REVIEW ARTICLE

Introduction to COVID-19, History, Impact, Symptoms and Prevention

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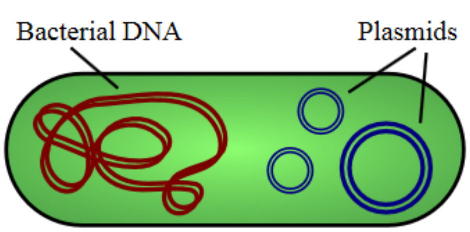
ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic continues to unfold. The situation varies greatly from country to country. COVID-19 pandemic has caused unprecedented human health and economic consequences. Almost all countries have been affected1. The spread of this novel virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues relentlessly. COVID-19 pandemic, and previous pandemics during this millennium, have demonstrated that the current state of global preparedness is inadequate for an effective response and to prevent local outbreaks from becoming international health emergencies. It is essential to strengthen biomedical research, improve healthcare delivery system, establish a permanent 'watch-dog' body and create an improved communication and coordination mechanism for the diverse agencies responsible for mitigating the broader adverse consequences of pandemics.
Keywords: COVID-19, SARS, Virology, Symptoms

INTRODUCTION

Viruses are a type of non-cellular infectious pathogen that replicates only inside the living cells of an organism. A **virus** is a tiny infectious agent that reproduces inside the cells of living hosts. When infected, the host cell is forced to rapidly produce thousands of identical copies of the original virus. Unlike most living things, viruses do not have cells that divide; new viruses assemble in the infected host cell. But unlike simpler infectious agents like prions (**Prions** are misfolded proteins with the ability to transmit their misfolded shape onto normal variants of the same protein. They characterize several fatal and transmissible neurodegenerative diseases in humans and many other animals). The origin of viruses is unclear; some may have evolved from plasmids (pieces of DNA that can move between cells), while others may have evolved from bacteria1.

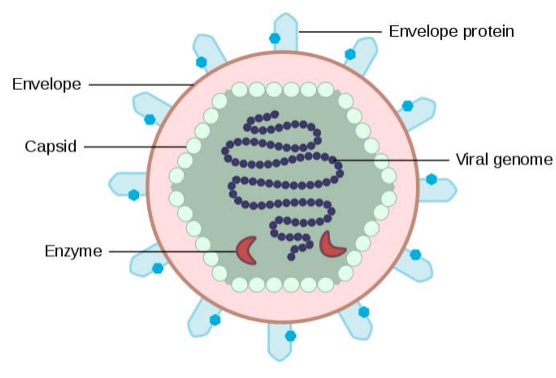
Fig. 1: Illustration of a bacterium showing chromosomal DNA and plasmids [(1)]



Viruses are made of either two or three parts. All include genes. These genes contain the encoded biological information of the virus and are built from either DNA or RNA. All viruses are also covered with a protein coat to protect the genes. Some viruses may also have an envelope of fat-like substance that covers the protein coat, and makes them vulnerable to soap. A virus with this "viral envelope" uses it along with specific receptors to enter a new host cell. Viruses vary in shape from the simple helical and icosahedral to more complex structures. Viruses range in size from 20 to 300 nanometers; it would take 33,000 to 500,000 of them, side by side, to stretch to 1 centimeter (0.4 in). Viruses spread in many ways and are very specific about which host species or tissue they attack, each species of virus relies on a particular method to copy itself.

Viruses such as influenza are spread through the air by droplets of moisture when people cough or sneeze. Viruses such as norovirus are transmitted by the faecal-oral route, which involves the contamination of hands, food and water. Rotavirus is often spread by direct contact with infected children. The human immunodeficiency virus, HIV, is transmitted by bodily fluids transferred during sex. Others, such as the dengue virus, are spread by blood-sucking insects. Figure 2 shows a general diagram of the virus[2].

Fig. 2: Simplified diagram of the structure of a virus [2]



Classification of viruses: Viruses are classified on the basis of morphology, chemical composition, and mode of replication. The viruses that infect humans are currently grouped into 21 families, reflecting only a small part of the spectrum of the multitude of different viruses whose host ranges extend from vertebrates to protozoa and from plants and fungi to bacteria.

In general, four characteristics were to be used for the classification of all viruses:

- Type of the nucleic acid including size of the genome, strandedness (single or double), linear or circular, positive or negative (sense), segments (number and size), sequence and G+C content etc.

