Bernd Sebastian Kamps
Christian Hoffmann

COVID REFERENCE

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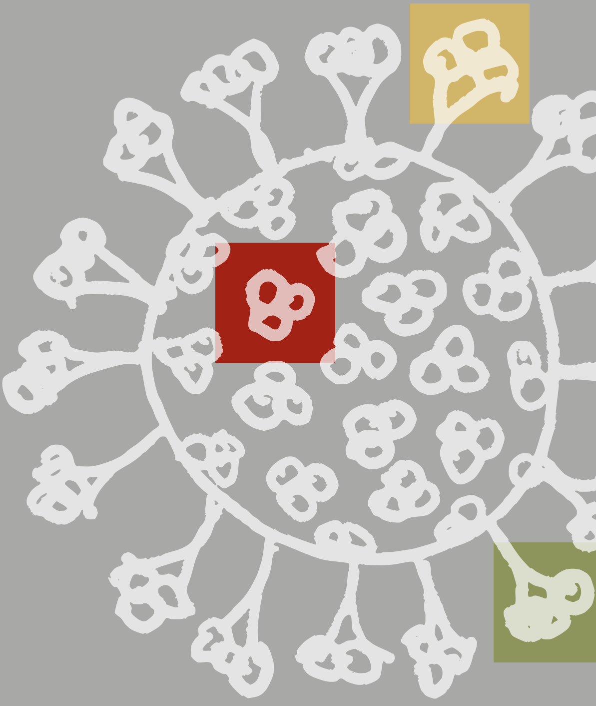

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Bernd Sebastian Kamps
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Preface

Seventeen years ago, in the middle of the outbreak, we decided to write a short medical text about the ongoing SARS drama, presenting the scientific data and providing real-time updates. After publishing three editions in 6 months, a scientific magazine concluded that our *SARS Reference* (www.SARSReference.com) was "not fancy", but presented "plenty of information". When we became aware of the new coronavirus epidemic in mid-January 2020, we immediately felt that time had come to repeat our millenium exercise.

While SARS-CoV-2 seems under control in China, the epidemic is moving west briskly. What only weeks ago seemed an impossible feat – imposing and enforcing strict quarantine measures and isolating millions of people – is now a reality in many countries. People all over the world will have to adapt and invent new lifestyles in what is the most disruptive event since World War II.

We believe that the current situation needs a new type of textbook. Humanity is confronting an unknown and threatening disease which is often severe and fatal. Health care systems are overwhelmed. There is no proven treatment and vaccines will not be available soon. Such a situation has not existed since the flu pandemic in 1918.

We believe a clear head is crucial in times of over-information, with dozens of scientific papers published *every day*, news about hundreds of studies being planned or already on the way and social media blending hard data with rumors and fake news. The tedious work of screening the scientific literature and the scientific data has to be done – regularly & constantly, like a Swiss watch.

Over the coming months, COVID Reference will be presenting updates on a weekly basis and narrating the scientific data as coherently as possible.

Remember Science Magazine. It isn't fancy.

Bernd Sebastian Kamps & Christian Hoffmann

29th March 2020

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1. Timeline

Thursday, 12 December

In **Wuhan**, health officials start investigating patients with viral pneumonia. They eventually find that most patients have visits to the Huanan Seafood Wholesale Market in common. The market is known for being a sales hub for poultry, bats, snakes, and other wildlife animals.

Monday, 30 December 2019

Li Wenliang (en.wikipedia.org/wiki/Li_Wenliang), a 34-year-old ophthalmologist from Wuhan, posts a message on a WeChat group alerting fellow doctors to a new disease at his hospital in late December. He writes that seven patients have symptoms similar to SARS and are in quarantine. Li askes his friends to inform their families and advises his colleagues to wear protective equipment.

Tuesday, 31 December 2019

The Wuhan police announce that they are investigating eight people for spreading rumors about a new infectious diseases outbreak (see 30 December).

The Wuhan Municipal Health Commission reports 27 patients with viral pneumonia and a history of exposure to the Huanan Seafood Wholesale Market. Seven patients are critically ill. The clinical manifestations of the cases were mainly **fever**, a few patients had **difficulty breathing**, and chest radiographs showed **bilateral lung infiltrative lesions**. The report says that the “disease is preventable and controllable”. WHO is informed.

http://wjw.wuhan.gov.cn/front/web/showDetail/2019123108989

Thursday, 1 January

The Huanan Seafood Wholesale Market is shut down.

Friday, 3 January

Li Wenliang is summoned to a local public security office in Wuhan for “spreading false rumours”. He is forced to sign a document where he admits having made “false comments” and “disrupted social order.” Li signs a statement agreeing not to discuss the disease further.

On the Weibo social network, Wuhan police say they have taken legal action against people who “published and shared rumors online”, “causing a negative impact on society”. The following day, the information is taken up by CCTV, the state television. CCTV does not specify that the eight people accused of “spreading false rumors” are doctors.

Sunday, 5 January

WHO alerts that 44 patients with pneumonia of unknown etiology have been reported by the national authorities in China. Of the 44 cases reported, 11 are severely ill while the remaining 33 patients are in stable condition. https://www.who.int/csr/don/05-january-2020-pneumonia-of-unkown-cause-china/en/

Tuesday, 7 January

Chinese officials announce that they have identified a **new coronavirus** (CoV) from patients in Wuhan (pre-published 17 days later: https://doi.org/10.1056/NEJMoa2001017). Coronaviruses are a group of viruses that cause diseases in mammals and birds. In humans, the most common coronaviruses (HCoV-229E, -NL63, -OC43, and -HKU1) continuously circulate in the human population; they cause colds, sometimes associated with fever and sore throat, primarily in the winter and early spring seasons. These viruses are spread by inhaling droplets generated when infected people cough or sneeze, or by touching a surface where these droplets land and then touching one's face.

Sunday, 12 January

The genetic sequence of the new coronavirus has been made available to WHO. Laboratories in different countries start to produce specific **diagnostic PCR tests**. (The Chinese government reports that there is no clear evidence that the virus passes easily from person to person.)

Two days after starting coughing, Li Wenliang (see 30 December) is hospitalized. He will later be diagnosed with COVID.

Monday, 13 January

Thailand reports the first case outside of China, a woman who had arrived from Wuhan. Japan, Nepal, France, Australia, Malaysia, Singapore, South Korea, Vietnam, Taiwan, Thailand and South Korea report cases over the following 10 days.

Saturday, 18 January

The Medical Literature Guide **Amedeo** (www.amedeo.com) draws the attention of 50,000+ subscribers to a study from Imperial College London, *Estimating the potential total number of novel Coronavirus cases in Wuhan City, China*, by Imai et al. The authors estimate that "a total of 1,723 cases of 2019-nCoV in Wuhan City (95% CI: 427 – 4,471) had onset of symptoms by 12th January 2020". Officially, only 41 cases were reported by 16th January.

Monday, 20 January

China reports three deaths and more than 200 infections. Cases are now also diagnosed outside Hubei province (Beijing, Shanghai and Shenzhen). Asian countries begin to introduce mandatory screenings at airports of all arrivals from high-risk areas of China.

Thursday, 23 January

In a bold and unprecedented move, the Chinese government puts tens of millions of people in **quarantine**. Nothing comparable has ever been done in human history. Nobody knows how efficient it will be.

All events for the Lunar New Year (starting on January 25) are cancelled.

WHO declares that the outbreak does not yet constitute a public emergency of international concern as there is "no evidence" of the virus spreading outside of China.

Friday, 24 January

At least 830 cases have been diagnosed in nine countries: China, Japan, Thailand, South Korea, Singapore, Vietnam, Taiwan, Nepal, and the United States.

Zhu et al. publish their comprehensive report about the isolation of a **novel coronavirus** which is different from both MERS-CoV and SARS-CoV (full-text: https://doi.org/10.1056/NEJMoa2001017). They describe sensitive assays to detect viral RNA in clinical specimens.

Wang et al. publish the **clinical features** of 41 patients (full-text: doi.org/10.1016/S0140-6736(20)30185-9).

Chan et al. describe a **familial cluster** of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission (full-text: doi.org/10.1016/S0140-6736(20)30154-9).

Saturday, 25 January

The Chinese government imposes travel restrictions on more cities in Hubei. The number of people affected by the quarantine totals **56 million**.

Hong Kong declares an emergency. New Year celebrations are cancelled and links to mainland China restricted.

Thursday, 30 January

The WHO declares coronavirus a global emergency. In the meantime, China reports 7,711 cases and 170 deaths. The virus has now spread to all Chinese provinces.

Friday, 31 January

Li Wenliang publishes his experience with **Wuhan police station** (see 3 January) with the letter of admonition on social media. His post goes viral.

India, the Philippines, Russia, Spain, Sweden, the United Kingdom, Australia, Canada, Japan, Singapore, the US, the UAE and Vietnam confirm their first cases.

Sunday, 2 February

The first death outside China, of a Chinese man from Wuhan, is reported in the **Philippines**. Two days later a death in Hong Kong is reported.

Thursday, 6 February

Li Wenliang, who was punished for trying to raise the alarm about coronavirus, dies. His death sparks an explosion of anger, grief and demands for freedom of speech: https://www.theguardian.com/global-development/2020/feb/07/coronavirus-chinese-rage-death-whistleblower-doctor-li-wenliang.

Friday, 7 February

Hong Kong introduces **prison sentences** for anyone breaching quarantine rules.

Monday, 10 February

Amedeo launches a weekly Coronavirus literature service which would later be called ***Amedeo COVID-19***.

Tuesday, 11 February

Less than three weeks after introducing mass quarantine measures in China, the number of daily **reported cases starts dropping**.

The WHO announces that the new infectious disease would be called **COVID-19** (**Co**rona**vi**rus **d**isease 20**19**).

Wednesday, 12 February

On board the Diamond Princess **cruise ship** docked in Yokohama, Japan, 175 people are infected with the virus. Over the following days and weeks, almost 700 people will be infected onboard.

Wednesday, 19 February

Iran reports two deaths from the coronavirus.

At the San Siro stadium in Milan, the Atalanta soccer team from Bergamo wins the Champions League match against Valencia 4 to 1 in front of 44,000 fans from Italy (2,000 from Spain). The mass transport from Bergamo to Milan and return, hours of shouting as well as the following festivities in innumerable bars have been considered by some observers as a coronavirus 'biological bomb'.

Thursday, 20 February

A patient in his 30s admitted to the intensive care unit (ICU) in **Codogno** Hospital (Lodi, Lombardy, Italy) tested positive for SARS-CoV-2. Over the next 24 hours, the number of reported cases would increase to 36, without links to the Codogno patient or previously identified positive cases. It is the beginning of the Italian epidemic. jamanetwork.com/journals/jama/fullarticle/2763188

Sunday, 23 February

Venice Carnival is brought to an early close and sports events are suspended in the most-hit Italian regions.

Monday, 24 February

Bahrain, Iraq, Kuwait, Afghanistan and Oman report their first cases.

Tuesday, 25 February

A report of a joint mission of 25 international and Chinese experts is presented to the public. The mission travelled to several different Chinese provinces. The most important findings are that the Chinese epidemic peaked and plateaued between the 23rd of January and the 2nd of February, and declined steadily thereafter (Table 1).

https://www.who.int/publications-detail/report-of-the-who-china-joint-mission-on-coronavirus-disease-2019-(covid-19)

This was the first sign that the **aggressive use of quarantine** ordered by the Chinese government was the **right thing to do**. Unfortunately, European countries which did not experience the SARS epidemic in 2003, would lose precious time before following the Chinese example.

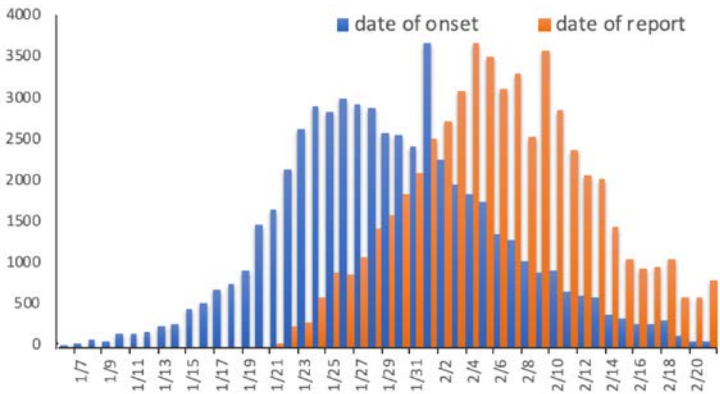

Figure 1. COVID-19 cases in China, January/February 2020. Epidemic curves by symptom onset and date of report on 20 February 2020 for laboratory confirmed COVID-19 cases for all of China. Modified from *Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19).* 16-24 February 2020. https://www.who.int/publications-detail/report-of-the-who-china-joint-mission-on-coronavirus-disease-2019-(covid-19)

Wednesday, 26 February

A president, fearing for his chances to be re-elected, downplays the threat from the coronavirus pandemic, twittering: "Low Ratings Fake News . . . are doing everything possible to make the Caronavirus [sic] look as bad as possible, including panicking markets, if possible."

https://www.bmj.com/content/368/bmj.m941

Two days later, the same individual invokes magic: "It's going to disappear. One day, it's like a miracle, it will disappear."

Friday, 28 February

A quick look at European cases diagnosed outside of Italy from February 24-27 reveals that 31 of 54 people (57%) had recently travelled to **Northern Italy**. Epidemiologists immediately realize that an unusual situation is building up and inform the Italian government.

Saturday, 7 March

Official data show that **China's exports** plunged 17.2 percent in the first two months of the year.

Sunday, 8 March

Italy imposes a strict quarantine on 16 million people in the state of Lombardy and 14 other areas in the north.

Monday, 9 March

Italy extends strict quarantine measures to the entire country of 60 million people. It declares the Italian territory a "security zone" with strict quarantine measures. All people are told to stay at home unless they need to go out for "valid work or family reasons". Schools are closed.

