JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Coronavirus Pandemic

The novel zoonotic COVID-19 pandemic: An expected global health concern

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Abstract

18 years ago, in 2002, the world was astonished by the appearance of Severe Acute Respiratory Syndrome (SARS), supported by a zoonotic coronavirus, called SARS-CoV, from the Guangdong Province of southern China. After about 10 years, in 2012, another similar coronavirus triggered the Middle East Respiratory Syndrome (MERS-CoV) in Saudi Arabia. Both caused severe pneumonia killing 774 and 858 people with 8700 cases of confirmed infection for the former, and 2494 for the latter, causing significant economic losses. 8 years later, despite the MERS outbreak remaining in certain parts of the world, at the end of 2019, a new zoonotic coronavirus (SARS-CoV-2) and responsible of coronavirus Disease (COVID-19), arose from Wuhan, Hubei Province, China. It spread rapidly and to date has killed 3,242 persons with more than 81,000 cases of infection in China and causing over 126,000 global cases and 5,414 deaths in 166 other countries around the world, especially Italy. SARS-CoV-2 would seem to have come from a bat, but the intermediate reservoir continues to be unknown. Nonetheless, as for SARS-CoV and MERS CoV, the Spillover effect linked to animal-human promiscuity, human activities including deforestation, illegal bush-trafficking and bushmeat, cannot be excluded. Recently, however, evidence of inter-human only transmission of SARS-CoV-2 has been accumulated and thus, the outbreak seems to be spreading by human-to-human transmission throughout a large part of the world.
Herein we will provide with an update on the main features of COVID-19 and suggest possible solutions how to halt the expansion of this novel pandemic.

Key words: SARS CoV; MERS CoV; SARS-CoV-2; COVID-19; spillover; drugs.

J Infect Dev Ctries 2020; 14(3):254-264. doi:10.3855/jidc.12671

(Received 15 March 2020 – Accepted 17 March 2020)

Coronavirus characteristics

Coronaviruses are members of the subfamily Coronavirinae from the family Coronaviridae and the order Nidovirales. Based on phylogenetic relationships and genomic structures, the subfamily Coronavirinae is divided into four genera - *Alphacoronavirus, Betacoronavirus, Gammacoronavirus and Deltacoronavirus*. *Alphacoronaviruses and betacoronaviruses* only infect mammals. *Gammacoronaviruses and deltacoronaviruses* infect birds and sometimes even infect mammals including rodents and bats. *Gammacoronaviruses and Betacoronaviruses* are known to cause respiratory diseases in humans and gastroenteritis in animals [1].

Coronaviruses are enveloped and have single stranded positive sense RNA genomes that range in size from 26 to 32 kilobases. This can lead to a greater possibility of errors, which can result in very rapid mutations. Some of these mutations can give the virus new properties, such as the ability to infect new cell types or even new species that can generate serious lung disease [2]. A coronavirus particle consists of four structural proteins: the nucleocapsid, envelope, membrane and spike [3]. The Spike (S) protein forms club-shaped protrusions that stick out all over the virion, resembling a crown or the sun's corona hence the name. These protrusions bind to receptors on host cells thus determine the cell types and the range of species that the virus can infect.

Transmission of the Coronavirus is usually via airborne droplets to the nasal mucosa in closed environments and through close contact between people, unwashed hands, and rarely as a result of touching contaminated surfaces. No other route of

transmission of coronavirus infection has been documented, thus far. The virus replicates locally in cells of the ciliated epithelium, causing cell damage and inflammation. Incidence peaks occur in the winter, taking the form of local epidemics lasting a few weeks or months. The same serotype may return to an area after several years [4].

Coronaviruses generally cause acute and chronic respiratory, enteric, and central nervous system diseases in many species of animals, including humans. There has also been much speculation about the association of human-man Coronaviruses with more serious human diseases such as multiple sclerosis [5], hepatitis or enteric disease [6] in infants. However, none of these early associations have been demonstrated [2].

Most humans in the world have encountered the coronavirus. In particular, the milder forms of the four strains of such viruses, cause about one fifth of common colds without leaving permanent immunity. Other types cause endemic diseases in some animal populations. In spite of this, until less than two decades ago, all known human varieties caused such mild diseases that they did not stimulate further advanced coronavirus research.

