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Will COVID-19 or Humanity Win the Global "Health" Challenge? A Global Prospective

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Abstract

The recent ongoing outbreak of highly contagious viral disease, COVID-19 due to SARS-CoV-2 has sparked worldwide concern. Originally emerged in December 2019 in Wuhan, Hubei Province, Central China; spread quickly across other areas and caused a major epidemic. In response to this serious situation, the World Health Organization (WHO) declared it a global public health emergency of international concern on 30th January, 2020, putting all health organizations on high alert. In China 84, 287 people infected with nCoV-19, which include 4,642 deaths as on 22nd April 2020. Although in China there has been a decline in the spread of the disease, the virus has spread rapidly to 200 countries around the world resulting in over 30 lakhs confirmed infections and 2.50 lakh deaths, and the trend raising on each passing day. Since there are no clinically approved vaccines or specific therapeutic antivirals available, globally most government authorities implemented some unprecedented measures to combat the nCoV-19 transmission. These include the suspension of public transportation, the closing of public spaces and management of communities, isolation and care for infected and suspected cases, and complete locked down to avoid contacting of residents with others. In this article, we systematically review currently available updated literature regarding nCoV-19 epidemic and clinical characteristics, highlighting the strategies adopted successfully by some countries to control the epidemic, which would help other countries respond to the outbreak.

Keywords: Coronavirus • Novel coronavirus • nCoV-2019 • Outbreak • Wuhan

Introduction

History of nCoV-19

Coronaviruses (CoVs) belong to the subfamily Orthocoronavirinae in the family Coronaviridae, Order Nidovirales. There are four genera within the subfamily Orthocoronavirinae, namely α-coronavirus (α-CoV), β-coronavirus (β-CoV), γ-coronavirus (γ-CoV) and δ-coronavirus (δ-CoV) [1]. The CoV genome is an enveloped, positive-sense, single-stranded RNA with a size varying between 26-32 kb, the largest genome of known RNA viruses. Both α-and β-CoV genera are known to infect mammals, whilst δ-and γ-CoVs infect birds. In the 21st century, 2 highly pathogenic β-CoVs are severe acute respiratory syndrome-coronavirus (SARS-CoV) and Middle East respiratory syndrome-coronavirus (MERS-CoV) emerged from animal reservoirs to cause global epidemic with significant morbidity and mortality [2]. In 2002, an outbreak of SARS was first reported in China and then spread quickly worldwide, resulting in hundreds of deaths with 11% mortality rate [3]. In 2012, MERS first emerged in Saudi Arabia and subsequently spread to other countries, with a fatality rate of 37% [4]. In both of these epidemics, the viruses likely originated from bats and then infected humans through other intermediate animal hosts [e.g. the civet cat (*Paguma larvata*)] for SARS-CoV and the camel for MERS-CoV [5].

Coronaviruses have long been considered inconsequential pathogens causing "common cold" in otherwise healthy people. However, in December 2019, a number of patients with pneumonia of unknown aetiology emerged in Wuhan City, Hubei Province, Central China. The Chinese public health, clinical and scientific communities have responded to identify what the new virus is? Based on phylogeny, taxonomy, genome sequencing, and established practices of viruses, on February 11th, 2020, the Coronavirus Study Group (CSG) of the International Committee designated this novel coronavirus as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [6] previously known as 2019 novel coronavirus (2019-nCoV) [7]. SARS-CoV-2 infections spread across China and the outbreak shows no signs of decrease, partly because transmission is not fully known [8]. Soon later, on February 12th, 2020, WHO named the SARS-CoV-2 as a novel Coronavirus disease-2019 or novel COVID-2019 (hereafter we call as nCoV-19). Considering the global threat, on January 30th, 2020 the World Health Organization (WHO) has declared nCoV-2019 a Public Health Emergency of International Concern (PHEIC).

Methodology Adopted

It has been four months since China's health officials reported a mysterious virus spreading in China. Cases of the nCoV-19 seem to be leveling off in China. But elsewhere, infections and deaths are rising. According to the John Hopkins University report as of 30th April, nCoV-19 has infected nearly 31,17,756 people globally and 2,17,217 deaths across 200 countries. The United States is the country with the most deaths at 58, 964. The other countries with over 1000 deaths are shown (Table 1). Italy 27,359, Spain 23,882, France 23,660, UK 17682, Belgium 7,331, Germany 6,314, 5877, Brazil 5083, Netherlands 4, 566, China 4,512, Turkey 2992, Sweden 2355, Switzerland 1699, Canada

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Table 1. Number of nCoV-19 infected cases (confirmed, recovered and dead) in some of the severely affected countries by the epidemic as on 30th April 2020.

Country	Confirmed cases	Deaths	Recovered cases	Deaths/100 infected cases	Death/100 closed cases
USA	10,36,657	59,266	118K	1.6	65.70
Italy	2,01,505	27,359	68,941	10.60	45.50
Spain	2,32,128	24,275	109K	7.8	35.50
France	1,69,053	23,660	46,886	6.0	25.90
UK	1,62,350	21,678	-	5.20	83.40
Belgium	47,334	7,501	11,283	11.80	74.80
Germany	1,59,912	6314	110K	0.70	5.0
Iran	92,584	5,877	72,439	7.40	17.60
Brazil	73,325	5,083	32,544	-	-
Netherlands	38,802	4,711	-	6.30	98.90
China	83,940	4,633	77,578	4.0	4.20
Turkey	1,14,653	2,992	38,809	-	-
Canada	50,373	2,904	19,190	-	-
Sweden	20,302	2,642	1,005	3.40	86.80
Switzerland	29407	1,699	22,600	1.80	13.10
Mexico	16,752	1,569	11,423	-	-
Ireland	19877	1569	9233	-	-
India	31,787	1,008	8,642	-	-

1683, Mexico 1569, and India 1008 (Table 1), and the situation is getting complicated with time. Globally analyzed data so far suggests that most cases are ending in recovery. According to the WHO, bout 5 in 100 infections led to death and 17 of every 100 closed cased ended in death.