Iran releases 70,000 prisoners because of the coronavirus outbreak in the country.

Tuesday, 10 March

Xi Jinping tours the city of **Wuhan** and claims a provisional victory in the battle against COVID-19. The last two of 16 temporary hospitals in the city are shut down.

Wednesday, 11 March

WHO declares the coronavirus outbreak a pandemic.

All schools in and around **Madrid**, from kindergartens to universities, are closed for two weeks.

Thursday, 12 March

Italy closes all shops except grocery stores and pharmacies.

In **Spain**, 70,000 people in Igualada (Barcelona region) and three other municipalities are quarantined for at least 14 days. This is the first time Spain adopts measures of isolation for entire municipalities.

Emmanuel Macron, the **French** president, announces the closure of nurseries, schools and universities from Monday, 16 March. He declares: “One principle guides us to define our actions, it guides us from the start to anticipate this crisis and then to manage it for several weeks, and it must continue to do so: it is **confidence in science**. It is to listen to those who know.” Some of his colleagues should have listened, too.

Friday, 13 March

The prime minister of an **ex-EU country** introduces the notion of ‘herd immunity’ as a solution to repeated future episodes of coronavirus epidemics. The shock treatment: accepting that 60%

of the population will contract the virus, thus developing a collective immunity and avoiding future coronavirus epidemics. The figures are dire. With a little over 66 million inhabitants, some 40 million people would be infected, 4 to 6 million would become seriously ill, and 2 million would require intensive care. Around 400,000 Britons would die. The prime minister projects that “many more families are going to lose loved ones before their time.”

Saturday, 14 March

The **Spanish** government puts the whole country into lockdown, telling all people to stay home. Exceptions include buying food or medical supplies, going to hospital, work or other emergencies.

The **French** government announces the closure of all “non-essential” public places (bars, restaurants, cafes, cinemas, nightclubs) after midnight. Only food stores, pharmacies, banks, tobacconists and petrol stations may remain open.

Sunday, 15 March

France calls 47 million voters to the poll. Both government and opposition leaders seem to be in favor of maintaining the municipal elections. Is this a textbook example of unacceptable interference of party politics with the sound management of a deadly epidemic? Future historians will have to investigate.

Monday, 16 March

Ferguson et al. publish a new modelling study on likely UK and US outcomes during the COVID-19 pandemic. In the (unlikely) absence of any control measures or spontaneous changes in individual behaviour, the authors expect a peak in mortality (daily deaths) to occur after approximately 3 months. This would result in 81% of the US population, about 264 million people, contracting the disease. Of those, 2.2 million would die, including 4% to 8% of Americans over age 70. More important, by the second week in April, the demand for critical care beds would be 30 times greater than supply.

The model then analyzes two approaches: mitigation and supression. In the mitigation scenario, SARS-CoV-2 continues to spread at a slow rate so as to avoid a breakdown of hospital systems. In the suppression scenario, extreme social distancing measures and home quarantines would stop the spread of the virus. The study also offers an outlook at the time when strict "Stay at home" measures are lifted. The perspective is grim: the epidemic would bounce back.

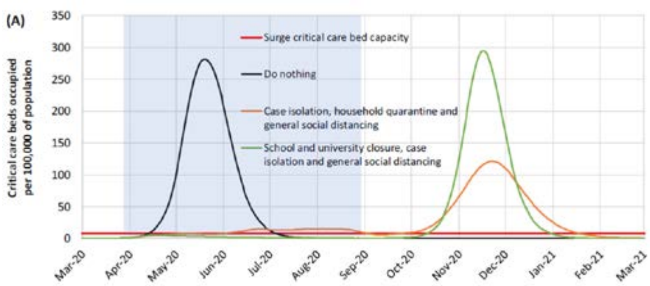

Figure 2. Impact of non-pharmaceutical interventions (NPIs) to reduce COVID-19 mortality and healthcare demand. (by Ferguson et al.)

France imposes strict confinement measures.

Tuesday, 17 March

Seven million people across the **San Francisco Bay Area** are instructed to "shelter in place" and are prohibited from leaving their homes except for "essential activities" (purchasing food, medicine and other necessities). Most businesses are closed. The exceptions: grocery stores, pharmacies, restaurants (for takeout and delivery only), hospitals, gas stations, banks.

Thursday, 19 March

For the first time since the beginning of the coronavirus outbreak, there have been **no new cases in Wuhan** and in the Hubei province.

Californian Governor Gavin Newsom orders the entire population of **California** (40 million people) to “stay at home”. Residents can only leave their homes to meet basic needs like buying food, going to the pharmacy or to the doctor, visiting relatives, exercising.

Friday, 20 March

Italy reports 6,000 new cases and 627 deaths in 24 hours.

In **Spain**, the confinement due to the coronavirus reduces crime by 50%.

China reports no new local coronavirus cases for three consecutive days. Restrictions are eased, **normal life resumes**. The entire world now looks at China. Will the virus spread again?

The state of **New York**, now the center of the U.S. epidemic (population: 20 million), declares a general lockdown. Only essential businesses (grocers, restaurants with takeout or delivery, pharmacies and laundromats) will remain open. Liquor stores? Essential business!

Monday, 23 March

Finally, too late for many observers, the UK puts in place containment measures. They are less strict than those in Italy, Spain and France.

German Chancellor Angela Merkel self-quarantines after coming into contact with a person who tested positive for coronavirus.

Tuesday, 24 March

Off all reported cases in Spain, 12% are among health care workers.

The Tokyo Olympics are postponed until 2021.

India orders a nationwide lockdown. Globally, three billion people are now in lockdown.

Wednesday, 25 March

After weeks of stringent containment measures, Chinese authorities lift travel restrictions in Hubei province. In order to travel, residents will need the “Green Code” provided by a monitoring system that uses the AliPay app.

A 16-year-old young woman dies in the south of Paris from COVID-19. She had no previous illnesses.

Thursday, 26 March

America First – the US is now the country with most known coronavirus cases in the world.

SARS-CoV-2 is spreading aboard the aircraft carrier USS Theodore Roosevelt.

For fear of reactivating the epidemic, China bans most foreigners from entering the country.

Friday, 27 March

The Prime Minister and the Ministre of Health of an ex-EU country tests positive for coronavirus.

The Lancet publishes *COVID-19 and the NHS—"a national scandal"*.

A paper by McMichael et al. describes a 33% case fatality rate for SARS-CoV-2 infected residents of a long-term care facility in King County, Washington, US.

Sunday, 29 March

In Italy, 50 doctors have died from COVID, half of them family doctors.

The Guardian publishes an article asking if US coronavirus deniers have blood on their hands. The SARS-CoV-2 epidemic is the worst intelligence failure in US history.

2. Epidemiology

Bernd Sebastian Kamps

In December 2019, several patients from Wuhan, People's Republic of China, developed pneumonia and respiratory failure reminiscent of the SARS epidemic in 2003 (WMHC 2019, www.SARSReference.com). In early January 2020, a new virus was grown from bronchoalveolar lavage fluid samples and found to be a betacoronavirus (Zhu N 2020). Between then and the time of this writing (29 March), the virus has spread to every corner of the world. More than 700,000 cases have been diagnosed, 30,000 people died. By the time you read this, the numbers will have increased again.

Transmission

Person-to-person spread

Transmission of coronaviruses is airborne, fecal-oral or through fomites. (A fomite is any inanimate object that, when contaminated with or exposed to infectious agents such as a virus, can transfer a disease to another person, for example elevator buttons, restroom taps etc. [Cai J 2020]). It is assumed that SARS-CoV-2 is spread mainly through person-to-person contact via respiratory droplets generated by coughing and sneezing. Whether and to what extent other transmission routes are epidemiologically relevant, is unclear. The virus has been isolated from toilet bowl and sink samples, suggesting that viral shedding in stool could be a potential route of transmission (Young 2020, Tang A 2020). The issue of fomites is even more a topic of public anxiety: can SARS-CoV-2 be spread via a French baguette or items bought in a supermarket? One study (van Doremalen 2020) showed that the virus can be detectable as an aerosol (in the air) for up to three hours, up to four hours on copper, up to 24 hours on cardboard and up to two to three days on plastic and stainless steel. Hence the imperative advice for regular and thorough handwashing.

Human-to-human transmission of SARS-CoV-2 was proved within weeks (Chan JF 2020, Rothe 2020). Even asymptomatic individuals can transmit the virus and a substantial proportion of secondary transmission is believed to occur prior to onset of illness (Nishiura 2020).

The SARS-CoV-2 virus is highly contagious, with a basic reproduction number R of around 2.5 (Chan JF 2020, Tang B 2020, Zhao S 2020) (R indicates the average number of infections one case can generate over the course of the infectious period in a naïve, uninfected population.)

The mean incubation is around 5 days (Li Q 2020, Lauer 2020). The serial interval of COVID-19 – defined as the duration of time between a primary case-patient having symptom onset and a secondary case-patient having symptom onset – has been estimated to be between 5 and 7.5 days (Cereda 2020).

Nosocomial spread

Nosocomial spread of the virus is well documented and seems to fuel the epidemic in some places. Within the first 6 weeks of the epidemic in China, 1,716 cases among health care workers were confirmed by nucleic acid testing, and at least 5 died (0.3%) (Wu Z 2020. Although appropriate hospital infection control measures can prevent nosocomial transmission of SARS-CoV-2 (Chen VCC 2020), working in a high-risk department, longer duty hours, and suboptimal hand hygiene after contacting with patients were all associated with an increased risk of infection

(Ran L 2020). At one time during the early epidemic in March 2020, around half of 200 cases in Sardinia were among hospital and other health care workers. At the end of March, medical personnel represented 12% and 8% of reported Spanish and Italian infections, respectively. Most European countries seem to be ill-prepared for the epidemic. As of 28 March, 51 doctors had died in Italy (roughly half of them family doctors) and five in France.

Long-term care facilities

Long-term care facilities are high-risk settings for infectious respiratory diseases. In a skilled nursing facility in King County, Washington, US, 167 cases of COVID-19 were diagnosed within less than three weeks after the identification of the first case: 101 residents, 50 health care personnel and 16 visitors (McMichael 2020) (Table 1).

Table 1. COVID outbreack in a long-term care facility

	Residents (N = 101)	Healthcare personnel (N = 50)	Visitors (N = 16)
Median age (range)	83 (51-100)	43.5 (21-79)	62.5 (52-88)
Female (%)	68.3	76	31.2
Hospitalized (%)	54.5	6.0	50.0
Died (%)	33.7	0	6.2
Chronique underlying conditions (%)			
Hypertension	67.3	8.0	12.5
Cardiac disease	60.4	8.0	18.8
Renal disease	40.6	0	12.5
Diabetes mellitus	31.7	10.0	6.2
Obesity	30.7	6.0	18.8
Pulmonary disease	31.7	4.0	12.5

Among residents (median age: 83 years), the case fatality was 33.7%. Chronic underling conditions included hypertension, cardiac disease, renal disease, diabetes mellitus, obesity and pulmonary disease. The study demonstrates that once introduced in a long-term care facility, SARS-CoV-has the potential to spread rapidly and widely.

Cruise ships

Cruise ships carry a large number of people in confined spaces. On 3 February 2020, 10 cases of COVID-19 were reported on the Diamond Princess cruise ship. Within 24 hours, ill passengers were isolated and removed from the ship and the rest of the passengers quarantined. Over time, more than 700 of 3,700 passengers and crew tested positive (~20%). One study suggested that without any interventions 2,920 individuals out of the 3,700 (79%) would have been infected (Rocklov 2020). The study also showed that an early evacuation of all passengers on 3 February would have been associated with only 76 infected. Today, all cruise ships are idle in ports around the world and face an uncertain future. Shipping village-loads of people from one place to another may not be a viable business model for years to come.

The Pandemic

The COVID-19 epidemic started in Wuhan, in Hubei province, China, and spread within 30 days from Hubei to the rest of mainland China, to neighboring countries (in particular, South Korea, Hong Kong and Singapore) and west to Iran, Europe and the American continent. The first huge outbreaks occurred in regions with cold winters (Wuhan, Iran, Northern Italy).

China

The nationwide spread to all provinces in January 2020 was favored by travelers departing from Wuhan before the Chinese Spring Festival (Zhong P 2020). In a study on cases reported through 11 February, among 44,672 confirmed cases, most were aged 30-79 years (86.6%), diagnosed in Hubei (74.7%), and considered mild (80.9%) (Wu 2020). A total of 1,023 deaths occurred among confirmed cases for an overall case-fatality rate of 2.3%.

Lombardy and Europe

Italy was the first European country struck by the pandemic. Complete genome analysis of SARS-CoV-2 isolates suggests that the virus was introduced on multiple occasions (Giovanetti 2020). Although the first local case was diagnosed only on 20 January, the force of the outbreak also suggests that the virus had been circulating for weeks. People from Milan remember discussing unusual frequent occurrence of pneumonia as early as mid-January (Dario Barone, personal communication).

Figure 1 shows the number of coronavirus cases per million population. Day 1 of the x-axis reflects the first day of *cases per million population >= 10* (Table 2). The data suggest that the epidemics in Spain, France and Germany lag behind Italy by about 10 days. Figure 2 zooms into the lower 20% of Figure 1. It would seem that no country will be spared.

