

RAPID RISK ASSESSMENT

Coronavirus disease 2019 (COVID-19) in the EU/EEA and the UK — eighth update

8 April 2020

Summary

Since 31 December 2019 and as of 7 April 2020, over 1.3 million (1 316 988) cases of COVID-19 have been reported worldwide, and more than 70 000 (74 066) deaths. Half of these cases (608 500) have been reported from the EU/EEA countries and the UK, and over 50 000 (51 059) of them have died.

Overall, large increases in COVID-19 cases and deaths continue to be reported from the EU/EEA countries and the UK. In addition, in recent weeks, the European all-cause mortality monitoring system showed all-cause excess mortality above the expected rate in Belgium, France, Italy, Malta, Spain, Switzerland and the United Kingdom, mainly in the age group of 65 years and above.

Recently, in a few EU/EEA countries, the number of new cases and new deaths reported daily appears to have decreased slightly. However, many EU/EEA countries are currently only testing severe or hospitalised cases, therefore these trends should be interpreted with caution. Despite early evidence from Italy and Austria that the number of cases and deaths are declining, there is currently **no indication at EU/EEA level that the peak of the epidemic has been reached**.

Based on data from EU/EEA countries, 32% of the diagnosed cases have required hospitalisation and 2.4% have had severe illness requiring respiratory support and/or ventilation. The crude fatality rate was 1.5% among diagnosed cases and 11% among hospitalised cases. The likelihood of hospitalisation, severe illness and death increases in persons over 65 years of age and those with defined risk factors including hypertension, diabetes, cardiovascular disease, chronic respiratory disease, compromised immune status, cancer and obesity.

Strain on health and social care systems and healthcare workers continues, with shortages reported in laboratory and testing capacity, personal protective equipment and healthcare capacity (including ICU ventilator and healthcare workforce capacity). In several EU/EEA countries with available data, between 9% and 26% of all diagnosed COVID-19 cases are in healthcare workers. There are also increasing reports of COVID-19 outbreaks in nursing homes across Europe, highlighting the vulnerability of the elderly in long-term care settings and the importance of infection control measures to protect vulnerable populations.

In the present situation, where continuous spread of the virus can be expected, the assessment is

- that the risk of severe disease associated with COVID-19 in the EU/EEA and UK is currently considered
 moderate for the general population and very high for populations with defined risk factors associated
 with elevated risk;
- that the risk of increasing community transmission of COVID-19 in the EU/EEA and the UK in the coming
 weeks is **moderate** if mitigation measures are in place, and **very high** if insufficient mitigation measures
 are in place;

that the risk of health and social care system capacity in the EU/EEA and the UK being exceeded in the
coming weeks is considered **high** with mitigation measures in place and **very high** if insufficient
mitigation measures are in place.

Over the past few weeks, EU/EEA countries and the UK have implemented a range of measures to reduce further transmission of the virus, focussing in particular on physical distancing to decrease the burden on healthcare services, protect populations at risk of severe disease and reduce excess mortality. There is evidence from countries in Asia that were affected early in the pandemic, which is supported by modelling studies, and preliminary signs from Italy and Austria, that a combination of stringent measures can achieve meaningful reductions in transmission.

In the current situation, a strong focus should remain on comprehensive testing and surveillance strategies (including contact tracing), community measures (including physical distancing), strengthening of healthcare systems and informing the public and health community. The promotion of mental wellbeing among people living under physical distancing measures is necessary to ensure that populations have the resilience to maintain adherence to these measures.

Stringent physical distancing measures are highly disruptive to society, both economically and socially. There is therefore significant interest in defining a sound approach to de-escalation. However, unless the incidence of infections is reduced to a very low level in a given setting, transmission will continue until a population protection threshold is reached. Current estimates suggest that no EU/EEA country is close to achieving the necessary population protection threshold, meaning that sustained transmission of the virus is to be expected if current interventions are lifted too quickly. In the absence of a vaccine, physical distancing measures of some kind will therefore need to remain in place for at least some months, in order to ensure that demand for healthcare does not exceed availability.

Plans for de-escalation should therefore ensure that appropriate capacities and safeguards, based on public health principles underscored by scientific evidence, are in place to mitigate the risk of an overwhelming recurrence of increased transmission and the risk to vulnerable members of the population. Considerations for de-escalation should take into account the fact that the reported new infections on any given day reflect the measures that were in place around one week earlier, while the deaths reported on any given day reflect the epidemiological situation and measures in place two to three weeks earlier. This time lag complicates assessment of the impact of measures, and it may present a particular challenge when communicating to the public about the need to sustain the current restrictions and measures.

Based on the available evidence, it is currently too early to start lifting all community and physical distancing measures in the EU/EEA and the UK. Before considering the lifting of any measures, Member States should ensure enhanced population and hospital-based testing and surveillance systems are in place to inform and monitor escalation/de-escalation strategies and assess the epidemiological consequences.

Solidarity and coordination between Member States will remain essential in the de-escalation phase in order to increase the effect of measures taken and minimise the risk of infection 'spill-over' between countries if they de-escalate at different rates and in different ways.

What is new in this update?

- Updated data on the epidemiological situation in the EU/EEA and the UK.
- Updated data on disease and case severity from Europe.
- Current risk of severe disease associated with COVID-19 in the EU/EEA and UK for the general population and for those with defined risk factors associated with elevated risk.
- Risk of further increases in community transmission of COVID-19 in the EU/EEA and the UK in the coming weeks, with or without mitigation measures in place.
- Risk of health and social care systems capacity being exceeded in the EU/EEA and the UK in the coming
 weeks, with or without mitigation measures in place.
- Response measures in place in the EU/EEA and the UK.
- Considerations regarding surveillance and testing strategies, including updated contact tracing options.
- Considerations regarding de-escalation of measures.

Regularly updated information on the coronavirus disease 2019 (COVID-19) outbreak is available on <u>ECDC's website</u> [1], the European Commission <u>website</u>, and the World Health Organization (WHO) <u>website</u> [2]. This risk assessment is based on published information available as of 8 April 2020. The latest ECDC publications on COVID-19 are listed in Annex 1.

1 Event background

Since ECDC's seventh risk assessment published on 25 March 2020, and as of 7 April 2020, 900 072 new cases and 74 066 new deaths have been reported worldwide, out of a total of 1 316 988 reported cases and 74 066 reported deaths since 31 December 2019 (Figure 1, Annex 2).

In the last two weeks (as of 7 April 2020), the proportion of new cases reported in Asian countries previously heavily affected (e.g. China, Iran, South Korea), has been limited compared to those reported in the EU/EEA and the United Kingdom (377 624 new cases and 35 931 new deaths, Figure 1), and in the United States of America (312 965 new cases and 10 188 new deaths).

The main developments since the risk assessment dated 25 March 2020 can be summarised as follows:

- Most of the new cases in the EU/EEA and the UK have been reported in Spain (95 359; 25.3% of total new cases in EU/EEA/UK), Germany (n=67 671; 17.9%), Italy (63 371; 16.8%) and France (52 088; 13.8%), as of 7 April 2020.
- The incidence of reported COVID-19 cases is heterogeneous among EU/EEA countries and the UK (Figure 2). High heterogeneity is also reported within countries with densely populated areas, such as Lombardy in Italy [3], Comunidad de Madrid in Spain [4] and the Stockholm region in Sweden [5] which have been seeing much higher incidence than other areas in the same countries. As of 7 April 2020, the incidence of COVID-19 cases reported since 1 January is 117 cases per 100 000 for the EU/EEA and the UK as a whole.
- The 14-day incidence of COVID-19 reported cases in the EU/EEA, providing an estimate of the prevalence of active cases in the population, is 82.1 per 100 000 population, ranging from 5.0 in Bulgaria to more than 100 cases per 100 000 in Belgium (149.5), Iceland (275.5), Italy (113.6), Luxembourg (323.8) and Spain (218.2) (Figure 1, Annex 3).
- Comparing the current 14-day incidence with that from two weeks ago, the largest increase is observed in Luxembourg, Spain, Belgium and Iceland. Liechtenstein is the only EU/EEA country which has seen a decrease (Figure 3).
- In some EU/EEA countries, the number of new cases and new deaths reported daily appears to be decreasing; however, many EU/EEA countries are only testing severe or hospitalised cases and therefore the trends should be interpreted with caution. In Italy, the highest number of new cases per day was reported on 21 March (6 557) and the highest number of deaths on 27 March (969), 10 and 16 days respectively after control measures (enforced stay-at-home orders) had been implemented in the country as a whole (measures were implemented two days earlier in northern Italy only). In Austria, the highest number of daily new cases was reported on 27 March (1 141) and the highest number of deaths on 31 March (22), 11 and 15 days respectively after control measures (stay-at-home restrictions) had been implemented on 16 March.
- There are several reports of COVID-19 outbreaks in nursing homes across Europe. In Italy, in the Province of Bergamo, long-term care facilities have reported around 600 deaths among 6 400 residents during the past 20 days and 2 000 out of 5 000 staff being absent due to illness, quarantine or isolation [6]. In France, COVID-19 cases have been reported in 511 nursing homes, with a total of over 3 000 cases and 254 deaths among the residents [7]. Similar reports from the Netherlands [8], Belgium [9] Germany [10] and Sweden [11] highlight the vulnerability of the elderly in long-term care settings and the importance of infection control measures to protect the vulnerable population in nursing homes [8,9,12].
- In week 13 (23–29 March 2020), the European all-cause mortality monitoring system (EuroMOMO) showed all-cause excess mortality in the 24 participating countries [13]. All-cause excess mortality above the expected has been observed in recent weeks in Belgium, France, Italy, Malta, Spain, Switzerland and the United Kingdom (England). The excess was mainly observed in the age group of 65 years and above [13]. The number of deaths in the recent weeks should, however, be interpreted with caution as adjustments for delayed registrations may be imprecise.