Structure of nCoV-19

Coronaviruses are enveloped viruses with a positive-sense single-stranded ribonucleic acid (RNA) genome named for its solar corona like appearance [9]. Their helical symmetry nucleocapsid is approximately 26-32 kb in size, making it the largest investigated genome among RNA viruses [10]. Like other SARS-CoV, nCoV-19 particles are spherical and have 9-12 nm long special glycoproteins called a "spike" (peplomer) protruding from their surface (Figure 1). Recent studies showed that like α-coronavirus (e.g.HCoV-NL63) [11,12] the spikes of nCoV-19 latch onto cell surface, then undergo a structural change that mediates fusion between the envelope and host cell membranes via a metallopeptidase like angiotensin-converting enzyme 2 (ACE2) as host cell entry receptor [13], which facilitate replication of viral genes thereby produced more copies of viral particles [14].

Structural analysis by Cryogenic Electron Microscopy (Cryo-EM) revealed nCoV-19 binds to human ACE2 with 10-20 folds higher affinity, suggesting nCoV-19 is more infectious to human than the SARS-CoV, or spread easily from onindividual to another than the SARS-CoV [15]. Homology modeling studies revealed that nCoV-19 is capable of using the same cell entry receptor, ACE2 as SARS-CoV, but not CD26 as MERS-CoV [12] to infect humans [12]. These studies are in agreement with Lu et al. [16] wherein these authors reported that similar to SARS-CoV, nCoV-19 primarily infects ciliated bronchial epithelial cells and type II pneumocytes, where it binds to ACE2 and initiates fusion with the host cells [16]. ACE2+ cells are abundantly present all over the respiratory tract. ACE2+ epithelial cells present in the salivary glands were considered one of the main targets of SARS-CoV infection [17]. Similarly, nCoV-19 may also use the same mechanism to induce infection, although definitive evidences are not available, this issue needs further investigation. In contrast to SARS-CoV, MERS-CoV exploits dipeptidyl peptidase-4 (DPP4), a transmembrane glycoprotein to infect pneumocytes and unciliated bronchial epithelial cells [18].

Molecular aspects of nCoV-19

A full-length genome sequence ranges from 29891 to 29903 nucleotides (nt) of nCoV-19 was deduced from bronchoalveolar lavage of critically ill nCoV-19 infected pneumonia patients [12,19] using next generation sequencing.

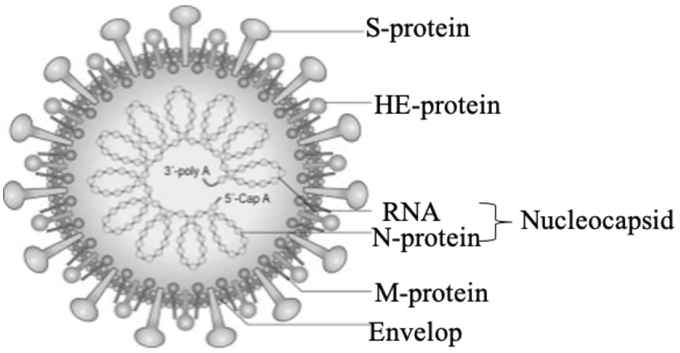

Figure 1. The Spherical enveloped particles studded with club-shaped glycoprotein projections, and surround a core matrix protein enclosed within which a single-stranded RNA (Mr 6 × 10^6) is associated with nucleoprotein. The envelope glycoproteins are responsible for attachment to the host cell and carry antigenic epitopes recognized by neutralizing antibodies.

nCoV-19 share 79.0% nt sequence identity to SARS-CoV and ~50% to MERS-CoV [12]. The nCoV-19 sequence is 96.30% identical at the whole-genome level to a horseshoe bat (*Rhinolophus affinis*), and bat coronavirus isolate RaTG13, and is 88% identical to two bat-derived SARS-like coronaviruses (bat-SL-CoVZC45 and bat-SL-CoVZXC21) [20,21]. The close phylogenetic relationship to RaTG13 suggests bats are probably natural hosts for nCoV-19 [12]. Human nCoV-19 has a unique furin-like cleavage site, RRAR motif in the spike protein which is not found in coronaviruses isolated from pangolins, indicating nCoV-19 may not originated directly from pangolins [7]. Of note, three mutations (D354, Y364, and F367) were located in the spike surface glycoprotein receptor-binding domain, which suggested nCoV-19 may rapidly evolve to evade immune response and adapt to other hosts in the future. The receptor binding protein spike (S) gene of nCoV-19 is highly divergen [20].

Etiology of nCoV-19

Coronaviruses (CoVs) have been identified as human pathogens since early 1960's. Previously, it was thought that CoVs only cause enzootic infections in a number of animals, including certain birds and mammals, but recent findings indicate that a variety of these viruses, including HCoV-229E, HCoV-NL63, HCoV-OC43 & HCoV-HKU1) cause various respiratory diseases. Of these HCoV-229E and HCoV-NL6 classified as antigenic group 1, whereas HCoV-OC43 and HCoV-HKU1 belonging to group 2

typically leading to an upper respiratory tract infection (URI) manifested by common cold symptoms [22].