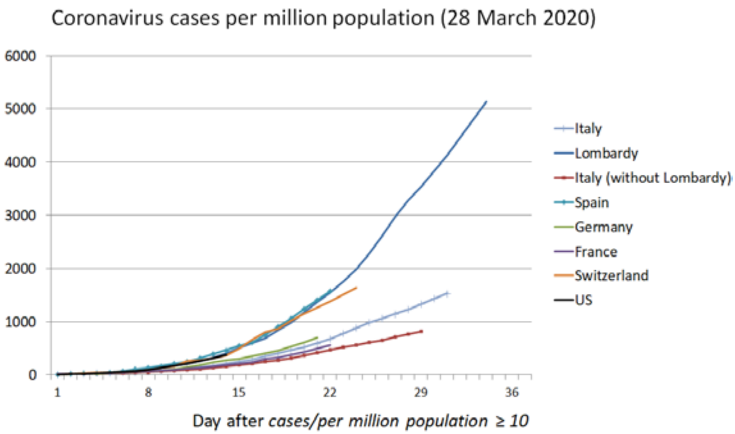

Figure 1. Coronavirus cases (per million population) in Italy, Spain, Germany, France and Switzerland. The Italian data are further divided into *Lombardy* and *without Lombardy*.
Source: Robert Koch Institute, worldometers.info, Johns Hopkins CSSE

Table 2. Day 1: Cases ≥ 10 per million population

Region/Country	**Day 1**	Cases	Cases/million population
Lombardy	**24 February**	126	12.6
Italy (without Lombardy)	**29 February**	500	10.0
Italy	**27 February**	650	10.7
France	**7 March**	949	14.2
Spain	**8 March**	673	14.4
Germany	**8 March**	847	10.2
Switzerland	**9 March**	102	11.9
US	**15 March**	3553	10.8

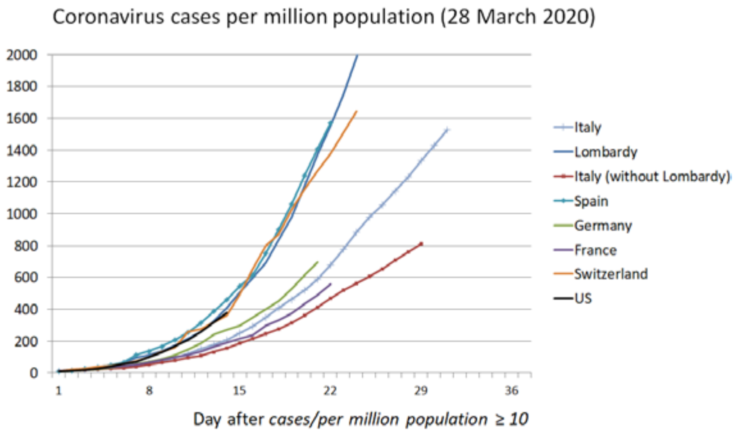

Figure 2. The same as Figure 1, but y-axis cut at 2000.

It is as yet unclear why the epidemic has taken such a dramatic turn in the northern part of Italy, especially in Lombardy, while other areas, especially the southern provinces, are relative spared. One super-spreader event may have been the Champions League match between Atalanta (Bergamo and Valencia) on 19 February at the San Siro stadium in Milan. Forty-four thousand fans from Italy and Spain witnessed the 4-to-1 win of the Italian team. The mass transport from Bergamo to Milan and return, hours of shouting as well as the following festivities in innumerable bars have been considered by some observers as a coronavirus 'biological bomb'. A more scientific explanation is that SARS-CoV-2 had been circulating in Northern Italy between 1 January 2020 (Cereda 2020) and 15 January.

How could the beginning of such an important epidemic be missed? Pointing out professional negligence of doctors and hospitals is a populist move. However, the signs on the wall could have been well hidden. During the yearly flu season, COVID-19 deaths in elderly people could easily be interpreted as flu deaths, and the rapid spread in the most active social age group – young people crowded in bars, restaurants and discos – would not have caused life-threatening symptoms. Future serological surveys may answer the question why Lombardy was so badly hit.

North America

Due to failed leadership, the number of cases in the US seems to be bound for a Lombardy-type epidemic and will probably be more severe than the epidemic in Hubei, China's most hit area. Only a few states have thus far declared a general lockdown. New York is currently the epicenter of the country's outbreak.

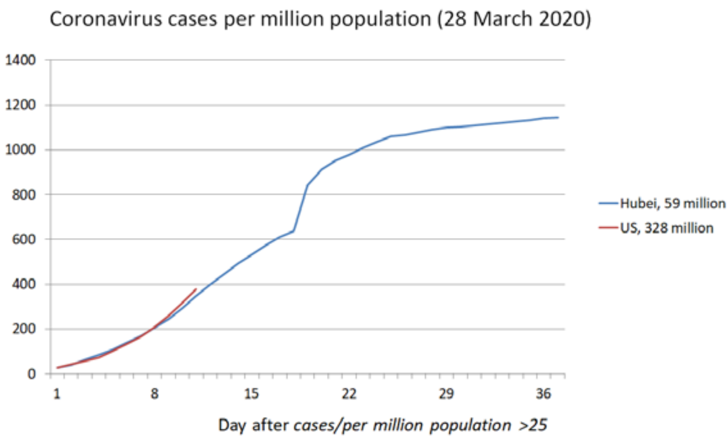

Figure 3. Failed US leadership. The US epidemic on track to be more deadly than the epidemic in Hubei, China's most hit province.

Africa and South America

New cases are reported from around the world, but the figures are still comparatively low in Africa and South America. One study estimated the risk of transmission of the SARS-CoV-2 through human passenger air flight from four major cities of China (Wuhan, Beijing, Shanghai and Guangzhou) (Haider 2020). From 1-31 January, 388,287 passengers were destined for 1,297 airports in 168 countries or territories across the world. In January, the risk of transmission of the virus to Africa and South America seemed to be low. However, a three-week lockdown began in South Africa which so far has the highest number of detected infections in sub-Saharan Africa at more than 1,000, with two deaths.

Outcome

Patient outcome

See chapter *Clinical Presentation*.

Country outcome

Starting on 23 January, China imposed a lockdown of the population of Wuhan and later of the entire Hubei province. This astonishing first in human history achieved what even specialists didn't dare dream: curbing an epidemic caused by a highly contagious virus (Lau 2020). The recipe of stringent confinement of people in high-risk areas, is now being re-combined by nations around the world, everyone adding some more or some less efficient ingredients.

Three months after the beginning of the epidemic, Chinese authorities started lifting travel restrictions, slowly restoring life to normal even in the most hard-hit provinces. At the same time, the epidemic is exploding in the US because of an unprecedented vacuum in leadership.

The outcome of the pandemic

The future of the COVID epidemic depends on the measures adopted by different countries and states. In the absence of any control measures, a peak in mortality (daily deaths) is expected to occur after approximately 3 months (Ferguson 2020). This would result "in 81% of the US population, about 264 million people, contracting the disease. Of those, 2.2 million would die, including 4% to 8% of Americans over age 70."

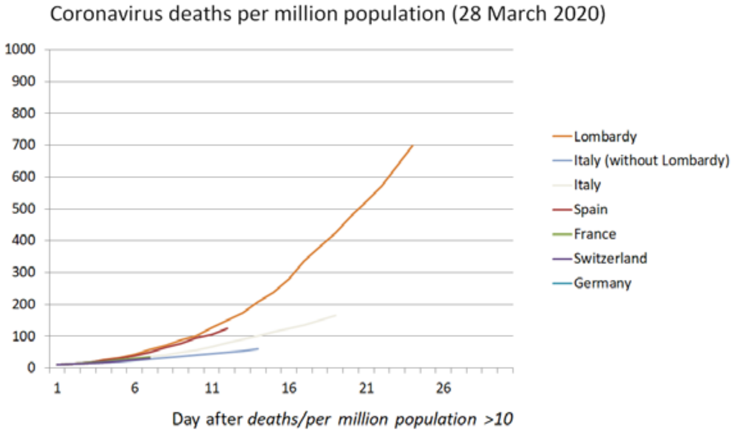

Figure 4. Coronavirus deaths (per million population) in Italy, Spain, France, Switzerland and Germany. The Italian data are further divided into *Lombardy* and *without Lombardy*.
Source: Robert Koch Institute, worldometers.info, Johns Hopkins CSSE

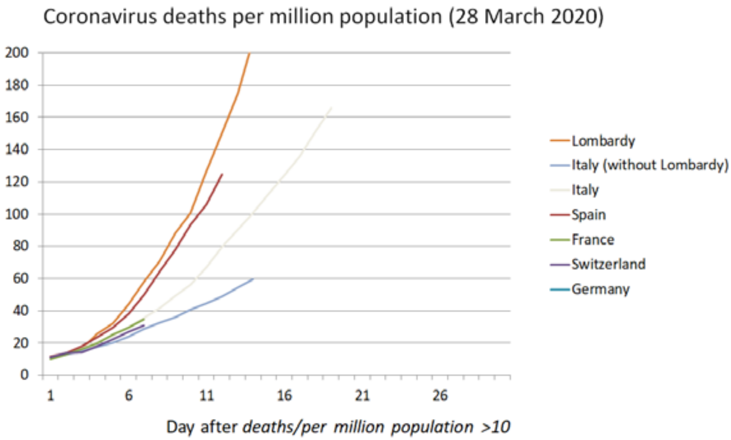

Figure 5. The same as Figure 5, but y-axis cut at 200

Some politicians have considered such a "let-the-virus-loose" strategy seriously, speculating on a heavy return on investment. After three months, when the whole pandemonium is over:

- The country would avoid the dramatic economic downturn that seems unavoidable in countries and states which opted for strict containment measures (Italy, Spain, France, California, New York, India, to name but a few).
- 70% of the population would be immunized against further outbreaks (through infection with SARS-CoV-2) and will be able to look ahead to the next winter season with an even temper. (How long would such acquired immunity last? Maybe only a few years. See the *Immunology of SARS-CoV-2 infection* chapter, page 47.)

On the other end of the spectrum of public intervention, countries like China, Italy, Spain and France introduced draconian containment measures. Within 8 weeks, China reduced the number of new infections in China to the two-digit range.

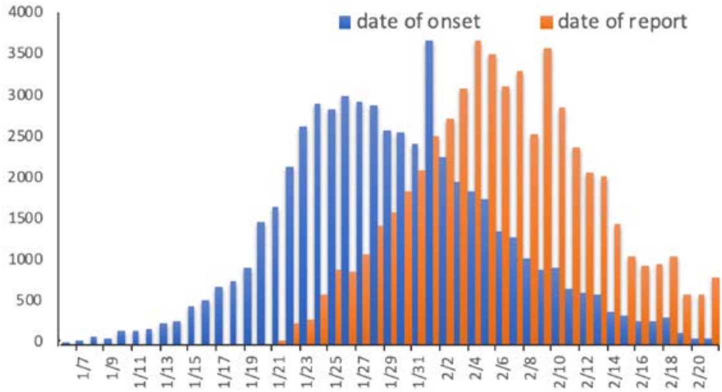

Figure 6. The Chinese outbreak in January/February 2020. Epidemic curves by symptom onset and date of report on 20 February 2020 for laboratory confirmed COVID-19 cases for all of China. Modified from *Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19).* 16-24 February 2020. https://www.who.int/publications-detail/report-of-the-who-china-joint-mission-on-coronavirus-disease-2019-(covid-19)

At the time of writing, 28 March, Figure 6 is the most important figure of the epidemic. It proves that strict containment measures are capable of curbing a SARS-CoV-2 epidemic. The figure presents the Chinese COVID-19 epidemic curves of laboratory-confirmed cases, by symptom onset (blue) and – separately – by date of report (orange). The data were compiled on 20 February 2020, four weeks after the beginning of the containment measures which included a lockdown on nearly 60 million people in Hubei province as well as travel restrictions for hundreds of millions of Chinese citizens. The blue columns show that (1) the epidemic rapidly grew from 10-22 January, (2) reported cases (by date of onset) peaked and plateaued between 23 January and 28 January and (3) steadily declined thereafter (apart from a spike reported on 1 February). Based on these data, we could expect a decline in reported cases around three weeks after the implementation of strict containment measures.

Italy is expected to see the number of daily reported new cases go down around 31 March while Spain, France and Germany will enter a descending phase in early April. The UK entered lockdown later (Table 3).

Table 3. When should we expect the number of reported new SARS-CoV-2 cases to decline?

Country	Implementation of containment measures	Expected decline in number of new reported cases
Italy	10 March	31 March
Spain	14 March	4 April
Germany	16 March	6 April
France	17 March	7 April
San Francisco	19 March	9 April
New York	20 March	10 April
UK	23 March	13 April

The question everyone has in mind today: how long would the effects of three-month- or even five-month-long containment measures last? The above-mentioned study (Ferguson 2020) predicts that after lifting strict “Stay at home” measures (extreme social distancing measures and home quarantines), the epidemic would simple bounce back (Figure 7)!

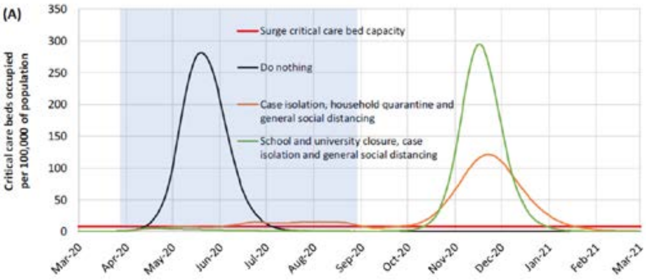

Figure 7. Impact of non-pharmaceutical interventions (NPIs) to reduce COVID-19 mortality and healthcare demand (Source: Ferguson 2020).

The study has a number of unknown variables. First of all, people have the ability to learn. In any second "wave" of the coronavirus epidemic, there will be no mass gatherings, no 2020 UEFA European Football Championship and no 2020 Summer Olympics in Tokyo. Discos, pubs and all other places which weeks ago brought people into close contact would be closed until further notice. In daily life, everyone would take action when experiencing fever and cough and suggesting action when witnessing it. There will be testing on a massive scale with extensive contact tracing and ensuing quarantine measures. Even after lockdown, life will not be as it was before 2020.

World Outlook

The next weeks will be outstandingly intense. We will watch, day by day, what happens in China as it cautiously lifts, one after the other, its still existing containment measures. We will eagerly await the peak of the Italian epidemic and, later, the evolution in Spain, France, Germany, the UK and all other countries around the world which enacted a lockdown of their populations. We will rejoice when the "Stay at home" order gives way to "Go out again”. And we all will be frightened by the prospect of seeing the number of new SARS-CoV-2 cases climb once again.

