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COVID-19: test, trace and isolate-new epidemiological data

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Summary

In the absence of an efficient drug treatment or a vaccine, the control of the COVID-19 pandemic relies on classic infection control measures. Since these means are socially disruptive and come with substantial economic loss for societies, a better knowledge of the epidemiology of the new coronavirus epidemic is crucial to achieve control at a sustainable cost and within tolerable restrictions of civil rights.

COVID-19 in children

Two important questions for the transmission of the pandemic have been: do children get infected with SARS-CoV-2 and do they become a motor for transmission of the infection? This has been affirmed in the context of influenza virus epidemics, and so it underlies the rationale for school closures.

In the early phase of the epidemic, COVID-19 was not widely distributed in children. Out of 366 children with respiratory infection who were hospitalized in Wuhan in early January, where the epidemic started, only six children tested positive for SARS-CoV-2. These children showed fever, cough, vomiting and radiological signs of viral pneumonia. One child from Huangshi was hospitalized on January 2 suggesting that, at this early date, the virus had already spread beyond Wuhan in the Hubei province (Zhang *et al*., 2020c). Later on, 1391 children from Wuhan who had contact with COVID-19 patients were screened. It turned out that 12% of them had become infected. However, more than half of them showed no fever. In fact, 16% displayed no symptoms at all. Three children with serious comorbidity needed intensive care, and one of them died (Lu *et al*., 2020b). A similar situation was observed in Italy which is, after China, the second hotspot of the COVID-19 pandemic. Only 1% of the registered Covid-19 cases were comprised of children. More than half of the infected children had acquired the infection from outside of the family. Common symptoms were cough and difficulty when eating or being fed. Overall, 21% of the infected children were asymptomatic, while 58% had mild disease; 12% were hospitalized, and 1% of the infected Italian children were in critical condition, but there were no fatalities (Parri *et al*., 2020).

According to these data, children can be infected with SARS-CoV-2, but further studies showed that children are infected less often than adults. In a study from Iceland, children under 10 years showed a 7% viral RNA detection rate compared with 14% in subjects older than 10 years, although both had had comparable exposure. No infected children were detected in a population wide survey from Iceland comprising 10 800 participants (Gudbjartsson *et al*., 2020). Very similar information was reported in data describing household transmission in Wuhan, where children showed a 4% infection rate compared with 17% in adults (Li *et al*., 2020). Likewise, in a study from Hunan children had a threefold lower infection risk than adults (Zhang *et al*., 2020b). In contrast, the infection risk in children from Shenzhen, China was similar to that in adults (Bi *et al*., 2020). However, all studies concur that disease in children is generally mild, if not asymptomatic. Asymptomatic cases raise problems for contact tracing and containment, but it is currently not clear to what extent infected children transmit the disease. Three asymptomatic SARS-CoV-2-positive adolescents showed transmission to family members (Liao *et al*., 2020) while data for transmission from children are still absent.

One special problem should still be mentioned in this context: in Italy, paediatric hospitalization decreased substantially during the COVID-19 epidemic. When the general population avoids hospitals for fear of infection, it can have a negative health impact. An increased number

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of deaths occurred in Italy due to delayed arrival of children in hospitals, while no child died from COVID-19 in Italy (Lazzerini *et al*., 2020). The fear of hospitals has also been responsible for a deficit in the treatment against stroke in adults in the United States (Kansagra *et al*., 2020).

COVID-19 in nursing homes

The statistics for the COVID-19 epidemic have shown that the older population has suffered the greatest loss of life, and that nursing homes have been hotspots for transmission. Two detailed studies from the U.S. document these given facts. At the end of February 2020, a cluster of 167 epidemiologically linked COVID-19 cases were reported in several long-term care facilities in Washington state. Of those, 144 cases were residents (median age 83 years), 55% of them were hospitalized, and 33% died. In comparison, only 16 cases had been visitors, 50% of whom were hospitalized, but none died. Further 50 cases were among the health care personnel, of whom only 6% were hospitalized, but again none died. Factors favouring the outbreak were health care personnel who showed up to work with symptoms; some of the personnel worked at more than one facility; and some residents were transferred between facilities. In the early stages of the epidemic, contributing factors to this outbreak were: an unawareness of the risk; a lack of diagnostic tests; and inadequate personal protection equipment (McMichael *et al*., 2020).

Currently, 1.3 million U.S. Americans reside in nursing homes. One in 10 of >1300 accredited nursing facilities reported COVID-19 cases. An epidemiological survey in such a facility demonstrated the extent of the problem: the first infection in this nursing home was introduced by a symptomatic nurse, and then a week later the first resident tested positive. A further 5 days later, half of the residents from this unit tested positive for viral RNA. During the following 2 weeks, 30–70% of the residents in other units of this home became infected, along with 19% of the staff. Notably, more than half of the residents were asymptomatic when they tested positive for viral RNA. Four days later, 89% of them had developed symptoms. The rest remained asymptomatic. Mortality was high at 26%. Importantly, asymptomatic, pre-symptomatic, and symptomatic residents did not differ with respect to viral load and infectious virus release. All viruses showed identical genome sequences except for one nucleotide difference, which defined two clusters in this home (Arons *et al*., 2020; Gandhi *et al*., 2020).