Coronavirus genetic evolution and the SARS global emergency

Over the last two decades, three new Coronaviruses with different genomic characteristics than those described above have emerged causing epidemics of such magnitude as to provoke a considerable global health concern. In 2003, the world experienced the Severe Acute Respiratory Syndrome (SARS) caused by a new coronavirus (SARS-CoV). The SARS-CoV outbreak started in Guangdong, South China in late 2002, and spread rapidly around different parts of the the world countries in many including Southeast Asia, Europe, South Africa and North America, most notably Toronto, Canada. It is believed to have been transmitted along international air-travel routes and resulting in 8,700 cases and 744 deaths in 33 countries and areas on 5 continents [7]. The Canadian outbreak presented an impressive challenge to public health services. There were 438 probable and suspected SARS cases reported, including 44 deaths, over a relatively short period of time, i.e., five months [8]. The transmission of SARS-CoV, which started from the bat and passed into some intermediate guests, including palm civets, occurred mainly person-to-person through direct contact, Flügge's large drop-to-drop contact and indirect contact by fomites, unwashed hands, and rarely touching contaminated surfaces or air travel [9].

The disease had a mortality rate of about 10%, but reached nearly 50% in elderly people, which is a very high rate when compared to other viral diseases [10].

This SARS outbreak was the first human pandemic to break in the 21st century. The severity of the illness associated with SARS-CoV infection and its rapid global spread, led to an intensive response including a wide range of highly productive research efforts directed toward understanding the molecular biology of the infection and the pathogenesis of the disease. The ability of the WHO to coordinate an intensely collaborative global response to SARS was impressive. Case identification and isolation followed by contact identification and management were responsible for limiting the spread of and ultimately the halting of the SARS outbreak. In particular, recognition of all potential contacts and implementation of measures to rapidly identify and isolate those that had become infected prevented further spread of disease.

Most of people who were severely infected with SARS-CoV had lower respiratory tract severe illness, an atypical infiltrate on chest radiograph and were hospitalised. SARS-CoV attacks human angiotensin-converting enzyme 2 (ACE-2), a metallopeptidase expressed in numerous tissues and mostly distributed in ciliated bronchial epithelial cells and type II pneumocytes from lower bronchi [10,11]. The S protein of SARS-CoV located on the outer envelope of the virion is the major inducer of neutralizing antibodies and it would appear to be an ideal SARS vaccine antigen [2,12]. S protein binding to ACE-2 and its subsequent downregulation of this receptor contribute to lung injury during SARS [13,14]. Atypical pneumonia with rapid respiratory deterioration and failure can be induced by SARS-CoV infection because of increased levels of activated proinflammatory cytokines [10].

In late 2003 and early 2004, new infections were reported in Guangdong, China, in people who had contact with animals infected with SARS-CoV strains which were significantly different from those that caused the 2002-2003 outbreak [11,12]. These events indicate that a SARS outbreak could occur at any time in the future due to SARS-CoV isolates evolving from SARS-CoV-like virus in host animals.

The emergence of the MERS and its global spread

After SARS, it was the turn of the Middle East Respiratory Syndrome (MERS) which occurred as a new challenging infection threatening the global health worldwide. The MERS Coronavirus (MERS-CoV), a

lethal zoonotic pathogen that was first identified in humans in the Kingdom of Saudi Arabia in 2012, continues to emerge and re-emerge through intermittent sporadic cases, community clusters and nosocomial outbreaks [15]. The first case resulting from MERS-CoV was identified in 2012 and defined in early research as a "SARS-like" or "SARS Arabica virus" [16]. According to virologists, the zoonotic virus MERS-CoV emerged between the summer of 2007 and the autumn of 2012 through mutations and transmissions between various animals, and could have originated among bats and been transmitted by air or direct contact to humans from dromedary camels or camel products [17,18] or other ways which also include water and insects but the ways of transmission are not yet full known and cannot definitely be established (Figure 1).

