

REVIEW ARTICLE

Coronavirus: A threat to Global Public HealthSoni Singh¹, Anil Kumar Singh², Pankaj Kumar Jain³, Naresh Pal Singh⁴, Prashant Kumar Bajpai⁵, Pradip Kharya⁶

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Abstract

Previously considered of meagre significance to the human race, coronaviruses have effectively evolved to jump the species barrier and cause widespread contagion in mankind. The SARS pandemic, the MERS situation in the middle-east and the ongoing COVID 2019 epidemic are all attributed to this evolving virus. COVID 2019 is the seventh coronavirus isolated successfully and the third beta-coronavirus that causes a fatal illness in humans; the other two beta-coronaviruses being severe acute respiratory syndrome (SARS) CoV and middle east respiratory syndrome (MERS) CoV. Having a natural reservoir in bats these viruses infect humans through an intermediate host and then rapidly adapt and mutate for human to human transmissions. Four other known alpha coronaviruses cause only common cold in humans. Although mortality rate of COVID 2019 epidemic is lower at 2.5% than the previous two CoV outbreaks, that is, 9.6% in SARS and 34.4% in MERS, but rapid transmissibility points towards a sustained epidemic of epic proportions. In the absence of any specific treatment protocols and experimental vaccines still under research, management largely depends upon symptomatic therapy, strict infection control and quarantine measures. Restriction of human interactions with known animal sources of the virus as a measure of prevention is essentially required. Owing to huge genetic diversity and frequent genomic recombination, novel coronaviruses might emerge periodically, warranting the need for extensive research and development of effective treatments and vaccines.

Keywords

COVID-19; Coronavirus; nCoV-2019; SARS; MERS

Introduction

Evolving, reemerging and adaptive pathogens have emerged as a threat to global public health.(1) One such pathogen climbing the ladder in the 21st century is the coronavirus. Several known coronaviruses are found in animals and were previously understood to be relatively benign. The outbreak caused by SARS CoV in 2002-03 demonstrated that animal coronaviruses could jump the species barrier and turn into a pandemic threat infecting thousands of people across the globe and killing hundreds. Another highly pathogenic coronavirus was recognized a decade later in 2012 as MERS CoV which

caused explosive nosocomial transmission events and more than 800 deaths in the middle-east till date. A third strain of coronavirus, CoVID 2019 has been identified in the current outbreak which started in early December of 2019 in the city of Wuhan in the Hubei Province of China and infected 6,93,224 people globally with 33106 deaths as on 30th March 2020.(2) Owing to high pathogenicity, adaptive and mutative behavior of coronavirus and rapid human to human spread, specific treatments are not yet available and management is dependent on symptomatic and supportive care.

Material and methods

The review includes peer reviewed scientific publications as well as authentic reports of leading health organizations. Advanced searches in the databases of Pubmed; Cochrane Library; Embase; and Google Scholar were conducted to identify published literature. 'Grey' literature search included open source documents of international organizations working in the health sector like World Health Organization (WHO), Centre for disease control and prevention (CDC) American society of microbiology as well as news reports till 30th of March, 2020

Coronavirus Genetics

A Coronavirus is an enveloped virus having non-segmented positive-sense RNA genome and belongs to the family Coronaviridae and the order Nidovirales which is broadly distributed in humans, other mammals, and birds causing respiratory, enteric, hepatic and neurologic diseases.(3,4) Coronaviruses are further classified into four genera namely alpha, beta, gamma and delta, of which only alpha and beta varieties are known to cause infections in humans. Until recent decades, Human coronaviruses were considered inconsequential pathogens rarely causing any disease more severe than the common cold and four alpha HCoVs (HCoV 229E, NL63, OC43, and HKU1) accounted for 10-30 percent of colds (upper respiratory tract infections) worldwide. However, relatively recently two new varieties of beta coronaviruses were discovered known as SARS CoV and MERS CoV, which are zoonotic in origin and found to cause severe lower respiratory disease with fatal consequences in humans.(5) The isolation of first coronavirus was done in 1937.(6) Culture of first human coronavirus, with specimen from nasal cavities of people with common cold was done in the 1960s.(6) Coronaviruses, are spherical in shape with club-shaped spike projections emanating from the surface which look like halos or a crown under the electron microscope and hence the name coronavirus.(7)A coronavirus typical generic genome is 32 kilobases long and is the largest known RNA virus genome.(7) Amongst positive-strand RNA viruses Coronaviruses have the highest known frequency of recombination. On infecting a host it rapidly and indiscriminately combines genetic information from different sources.(7) It is also known for its ability to recombine using both homologous and non-homologous recombination which presumably plays a key role in virus evolution.(8) The average evolutionary rate for coronaviruses is roughly 10^{-4} nucleotide substitutions per site per year,(9) with mutations taking place during every replication cycle.(8) In other words, these viruses have a tendency of mutating and changing at a high rate, wreaking havoc for both, diagnosis as well as treatment and vaccine regimens. It is, however, striking that the sequences of COVID 2019 from different patients were

