acute Diarrhoea Syndrome Coronavirus, IBV: Avian Infectious Bronchitis Virus)

CA for these four genera would at least be around 55.8 million years, but as per them (15) it is highly possible that these genera separated 300 million years ago, which allowed the co-evolution of viruses and hosts (9,15).

Many studies (8-9,14,16-18) have analysed the genomes of coronaviruses to understand the origin, genetic recombination, and molecular evolution of these viruses. A study proposed a model for diversification and cross-transmission of these viruses. As per them (14), there exists a huge diversity of bat CoVs in *Alphacoronavirus* and *Betacoronavirus* but not in the rest two genera. Similarly, a huge diversity of bird CoVs is found in *Gammacoronavirus* and *Deltacoronavirus,* but not in the previous two genera, hence pointing bats and birds as gene sources for *Alpha-Betacoronavirus* and *Gamma-Deltacoronavirus* respectively (Figure 1) (14).

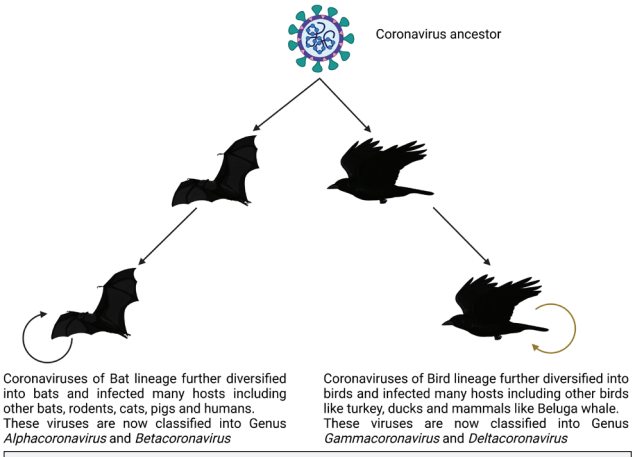

Figure 1. Diversification and cross-transmission of coronaviruses ("created with BioRender.com")

After having jumped between species of bats and given rise to *Alpha-Beta* coronaviruses, bat lineage CoV further jumped to other mammalian species, including species of other bats, pigs, giraffes, rats, and humans, and each jump to different species evolved dichotomously. Similarly, the bird lineage CoV jumped to other species of birds, generating *Gamma-Delta* coronaviruses, which further jumped to other birds and occasionally entered certain mammalian species like beluga whale or pigs, and, like bat lineage CoV, each jumping event evolved dichotomously (8-9,14). Estimated time and region of emergence of HCoVs are shown in Table 3.

HUMAN CoVs

There are seven members of the corona family which are known to infect humans. Four of them cause relatively minor ailments whereas three of them became medical emergencies either in specific regions of the world or even globally as described below.

HCoV-229E

HCoV-229E was first isolated from medical students having respiratory illness who were enrolled in University of Chicago (19). Adults infected with the virus showed common cold-like symptoms (20). However, nosocomial viral respiratory infections among high-risk infants are also linked with it (21). In a recent study, this virus has been detected in infection of lower respiratory tract in an adult individual having acute respiratory distress syndrome with no co-morbidities (22). It appears that HCoV-229E has different clinical manifestations in different patients and the reason for these different manifestations is still not clear.

It is speculated that this virus originated in bats, which might be the primary host, as sequences closely related to this virus were found in a study in bats in Kenya (23). HCoV-229E related

Table 3. Time and area of emergence of Human CoVs.

HCoVs	Estimated time of emergence (year)	Area of origin or first report	Reference
HCoV-229E	~220-330 years ago (1686-1800)	Isolated from students of Chicago University	(19, 103)
HCoV-OC43	~130 years ago (1890s)	Isolated in viral diseases lab. in Maryland, USA	(33, 36)
HCoV-HKU1	~70 years ago (1950s)	Isolated in Hong Kong in late 2004	(39, 104)
HCoV-NL63	~563-822 years ago	Isolated from a 7-month old in the Netherlands	(27, 105)
SARS-CoV	~20 years ago (4 years before outbreak)	Originated in the Guangdong province of China	(42, 106)
	~35 years ago (17 years before outbreak)		(107)
MERS-CoV	~10 years ago (2010)	Originated in Arabian Peninsula	(42, 108)
SARS-CoV-2	Not defined	First reported in Wuhan city of China	(62)