So what will our future look like? A pendulum existence of three months “Stay at home” interspersed with a few months “Go out again”? Economically, this is unsustainable. What can be done this time – the current month-long isolation of the entire population – cannot be repeated. A recession of unseen proportions would stir social turmoil, and social turmoil would undermine any containment measures. There could even be social upheaval.

Unless a miraculous drug or vaccine is/are developed and produced quickly in sufficient quantities, the people of the world will have to invent intermediate measures. Some epidemiologists are speculating that “granny quarantine” might be the last resort of the COVID dilemma: quarantine all people over 60 as well as those who have serious medical conditions for three months. (In older age, time flies, flying faster every year. Tell your grandparents it won’t be long.) Tell those over 50 to stay at home as often as possible. Now let the virus loose to infect the rest of the population. After three months, more than half of the population would have antibodies against SARS-CoV-2, the epidemic could be over and Granny and Grandpa might make a comeback.

Is “granny quarantine” the magic bullet? We might know soon because some countries are tempted to try such an approach; however, the capacity of intensive care units might be streched beyond capacity even with all people over 40 being quarantined. In the meantime, all options are on the table and are being evaluated. We are walking on quicksand. In the coming weeks, humanity will need to be flexible, no rules are set in stone, all stones will be turned upside down. If we leapt three years into the future and read the story of COVID-19, we wouldn’t believe it.

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3. Immunology of SARS-CoV-2

Thomas Kamradt

To date, despairingly little is known about immune responses against SARS-CoV-2. Some of the most important and most urgent questions are:

- Is someone who has overcome COVID-19, the disease caused by SARS-CoV-2, protected from a second round of COVID-19 disease?
- If yes, how long does the immune protection last?
- What are the correlates of protection?
- Why do children and young adults seem to develop only mild, if any, signs and symptoms of COVID-19, and why is the disease so much more severe in the elderly?
- How does the immune response against SARS-CoV-2 contribute to disease development? Are there pathogenic immune responses?
- Can we use immunological parameters to predict an individual patient's risk in developing severe disease?
- Can we develop a vaccine against SARS-CoV-2?

We do not know the answer to any of these questions today.

Protective Antibodies

In the absence of robust experimental or clinical data on SARS-CoV-2-induced immune responses we can make some educated guesses based on prior experiences with endemic coronaviruses (e.g. 229E or OC43), the SARS-CoV and the MERS-CoV viruses. Experimental, serological and sero-epidemiological studies strongly suggest that coronaviruses, including SARS-CoV induce neutralising and protective antibodies. These studies also seem to indicate that antibody-mediated protection is short-lived.

Cellular Immune Response

Less is known about cellular immune responses, i.e. T-cell responses against coronaviruses. Experimental evidence from studies in mice suggests that T cells residing in the mucosa of the respiratory tract could be an important correlate of protection. However, although mice can be infected with coronaviruses including SARS-CoV, they do not develop the severe pulmonary symptoms that are characteristic of SARS and COVID-19. Therefore, these results have to be interpreted with caution. Human T cells from the respiratory mucosa of diseased and convalescent humans would be necessary to clarify the issue but are difficult to come by.

These questions are not simply of an academic nature. Rational vaccine design is based on solid knowledge about protective immunity. As long as we do not know which protective immune response we need to induce by vaccination, vaccine development remains guesswork.

Vaccine-induced disease enhancing antibodies

To make matters more complicated, we cannot even be sure that vaccine-induced anti-SARS-CoV-2 immune responses will not cause harm. There is ample evidence in other viral diseases, most prominently RS-Virus and Dengue virus, that some antibodies can enhance disease instead of protecting the host. Whereas vaccine-induced disease-enhancing antibodies are known to occur against a feline coronavirus, there is currently no *in vivo* proof for such disease-enhancing antibodies in SARS or COVID-19. However *in vitro* data obtained with human cells indicate that some antibodies might enable the virus to enter B lymphocytes. Antibody-dependent enhancement is certainly a possibility that needs to be ruled out in any SARS-CoV-2 vaccine development.

Taken together, we need to rapidly acquire solid knowledge on protective and pathogenic immune responses against SARS-CoV-2 in order to

- identify patients at risk for the development of severe disease and
- develop effective and safe vaccines against this pandemic virus.

*** The current draft version will be expanded soon. ***

4. Diagnostic Tests and Procedures

Bernd Sebastian Kamps
Christian Hoffmann

Diagnosis

Rapid identification and isolation of infected individuals is crucial. Diagnosis is made using clinical, laboratory and radiological features. However, screening protocols should be adapted to the local situation. As symptoms and radiological findings of COVID-19 are non-specific, SARS-CoV-2 infection has to be confirmed by nucleic acid-based polymerase chain reaction (PCR), amplifying a specific genetic sequence in the virus. There is an interim guidance for laboratory testing for coronavirus disease (COVID-19) suspected human cases, published by WHO on March 19, 2020 (WHO 2020).

PCR

Several different qPCR-based detection kits are available as labs worldwide have customized their PCR tests for SARS-CoV-2, using different primers targeting different sections of the virus's genetic sequence. A protocol for real-time RT-PCR assays for the detection of SARS-CoV-2 for two RdRp targets (IP2 and IP4) is described at https://www.who.int/docs/default-source/coronaviruse/real-time-rt-pcr-assays-for-the-detection-of-sars-cov-2-institut-pasteur-paris.pdf?sfvrsn=3662fcb6_2

Novel real-time RT-PCR assays targeting the RNA-dependent RNA polymerase (RdRp)/helicase, spike and nucleocapsid genes of SARS-CoV-2 may help to improve the laboratory diagnosis of COVID-19. Compared to the reported RdRp-P2 assay which is used in most European laboratories, these assays do not crossreact with SARS-CoV in cell culture and may be more sensitive and specific (Chan 2020).

Qualitative PCR

According to WHO, respiratory material for PCR should be collected from upper respiratory specimens (nasopharyngeal and oropharyngeal swab or wash) in ambulatory patients (WHO 2020). Lower respiratory specimens may include sputum (if produced) and/or endotracheal aspirate or bronchoalveolar lavage in patients with more severe respiratory disease. However, a high risk of aerosolization should be considered (adhere strictly to infection prevention and control procedures). Additional clinical specimens may be collected as COVID-19 virus has been detected in blood and stool (see below).

Several studies have shown that asymptomatic patients may transmit the virus and will have positive PCR testings (Bai 2020, Cereda 2020, Rothe 2020). There is also a small case series on four patients with COVID-19 who met criteria for hospital discharge or discontinuation of quarantine (absence of clinical symptoms and radiological abnormalities and 2 negative RT-PCR test results) who had positive RT-PCR test results 5 to 13 days later (Lan 2020).

Several reasons for false negative PCR results have to be considered, including laboratory errors or, more importantly, insufficient viral material in the specimen. In addition, several patients have been reported, in whom isolated infection of lower respiratory tract was evident (Hao 2020, Xie 2020). These patients show characteristic radiological features of COVID-19 pneumonia and initial negative or weakly positive PCR. In these cases, repeated testing can be used because over time, the likelihood of the SARS-CoV-2 being present in the nasal-pharynx increases.

Gathering specimens from nasopharyngeal and throat swabs can cause discomfort for patients and put health-care workers at risk. The virus is present in saliva and one large study has shown that posterior oropharyngeal (deep throat) saliva samples are feasible and more acceptable to patients and healthcare workers (To 2020).

Although no cases of transmission via fecal-oral route have yet been reported, there is also increasing evidence that SARS-CoV-2 is actively replicating in the gastrointestinal tract. A larger study from Zhuhai/China showed prolonged presence of SARS-CoV-2 viral RNA in fecal samples. Of the 41 (55%) of 74 patients with fecal samples that were positive for SARS-CoV-2 RNA, respiratory samples remained positive for SARS-CoV-2 RNA for a mean of 16.7 days and fecal samples remained positive for a mean of 27.9 days after first symptom onset (Wu 2020). There are also case reports with positive fecal and negative oropharyngeal tests (Chen 2020).

Quantification of viral load

Several studies have evallated the SARS-CoV-2 viral load in different specimens. In a small prospective study, the viral load in nasal and throat swabs obtained from the 17 symptomatic patients was analyzed in relation to day-of-onset of any symptoms (Zou 2020). Of note, the viral load that was detected in the asymptomatic patient was similar to that in the symptomatic patients, which suggests the transmission potential of asymptomatic or minimally symptomatic patients. In another study on 82 infected individuals, the viral loads in throat swab and sputum samples peaked at around 5–6 days after symptom onset, ranging from around 10^4 to 10^7 copies per mL during this time (Pan 2020). In a study on oropharyngeal saliva samples, unlike SARS, patients with COVID-19 had the highest viral load near presentation, which could account for the fast-spreading nature of this epidemic (To 2020). The median viral load in posterior oropharyngeal saliva or other respiratory specimens at presentation was 5.2 $\log_{10}$ copies per mL (IQR 4.1-7.0) in this study.

Higher viral loads might be associated with severe clinical outcomes. In a study evaluating serial samples from 21 mild and 10 severe cases (Liu 2020), mild cases were found to have an early viral clearance, with 90% of these patients repeatedly testing negative on RT-PCR by day 10 post-onset. By contrast, all severe cases still tested positive at or beyond day 10 post-onset. However, large and prospective trials are needed to evaluate the role of SARS-CoV-2 viral load as a marker for assessing disease severity and prognosis.

Diagnosis in the setting of shortage of PCR test kits

There is no doubt that the overall goal must be to detect as many infections as possible. However, in many countries, a shortage of supply test kits does not meet the need a growing infected population. A large retrospective case-control study from Singapore has evaluated predictors for SARS-CoV-2 infection, using exposure risk factors, demographic variables, clinical findings and clinical test results (Sun 2020). Even in the absence of exposure risk factors and/or radiologic evidence of pneumonia, clinical findings and tests can identify subjects at high risk of COVID-19. Low leucocytes, low lymphocytes, higher body temperature, higher respiratory rate, gastrointestinal symptoms and decreased sputum production were strongly associated with a positive SARS-CoV-2 test. However, those preliminary prediction models are very sensitive to the local epidemiological context and phase of the global outbreak. However, the nucleic acid test or genetic sequencing serves as the gold standard method for confirmation of infection. Whenever PCR is available, PCR should be performed.

Serology

Detection of past viral infections by looking for antibodies an infected person has produced will be among the most important goals in the fight against the COVID-19 pandemic. These serological assays are of critical importance to determine seroprevalence, previous exposure and identify highly reactive human donors for the generation of convalescent serum as therapeutic. They will also support screening of health care workers to identify those who are already immune. Several groups are working towards such a test (Amanat 2020) which will be commercially available in a short time.

Up to now (end of March) however, there are still no valid serological testings for routine use. Cross reactivity to other coronaviruses can be challenging. Preliminary data suggest that the profile of antibodies to SARS-CoV-2 is similar to SARS-CoV (Xiao 2020). For SARS-CoV, antibodies were not detected within the first 7 days of illness, but IgG titre increased dramatically on day 15, reaching a peak on day 60, and remained high until day 180 from when it declined gradually until day 720. IgM was detected on day 15 and rapidly reached a peak, then declined gradually until it was undetectable on day 180 (Mo 2006). The first larger study on the host humoral response against SARS-CoV-2 has shown that humoral response to SARS-CoV-2 can aid to the diagnosis of COVID-19, including subclinical cases (Guo 2020). In this study, IgA, IgM and IgG response used an ELISA based assay on the recombinant viral nucleocapsid protein was analyzed in 208 plasma samples from 82 confirmed and 58 probable cases (Guo 2020). The median duration of IgM and IgA antibody detection were 5 days (IQR 3-6), while IgG was detected on 14 days (IQR 10-18) after symptom onset, with a positive rate of 85.4%, 92.7% and 77.9% respectively. The detection efficiency by IgM ELISA was higher than that of qPCR after 5.5 days of onset of symptoms.

Radiology

Computed tomography

Computed tomography (CT) can play an important role in both diagnosing and assessment of disease extent and follow-up. Chest CT has a relatively high sensitivity for diagnosis of COVID-19 (Ai 2020, Fang 2020). However, around half of patients may have a normal CT during the first 1-2 days after symptom onset (Bernheim 2020). On the other hand, a considerable proportion of subclinical patients (scans done before symptom onset) may already have pathological CT findings (Shi 2020).

If pathological, images usually show bilateral involvement, with multiple patchy or ground-glass opacities (GGO) with subpleural distribution in multiple bilateral lobes. Lesions may display significant overlap with those of SARS and MERS (Hosseiny 2020).

A systematic review of imaging findings in 919 patients found bilateral multilobar GGO with a peripheral or posterior distribution, mainly in the lower lobes and less frequently within the right middle lobe as the most common feature (Salehi 2020). In this review, atypical initial imaging presentation of consolidative opacities superimposed on GGO were found in a smaller number of cases, mainly in the elderly population. Septal thickening, bronchiectasis, pleural thickening, and subpleural involvement were less common, mainly in the later stages of the disease. Pleural effusion, pericardial effusion, lymphadenopathy, cavitation, CT halo sign, and pneumothorax were uncommon (Salehi 2020).

With a longer time after the onset of symptoms, CT findings are more frequent, including consolidation, bilateral and peripheral disease, greater total lung involvement, linear opacities, "crazy-paving" pattern and the "reverse halo" sign (Bernheim 2020). Some experts have proposed that imaging can be sorted into four different phases (Li 2020). In the early phase, multiple small patchy shadows and interstitial changes emerge. In the progressive phase, the lesions increase and enlarge, developing into multiple GGOs as well as infiltrating consolidation in both lungs. In the severe phase, massive pulmonary consolidations and “white lungs” are seen, but pleural effusion is rare. In the dissipative phase, the GGOs and pulmonary consolidations were completely absorbed, and the lesions began to change into fibrosis.