SARS-CoV (identified in China's Guangdong Province in 2002) and MERS-CoV (identified in Saudi-Arabia in 2012) responsible for causing two large-scale pandemics in the last two decades [23,24]. SARS-CoV mainly found in natural reservoir host, horseshoe bats and cause disease outbreak [25,26]. Human transmission for SARS-CoV was facilitated by intermediate hosts like palm civet cats and raccoon dogs, which are frequently sold as food sources in Huanan seafood market, China [27]. For MERS-CoV dromedary camels are the host reservoirs for human infections. When it comes to nCoV-19, scientists discovered that bats were likely not the only animal involved, because nCoV-19 has genetic similarities to coronaviruses found in pangolins. At some point before the first case of nCoV19 in December 2019 surfaced in Wuhan, a bat coronavirus and a pangolin coronavirus might have exchanged genetic information, which gave birth to the new strain, i.e. nCoV-19. At the moment this seems to be the most plausible explanation that science can give us.

Clinical symptoms of nCoV-19

We now have a better idea of just how contagious nCoV-19 is, and the main symptoms to look out for. But there is still a lot to learn. How much do symptoms vary? And will there be lasting consequences for those who recover from an infection? Understanding the clinical symptoms of nCoV-19 is crucial; although the symptoms are vary among patients. The main clinical signs and symptoms reported are fever (98%), a runny nose, sore throat, dry cough (76%), headache, dyspnoea or shortness of breath (~50%), malaise, myalgia, fatigue (44%) [28,29]. Many individuals will just get a runny nose or a sore throat. Some people with the virus don't seem to show any symptoms at all due to stronger immune systems. Vomiting and diarrhoea tend to appear in few cases. Some patients rapidly develop severe pneumonia symptoms and complications including acute respiratory distress syndrome (ARDS), pulmonary oedema or multiple organ dysfunction (e.g. acute cardiac and kidney injury) and death in severe cases [30]. Some patients may show normal or lower white blood cell (WBC) counts, lymphopenia, or thrombocytopenia with extended activated thromboplastin time and increased C-reactive protein level [31].

Virology of nCoV-19

Four corona viruses commonly infect humans and cause severe flu like symptoms, though flu belongs to different virus family. These are believed to have evolved in humans to maximize their own spread. It is interesting to know whether nCoV-19 can be compared with the flu. The flu kills people. This is not an Ebola, nor SARS-CoV, MERS-CoV or Influenza virus. Yes, the flu is terrible, that is exactly why scientists don't want another contagious respiratory disease to take root. In many ways the flu is the best argument for throwing everything at the nCoV-19. AS on 30th April 28th, 2020 it is not even known how many people are actually infected with nCoV-19 and succumbed to the disease. nCoV-19 has spread over 200 countries, and over 3 million people contracted the disease globally and over 2.20 lakh people lost their lives (Figure 2). The Johns Hopkins University tracker says, globally, high mortality were recorded in USA followed by Italy, Spain, France, UK, Belgium, Iran etc. (Table 1). This is more than SARS-CoV (8273 cases, 775 deaths) and MERSCoV (1139 cases, 431 deaths) caused in 2002 and 2012 respectively. Based on published data from Chinese Center for Disease Control and Prevention (China CDC), the case-fatality rate for nCoV-19 infection in China is estimated to be is 2.4 to 3.4%, which is far lower than that of his cousin, SARS-CoV and MERS-CoV [32,33].

The populations in every age group are generally susceptible to nCoV-19 infection. The data from China and other countries reveal that over 70% of infected people are between 60-70 yrs age group. Young people, on the other hand, appear to be better protected against the virus. We don't yet know if children aren't catching the virus at the same rate as adults, or if they just don't show symptoms when they do have the virus. Infections from Asian countries, particularly from India show all groups of people including children are infected with nCoV-19, and recovery rate is better and deaths are minimal among younger age group. People who are older than 60, and have chronic illness such as heart, kidney, diabetes, blood pressure (BP), or a week immune system are more at risk, and likely to have respiratory failure [34]. The majority of patients can recover, however, about 20% of patients will progress into severe complications including ARDS, which may worsen rapidly into respiratory failure, need an intensive care unit (ICU) and even cause multiple organ failure [30].

