

COVID-19: a brief history and treatments in development

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Coronavirus disease (COVID-19) is now dominating the lives of everyone, and its history is constantly being rewritten. This article gives a brief account of the story so far: where SARS-CoV-2 might have originated, how it compares with other viruses that cause major respiratory disease, and some of the treatments and vaccines currently being investigated to combat it.

On 31 December 2019, the World Health Organization (WHO) was formally notified about a cluster of cases of pneumonia in Wuhan City, home to 11 million people and the cultural and economic hub of central China. By 5 January, 59 cases were known and none had been fatal.¹ Ten days later, WHO was aware of 282 confirmed cases, of which four were in Japan, South Korea and Thailand.² There had been six deaths in Wuhan, 51 people were severely ill and 12 were in a critical condition. The virus responsible was isolated on 7 January and its genome shared on 12 January.³ The cause of the severe acute respiratory syndrome that became known as COVID-19 was a novel coronavirus, SARS-CoV-2. The rest is history, albeit history that is constantly being rewritten: as of 12 May, 82,591 new cases of COVID-19 worldwide were being confirmed daily and the death rate was over 4200 per day.⁴

Coronaviruses in man

Phylogenetic analysis suggests that SARS-CoV-2 originated in animals, probably bats, and was transmitted to other animals before crossing into humans at the Huanan wet market in Wuhan City.^{5,6} There is some evidence that the intermediate vector may have been pangolin, a type of nocturnal anteater imported illegally for its flesh. This animal carries a coronavirus that is very similar to SARS-CoV-2 but differs in a crucial region that determines viral infectivity and host range. It is therefore possible that the virus passed into humans and then, through adaptation as it infected more people, mutated to acquire the characteristics that made it spread so quickly.

SARS-CoV-2 is not the first coronavirus to cause outbreaks of respiratory infection in humans. Six others have been identified so far, all believed to have originated in animals.^{6,7} The four coronaviruses that are now endemic in humans cause 10–15% of common colds, mostly peaking between December and April

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in temperate climates.⁸ NL63 and 229E probably came from bats; OC43 and HKU1 seem to have originated in rodents. Each of these causes mild symptoms, though OC43 has ancestry as a bovine coronavirus that may have caused a pandemic at the end of the 19th century.

Two non-endemic coronaviruses have caused serious disease. SARS-CoV was the first to be recognised, occurring first in November 2002 in China (though not known at the time) and coming to the attention of WHO early in 2003 in Viet Nam.⁹ The outbreak was largely over by July, and the last cases were reported in China in April 2004. This virus was responsible for Severe Acute Respiratory Syndrome (SARS), a flu-like illness, though diarrhoea was common. It could progress to pneumonia and respiratory failure in two weeks and 25% of people infected required intensive care. A total of 8098 cases and 774 deaths were notified.¹⁰ SARS-CoV appears to have originated in horse-shoe bats and possibly transmitted to humans via palm civet cats, traded in China for their meat.

The second serious infection due to a coronavirus was Middle Eastern Respiratory Syndrome (MERS). The MERS-CoV virus was first identified as the cause of a fatal infection in Saudi Arabia in 2012.¹¹ It spread to 27 countries. Unlike SARS, MERS is still prevalent and, as of November 2019, 2494 infections had been notified, of which 858 proved fatal.¹² Like SARS, MERS causes a flu-like illness with symptoms ranging from mild (with about one-quarter of people also having diarrhoea) to severe pneumonia, acute respiratory distress syndrome, septic shock and multiorgan failure. MERS-CoV is believed to have reached humans via dromedary camels, which appear to be a reservoir in several Middle East states. The original source species is not known, but bats are the most likely.

SARS-CoV-2 more closely resembles the bat wild virus than it does either SARS-CoV or MERS-CoV, strongly suggesting that it is a novel coronavirus in humans.⁵ The coronavirus spike protein – the structure that binds the virus to the target receptor and mediates cell entry – requires six amino acids: SARS-CoV-2 shares only one of these with SARS-CoV. This spike protein confers high affinity for angiotensin-converting enzyme 2 (ACE2), the host receptor in humans (and many other species, including pigs, primates and cats).¹³ The second major structural difference from SARS-CoV is a unique subunit of the spike protein that determines viral infectivity and host range. It may have been a mutation of this feature during human infection that led to the rapid spread of COVID-19 in humans. There is currently no evidence that any of the mutations identified since SARS-CoV-2 virus emerged in humans have altered the key characteristics of COVID-19.⁸

How do major respiratory viral infections compare?