almost identical, with greater than 99-9% sequence identity.(9) This finding suggests that COVID 2019 originated from one source within a very short period and was detected relatively rapidly.(10) As the virus transmission to more individuals occurs, constant surveillance of any mutations arising is needed. (Figure 1)

History of coronavirus Outbreaks

SARS outbreak: The Severe Acute Respiratory Syndrome caused by SARS CoV was the first contagion pandemic of the 21st century. In November, 2002 cases of unusual atypical pneumonia first emerged in Foshan, Guangdong province, China.(11) By the time WHO was notified, on February 11, 2003, number of cases were already 305 with 5 deaths.(12) A doctor from the Guangdong province, who was ill, travelled to Hongkong and stayed at the Hotel Metropole in February 2002, infecting 17 other guests at the hotel.(13) From here, as the infected guests travelled, onwards to their home countries, the disease spread to Vietnam, Singapore, Canada, Taiwan and elsewhere.(14) SARS has a very non-specific flu-like presentation with symptoms including fever, malaise, headache, myalgia, chills and diarrhea.(15,16,17) In the first and/or second week of illness there might be cough with shortness of breath and diarrhea. There is progression to respiratory distress in severe cases, requiring intensive care. Risk of death is high in patients with co-morbid conditions especially diabetes and heart disease.(18) Mortality rate is over 50% in patients more than 65 years of age.(19) Affected children below 12 years of age usually have good disease outcome.(20) Transmission of the disease primarily occurs from one person to another through direct or indirect contact of mucous membranes (eyes, nose or mouth) by means of respiratory droplets or fomites.(21) First to get infected were the medical professionals and health care workers attending the infected individuals, followed closely by family clusters.(22) Amoy Gardens apartment complex in Kowloon Bay, Hongkong witnessed a community outbreak, wherein an infected person from Shenzhen while visiting a relative living in the apartment used his toilet because of diarrhea which contaminated the sewage.(23) Virus containing droplets, were hypothesized to be the possible mode of transmission, from this contaminated sewage reaching the bathrooms of residents through dried up U-traps.(24) A total of 321 residents were infected and the whole apartment complex was evacuated for disinfection.(25) WHO issued a global alert on March 12, 2003. Soon thereafter, in April 2003 the full genome mapping of SARS related coronavirus was completed and WHO announced the causative agent as SARS CoV. The SARS CoV, previously not known to cause endemics in humans, is thought to be a virus of animals, with bats as their reservoirs and raccoon dogs and civet cats as their intermediate hosts which pass on the infection to humans.(26) Within a few

months after its first emergence, it had affected over 8,098 patients with 774 deaths with case fatality rate of 9.6% in 26 countries.(27) Symptomatic treatment and supportive care along with broad-spectrum anti-virals like ribavirin are the mainstay of management of SARS as no known drugs have proven complete efficacy.(28) SARS outbreak was declared as contained, when Taiwan reported no new cases for 20 days, in July 2003, after which only sporadic cases of SARS have been reported worldwide till date. Experimental vaccines are under development.