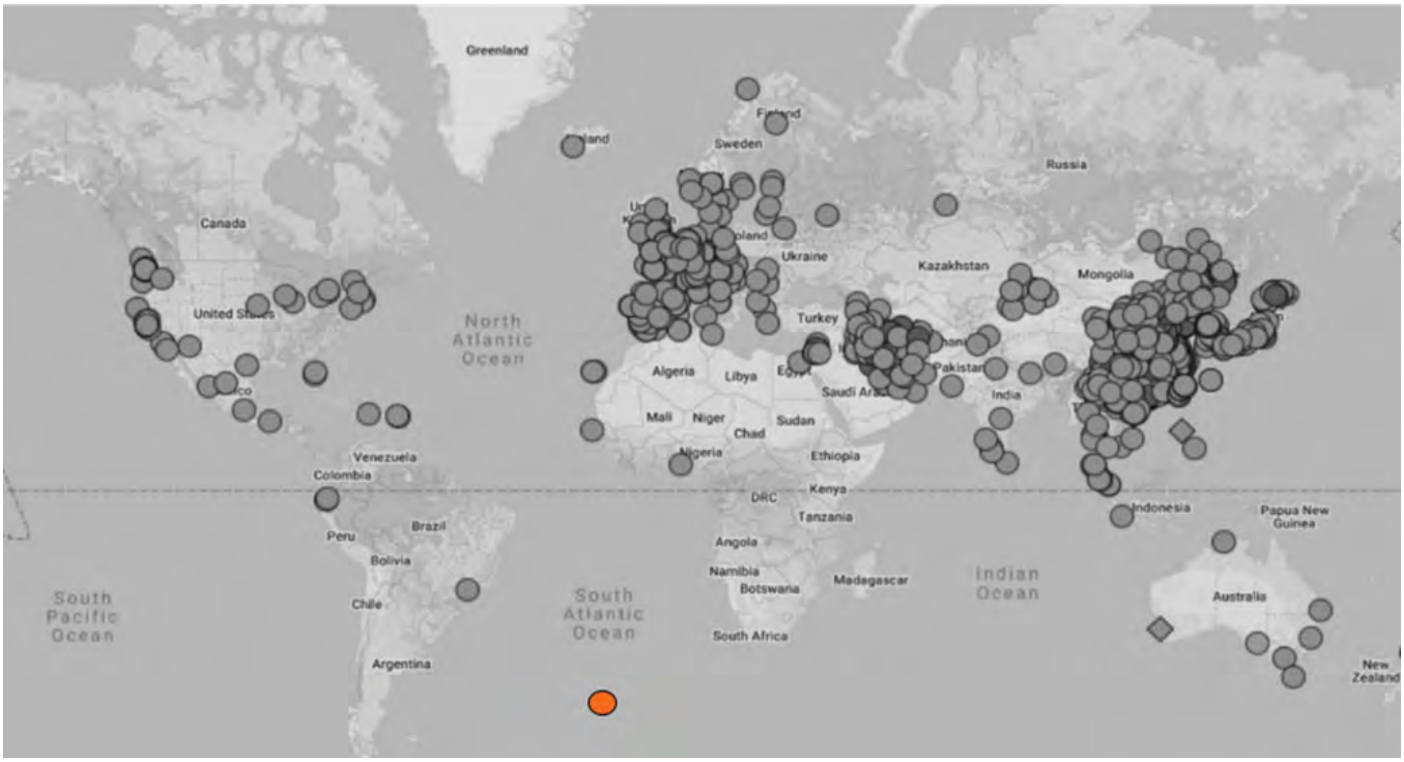

Figure 2. Countries, territories or areas with reported confirmed cases of COVID-19, as on 1st March 2020. Countries, territories or areas with reported confirmed COVID-19, March 1st, 2020. Data in Panel is from World Health Organization (WHO).

It was reported that, globally higher number of males (~64%) infected with nCoV-19 than females [28]. Similar trend was observed for SARS-CoV and MERS-CoV outbreaks [35]. Mortality rates in older men are higher than infected younger people due to higher immune status in the later. Mortality rates in men are higher than women. The reason for such a gender discrepancy is not known, although men do smoke more often resulting in compromised lung function [28]. It has also been reported that Asian populations may be more susceptible to nCoV-19 than other races [11,12], although more evidence is needed to draw such a conclusion.

In limited studies on lactating mothers with nCoV-19 and SARS-CoV infection, the virus has not been detected in breast milk. However we do not know whether mothers with CoV-19 can transmit the virus via breast milk. Chen et al. [28] investigated pregnant women with COVID-19 in their third trimester that underwent caesarean section. nCoV-19 was tested in the amniotic fluid, cord blood, neonatal throat swab, and breastmilk samples and got all negative results. None of the neonates has clinical signs of infection. This result suggested no intrauterine fatal infections occurred as a result of nCoV-19 infection during the late stage of pregnancy. Previous studies also showed no evidence of perinatal infection of SARS-CoV and MERS-CoV during pregnancy [36]. However, a neonate born to a pregnant woman with nCoV-19 pneumonia tested positive 36 hr after birth at Wuhan Tongji Hospital [28]. It is reasonable to assume that a new-born could be infected either in-utero or perinatally, and thus newborns should be placed in isolation to avoid exposure to any source of infection.

Epidemiology of nCoV-19

A series of patients with pneumonia of unknown cause were initially reported by the Health Commission of Wuhan, Hubei province, China in December 2019. Although patients were initially announced to be afflicted with this mysterious pneumonia, the number rose and few have become critically ill, one death was noted in the subsequent report on January 11th, 2020 (CHP information on cluster of pneumonia cases in Wuhan, 2020). The Chinese authorities reported to WHO stated that several patients were dealers/vendors selling live and freshly slaughtered hunted animals in the Huanan seafood market [31]. Several reports of clusters of cases among families and infection of several health care workers pointed to human-to-human transmission of the nCoV-19 [9,31]. Peak travel season due to the Chinese New Year was probably an important factor that led to the spread of the infection. As of April 30th, 2020, Chinese authorities reported 83,940 nCoV-19 infected cases with a death toll of 4,633. Within a few weeks after recognition of the outbreak, Chinese authorities could prevent the spread infection to a greater extent using their efficient surveillance network and laboratory infrastructure.

According to the sixth version of the guidance for diagnosis and treatments for nCoV-19 issued by the National Health Commission of China, nCoV-19 was transmitted through respiratory aspirates, droplets, contacts, and feces. Similar to SARS-CoV and MERS-CoV, nosocomial transmission was a severe problem to nCoV-19, and even worse. Nosocomial infections extremely burdened the health system and hindered early infected individuals from getting immediate medical supports, therefore resulting in high case fatality rate. The nCoV-19 is 10 times more contagious and deadlier than most strains of the flu known so far. On an average, seasonal flu strains kill 0.1% of people who become infected. The mean incubation period of nCoV-19 is estimated to be 3-7 days (range 1–14 days) indicating a long transmission period. These data fully support the current period of active monitoring recommended by the WHO of 14 days [37,38].