(HCoV: Human Coronavirus, SARS: Severe Acute Respiratory Syndrome, MERS: Middle East Respiratory Syndrome)

viruses have been isolated from dromedaries where anti-HCoV-229E antibodies from human sera are found to neutralise dromedary-derived virus *in-vitro* (24). A potential role of camels in transmission of this virus to humans can be hence speculated. This role of camels can be of very high significance as they have been an important link in the chain of transmission of MERS-CoV from dromedaries to humans, which is discussed ahead (25).

HCoV-229E uses human aminopeptidase N as its receptor, which is a cell surface metalloprotease present on epithelial cells of lung, kidney, and intestine (26). After infecting an individual, this virus, like others, replicates and gets transmitted to other individuals. Transmission between individuals occurs via respiratory droplets or coming in contact with contaminated objects (20,21).

HCoV-NL63

HCoV-NL63 was first isolated from a seven-month old child suffering from bronchiolitis in the Netherlands (27). This virus is associated with respiratory tract illnesses involving both the upper and lower respiratory tract (28). The virus mostly affects the young children, adults, and immune-compromised individuals (29), and its symptoms involve fever, rash, bronchiolitis, bronchitis, sore throat, congestion, and malaise (30).

It has been demonstrated that HCoV-NL63 is a recombinant between viruses similar to NL63 circulating in *Triaenops* bats and 229E like viruses circulating in *Hipposideros* bats (23). The bats might be the primary hosts; however, the intermediate host remains unidentified (31). HCoV-NL63 uses angiotensin-converting enzyme 2 (ACE2) as its receptor for cellular entry (32). The mode of transmission is the same as that of HCoV-229E.

HCoV-OC43

HCoV-OC43 was first isolated in laboratory of viral diseases in Maryland (33). Infected individuals demonstrate common cold-like symptoms (34). This virus is majorly involved in upper respiratory tract infections. However, in cases of children and individuals co-infected with other respiratory viruses, lower respiratory tract infections are common (35).

Rodents are speculated to be the natural or primary host of this virus (9-10), whereas a recent zoonotic transmission is suggested which involved bovines (36), suggesting that bovines are its intermediate hosts.

The protein receptor for the virus still remains unknown, but N-acetyl-9-O-acetylneuraminic acid is identified as the receptor determinant (37). OC43 utilises endocytic route for entry inside the cells and this entry is caveolin-1 dependent. After entering the cell via caveolae, the virus is transported through actin cytoskeleton. There are also other entry pathways to the cells; however, they do not lead to productive infection (38).

HCoV-HKU1

HCoV-HKU1 was isolated in late 2004 in Hong Kong (39). Similar to the three previously described HCoVs, this virus leads to common cold-like symptoms. As compared to other HCoVs, relatively less information is available about this virus. Like HCoV-OC43, rodents are speculated to be its primary host; however, the intermediate host still remains elusive (10,31). Though the protein receptor is still not identified but O-acetylated sialic acid is identified as a receptor determinant (37,39).

SARS-CoV

SARS-CoV emerged about 20 to 35 years ago in the Guangdong province of China (Table 3). SARS-CoV is responsible for the first pandemic of the 21st century, which broke out at the end of February 2003, though no outbreak or transmission has been reported since May 2004 (40). This virus causes SARS, which is characterized by severe pneumonia and diffuse alveolar damage (41-43).

SARS-CoV originated in horseshoe bats by recombination events in SARS related CoVs (41). A study proposed that after its origin, SARS-CoV was transmitted to farmed civet (or another mammal), which got transmitted to other civets (intermediary host) by oral-fecal mode of transmission. These 'virus-carrying' civets were then transported to Guangdong market, leading to the spread of the virus there. The virus acquired more mutations and finally spilled over to humans (10). The mode of transmission from animals to humans remains mysterious; however, contacts with intermediary host in the form of uncooked meat or urine are some of the main suppositions. Respiratory secretions, like droplets, can transmit this virus by direct person to person contact (42).