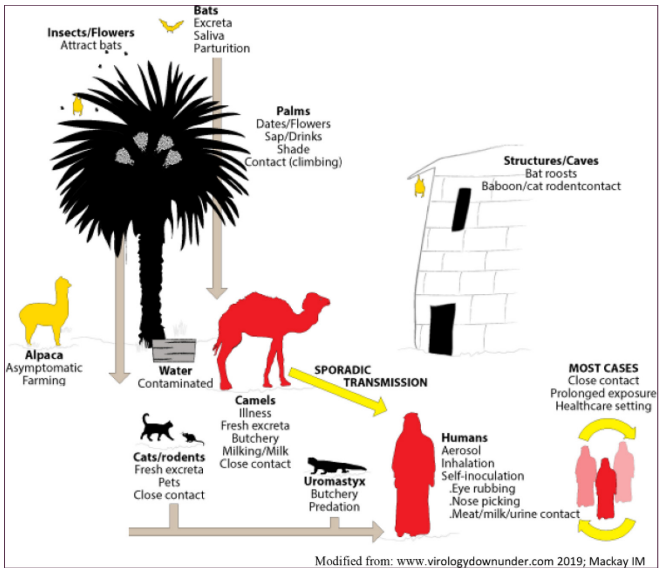
Camels are suspected to be a reservoir of MERS-CoV since the virus has originated in the Middle East and some patients had had contact with camels prior to symptom onset [19]. Further research has conducted that the MERS CoV has been quite frequent among camels and has been spreading from camels to humans for at least the last 20 years, although it is not yet clear how. Other camelid animal such as alpacas and Lamas are probably involved too [20].

MERS-CoV has an incubation period of about 7-12 days, which means that it takes approximately 10 days after infection before the first symptoms become apparent. This coronavirus initially causes flu-like problems, with fever, chills, muscle pain and in some cases dysentery [21]. As the infection progresses, respiratory problems may occur including interstitial pneumonia up to severe respiratory insufficiency requiring mechanical ventilation in the most severely affected cases (Table 1). The MERS-CoV virus can also cause acute renal failure, which further compromises the patient's clinical picture [22].

The mean age of all cases of MERS reported worldwide was 50.21 ± 18.73 years, and ranged from 2 to 109 years of age [15-17].

Although studies have been ongoing on for three years, information on how MERS-CoV works is still unclear. This is partly due to the number of people who have contracted it and have undergone analysis being resulting the lack of availability of relevant and reliable statistical data. MERS-CoV binds to a receptor called DPP4 also known as CD26, highly expressed in unciliated bronchial epithelial cells and type II pneumocytes from lower bronchi and lung cells in the kidney, alveoli, small intestine, liver, and prostate, and on activated leukocytes [22,23]. Differences in the

Figure 1. Most known Ways of MERS-CoV exposure and Transmission in Humans. Modified form: www.virologydownunder.com, Mackay IM 2019.



distribution of these receptors in tissues and organs may account for differences between the two diseases, such as the fact that MERS is more lethal than SARS and exhibits also prominent gastrointestinal symptoms and renal failure too. MERS CoV is not highly infectious, although this may also be a receptor-related trait. As DPP4 is mainly expressed in the lower bronchi, prolonged and intense exposure is necessary to reach the lungs. This would explain how those working closely with camels fall ill [17-20;24].

According to a 2013 study, Infection with MERS-CoV can cause severe disease with high mortality. MERS disease has in fact a case fatality rate of close to 35-40 percent, which is much higher than SARS, which in turn estimated around 9.6 % [25,23]. Research has also assumed that it takes about 8 days for the virus to spread inter-humanly from one infected person to another but transmission routes are, as yet, unknown [7-8;14,23].

A total of 2499 MERS cases were confirmed from 2012 to 30 November 2019. In this period, 858 associated deaths were reported to the WHO [26]. These statistics for total deaths include those which have been reported, thus far, to the WHO, after identification during follow-up by affected Member States. 8 years after the emergence of the MERS-CoV based on our analyses of the WHO data, Saudi Arabia still has the highest rate of infection [14,15,20].

SARS-CoV-2 and the new Coronavirus disease (COVID-19) pandemic

In December 30th, 2019, while the MERS-CoV epidemic was still ongoing, a cluster of patients with pneumonia of unknown etiology were observed in Wuhan, China (Hubei Province). These individuals were associated in some way with visits to Wuhan market.

In contrast to the SARS virus that was isolated 6 months after the SARS outbreak [27], Chinese scientists were able to isolate the new coronavirus (formerly 2019-nCoV, then SARS-CoV-2) as belonging to the Coronaviridae family, from respiratory samples of a Wuhan patient in just a few days. These results were gained on January 9th, 2020 and after sequencing the SARS-CoV-2 genome, were made available to the WHO on January 12th, 2020 [28].

SARS-CoV-2 is classified as a novel *Betacoronavirus* belonging to the *Sarbecovirus* subgenus of Coronaviridae family. This virus has never previously been identified in humans. Neverthless, information coming from the scientific world is constantly evolving.