In a longitudinal study analyzing 366 serial CT scans in 90 patients with COVID-19 pneumonia, the extent of lung abnormalities progressed rapidly and peaked during illness days 6-11 (Wang 2020). The predominant pattern of abnormalities after symptom onset in this study was ground-glass opacity (45-62%). As pneumonia progresses, areas of lesions enlarge and developed into diffuse consolidations in both lungs within a few days (Guan 2020).

Most patients discharged had residual disease on final CT scans (Wang 2020). Studies with longer follow-up are needed to evaluate long-term or permanent lung damage including fibrosis, as is seen with SARS and MERS infections.

Of note, chest CT is not recommended in all COVID-19 patients, especially in those who have who are well enough to be sent home or those with only short periods of symptoms (< 2 days). In case of COVID-19, a large number of patients with infection or suspected infection swarm into the hospital. Consequently, the examination workload of the radiology department increases sharply. Because the transmission route of SARS-CoV-2 is through respiratory droplets and close contact transmission, unnecessary CT scan should be avoided. An overview of the prevention and control of the COVID-19 epidemic in the radiology department is given by An et al.

Ultrasound and PET

Some experts have postulated that lung ultrasound (LUS) may be helpful, since it can allow the concomitant execution of clinical examination and lung imaging at the bedside by the same doctor (Buonsenso 2020, Soldati 2020). Advantages of LUS include portability, bedside evaluation, safety and possibility of repeating the examination during follow-up. However, the diagnostic and prognostic role of LUS in COVID-19 is uncertain. Whether there is any potential clinical utility of other imaging techniques such as 18F-FDG PET/CT imaging in the differential diagnosis of complex cases also remains unclear (Deng 2020, Qui 2020).

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5. Clinical Presentation

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After an average incubation time of around 5 days (range: 2-14 days), a typical COVID-19 infection begins with dry cough and low-grade fever (38.1–39°C or 100.5–102.1°F). In a more advanced stage, patients may experience shortness of breath and require mechanical ventilation.

Laboratory findings include lymphocytopenia. In patients with a fatal outcome, levels of D-dimer, serum ferritin, serum lactate dehydrogenase and IL-6 were elevated compared to survivors.

The predominant CT abnormalities are bilateral, peripheral and basal predominant ground-glass opacity, consolidation, or both.

The outcome of COVID-19 is often unpredictable, especially in older patients with comorbidities.

Symptoms and findings

Incubation period

A pooled analysis of 181 confirmed COVID-19 cases with identifiable exposure and symptom onset windows estimated the median incubation period to be 5.1 days with a 95% CI of 4.5 to 5.8 days (Lauer 2020). The authors estimated that 97.5% of those who develop symptoms will do so within 11.5 days (8.2 to 15.6 days) of infection. Fewer than 2.5% of infected persons will show symptoms within 2.2 days, whereas symptom onset will occur within 11.5 days in 97.5%. However, these estimates imply that, under conservative assumptions, 101 out of every 10,000 cases will develop symptoms after 14 days of active monitoring or quarantine. Another analysis of 158 confirmed cases outside

Wuhan estimated a very similar median incubation period of 5.0 days (95 % CI, 4.4 to 5.6 days), with a range of 2 to 14 days (Linton 2020). In a detailed analysis of 36 cases linked to the first three clusters of circumscribed local transmission in Singapore, the median incubation period was 4 days with a range of 1-11 days (Pung 2020). Taken together, the incubation period of around 4-6 days is in line with that of other coronaviruses causing SARS or MERS (Virlogeux 2016). Of note, the time from exposure to onset of infectiousness (latent period) may be shorter. There is little doubt that transmission of SARS-CoV-2 during the late incubation period is possible (Li 2020). However, the degree to which presymptomatic persons can transmit SARS-CoV-2 is a matter of debate.

Symptoms

Symptoms occur in the majority of cases (for symptomatic, see below). In the largest study published to date (Guan 2020, see Table 1 and 2), fever was the most common symptom in 88.7%, with a median maximum of 38.3 C; only 12.3% had a temperature of > 39 C. The absence of fever seems to be somewhat more frequent than in SARS or MERS; fever alone may therefore not be sufficient to detect cases in public surveillance. The second most common symptom is cough, occurring in about two thirds of all patients.

In the study from Wuhan on 191 patients hospitalized with severe COVID-19 (Zhou 2020), among survivors, median duration of fever was 12.0 days (8-13 days) and cough persisted for 19 days (IQR 12-23 days). Shortness of breath is also common, especially in severe cases (Table 2).

Table 1. Outstanding clinical studies, main characteristics

	Guan 2020	Wu 2020	Mizumoto 2020	Zhou 2020
n	1,099	73,314	634	191
	China	China	Japan	Wuhan (China)
Median age	47 (IQR 35-58)	NA	58	56 (IQR 46-67)
“Older” age	15.1% (> 65 yrs)	11.9% (> 70 yrs)	75.1% (> 60 yrs)	NA
Female	41.9%	NA	49.4%	37.7%
Severe Dis.	15.7%	18.6%	NA	NA
	(CAP definition)	(more than mild pneumonia)		
Death	1.4% (15)*	2.3% (1,023)	1.1% (7**)	28.3%

*short FU, outcomes unknown at time of data cut-off. **longer FU expected

The study by Guan (N Engl J Med) is the largest clinical cohort to date with 1,099 relatively well documented patients from 552 hospitals in 30 Chinese provinces, admitted as of January 29 (Guan 2020).

The second study (Wu 2020) is a report from the Chinese Center for Disease Control, summarizing briefly what happened in China during the first weeks and which population groups were affected.

The third study describes an outbreak onboard the Diamond Princess cruise ship (Mizumoto 2020).

The fourth study reports from hospitalized patients in Wuhan with severe COVID-19 who have a definite outcome (Zhou 2020).

In a meta-analysis of COVID-19 in papers published until February 23, fever (88.7%), cough (57.6%) and dyspnea (45.6%) were the most prevalent clinical manifestations (Rodrigues-Morales 2020). In another review, the corresponding percentages were 88.5%, 68.6% and 21.9%, respectively (Li 2020). As shown in Table 1, some differences between severe and non-severe cases are evident. In the Wuhan study on patients with severe COVID-

19, multivariate analysis revealed that a respiratory rate of > 24 breaths per minute at admission was higher in non-survivors (63% versus 16%). Other studies found higher rates of shortness of breath, and high temperature of > 39.0 in older patients compared with younger patients (Lian 2020).

In contrast, nasal congestion, diarrhea, nausea or vomiting only occur in small percentages. Other signs of infection such as throat congestion, tonsil swelling, enlargement of lymph nodes or rash were almost inexistent. All symptoms are non-specific so that the differential diagnosis includes a wide range of infections, respiratory disorders that may not be distinguished clinically.

Upper respiratory tract symptoms such as rhinorrhea, nasal congestion, sneezing and sore throat are relatively unusual. However, some researchers have reported on anosmia and hyposmia as an early sign (Luers 2020).

Laboratory findings

The most evident laboratory findings in the large cohort study from China (Guan 2020) are shown in Table 2. On admission, lymphocytopenia was present in 83.2% of the patients, thrombocytopenia in 36.2%, and leukopenia in 33.7%. In most patients, C-reactive protein was elevated to moderate levels; less common were elevated levels of alanine aminotransferase, and D-dimer. Most patients have normal procalcitonin on admission.

Table 2. Percentage of symptoms in the largest cohort to date (Guan 2020). Disease severity was classified according to American Thoracic Society (Metlay 2019) guidelines

Clinical symptoms	All	Severe Disease	Non-Severe
Fever,%	88.7	91.9	88.1
Cough,%	67.8	70.5	67.3
Fatigue,%	38.1	39.9	37.8
Sputum production,%	33.7	35.3	33.4
Shortness of breath,%	18.7	37.6	15.1
Myalgia or arthralgia,%	14.9	17.3	14.5
Sore throat,%	13.9	13.3	14.0
Headache,%	13.6	15.0	13.4
Chills,%	11.5	15.0	10.8
Nausea or vomiting,%	5.0	6.9	4.6
Nasal congestion,%	4.8	3.5	5.1
Diarrhea,%	3.8	5.8	3.5
Radiological findings			
Abnormalities on X-ray,%	59.1	76.7	54.2
Abnormalities on CT,%	86.2	94.6	84.4
Laboratory findings			
WBC < 4,000 per mm^3,%	33.7	61.1	28.1
Lymphocytes < 1,500 per mm^3,%	83.2	96.1	80.4
Platelets < 150,000 per mm^3,%	36.2	57.7	31.6
C-reactive protein ≥ 10 mg/L,%	60.7	81.5	56.4
Lactate dehydrogenae ≥ 250 U/L,%	41.0	58.1	37.1
AST > 40 U/L,%	22.2	39.4	18.2
D-dimer ≥ 0.5 mg/L,%	46.6	59.6	43.2

Patients with severe disease had more prominent laboratory abnormalities (including lymphocytopenia and leukopenia) than those with non-severe disease. This was also seen in a large retrospective study of hospitalized patients in Wuhan where lymphocyte and leukocyte count was significantly lower in non-survivors. In these, also levels of D-dimer, serum ferritin, high-sensitivity cardiac troponin I, serum lactate dehydrogenase and

IL-6 were clearly elevated compared to survivors (Zhou 2020). In particular, D-dimer seemed to be of prognostic value. In the Wuhan study, all patients surviving had low D-dimer during hospitalization, whereas levels in non-survivors tended to increase sharply at day 10. In a multivariate analysis, D-dimer of > 1 µg/mL remained the only lab finding which was significantly associated with in-hospital death, with an odds ratio of 18.4 (2.6-129, p=0.003). However, D-dimer has a reported association with mortality in patients with sepsis. Many of these died from sepsis in the Wuhan study.

In addition to D-dimer, a meta-analysis of 341 patients found that cardiac troponin I levels are significantly increased only in patients with severe COVID-19 (Lippi 2020). It remains to be seen whether troponin levels can be used as a prognostic factor. In another retrospective observational study of 69 patients with severe COVID-19, the decrease of interleukin-6 (IL-6) levels was closely related to treatment effectiveness, while the increase of IL-6 indicated disease exacerbation. The authors concluded that the dynamic change of IL-6 levels can be used as a marker in disease monitoring in patients with severe COVID-19 (Liu 2020).

Radiological findings

The primary findings on chest x-ray and CT are those of atypical pneumonia. The predominant CT abnormalities are bilateral, peripheral and basal predominant ground-glass opacity, consolidation, or both (Pan 2020). Patterns of radiological findings are described in a more detail in the chapter *Diagnosis*.

Asymptomatic cases

While physicians need to be aware of asymptomatic cases (Bai 2020), the true percentage is difficult to assess. The probably best data come from 3,600 people on board the cruise ship Diamond Princess (Mizumoto 2020) who became involuntary actors in a "well-controlled experiment" where passengers and crew comprised an environmentally homogeneous cohort. Due to insufficient hygienic conditions, >700 people became infected while the ship was quarantined in the port of Yokohama, Japan for several weeks. After systematic testing, 328 (51.7%) of the first 634 confirmed cases were found to be asymptomatic. Considering the varying of the incubation period between 5.5 and 9.5 days, the authors calculated the true asymptomatic proportion at 17.9% (Mizumoto 2020).

From a total of 565 Japanese citizens evacuated from Wuhan, the asymptomatic ratio was estimated to be 41.6% (Nishiura 2020). In another study on 55 asymptomatic patents with confirmed SARS-CoV, the majority was of middle age and had close contact with infected family members (Wang 2020).

Taken together, these preliminary studies indicate that around 20-40% of all COVID-19 infected subjects may be asymptomatic.

Asymptomatic patients may transmit the virus (Bai 2020, Rothe 2020). In a study from Northern Italy viral loads in nasal swabs between asymptomatic and symptomatic subjects did not differ significantly, suggesting the same potential for transmitting the virus (Cereda 2020).

Clinical classification

There is no broadly accepted or valid clinical classification for COVID-19. The largest clinical study distinguished between severe and non-severe cases (Guan 2020), according to the Diagnosis and Treatment Guidelines for Adults with Community-acquired Pneumonia, published by the American Thoracic Society and Infectious Diseases Society of America (Metlay 2019). In these validated definitions, severe cases include either one major criterion or three or more minor criteria. Minor criteria are a respiratory rate > 30 breaths/min, PaO2/FIO2 ratio < 250, multilobar infiltrates, confusion/disorientation, uremia, leukopenia, low platelet count, hypothermia, hypotension requiring aggressive fluid resuscitation. Major criteria comprise septic shock with need for vasopressors or respiratory failure requiring mechanical ventilation.

Some authors (Wang 2020) have used the following classification including four categories:

1. Mild cases: clinical symptoms were mild without pneumonia manifestation through image results
2. Ordinary cases: having fever and other respiratory symptoms with pneumonia manifestation through image results
3. Severe cases: meeting any one of the following: respiratory distress, hypoxia ($SpO_2 \leq 93\%$), abnormal blood gas analysis: ($PaO_2 < 60mmHg$, $PaCO_2 > 50mmHg$)
4. Critical cases: meeting any one of the following: Respiratory failure which requires mechanical ventilation, shock, accompanied by other organ failure that needs ICU monitoring and treatment.

In the report of the Chinese CDC, estimation of disease severity used almost the same categories (Wu 2020) although numbers 1 and 2 were combined. According to the report, there were 81% mild and moderate cases, 14% severe cases and 5% critical cases. There are preliminary reports from the Italian National Institute of Health, reporting on 24.9% severe and 5.0% critical cases (Livingston 2020). However, these numbers are believed to strongly overestimate the disease burden, given the very low number of diagnosed cases in Italy at the time.

Outcome

We are facing rapidly increasing numbers of severe and fatal cases in the current pandemic. The two most difficult but most frequently asked clinical questions are 1. how many patients result with severe or even fatal courses of COVID-19? 2. how many remain asymptomatic but unreported?