MERS Outbreak: A patient from Saudi Arabia with multiorgan dysfunction and hypoxemic respiratory failure led to the identification of MERS CoV, in September 2012.(29) This was followed by numerous sporadic cases across the Arabian Peninsula, occasional importations to other regions and sometimes associated clusters. So far 27 countries have reported laboratory-confirmed cases of MERS in the region including Bahrain, Islamic Republic of Iran, Jordan, Kuwait, Oman, Qatar, Saudi Arabia, and United Arab Emirates.(30) Imported cases associated with travel were reported from Egypt, Lebanon, Tunisia and Yemen. Non-sustained and infrequent human to human transmission has been seen.(31) Health care-associated outbreaks have occurred in the Republic of Korea, Saudi Arabia and the United Arab Emirates.(32) From 2012 to December 2019, there have been 2,499 cases of MERS with 861 associated deaths globally and a case fatality rate of 34.4%.(33) Unlike SARS, MERS is a severer form of respiratory illness. It manifests with low grade fever, runny nose, sore throat, muscle aches and diarrhea initially, and rapidly progresses to acute respiratory distress syndrome. People with underlying chronic illnesses are at greater risk. Bats are the natural reservoirs whereas Dromedary camels are the animal hosts(34) for the virus and remain asymptomatic or develop only mild upper respiratory illness.(35)

COVID 2019 outbreak

In December 2019, severe cases of pneumonia of unknown etiology were reported in the city of Wuhan, in the Hubei province of Republic of China.(36)The WHO country office of China was notified about these pneumonia cases on December 31st, 2019 and thereafter within a span of four days 44 new cases were reported by the National authorities of China. Of the first 41 people with laboratory-confirmed coronavirus infection and hospitalized for pneumonia, two third had history of exposure to the Huanan seafood market of Wuhan.(37) The Centre of disease control and prevention in China, isolated a new type of corona virus on January 7, 2020 which was named as nCoV 2019 by WHO and later changed to COVID 2019.(38) Outside China, the first case was reported from Thailand on 13th January 2020, with a travel history to Wuhan city. This was followed by reports of cases, from more than two dozen countries, most of

whom had travelled to or had been in close contact with someone who had travelled to Wuhan. As of 30th March 2020, there were 6,93,224 laboratory confirmed cases globally with 33106 deaths with an estimated mortality rate of 2.5% in China .(2) Mortality rate is higher at around 10.5% for persons over 80 years of age with chronic illnesses. A total of 712 cases were confirmed on a cruise ship called “Diamond Princess” which was quarantined off-shore with 3600 passengers and crew on-board.(2) Despite numerous travel bans this outbreak which was at first limited mainly to the Hubei province in China, spread like wildfire to multiple countries and was declared a pandemic by WHO on 11th March 2020.

All of the 196 countries of the world are currently affected with COVID 19 with number of cases and deaths exceeding that of China, which was the epicentre of the outbreak at first. Countries which are hardest hit include Italy with 9,76,89 cases and 10781 deaths, Spain with 78797 cases and 6528 deaths, Iran with 38309 cases and 2640 deaths and United States of America with 1,22,653 cases and 2112 deaths as of 30th March 2020.(2) ([Figure 2](#))

COVID 2019 in India

The first three imported cases in India were amongst the citizens rescued from Wuhan and were reported from Kerala. Throughout the month of February few only few other sporadic imported cases were reported. The government authorities were prompt in identifying and isolating the cases. However, owing to rampant spread throughout Europe and United Kingdom, despite numerous travel advisories and bans the infection could not be contained. Although still in its initial stages, the outbreak is on the rise in India. A total of 1251 cases in 27 states and union territories of India were reported till 30th march 2020, out of which 102 were cured, discharged or migrated and 32 died. (39) As we finish writing this article the number of cases rise.

Clinical features

COVID 2019, just like previous CoV outbreaks manifests with non –specific flu-like symptoms such as Fever, cough and shortness of breath.(40) Muscle ache, headache, nausea and vomiting are less common presenting symptoms.(41) In patients with co-morbid conditions and over 80 years of age, the disease might rapidly progress to acute respiratory distress with bilateral pneumonia and death.(41)

Transmission:

Initial studies are consistent with a bat reservoir for COVID 2019 in particular and coronaviruses in general.(9) However direct transmission from bats seems improbable and several facts indicate the presence of an intermediate host between bats and humans. Firstly, most bat species in Wuhan are hibernating during late December in Wuhan, when the outbreak first occurred.(9) Secondly, several non-aquatic animals including mammals are sold at the Huanan seafood market but bats are neither sold nor

found there.(9) Thirdly, phylogenetic analysis showed that bat derived coronaviruses are not direct ancestors of COVID 2019.(9) Fourthly, both SARS CoV and MERS CoV have natural reservoirs in bats with an intermediate host (civet cats in SARS(42) and dromedary camels in MERS(43)) and humans as terminal hosts.(9) All this makes it highly likely that currently unknown wild animals, acted as intermediate host for COVID 2019. Infection of healthcare professionals including death of whistleblower Dr Li Wenliang in Wuhan provides evidence of human to human transmission.(44) Human-to-human transmissions have been confirmed via droplets, contaminated hands or surfaces.(39) Rapid progression in number of infected patients suggests that COVID 2019 is more contagious than SARS CoV and MERS CoV(37) with a great potential for a sustained epidemic. Incubation period is 2-14 days.(45) Transmission also occurs from infected but asymptomatic person.(46) (Figure 3)

Prevention

At present prevention seems to be the only effective measure against COVID 2019. Maintenance of Hand hygiene, use of face masks, sanitisation of exposed surfaces and social distancing are the most widely used methods of prevention. Multiple countries including India resorted to complete lockdowns and ban of all domestic and international travels to limit spread. Contact tracing of infected individuals and rapid isolation and quarantine have proven effective to some extent. Healthcare workers who are at higher risk of infection use hazmat suits and personal protective equipments (PPE) to limit exposure.

Diagnosis and Treatment

Diagnosis is based on history of exposure followed by Virus specific Reverse Transcriptase Polymerase chain reaction (RT-PCR) tests using upper and lower respiratory tract specimens. Symptomatic treatment is instituted because of lack of any specific treatments or vaccine till date.

Conclusion

Viruses have known to be notorious pathogens that cause a range of mild to severe and even fatal infections with frequently mutative behavior that often lead to problems of diagnosis and treatment. Beta coronaviruses known to humans till date pose a significant threat to global health and economy. A greater element of alarm arises from the fact that medical science is still not familiar with many such fatal coronaviruses and current outbreaks might only be the tip of the iceberg. Ongoing research with broad-spectrum antivirals such as remdesivir, lopinavir or ritonavir and interferon beta have elicited promising results against MERS CoV and also being tested against COVID 2019.(47) Nucleic Acid Vaccine platform approaches and messenger RNA vaccine technologies are being pursued for developing effective vaccines within a compressed timeframe.(48) Infection control and

outbreak preparedness are our best bet at dealing with such outbreaks in the absence of effective treatments. Animal sources known to harbor such viruses should best be kept away from human settlements as a preventive measure. Effective public health strategies and outbreak containment remains mainstay of management until targeted and effective treatments are available.

Limitation of the study

COVID-19 outbreak is still ongoing and the prediction of exact trajectory of the outbreak is not available at present.

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Figures

FIGURE 1 STRUCTURE OF CORONAVIRUS (SOURCE: WIKIMEDIA)