The novel coronavirus sequencing enabled the laboratories from different countries to produce specific diagnostic real-time RT-PCR methods for detecting the SARS-CoV-2 infection [26]. The genome sequence of SARS-CoV-2 is about 89% identical to bat SARS-like-CoV and 82% identical to human SARS-CoV [29]. SARS-CoV-2 is reported as using the same cell entry receptor as SARS-CoV [30], ACE2, to infect humans, so clinical similarities between the two viruses are expected, particularly in severe cases.

Phylogenetic analysis of novel SARS-CoV-2 has shown that it is a product of recombination with previously identified bat coronaviruses. However, significantly, SARS-CoV-2 is only closely related to the specific bat SARS-like coronavirus isolated from *Rhinolophus sinicus* in 2015 in China (MG772934.1). Further structural analysis of two important viral proteins, the nucleocapsid (N protein) involved in virion assembly and the S-protein-like nucleoprotein (S

Table. 1 Characteristics of the Emergent Zoonotic Coronaviruses of the Century Responsible for Severe Acute Respiratory Syndrome (SARS-CoV), Middle Eastern Respiratory Syndrome (MERS-CoV) and SARS-2-CoV-19 (COVID 19).

Epidemiological, clinical and biological characteristics	SARS-CoV	MERS-CoV	SARS-CoV-2 (Covid-19)
Distribution	Pandemic	Epidemic	Pandemic
Origin	Guangdong province, South China	Saudi Arabia	Wuhan, Hubei province, China
Natural reservoir	Bat*	Bat*	Bat*
Viral sequence	Reference [2,11]	Reference [20,23]	89% similarity with SARS-CoV, 64% with MERS-CoV [29,31]
Probable/suspected intermediary host	Palm-civet Others**	Camel/dromedary llama, alpaca, market civets	Not-known Pangolins?
Transmission	Human-to human spread°	Human-to human spread Other°°	Human-to human spread Other°
Pathogenicity (involved receptor)	ACE-2§	DPP4 or CD26§§	ACE-2§
Total number of infected persons in the World	More than 8,098	2,490^	More than 207,800
Incubation period	2-7 days	7-12 days	2-14 days
Global deaths	774	858^	More than 8,657
Main symptoms	Influenza-like symptoms, fever, chills, dry cough, shortness of breath	Fever, chills, cough, shortness of breath, myalgia, and malaise	Influenza-like symptoms, fever, dry cough, headache, myalgia malaise, diarrhoea, shortness of breath
Lethal disease	Acute Respiratory Distress Syndrome (ARDS)	Rapidly progressing pneumonia, possible renal failure	Severe pneumonia†
Patients facing life-threatening and or death	Elderly and persons with pre-existing conditions	Elderly and persons with pre-existing conditions	Elderly and persons with pre-existing conditions
R0 ††	2-5	< 1	1.4-5.5
Case Fatality Rate	9.6%	34.5%	05-3% ¥
Children	5.7%	1%	Infrequently reported ¥¥

Horseshoe bats* *(Rhinolophus Hypposideros* Bat); raccoon dogs and Chinese ferret-badger**; droplets, via direct person-to-person contact°; close contact with: respiratory secrets, urine, unpasteurized milk, saliva, uncooked meat of camels and/or dromedaries or other camelids°°; ACE-2, Human angiotensin-converting enzyme-2 §; DPP4 or CD-26, Human dipeptidyl peptidase §§; reported by WHO from 2012 through 30 November 2019 ^; 14.9% of those who have comorbidity such as hypertension, diabetes, cancer, immunosuppression, hearth or renal failure†; R0; viral transmissibility†† (if *R*0 is less than 1, each existing infection causes less than 1 new infection); in Wuhan, 2.9-3-5%; 0.4% in rest of China ¥; no death under 10 years ¥¥.

protein) responsible for virus entry into the cell after, has confirmed a significant similarity between the new coronavirus and the bat-like SARS-CoV while undelining its difference from the SARS-CoV [31,32]. If these proteins undergo mutations, the result could lead to a greater ability to infect than the bat-like SARS-CoV, but a lower pathogenicity than the SARS-CoV. This may explain its initial lower severity when compared to SARS epidemic [33].

Amino acid analyses have also indicated that SARS-CoV-2 uses the ACE-2 less efficiently than the SARS-CoV, but more efficiently than this [12-13]. In SARS-CoV-2, the presence of asparagine at position 501, which is compatible with, but not ideal for binding human ACE-2, suggests that the virus has acquired the ability for human-to-human transmission, but this appears to be more limited than in the SARS-CoV strain [33].