Case fatality rates

The case fatality rates (CFR) or infection fatality rates (IFR) are difficult to assess in such a dynamic pandemic. CFR can be biased upwards by underreporting of cases and downwards by insufficient follow up or unknown outcome. A downward trend may also indicate improvements in epidemiological surveillance. COVID-19 fatality is likely overestimated and especially early estimates are susceptible to uncertainty about asymptomatic or subclinical infections and several biases, including biases in detection, selection or reporting (Niforatos 2020).

Just dividing the number of deaths by the number of total confirmed cases (March 28 for Italy: 10.8%, Spain 8.2%, South Korea 1.5%, Germany 0.8%) is not appropriate. This probably only reflects the testing policies (and capacities) in a country. In addition, death rates only reflect what had happened 2-3 weeks earlier. In the large retrospective study from Wuhan, the time from illness onset to death was 18.5 days (IQR 15-22 days).

The summarizing report from the Chinese CDC found a death rate of 2.3%, representing 1,023 among 44,672 confirmed cases (Wu 2020). Mortality increased markedly in older people. In the cases aged 70 to 79 years, CFR was 8.0% and cases in those aged 80 years older had a 14.8 % CFR. CFR was also elevated among those with cardiovascular diseases (10.5 %), chronic respiratory diseases (6.3%) for hypertension (6.0%) and cancer (5.6%). Among 1,716 health care workers, 14.8% of confirmed cases were classified as severe or critical and 5 deaths were observed.

A more recent in-depth analysis of 48,557 cases and 2,169 deaths from the epicenter, Wuhan, found lower rates (Wu 2020). The authors estimated an overall symptomatic case fatality risk (SCFR, the probability of dying after developing symptoms) of only 1.4% (0.9–2.1%). Compared to those aged 30–59 years, those aged below 30 and above 59 years were 0.6 (0.3–1.1) and 5.1 (4.2–6.1) times more likely to die after developing symptoms (Wu 2020).

Again, the most valid data seem to come from the Diamond Princess. As of March 19, the total number of infected reached 712, and 9 patients have died from the disease leading to a CFR of 1.3%. However, this rate may yet increase as at least 14 patients were in serious condition (Moriarty 2020). If all patients seriously ill at the last follow up will die, this would result in CFR of 3.2%. On the other hand, around 75% of the patients on the Diamond Princess were of 60 years or even older, many of them in their eighties, suggesting that the risk in the "general" population may be lower.

Risk factors for severe disease

From the beginning of the epidemic, older age has been identified as an important risk factor for disease severity (Huang 2020, Guan 2020). In Wuhan, there was a clear and considerable age dependency in symptomatic infections (susceptibility) and outcome (fatality) risks, by multiple folds in each case (Wu 2020). According to the Italian National Institute of Health, an analysis of the first 2,003 death cases, median age was 80.5 years (IQR 74.3-85.9). Only 17 (0.8%) were 49 years or younger, and 87.7% were older than 70 years (Livingston 2020).

Beside older age, several risk factors have been evaluated in the current pandemic. In the largest clinical study to date, some comorbidities such as hypertension have been identified as the main risk factors for severe disease and death (Table 3).

Others have confirmed a higher rate for patients with comorbidities such as hypertension or diabetes. In multivariate analysis of hospitalized patients with severe COVID-19, however, no comorbidity remained significantly associated with outcome (Zhou 2020).

Table 3. Age and comorbidities in the NEJM paper (Guan 2020)

	All	Severe Disease	Non-Severe
Age > 65	15.1	27.0	12.9
Age < 50	56.0	41.7	58.7
Never smoker	85.4	77.9	86.9
Former or current smoker	14.5	22.1	13.1
COPD,%	1.1	3.5	0.6
Diabetes,%	7.4	16.2	5.7
Hypertension,%	15.0	23.7	13.4
Coronary heart disease,%	2.5	5.8	1.8
Cerebrovascular disease,%	1.4	2.3	1.2
Hepatitis B infection,%	2.1	0.6	2.4
Cancer,%	0.9	1.7	0.8
Chronic renal disease,%	0.7	1.7	0.5
Immune deficiency,%	0.2	0	0.2

In another retrospective cohort of 487 COVID-19 patients in Zhejiang Province of China with detailed clinical data, severe cases were also older and more male. Severe cases had a higher incidence of hypertension, diabetes, cardiovascular diseases, and malignancy, and less exposure to epidemic area, but more infected family members. In a multivariate analysis, older age (OR 1.06, 95% CI 1.03–1.08, p<0.001), male (OR 3.68, 95% CI 1.75–7.75, p=0.001), and presence of hypertension (OR 2.71, 95% CI 1.32–5.59, p=0.007) were independently associated with severe disease at admission, irrespective of adjustment of time to admission (Shi 2020).

As shown in Table 3, there was a slightly higher rate of current smokers in patients with severe disease. However, a meta-analysis of 5 studies comprising 1,399 patients, only a trend but no significant association could be found between active smoking and severity of COVID-19 (Lippi 2020).

More research is needed on the deleterious effect of comorbidities, especially with regard to the renin-angiotensin system (RAS). Hypertension, cardiovascular disease and diabetes share underlying RAS pathophysiology that may be clinically insightful. In particular, activity of the angiotensin-converting enzyme 2 (ACE2) is dysregulated (increased) in cardiovascular disease (Hanff 2020). As SARS-CoV-2 cell entry depends on ACE2 (Hoffmann 2020), increased ACE2 levels may increase the virulence of SARS-CoV-2 within the lung and heart.

Overburdened health care systems

Mortality may be also higher in situations where hospitals are unable to provide intensive care to all the patients who need it, in particular ventilator support. Mortality would thus also be correlated with health-care burden. Preliminary data show clear disparities in mortality rates between Wuhan (> 3%), different regions of Hubei (about 2.9% on average), and across the other provinces of China (about 0.7% on average). The authors have postulated that this is likely to be related to the rapid escalation in the number of infections around the epicenter of the outbreak, which has resulted in an insufficiency of health-care resources, thereby negatively affecting patient outcomes in Hubei, while this has not yet been the situation in other parts of China (Ji 2020). Another study estimated the risk of death in Wuhan as high as 12% in the epicentre and around 1% in other more mildly affected areas (Mizumoto 2020).

The nightmare of insufficient ressources is currently the reality in Northern Italy. In Italy, on March 15, the cumulative death numbers exceeded for the first time those of admissions to intensive care units – a clear sign for a collapsing health care system. Other countries or regions will face the same situation soon.

Outlook

Over the coming months, serological studies will give a clearer picture of the true number of asymptomatic patients and those with unusual symptoms. More importantly, we have to learn more about risk factors for severe disease, in order to adapt prevention strategies. Age is not the only risk factor. The precise mechanisms how comorbidities (and comedications) may contribute to an increased risk for a severe disease course have to be elucidated. Genetic and immunological studies have to reveal susceptibility and predisposition for both severe and mild courses.

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6. Treatment

Christian Hoffmann

The number of people infected with SARS-CoV-2 is increasing rapidly. Because up to 5-10% can have a severe, potentially life-threatening course, there is an urgent need for effective drugs. The time in this pandemic is too short for the development of new, specific agents; a vaccine will also be a long time coming. Thus, existing antivirals or immune modulators with known safety profiles will gain traction as the fastest route to fight COVID-19. Those compounds that have already been tested in other indications now have priority, in particular those that have been shown to be effective in other beta-coronaviruses such as SARS and MERS.

Many current suggestions have emerged from animal models, cell lines or even virtual screening models. While some approaches have at least some evidence for clinical benefit, for others this remains highly speculative. A brief look at the International Clinical Trials Registry Platform (ICTRP) of the World Health Organization (WHO) may illustrate the intensive research efforts that are underway: on March 15, the ICTRP listed a total of 392 clinical studies addressing COVID-19, of which 181 were currently recruiting. Within 5 days, this number has increased to 508 (244 recruiting).

Several very different therapeutic approaches are in the treatment pipeline for COVID-19: antiviral compounds that inhibit enzyme systems, those inhibiting the entry of SARS-CoV-2 into the cell and, finally, immunomodulators that are supposed to reduce the cytokine storm and associated pulmonary damage that is seen in severe case. Of note, no drug is approved for COVID-19. In an interim guidance, the WHO stated on March 13, that "there is no current evidence to recommend any specific anti-COVID-19 treatment" and that use of investigational therapeutics "should be done under ethically approved, randomized, controlled trials" (WHO 2020).

However, enrolling patients in clinical trials will not be possible everywhere. For these, this chapter may support in decision-making. The following agents will be discussed here:

1. Inhibitors of viral RNA synthesis

Remdesivir

Lopinavir (and Darunavir)

Favipiravir

Ribavirin

Sofosbuvir

2. Antiviral Entry Inhibitors

Camostat

Hydroxychloroquine and Chloroquine

Oseltamivir

Umifenovir

Baricitinib

3. **Immunomodulators and other immune therapies**

Corticosteroids

Tocilizumab

Siltuximab

Interferons

Passive immunization

1. Inhibitors of the viral RNA synthesis

SARS-CoV-2 is a single-stranded RNA beta-coronavirus. Potential targets are some non-structural proteins such as protease, RNA polymerase and helicase, but also accessory proteins. Coronaviruses do not use reverse transcriptase. There is only a total of 82% genetic identity between SARS-CoV and SARS-CoV-2. However, the strikingly high genetic homology for one of the key enzymes, the RNA-dependent RNA polymerase (RdRp) which reaches around 96% (Morse 2020), suggests that substances effective for SARS may also be effective for COVID-19.

Remdesivir

Remdesivir (RDV) is a nucleotide analogue and the prodrug of an adenosine C nucleoside which incorporates into nascent viral RNA chains, resulting in premature termination. *In vitro* experiments have shown that remdesivir has a broad anti-CoV activity by inhibiting RdRp in airway epithelial cell cultures, even at submicromolar concentrations (Sheahan 2017). This RdRp inhibition also applies to SARS-CoV-2 (Wang 2020). The substance is very similar to tenofovir alafenamide, another nucleotide analogue used in HIV therapy. Remdesivir was originally developed by Gilead Sciences for the treatment of the Ebola virus but was subsequently abandoned, after disappointing results in a large randomized clinical trial (Mulangu 2019). However, remdesivir is currently being tested in two large randomized phase III studies in around 1,000 patients with both mild-to-moderate and with severe COVID-19 disease. The studies recruiting patients in China and several European countries are planned to be completed by the end of April 2020.

From WHO, remdesivir has been ranked as the most promising candidate for the treatment of COVID-19. Experimental data from mouse models showed better prophylactic and therapeutic efficacy in MERS than a combination of lopinavir/ritonavir (see below) and interferon beta. Remdesivir improved lung function and reduced viral load and pulmonary damage (Sheahan 2020). The first US patient with SARS-CoV-2 also improved dramatically after intravenous treatment with remdesivir (Holshue 2020). Resistance to remdesivir in SARS was generated in cell cultures, but was difficult to select and seemingly impaired viral fitness and virulence (Agostini 2018). The same is seen with MERS viruses (Cockrell 2016). Animal models suggest that a once-daily infusion of 10 mg/kg remdesivir may be sufficient for treatment; pharmacokinetic data for humans are still lacking. In the two large phase III studies on COVID-19, an initial dose of 200 mg is started on day 1, similar to the Ebola studies, followed by 100 mg for another 9 days. The safety of the drug seems to be good. Due to an exponential increase in compassionate use requests, this program is now limited to pregnant woman and children less than 18 years of age. However, Gilead is currently in the process of transitioning from individual requests to expanded access programs (refer to gilead.com).

Lopinavir and Darunavir

The two HIV protease inhibitors (PI) lopinavir and darunavir are thought to inhibit the 3-chymotrypsin-like protease of coronaviruses. Both are administered orally. Lopinavir was used in many patients in China at the beginning of the outbreak (Chen 2020). At least two case-control studies on SARS (Chan 2003, Chu 2004) and one prophylactic study on MERS (Park 2019) have indicated a beneficial effect, but the evidence remains poor. All studies were small and non-randomized. It therefore remained unclear, whether all prognostic factors were matched appropriately. However, a small substudy indicated that SARS-CoV-2 viral load seems to decrease more quickly with lopinavir than without (Chu 2004).

A sharp decline has also been seen in individual cases with COVID-19 treated with lopinavir/r (Lim 2020, Liu 2020, Wang 2020). However, given the rapid kinetics and the rapid decreasing viral load even without therapy in patients recovering, case reports are not very meaningful. In a small study from Singapore study, lopinavir showed no effect on SARS-CoV-2 clearance in nasal swabs (Young 2020). In addition, the first randomized open-lable trial in 199 adults hospitalized with severe COVID-19 did not find any clinical benefit with lopinavir/r treatment beyond standard care (Cao 2020) in patients receiving the drug 10 to 17 days after onset of illness. The percentages of patients with detectable viral RNA at various time points were similar, suggesting no discernible effect on viral shedding. Although PK data is lacking, it seems to be possible that concentrations of protein-unbound lopinavir achieved by current HIV dosing is too low for inhibiting viral replication. It remains to be seen whether levels will be sufficient for (earlier) treatment of mild cases or as post-exposure prophylaxis. There is one retrospective study on 280 cases in which early initiation of lopinavir/r and/or ribavirin showed some benefits (Wu 2020)

There are also press releases on the antiviral effects of darunavir in cell cultures (PR 2020). Darunavir is another protease inhibitor which is more effective than lopinavir in HIV infection. However, the manufacturer Janssen-Cilag published a letter to the European Medical Agency on March 13, pointing out that "based on preliminary, unpublished results from a previously reported *in vitro* experiment, it is not likely darunavir will have significant activity against SARS-CoV-2 when administered at the approved safe and efficacious dose for the treatment of HIV-1 infection." Nevertheless, a large study (CQ4COV19) with 3,040 participants was started on March 18 in Spain for darunavir. Patients with mild symptoms are treated with darunavir/ritonavir and chloroquine immediately after a positive SARS-CoV-2 test.