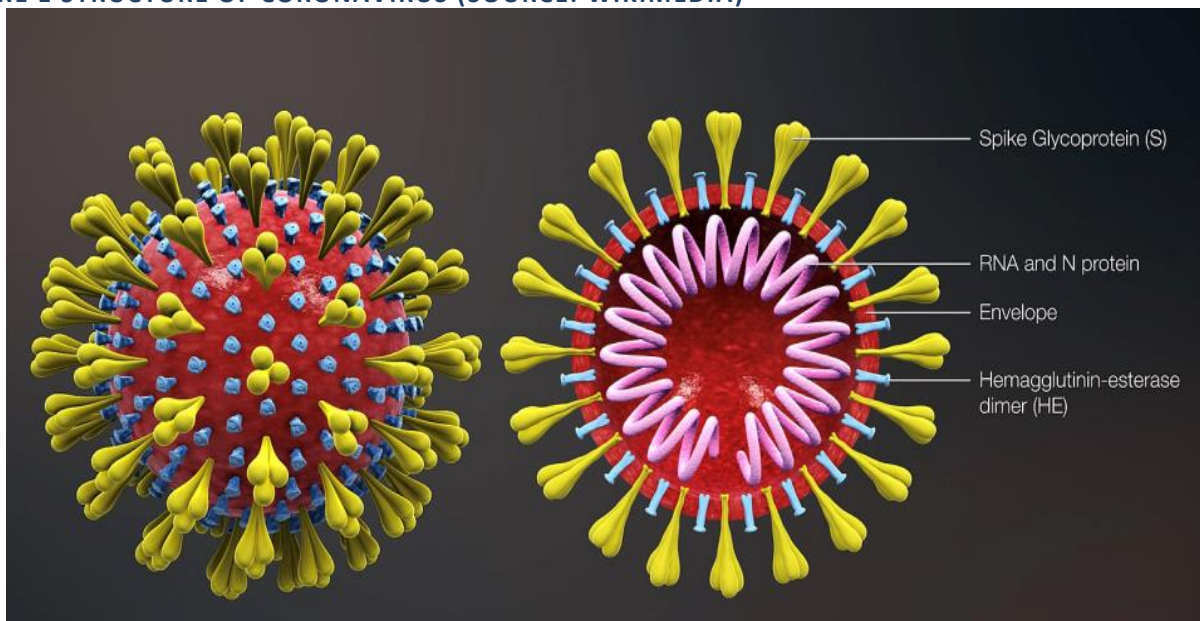


FIGURE 2 COUNTRIES, TERRITORIES OR AREAS WITH REPORTED CONFIRMED CASES OF COVID-19, AS ON 30 MARCH 2020 (SOURCE: WORLD HEALTH ORGANIZATION SITUATIONAL REPORT-70)

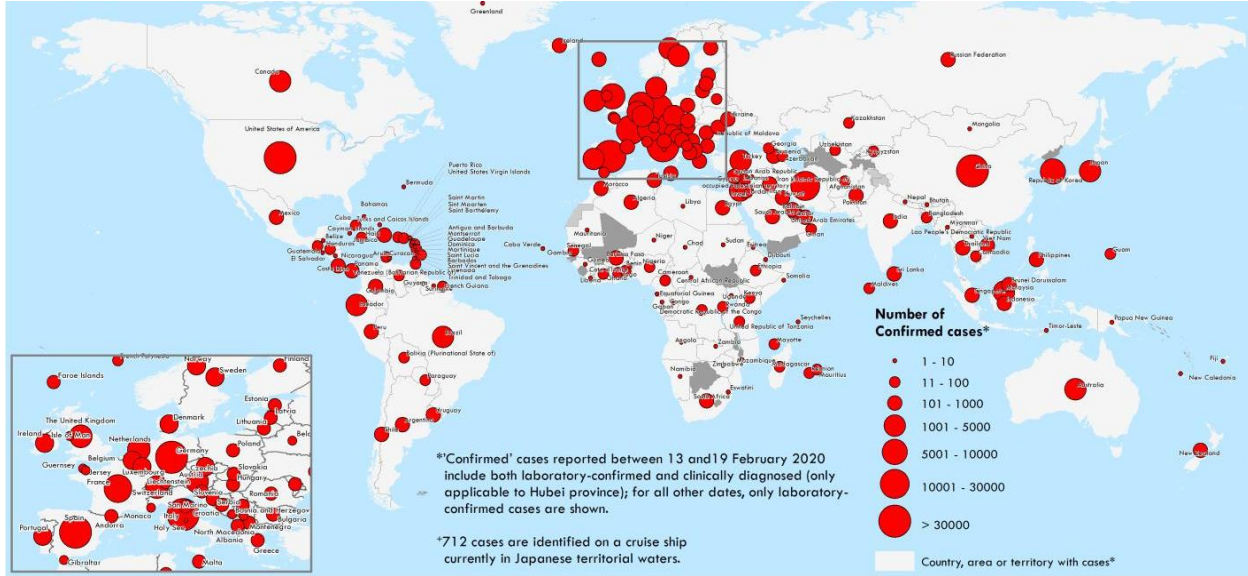


FIGURE 3 EPIDEMIC CURVE OF CONFIRMED COVID-19, BY DATE OF REPORT AND WHO REGION THROUGH 30 MARCH 2020 (SOURCE: WORLD HEALTH ORGANIZATION SITUATIONAL REPORT-70)