Other important factors such as case fatality rate (CFR), basic reproduction number (R0 or 'R nought' in the jargon) and the reservoir hosts are crucial in influencing viral endemicity. The basic reproduction number is important threshold related to the transmissibility of the virus, which is expressed as R0. The R0 is defined as the average number of secondary infections produced by an infectious person. The general belief is that if 'R' 0 is >1, the number of infected cases will increase exponentially and cause an epidemic or even a pandemic. It has been estimated that the R0 of nCoV-19 is in the range of 1.4-5.49, with a mean of 2.8 meaning 10 infected persons will infect 28 more (Flu has an R0 of 1.3) regardless of prediction models, which is higher than SARS-CoV and MERS-CoV (R0 of 2-5) [39]. Further, it was reported that viruses with higher CFR (CFR >5%) die out after few passages of infections sooner or later, whereas viruses with low CFR remain endemic with a seasonal outbreak like common flu. Although it is very difficult to calculate actual CFR until the outbreak ends, an initial estimate suggests that CFR for nCoV-19 is 2.58%, much closer to seasonal flu than SARS-CoV and MERs-CoV i.e., 10% and 35%, respectively indicating the ability of the nCoV-19 to remain in circulation with low CFR [40].

How deadly is nCoV-19?

nCoV-19 is one of the most alarming highly infectious diseases in the globe at this moment. It is also difficult to estimate how fatal the virus is, because the fatality rate differs in each country, even within the countries. Most estimates put the rate at somewhere between 1 and 2% of infections. This is higher in older populations put the fatality rate at 8% for those in their 70s and 14% for people aged 80 or over. But the exact figure is impossible to calculate, because we can't be sure how many people have caught the virus.

If there is one thing about nCoV-19 that has become point of contention for scientists all over the world, it is the deepening conundrum about how easily does nCoV-19 spread? The rate of spread would depend on how contagious the disease is in milder cases. The virus spread silently between people before the cluster of cases discovered. The variation in mortality rate depends on various local factors like access to quality healthcare, infrastructure, general preparedness, proportion of malnourishment, and overall health profile of the population. So most countries were able to mobilize their health care systems to rapidly test and bring down fatality rates. For instance, in the Central China City of Wuhan, where the nCoV-19 first exploded, ~1.4% of patients was died according to the WHO. But in the rest of hard hit China, the death rate was strikingly as low as 0.70%. There is nothing different about the virus from one place to another. Instead, they never before seen strain of nCoV-19 struck fast, before anyone could realize what the illness was.

To give a statistical answer, the simplest formula would be to divide the number of deaths by the total number of identified cases (e.g. if 10 people have died out of 1,000 infected then the death rate is 10/1000 X100=1%. That is 1 out of every 100 confirmed cases is going to die. But experts say there are issues with this formula as the death rate can be misleading. WHO sums it by saying "The infection fatality rate to a large extent determined by access to and quality of healthcare (Johns Hopkins University Ministry of health note).

As on 30th April 2020, 18 countries have reported more than 1000 deaths (Table 1). In China the figure for deaths /100 infected and the deaths /100 closed cases have almost converged. China has one of the highest rates of recovery, and this convergence show how China has managed to treat its nCoV-19 patients while controlling the spread of the disease. Almost a third of the confirmed cases are in the USA, which remains the worst affected country with more than 56,000 deaths, though the true number will be much higher. USA and Germany seeing most closed cases ending in death. The comparison of deaths/100 infected cases in these countries shows that the death rate for Germany is the lowest in this category. The situation appears to be worst in USA, Italy, Netherlands, Belgium, Sweden and UK. While Belgium has the highest infected/deaths cases; the Netherland has the highest deaths/closed cases. Germany reported 0.69 deaths /100 (0.69%) infected cases. Italy on the other hand has reported 8.56 deaths/100 infected people. About 5 in 100 infections led to death and 17 of every 100 closed cased ended in death. Both these figures are likely to drop as countries scale-up testing, suggesting globally, most cases are ending in recovery.

Discussion

The last century, the world population has witnessed several assaults from RNA viruses, resulting in millions of deaths. The 21st century appears no longer an exception, with the trend continued with significant fear of SARS-COV first appeared in 2002 and rapidly spread to 32 countries and regions, after which the world then experienced the outbreak novel influenza virus pandemic in 2009 and MERS-CoV in 2012. Recently, a newly emerged severe pneumonia-

associated respiratory syndrome caused by nCoV-19, spread rapidly and has become a world-wide public health challenge. Much is unknown about how nCoV-19 is spread. Person-to-person spread is thought to occur mainly via respiratory droplets produced when an infected person coughs or sneezes, like how influenza (flu) and other respiratory pathogens spread. About 5% of nCoV-19 patients experience ARDS, and even progressed into ICU admission. At the moment, the causes for the mortality and identification of novel therapeutic options for nCoV-19 are crucial. The illness caused by the nCoV-19, people may contagious before symptoms develop, making it difficult or even impossible to control the spread. Moreover, asymptomatic patients during their incubation periods can effectively transmit nCoV-19 infection [41]. On an average, a person with nCoV-19 appears to infect 2-3 other people (WHO 2020-situation report12). But the figure is skewed by the fact that the epidemic was not managed well in the beginning and infections soared. Globally, 80% of patients are mildly ill when the virus is detected, compared to 15%, who already are severely ill. While the sickest to start with are at highest risk of death, a fraction of the mildly ill does go on to die for unknown reasons. Morbidity varies in different environments, depending on factors like temperature, population density and susceptibility to the disease in a population. Due to these factors, several researchers around the globe are providing inconsistent results on the number of infection and mortality rate. Much remain unknown about the nCoV-19 burst through the world, but at the moment, we only have informed guesses, which are likely to solidify in the coming weeks and months. But what we know so far can shed some light on the characteristics of the virus, and offer some instructions on dealing with the rapidly growing pandemic.