Both lopinavir and darunavir must be boosted by pharmacoenhancers in order to achieve adequate levels; this is usually done with ritonavir which has a high risk of drug-drug interactions. Numerous studies on both HIV PIs (and other investigational PIs) have started, some of them combined with other agents.

It is hoped that the recently published pharmacokinetic characterization of crystal structure of the main protease SARS-CoV-2 may lead to the design of optimized protease inhibitors (Zhang 2020).

Favipiravir

Favipiravir is another broad antiviral RdRp inhibitor that has been approved for influenza A and B in Japan and other countries (Shiraki 2020). Favipiravir is converted into an active form intracellularly and recognized as a substrate by the viral RNA polymerase, acting like a chain terminator and thus inhibiting RNA polymerase activity (Delang 2018). In an *in vitro* study, this compound showed no strong activity against a clinical isolate of SARS-CoV-2. On February 14, however, a press release with promising results was published in Shenzhen (PR Favipiravir 2020). Preliminary results from a total of 80 patients showed that favipiravir had a stronger antiviral effect than lopinavir/ritonavir, and significantly fewer side effects were observed. Another press release by Chinese officials reported on encouraging results in 340 COVID-19 patients in Wuhan and Shenzhen. With favipiravir, patients showed shorter periods of fever (2.5 versus 4.2 days), faster viral clearance (4 versus 11 days) and improvement in radiological findings (Bryner 2020). Although no scientific data are available to date, favipiravir has been granted five-year approval in China under the trade name Favilavir® (in Europe: Avigan®).

Ribavirin

Ribavirin is a guanosine analogue and RNA synthesis inhibitor that was used for many years for hepatitis C infection and is also thought to inhibit RdRp (Elfiky 2020). In SARS and MERS, ribavirin was mostly combined with lopinavir/ritonavir or interferon; however, a clinical effect has never been shown (Arabi 2017). Ribivarin is now available generically. Its use is limited by considerable side effects, especially anemia.

Sofosbuvir

Sofosbuvir is a polymerase inhibitor which is also used as a direct-acting agent in hepatitis C. It is usually very well tolerated. Modelling studies have shown that sofosbuvir could also inhibit RdRp by competing with physiological nucleotides for RdRp active site (Elfiky 2020). Sofosbuvir could be combined with HCV PIs. Among these, the fixed antiviral combinations with ledipasvir or velpatasvir could be particularly attractive as they may inhibit the both RdRp and protrease of SARS-CoV-2 (Chen 2020). Studies are planned but not yet officially registered.

2. Antiviral Entry Inhibitors

Most coronaviruses attach to cellular receptors by their spike (S) protein. Within a few weeks, several groups have elucidated the entry of SARS-CoV-2 into the target cell (Hoffmann 2020, Zhou 2020). Similar to SARS-CoV, SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as a key receptor, a surface protein that is found in various organs and on lung AT2 alveolar epithelial cells. The affinity for this ACE-2 receptor appears to be higher with SARS-CoV-2 than with other coronaviruses. The hypothesis that ACE inhibitors promote severe COVID-19 courses through increased expression of the ACE2 receptor remains unproven (Hanff 2020). In the largest study to date of 1,099 patients with COVID-19, hypertension was associated with an increased risk (24% versus 13%) of severe course of disease (Guan 2020). However, comedication was not recorded in this study, and several medical societies explicitly advise against discontinuing ACE inhibitors (ESH 2020). Furthermore, the binding of SARS-CoV-2 to ACE2 appears to lead to an imbalance in the RAS system. Animal studies have shown that this imbalance could even be influenced favourably by ACE inhibitors in the course of pneumonia (Gurwitz 2020, Sun 2020).

Camostat

In addition to binding to the ACE2 receptor, priming or cleavage of the spike protein is also necessary for viral entry, enabling the fusion of viral and cellular membranes. SARS-CoV-2 uses the cellular protease transmembrane protease serine 2 (TMPRSS2). Compounds inhibiting this protease may therefore inhibit viral entry (Kawase 2012). The TMPRSS2 inhibitor camostat, which was approved in Japan for the treatment of chronic pancreatitis (trade name: Foipan®), may block the cellular entry of the SARS-CoV-2 virus (Hoffmann 2020). Clinical data are pending.

Hydroxychloroquine (HCQ) and Chloroquine (CQ)

Chloroquine is used for prevention and treatment of malaria and is effective as an anti-inflammatory agent for rheumatoid arthritis and lupus erythematosus. The potential broadly antiviral effect is due to an increase in the endosomal pH value, which disrupts the virus-cell fusion. The glycosylation of cellular receptors of SARS-CoV is also disturbed (Savarino 2003, Vincent 2005, Yan 2013). In SARS-CoV-2 infection, chloroquine may possibly also inhibit post-entry steps (Wang 2020). In addition to the antiviral effect, anti-inflammatory effects could also be beneficial in COVID-19 pneumonia. A Chinese consensus paper dated March 12 recommended chloroquine for patients with both mild and severe pneumonia (EC 2020). Various studies are planned, including as treatment and prophylaxis, including a Spanish study with 3,040 patients and healthcare workers.

Hydroxychloroquine may be more effective than chloroquine (Yao 2020); it is also better tolerated. According to *in vitro* data, hydrochloroquine is recommended in a loading dose of 400 mg twice daily, followed by maintenance therapy of 200 mg twice daily (Yao 2020). A mini-review stated that "results from more than 100 patients" showed that chloroquine phosphate would be able to alleviate and shorten the course of the disease (Gao 2020). To date, valid clinical data are not available, and other experts have raised considerable doubts (Touret 2020). A benefit of chloroquine would be the first positive signal, after decades and hundreds of unsuccessfully studies conducted in a huge number of acute viral diseases. There are also experts arguing that CQ/HCQ could not only be useless but even harmful, as it was seen for Chikuyunga virus infection which may be explained by a delay in immune adaptive response (Guastalegname 2020).

On March 17, a preliminary report from Marseille, France (Gautret 2020) appeared to show some benefit in a small non-randomized trial on 36 patients. Patients who refused treatment or had an exclusion criteria, served as controls. At day 6, 70% were virologically cured (100% when azithromycin was added) as assessed by nasopharyngeal swabs, compared to 13% in the control group. However, several methodological issues have raised doubts on validity of the data. A small randomized trial from China on 30 patients failed to show any clinical or virological benefit (Chen 2020). Precautions for hydroxychloroquine include QTc > 500 msec and several diseases such as myasthenia gravis, epilepsy etc.

Oseltamivir

Oseltamivir (Tamiflu®) is a neuraminidase inhibitor that is also approved for the treatment and prophylaxis of influenza in many countries. Like lopinavir, oseltamivir has been widely used for the current outbreak in China (Guan 2020). Initiation may be crucial immediately after the onset of symptoms. Oseltamivir is best indicated for accompanying influenza coinfection, which has been seen as quite common in MERS patients at around 30% (Bleibtreu 2018). There is no valid data for COVID-19. It is more than questionable whether there is a direct effect in influenza-negative patients with COVID-19 pneumonia. SARS-CoV-2 does not require neuramidases to enter target cells.

Umifenovir

Umifenovir (Arbidol®) is a broad-spectrum antiviral drug which is approved as a membrane fusion inhibitor in Russia and China for the prophylaxis and treatment of influenza. Chinese guidelines recommend it for COVID-19, according to a Chinese press release it is able to inhibit the replication of SARS-CoV-2 in low concentrations of 10-30 µM (PR 2020).

In a small retrospective and uncontrolled study in mild to moderate COVID-19 cases, 16 patients who were treated with oral umifenovir 200 mg TID and lopinavir/r were compared with

17 patients who had received lopinavir/r as monotherapy for 5–21 days (Deng 2020). At day 7 (day 14), in the combination group, SARS-CoV-2 nasopharyngeal specimens became negative in 75% (94%), compared to 35% (53%) with lopinavir/r monotherapy. Chest CT scans were improving for 69% versus 29%, respectively. However, a clear explanation for this remarkable benefit was not provided.

Baricitinib

Baricitinib (Olumiant®) is a Janus-associated kinase (JAK) inhibitor approved for rheumatoid arthritis. Using virtual screening algorithms, baricitinib was identified as a substance that could inhibit ACE2-mediated endocytosis (Stebbing 2020). Like other JAK inhibitors such as fedratinib or ruxolitinib, signaling inhibition may also reduce the effects of the increased cytokine levels that are frequently seen in patients with COVID-19. There is some evidence that baricitinib could be the optimal agent in this group (Richardson 2020). Studies are not yet registered (as of March 25th).

3. Immunomodulators and other immune therapies

While antiviral drugs are most likely to prevent mild COVID-19 cases from becoming severe, adjuvant strategies will be particularly necessary in severe cases. Coronavirus infections may induce excessive and aberrant, ultimately ineffective host immune responses that are associated with severe lung damage (Channappanavar 2017). Similar to SARS and MERS, some patients with COVID-19 develop acute respiratory distress syndrome (ARDS), often associated with a cytokine storm (Mehta 2020). This is characterized by increased plasma concentrations of various interleukins, chemokines and inflammatory proteins.

Various host-specific therapies aim to limit the immense damage caused by the dysregulation of pro-inflammatory cytokine and chemokine reactions (Zumla 2020). Immunosuppressants, interleukin-1 blocking agents such as anakinra or JAK-2 inhibitors are also an option (Mehta 2020). These therapies may potentially act synergistically when combined with antivirals. Several marketed drugs are discussed, including those for lowering cholesterol, for diabetes, arthritis, epilepsy and cancer, but also antibiotics. They are said to modulate autophagy, promote other immune effector mechanisms and the production of antimicrobial peptides. However, clinical data is pending for most strategies.

Corticosteroids

Corticosteroids are often used, especially in severe cases. In the largest uncontrolled cohort study to date of 1,099 patients with COVID-19, a total of 19% were treated with corticosteroids, in severe cases almost half of all patients (Guan 2020). However, according to current WHO guidelines, steroids are not recommended outside clinical trials.

A systematic review of several observational SARS studies (Stockman 2006) yielded no benefit and various side effects (avascular necrosis, psychosis, diabetes). However, the use of corticosteroids COVID-19 is still very controversial (Russell 2020, Shang 2020). In a retrospective study of 401 patients with SARS, it was found that low doses reduce mortality and are able to shorten the length of hospital stay for critically ill patients, without causing secondary infection and/or other complications (Chen 2006).

In another retrospective study involving a total of 201 COVID-19 patients, methylprednisolone reduced mortality in patients with ARDS (Wu 2020). On the other hand, there is strong evidence of a delayed viral clearance (Ling 2020), which has also been observed with SARS (Stockman 2006). In a consensus statement by the Chinese Thoracic Society on February 8, corticosteroids should only be used with caution, after careful consideration, at low doses (≤ 0.5–1 mg/kg methylprednisolone or equivalent per day) and, last but not least, as short as possible (≤ 7 Days) (Zhao 2020).

Tocilizumab

Tocilizumab is a monoclonal antibody that targets the interleukin-6 receptor. Tocilizumab (RoActemra® or Actemra®) is used for rheumatic arthritis and has a good safety profile. At least one uncontrolled, retrospective study has been published, showing encouraging results in 20 patients with severe COVID-19 and elevated IL-6 levels (Xu 2020). The initial dose should be 4-8 mg/kg, with the recommended dosage being 400 mg (infusion over more than 1 hour). Controlled trials are underway as well as for sarilumab (Kevzara®), another IL-6 receptor antagonist. There is no doubt that tocilizumab should be reserved for patients with severe disease who have failed other therapies.

Siltuximab

Siltuximab (Sylvant®) is another anti-IL-6-blocking agent. However, this chimeric monoclonal antibody targets interleukin-6 directly and not the receptor. Siltuximab has been approved for idiopathic multicentric Castleman's disease. First results of a pilot trial in Italy ("SISCO trial") have shown encouraging results but have not been published yet.

Interferons

In patients with MERS, interferon studies were disappointing. Despite impressive antiviral effects in cell cultures (Falzarano 2013), no convincing benefit was shown in clinical studies in combination with ribavirin (Omrani 2014, Shalhoub 2015, Arabi

2019). Nevertheless, inhalation of interferon is still recommended as an option in Chinese treatment guidelines.

Passive immunization

A meta-analysis of observational studies on passive immunotherapy for SARS and severe influenza indicates a decrease in mortality, but the studies were commonly of low or very low quality and lacked control groups (Mair-Jenkins 2015). In MERS, fresh frozen convalescent plasma or immunoglobulin from recovered patients have been discussed (Zumla 2015, Arabi 2017). Recovered SARS patients develop a neutralizing antibody response against the viral spike protein (Liu 2006). Preliminary data indicate that this response also extends to SARS-CoV-2 (Hoffmann 2020), but the effect on SARS-CoV-2 was somewhat weaker. Others have argued that human convalescent serum could be an option for prevention and treatment of COVID-19 disease to be rapidly available when there are sufficient numbers of people who have recovered and can donate immunoglobulin-containing serum (Casadevall 2020).

In a preliminary uncontrolled case series of 5 critically ill patients with COVID-19 and ARDS, administration of convalescent plasma containing neutralizing antibody was followed by improvement in their clinical status (Shen 2020). All 5 patients were receiving mechanical ventilation at the time of treatment and all had received antiviral agents and methylprednisolone. On March 26, the FDA has approved the use of plasma from recovered patients to treat people who are critically ill with COVID-19 (Tanne 2020). This method has been used in the past to treat diseases such as polio, measles or even the 1918 flu epidemic.

Other immunomodulatory and other approaches in clinical testing include bevacizumab, brilacidin, cyclosporin, fedratinib (Wu 2020), fingolimod, lenadilomide and thalidomide, sildenafil, teicoplanin (Baron 2020), monoclonal antibodies (Shanmugaraj 2020) and many more. Cellular therapy approaches are also being discussed. However, there is no doubt that these strategies are still far away from broad clinical use.