Upon exposure to the host, the virus binds to the virus receptors, expressed by the target cells (43). ACE2 is the main functional receptor for SARS-CoV (44), whereas it also binds to an alternative receptor, CD209L, but with a greatly reduced affinity (44). ACE2 is widely distributed in respiratory tract epithelium, alveolar monocytes, and macrophages, whereas CD209L is expressed in human type II alveolar cells and endothelial cells (42,45). The virus infects these target cells and multiplies. ACE2 is a surface receptor which provides the virus with an advantage of infecting diverse range of cells. As ACE2 is also expressed in arterial and venous endothelia, arterial smooth muscle, cells of small intestine, cerebral neurons, epithelial cells of the distal renal tubules (46). Hence, virus can infect all these cells.

Atypical pneumonia sets in along with respiratory deterioration, which can lead to respiratory failure. These virus particles can be found in urine, faeces and sweat as the virus has the potential to infect kidneys, intestines, and sweat glands, thereby providing the virus with additional means of spreading along with the respiratory droplets (46,47). A total of 27 nations (including Russian Federation and Taiwan) and two administrative regions of China (Macao and Hong Kong) were affected by SARS-CoV. In total, 8096 individuals were infected, out of which 774 died, leading to a high mortality rate of 9.60% (48).

MERS-CoV

MERS-CoV possibly emerged around 2010 in the Arabian Peninsula (Table 3). The second pandemic of this century is attributed to MERS-CoV. This virus leads to life-threatening MERS disease,

which first broke out in 2012 in Saudi Arabia. Certain cases are reported every year highlighting the fact that virus still remains in circulation (49). MERS-CoV can lead to highly lethal pneumonia and renal dysfunction, though certain individuals infected with it might remain asymptomatic (50).

MERS related CoVs (MERSr-CoVs) have been reported in 14 species of bats, but as the S protein of these MERSr-CoVs is significantly different from MERS-CoV, none of these can be identified as a direct progenitor of MERS-CoV (51,52). Emergence of this virus involved an exchange(s) of genetic elements between different viral ancestors which might have taken place either in bat ancestors or dromedaries (intermediate hosts) which acted as 'mixing vessels' for viruses thriving in different hosts (51,53). All the known MERSr-CoVs bat strains, though, suggest that MERS-CoV originated in bats. But as there exists a phylogenetic gap between MERSr-CoVs and MERS-CoV isolated from humans and camels, some 'yet-to-be identified' viruses must be present in the environment, which led to emergence of MERS-CoV of human and camels (10).

As in the case of SARS, the animal to human mode of transmission could not be fully understood even for MERS. Customs involving consuming uncooked meat, milk and urine might have led to animal to human transfers (43). However, human to human transmission is reported. Reports suggest that unless there is a close contact between two persons, like a healthcare worker providing unprotected care to patient, the virus does not easily pass (54,55). "Simple proximity" and "casual contact" are not generally associated with MERS transmission, but close contact like sharing or sleeping in the room of infected patient or direct patient contact increases this risk (56). Many of the MERS infections were nosocomial in nature (57,58). Further, a study found that the spread of virus by an asymptomatic individual is highly unlikely. However, the study itself calls for more data collection to reach a definitive conclusion (59).

The virus receptor in the case of MERS is dipeptidyl peptidase 4 (DPP4, alternatively known as CD 26), a multi-functional surface protein of cell (Table 4), which is expressed in lower respiratory tract in humans including type-1 and 2 alveolar cells of lung parenchyma, endothelial cells, and macrophages, whereas the expression in nasal cavity and conducting airways is weak and scattered (60,61). On the contrary, in the case of camels, this receptor is expressed in the upper respiratory tract (61).