Emerging trends of nCoV-19

The emerging nCoV-19 pandemic poses a massive crisis to global public health. While the nCoV-19 has extended its reach quickly across the world, definite geographic clusters of infections were emerging. We used data from December-2019 to 30th April, 2020 on the number of cases exported from Wuhan to infer the number of infections in the world. The number of nCoV-19 infected cases outside China exceeded the number within the country. Amid fear about where next outbreak of a fast spreading nCoV-19 would appear, infections and deaths continued to rise across the globe. Worryingly, it seems that somebody who survives one bout of nCov-19 doesn't develop immunity, people can be re-infected. We don't know how the infection propagates (for example, is it aerial or waterborne) and there may be a long period when carriers have no symptoms. The big question is whether nCoV-19 will be establishing itself in an endemic form or will it eventually die out? Endemic viruses during circulation may acquire mutations to infect naïve, as well as individual with pre-existing immunity.

Containment of nCoV-19

The CoV-19 outbreak cause significant public threat and we need to understand more about the disease to overcome it. One of the most worrying things about any outbreak is the spreading of viruses from mild or asymptomatic individuals, which is currently happening in case of nCoV-19 infection. If this trend continues then the virus may establish itself in the population and quarantine will be very difficult to stop the virus spread.

Containment is the first step in responding to any outbreak to ensure rapid evaluation and care of patients, limit further transmission. To mitigate community spread of the nCoV-19, an effective prevention and control measurements are crucial. This must include early detection, diagnosis, and quarantine to block person-to-person transmission as well as reducing secondary infections among household members and health care providers in combination with contact tracing activities from the date of onset of clinical symptoms. In an effort to stem the spread of the virus, transport bans were instituted globally. Officials from various countries said they had temporarily closed the area's outgoing airport and railway stations, and suspended all public transport. One must strictly follow government guidelines like home isolation, maintain safe distance, wear nose masks, and sharing of information. But the concern is, this virus may be beyond containment that it may be with us indefinitely.

Immunological aspects of nCoV-19

Humans rely on immune systems to keep their cool when facing a threat. It has been shown that patients infected with nCoV-19, its severity and outcomes are linked not only to host genetic makeup but also its immune status. Very few immunological studies have been carried out in nCoV-19 infected humans, which attribute dysregulated/exuberant immune responses as a leading contributor to nCoV-19 mediated infection. nCoV-19 infected persons can go for 14 days or more without symptoms. Although the major clinical manifestations of the nCoV-19 involve the lungs, the key component of the pathogenesis appears to be immune system.

SARS-CoV can infect and kill airway ciliated cells, which then sloughed off and filled patients' airways with debris and fluids [2], therefore we believe that the same could happen with the nCoV-19. That is because studies on nCoV-19 have shown that many patients develop pneumonia, accompanied by symptoms like shortness of breath. That is when phasing the immune system kicks in. Waken by the presence of a viral invader, our bodies' step-up to fight the virus by flooding the lungs with immune cells to clear away the damage and restore the lung function. Cytokines are the known inflammatory markers, used by the immune system as alarm beacons, and they recruit immune cells to the site of infection in the lung [42]. Upon entry into alveolar epithelial cells, nCoV-19 replicates rapidly and triggers a strong immune response, resulting in cytokine storm syndrome and pulmonary tissue The immune cells then kill-off the infected alveolar cells in a bid to save them. But during a runaway nCoV-19 infection, when the immune system dumps pro- inflammatory cytokines in excess (hypercytokinaemia) into the lungs, this culling becomes a free-for-all, instead of shooting at a target with a gun, cytokines act as missile launcher. That's where the problem arises. When working properly, inflammatory process is tightly regulated and confined only to infected areas. But sometimes our immune system goes haywire and those cells kill anything in their way, including healthy cells. Therefore, a compromised immune response can lead to aggravation of nCoV-19 induced lung injury. The uncontrolled production of pro-inflammatory cytokines can lead to ARDS and multiple organ failure [43].

Further, it has also been demonstrated that increased alveolar exudates caused by aberrant host immune response and inflammatory cytokine storm impedes alveolar gas exchange and contributes to the high mortality of nCoV-19 patients [44]. Similar to the inflammatory cytokine profile in SARS-CoV and MERS-CoV, patients with nCoV-19 also have increased plasma levels of pro-inflammatory cytokines such as tumour necrosis factor α (TNF-α), interleukins-IL-1,-2,-6,-8,-7,-10,-12, CXCL-10, granulocyte-colony stimulating factor (G-CSF), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1α (MIP-1α), and interferon-γ-inducible protein-10, which suggests a cytokine storm occurred [30,45]. Such an abnormal production of inflammatory cytokine is accompanied by infiltration of inflammatory monocytes/macrophages (IMM) into the lung that weakens blood vessels in the lungs and causes fluid to seep through to the air sacs. The storm spills into circulatory system and creates systemic issues across multiple organs. From there things can take a sharp turn for the worse. In some of the most severe nCoV-19 patients, the cytokine response, combined with a diminished capacity to pump oxygen to the rest of the body, can result in multi-organ failure and death [46]. It is not known exactly why some patients experience complications outside of the lung, but it might be linked to underlying conditions like cardiac, diabetic or co-morbid complications.