Outbreaks of MERS-CoV now occur mostly due to animal-to-human transmission (probably during the camel calving season).¹⁴ Person-to-person spread seems to depend on close contact, such as providing care to an infected person or within a hospital setting. In all, 40% of confirmed cases have been acquired nosocomially – on one day in May 2015, an individual

with MERS visited several hospitals in Korea and infected 186 people.¹¹

SARS-CoV is transmitted via droplets in respiratory aerosol, contact with surfaces and possibly via faecal-oral contact.¹⁰ Within one month of 55 index cases being recognised in Hong Kong, Hanoi and Singapore, a total of 3000 cases had been confirmed globally with a peak reporting rate of 200 new cases per day.¹⁵ At the time, this was described as devastating. For comparison, one month after 5 January when the first 59 cases of COVID-19 were recognised, 24,554 cases had been confirmed globally.¹⁶

These figures are influenced by the restrictions on travel and lockdown measures recommended by WHO in liaison with governments to control the spread of infection. They are not, therefore, solely an indicator of the natural pathogenicity of the viruses.

The COVID-19 pandemic has often been compared with global influenza outbreaks in an attempt to put this new threat in an historical context. According to WHO data, seasonal flu causes three to five million cases of severe illness and 290,000–650,000 deaths from respiratory disease each year.¹⁷ H1N1, the virus that caused the swine flu pandemic of 2009/10, infected 11–21% of the global population (750 million – 1.4 billion people) and caused around 280,000 deaths from respiratory disease and cardiovascular disorders; about two thirds of those deaths occurred in people aged 18–64 years.^{18,19} As of 12 May, the number of deaths attributed to COVID-19 worldwide has already surpassed 280,000.⁴

COVID-19 infection

Like SARS-CoV, the SARS-CoV-2 virus responsible for COVID-19 can survive in aerosols for hours and on surfaces including stainless steel, plastic and cardboard for days,²⁰ although washing with soap or detergent will destroy the virus. It can be transmitted during the asymptomatic incubation phase (this is estimated to occur in 50–60% of cases) and for up to two weeks after the onset of symptoms.²¹ Each person infected passes the virus on to an average of three others.⁸ The incubation period is about 5–6 days (range 1–14 days). Clinical presentation varies from asymptomatic, subclinical infection and mild illness to severe or fatal illness; deterioration can occur rapidly, often during the second week of illness.⁸ Viral load is up to 60 times greater in people with severe symptoms compared with mild cases. Death is due to pneumonia and possibly hyperinflammation associated with cytokine storm syndrome.²² Hospitalisation rates and crude mortality rates in Europe up to 22 April, showing the influence of increasing age, are shown in Figures 1 and 2.

As reported on 21 April, the most common symptoms of COVID-19 reported in Europe are fever/chills (49%), dry or productive cough (24%), sore throat (12%), general weakness (8%), pain (7%), rhinorrhoea (4%) and diarrhoea (2%).⁸ These data are largely from Germany and may not be representative of all COVID-19 cases. Complications include cardiomyopathy, thrombosis, acute kidney injury and encephalitis.

Probable risk factors for severe disease and death include increasing age, being of minority ethnic background, immunosuppression, hypertension, diabetes, cardiovascular disease, chronic respiratory disease, obesity, smoking and cancer. Men in these groups appear to be at higher risk. Chronic obstructive pulmonary disease (COPD), cardiovascular disease and hypertension are strong predictors of admission to intensive care.^{23,24}

Some risk factors may be explained by the virus's affinity for ACE2, which is expressed by the epithelial cells of the lung, intestine, kidney and vasculature.²⁵ ACE2 expression is upregulated in older people, tobacco smokers, and people with diabetes or hypertension, many of whom are treated with ACE inhibitors, and by the glitazones and ibuprofen. However, two recent studies from Italy and the USA^{26,27} have shown that treatment with an ACE inhibitor or angiotensin II-receptor blocker (or indeed any other single antihypertensive agent) is not associated with an increased risk of contracting COVID-19, severe symptoms or a fatal outcome. The link therefore appears to be simply due to the higher risk associated with cardiovascular disease.