Figure 1. Distribution of new COVID-19 cases reported daily in EU/EEA countries and the UK, 7 April 2020

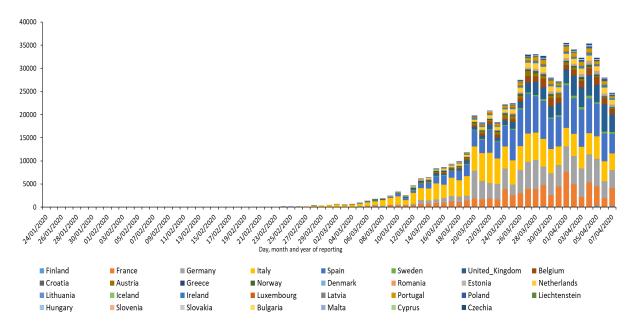
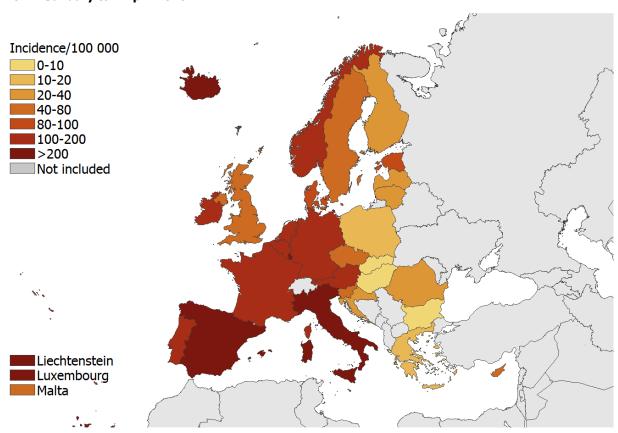


Figure 2. Incidence of reported COVID-19 cases/100 000 population in EU/EEA countries and the UK, from 1 January to 7 April 2020



Spain Spain Belgium Luxembourg Iceland Germany United Kingdom France Belgium Netherlands Portugal Ireland United Kingdom Portuga Italy France Sweden Ireland Poland Netherlands Denmark Romania Sweden Czechia Austria Estonia Cyprus Denmark Norway Luxembourg Czechia Norway Finland Lithuania Croatia Romania Lithuania Estonia Finland Croatia Hungary Greece Iceland Latvia Poland Cyprus Latvia Slovenia Hungary Greece Slovakia Bulgaria Slovakia Bulgaria Malta Liechtenstein Liechtenstein 25000 75000 100000 14-day cumulative reported cases 14-day incidence / 100 000 population

Figure 3. Change in 14-day reported COVID-19 cases (A) and in 14-day incidence of reported COVID-19 cases/100 000 population (B) in EU/EEA countries and the UK, from 24 March to 7 April 2020

For more detailed event background information, please visit ECDC's website [14].

For the most recent information on the current epidemiological situation regarding COVID-19, please visit this <u>page</u> and ECDC's situation <u>dashboard</u> [15].

2 Disease background

Coronavirus disease (COVID-19)

On 31 December 2019, a cluster of pneumonia cases of unknown aetiology was reported in Wuhan, Hubei Province, China. On 9 January 2020, China CDC reported a novel coronavirus as the causative agent of this outbreak, coronavirus disease 2019 (COVID-19).

Disease

Symptoms: By 6 April 2020, 325 843 laboratory-confirmed cases had been reported to The European Surveillance System (TESSy). Information on symptoms was available for 58 277 cases from 11 countries; the majority (99.8%) of these cases were reported by Germany. Among these cases, the most commonly reported clinical symptom was fever (35.0%), dry or productive cough (16.0%), sore throat (9.1%), general weakness (5.3%) and pain (3.5%). The frequency of these symptoms differs notably from those reported from China [16], summarised in the sixth update of ECDC's Rapid Risk Assessment [17]. Data on cases reported to TESSy may be biased depending on the testing approaches chosen in countries (e.g. widespread testing of milder cases in the general population or testing only of hospitalised cases, including long-term care facilities.)

Severity: In China and the United States (US), hospitalisation has occurred in 10.6% and 20.7–31.4% of cases reported [18,19]. Median length of stay in intensive care units (ICU) has been reported to be around seven days for survivors and eight days for non-survivors, though evidence is still limited [18,20-22]. The UK's Intensive Care National Audit and Research Centre, reports 690 patients in critical care, with a length of stay in ICU of four days for survivors and five days for non-survivors (interquartile range (IQR) 2–8 days for survivors and 3–8 days for non-survivors)

Preliminary estimates of severity were based on the analysis of data from EU/EEA countries and the UK available in TESSy and online country reports (for countries whose data was incomplete or missing in TESSy).

Among all cases:

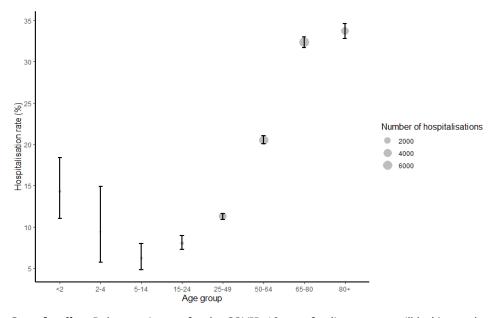
- Hospitalisation occurred in 32% (48 755 of 152 375) of cases reported from 26 countries (median country-specific estimate, interquartile range (IQR): 28%, 14–63%)
- Severe illness (requiring ICU and/or respiratory support) accounted for 2 859 of 120 788 (2.4%) cases reported from 16 countries (median, IQR: 1.4%, 0–33%).

Among hospitalised cases:

- Severe illness was reported in 9.2% (3 567 of 38 960) of hospitalised cases from 19 countries (median, IQR: 15%, 3.8–35%).
- Death occurred in 1 005 of 9 368 (11%) hospitalised cases from 21 countries (median, IQR: 3.9%, 0–13%).

Age-specific hospitalisation rates among all cases based on TESSy data showed elevated risk among those aged 60 years and above (Figure 4).

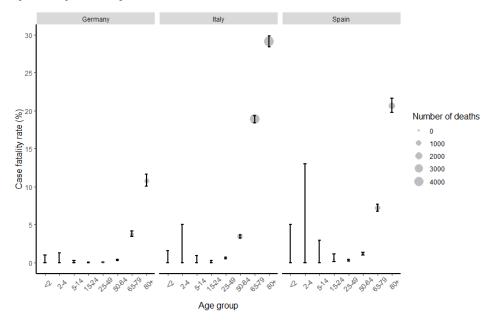
Figure 4. Age-specific hospitalisation rates among all cases, data from 20 countries in TESSy with >50% data completeness for hospitalisation, 6 April 2020



Case fatality: Robust estimates for the COVID-19 case fatality rate are still lacking and potentially biased by incomplete outcome data and differences in testing policies. The mean crude case-fatality (proportion of deaths among total cases reported) from the EU/EEA and the UK by 6 April 2020 was 1.5% (median country-specific estimate: 1%; range: 0.0–25%).

The absolute number of deaths was higher among those aged over 65 years. Persons aged 65–79 years accounted for 44% of all deaths and those aged 80 years and above for 46%. Similarly, age-specific estimates of crude case-fatality for Germany, Italy and Spain increased with age, particularly among those aged over 65 years (Figure 4). The male-to-female ratio for deaths was 2.1 and the highest male-to-female ratio among deaths was observed for 50–65 year-olds (3.9). There were more deaths among males overall for all age groups where the outcome of cases was reported.

Figure 5. Age-specific crude case-fatality (deaths/all cases) in Germany, Italy and Spain (TESSy data up to 6 April 2020)



Infection and transmission

Basic reproduction number (R₀)

 R_0 is proportional to the contact rate and will vary according to the local situation. A recent review of 12 modelling studies reports the mean basic reproductive number (R_0) for COVID-19 at 3.28, with a median of 2.79. This is in accordance with estimates of R_0 from Italy, ranging between 2.76 and 3.25. The introduction of mitigation measures has been reported to decrease R_0 [23]. Further research is needed to obtain a more accurate estimate of R_0 in the various outbreak settings [23].