DPP4 is also expressed on endothelium of venules as well as in the venous part of capillary bed. It is also expressed in kidney cortex, small intestine (especially ileum) and prostate gland (62). Further, what makes MERS-CoV more dangerous is its ability to efficiently infect the T cells in peripheral blood as well as the T cells of lymphoid organs like tonsils and spleen. The virus induces both intrinsic and extrinsic pathways of apoptosis in T cells leading to its death (63). As a result of virus receptor expression, MERS-CoV leads to pneumonia and renal dysfunction as well as immune system deregulation, which gives rise to a life threatening situation requiring immediate medical care. Owing to the receptor distribution, it is possible that along with respiratory droplets, virus particles may also be found in the urine, stool, and semen of an infected individual. As on 8th May, 2022, a total of 2494 MERS cases have been reported from 27 countries out of which 858 people died, leading to a high mortality rate of 34.40% (64).

SARS-CoV-2

SARS-CoV-2 virus is responsible for the latest pandemic of the 21st century to date. It has brought the human civilisation at a partial halt. Humans are discouraged or even blocked from gathering outside or travelling. Partial or complete lockdowns are in force in many places. Owing to the possibility of more infection waves, it is a great emerging threat for most countries (65).

SARS-CoV-2 was first reported in Wuhan, China in December 2019. As this is an emerging virus, relatively little is known about it. Similar to SARS-CoV, SARS-CoV-2 has 29903 nucleotides in its RNA genome (GenBank: NC_045512.2). This virus causes COVID-19 in humans, and its clinical manifestations range from mild pneumonia to respiratory failure, septic shock, and multiple organ dysfunction (66).

Table 4. Cellular receptors of Human CoVs.

HCoV	Receptor on human cells
HCoV-229E	Aminopeptidase N (AP-N)
HCoV-OC43	Unknown; N-acetyl-9-O-acetylneuraminic acid (receptor determinant)
HCoV-HKU1	Unknown; O-acetylated sialic acid (receptor determinant)
HCoV-NL63	Angiotensin-converting enzyme 2 (ACE2)
SARS-CoV	Angiotensin-converting enzyme 2 (ACE2); CD209L (another receptor with reduced affinity)
MERS-CoV	Dipeptidyl peptidase 4 (DPP4, also known as CD 26)
SARS-CoV-2	Angiotensin-converting enzyme 2 (ACE2)

(HCoV: Human Coronavirus, SARS: Severe Acute Respiratory Syndrome, MERS: Middle East Respiratory Syndrome)

SARS-CoV-2 has about 80% sequence similarity with SARS-CoV and is more than 96% similar to that of bat CoVs RaTG13 and BANAL-52 on whole genome level, suggesting bats to be its natural hosts (18,67,68). Another study showed that Malayan Pangolins associated CoVs have 85.5 to 92.4% similarity to SARS-CoV-2, suggesting these to be the intermediate host (69,70). Other studies have also suggested snakes and turtles as intermediate hosts (71,72), but this possibility has been ruled out by another study which advocates for screening of rodents and bovine animals as potential intermediate hosts (73). Owing to its recent emergence, little is known about animal to human transfer of the virus, but WHO recommends to avoid eating raw or uncooked animal products.

Human to human transmission through droplets, formites and contaminated frozen meat and seafood is widely documented (74). In contrast to what was observed for MERS-CoV, asymptomatic individuals infected from SARS-CoV-2 have a high potential to transmit the virus to healthy individuals (75,76). Interestingly, human to animal transmissions of SARS-CoV-2 are reported. A tigress in the Bronx Zoo in New York appears to be the first such case where it has tested positive for COVID-19, and it seems that she acquired the infection from an asymptomatic care taker. A study carried out in this regard showed that cats are highly susceptible to this air born infection (77). Human to animal transmissions have also been reported in dogs, cats, minks, lions, and puma (78).

SARS-CoV-2, like SARS-CoV, uses ACE2 as the virus receptor (67) as a result of which all the cellular types (expressing ACE2), which were susceptible to SARS-CoV infection, can be infected by SARS-CoV-2 as well. Though COVID-19 might only cause flu-like symptoms in some individuals but in critical cases, it can lead to respiratory distress, respiratory failure, multiple organ dysfunction, and multiple organ failure, which may finally lead to death. The virus can be detected in oral and anal swabs as well as the blood of the patients indicating the presence of multiple shedding routes (79).