The latest advice (14 April) from the Commission on Human Medicines (CHM) is that there is insufficient evidence to establish a link between NSAIDs/ibuprofen and susceptibility to COVID-19 or worsening of symptoms, and it says patients can take either paracetamol or ibuprofen when self-medicating for symptoms of COVID-19. However, additional risks are plausible, and a rapid evidence summary from NICE rounds up all the evidence on this topic to date (ES23).²⁸

Treatments under evaluation for COVID-19

Management of the complications of COVID-19 relies on supportive care and oxygen supplementation via non-invasive or mechanical ventilation. Patients who are critically ill may require vasopressor support and antibiotics for secondary bacterial infections.⁸

The search for drugs and vaccines to treat or prevent COVID-19 began quickly but, with many studies carried out independently in small numbers of people, there is a risk that the trials will lack statistical rigour. WHO has launched a non-blinded clinical trial (SOLIDARITY) to evaluate four candidate treatments (remdesivir, lopinavir/ritonavir, lopinavir/ritonavir/interferon beta-1a, and chloroquine or hydroxychloroquine) versus standard of care in 18 countries worldwide. France is coordinating the Discovery trial to compare the same drugs with standard care in 3200 patients in Belgium, France, Germany, Luxembourg, the Netherlands, Spain, Sweden and the UK. This will be randomised but non-blinded and will assess outcomes at 15 days.^{29,30}

Table 1 lists some of the drugs currently reported as under investigation specifically for treating COVID-19; others that have shown potential for the treatment of SARS and MERS are also being evaluated on the basis that the viruses share structural similarities with SARS-CoV-2. These include novel agents in development and antivirals currently in use for other indications, and several studies have also evaluated potential treat-

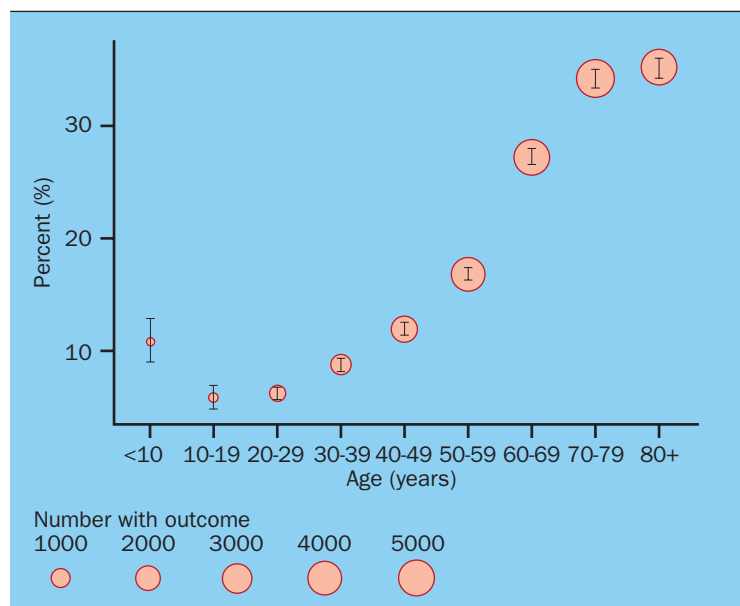


Figure 1. Age-specific hospitalisation rates among all reported cases of COVID-19, data from 14 countries in the European Surveillance System up to 22 April 2020⁸

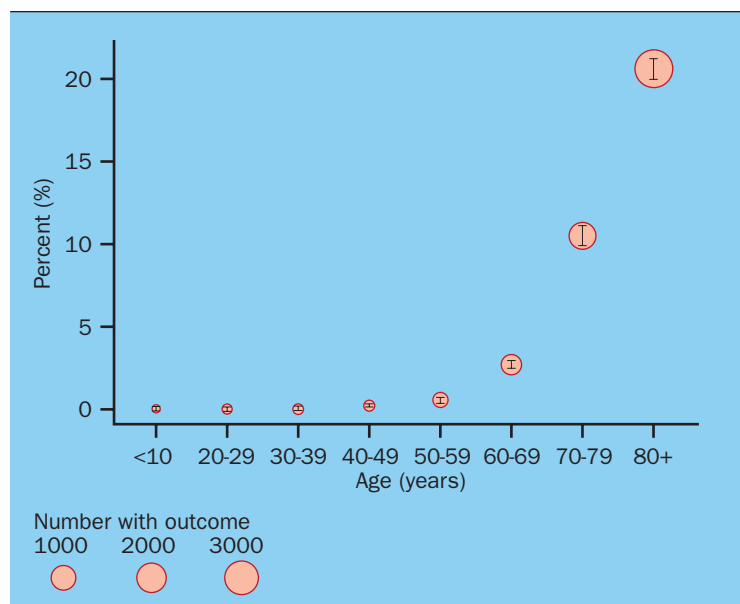


Figure 2. Age-specific crude case fatality (deaths/all reported cases of COVID-19), data from 13 countries in the European Surveillance up to 22 April 2020⁸