Incubation period

Current estimates suggest a median incubation period from 5–6 days for COVID-19, with a range from 1–14 days. One study reported that in 97.5% of people with SARS-CoV-2 infection, COVID-19 compatible symptoms will appear within 11.5 days [24]. A recent modelling study confirmed that it remains prudent to consider the incubation period to be up to 14 days [25,26].

Viral sheddina

Over the course of infection, the virus has been identified in respiratory tract specimens 1–2 days before the onset of symptoms, and it can persist for up to eight days after the onset of symptoms in mild cases [27] and for longer periods in more severe cases, peaking in the second week after infection [27,28]. The high viral load close to symptom onset suggests that SARS-CoV-2 can be easily transmissible at an early stage of infection [29]. Viral RNA has been detected in faeces [30], whole blood [20], serum [31,32], saliva [26,29], nasopharyngeal specimens [21] and urine [33]. It should be noted that detection of viral RNA by PCR does not equate with infectivity, unless infectious virus particles have been confirmed through virus isolation and cultured from the particular samples. For more information on viral shedding, please refer to ECDC's seventh update of the risk assessment [34].

Infection in asymptomatic individuals

Asymptomatic infection at time of laboratory confirmation has been reported from many settings [35-38]. Some of these cases developed some symptoms at a later stage of infection, however, the proportion is not yet fully understood [39,40]. There are also reports of cases remaining asymptomatic throughout the whole duration of laboratory monitoring, which revealed viral RNA shedding in various sample types. A recent modelling study suggested that asymptomatic individuals might be major drivers for the growth of the COVID-19 pandemic [41]. For more information on asymptomatic infection, please refer to the ECDC's seventh update [34].

Transmission by pre-symptomatic individuals

Pre-symptomatic transmission has been reported; exposure in these cases occurred 1–3 days before the source patient developed symptoms [42]. It has been inferred through modelling that, in the presence of control measures, pre-symptomatic transmission contributed to 48% and 62% of transmissions in Singapore and China (Tianjin data), respectively [43]. Although transmission from asymptomatic patients has also been reported, the risk of transmission from pre-symptomatic or symptomatic patients is considered to be higher; viral RNA shedding is higher at the time of symptom onset and declines after days or weeks [29]. For more information on pre-symptomatic infection, please refer to the ECDC's seventh update [34].

Virus and blood donation

Four SARS-CoV-2 RNA-positive blood donations from asymptomatic donors were detected during a routine and retrospective laboratory screening in Wuhan Blood Centre, China [44]. While the two donors were asymptomatic at the time and after donation, another two developed symptoms after donation. One of the donations was discarded. The transfusion history of the other three donations is missing. At the time of donation, donors tested negative for specific IgG and IgM against SARS-CoV-2 by ELISA. The RNA-positive blood was not tested for the presence of infectious SARS-CoV-2 virions. This documented occurrence of SARS-CoV-2 RNA-positive donations from asymptomatic and pre-symptomatic blood donors indicates that SARS-CoV-2 RNA positive blood, donated by an asymptomatic donor, may enter the blood supply. However, to assess the risk of COVID-19 transmission through the transfusion of SARS-CoV-2 RNA-positive donations, it is necessary to prove whether the detectable RNA in blood donations is infectious. Transfusion-transmitted COVID-19 has not been reported yet. It is therefore suggested that existing blood safety measures should be maintained.

Infection and transmission in different population groups

Healthcare workers

Of the confirmed cases in China, 3.8% (1 716/44 672) were healthcare workers. Of those, 14.8% were severely or critically ill and 5% of the severe cases died [45]. Latest figures reported from Italy show that 9% of COVID-19 cases are healthcare workers, with Lombardy region reporting up to 20% of cases in healthcare workers [46,47]. In Spain, the latest COVID-19 situation overview from the Ministry of Health reports that 26% of COVID-19 cases are in healthcare workers [48]. In a Dutch study, healthcare workers were tested voluntarily for COVID-19 and 6% tested positive [49]. In a report on 30 cases in healthcare workers in China, all cases had a history of direct contact (distance within 1 metre) with COVID-19 patients, with an average number of 12 contacts (7, 16), and the average cumulative contact time being two hours (1.5, 2.7) [50]. In the Dutch study, only 3% of the healthcare workers reported being exposed to hospital patients with COVID-19 prior onset of symptoms and 63% had worked while asymptomatic [49].

Children

Children made up a very small proportion of the 266 393 cases reported to TESSy as of 6 April (with known age (<10 years (1.1%), 10-19 years (2.5%)). The male-to-female ratio in children and young people (19 years or below) was 1.0:1, compared to 1.1:1 overall. The age distribution observed in the EU/EEA and the UK reflects testing policies and case definitions which usually include symptoms, and it is possible that the small proportion of infected children reflects a lower risk of children developing COVID-19 symptoms [51].

Mild respiratory or gastrointestinal symptoms are predominant among children [52,53]. Zheng et al reported two cases of severe disease in children with underlying conditions, requiring invasive mechanical ventilation. Both of them had recovered partially or fully by the end of the study period [54]. A network of paediatric ICUs (PICU) have reported 106 critically children in the USA since the beginning of the COVID-19 outbreak and one death [55]. Health authorities and media have reported few fatal paediatric cases: one case in Panama (13 years of age), two cases in USA (an infant and a five-year old), one case in Belgium (12 years of age), one case in the UK (13 years of age) and one case in France (16 years of age) [56-60].

Data in TESSy show no difference between age groups in terms of the most common symptoms, but fever was less commonly reported among those aged 10-19 years of age (38%, compared to 48% for all ages) and a sore throat was less common among those aged <10 years (6%, compared to 13% for all ages).

Asymptomatic cases in infants and children have also been reported [61-64]. Two studies on patients with positive laboratory results reported that 10 out of 15 (66.7%) and four out of 31 (13%) of the children were asymptomatic [65,66]. Exposure to COVID-19 among children has been reported in a household context [67,68].

Pregnant women and neonates

Clinical manifestations in pregnant women range from asymptomatic to mild symptoms, sometimes with atypical findings such as leucocytosis and higher prevalence of consolidation lesions in the computed tomography (CT) images [69-71].

In addition to two previous reports on critically-ill pregnant women [72], the Public Health Agency of Sweden has reported two pregnant women being admitted to an ICU, without further details on the gestational week at admission or disease severity [11]. Two maternal deaths due to acute respiratory distress syndrome (ARDS) have been reported from Iran [73]. To our knowledge, these are the only fatal maternal cases known to date. Overall, it seems that pregnancy and delivery do not aggravate the severity and maternal outcomes of COVID-19 pneumonia [74].

Intrauterine transmission, although apparently unlikely, cannot be ruled out and reports of perinatal transmission are emerging [75-78]. Elective Caesarean section deliveries have been commonly reported as a precautionary method to avoid perinatal transmission [72,75,76]. There are few reported cases of vaginal deliveries without perinatal transmission [74,77,79]. A recent study on 30 neonates delivered by COVID-19 rtRT-PCR positive women showed no SARS-CoV-2 infection in the neonates; despite the fact that some of the neonates had perinatal complications. The placenta of those neonates with perinatal complications was SARS-CoV-2 positive [80].

Groups with elevated risk

Data from Italy, Spain, Sweden, Switzerland and the Netherlands support previous identifications of population groups at higher risk of having severe disease and death [11,48,81,82]. Overall, the male to female ratio in critically ill patients is 2.7. Risk factors for critical illness include elderly people above 70 years of age, and people with underlying conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, immune compromised status, cancer and obesity (73.4% of critically ill patients with BMI 30-40+) [16,21,32,83,84]. Strong predictors for ICU admission, such as diabetes, chronic lung disease, cardiovascular diseases, and hypertension, have been identified in surveillance data from Italy, the US, Sweden and Spain as shown in Table 1 [11,48,85].

Table 1 Underlying health conditions in hospitalised COVID-19 ICU patients

Underlying condition (ICU patients)	Italy (%)ª	United States (%) ^b	Sweden (%) ^c	Spain (%) ^d
Diabetes	17	32	23	17
Hypertension	49	I/O	34	NA
Chronic lung disease	4	21	16	6
Cardiovascular disease	21	23	11	30
Immunocompromised condition	I/O	9	6	NA
Chronic renal disease	3	12	4	NA
Chronic liver disease	3	2	1	NA
Pregnancy	NA	1	1	NA
Former smoker	NA	7	NA	NA
Current smoker	NA	1	NA	NA
Other	20	22	9	23

^a Data from 1 043 patients with COVID-19 admitted to ICU with data on comorbidities in Lombardy, Italy. ^b Data from 1 069 patients with COVID-19 admitted to ICU. ^c Percentage of ICU patients with COVID-19 per risk group (one patient may belong to several risk groups). ^d Data from 2 159 patients admitted to ICU with COVID-19. NA=Not Available. I/O=Included in Other.

Virus

Virus evolution

There is currently no evidence that any of the mutations accumulated since the introduction of the SARS-CoV-2 virus in the human population have any effect on disease characteristics. Over 3 000 genome sequences have been deposited in the GISAID EpiCoV database to date (www.gisaid.org). Mutations in the receptor-binding domain of the spike glycoprotein are of interest as they may affect infectivity and host-specificity [86]. Some mutations in this domain have been reported [87], but these have so far been rare and are not present in any of the major SARS-CoV-2 clades. Mutations in primer binding sites for published RT-PCR detection assays have so far been rare [88].