On January 24th, 2020, the French Ministry of Health confirmed the first three cases of patients affected by the Wuhan coronavirus. On January 29th, 2020, the Institute Pasteur, responsible for monitoring respiratory viruses in France, sequenced the whole genome of the coronavirus known as "SARS-CoV-2", becoming the first institution in Europe to sequence the virus since the start of the initial outbreak. A few days later, in the laboratories of Lazzaro Spallanzani (Rome, Italy), the virus was again isolated from another Chinese couple on vacation in Italy and announced to the world as being named 2019-nCoV/Italy-INMI1, on January, 30th. The viral sequence has already been deposited in the GenBank database, and it is currently available to the international scientific community for development of more sensitive diagnostic tests which will be capable of intercepting the virus rapidly. As a consequence, it is hoped that a way to contain it and possibly, combat it will be found rapidly and consequently, finding a way to contain it and possibly, better fight it.

The SARS-CoV-2 origin is still discussed although the initial cases have been associated with the Huanan South China Seafood Market. As with SARS-CoV and MERS-CoV, SARS-CoV-2 almost certainly originated in bats [30]. The most recent analysis of the SARS-CoV-2 genome has found that it shares 96 percent of its RNA with a coronavirus which was previously identified in a specific bat species in China [31,32]. Such hosts may increase the viruses' genetic diversity by facilitating greater numbers of different mutations.

Although SARS-CoV-2 can cause a severe respiratory illness like SARS and MERS, evidence from clinics has suggested that this virus is generally less pathogenic than SARS-CoV, and much less than MERS-CoV [34].

The Covid-2019 pandemic emerged as an outbreak rapidly and spread to China and other countries, including the United States, killing at the time of writing 3,194 people with more than 81,000 confirmed cases of infection of Chinese nationality (99%), along with approximately 5,415 deaths in predominantly elderly people (age range 58-101 years) and more than 126,000 confirmed cases in 166 countries [35]. In just 2 and a half months SARS-CoV-2 has caused more victims than SARS-CoV in about 8 months and MERS-CoV in eight years [36].

On January 30th, the WHO declared the outbreak of Coronavirus as a Chinese International Public Health Emergency. For the first time in the recent history of infectious diseases, drastic preventive emergency measures were put into practice by the Chinese government to support population prevention and clinical treatment after the outbreak and made remarkable progress in responding to disease control, including quarantine for over 60,000,000 people, contact tracing, social removal measures commensurate with risk, while leading incalculable repercussions for the economy [37]. Two hospitals with other than 1,600 beds each were also built. Moreover, in an attempt to contain the epidemic, the Chinese authorities have blocked transport with 12 Chinese cities, isolating 43 million people. The measure was taken during the Chinese New Year, a period that marks the displacement of hundreds of millions of people within and outside the country .

The rate of increase of infected people in China and the rest of the world compared to January 24th is 555% [35]. While cases in China seem to be decreasing, in other countries of the world particularly Italy, Iran, South Korea and they are increasing day by day. At moment of writing, Italy is in 2nd place globally for the number of COVID-19 infections after China. From 3 cases of infection in Italy prior to February 21th, over 28,600 confirmed cases and 2,978 deaths have been recorded after this date in recent weeks, mainly concentrated in Lombardy, Emilia Romagna, Veneto, Piedmont and Marche, and advancing rapidly in all Italian regions day by day. The majority of deaths were found in people over 65 years of age (between 50 and 101 years of age) suffering from comorbidities and hospitalised in intensive care units (ICU).

To date, one explanation that could justify such a high number of infections could be the fact that in Italy more swabs (more than 1000 per day) are carried out than in any other European country after the COVID-

19 epidemic, or that the virus was circulating in Italy even before flights to China were blocked. In fact, a recent study based on a phylogenetic temporal reconstruction of SARS-CoV-2 phylogeny suggested that the COVID-19 outbreak in Italy started between November and December 2019, several weeks before the first cases were described [38]. A possible reason could be that many people left Wuhan for the traditional Chinese New Year before the closure of the city and went on holiday to other countries including Germany from where the outbreak may have spread to our country. Molecular and viral phylogeny studies are underway to establish and verify this possibility.

If one of these people had already been infected with SARS-CoV-2, potentially the virus could have been transmitted at any time. Finally, another hypothesis concerns the existence of so-called super-spreaders that could have infected a large number of people.