As on 8th May, 2022, 226 countries and territories of the world have been affected by SARS-CoV-2. A total of 517,095,499 cases have been reported worldwide, out of which 6,276,097 individuals have died of the disease and 471,780,006 individuals have recovered with the rest being currently infected (Table 5). This brings the mortality to 1.21% (80). However, this percentage will change depending upon the reports of new cases and the death of currently infected individuals who are in critical state.

Various pharmaceutical companies distributed worldwide have been working hard for development, trials and safety assessment and mass production of Covid-19 vaccines. About 300 vaccine projects are in development with a significant number of them under trials (81). Regulatory bodies of many countries have now approved few vaccines for mass administration like Covaxin, Covishield, Sputnik V, CoronaVac, and others.

ECONOMIC IMPACT OF CoVs

Members of coronavirus family have made a huge dent in regional as well as global economies. A standardised system or a set of rules/guidelines to calculate the projected or actual economic loss incurred as result of an epidemic or a pandemic is not available. Hence, an array of parameters and methodologies are used by different economists in different studies to reach a figure. Here, we try to give a sense of the economic losses that nations incurred due to these minute pathogenic 'creatures'.

Human CoVs

The four HCoVs (namely 229E, OC43, NL63, HKU1) are not life-threatening, and once they infect the host, the symptoms are very much similar to common colds along with fever, cough, headache, and sore throat (8). Owing to such clinical presentations, the economic impact of these CoVs in terms of providing medical support and health care is relatively miniscule. On the other hand, the rest three HCoVs caused global pandemics of varying severity and hence led to massive economic losses (82-85).

The SARS outbreak initiated in Guangdong and as a result of it, the major economic blow was faced by China and Hong Kong. Other countries also bear the burnt; however, the impact was relatively less. The global macroeconomic impact of SARS was estimated at USD 3-10 million per case (USD 30-100 billion in total). 1% of Chinese GDP declined as an outcome of SARS (82). However, in Hong Kong, the impact of SARS on tourism, travel, and consumption was short-lived, and as soon as the outbreak came under control, the panic and fear subsided quickly (83).

Table 5. Description of HCoVs that caused pandemics. (A: Animal, H: Human, '}' shows transmission direction).

HCoV	Disease	Mode of transmission	Cases reported (as on 8th May, 2022)	Mortality (as on 8th May, 2022)
SARS-CoV	SARS	A} H H} H	8,096	09.60%
MERS-CoV	MERS	A} H H} H	2,494	34.40%
SARS-CoV-2	COVID-19	A} H H} H H} A	517,095,499	01.21%

(SARS: Severe Acute Respiratory Syndrome, MERS: Middle East Respiratory Syndrome)

In the case of MERS, the average cost of managing each MERS case in the Saudi Arabia's hospital was around USD 12,947.03 ± 19,923.14 (84). The major industrial sectors of the Republic of Korea faced a loss of USD 3.61 billion (85).

SARS-CoV-2, which is still emerging as a medical and economic emergency, has led to a global economic crisis. As it is an emerging virus, it is extremely difficult to assess the size of the final impression it will leave on global economy, not to mention its adverse effects on different cultures and society. Some initial figures of this pandemic are dismaying. COVID-19 has the potential to bring a global recession and plunge world economies into a chasm (86). As this virus seems to be highly contagious, has led to hospitalization in many cases and has created a fear among the masses, most nations are either facing a partial or complete lockdown or some other form of restrictions to avoid the spread and to avert an exponential burden on the health care machinery.

As a result, sectors like manufacturing and sales, hospitality and tourism, entertainment and others are shut at various levels. A sector wise impact analysis of COVID-19 has been done in a recent study (87). Poor and under developed nations, which lack basic medical facilities, are badly hit. The International Monetary Fund has said that the cumulative loss of COVID-19 pandemic will range around USD 9 trillion. This figure is greater than the sum of economies of Japan and Germany (88).