For information on seasonality and survival in the environment, please refer to the ECDC's seventh update of the risk assessment and the page on COVID-19 disease background [89] on ECDC's website.

Protection, immunity and treatment

Vaccines

Several potential COVID-19 vaccines are under development and two have entered phase I clinical trials [90]. The European Medicines Agency (EMA) expects that it may take at least one year before a vaccine is approved and available for widespread use.

Immunity

It is too early to know how long the protective immune response against SARS-CoV2 will last, as this will require longitudinal serological studies that follow patients' immunity over an extended period of time [91]. Based on the currently available data, the IgM and IgG antibodies to SARS-CoV-2 develop between 6–15 days post disease onset [92-97]. However, clinically validated laboratory assays for detection of antibodies are still lacking and therefore these results need to be interpreted with caution. In addition, correlates of protection are still to be defined to assess the possibility of re-infection and the duration of immunity. Primary infection with SARS-CoV-2 was shown to protect rhesus macaques from subsequent challenge and casts doubt on reports that the re-positivity observed in discharged patients is due to re-infection [98].

Treatment

Moderate to severely ill patients require supportive care and oxygen supplementation. At present, no medicine has demonstrated efficacy in the treatment of COVID-19. A number of pharmaceuticals are undergoing clinical trials to assess their safety and efficacy as potential treatments for COVID-19, including the antiviral nucleotide analogue remdesivir; systemic interferons and, in particular, interferon β -1a; the antiviral combination lopinavir/ritonavir; the antimalarial chloroquine/hydroxychloroquine and monoclonal antibodies against components of the immune system such as interleukin-6 (IL-6) and IL-4 [90]. It is important that the potential treatments are carefully assessed in randomised controlled trials (RCTs). EMA has published recommendations on compassionate use of the investigational antiviral agent remdesivir [99].

A randomised, controlled, open-label trial of lopinavir/ritonavir in 199 COVID-19 patients in China failed to show any statistically significant favourable effect on the clinical course or mortality when compared to standard treatment [100]. Hydroxychloroquine has been shown in vitro to alter the uptake of the virus in cells, and small case series and a small trial have reported its use in patients during this outbreak in China and Europe in combination with azithromycin, with conflicting results. It remains one of the possible therapies that needs to be evaluated through adequately sized RCTs. Caution is therefore advised against its widespread off-label use in light of potential adverse reactions [101-103]. Systemic use of steroids for COVID-19 pneumonia is not recommended, because they might increase the viral replication and shedding of the virus, along with other steroid-related side effects [104].

Convalescent plasma (plasma with antibodies from recovered COVID-19 patients) is under investigation for the treatment of patients with COVID-19. Despite some study limitations, the improved outcomes in recipients of convalescent plasma obtained in two recent small studies in China [105,106] support the possibility of investigating this therapy further in adequately designed clinical trials. Blood services in several EU countries and the USA [107] reported preparation activities for collection and transfusion of convalescent plasma and some have already started or plan to start studies soon. The EU Commission, in cooperation with ECDC, national competent authorities for blood safety and national blood establishments, is working on an EU programme of COVID-19 convalescent plasma collection and supply. It aims to launch a co-ordinated and effective approach to the collection of convalescent plasma across the EU, supporting the possible treatment of seriously ill patients within observational studies or randomised and case-control clinical trials, and the development of immune globulin concentrates by industry in the longer term. The programme includes the development and hosting of a database to monitor convalescent plasma donation and use. The database will be developed and hosted by the European Commission (DG DIGIT), in compliance with Regulations 2016/679 and 2018/17/25 and will be designed in collaboration with the European Blood Alliance (EBA).

Reports that non-steroidal anti-inflammatory drugs worsen COVID-19 through increased expression of angiotensin-converting enzyme 2 (ACE2), whose receptor is used by SARS-CoV-2 to enter the target cells, are not supported by evidence [108]. ACE-inhibitors and angiotensin receptor blockers are used for the treatment of hypertension, heart failure or renal disease. Patients receiving these agents are advised not to interrupt their treatment and there is no need to switch to other medicines [109].

For more information on COVID-19, please visit the page on COVID-19 disease background [89] on ECDC's website.

3 ECDC risk assessment

Many uncertainties remain regarding infectivity during the incubation period, the level of population immunity, agestratified risk factors for severe illness, the effectiveness of treatment regimens, and the impact and duration of individual or population-based physical distancing preventive measures implemented at different points in time and with different intensity across countries.

This assessment is based on information available to ECDC at the time of publication and unless otherwise stated, the assessment of risk refers to the risk that existed at the time of writing. It follows the ECDC rapid risk assessment methodology, with relevant adaptations [110].

Risk assessment questions

- What is the overall risk, as of 8 April 2020, of severe disease in the general population and in populations with defined factors associated with elevated risk for COVID-19 in the EU/EEA and UK?
- What is the risk of increasing community transmission in the EU/EEA and the UK in the coming weeks, with and without mitigation measures?
- What is the risk that the capacity of health- and social care systems will be exceeded in the EU/EEA and the UK in the coming weeks, with and without mitigation measures?

What is the overall risk, as of 8 April 2020, of severe disease in the general population and in populations with defined factors associated with elevated risk for COVID-19 in the EU/EEA and UK?

The risk of severe disease associated with COVID-19 in the EU/EEA and UK is currently considered **moderate** for the general population and **very high** for populations with defined risk factors associated with elevated risk.

This assessment is based on the following factors:

- Ongoing increase of mild, severe and fatal COVID-19 cases have been reported in most EU/EEA countries and the UK. The overall 14-day incidence for the EU/EEA and the UK has increased from 36 cases per 100 000 population on 25 March to 82 cases per 100 000 population on 7 April 2020, while the total cumulative incidence has increased from 40 per 100 000 population to 117 per 100 000 population. Cumulative COVID-19 mortality per 1 million population has increased from 23 per million on 25 March 2020 to 98 per million on 7 April 2020. Uncertainty remains about the extent to which the prevention and control measures introduced may slow the rate of transmission, making the probability of continued transmission in the EU/EEA and the UK in the coming weeks very high. Recent data from EU/EEA and the UK indicate that 32% of cases require hospitalisation, and 2.4% require critical care. The likelihood of severe illness and death rises significantly in persons over 65 years of age and in those with defined risk factors including hypertension, diabetes, cardiovascular disease, chronic respiratory disease, compromised immune status, cancer and obesity. These risk groups account for the majority of severe disease and fatalities to date.
- Mitigation measures to slow transmission through infection prevention and control and physical distancing have been introduced at different points in time and at varying intensities across EU/EEA and the UK. The efficiency of these measures in slowing the transmission of COVID-19 in the general population and, more specifically, in defined risk groups of older adults and individuals with chronic underlying conditions, cannot yet be evaluated. Once infected, no specific treatment for COVID-19 exists, however early supportive therapy, if healthcare capacity for this exists, can improve outcomes. In summary, the impact of COVID-19, if acquired, is assessed as moderate for the general population and as very high for elderly and individuals with defined risk factors.

What is the risk of increasing community transmission in the EU/EEA and the UK in the coming weeks, with and without mitigation measures?

The risk of increasing community transmission of COVID-19 in the EU/EEA and the UK in the coming weeks is **moderate** if mitigation measures are in place, and **very high** if insufficient mitigation measures are in place.

This assessment is based on the following factors:

There are rapidly growing numbers of severe and fatal cases in many EU/EEA countries, and several countries in Europe have already reported nationwide community transmission. Mitigation measures to slow transmission have been introduced at different points/varying intensities across all EU/EEA countries and the UK. The effect of these measures in slowing virus transmission in the general population and defined risk groups cannot yet be fully evaluated, given the time lag between the introduction of measures and the reduction in cases, deaths and healthcare saturation. However, it is known that the virus spreads very quickly in the absence of effective mitigation measures. Based on the high transmissibility of the virus and the continued increase in the notification rate in all EU/EEA countries, the probability of increased community transmission is considered moderate if effective mitigation measures are in place, and very high in the absence of effective mitigation measures. If mitigation measures are lifted suddenly or too early, a resurgence of cases is likely.

• The impact of increased community transmission would be high, especially if healthcare capacity is exceeded or if hospitals are affected and a large number of healthcare workers need to be isolated or become infected. The impact on vulnerable groups would be very high, in particular for the elderly and individuals with defined risk factors associated with elevated risks.

What is the risk that the capacity of health and social care systems will be exceeded in the EU/EEA and the UK in the coming weeks, with and without mitigation measures?

The risk that the capacity of health and social care systems in the EU/EEA and the UK will be exceeded in the coming weeks, is considered **high** with mitigation measures in place and **very high** if insufficient mitigation measures are in place.