Table 1 describes the most salient features of COVID-19 compared to SARS and MERS CoV. Regarding transmission of COVID-19 infection, apart from respiratory infection by droplets, no other means of transmission for this virus has been definitely proven. It would seem, for instance, that SARS-CoV-2 does not pass into the placenta, fetal blood or breast milk and has not been found in amniotic fluid of pregnant women [39]. In addition, a recent study conducted on women in their third trimester who were confirmed to be infected with the coronavirus, there was no evidence that there was transmission from mother to child probably because pregnant mothers are relatively more susceptible to infection by respiratory pathogens and severe pneumonia [40]. Uncertainties still remain about fecal-oral transmission [35] and too little scientific evidence is still available on this issue.

For COVID-19, the attack rate or transmissibility (Ro) indicating how rapidly the disease spreads, is estimated as being between 1.4 and 2.5 (range 2.2 to 3.58) [41]. In comparison, the Ro for the common flu is 1.3 and for SARS and MERS it was 2.0 and < 1, respectively [4243]. The novel COVID-19 case fatality rate has been estimated at around 2.79% [43], whereas for SARS it was 9.6% and for MERS 34.5% [44].

Available data suggest that COVID-19 has an incubation period of ~5-7 days (range-2-14 days). The complete clinical picture of COVID-19 is not fully understood. Symptoms may appear in as few as 2 days or after as many as 14 (estimated ranges vary from 2-10 days, 2-14 days, and 10-14 days), during which the virus is contagious but the patient does not display any symptom (asymptomatic transmission). Clinical presentation closely resembles diseases from SARS-CoV or MERS-CoV [44]. The most common symptoms are fever, cough, dyspnea, myalgia and asthenia, rarely kidney failure, suggesting fever is dominant but not the main symptom of infection. A small number of patients can have headache or hemoptysis or diarrhea and even be relatively asymptomatic [45]. Mortality is high especially in patients over 65 years with underlying health conditions such as diabetes, hypertension, cardiovascular disease, cancer or other conditions that may compromise their immune systems. As for SARS, no deaths have been reported in the pediatric age group especially under 10 years [44]. Regarding laboratory studies, patients might show normal or lower white blood cell counts, leuko-lymphopenia, or thrombocytopenia, with extended activated thromboplastin time and increased C-reactive protein level [44,46]. Patients presenting with fever together with upper respiratory tract symptoms with leuko-lymphopenia should be suspected, especially for those patients with Wuhan exposure or a close contact history.

Generally, on the basis of existing Chinese data published so far, 80.9% of patients infected with the virus develop mild infection; 13.8% severe pneumonia; 4.7% respiratory failure, septic shock or multi-organ failure. 3% of these are fatal [44-46]. Patients with severe illness have shown to develop ARDS and required ICU admission and oxygen therapy. The average age of hospitalised patients is 57-79 years, with a third to half with an underlying illness. The time between hospital admission and ARDS was as short as 2 days [44]. There is a higher risk of death for men at 2.8% while it remains at 1.7% for women [44]. Although the fatality rate will continue to change until all infected people recover, it appears that the novel SARS-CoV-2 is less pathogenic than SARS-CoV (~10%), and much less than MERS-CoV (~40%) [28,37].

The Spillover Consequences

As happened with measles, rabies, Ebola, Dengue, HIV-1, Marburg and Lassa fever, Swine and avian Flu (H1-N1and H3-N7 respectively), the new coronavirus diseases that have come to the forefront lately such as SARS in 2003, also recognize an animal origin [4,14,47]. Viruses from certain animals (e.g. wild birds, bats, monkeys) have reached humans through species jump (spillover). Deforestation (which provides space for livestock farms and our overcrowded cities), altered ecosystems (which provide shelter for wildlife), illegal trading with wildlife (Bushmeat), intensive domestic

animal husbandry, and large-scale distribution of uncontrolled food of animal origin are all factors that may have contributed to the consequences of such spillover. Rapid world population growth and intercontinental travel ('virus shift' on low cost flights) have also provided a significant contribution [47].

The origin of SARS-CoV, still remains yet elusive. SARS-CoV virus has been identified in palm civets, raccoons, dogs and Chinese ferret-badgers (intermediary source) found in live animal markets from Guangdong, China and some bats species (horseshoe bats) which are the primary reservoir of coronaviruses, and were found to be closely related to those responsible for the SARS outbreak [46,48]. MERS-CoV was believed to originate in horse bats that reside in China, Europe and Africa and these infections were transmitted directly to humans from market civets and dromedary/camels, respectively [48]. Extensive research on MERS-CoV led to the discovery of many MERS-like coronaviruses in bats which being SARS-like, are likely to emerge periodically in humans owing to frequent cross-species infections and occasional spillover events. In addition, recent studies indicated that bats have unique defense mechanisms that allow them to be persistently or latently infected with viruses [14]. Less recent findings have demonstrated that several bat Coronavirus are capable of infecting human cells without a need for intermediate adaptation [24;49]. Since the mutation in the original strain could have directly triggered virulence towards humans, it is not certain that this intermediary exists.