ANIMAL CoVs

Porcine Epidemic Diarrhoea Virus (PEDV)

The PEDV outbreak was first reported in the 1970s in Europe and since then, sporadic occurrences have been observed in many countries including major ones in China (2010) and the USA (2015). PEDV is responsible for causing lethal diarrhoea in pigs at neonatal stage whereas weight reduction is observed in hogs (89). In suckling piglets in China, a death rate of 80-100% was reported (90). PEDV led to a decrease of USD 900 million to USD 1.8 billion for the U.S. economic welfare. Similarly, there was an annual reduction in income of pork packers, and as a result of declined supply, pork consumers not only had to pay more for limited supply of pork, but also for other meats as well, as prices strengthened due to PEDV (91).

Porcine Delta Coronavirus (PDCoV)

PDCoV was first detected in Hong Kong in 2012 and since then, it has reached Canada, the USA, Laos, Vietnam, Thailand, South Korea, and China. Though the clinical severity is less than PEDV, it still causes serious diseases (89). It causes vomiting, dehydration and diarrhoea in neonatal piglets which can be lethal and has a 40% mortality rate (92). The economic impacts are somewhat similar to that of PEDV albeit low in nature owing to its low mortality rate. However, as it is a new and emerging virus, more studies are required to exactly estimate the economic losses happening as a result of it.

Apart from these two porcine coronaviruses, there are many more porcine coronaviruses, like Transmissible gastroenteritis virus (TGEV), porcine respiratory coronavirus (PRCoV), porcine hemagglutinating encephalomyelitis virus (HEV), and swine acute diarrhoea syndrome (SADS-CoV), and they have a huge impact on agricultural returns.

Avian Infectious Bronchitis Virus (IBV)

IBV mainly causes a respiratory infection in chickens, but it can have multiple clinical infestations including reproductive disease, and nephritis along with respiratory disorders. IBV was first reported in the 1930s, but all countries having intensive poultry industries are affected by it. Though a morbidity of 100% is reported but mortality is around 20-30% and almost always occur as a result of co-infection with a bacterium or mycoplasma (93). As a result of morbidity and mortality, agricultural economy is significantly impacted. A study conducted in Brazil with breeders and broilers showed that with breeders of about 6 months of age, a total loss of USD 3567.40 per 1000 birds was incurred. The same statistic became USD 4210.80 per 1000 birds in 10 months old breeders, showing an increase in loss with increased age of birds. In the case of 48 days old broilers, the loss per 1000 birds was estimated at USD 266.30 (94).

Turkey Coronavirus (TCoV)

Another coronavirus which infects turkeys is commonly known as TCoV. It causes severe diarrhoea in young turkey poults. Though a direct estimate of economic loss from TCoV couldn't be found but a high field-prevalence ranging between 60-74% among different turkey classes like meat turkeys and breeders was reported (95).

CoVs are also reported from other animals used in agriculture like Pheasant CoV, Duck CoV, Goose CoV, and Pigeon CoV. Though it seems impossible to estimate all the economic losses which occur as a result of CoVs, but the examples cited above give a clear picture about how badly these CoVs impact economies and hence warrant extensive research to prevent human lives, animal lives as well as the agriculture industry.

CURRENT STATUS AND FUTURE PROSPECTS

HCoVs like 229E, OC43, NL63, HKU1 never lead to life-threatening manifestations alone, whereas SARS-CoV, MERS-CoV and SARS-CoV-2 not only threaten life but also have serious economic manifestations. However, infections with the former CoVs can be fatal if patients have low haemoglobin concentration, serum albumin levels or other such issues (96). Similarly, infants, immune-compromised individuals, and people with co-morbidities or those in old age are at high risk of developing serious clinical manifestations if infected with the former four HCoVs (22,29).

Three of these seven HCoVs, namely HCoV-NL63, SARS-CoV, and SARS-CoV-2 use similar receptor-ACE2; however, not only do these viruses have different infection potential, but the mortality rates are also very different (Tables 4 and 5). Mortality with NL63 is rarely reported, SARS-CoV has about 10% mortality, whereas around 1.21% mortality is currently observed for SARS-CoV-2. Similarly, the number of infected individuals also

varies greatly, where SARS-CoV infected about 8100 individuals, SARS-CoV-2 has globally infected 517.10 million people as on 8th May, 2022 (Table 5). This indicates that mere use of the similar receptor doesn't define the capacity or severity of infection and mortality rates. Possible factors for these observed differences probably involve varying demographic structures as mortality is skewed towards older people (97), prevalent climatic conditions, population density, and access to medical care among many.