ments *in vitro*.³¹⁻³³ Treatments appear to have been introduced in China but are not well reported in English language scientific literature. China, as the country with the longest experience of managing COVID-19, is likely to have valuable expertise to share with other states. To date (early May), no drug treatment has been proven to be effective.

A trial claiming to show efficacy with hydroxychloroquine plus azithromycin received wide coverage in the lay media.³⁴

This study had important methodological flaws and its conclusions have been disputed.³⁵ In addition, this combination is associated with an increased risk of QT prolongation. A controlled trial indicated that the combined viral protease inhibitor formulation of lopinavir/ritonavir is ineffective.³⁶ An uncontrolled trial of remdesivir, which has *in vitro* activity against SARS-CoV-2, achieved improvement in 36 of 53 (68%) severely ill patients (oxygen saturation \leq 94% or receiving oxygen sup-

port).³⁷ More recently (29 April), a randomised control trial has been published from China (n=237),³⁸ and headline results released from a global phase 3 trial (ACTT, n=1063).³⁹ Both included hospitalised patients with pneumonia and confirmed COVID-19. In the Chinese study, remdesivir did not significantly reduce time to clinical improvement, though there was a trend towards faster improvement in patients with a symptom duration of 10 days or less. By contrast, the ACTT study suggested

Candidate	Possible mechanism(s) of action	Development status
Chloroquine or hydroxychloroquine	<ul style="list-style-type: none"> Impairs virus release after cell entry Impairs virus binding to cell receptor Modulates immune response Hydroxychloroquine is associated with fewer adverse effects than chloroquine 	Given FDA Emergency Use Authorisation in the USA, but the MHRA states it should only be used within a clinical trial. Being investigated in the WHO SOLIDARITY trial
Hydroxychloroquine + azithromycin	<ul style="list-style-type: none"> Hydroxychloroquine as above Azithromycin – possible antiviral activity and prevention of secondary bacterial infection 	One trial suggests reduction in viral nasopharyngeal carriage at 6 days in 20 patients compared with unmatched untreated cohort, with azithromycin reinforcing the effect of hydroxychloroquine ³⁴
Lopinavir/ritonavir	<ul style="list-style-type: none"> Viral protease inhibitors May inhibit SARS virus and reduce adverse outcomes of infection 	Randomised trial (n=200) suggested no benefit. ³⁶ Trial now underway in combination with steroids. Being investigated in the WHO SOLIDARITY trial
Interferon beta-1a	<ul style="list-style-type: none"> May counter suppression of interferon beta by SARS-CoV-2 	Administered by inhalation; trial underway to determine impact on severity of complications
Remdesivir	<ul style="list-style-type: none"> Blocks viral RNA synthesis Broad-spectrum activity against coronaviruses 	Given Emergency Use Authorisation in the USA; EMA rolling review underway. Clinical trials now reporting preliminary results; ^{38,39} ACTT trial indicates beneficial effect on time to recovery. One of the drugs in the WHO SOLIDARITY trial
Tocilizumab	<ul style="list-style-type: none"> Blocks interleukin-6 signalling, which may counter cytokine release syndrome in severe COVID-19 	Trial supported by US FDA underway (COVACTA) in patients with severe COVID-19 pneumonia
Favipiravir + interferon alpha	<ul style="list-style-type: none"> Blocks viral RNA synthesis Stimulates innate antiviral response 	Trials underway in China
Favipiravir + baloxavir marboxil	<ul style="list-style-type: none"> Blocks viral RNA synthesis Baloxavir licensed in USA for flu 	
Favipiravir vs umifenovir	<ul style="list-style-type: none"> Blocks viral RNA synthesis Blocks virus-cell fusion 	In an unreviewed randomised non-blinded trial (n=240), clinical recovery rates at 7 days were similar for favipiravir and umifenovir. ⁴⁰ Trials of favipiravir underway in India
Ribavirin + interferon alpha, lopinavir/ritonavir + interferon alpha, and ribavirin + lopinavir/ritonavir + interferon alpha	<ul style="list-style-type: none"> Ribavirin may reduce viral replication Triple therapy recommended by National Health Commission of the People's Republic of China. Guidelines for diagnosis and treatment of novel coronavirus pneumonia (Trial Version 5) 2020 	Trials underway in China ⁴¹