Pre-symptomatic virus excretion

The Munich cluster

A cluster of COVID-19 cases in Munich, Germany was analysed in detail. A chain of infection was established that linked parents from Wuhan who visited their child in Shanghai, who then had had to travel for business to Munich. In Munich, the index case – while still in the pre-symptomatic stage – went on to infect 16 people, totalling four transmission generations. In nine of the German cases, patients developed mild disease characterized by cough, sinusitis and loss of smell. A high viral load was measured in nasopharynx and oropharynx swabs, with a peak titre in excess of 10^8 viruses per ml before symptom onset. High viral RNA titers were also detected in sputum and stool. Infectious virus was isolated from the respiratory but not from the stool samples. Infectious virus was only observed during the first week after symptom onset, while viral RNA was detected much longer. Active viral replication, as documented by the presence of sub-genomic RNA, was detected in the respiratory tract and in the gut. Independent viral replication processes apparently occurred in the upper and lower respiratory tract, as deduced from viral populations differing by a point mutation. Half of the patients had seroconverted for IgG antibodies 1 week after symptom onset and all patients had developed neutralizing antibodies after 2 weeks. The serum antibodies cross-reacted with seasonal cold coronaviruses. Viral RNA, but not infectious virus, was detected after seroconversion and clinical recovery of the patients (Böhmer *et al*., 2020; Wölfel *et al*., 2020).

China

The dynamics of viral shedding was also evaluated in 94 Chinese COVID-19 patients who provided 414 throat swabs. The highest viral load was found directly at symptom onset and did not differ with the severity of disease, age and sex of the patient. In a separate set of 77 infectors-infectees transmission pairs, the serial interval (duration between symptom onset of successive cases in a transmission chain) was 5.2 days. The incubation period (time between infection and symptom onset) was also 5.2 days. It was deduced from this observation that the infectiousness of COVID-19 patients peaked on, or slightly before, symptom onset and that 44% of the secondary infections occurred in the pre-symptomatic phase of the index patient. This characteristic contrasts with that of SARS-CoV which showed peak viral titers only 10 days after symptom onset. SARS-CoV-2 resembles seasonal influenza in that viral excretion peaks 1 day after symptom onset. Increased personal hygiene and social distancing for everyone are, therefore, key instruments for COVID-19 disease control in the community (He *et al*., 2020).

United Kingdom

At the height of the UK COVID-19 epidemic asymptomatic health care workers (HCW) from London were repeatedly tested for viral RNA over 6 weeks. The infection rate in asymptomatic HCW was 7% at the peak of the epidemic, and it decreased to 1% with the lessening of the epidemic in the population, suggesting that infection was contracted in the community, and not in the hospital, since HCW remained exposed to COVID-19 patients during work (Treibel *et al*., 2020).

Molecular epidemiology of viral genomes

Guangdong cases

In Guangdong province of China, all return visitors from Wuhan/Hubei province, their contacts, and all of the local hospitalized patients were tested for viral RNA. About 1.6 million tests were used to identify 1400 SARS-CoV-2-positive cases; 1000 patients had had exposure to infected people from Hubei. Half of the local transmissions occurred within households. By mid-February, the local spread was controlled, but in March, new cases were imported from abroad. Sputum samples showed the highest viral titers, followed by oropharynx, stool, and finally nasopharynx samples. Critical and severe cases showed higher viral titers than moderate and mild cases, but the differences were small. Viruses from 53 patients were sequenced and compared with 177 SARS-CoV-2 sequences deposited in the database. Single nucleotide polymorphisms (SNPs) were detected at 97 nucleotide positions scattered through the viral genome; 77 variant sites were only seen in a single virus isolate. On a phylogenetic tree, the Guangdong sequences were interspersed between the viral sequences from Wuhan and those isolated abroad, documenting a recent, single source outbreak of a virus showing a low mutation rate (Lu *et al*., 2020a).