This assessment is based on the following factors:

- Many EU/EEA countries are experiencing demands that far exceed currently available health and social care, including ICU capacity and, if the pandemic continues on its current course without strong countermeasures and surge capacity enacted, there is a strong probability that other EU/EEA countries will also reach this point. Furthermore, there have been reports of additional constraints or shortages in the following areas: ventilator availability; personal protective equipment; sampling material and laboratory materials affecting diagnostic capacity for COVID-19 testing (which also affects other laboratory services); contact tracing; surveillance; risk communication; shortages of space due to increased needs for triage and isolation of suspected cases. Health worker shortages are also reported, due to increased demand and also because healthcare workers are being infected with COVID-19 at high rates in some settings (20% of all reported cases in Lombardy, 26% in Spain; 19.6% of all health workers in a sample tested in the Netherlands) [47-49].
- Sub-regions of Italy, France, the Netherlands and Spain have already reported healthcare system saturation due to very high patient loads requiring intensive care. Increased duration of hospital and ICU bed occupation by COVID-19 patients has been observed. This may cause further strain on the available capacity. The increased pressure caused by COVID-19 on many EU/EEA health systems is dependent on the level of preparedness and surge capacity that a given country or area has available or can quickly implement. If the incidence of COVID-19 cases increases quickly, and if additional surge capacity for resources, staff and hospital beds are not ensured, the impact of COVID-19 will be very high and probably result in considerable additional morbidity and mortality. Particularly high all-cause excess mortality has been observed in some countries (Italy, Spain) and was above the expected rate in the Netherlands and UK (England) during week 13 (23–28 March 2020), primarily in the age group of 65 years and above. The impact of over-stretched health and social care systems will be mostly concentrated in vulnerable populations of the elderly and persons with defined risk factors. Healthcare capacity, which is already stretched, would be further affected if substantial numbers of healthcare workers became infected.

It is essential to introduce and maintain measures to slow down the spread of the virus in the population in order to allow healthcare systems to put surge capacity measures in place to absorb more severe COVID-19 cases, as well as to respond to non-COVID-19 health needs. These options are listed under 'Preparedness and public health response' and recent ECDC guidance documents [111]. The implementation of these mitigation measures will determine the eventual level of impact of the epidemic on individuals, populations and healthcare system capacity.

4 Considerations and options for response

Five scenarios describing the possible progression of the COVID-19 outbreak in EU/EEA countries were presented in ECDC's fifth Rapid Risk Assessment on COVID-19 (Annex 5) [112]. Currently, the epidemiological situation in the EU/EEA and the UK varies by region and country, but an analysis of the epidemic progression indicates that all countries are generally following quite similar epidemic curves (Annex 3). Most countries in the EU/EEA and the UK are currently in scenarios 3 or 4.

At this stage, all measures in the Member States should be aimed at the containment and mitigation of further transmission of the virus. A focus on vulnerable groups and populations with defined risk criteria is paramount. Options for scenarios 0, 1 and 2 can be found in ECDC's sixth risk assessment [112]. The options provided here focus on scenarios 3 and 4, which describe local and nationwide transmission scenarios, and include: i) community measures and physical distancing; ii) measures in hospital settings; iii) surveillance and testing. The final subsection of this risk assessment sets out considerations regarding de-escalation measures for EU/EEA countries and the UK.

Community measures and physical distancing

ECDC's <u>quidelines</u> for the use of non-pharmaceutical countermeasures to delay and mitigate the impact of the COVID-19 pandemic include a description of community measures, such as infection prevention and control, and physical distancing [111].

Infection prevention and control in the community

There is evidence from other respiratory infections that measures taken by individuals, such as rigorous hand hygiene, respiratory etiquette, and use of face masks when sick, contribute to reducing the risk of transmitting/acquiring COVID-19 infections.

- Rigorous handwashing, avoiding touching face, eyes and mouth and respiratory etiquette are still advised as some of the main community infection prevention and control measures [34].
- The use of medical face masks should be prioritised for healthcare workers. In addition, when worn by a person with respiratory symptoms, the mask decreases the risk of infecting others before seeking medical advice, while being assessed and until being placed in isolation.
- The use of face masks in public may serve as a means of source control to reduce the spread of the infection in the community by minimising the excretion of respiratory droplets from infected individuals who have not yet developed symptoms or who remain asymptomatic [111].
- The use of face masks in the community should be considered only as a complementary measure and not as a replacement of the preventive measures already recommended including physical distancing, respiratory etiquette, meticulous hand hygiene and avoiding touching the face, nose, eyes and mouth.
- The use of non-medical face masks could be considered, especially if due to supply problems medical face masks must be prioritised for use as personal protective equipment by healthcare workers. This is based on limited indirect evidence supporting the use of non-medical face masks as a means of source control. [113,114].
- Appropriate use of face masks is the key to the effectiveness of the measure and can be improved through education campaigns.

A recent ECDC technical report with further information on using face masks in the community provides additional considerations and information on this topic [115].

Risk groups, especially the elderly, should be encouraged to stay home and avoid physical contact. If they have symptoms compatible with COVID-19, they should seek medical advice early, given the stronger possibility of progression to severe disease [116]. While people with mild symptoms are usually advised to self-isolate at home [116], anyone with acute respiratory symptoms that are worsening should seek medical attention promptly, ideally first by phone. Household contacts of a person confirmed to have COVID-19 should quarantine themselves for 14 days after their last contact with the case, while household contacts of a person displaying symptoms compatible with COVID-19 should be encouraged to quarantine at home for 14 days after the symptoms of the household contact have resolved.

Physical distancing measures

The term 'social distancing' has been used by many authorities over the course of the COVID-19 pandemic. It refers to efforts that aim, by a variety of means, to decrease or interrupt transmission of COVID-19, by minimising physical contact between potentially infected individuals and healthy individuals, or between population groups with high rates of transmission and population groups with no or low-level transmission. However, it is increasingly recognised that 'social distancing' as a term does not reflect the actual intention of the actions taken, which is to create physical distance between people, while not separating them socially. ECDC is now therefore using the term 'physical distancing' to describe these measures.

- Community-level physical distancing measures should be implemented in parallel with containment efforts (e.g. contact tracing) [117]. Such physical distancing measures can include individual-level measures:
 - Isolation of COVID-19 cases or people with respiratory symptoms;
 - Quarantine of their contacts;
 - Stay-at-home policies targeting people who are at high-risk of severe disease.
- Measures affecting multiple people:
 - The closure of educational institutions and workplaces;
 - Measures to limit outside visitors and limit the contact between the residents of confined settings, such as long-term care facilities and prisons;
 - Cancellation, prohibition and restriction of mass gatherings and smaller meetings;
 - Mandatory quarantine of all inhabitants of buildings or residential areas;
 - Internal and/or external border closures:
 - Stay-at-home restrictions for entire regions or countries.

The physical distancing measures implemented across the EU/EEA have had a marked impact on people's movements, as shown by aggregated, anonymous data that chart mobility trends over time by geographical location [118]. Evidence from a number of modelling studies indicate that this has had a substantial impact on transmission [119-123]. One study calculated that 59 000 [21 000–120 000] deaths had been averted by these measures in 11 EU/EEA countries up until the end of March [124]. Modelling evidence has also indicated that physical distancing interventions may delay the peak of the epidemic, thereby significantly alleviating pressure on national health systems [125]. However, it has been noted that adherence to physical distancing measures needs to be high in order for them to be effective [126].

Physical distancing measures in place in EU/EEA Member States and the UK

A variety of response measures have been progressively implemented across the EU/EEA countries and the UK as the transmission of COVID-19 has increased. An overview showing both the number of reported cases and deaths related to COVID-19, and the main public health response measures at national level reported from public sources over time, is presented in Annex 4. As of Friday 3 April 2020, all 31 EU/EEA countries and the UK had implemented measures to cancel mass gatherings (31/31, 100%). This includes the cancellation of specific events or a ban on gatherings of a particular size. Generic measures to close public spaces are ongoing in 30 countries (30/31, 97%) and include the closure of cafes or restaurants, non-essentials shops, or various entertainment venues. EU/EEA countries and the UK have also implemented measures to close educational institutions including the closure of secondary schools or higher education (31/31, 100%), the closure of primary schools (29/31, 94%) and the closure of day-care or nursery schools (25/31, 81%). Stay-at-home orders for the general population (also known as 'lockdown') have been implemented in more than half of EU/EEA countries and the UK (18/31, 58%). In the countries not issuing stay-at-home orders, six issued stay-at-home recommendations to the general population (6/31, 19%), and 17 issued stay-at-home recommendations for risk groups (17/31, 55%).

Considerations when implementing physical distancing measures

Some key points for consideration when implementing physical distancing measures include the following:

- ensuring the continued provision of essential services and supplies to everyone who is subjected to the measures (e.g. food, medication and access to healthcare) [127,128];
- coordinating with and supporting civil society and religious groups who work with vulnerable groups, such as
 the elderly, people with underlying health conditions, physically disabled people, people with mental health
 problems, homeless people, people living in abusive household settings, prisoners and undocumented
 migrants [17,129];
- officially acknowledging and promoting gestures of solidarity and mutual support that have spontaneously
 emerged in communities under quarantine [130];
- providing financial compensation for lost income and employment, as this will probably facilitate adherence to the prescribed public health measures [131,132].