- Symmetry of the protein shell
- Presence or absence of a lipid membrane
- Dimensions or the size of the virion and capsid

Other properties include the physicochemical properties including molecular mass, pH, thermal stability, susceptibility to chemicals and physical extremes and to ether and detergents. Table 1 describes some of the medically important viruses[8].

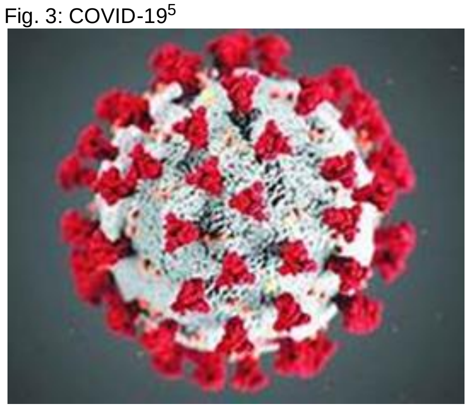
Table 1: Classification of viruses [(3)]

Properties	Viral Family	Size	Example
single-stranded DNA; naked; polyhedral capsid	Parvoviridae	18-25 nm	parvoviruses (roseola, fetal death, gastroenteritis; some depend on coinfection with adenoviruses)
double-stranded, DNA; naked; polyhedral capsid	Papovaviridae; circular dsDNA	40-57 nm	human papilloma viruses (HPV; benign warts and genital warts; genital and rectal cancers)
	Adenoviridae; dsDNA	70-90 nm	adenoviruses (respiratory infections, gastroenteritis, infectious pinkeye, rashes, meningoencephalitis)
double-stranded, circular DNA; enveloped; complex	Poxviridae	200-350 nm	smallpox virus (smallpox), vaccinia virus (cowpox), molluscipox virus (molluscum contagiosum-wartlike skin lesions)
double-stranded DNA; enveloped; polyhedral capsid	Herpesviridae	150-200 nm	herpes simplex 1 virus (HSV-1; most oral herpes; herpes simplex 2 virus (HSV-2; most genital herpes), herpes simplex 6 virus (HSV-6; roseola), varicella-zoster virus (VZV; chickenpox and shingles), Epstein-Barr virus (EBV; infectious mononucleosis and lymphomas), cytomegalovirus (CMV; birth defects and infections of a variety of body systems in immunosuppressed individuals)
	Hepadnaviridae	42 nm	hepatitis B virus (HBV; hepatitis B and liver cancer)
(+)single-stranded RNA; naked; polyhedral capsid	picornaviridae	28-30 nm	enteroviruses (poliomyelitis), rhinoviruses (most frequent cause of the common cold), Noroviruses (gastroenteritis), echoviruses (meningitis), hepatitis A virus (HAV; hepatitis A)
(+)single-stranded RNA; enveloped; usually a polyhedral capsid	Togaviridae	60-70 nm	arboviruses (eastern equine encephalitis, western equine encephalitis), rubella virus (German measles)
	Flaviviridae	40-50 nm	flaviviruses (yellow fever, dengue fever, St. Louis encephalitis), hepatitis C virus (HCV; hepatitis C)
	Coronaviridae	80-160 nm	coronaviruses (upper respiratory infections and the common cold; SARS)
(-)single-stranded RNA; enveloped; pleomorphic	Rhabdoviridae; bullet-shaped	70-189 nm	rabies virus (rabies)
	Filoviridae; long and filamentous	80-14,000 nm	Ebola virus, Marburg virus (hemorrhagic fevers)
	Paramyxoviridae; pleomorphic	150-300 nm	paramyxoviruses (parainfluenza, mumps); measles virus (measles)
(-) strand; multiple strands of RNA; enveloped	Orthomyxoviridae	80-200 nm	influenza viruses A, B, and C (influenza)
	Bunyaviridae	90-120 nm	California encephalitis virus (encephalitis); hantaviruses (Hantavirus pulmonary syndrome, Korean hemorrhagic fever)
	Arenaviridae	50-300 nm	arenaviruses (lymphocytic choriomeningitis, hemorrhagic fevers)
produce DNA from (+) single-stranded RNA using reverse transcriptase; enveloped; bullet-shaped or polyhedral capsid	Retroviridae	100-120 nm	HIV-1 and HIV-2 (HIV infection/AIDS); HTLV-1 and HTLV-2 (T-cell leukemia)
dsRNA; naked; polyhedral capsid	Reoviridae	60-80 nm	reoviruses (mild respiratory infections, infant gastroenteritis); Colorado tick fever virus (Colorado tick fever)

In this review article the focus and emphasize was placed on human viruses in general and on corona viruses in particular, precisely COVID-19.