Table 1. Drugs under investigation for the treatment of COVID-19^{29,32}

that treatment with remdesivir was associated with a more rapid recovery compared with placebo (median time to recovery 11 vs 15 days, $p < 0.001$), and there was a trend towards improved mortality (8.0 vs 11.6%; $p = 0.059$). More data is needed to provide a clearer picture on its benefits.

Work on vaccines is also developing quickly. In March, WHO identified two vaccines in phase 1 trials and 42 in preclinical development.⁴² A review published on 9 April described 115 candidate vaccines, of which the development status is unknown for 37.⁴³ Of the 78 projects known to be progressing, 73 were noted to be in exploratory or preclinical stages and five in phase 1 trials.

These vaccines are being developed using a diverse range of delivery platforms, including DNA and RNA, self-amplifying RNA, virus-like particle, peptide, viral vector, recombinant protein, live attenuated virus and inactivated virus. RNA and DNA delivery platforms offer rapid development of a vaccine from sequencing the virus to beginning a clinical trial. In the case of one vaccine now in trials, the interval between sequencing the virus genome and beginning the clinical trial was only 10 weeks. Others, including the Oxford Vaccine Centre's ChAdOx1nCoV-19 vaccine, for which phase 1 clinical trials are now underway in the UK, use a non-replicating viral vector such as an adenovirus.

Specialists at the Coalition for Epidemic Preparedness and Innovation have highlighted three challenges to vaccine development.⁴⁴ There is uncertainty about which is the optimal target antigen on SARS-CoV-2. Experience with vaccines against SARS and MERS infections revealed a risk of exacerbating lung disease, therefore testing in animal models is essential. And the duration of immunity and effectiveness of single-dose vaccines is unknown. To this can be added the challenge of upscaling production to meet the urgent global demand. Given the seriousness of the challenge posed by COVID-19, there may be calls to waive some of the usual requirements for evidence of safety to accelerate access to a vaccine. For example, an experimental vaccine was used to control an outbreak of Ebola virus disease in Guinea in 2015.⁴⁵

The idea that herd immunity might protect the population from SARS-CoV-2 has proved controversial, largely because it is a concept normally applied to immunisation programmes rather than a pandemic with a high mortality rate. For herd immunity to be effective in the UK, the proportion of the population with immunity must exceed the threshold of about 65%.⁴⁶ Achieving that level by national exposure to the virus would be associated with an unacceptable number of deaths. However, the extent to which lockdown measures can ultimately prevent rather than delay infection is uncertain, and it is unknown how the death rate would compare with the final mortality after the pandemic has run its course.

The preferred way to build herd immunity is through vaccination. It is currently uncertain when a vaccine will be available to the general population; it is likely that frontline health workers would be the first to receive it, then high-risk individuals. How quickly production can be scaled up to meet inter-

national demand is another unknown. There has been some anxiety in the media that infection may not confer lasting protection against SARS-CoV-2. However, evidence from an animal study⁴⁷ suggests that reinfection will not occur, and some cases of alleged re-infection have been errors due to unreliable testing or relapse. It has also been suggested⁴⁸ that prior infection by established coronaviruses might confer partial immunity, and that may partially explain why some people have only very mild symptoms. However, more evidence is needed.

Summary

COVID-19 presents an enormous global challenge that has required levels of intervention on a scale that is unprecedented. In one sense, it is a new threat: SARS-CoV-2 emerged as a novel virus to which humans had no immunity, it spreads exceptionally quickly, carries a high mortality and can overwhelm the capacity of health services to treat the most seriously ill. But it is not incomparable: similarities with other coronaviruses and recent epidemics mean that infection control measures are well-rehearsed and existing technologies can be deployed to speed the development of new vaccines and treatments.

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Declaration of interests

None to declare.

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