With restrictions on movement likely to be in place throughout the EU/EEA for an unforeseeable, but potentially prolonged, length of time, the promotion of mental wellbeing is increasingly recognised as a central component of the response to COVD-19. Not only is good mental health critically important in its own right, but populations suffering from poor mental health may not have the resilience to maintain adherence to the restrictions that they face, thereby potentially compromising the effectiveness of the public health measures that are needed to bring the pandemic under control. Psychologists have proposed a number of strategies to promote the mental health of the general population while COVID-19 physical distancing measures are being implemented. These include:

- Encouraging people to maintain close social contact with friends, family and other networks via internetbased communications systems, social media and phone [133,134]. We may be in physical isolation, but we need not feel alone.
- Maintain routines as a means of managing anxiety [135], while accepting that some degree of anxiety is a natural response to the current situation [136].
- Engage in physical activity, whether in their homes, alone or outside [137]. This is important both for physical health and mental wellbeing.
- Prioritise quality sleep. Getting enough good sleep underpins every aspect of physical and mental health [138].
- Be kind to ourselves, and to those around us [138].

Children who have been isolated or quarantined during previous pandemics have been found to be at increased risk of developing acute stress disorder, adjustment disorder, and grief, with 30% meeting the clinical criteria for post-traumatic stress disorder. Extra efforts must be made to minimise the impact of physical distancing on children's mental health, as these impacts can be lifelong [139]. Child-friendly messages from leaders may help children to understand the reasons for the restrictions, and thereby protect their mental health [140].

Healthcare workers treating COVID-19 patients have been reported to suffer extreme stress, which can lead to burnout and a reduced capacity to continue work. One reason for this is the 'moral injuries' they endure when, for example, deciding which patient should receive a life-saving therapy that is in short supply, at the expense of another dying patient. It has been recommended that managers are frank with their staff about the situations they are likely to face; that regular meetings are held to discuss such decisions and to check on staff wellbeing; and that, once the crisis begins to recede, staff must be actively monitored, supported, and, where necessary, provided with treatment for any mental health-related issues they may have developed [141].

Measures for healthcare settings

Preparedness

Hospital preparedness is an absolute and immediate priority when countries/regions find themselves in scenario 3 or 4. In healthcare settings, surge capacity plans must be enacted to meet the expected high demand for care of patients with moderate or severe respiratory distress [17]. Emergency wards and intensive care wards are likely to exceed capacity very rapidly if service delivery is not reorganised [16,40]. For more details on contingency planning in healthcare settings (primary care and hospital settings), please consider previous ECDC rapid risk assessments [17], the related 'Guidance for health system contingency planning during widespread transmission of SARS-CoV-2 with high impact on healthcare services' [142] and hospital preparedness checklists [59].

Infection prevention and control in healthcare settings

Up to 9% of all cases in Italy, 20% in Lombardy and 26% in Spain were among healthcare workers [143]. It is probable that nosocomial outbreaks are important amplifiers of the local outbreaks, and they disproportionately affect the elderly and vulnerable populations. Infection prevention and control (IPC) practices are of critical importance in protecting the function of healthcare services and mitigating the impact on vulnerable populations.

Measures to prevent transmission in healthcare facilities are an immediate priority in order to slow the demand for specialised healthcare, such as ICU beds; safeguard risk groups; protect healthcare workers and minimise the export of cases to other healthcare facilities and the wider community.

Due to the likelihood of virus transmission by persons with few or no symptoms, healthcare facilities should ensure that physical distancing measures are implemented by staff, visitors and patients, particularly in settings with widespread community transmission. The use of medical masks by healthcare workers not taking care of COVID-19 patients for personal protection and source control can reduce transmission within healthcare settings [144]. Optimal strategies have not been defined but any strategy needs to take into account the availability of medical masks, the extent of community transmission and other measures in place. Some healthcare facilities require that all healthcare providers wear a medical mask while at work. Standard precautions, and in particular meticulous hand hygiene, should be emphasised.

For more guidance on measures in healthcare settings, please refer to the 'Measures for health care settings' section of ECDC's seventh update of the risk assessment [34] and ECDC's technical report on infection prevention and control for the care of patients with COVID-19 in healthcare settings [145], the technical report on personal protective equipment (PPE) needs in healthcare settings [146], ECDC 'Guidance for wearing and removing personal protective equipment in healthcare settings for the care of patients with suspected or confirmed COVID-19' [147,148] and WHO's 'Five Moments for Hand Hygiene' approach before touching a patient [149].

Home care and isolation of cases

Clinical presentation among reported cases of COVID-19 varies in severity from asymptomatic, subclinical infection and mild illness to severe or fatal illness. Reports show that clinical deterioration can occur rapidly, often during the second week of illness [16,32,150,151]. For a description of the clinical presentation and risk groups, see the 'Disease background' section.

Patients with a mild clinical presentation (mainly fever, cough, headache and malaise) will not initially require hospitalisation and may be safely managed in dedicated isolation facilities or at home. The majority of these cases will spontaneously recover without complications. However, as clinical signs and symptoms may worsen with progressive dyspnoea due to lower respiratory tract disease in the second week of illness, patients treated at home should be provided with instructions if they experience difficulties breathing. Sufficient call and reception capacity, as well as hospitalisation capacity have to be established to guarantee good access. According to data from China, an estimated 10–15% of mild cases progress to severe, and 15–20% of severe cases become critical [16]. Home care could also be considered for symptomatic patients no longer requiring hospitalisation, or in the case of informed refusal of hospitalisation [152]. ECDC has proposed criteria for hospital discharge of confirmed COVID-19 cases [153].

Persons with mild COVID-19 not requiring hospitalisation should stay in home isolation for eight days after onset of symptoms and for at least three days until resolution of fever and clinical improvement of other symptoms, or seek medical care, if symptoms worsen [153].

Guidance for clinical care of severe cases is available from WHO [104] and from the US CDC [154]. IPC measures for homecare are outlined in WHO [152] and ECDC guidance [116].

Testing and surveillance

Surveillance

Surveillance for COVID-19 should occur in both community and hospitals. The objectives at national and EU/EEA level are to:

- monitor the intensity and geographical spread of the virus in the population;
- identify risk groups for severe disease;
- measure the impact on the population and the healthcare system; and
- measure the impact of the mitigation measures and identify triggers for measure escalation/de-escalation strategies.

These objectives can be addressed by sentinel syndromic and virological surveillance in primary care, hospital-based surveillance and all-cause excess mortality monitoring. In countries recommending that patients with acute respiratory infection (ARI)/influenza-like illness (ILI) should not visit general practitioners (GPs), sentinel syndromic surveillance should include the collection of the number of calls made to sentinel general practices by patients. Phone calls received at regional/national healthcare hotlines can be an additional source of data. Hotlines and helplines could also be used to sample a proportion of cases fitting the ARI/ILI case definition, which would provide additional data on community transmission of COVID-19. In addition, surveillance should include sites to which patients with COVID-19-like symptoms are guided and where they are tested (e.g. dedicated testing centres). Hospital-based surveillance should include testing data of SARI cases in all hospital wards and/or SARI cases in intensive care units as well as either enhanced surveillance of SARI cases or, if resources do not allow, enhanced surveillance of hospitalised confirmed COVID-19 cases in all wards or those in ICU. Given the risk of significant mortality in long-term care facilities, Member States should include these settings in their surveillance systems and ensure capacity to test symptomatic people, as recommended above.

In addition, Member States should consider specific studies to supplement surveillance data in order to have a more comprehensive understanding of the prevalence of SARS-CoV-2 in the community. While serological assays are still being validated, an approach using pooled PCR tests of a random community sample could allow for a relatively rapid assessment of the prevalence in the community and give an indication of the proportion of asymptomatic cases [155,156]. Seroepidemiological population surveys can estimate population immunity and the speed of immunity developing during community outbreaks, providing key information to guide decisions on deescalation strategies. A protocol from WHO is available [157].

All deaths among confirmed cases should be monitored, irrespective of whether they occur in hospitals, in the community or in long-term care facilities. In addition, all deaths should be recorded where COVID-19 was the main or contributing cause of death. Hospitalised cases should include deaths which occur during the hospitalisation and in the 30 days following discharge. However, these data will not include all deaths caused by COVID-19, particularly in countries where testing in settings outside of hospitals is limited (for example in long-term care facilities). Testing approaches also affect the overall reported case fatality rates, as more widespread testing in the community will pick up additional milder cases (compared to testing strategies focused on SARI cases) which will lead to lower apparent case fatality rates for all age groups. Therefore, monitoring of all-cause or specific excess mortality is essential to assess the impact of the epidemic and identify the most affected age groups in a timely manner [13].

Post-mortem testing can be considered for people that showed symptoms compatible with COVID-19 prior to death but were not tested (e.g. in settings such as long-term care facilities containing vulnerable populations.)