Coronavirus, is any virus belonging to the family Coronaviridae (+)single-stranded RNA; enveloped; usually a polyhedral capsid) that have enveloped vitions (an entire virus particle, consisting of an outer protein shell called a capsid and an inner core of nucleic acid (either RNA or DNA), the core confers infectivity, and the capsid provides specificity to the virus). Coronavirus diameter approximately 120 nanometer and has a club-shaped glycoprotein spikes in the envelope give the viruses a crownlike, or coronal, appearance. The nucleocapsid, made up of a protein shell known as a capsid and containing the viral nucleic acids, is helical or tubular. The coronavirus genome consists of a single strand of positive-sense RNA (ribonucleic acid). Coronaviruses are a group of related viruses that cause diseases in mammals and birds. In humans, coronaviruses cause respiratory tract infections that can range from mild to lethal. Figure 3 shows the most familiar shape of COVID-19[4].

Fig. 3: COVID-19[5]



Six coronaviruses have been known to infect human hosts and cause respiratory diseases. Among them, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) are zoonotic and highly pathogenic coronaviruses that have resulted in regional and global outbreaks. According to the International Committee on Taxonomy of Viruses, coronaviruses are classified under the order *Nidovirales*, family *Coronaviridae*, subfamily *Coronavirinae*. Based on early serological and later genomic evidence, *Coronavirinae* is divided into four genera:

- ✓ *Alphacoronavirus*,
- ✓ *Betacoronavirus*,
- ✓ *Gammacoronavirus*, and
- ✓ *Deltacoronavirus* [(5)].

In November 2002, a viral respiratory disease first appeared in southern China and quickly spread to other countries, leading to over 8,000 confirmed cases at the end of the epidemic in June 2003, with amorality rate of ∼9.6%[6]. The etiologic agent was identified as SARS-CoV, azoonotic betacoronavirus originated in horseshoe bats that later adapted to infect the intermediate host palm civet and ultimately humans[7]. After an incubation period of 4-6 days, SARS patients develop flu-like symptoms and pneumonia, which in severe cases lead to fatal respiratory failure and acute respiratory distress syndrome. Although SARS-CoV infects multiple organs and causes systemic disease, symptoms indeed worsen as the virus is cleared, suggesting that aberrant immune response may underlie the pathogenesis of SARS-CoV[8]. While no cases of SARS have been reported since 2004, a rich gene pool of bat SARS-related coronaviruses was discovered in a cave in Yunnan, China, highlighting the necessity to prepare for future reemergence[9].

In June 2012, MERS-CoV emerged in Saudi Arabia as the causative agent of a SARS-like respiratory disease[10]. Although human-to-human transmission is considered limited, MERS-CoV has caused two major outbreaks in Saudi Arabia (2012) and South Korea (2015), with the global confirmed cases exceeding 2,000 and a mortality rate of ∼35%[11]. Elderly people infected with MERS-CoV, particularly those with comorbidities, usually develop more severe and sometimes fatal disease [(12)]. Similar to SARS-CoV, MERS-CoV originated in bats, but it later adapted to dromedary camels as intermediate hosts[13].

Currently, no vaccine or specific antiviral drug has been approved for either SARS-CoV or MERS-CoV.Prior to the emergence of SARS-CoV, only two HCoVs (HCoV-229E and HCoV-OC43) were known, both causing mild upper respiratory symptoms when inoculated to healthy adult volunteers [(14)]. Importantly, a majority of alpha coronaviruses and beta coronaviruses were identified only in bats, and many coronaviruses phylogenetically related to SARSCoV and MERS-CoV was discovered in diverse bat species [(15)]. Therefore, emerging zoonotic HCoVs such as SARS-CoV and MERS-CoV likely originated in bats through sequential mutation and recombination of bat coronaviruses, underwent further mutations during the spillover tointermediate hosts, and finally acquired the ability to infect human hosts[16].

In this review, firstly revisit the replication cycle of HCoV, with a particular focus on the host factors co-opted during individual stages of HCoV replication. Next, we summarize the current knowledge of important signaling pathways activated during HCoV infection, including stress response, autophagy, apoptosis, and innate immunity. The cross talk among these pathways and the modulatory strategies utilized by HCoV are also discussed.