USA west-to-east spread

The first case of COVID-19 in the United States was reported on January 19 at the northwest coast of Washington State and was imported from China. From March 1–19, the number of cases in the United States increased from 70 to 13 000. Epidemiologists investigated the first nine COVID-19 cases on the East coast (Connecticut) that were observed in mid-March with genome sequencing. Only one sequence exactly matched the viral sequences from China, but the patient had not travelled to China. The viral sequences from seven further patients, clustered with a large U.S. clade known from Washington State, documented a rapid west-to-east national spread of the novel coronavirus in the United States. International air travel restrictions had no, or low, impact on the epidemic spread in the United States. The viral genome was rooted in a single ancestor coronavirus in Wuhan by fewer than 10 mutations, and it had accumulated about two nucleotide changes per month during its spread across the United States, which is a low mutation rate for a 30 000 nucleotide long viral RNA genome. With the portable Oxford Nanopore Technologies MinION platform, viral genomes were sequenced within 14 h after having received the sample, theoretically allowing near real-time molecular epidemiology of the epidemic spread (Fauver *et al*., 2020).

Transmission chains and risk factors

China

In Wuhan, 105 index cases of patients suffering from moderate COVID-19 symptoms (fever, cough, fatigue) were investigated for secondary transmission to 392 household contacts. The average household size was four persons. The index case persons remained at home for a documented number of days before seeking medical advice. In total, 64 contacts (16%) were infected, nine without symptoms, and the rest experienced moderate disease. The time lapse between primary and secondary infections was 6 days. The transmission probability was age-dependent: it was 4% in children and 17% in adults. The highest transmission rate was seen in 50–60 year old, but not in >60 year-old household members. Spouses experienced a 28% infection transmission rate. When the index case was quarantined directly after symptom onset, transmission rate was 0% (Li *et al*., 2020).

In Shenzhen, 391 cases were recorded, 77% of which were detected through the surveillance of symptoms. Most cases were mild (26%) or moderate (65%). Only 9% of infections were associated with severe disease, which correlated with male sex and older age; three patients died. The researchers identified 1281 close contacts for the index cases; 8% of these had become infected. An increase to 16% in the rate of infection was seen in those who lived or travelled with index case persons. Interestingly, infection risk was comparable for all age groups ranging from 0 to 70 years old. However, half of the children showed no fever, and severe infections were rare in people under the age of 40. Notably, 80% of secondary infections were traced to only 9% of the index case persons (Bi *et al*., 2020) suggesting an important role of 'super-spreaders" in infection transmission. It would be helpful for public health if characteristic traits of super-spreaders were known.

Serology in Singapore

Adding viral-specific IgG antibody tests to the toolbox of COVID-19 epidemiology have allowed the connection between three previously separated infections clusters in Singapore. An infected traveller from Wuhan attended a church meeting, thereby infecting a secondary person (case X), who transmitted the virus to another subject during a family gathering, who then transmitted the virus to a large number of people in a second church. Case X tested negative for viral RNA and represented the missing link between the events. Case X showed a strong serological response to SARS-CoV-2, then connecting the links in the chain (Yong *et al*., 2020).

Iceland

From among 9000 high-risk Icelanders (persons who were symptomatic, or had contact with infected persons, or who travelled to a high-risk country), 13% tested positive for SARS-CoV-2 RNA. Children under 10 years from that high-risk group showed a 7% RNA detection rate compared with 14% in subjects older than 10 years. Before mid-March, travel exposure to Austria and Italy was a common denominator in the positive subjects. After mid-March, travel to United Kingdom was the biggest risk factor. In mid-March, a representative sample of 11 000 subjects from the general population of Iceland (360 000 inhabitants) was tested, and 0.8% tested positive for SARS-CoV-2 RNA. In April, another sample of 2000 subjects from the general population showed a similar rate of viral excreters. In the general population, males were more frequently virus-positive than females. The highest prevalence was seen in 40 year-old subjects, while no children under 10 years were infected. Five hundred viral genomes, isolated from infected Icelanders, were sequenced. The genomes were clustered into 42 distinct clades. During the early epidemic phase in Iceland, nearly all SARS-CoV-2 isolates belonged to the A2 clade, which was also frequently found in central European populations. Viral genome sequencing identified networks of up to 14 linked infections. Transmission occurred in the early phase via international travel, but later via infection from family members (Gudbjartsson *et al*., 2020).

Transmission modes

Airborne: cough, sneeze and speech

Australian engineers evaluated the literature about the reach of pathogen transmission by coughing and sneezing. The 1–2 m rule has been set since the 1940s by photography, physical calculations, and through simulations. Distinct models (turbulent jets vs. puffs) have been used, but not all used appropriate parameters for humidity and temperature. It remains unclear which conditions apply to the human respiratory excretions when handling infected patients in a clinic (Bahl *et al*., 2020). Newer high-speed pictures of a coughing volunteer show a turbulent jet plume that extends over 0.5 m (Tang and Settles, 2008). High-speed pictures of a sneezing volunteer revealed exhaled air, muco-salivary filaments and drops. The turbulent puff cloud disintegrated into droplets that settled within 1–2 m distance. Some droplets evaporate and become suspended in the puff and travel a room within a few minutes to land 6–8 m away from the sneezing person (Bourouiba, 2016) Speech generated droplets in front of the mouth increased with the loudness of the voice. Holding a cloth in front of the mouth suppressed the droplet detection (Anfinrud *et al*., 2020).