Outlook

It is hoped that local health systems can withstand the current outbreak and that at least some of the options given in this overview will show positive results over time. It is also important that in this difficult situation, despite the immense pressure, the basic principles of drug development and research including repurposing are not abandoned.

Four different options, namely lopinavir/r, alone and in combination with interferon, remdesivir and (hydroxy) chloroquine will be tested in the SOLIDARITY study launched on March 18 by the WHO. Results of this large-scale, pragmatic trial will generate the robust data we need, to show which treatments are the most effective (Sayburn 2020).

So in the present dark times, which are the best options to offer patients? There is currently no evidence from controlled clinical trials to recommend a specific treatment for SARS-CoV-2 coronavirus infection. A task force of diverse groups of Belgian clinicians has developed "Interim Guidelines for patients suspected of/confirmed with COVID-19 in Belgium" that were published on March 24. They also refer to other Interim Guidelines, as shown in Table 1.

We predict that within months, we will shake our heads in disbelief at these recommendations but this is no reason to remain inactive today. The task of medicine is to offer the best known treatment at a given moment. At present, the best treatment is supportive care for respiratory failure and hope that some of the above mentioned drugs have a marginal benefit.

Even a marginal benefit might help patients to surpass *in extremis* the divide between life and death.

Table 1. Preliminary guidelines for COVID-19 in different countries, according to disease severity (https://epidemio.wiv-isp.be)

Disease severity	Italy (Lombardia protocol)	France	Netherlands	Belgium
Mild to moderate, no risk factors	No	No	No	No
Mild to moderate, risk factors	LPV/r + (H)CQ for 5-7 days	Consider LPV/r, duration depending on viral shedding	Consider CQ for 5 days	Consider HCQ 400 BID, then 200 mg BID for 4 days
Severe	RDV + (H)CQ for 5-20 days	RDV, duration depending on viral shedding	CQ (600 mg, then 300 mg) for 5 days	HCQ 400 BID, then 200 mg BID for 4 days
Severe, 2nd Choice	LPV/r with CQ	No	LPV/r for 10-14 days	LPV/r for 14 days
Critical	RDV + (H)CQ for 5-20 days	RDV, duration depending on viral shedding	RDV for 10 days + CQ for 5 days	RDV
Critical, 2nd Choice	LPV/r with CQ	LPV/r		HCQ (TOC within RCTs)

RDV Remdesivir, LPV/r Lopinavir/ritonavir, (H)CQ (Hydroxy) Chloroquine, TOC tocilizumab. Risk factors: age > 65 years and/or underlying end organ dysfunction (lung, heart, liver), diabetes, CVD, COPD, hypertension

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7. Severe COVID-19

This chapter about severe COVID-19 in the hospital/ICU is still under construction. In the meantime, please find the following recommendations.

Checklists for hospitals

European Centre for Disease Prevention and Control. **Checklist for hospitals preparing for the reception and care of coronavirus 2019 (COVID-19) patients.** ECDC: Stockholm; 2020. https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-checklist-hospitals-preparing-reception-care-coronavirus-patients.pdf

Patient admission to ICUs

Swiss Society Of Intensive Care Medicine. **Recommendations for the admission of patients with COVID-19 to intensive care and intermediate care units (ICUs and IMCUs).** Swiss Med Wkly. 2020 Mar 24;150:w20227. Fulltext: https://doi.org/10.4414/smw.2020.20227

Management of critically ill patients

Excellent detailed update for anesthesiologists and intensivists:

Thomas-Ruddel D, Winning J, Dickmann P, et al. **Coronavirus disease 2019 (COVID-19): update for anesthesiologists and intensivists March 2020.** Anaesthesist. 2020 Mar 24. pii: 10.1007/s00101-020-00760-3. Fulltext: https://doi.org/10.1007/s00101-020-00760-3

Short recommendations, made by the Surviving Sepsis Campaign:

Poston JT, Patel BK, Davis AM. **Management of Critically Ill Adults With COVID-19.** JAMA. 2020 Mar 26. pii: 2763879. Fulltext: https://doi.org/10.1001/jama.2020.4914

Pragmatic recommendations from Italy on mechanical ventilation and management of sepsis: https://www.esicm.org/blog

Endotracheal intubation and staff safety

Orser BA. **Recommendations for Endotracheal Intubation of COVID-19 Patients.** Anesth Analg. 2020 Mar 23. Abstract: https://pubmed.gov/32209810. Fulltext: https://doi.org/10.1213/ANE.0000000000004803

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Triage for intensive-care treatment

Swiss Academy Of Medical Sciences. **COVID-19 pandemic: triage for intensive-care treatment under resource scarcity.** Swiss Med Wkly. 2020 Mar 24;150:w20229. Abstract: https://pubmed.gov/32208495. Fulltext: https://doi.org/Swiss Med Wkly. 2020;150:w20229

Patients in the radiology department

An P, Ye Y, Chen M, Chen Y, Fan W, Wang Y. **Management strategy of novel coronavirus (COVID-19) pneumonia in the radiology department: a Chinese experience.** Diagn Interv Radiol. 2020 Mar 25. Abstract: https://pubmed.gov/32209526. Fulltext: https://doi.org/10.5152/dir.2020.20167

Recommendations for conducting autopsies

Hanley B, Lucas SB, Youd E, Swift B, Osborn M. **Autopsy in suspected COVID-19 cases.** J Clin Pathol. 2020 Mar 20. pii: jclinpath-2020-206522. Abstract: https://pubmed.gov/32198191. Fulltext: https://doi.org/10.1136/jclinpath-2020-206522

European Centre for Disease Prevention and Control. **Considerations related to the safe handling of bodies of deceased persons with suspected or confirmed COVID-19.** Stockholm: ECDC; 2020. https://www.ecdc.europa.eu/sites/default/files/documents/COVID-19-safe-handling-of-bodies-or-persons-dying-from-COVID19.pdf

8. Comorbidities / Special Populations

The following topics will be expanded in future editions. In the meantime, click the full-text links to read the following articles.

Cardiovascular diseases

Patel AB, Verma A. **COVID-19 and Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers: What Is the Evidence?** JAMA. 2020 Mar 24. pii: 2763803. Fulltext: https://doi.org/10.1001/jama.2020.4812

Clerkin KJ, Fried JA, Raikhelkar J, et al. **Coronavirus Disease 2019 (COVID-19) and Cardiovascular Disease.** Circulation. 2020 Mar 21. Fulltext: https://doi.org/10.1161/CIRCULATIONAHA.120.046941

HIV infection and immunosuppression

U.S. Department of Health and Human Services. **Interim Guidance for COVID-19 and Persons with HIV.** https://aidsinfo.nih.gov/guidelines/html/8/covid-19-and-persons-with-hiv--interim-guidance-/554/interim-guidance-for-covid-19-and-persons-with-hiv

EACS & BHIVA **Statement on risk of COVID-19 for people living with HIV (PLWH).** https://www.eacsociety.org/home/covid-19-and-hiv.html

Bashyam AM, Feldman SR. **Should patients stop their biologic treatment during the COVID-19 pandemic.** J Dermatolog Treat. 2020 Mar 19:1-2. Fulltext: https://doi.org/10.1080/09546634.2020.1742438

Conforti C, Giuffrida R, Dianzani C, Di Meo N, Zalaudek I. **COVID-19 and psoriasis: Is it time to limit treatment with immunosuppressants?** A call for action. Dermatol Ther. 2020 Mar 11:e13298. Fulltext: https://doi.org/10.1111/dth.13298

Oncology

Francesco C, Pettke A, Michele B, Fabio P, Helleday T. **Managing COVID-19 in the oncology clinic and avoiding the distraction effect.** Ann Oncol. 2020 Mar 19. pii: S0923-7534(20)36373-0. Fulltext: https://doi.org/10.1016/j.annonc.2020.03.286

Ueda M, Martins R, Hendrie PC, et al. **Managing Cancer Care During the COVID-19 Pandemic: Agility and Collaboration Toward a Common Goal.** J Natl Compr Canc Netw. 2020 Mar 20:1-4. Fulltext: https://doi.org/jnccn1804COVID

Dholaria B, Savani BN. **How do we plan hematopoietic cell transplant and cellular therapy with the looming COVID-19 threat?** Br J Haematol. 2020 Mar 16. Fulltext: https://doi.org/10.1111/bjh.16597

Xia Y, Jin R, Zhao J, Li W, Shen H. **Risk of COVID-19 for cancer patients.** Lancet Oncol. 2020 Mar 3. pii: S1470-2045(20)30150-9. Fulltext: https://doi.org/10.1016/S1470-2045(20)30150-9

Liang W, Guan W, Chen R, et al. **Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China.** Lancet Oncol. 2020 Mar;21(3):335-337. Fulltext: https://doi.org/10.1016/S1470-2045(20)30096-6

Transplantation

Kumar D, Manuel O, Natori Y, et al. COVID-19: **A Global Transplant Perspective on Successfully Navigating a Pandemic.** Am J Transplant. 2020 Mar 23. Abstract: https://pubmed.gov/32202064. Fulltext: https://doi.org/10.1111/ajt.15876

Guillen E, Pineiro GJ, Revuelta I, et al. **Case report of COVID-19 in a kidney transplant recipient: Does immunosuppression alter the clinical presentation?** Am J Transplant. 2020 Mar 20. Abstract: https://pubmed.gov/32198834. Fulltext: https://doi.org/10.1111/ajt.15874

Andrea G, Daniele D, Barbara A, et al. Coronavirus Disease 2019 and Transplantation: a view from the inside. Am J Transplant. 2020 Mar 17. Abstract: https://pubmed.gov/32181969. Fulltext: https://doi.org/10.1111/ajt.15853

Dialysis

Basile C, Combe C, Pizzarelli F, et al. **Recommendations for the prevention, mitigation and containment of the emerging SARS-CoV-2 (COVID-19) pandemic in haemodialysis centres.** Nephrol Dial Transplant. 2020 Mar 20. pii: 5810637. Abstract: https://pubmed.gov/32196116. Fulltext: https://doi.org/10.1093/ndt/gfaa069

Other comorbidities

Favalli EG, Ingegnoli F, De Lucia O, Cincinelli G, Cimaz R, Caporali R. **COVID-19 infection and rheumatoid arthritis: Faraway, so close!** Autoimmun Rev. 2020 Mar 20:102523. Abstract: https://pubmed.gov/32205186. Fulltext: https://doi.org/10.1016/j.autrev.2020.102523

Figueroa-Parra G, Aguirre-Garcia GM, Gamboa-Alonso CM, Camacho-Ortiz A, Galarza-Delgado DA. **Are my patients with rheumatic diseases at higher risk of COVID-19?** Ann Rheum Dis. 2020 Mar 22. pii: annrheumdis-2020-217322. Abstract: https://pubmed.gov/32205336. Fulltext: https://doi.org/10.1136/annrheumdis-2020-217322

Pediatric

Shen K, Yang Y, Wang T, et al. **Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: experts' consensus statement.** World J Pediatr. 2020 Feb 7. pii: 10.1007/s12519-020-00343-7. Abstract: https://pubmed.gov/32034659. Fulltext: https://doi.org/10.1007/s12519-020-00343-7

Sun D, Li H, Lu XX, et al. **Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center´s observational study.** World J Pediatr. 2020 Mar 19. pii: 10.1007/s12519-020-00354-4

Ludvigsson JF. **Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults.** Acta Paediatr. 2020 Mar 23. Abstract: https://pubmed.gov/32202343. Fulltext: https://doi.org/10.1111/apa.15270

Brodin P. **Why is COVID-19 so mild in children?** Acta Paediatr. 2020 Mar 25. Abstract: https://pubmed.gov/32212348. Fulltext: https://doi.org/10.1111/apa.15271

Hong H, Wang Y, Chung HT, Chen CJ. **Clinical characteristics of novel coronavirus disease 2019 (COVID-19) in newborns, infants and children.** Pediatr Neonatol. 2020 Mar 10. pii: S1875-9572(20)30026-7. Abstract: https://pubmed.gov/32199864. Fulltext: https://doi.org/10.1016/j.pedneo.2020.03.001

Zeng L, Xia S, Yuan W, et al. **Neonatal Early-Onset Infection With SARS-CoV-2 in 33 Neonates Born to Mothers With COVID-19 in Wuhan, China.** JAMA Pediatr. 2020 Mar 26. pii: 2763787. Abstract: https://pubmed.gov/32215598. Fulltext: https://doi.org/10.1001/jamapediatrics.2020.0878

Pregnancy

Schwartz DA. **An Analysis of 38 Pregnant Women with COVID-19, Their Newborn Infants, and Maternal-Fetal Transmission of SARS-CoV-2: Maternal Coronavirus Infections and Pregnancy Outcomes.** Arch Pathol Lab Med. 2020 Mar 17. https://doi.org/10.5858/arpa.2020-0901-SA

Qiao J. **What are the risks of COVID-19 infection in pregnant women?** Lancet. 2020 Mar 7;395(10226):760-762.

Liu D, Li L, Wu X, et al. **Pregnancy and Perinatal Outcomes of Women With Coronavirus Disease (COVID-19) Pneumonia: A Preliminary Analysis.** AJR Am J Roentgenol. 2020 Mar 18:1-6. https://doi.org/10.2214/AJR.20.23072

Dong L, Tian J, He S, et al. Possible Vertical **Transmission of SARS-CoV-2 From an Infected Mother to Her Newborn.** JAMA. 2020 Mar 26. pii: 2763853. Abstract: https://pubmed.gov/32215581. Fulltext: https://doi.org/10.1001/jama.2020.4621

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Notes

A print edition will be available soon

Notes

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While SARS-CoV-2 seems under control in China, the epidemic is moving west briskly. What only weeks ago seemed an impossible feat – imposing and enforcing strict quarantine measures and isolating millions of people – is now reality in many countries. People all over the world will have to adapt and invent new lifestyles in what is the most disrupting event since World War II.

Over the coming weeks, COVID Reference will be presenting regular updates and narrating the scientific data as coherently as possible.

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