Origin and Spread of COVID-19[17]: In December 2019, adults in Wuhan, capital city of Hubei province and a major transportation hub of China started presenting to local hospitals with severe pneumonia of unknown cause. Many of the initial cases had a common exposure to the Huanan wholesale seafood market that also traded live animals. The surveillance system (put into place after the SARS outbreak) was activated and respiratory samples of patients were sent to reference labs for etiologic investigations. On December 31st 2019, China notified the outbreak to the World Health Organization and on 1st January the Huanan sea food market was closed. On 7th January the virus was identified as a coronavirus that had >95% homology with the bat coronavirus and > 70% similarity with the SARSCoV. Environmental samples from the Huanan sea food market also tested positive, signifying that the virus originated from there[18].

The number of cases started increasing exponentially, some of which did not have exposure to the live animal market, suggestive of the fact that human-to-human transmission was occurring[19]. The first fatal case was reported on 11th Jan 2020. The massive migration of Chinese during the Chinese New Year fuelled the epidemic. Cases in other provinces of China, other countries (Thailand, Japan and South Korea in quick succession) were reported in people who were returning from Wuhan. Transmission to healthcare workers caring for patients was described on 20th Jan, 2020. By 23rd January, the 11 million population of Wuhan was placed under lock down with restrictions of entry and exit from the region. Soon this lock down was extended to other cities of Hubei province. Cases of COVID-19 in countries outside China were reported in those with no history of travel to China suggesting that local human-to-human transmission was occurring in these countries [(20)]. Airports in different countries including India put in screening mechanisms to detect symptomatic people returning from China and placed them in isolation and testing them for COVID-19.

Soon it was apparent that the infection could be transmitted from asymptomatic people and also before onset of symptoms. Therefore, countries including India who evacuated their citizens from Wuhan through special flights or had traveler sreturning from China, placed all people symptomatic or otherwise in isolation for 14 d and tested them for the virus.

Cases continued to increase exponentially and modeling studies reported an epidemic doubling time of 1.8 d[21]. In fact on the 12th of February, China changed its definition of confirmed cases to include patients with negative/pending molecular tests but with clinical, radiologic and epidemiologic features of COVID-19 leading to an increase in cases by 15,000 in a single day[22]. As of 05/03/2020 96,000 cases worldwide (80,000 in China) and 87 other countries and 1international conveyance (696, in the cruise ship Diamond Princess parked off the coast of Japan) have been reported 9[23]. It is important to note that while the number of new cases has reduced in China, in other countries have increased exponentially including South Korea, Italy and Iran. Of those infected, 20% are in critical condition, 25% have recovered, and 3310 (3013 in China and 297 in other countries) have died[24]. India, which had reported only 3 cases till 2/3/2020, has also seen a sudden spurt in cases. By 5/3/2020, 29 cases had been reported; mostly in Delhi, Jaipur and Agra in Italian tourists and their contacts. One case was reported in an Indian who traveled back from Vienna and exposed a larg number of school children in a birthday party at a city hotel. Many of the contacts of these cases have been quarantined. These numbers are possibly an underestimate of the infected and dead due to limitations of surveillance and testing. Though the SARS-CoV-2 originated from bats, the intermediary animal through which it crossed over to humans is uncertain. Pangolins and snakes are the current suspects Epidemiology and pathogenesis [(25, 26)]. All ages are susceptible. Infection is transmitted through large droplets generated during coughing and sneezing by symptomatic patients but can also occurs from asymptomatic people and before onset of symptoms[27].

Studies have shown higher viral loads in the nasal cavity as compared to the throat with no difference in viral burden between symptomatic and asymptomatic people [(28)]. Patients can be infectious for as long as the symptoms last and even on clinical recovery. Some people may act as super spreaders; a UK citizen who attended a conference in Singapore infected 11 other people while staying ina resort in the French Alps and upon return to the UK[29]. These infected droplets can spread 1-2 m and deposit on surfaces. The virus can remain viable on surfaces for days in favorable atmospheric conditions but are destroyed in less than a minute by common disinfectants like sodium hypochlorite, hydrogen peroxide etc. [(30)]. Infection is acquired either by inhalation of these droplets or touching surfaces contaminated by them or then touching the nose, mouth and eyes. The virus is also present in the stool and contamination of the water supply and subsequent transmission via aero solization/feco oral route is also hypothesized[31]. As per current information, transplacental transmission from pregnant women to their fetus has not been described[32]. However, neonatal disease due to post natal transmission is described [(33)]. The incubation period varies from 2 to 14 d [median 5 d]. Studies have identified angiotensin (peptide hormone) receptor 2 (ACE2) as the receptor through which the virus enters the respiratory mucosa [(34)]. The basic case reproduction rate (BCR) is estimated to range from 2 to 6.47 in various modeling studies [(35)]. In comparison, the BCR of SARS was 2 and 1.3 for pandemic flu H1N1 2009[36].