A WHO communication led to a controversy saying that there is not enough evidence that SARS-CoV-2 transmission is airborne. WHO defines airborne transmission as being via aerosols as opposed to transmission by droplets. Since most COVID-19 transmission seems to occur through close contact, droplets have been considered to be the more likely vehicles. Whatever the exact transmission route by air, avoiding crowds or standing next to a person for too long, and increasing the rate of ventilation in closed rooms without air recirculation are reasonable precautions (Lewis, 2020).

Face mask use

Physicians recommended face mask use, even when scientific evidence for its effectiveness is lacking, in comments to leading medical journals. Recent reviews have concluded that: no randomized trials with masks have been conducted; that the benefit of masks over no masks (but not of respirator masks over paper masks) was shown in an influenza epidemic in Australia; that some benefit of masks was seen when worn by symptomatic, but not by asymptomatic cases during an influenza epidemic; that no data exist which directly support the use of mask wearing by the public; that no significant effect was seen for household use of masks against influenza transmission. Therefore, WHO initially recommended masks only for symptomatic cases. CDC first advised against mask use by the public but have now changed their policy by recommending even self-made cloth masks for wide use. Harm (e.g. increase of CO_2 level under the mask) is low if not used by small children or elderly people with disabilities (Chen *et al*., 2020; Greenhalgh *et al*., 2020).

Wuhan hospital

As assessed by viral RNA detection, air and surfaces in a Wuhan hospital were widely contaminated during the height of the epidemic in China. Contamination levels were greater on the intensive care unit ward than on the general ward. The transmission of SARS-CoV-2 might reach up to 4 m distance. However, no medical staff in that particular hospital was infected. The authors admit two limitations of the study which prevent firm conclusions from being made. First, viral RNA detection does not mean infectious virus detection, and second, the minimum infectious dose of SARS-CoV-2 for humans is unknown (Guo *et al*., 2020). When reviewing the official recommendations, the consensus seems to be to use a respirator for high-risk interventions, which create aerosols in the ICU, and to use surgical masks on the general ward with low-risk activities (Bahl *et al*., 2020).

Singapore hospital

The environment of three COVID-19 patients from a ventilated hospital infection ward in Singapore was tested for viral RNA presence by RT-PCR. After routine cleaning of high touch areas and of the floor, no viral RNA was found in the air, on hospital room surfaces or on the personal protection equipment of the treating physician. Before routine cleaning, however, 16 of 20 room sites (table, chair, floor, window, toilet) and the shoe protection of a physician tested positive. Room air samples and hospital corridor floors were, however, negative for viral RNA. For infection control, regular room cleaning and handwashing were judged to be essential (Ong *et al*., 2020).

PRIMIT study

It is more problematic to establish a control when a family member with mild infection remains at home. There is only one behavioural intervention study that has proved to reduce respiratory viral transmission within households, the PRIMIT germ defence study. The key interventions are web-based instructions about handwashing given to 10 000 intervention subjects in the United Kingdom, but not to 10 000 controls. Infection transmission was reduced by 20% and infection severity was also reduced, albeit modestly (Little *et al*., 2015). The rationale behind the idea was to reduce the viral load by which contacts are particularly exposed, such as through hand-to-eye contact, since the conjunctiva supports SARS-CoV-2 replication (Hui *et al*., 2020; Little *et al*., 2020).

Different control strategies

COVID-19 in Italy

In Italy, the epidemic started in Lombardy and Veneto. Lombardy strengthened their hospital capacity and increased ICU beds, while Veneto opted for strict containment and mass testing in 4% of the population. Lombardy experienced 47 000 more cases than Veneto and also had a much higher crude case fatality rate (18% vs. 6%). The higher death rate is probably explained by the delayed public health response (Odone *et al*., 2020) as also seen in the United States (Anonymus, 2020).

COVID-19 in Sweden

The Swedish government had recommended a number of trust based measures (social distancing from old people, handwashing, home office, travel reduction), but refrained from closing borders, schools, restaurants and bars, partly because the Swedish law does not allow lockdowns. The case reduction of seasonal influenza and Norwalk diarrhoea provided documented effectivity of the measures taken (Paterlini, 2020). However, compared with neighbouring Finland and Norway, Sweden experienced a tenfold higher number of deaths for a 1.5-fold larger population, but the absolute numbers are still small (3700 vs. 300 for Sweden and Finland, respectively, May 18).