As for SARS-CoV-2 it cannot be excluded that a spillover effect comes into play, *i.e.*, a biological mechanism linked to animal-human promiscuity. In fact, many Chinese patients claim to have visited the southern China seafood and wildlife market in Wuhan in November 2019. In addition to seafood, it was reported that snakes, birds and small mammals including marmots and bats, were reportedly sold at the Wuhan Market. To this end, the WHO has reported that environmental samples taken from the market were positive at PCR for the new coronavirus, but no specific animal association has been identified [50,51]. It also seems there were no bats being sold at the animal market in Wuhan, China, where the current outbreak is thought to have begun, suggesting an intermediate host species was likely involved, which is yet unknown. Although the snakes have been called into question, there is no historically evidence of any coronavirus being hosted by animals other than mammals and birds. However, on the basis of recent phylogenetic data it is not unlikely that SARS-CoV-2 passed directly from bats to humans without the intermediate host [31].

Whatever the intermediate animal, it cannot be excluded that the spillover effect may involve a mechanisms similar to those in SARS or MERS, although there may be other animals involved.

Conclusions

Started as an epidemic in China, and then spreading to other countries quickly, COVID-19 has now been officially declared a pandemic by the WHO on March, 11, 2020. This new pandemic, which is considered a global health emergency, prompts some considerations:

1. In the globalization era, no country can neglect or hide an emerging epidemic. From SARS, initially spreading unnoticed worldwide to SARS-2-CoV, China did not alert its citizens until late January despite researchers warned about a new epidemic in early December 2019. This may have delayed the implementation of containing strategies that could have reduced the viral spread, such as suspected cases without adequate restriction and continuing their work activity.

2. Animal health surveillance systems play an important role in anticipating, detecting and containing outbreaks and should be increasingly integrated with human public health surveillance systems. In this regard, Coronavirus outbreaks from the past and more ones recent teach us that such occurrences do not come out of nowhere, but always arise from inappropriate human activity. Examples arise from deforestation and the alteration of natural ecosystems, which, by offering shelter to wildlife, deprive viruses of their natural hosts, thus providing the basis for new infections to humans [52]. In addition, the intensive rearing of domestic animals, such as chickens and pigs, is considered under special surveillance by health authorities around the world. In fact, one of the last pandemics (between 2009 and 2010) was triggered by a virus of swine origin, H1N1, which caused more than 220,000 deaths worldwide [53]. Blaming bats or civets or camels is of little use and only serves to camouflage the underlying reasons for the next global health emergency.

3. Since 2002/2003, the new SARS pandemic has been raising questions about how these pathogens evolve and what makes infections mild or severe [20]. The fear and panic brought by the new COVID-19 outbreak has made us realise that the history of zoonotic diseases continues to repeat itself over time [54]. To stop the spread of the novel COVID-19, the Beijing government has temporarily banned the trade in wild animals. A similar measure was also introduced in 2003

for SARS, but after the emergency everything was back to normal. Continuous surveillance of mammals and birds will be essential for a better understanding of the ecology of coronaviruses and for the prevention of animal-to-human transmissions and epidemics in the future.

General Perspectives, Vaccine and Treatment Options

The morbidity, mortality, mental health impact and psychological effects due to the new COVID-19 are currently difficult to predict. Ad COVID-19 is now a pandemic, careful surveillance is essential to monitor its future host adaption, viral evolution, infectivity and transmissibility. Other critical issues include identifying reservoirs, defining exactly the incubation period, characterizing the clinical spectrum of the disease, exploring the potential for long-term health effects and understanding sensitive populations. Reducing the spread and transmission of the infection for this new coronavirus is today the best preventive strategy we can have in the absence of vaccine or specific drugs. The possibility of transmission before the development of symptoms cannot be excluded. This raises the problem that asymptomatic individuals could transmit the virus, suggesting that the use of isolation is the best way to contain this pandemic.

As soon as the COVID-19 outbreak began, China implemented impressive infection containment measures consisting of closing entire cities, blocking airports, ships, trains and car traffic, with quarantine for millions and millions of people. Thanks to these draconian measures, in more than a month and shortly after the discovery of the COVID-19 epidemic, the number of infected Chinese people has almost halved and deaths are decreasing day by day.