Etiology: The subfamily *Orthocoronavirinae* of the *Coronaviridae* family (order *Nidovirales*) classifies into four genera of CoVs: Alphacoronavirus (alphaCoV), Betacoronavirus (betaCoV), Deltacoronavirus (deltaCoV), and Gammacoronavirus (gammaCoV), the betaCoV genus divides into five sub-genera or lineages. Genomic characterization has shown that probably bats and rodents are the gene sources of alphaCoVs and betaCoVs. On the contrary, avian species seem to represent the gene sources of deltaCoVs and gammaCoVs. Members of this large family of viruses can cause respiratory, enteric, hepatic, and neurological diseases in different animal species, including camels, cattle, cats, and bats. To date, seven human CoVs (HCoVs) (capable of infecting humans) have been identified. Some of HCoVs were identified in the mid-1960s, while others were only detected in the new millennium.

Signs and symptoms: Table 2 shows the common symptoms that were noticed in the infected patients.

Table 2: Most familiar symptoms in patient with COVID-19[37]

Symptom	%
Fever	88
Dry cough	68
Fatigue	38
Sputum production	33
Loss of smell	15 to 30
Shortness of breath	19
Muscle or joint pain	15
Sore throat	14
Headache	14
Chills	11
Nausea or vomiting	5
Nasal congestion	5
Diarrhea	4 to 31
Haemoptysis	0.9
Pink eyes	0.8

Those infected with the virus may be asymptomatic or develop flu-like symptoms, including fever, cough, fatigue, and shortness of breath. Emergency symptoms include difficulty breathing, persistent chest pain or pressure, confusion, difficulty waking and bluish face or lips; immediate medical attention is advised if these symptoms are present[36]. Less commonly, upper respiratory symptoms, such as sneezing, runny nose or sore throat may be seen. Symptoms such as nausea, vomiting and diarrhea have been observed in varying percentages. Some cases in China initially presented only with chest tightness and palpitations[38].

In March 2020 there were reports indicating that loss of the sense of smell (anosmia) may be a common symptom among those who have mild disease, although not as common as initially reported[39], the disease may progress to pneumonia, multi-organ failure and death[39], and in severe symptoms, time from symptom onset to needing mechanical ventilation is typically eight days[40].

As is common with infections, there is a delay between the moment when a person is infected with the virus and the time when they develop symptoms. This is called the incubation period. The incubation period for COVID-19 is typically five to six days but may range from two to 14 days[41], 97.5% of people who develop symptoms will do so within 11.5 days of infection.

Reports indicate that not all who are infected develop symptoms, but their role in transmission is unknown[42]. Preliminary evidence suggests asymptomatic cases may contribute to the spread of the disease[43]. The proportion of infected people who do not display symptoms is currently unknown and being studied, with the Korea Centers for Disease Control and Prevention (KCDC) reporting that 20% of all confirmed cases remained asymptomatic during their hospital stay[44] China's National Health Commission began including asymptomatic cases in its daily cases on 1 April, of the 166 infections on that day, 130(78%) were asymptomatic[45].

Transmission: Respiratory droplets produced when a man is sneezing visualized using Tyndall scattering (colloid particles). Some details about how the disease is spread are still being determined[45]. The WHO and the US Centers for Disease Control and Prevention (CDC) say it is primarily spread during close contact and by small droplets produced when people cough, sneeze or talk; with close contact being within 1–3m[46].

A study in Hong Kong observed that the virus was present in most patients' saliva in quantities reaching 100 million virus strands per 1 mL. A study in Singapore found that an uncovered cough can lead to droplets travelling up to 4.5 meters [(47)]. A second study, produced during the 2020 pandemic, found that advice on the distance droplets could travel might be based on old 1930s research which ignored the protective effect and speed of the warm moist out breath surrounding the droplets. This study found that an uncovered cough or sneeze can travel up to 8.2 meters[48].