Emergency measures in the United States

In the United States, the individual states and CDC have many legal options for quarantine (for the segregation of exposed people) and isolation (separation of infected people from the general population) in such cases as with SARS. The establishment of broad sanitary cordons in which entire geographical areas are quarantined (as has happened in Wuhan) will raise constitutional questions in the United States. The U.S. recommendations say that patients who show mild symptoms should stay home and notify their employer electronically. Low-wage workers cannot afford to stay off work, but the U.S. senate is in the process of establishing bills for paid sick leave and unemployment insurance (Parmet and Sinha, 2020).

Control measures in Hong Kong

The control measures that stopped the epidemic locally have included: intense infection surveillance of incoming travellers; isolation of COVID-19 cases in hospitals; contact tracing and quarantine in holiday camps; and school closure but no lock-down, thus preventing the crisis from having a negative economic impact. A total of 715 cases were confirmed, half imported, and the rest locally transmitted with a reproduction number that quickly decreased to values around 1; and 13% of virus-positive subjects were asymptomatic. The control measures also stopped an ongoing seasonal influenza epidemic. Surveys showed that the population agreed to participate in the measures. They kept social distancing and made behavioural changes (99% wearing masks outside house, 93% increased hand hygiene, 83% staying at home as much as possible). The study could not differentiate the impact of each individual measure. Unfortunately, the full effect of school closure is still unknown because the susceptibility of children for COVID-19 and their capacity to transmit the infection has not yet been established (Cowling *et al*., 2020).

Non-pharmaceutical interventions in China

China has contained the COVID-19 epidemic through a combination of different measures including drastic ones. An international team of epidemiologists developed a computer model that described the dynamics of the epidemic and tested the impact of the different containment measures by using computer simulations. Without any intervention, a 100-fold higher number of cases would have occurred in China, resulting in over 10 million cases. Without travel restrictions, the epidemic would have expanded more widely over the western provinces. Early detection and isolation of patients reduced the number of cases by fivefold, while social distancing and contact reduction led to a 2.6-fold reduction. However, without contact reduction, the epidemic would have, over time, increased exponentially across the regions. Initiating the intervention 1 week earlier would have decreased the number of cases by 66% or, if done 1 week later the number of cases might have increased by threefold. A delay of 2 or 3 weeks would have increased cases by 7- and 18-fold, respectively. Lifting travel restrictions will result in a new rise in case numbers, but even moderate levels of social distancing could keep this increase in check. Partial maintenance of NPI may prevent, or at least delay, the arrival of second wave infections (Lai *et al*., 2020).

Contact reduction in China

Contact surveys were conducted in Wuhan and Shanghai during the height of the COVID-19 epidemic in China. Before the epidemic, people reported between 15 and 18 contacts (two-way conversations, physical contact) per day. This number was reduced to two during the containment period. Contact reduction was most significant for school-age children who, before the intervention, reported the greatest numbers of contacts out of all of the age groups, followed by adults at the workplace. During containment, contacts were mainly within families (80%–95%). The survey was consistent with data from inner city mobility.

All contacts of patients in Hunan province were placed under medical observation and tested for excretion of viral RNA. From these contact data, it was deduced that children (<14 years) had an infection rate that was only a third as high as adults (15–65 years), while older individuals had a 50% higher infection rate than young adults. Based on these data and on a mathematical infection model, the authors concluded that social distancing alone is sufficient to control COVID-19 spread. Proactive school closure alone cannot interrupt transmission but can reduce the peak incidence of the disease by half, and it can delay the epidemic (Zhang *et al*., 2020b). These are model simulations based on assumptions on infection transmission by children for which only few data are currently available. The reopening of schools in several countries will hopefully settle some questions with observational data.

Psychology

Psychologists argue that contact-seeking is a basic human response to danger. This inclination takes over when an invisible infection threat is perceived. This instinct is only opposed by disgust when infected persons show appalling clinical signs which is not the case for SARS-CoV-2 infected subjects in pre-symptomatic or asymptomatic state. It will be increasingly difficult for health authorities to impose social distancing, as proven by the street demonstrations against containment measures in the US and in European countries by differently motivated opposition groups. The authors argue that the increased use of the Internet as a substitute for contact can become an important public health tool to achieve physical distancing without social distancing (Dezecache *et al*., 2020).

Census

By May 18, the Johns Hopkins University registered 4.7 mio cases worldwide. The lion's share is from the United States with 1.4 mio cases, compared with 84 000 cases reported by China. One should interpret these data with caution. The definition for a confirmed case of COVID-19 was changed five times in China, which accounts for the increase in knowledge about the epidemic. Scientists from the WHO Collaboration Centre in Hong Kong calculated that when the fifth version is applied, the total number of cases in China would increase from 55 000 to 230 000, but the transmission patterns in mainland China would not change (Tsang *et al*., 2020). The case number also depends on the intensity of viral testing and the capacity of the public health system to report the number of cases.