Xu et al. reported desquamation of pneumocytes, hyaline membrane formation, and infiltration of interstitial mononuclear cells in the lung tissue suggests ARDS [11]. ARDS decreased immune function and secondary infection further worsens respiratory failure. Further, these authors showed the presence of multinucleated giant cells with atypical enlarged pneumocytes characterised by large nuclei, prominent nucleoli and amphophilic granular cytoplasm in the intra-alveolar spaces, indicated viral cytopathic-like changes. Diao et al. shown that total numbers of T-cells (CD4+T-cells and CD8+T-cells) are decreased in patients with nCoV-19 infection, and the surviving T-cells are functionally deranged, suggesting an altered immune function in these patients [47].

Pathological mechanism of nCoV-19

No detailed studies have been conducted to explain the mechanism involved in the pathogenesis of nCoVD on a molecular scale. It has been

confirmed that nCoV-19 enters lung cells by binding to ACE2 and infect them. Following infection, activated lung resident immune cells sense invading viral pathogens/antigens. At the site of infection, activated virus-specific cytotoxic T lymphocytes-TCLs (e.g. CD8+T-cell) produce antiviral cytokines (e.g. IFN-γ and TNF-α) and chemokines. These cytokines inhibit viral replication and enhance antigen presentation and kill infected alveolar epithelial cells, while chemokines recruit more innate immune cells to control pathogen burden (Figure 3).

Besides pulmonary tissue, ACE2 is also highly expressed in other tissues including bile duct, liver, small intestine, duodenum, oesophagus, testis and kidney [48,49]. Given the expression of nCoV-19 in other tissues apart from lung, it is tempting to speculate about infection beyond the respiratory tract. However, we are not aware of any data on this yet. Taken together, understanding the pathological characteristics of nCoV-19 could help to provide new insights into the pathogenesis of nCoV-19-infected pneumonia, which may help physicians to design treatment modalities to reduce mortality.

In addition, certain immune system genes like Human Leukocyte Antigen (HLA) known to be involved in recognizing pathogens vary from person to person. The individual HLA, haplotype, and genotype variability likely influence how well the immune system recognizes nCoV-19 infection. Poor recognition of nCoV-19 could cause a person to be more vulnerable to the virus. Following the development of a vaccine against nCoV-19, individuals with high-risk HLA types may be prioritized for vaccination. It is interesting to study how the variations in HLA affect patients susceptible to nCoV-19 infection. Probably, individual genetic variation may explain differences in the strength of immune responses. This could help identify individuals at higher risk from the nCoV-19 infection.

Clinical manifestations, diagnosis and treatment of nCoV-19

Overall, infection caused by the nCoV-2019 shares many clinical similarities with infection caused by SARS-CoV. There are currently no effective prophylactic or post exposure therapies. Antibody tests, can determine whether someone got infected, may eventually help to establish how many people had mild or asymptomatic nCoV-19 infection. A study from China CDC showed majority of patients (~80%) were considered asymptomatic or mild pneumonia but released large amounts of viruses at the early phase of infection, which can fool health workers, and posed enormous challenges for containing the spread of this epidemic. Following the outbreak, full nCoV-19 genomic sequence was released in public databases [50]. This, in turn, paved the way for the development of PCR assays to detect the virus. This method will hopefully allow identifying positive cases and treating them quickly. Enzyme-linked immunoassay (ELISA) and RT-PCR assays is also being used in some clinics for nCoV-19 detection using throat swabs or blood samples [12]. Chest X-ray and computed tomography (CT) are being used to confirm laboratory detection methods [51].

Till date, there are no medicines that work effectively to prevent nCoV-19 infection. WHO has recommend the use of acetaminophen (paracetamol) to relieve from pain and fever, fluids to avoid dehydration, complete rest and supportive care, oxygen therapy, administration of antimicrobials for treatment of bacterial infections to prevent end-organ dysfunction for ICU cases. For these patients, use of high-flow oxygen therapy, extracorporeal membrane oxygenation, mechanical ventilation (for life-threatening ARDS cases), glucocorticoid therapy and administration of convalescent plasma have been recommended. Some ARDS patients get benefit from short-term use of methylprednisolone (1-2 mg/kg body wt. per day), and passive immunotherapy reported tocilizumab (identified in USA as NCT04317092) effectively curb inflammatory storm (pathogenic T cells, inflammatory monocytes and cytokines) and to reduce nCoV-19 infected patients mortality [28,44]. Recently, a randomized controlled trial evaluating the efficacy and safety of lopinavir-ritonavir-ribavirin, interferon-α 2b, chloroquine phosphate and abidor has been initiated. Italian Pharmaceutical Agency (IFA) approved a Phase II trial in 330 patients with nCoV-19 induced ARDS using tocilizumab started on March 19, 2020. Passive immunization (PI) through pathogen-specific broadly neutralizing antibodies that bind to the specific antigens and block its interaction with ACE2 may be a potential option to address the immediate health threat of nCoV-19 pandemic while vaccines are being developed.

Vaccines

Currently, there are no approved specific antivirals for nCoV-19. Nonetheless, there are ongoing efforts for vaccine development. Vaccines