All the three diseases i.e. SARS, MERS, and COVID-19 can be lethal; however, the contagiousness of all the three viruses seems to be different. The SARS-CoV-2 seems to be highly contagious (98), whereas MERS-CoV requires a close contact between the infected and healthy person to get transmitted (54, 58). Further, transmission of SARS-CoV-2 is reported from asymptomatic individual, which is not the case in the case of MERS (59,75,76).

It is possible that the absence of MERS-CoV receptor, DPP4, in the upper respiratory tract of humans (60,61) is a major reason for this restricted human to human contact, hence requiring close proximity for transmission. As MERS had a high mortality rate (35%), one cannot even imagine the kind of calamity the human civilisation would have faced if MERS-CoV could have transmission rates as that of SARS-CoV-2 and if it could have been transmitted by asymptomatic individuals. On the contrary, it is also possible that SARS-CoV-2 has a high transmission rate as it has a relatively low mortality rate and it causes milder symptoms.

Acts like consumption of raw meat and sea food, wild life trade not only give a chance to newly evolved viruses to spill over but also brings these viruses in close contact with humans and other animals, which can lead to calamities as evident in the case of SARS-CoV-2. Live animals were on sale in Huanan seafood wholesale market in China, from where SARS-CoV-2 seems to have reached humans (74). Owing to the rich diversity of coronaviruses in bats and presence of wet markets in Asian countries, evolution and spillover of a more deadly virus than SARS-CoV-2 cannot be denied.

A high diversity of SARS and MERS related coronaviruses exists in primary and intermediate hosts (41,99), as a result of which evolution and emergence of new coronaviruses are very much possible in the near future. One study (6) showed that there existed a high probability of emergence of a SARS- and MERS-CoV like coronavirus in China itself, and in less than a year, it became true. It is of utmost importance to fill the phylogenetic gaps among the evolutionary stages of coronaviruses which will help in understanding the dynamics between primary and intermediate hosts, further helping in preventing the transmission of newly evolved coronaviruses in the future.

The COVID-19 crisis highlights the need for every country to fund research institutions as well as the need for scientific temperament among the masses. Similarly, it also emphasises the need for robust healthcare and pharmaceutical sectors along with equipping the medical staff, even in remote areas, to deal with highly contagious infectious agents.

CONCLUSION

Coronaviruses are the viruses of ancient lineage. Though the tMRCA is debated, it is highly possible that it originated about 300 million years ago and diversified further. HCoV infections manifest in a variety of ways, ranging from common cold-like symptoms in some cases to life-threatening concerns with others despite the fact that many of these HCoVs use the same receptors and infect the same cell types.

The primary and intermediary hosts play an extremely crucial role in virus propagation because they help the viruses to 'jump' between different species. Owing to this zoonotic potential of these viruses, more research is needed to understand the dynamics among the hosts as well as the urgency to fill the phylogenetic gaps which can allow to break the transmission chain of coronaviruses among humans in the future. The ramifications of HCoV propagation also call for an urgent regulation of wet markets in order to avoid further spill over of deadly viruses.

The economic impact of both HCoVs and animal CoVs is daunting. Not only do the animal CoVs have an impact on the agricultural aspects, but also the economic shutdown, especially due to SARS-CoV-2, will have far reaching consequences. COVID-19 forced countries to go into lockdown, causing various sectors such as tourism, sales, entertainment, manufacturing, and other businesses to suffer. The GDP growth of many major economies is projected to be negative. All these have been happening because of a sub-microscopic RNA particle enclosed in an envelope, demonstrating the need of allocation of bigger chunks of GDP to education, research, and healthcare.

As the emergence of new viruses is inevitable, human civilisation must learn from the current crisis not only to prevent deaths, but also to take care of the economy.

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