With nearly 90 000 deaths, the U.S. number greatly surpasses the 4600 deaths reported in China. It is still difficult to assess the morbidity and mortality impact of the COVID-19 pandemic on the population. Even mortality rate is not a clear figure since it is reported differently in different countries. While death is a clear diagnosis, the cause of death is not. It might not be evident whether somebody died with or from COVID-19, particularly in nursing homes. Some countries attribute death to COVID-19 if the virus was present at death. Others attribute each death in nursing homes to COVID-19 during the height of the epidemic – as was done in Belgium, which explains its high mortality data. Many deaths occurred while people also had underlying health problems (comorbidities); therefore, they were already at increased risk of death.

Excess mortality

An international consortium of demographers called for the publication of excess mortality data. By comparing mortality statistics for a given epidemic period with a corresponding time period during previous years without that epidemic, the absolute impact of an infection can be assessed. Such data are still largely lacking in the literature. Excess mortality rates should best be calculated for both sexes and for each 5-years age range separately (Leon *et al*., 2020). First data have just now been reported: In March/April, the care sector of England and Wales alone has seen 20 000 excess deaths over the figures of previous years. COVID-19 deaths at care homes were three times as high as COVID-19 deaths in hospitals (Burki, 2020).

Excess mortality calculations have been done globally for seasonal influenza, arriving at 300 000–600 000 influenza-associated deaths occurring annually (Iuliano *et al*., 2018). While the majority of influenza mortality applies to elderly people, the death rate is also substantial for children at an estimated 34 000 deaths in 2018 (Wang *et al*., 2020). In comparison, the global death toll of COVID-19 is now 315′000 (status May 18). A direct comparison of these two figures is difficult for two reasons: death levels are affected by vaccination campaigns against seasonal influenza and by strict containment measures for COVID-19. It seems plausible that without any containment measures COVID-19 mortality would surpass greatly the number of deaths from seasonal influenza. The presumption that the COVID-19 mortality is comparable to that of seasonal influenza deaths is fundamentally flawed because it compares numbers which are obtained by different methods. The death rate for COVID-19, which has just crossed the 100 000 figure in the United States, is an actual count of dead patients. In contrast, the 23 000–61 000 annual deaths from seasonal influenza quoted after influenza epidemics in the United States are estimates by the CDC of influenza deaths based on calculations from models. The death counts actually reported to U.S. health authorities ranged from 3400 to 15 000 deaths per year during an influenza epidemic in the United States. Expressed as deaths per peak week, influenza claimed a maximum 1616 deaths per week, while COVID-19 took about 15 000 lives per week at its peak in the United States (Faust and del Rio, 2020).

Computer model projections for a second epidemic wave

Wuhan

An international consortium of epidemiologists has estimated that 66 000 people were infected in Wuhan and that 2800 have died; 70% were infected through household contact, 25% through public contact, and 5% in hospitals. From a peak number of 2000 new infections, Wuhan currently has 10 or fewer new infections per day. Safe strategies are now needed for the exit from lockdown measures. When lifting the lockdown to a 100% pre-quarantine social contact level, a computer model showed that a 95% face mask wearing would be needed to ensure a complete elimination of infections. In contrast, with only 50% face mask use and a lifting date of strict measures before April 25 to pre-quarantine level, the conditions in this model would lead to a major second wave of infection. Maintaining a contact rate below pre-quarantine level combined with a high percentage of face mask wearing is essential while now the restrictions have been lifted in Wuhan – at least until a vaccine becomes available. However, face mask provision for such large populations represents logistical challenges and must not cause a shortage of protective gear for health personnel (Zhang *et al*., 2020a).

Mainland China

In mainland China, 13 400 confirmed cases and 120 deaths were reported by March 18. In Beijing and Shenzhen, most cases have been imported from Wuhan and the reproduction number R remained below 1.0. In Shanghai and Wenzhou, local cases dominated but R rose to greater than 1 for only one January week. Case fatality was 1% compared with 6% in Hubei. Relaxing the restrictions could lead to a second wave of exponential infection from imported cases in a non-immune, susceptible population. Maximizing economic productivity under the ≤1 constraint can, according to this study, only be possible with a real time prevalence determination of new infections through extensive testing (Leung *et al*., 2020).

Other epidemiologists working on outbreak data from mainland China observed a sub-exponential increase of cases from the beginning, instead of an expected exponential growth for an unconstrained epidemic. Model calculations showed that the containment measures (the quarantine of exposed, and the isolation of infected persons) reproduced the actually observed case development. Similar strategies are recommended in the event of a future outbreak (Maier and Brockmann, 2020).