When resources are limited, making it difficult to collect all data from confirmed cases, surveillance data requirements could be reduced. For example, hospital-based surveillance could be limited to key variables and, as an alternative, aggregate reporting could further limit the workload. If there is no capacity for testing specimens from the community for surveillance purposes, sentinel syndromic surveillance for ARI/ILI through sentinel general practices and/or telephone helplines should be used to assess the intensity and spread of infection. This might be challenging if other respiratory pathogens are co-circulating. If there is testing capacity in hospitals or ICU, then the focus should be on SARI/ICU surveillance and/or surveillance of hospitalised cases. In the event that no testing capacity remains in hospitals, qualitative indicators can be used.

For more details on surveillance approaches and reporting at EU/EEA level, please refer to the ECDC's seventh update of the risk assessment [34] and the ECDC document Strategies for the surveillance of COVID-19 [158].

Testing strategy for COVID-19

Timely and accurate laboratory testing of specimens from cases under investigation is an essential element of the response, supporting decisions on infection control strategies and patient management at healthcare facilities. Sufficient capacity for various testing strategies during the different phases of the outbreak is paramount and will continue to be essential when Member States begin de-escalating control measures. EU countries should follow EU and WHO guidance on testing strategies [159-162].

In situations where testing capacities are sufficient, all patients presenting to the healthcare system with symptoms of ARI should be considered as suspected cases according to the EU case definition and should be tested for SARS-CoV-2 virus as part of active case finding [163].

If the number of suspected cases exceeds the available testing capacity in a country or an area, testing of the following groups should be prioritised (in decreasing order of importance):

- testing of hospitalised patients with SARI in order to inform appropriate clinical management, including isolation and wearing of PPE to protect healthcare staff, as well as for surveillance purposes;
- testing all people with ARI in long-term care facilities (or, as a minimum, the first cases to confirm an outbreak in
 closed settings) in order to guide infection control and PPE use to protect vulnerable persons and healthcare
 staff, isolation and early treatment to prevent severe disease and fatal outcome in risk groups; AND testing of
 symptomatic healthcare staff, even those with mild symptoms, to guide decisions on exclusion from, and return
 to, work; the aim being to ensure continued health and social care services;
- elderly people and those with underlying chronic medical conditions such as lung disease, cancer, heart failure, cerebrovascular disease, renal disease, liver disease, hypertension, diabetes, and immunocompromising conditions who show signs of acute respiratory illness, since they may need respiratory support sooner than people who are not in a risk group;
- testing of subsets of patients with ARI or ILI in sentinel outpatient settings (see surveillance section for more details).

Member States should adapt these recommendations based on the national/local epidemiological situation and their resources, ensuring that testing also covers surveillance needs.

Contact tracing

Contact tracing is a core public health measure that plays an important role in the control of COVID-19 [164]. There is increasing evidence that the adoption of rigorous testing and contact tracing can change the trajectory of the outbreak in all transmission scenarios. Countries should adapt measures based on a regular review of their local epidemiological situation and available resources. For countries that have implemented strict physical distancing measures to interrupt the chain of transmission of the virus, contact tracing will be a major part of the public health response after these measures are lifted, to reduce the risk of further escalation. Before de-escalation measures are implemented, countries should review existing systems to determine the optimal implementation of an effective contract tracing strategy.

Several countries in Asia have been able to limit the size of their outbreaks and avoid overwhelming healthcare and high numbers of deaths through intensive contact tracing and quarantine measures [165-167]. Contact tracing in China and Singapore reduced the time from symptom onset to isolation substantially, thus reducing the likelihood of ongoing transmission [168,169].

To support public health authorities managing the contact tracing process, WHO has developed the <u>Go.Data</u> tool [170]. This software allows for the registration of cases and their contacts and facilitates the follow-up of the contacts. Go.Data also facilitates the summarisation, visualisation and analysis of data. Such analyses can provide key information to inform a more effective response. They can provide a better understanding of transmission and attack rates, help identify settings where transmission occurring and understand the effectiveness of different mitigation measures, such as physical distancing.

Other mobile applications ('apps') have been used in Iceland and Singapore to support the process of contact tracing by public health authorities [171,172], and modelling has shown the added value of using such technology to aid manual contact tracing efforts [173]. Similar technologies are starting to be used in the EU/EEA. Various apps have been developed that use GPS or Bluetooth technology to inform those who have been in close proximity to someone who tested positive for SARS-Cov2 for a certain period of time . The use of these apps causes significant challenges with regard to privacy and data protection. A working group of the EU eHealth network has been established to provide necessary guidance on these issues.

Laboratory testing

The current test reagent and equipment shortages affect laboratories in all EU/EEA countries and their diagnostic capacity, thereby hampering the epidemic response at national and local level. For EU/EEA countries that need help in testing, a pool of specialised laboratories have offered support [160,178]. The European Commission has launched a joint procurement to enable equitable access to SARS-CoV-2 RNA detection reagents, materials and equipment across the EU [179]. In the event of severe shortages of reagents, the following alternative approaches have been proposed and may be considered after thorough validation in the individual laboratory:

- RT-PCR screening of only a single discriminatory target, using one set of primers, instead of two [159]. Confirmatory testing (and additional sampling if necessary) should be performed only for specimens where the first result is technically not interpretable;
- performing a sample preheating step, instead of RNA extraction. This should be followed by the use of a human gene target as a control to ensure that sufficient RNA has been included in the RT-PCR reaction [179];

- pooling of low-risk samples from different individuals in one testing run (group testing); this can be used in
 prevalence studies or for testing mild/asymptomatic patients. For diagnosis, the samples will need to be retested separately if there is a positive result in the pooled sample [156,180];
- oropharyngeal and nasopharyngeal swabbing can be performed with one swab and combined into one diagnostic test [181];
- sterile saline can be used instead of viral transport media [181].

For information on biosafety guidelines, please refer to the ECDC's seventh update of the risk assessment [34].

Countries should continue to increase their primary SARS-CoV-2 diagnostic testing capacity in local clinics and laboratories and look for additional laboratory and personnel resources. If capacity in diagnostic laboratories is exhausted, support may be sought from research, teaching or commercial laboratories who may have the capacity to quickly update their laboratory systems for validated detection assays for SARS-CoV-2.

Testing methods and assays

The recommended diagnostic test method for SARS-CoV-2 infection is viral RNA detection with nucleic acid amplification tests (NAAT), such as RT-PCR [159,183]. The specimen types to be collected for testing are listed in WHO's laboratory guidance [159]. To evaluate the data quality and reliability of the testing assays, laboratories that are involved in the COVID-19 national response are encouraged to participate to the forthcoming ECDC and WHO external quality assessments. Representative viruses from different geographic locations, time of occurrence during the epidemic, age, gender and severity should be selected for sequencing to monitor the virus evolution and changes in the virus genome. RT-PCR with a Ct value less than 30 is considered a good source of sequencing material. Countries that do not have sequencing capacity through their national laboratories are encouraged to send specimens to referral laboratories or request sequencing support from ECDC (please send an email to influenza@ecdc.europa.eu with your request). The sequencing results should be deposited in GISAID. ECDC can support countries with raw whole genome sequence analysis if needed.

RT-PCR is the current test methodology applied in EU/EEA Member States. However, these tests require well-equipped laboratory facilities, highly skilled technologists and multiple reagents. Due to the infrastructure limitations and supply shortages, reliable rapid diagnostic tests for COVID-19, in particular rapid antigen or RNA detection tests, could alleviate the pressure on laboratories and expand testing capacity to meet the most urgent medical and public health needs.

Rapid tests may provide results in 10–30 minutes, they are relatively simple to perform and interpret and therefore require limited test operator training. They may be intended either for use in hospital laboratories or near the point-of-care. The availability of commercial in vitro diagnostic tests for SARS-CoV-2 infection is monitored by the Foundation for Innovative New Diagnostics (FIND), a WHO collaborating centre, at the following link: https://www.finddx.org/covid-19/pipeline/. Several commercial detection assays for SARS-CoV-2 are on the market, however information on their clinical performance is still limited.

Serological assays for SARS-CoV-2 specific antibodies are under development and available assays are listed in the FIND inventory. Research groups have developed and are validating in-house antibody detection tests for SARS-CoV-2. Preliminary reports on ELISA assays have shown good correlation of antibody titration result with virus-neutralising antibodies [94,184]. SARS-CoV-2 antibody detection tests have limited usefulness for early COVID-19 diagnosis as it can take 6–15 days after onset of symptoms for patients to become positive for detectable antibodies. However, the tests can be used for diagnosis of patients with delayed presentation to hospitals or retrospective diagnosis of milder cases. Once validated, commercial SARS-CoV-2 antibody tests will be essential for performing large-scale seroepidemiological population surveys, for assessing the immune status of first-line responders and healthcare personnel and for guiding safe return to work as part of de-escalation strategies when transmission begins to abate. Collecting paired serum specimens at symptom onset, at admission, during the convalescent stage, or upon discharge will be useful for subsequent testing in seroepidemiological studies. Sera biobanking should be undertaken, particularly for hospitalised patients and during outbreaks in schools or confined facilities. WHO has provided several different types of protocols to study immune response in the population and in targeted groups [185].