In Italy, the government has taken similar measures to contain the infection and contagion. Entire regions have been isolated as was the case for Lombardy. Now, the entire Italy. We still do not know whether these measures work as they do in China.

Another important point regards the super-spreader. The identification of possible super-spreaders, defined as contagious hosts that create more secondary contacts than most others in the population, will be a new objective to achieve, although it is thought that super-spreading may have already occurred in the current epidemic [55]. All these points will be a critical component of retrospective analyses to define the current pandemic [20].

So far, as with SARS and MERS, there is not a vaccine although several studies are currently underway [12]. Moreover, there are no proven and specific antiviral therapies for COVID-19 although there are agents that were used during the SARS and MERS. In this regard, although no specific anti-SARS-CoV-2 treatment is recommended because of the absence of evidence, several clinical trials, are underway to examine existing antiviral drugs to identify those that could be specific and effective against COVID-19 [56].

In this setting, two classes of potential targets are viral polymerases and protease inhibitors, both of which are components of human immunodeficiency virus (HIV) and hepatitis C virus (HCV) antiviral regimens. Chinese experimental studies suggest taking an antiviral therapy based on a cocktail of anti-HIV drugs with lopinavir/ritonavir together with inhalation of a nebulized interferon dose [56,57].

Lopinavir/ritonavir (LPV/r) (Mylan), belongs to the category of protease inhibitors and is currently being used in combination with other antiretroviral drugs such as Darunavir/ritonavir and darunavir/cobicistat, for the treatment of HIV infection, with limited side effects and a known safety profile. LPV/r has been associated with a possible clinical benefit in the treatment of patients affected by SARS and MERS by improving the clinical, radiological, pathological outcome and reducing the viral load in treated animals compared to untreated animals [10,12;58]. Similarly, although preliminary findings have shown that the administration of LPV/r is able to reduce the viral load of COVID-19 very rapidly [56,57], more recent findings suggest that in hospitalized adult patients with severe Covid-19, no benefit was observed with LPV/r treatment beyond standard care [59].

Remdesivir (RDV) (Gilead, USA), an experimental compound with a broad spectrum of activity against RNA viruses including SARS-CoV and MERS-CoV [58,60], has been tested in severely ill patients suffering from SARS-CoV-2, giving encouraging results in the USA and prompting further clinical trials especially in countries particularly affected by COVID-19 including Italy [60-62]. RDV is not yet approved by regulatory authorities for therapeutic use and is provided for compassionate use - outside clinical trials - for the emergency treatment of individual patients with COVID-19 in severe conditions and without valid therapeutic alternatives.

The use of chloroquine phosphate, an old drug for the treatment of malaria with immunomodulating activity, has been shown to have an apparent efficacy and acceptable safety against pneumonia associated with COVID-19 in multicentric clinical trials conducted in China [34;63]. The clinical evidence, however,

although increasing in the last months, needs to be assessed by further clinical trials.

Hopes may also arise from the use of Tocilizumab (Roche), already known for its effectiveness against rheumatoid arthritis and first tested at Naples' Pascale Hospital, Italy, on a few patients suffering from very severe forms of pneumonia from COVID-19. This monoclonal antibody, reducing the "cytokine storm" and especially IL-6, is able to reduce the time of assisted ventilation in ICU.

Attempts to use plasma obtained from previously infected patients have been made to treat COVID-19 in severely ill patients, as reported in patients with convalescent SARS [64]. The antibodies contained in the convalescent plasma could suppress viremia and thus improve the clinical response of these patients without the occurrence of severe adverse events, as demonstrated by other severe acute respiratory infections of viral etiology [65]. Patients with resolved infection should therefore produce high titres of polyclonal anti-SARS-COV-2 antibodies neutralising the virus and thus preventing new infectious cycles.

Further work is needed to improve strategies for prevention, diagnosis and treatment of this new emerging disease. Research also still needs to fully exactly clarify the pathogenetic mechanism of SARS-CoV-2 in order to build reproducible animal models to develop effective measures to combat not only the latter zoonotic viruses but also other potential emerging zoonotic infectious diseases potentially evolving into pandemics. In this context, new technologies have multiplied to address and improve the readiness to respond to the growing but unpredictable threat posed by emerging pathogens, as the recent past has taught us [66].

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Conflict of interests: No conflict of interests is declared.