Harvard model

Epidemiologists from Harvard University derived projections from model calculations about the future dynamics of the COVID-19 epidemic. When anticipating short-term immunity (as observed for seasonal common cold coronaviruses), they predict annual winter epidemics for SARS-CoV-2. With intermediate levels of immunity persistence, epidemics would become biannual. Long-term immunity (as in the case of SARS-CoV) would lead to the extinction of the virus, even in the absence of social distancing. They also calculated that it needed 20 weeks of social distancing to reduce the peak number of infected persons. If the reproduction of the virus is reduced by more than 60% through lockdowns, the infection peak is predicted to shift to the next winter season with high numbers because no herd immunity has been achieved (Kissler *et al*., 2020).

Herd immunity

A central concept of epidemiology is herd immunity; the percentage of persons with protective immunity needed in a population to stop the propagation of an infectious agent. When this threshold is crossed, the remaining susceptible persons are protected from infection. The threshold level depends on the 'force' of the infectious agent which is expressed by the basic reproduction number R_0, which is defined as the number of secondary infections caused by an index case. In infection modelling, herd immunity threshold and R_0 are linked by a simple mathematical function. SARS-CoV-2 has a higher R_0 'infectious force' than influenza virus, but a much lower one than 'flying infections" such as chickenpox or measles. It is anticipated that a population needs a herd immunity of 50–80% protected people to stop the COVID-19 epidemic.

The initial strategy of the UK government was to let the epidemic roll over the country to achieve this herd immunity, in contrast to containment policies which prevent exposure, but which also prevent immunity development in the population. This strategy has theoretical advantages (fewer economic losses when a lockdown is avoided, and a protected population in the event that no vaccine becomes available). However, it comes at a cost. If you allow, let us say, 60% of the population to get infected, you can calculate the cost of this strategy with the help of the infection fatality rate (IFR). In contrast to the case fatality rate (CFR) which expresses the number of deaths per clinically ill patients (which varies from 1.4% to 15% for COVID-19), IFR is the number of deaths per infected individual. The number is, of course, lower than CRF. While we know, approximatively, the number of COVID-19 deaths and COVID-19 cases, we do not definitively know the number of infected persons, since this would require large and systematic seroprevalence studies, but which are lacking. Current estimates suggest 0.6% as a realistic approximation for IFR. With that figure, one can calculate that achieving herd immunity through natural infection with SARS-CoV-2 would cost the lives of 150 000 UK citizen or more than 1 000 000 U.S. citizens. This death toll was considered as too high by the UK government, which then changed strategy by declaring a late containment strategy (Randolphe and Barreiro, 2020). Delays in imposing containment measures were predicted to lead to 10-fold or higher number of cases and fatalities. This prediction might explain why the United States and United Kingdom have such high case and death statistics in international comparison.

Controlling exit from lockdown

Mobile phone technology

Epidemiologists from the United Kingdom and United States have developed a real-time data-capture platform applicable for mobile phone use for the self-guided collection of population-level data (COPE consortium). The app queries location, age, health-risk factors and asks daily for new symptoms and diagnostic test results. A test run with 1.6 million users in United Kingdom showed that the most common symptoms were fatigue and cough. Anosmia (loss of smell) appeared as a strong predictor of COVID-19, while fever was not a diagnostic criterion unless combined with other symptoms. The reported symptoms predicted that there would be changes in the number of cases as indeed reported from health authorities 5–7 days later. The tool will be important for a controlled safe exit from confinement measures. Also, long-term effects of the disease, and the impact of the COVID-19 epidemic on social relations, mental health, and financial outcome can be evaluated with this tool. Machine learning could also reveal new disease manifestations of the epidemic (Drew *et al*., 2020).

Anosmia is an interesting symptom. A preliminary evaluation of a COVID-19 Symptom Tracker smartphone app from UK users showed that the loss of smell was reported by 59% of people with respiratory infection who tested positive for SARS-CoV-2, compared with 18% of respiratory patients who tested negative. Clinical criteria that allow a diagnosis of COVID-19 without a viral RNA test would be welcome for mass screening and telemedicine in an epidemic situation. French physicians have also reported that many COVID-19 patients reported loss of smell and loss of taste, without nasal congestion. When these criteria were combined in a retrospective questionnaire this combination of signs had a sensitivity of 42% and a specificity of 95% for detecting COVID-19 patients (Bénézit *et al*., 2020). These observations are not surprising since the highest expression level of the SARS-CoV-2 receptor ACE-2 was shown in the respiratory tract, more specifically in the nasal epithelia. U.S. physicians even suspected that SARS-CoV-2 might, in addition to the respiratory and alimentary tract, also infect cranial nerves (i.e. being neurotropic), which potentially explains the observation of neurological signs in 9% of COVID-19 patients (Chu *et al*., 2020).