Respiratory droplets may also be produced while breathing out, including when talking. Though the virus is not generally airborne[6], the National Academy of Science has suggested that bioaerosol transmission may be possible and air collectors positioned in the hallway outside of people's rooms yielded samples positive for viral RNA. The droplets can land in the mouths or noses of people who are nearby or possibly be inhaled into the lungs [(49)]. Some medical procedures such as intubation and cardiopulmonary resuscitation (CPR) may cause respiratory secretions to be aerosolized and thus result in airborne spread. It may also spread when one touches a contaminated surface, known as fomite transmission, and then touches one's eyes, nose or mouth, while there are concerns it may spread by feces, this risk is believed to be low [(50)]. The virus is most contagious when people are symptomatic; while spread may be possible before symptoms appear, this risk is low [(51)]. The European Centre for Disease Prevention and Control (ECDC) says while it is not entirely clear how easily the disease spreads, one person generally infects two to three others.

The virus survives for hours to days on surfaces[52]. Specifically, the virus was found to be detectable for one day on cardboard, for up to three days on plastic (polypropylene) and stainless steel (AISI 304) and for up to four hours on 99% copper[53]. This, however, varies based on the humidity and temperature[54]. Surfaces may be decontaminated with a number of solutions (within one minute of exposure to the disinfectant to achieve a 4 or more log reduction), including 78–95% ethanol (alcohol used in spirits), 70–100% 2-propanol (isopropyl alcohol), the combination of 45% 2-propanol with 30% 1-propanol, 0.21% sodium hypochlorite (bleach), 0.5% hydrogen peroxide, or 0.23–7.5% povidone-iodine. Soap and detergent are also effective if correctly used; soap products degrade the virus' fatty protective layer, deactivating it, as well as freeing them from skin and other surfaces. Other solutions, such as benzalkonium chloride and chlorhexidine gluconate (a surgical disinfectant), are less effective[(55].

Roadmap: The Roadmap identifies the following nine core research priorities:

1. Virus: natural history, transmission and diagnostics;
2. Animal and environmental research on the virus origin, and management measures at the human-animal interface;
3. Epidemiological studies;
4. Clinical characterization and management;
5. Infection prevention and control, including healthcare workers protection;
6. Candidate therapeutics R&D;
7. Candidate vaccines R&D;
8. Ethical considerations for research; and
9. Integrating social sciences in the outbreak response.

In each area, the WHO has identified key knowledge gaps, priorities and milestones. Researchers must focus their efforts and identify where they will have the greatest impact.

A coordinated and multidisciplinary approach is needed. The Global Research Roadmap is a critical tool, but only if transparency and collaboration are maintained. All researches must be carried out in the spirit of collaboration, solidarity and equitable access to all innovations. Research must also be applied in a context-specific way. Protocols, interventions, assessments and the translation of results must be adjusted to local needs and realities.

Hand hygiene and respiratory etiquettes are individual-oriented actions. Social distancing - the key to contain pandemic by interrupting the transmission of virus - has several dimensions. These include avoiding contact with patients of COVID-19, refraining from non-essential use of public transport, working from home and avoiding large and small gatherings namely dining out, socializing and visiting other places where infections can spread easily. It is well established that if NPIs are promptly and effectively implemented during pandemics, disease transmission can be reduced.

The COVID-19 pandemic has hit the world severely and unexpectedly. Time for effective response is at premium. Pandemic affects all. It is the responsibility of every citizen to join hands to mitigate its impact by using evidence-based NPIs and following guidance provided by the national authorities through various 24×7 mechanisms.

The WHO Director-General has recently said16,

"***This is a time for facts, not fear. This is the time for science, not rumors. This is the time for solidarity, not stigma. This outbreak is a test of solidarity - political, financial and scientific. We need to come together to fight a common enemy that does not respect borders***".

We must adhere to this philosophy to defeat the COVID-19 pandemic.

CONCLUSIONS

Microorganisms antedated human beings. They will continue to cause pandemics because of their ingenuity and basic survival instinct. It is obvious following the spread of COVID-19 that notwithstanding the phenomenal advances in epidemiology, disease biology, molecular biology, genomics and proteomics, humanity is still unable to predict and prevent the unsuspected onset of epidemics and pandemics of infectious diseases. It is also obvious that besides their disastrous effect on human morbidity and mortality, there are equally distressing socio-economic consequences for the affected countries and the whole world. It is essential to strengthen biomedical research, improve healthcare delivery system, establish a permanent 'watch-dog' body and create an improved communication and coordination mechanism for the diverse agencies responsible for mitigating the broader adverse consequences of pandemics. This will require not only national efforts but a coordinated global response through international agencies and development partners.

Conflict: No conflict of interest.

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