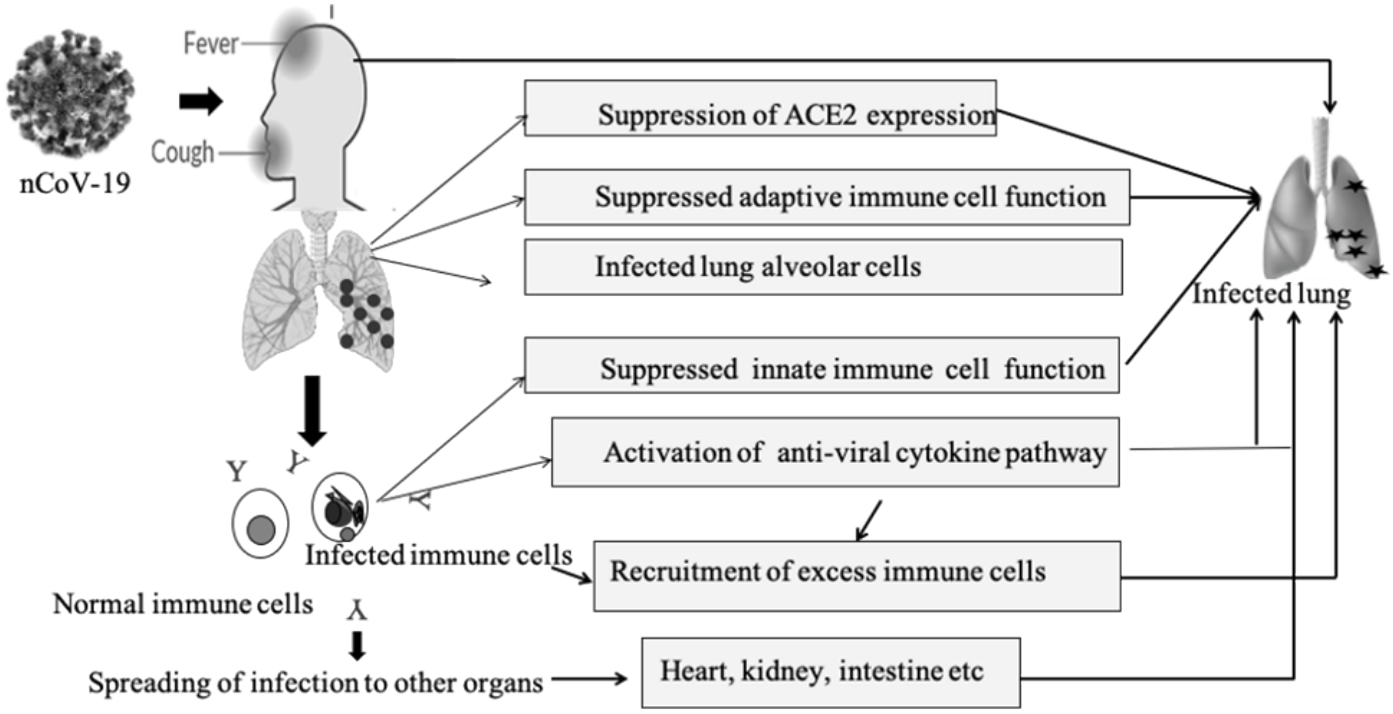

Figure 3. Possible mechanism involved in the pathogenesis of nCoVD-19 infection. Initiation of immune response against nCoV-19 begins with direct infection of lung alveolar epithelium. Following infection, lung resident immune cells acquire the invading pathogen or antigens from infected epithelial cells. The activated virus-specific effector T cells produce antiviral cytokines and chemokines. Cytokines regulate viral replication and enhance antigen presentation and kill infected alveolar epithelial cells. The chemokines produced by activated T cells recruit more immune cells to control pathogen load.

based on whole virus, spike (S) protein, nucleocapsid (N) protein, and membrane (M) protein, T cell epitopes and RBD (receptor binding domain) have been studied for SARS-CoV and MERS-CoV [52,53]. On Feb 24th, 2020, Moderna, a US based pharmaceutical company announced that its experimental mRNA nCoV-19 vaccine, known as mRNA-1273, was ready for clinical trials. A number of other vaccine candidates such as Ad5-nCoV (CanSino Biologics), ChAdOx1 (The University of Oxford), BNT162 (Pfizer and BioNTech), besides the antibody-based therapeutic candidates against SARS-CoV and MERS-CoV are in various stages of development [54,55]. If there is found to be substantial cross-reactivity between nCoV-19 and SARS-CoV and MERS-CoV or any other known coronavirus for which immuno-prophylactics and/or therapeutics, it may be quicker to repurpose these medical countermeasures for use against nCoV-19. However, creating an experimental vaccine for nCoV-19 may be ready for testing in human within a few months, but will take much longer, at least a year or two to become available in the market.

Conclusion and Future perspectives

It is important to discuss the theoretical potential for cross-reactivity between nCoV-19 and SARS-CoV based on available sequence/modeling data. So combining early research on the outbreak with past lessons from SARS-CoV and MERS-CoV can provide an answer. However, there is still much that is unknown about nCoV-19, including what actually happens to the body when it is infected by this virus?, and how long it can last for any period of time outside of the host. It's currently unclear if a person can get nCoV-19 by touching a surface or object that has the virus on it and then touching their own mouth, nose or eyes. This pandemic emphasizes the need to be constantly alert to shifts in both the global dynamics and the contexts of individual countries, making sure that all are aware of which approaches are successful for the prevention.

The association between the nCoV-19 and the disease has not been proved by animal experiments. We don't know the transmission method of this virus among hosts yet. We should closely monitor if the virus continue evolving to become more virulent. Owing to shortage of specific treatment and considering the relatedness between SARS-CoV and nCoV-2019, some drugs and pre-clinical vaccine against SARS-CoV probably can be applied to this virus. Considering the wide spread of nCoV-19, future research should be focused on active surveillance through a broader geographic regions. Most importantly, continuous monitoring of newly infected and those recovered individuals as re-infection may lead to the selection of escape mutants and subsequent dissemination to the public. Global co-ordinated action is essential to deal health challenges the pandemic poses to people. It is also important to share information on health technology developments vital to treat nCoV-19 patients who need them quickly. Lastly, strict regulations against the wildlife domestication and consuming should be implemented.

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