Seroprevalence studies

Antibody tests are an important tool in a staggered release of population groups out of lockdowns because such tests identify people who have been exposed to the infection and who are potentially immune to infection. So far, only preliminary data became available from 3300 volunteers from Santa Barbara county in California. One out of 66 (1.5%) showed antibodies to SARS-CoV-2. This number is 50-fold higher than the number of the official case count was for this area in early April. In a preliminary survey in Geneva, less than 5% of a population sample showed viral-specific antibodies in preliminary surveys. In a town with 12 000 inhabitants in Germany, 500 people were antibody tested following carnival parties and an infection rate of 15% was determined. These datasets cannot be extrapolated to the population at large. In addition, the antibody tests were only validated with a small set of positive and negative test samples, raising concerns about the reliability of the results (Mallapaty, 2020; Sood *et al*., 2020). The next challenge will be the acquisition of reliable antibody data for representative samples from entire populations.

Some public health considerations

The COVID-19 epidemic continues to challenge our societies by its toll in deaths, by the disruption of social life; by its disastrous impact on the world economy; by increasing the debt of many nations; by endangering the survival of many industries; and by reversing the worldwide trend for poverty relief. For microbiologists, the COVID-19 crisis has also revealed shortcomings in the public health sector, particularly in that of countries which were exemplary in this field during past decades.

In the United States, the COVID-19 epidemic has taken more lives in 1 month than over 8 years during the Vietnam War. With more than 1.7 million cases, and more than 100 000 deaths, the ‘America first’ slogan has become sadly ironic in the context of COVID-19. An article in the leading U.S. medical journal, The *New England Journal of Medicine*, attributes this calamity to insufficient diagnostic testing caused by the delivery of faulty tests by CDC; non-approval through the FDA of working tests by WHO resulting in a delayed start of viral detection activities; and then followed by a shortage of test reagents. Public health workers were therefore blind to the unfolding of the US epidemic and unable to design efficient containment measures, short of a lockdown. Epidemiologists were left without population data for modelling the epidemic in the United States at a moment when the country started reopening economic and public activity. In comparison with other countries, the United States has tragically ‘failed the test’. In the words of this article, ‘The US once a leader, seem oddly lost’ (Schneider, 2020). An editorial in the leading British medical research journal, *The Lancet*, comes to the same conclusion: The CDC, once a pillar and international reference for combating diseases worldwide, instrumental in eradicating smallpox and coping with AIDS or Ebola, has lost its technical competence and public trust due to contradictory scientific messages and the undermining of trust in scientific evidence by the current U.S. administration. According to the Lancet editors, the ‘US Administration is obsessed with magic bullets-vaccines, new drugs- while only basic public health principles, like test, trace, and isolate, will see the emergency brought to an end’ (The Lancet, 2020). The situation is not better in the United Kingdom, once also renowned for its excellent public health research, particularly in the field of respiratory infections (remember the Common Cold research unit). At the end of May, the United Kingdom directly follows the United States in the international mortality ranking list with more than 38 000 COVID-19 deaths. The late onset of large-scale testing, the lack of personal protective equipment, and a delayed introduction of containment measures have certainly contributed to this high death toll.

A correspondent to The Lancet deplores that the situation in Europe was no better with respect to the lack of a coordinated response to the pandemic. The European Centre for Disease Prevention and Control (ECDC), which was established in 2004 to create a complement to the U.S. CDC, failed to become a hub in Europe of knowledge for COVID-19 and a coordination centre for Europe-wide epidemic counter-strategies. ECDC is underfunded (CDC in 2020: 8 billion $, ECD 60 million $) and understaffed (CDC: 10 800, ECDC: 270 employees). An emergency structure for a pandemic was not set up, and ECDC played essentially no role in pandemic crisis management, which was done according to EU laws by national organizations without any European coordination

(Jordana and Triviño-Salazar, 2020). Even the city-state of Singapore, where the early handling of the COVID-19 was lauded as exemplary public health action, had 'blind spots' on their screen in overlooking the miserable living conditions of migrant workers that became hotspots of COVID-19 transmission. Of special global health concern are refugee camps from Bangladesh to Europe. A refugee camp on Lesvos/Greece has just one water tap per 1300 residents, making efficient handwashing an impossible mission (Newland, 2020). Governments plan to spend billions on rescuing what they consider to be essential national industries. It will be important that they also find the money needed for COVID-19 containment among migrant workers, refugees and populations at risk in developing countries. The beneficial epidemic effect of the lockdowns, obtained at enormous economic costs, would be cancelled out if a second wave epidemic should start from these settings with relatively unrestrained viral transmission. At present, it is not clear which institution, if not the United Nations' suborganizations, will be able to implement such measures. When the leading nation of the western hemisphere leaves now the WHO, this is a disastrous signal for global public health at this crucial moment of the COVID-19 pandemic.

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Conflict of interest

The author consults Nestlé, his former employer, on the scientific aspects of the COVID-19 epidemic, but he does not consider this as a conflict of interest.

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