Self-sampling approaches may provide an efficient way to screen patients for COVID-19 on a large-scale basis, while reducing the risk of contaminating workers at healthcare facilities and decreasing the risk of non-infected people becoming infected in waiting rooms. To date, there are no validated self-testing or community-based SARS-CoV-2 testing assays available.

Clinical validation of the diagnostic performance of rapid tests and serological assays for COVID-19 is important before introducing them into the routine as a stand-alone diagnostic test [186]. In addition, it is important to be vigilant about fraudulent commercial claims of test performance, as communicated by WHO in a Medical Product Alert on 31 March 2020 in relation to reports of falsified intro vitro diagnostics (IVDs) and laboratory reagents for the detection of SARS-CoV-2 [187]. ECDC is working closely with the European Commission, Member State authorities, FIND and WHO to monitor the ongoing validation of these rapid tests.

WHO has activated the Emergency Use Listing (EUL) procedure designed to expedite the availability of IVDs needed to detect SARS-CoV-2. According to IVD Directive 98/79/EC, to affix the CE-mark to COVID-19 diagnostic devices to be used by health professionals, the manufacturer has to specify device performance characteristics and

self-declare conformity with the safety and performance requirements listed in the Directive. The performance of compliant CE-marked rapid diagnostic tests may vary in the routine testing laboratory against the manufacturer's performance study done for the purposes of CE-marking [186].

FIND is performing validation studies and the results are being made available at https://www.finddx.org/covid-19/dx-data/. In addition, such studies are also being performed by WHO referral laboratories for COVID-19, and the European Commission and Member States are funding fast-track clinical validation studies of rapid diagnostic tests for COVID-19. Scientific publications of results should soon clarify the clinical performance and limitations of rapid diagnostic tests and indicate which tests can be used safely and reliably for specific medical or public health purposes.

5 Considerations regarding de-escalation of measures

Physical distancing measures have been implemented in all EU/EEA Member States during the COVID-19 pandemic, in different forms and to different degrees (Annex 4). Evidence is now accumulating to indicate that these measures are collectively reducing transmission. Modelling studies have shown that slowing transmission would reduce the overall number of cases and delay the peak of the epidemic, thereby significantly alleviating pressure on national health systems [188]. However, stringent physical distancing measures are highly disruptive to society, both economically and socially, and there are already signs that people in some countries are not adhering firmly to the recommended measures on account of 'isolation fatigue' [189]. There is therefore significant interest in defining a sound approach to de-escalation.

Unless the incidence of infections is reduced to a very low level in a given setting (i.e. re-establishment of the containment scenarios), transmission will continue until a population protection threshold is reached. For a basic reproduction number, R₀, of 3, this threshold is 67%. That is to say, on average, two out of every three people in every social setting or location would need to be immune to stop ongoing transmission. In the absence of a vaccine, this immunity will only be acquired as a result of infection with the virus. Current estimates suggest that no EU/EEA country or population is close to achieving the population protection threshold, meaning that if interventions are lifted too rapidly, sustained transmission of the virus is to be expected [121,122].

Some form of physical distancing interventions will therefore need to be in place for at least several months from now, otherwise healthcare demand will exceed availability [190]. Plans for de-escalation should be based on public health principles and underscored by scientific advice. Solidarity and coordination between Member States will remain essential in the de-escalation phase - i.e. if one Member State allows incidence to rise too rapidly, it may have a negative effect on the efforts of neighbouring countries.

ECDC is currently working to evaluate approaches to the de-escalation of physical distancing interventions. A baseline scenario is to maintain stringent measures until a 'game changer' is developed, for example a vaccine. Alternatives include:

- identifying a combination of measures that maintains incidence slightly below hospital capacity [17]:
- ensuring adequate protection of those most at risk of developing severe disease: the so-called 'cocooning' approach;
- widespread testing to facilitate the return to work of those who have recovered.

In practical terms, an optimal approach is likely to be a combination of these.

Although modelling studies to date have provided an insightful schematic representation of the dynamics of transmission, control and de-escalation [123], a significant degree of uncertainty remains.

When considering the lifting of control measures, the following questions should be addressed:

What proportion of the population is susceptible?

In order to estimate how long physical distancing measures will need to be in place, or how quickly incidence will rise following de-escalation, it is necessary to know the proportion of the population that is still susceptible to infection with the virus. Regions with higher levels of susceptibility may sustain larger localised outbreaks, acting as amplification centres and causing strain on their neighbours.

What we know: Modelling studies have used the reported number of deaths from ECDC data to back-estimate the total number of infections (observed and unobserved), postulating that trends in mortality are less influenced by differences in testing strategy or capacity than the number of reported confirmed cases [124,191]. However, these estimates are strongly influenced by published estimates of the case-fatality rate and differences in COVID-19 mortality reporting between countries.

What we need: large-scale age-stratified seroepidemiological population-based surveys would give the most accurate estimate of remaining susceptibility, and would give insight into regional heterogeneity. Increased production of valid serological assays, together with increased operational and lab capacity will be necessary to implement these.

Who is most in need of protection from the virus?

Not everyone is at equal risk of developing severe symptoms of COVID-19, of requiring hospital treatment (including ICU) or of dying. Identifying the risk profile associated with severe disease and death (e.g. in terms of age, smoking habits or co-morbidities) would allow control measures to become more targeted, focusing on the reduction of morbidity and mortality, rather than all transmission.

What we know: risk factors for critical illness include age above 65 years and underlying conditions including hypertension, diabetes, cardiovascular disease, chronic respiratory disease, immune compromised status, cancer and obesity [16,21,32,83,84]. Smokers may also be at elevated risk [192].

What we need: with increased completeness of data on co-morbidities and demography of confirmed cases reported to TESSy, it will be possible to describe the risk factors for the population in the EU/EEA and the UK and to tailor prevention measures more precisely to those in most need of protection from the virus.

Who can safely return to business as usual?

Assuming that infection results in lasting immunity in all those infected, people who have recovered or had an asymptomatic infection could return to work without risk of increased transmission. Identifying these individuals would be beneficial for planning rosters of healthcare workers, and for re-starting the economy in general. If current control measures are sustained, this proportion of the population will remain low in the coming months. Therefore, this should be considered as one component of a broader de-escalation strategy.

What we know: although many individuals have tested positive for the virus and returned to full health, there is limited information available about whether the protective immune response against SARS-CoV2 will last [91], whether asymptomatic cases develop a full immune response or whether some individuals are healthy carriers of the virus.

What we need: plans for de-escalation should be tempered with the warning that re-infection with SARS-CoV2 remains a possibility. Longitudinal studies with clinically validated antibody detection assays are necessary to assess the extent of this risk.

If naturally induced immunity is indeed long-lasting, validated sensitive and specific rapid antigen tests could be used to give a rapid diagnosis, allowing individuals to know that, once they have recovered from symptoms, they may return to work and life as usual. However, these would need to be produced on a massive scale and widely distributed.

How effective are the control measures at reducing transmission?

In order to estimate the impact of de-escalating measures, it is important to know how effective they have been. Since in many settings measures have been introduced in combination, it is difficult to assess which have had the strongest impact on transmission, morbidity and mortality. If the relative effectiveness of each measure is quantified, it becomes easier to identify a mixed approach that will keep the incidence rate of cases at equilibrium, which is important for minimising the total number of cases and for planning and optimising healthcare staffing and resources. The time lag between the introduction or removal of control measures and the subsequent impact on incidence of severe cases or mortality (the most robust surveillance indicators) is up to three weeks [124]. However, the impact of control measures on behaviour, such as mobility, can be observed almost instantly with the use of social media or telecommunication data.

What we know: in the UK, a longitudinal nationwide telephone survey is investigating changes in social behaviour following the introduction of physical distancing measures. Compared with the pre-epidemic period, the first round of the survey showed a 73.1% decrease in contacts, with little variation across age and gender. Under stringent control measures, the proportion of interpersonal contacts in the home increased from 33.7% to 57.6%. However, only 2.5% of the interviewed population decreased their frequency of visits to supermarkets and just 32.5% cancelled leisure activities, such as visiting the pub. The study estimates that the observed reduction in contacts may lower the effective reproduction number by 38% [11% - 63%] [193].

Digital and telecommunication providers have also collaborated to generate insights on the efficacy of control measures by analysing mobility data. Google is releasing open reports on mobility patterns, which show the impact of mobility restriction measures on a number of common activities at regional level. For example, data from Italy show a decrease in visits to retail and leisure institutions (-94%), groceries and pharmacies (-85%), parks (-90%), transportation hubs (-87%) and workplaces (-63%) [118].

What we need to know: although behavioural studies give a strong indication of how transmission may be reduced by physical distancing measures, studies using directly observed data on case numbers and mortality have been limited. Over the coming days and weeks, the impact of the first control measures to be implemented should be clearly evident in routinely collected epidemiological data.

The delay in observing the effect of these interventions should serve as a warning against de-escalating too rapidly. Removal of too many measures too quickly may cause an upsurge in infections which will not be observed until weeks later, and at that point, transmission will once again be sustained at higher levels.

How much targeted protection do the control measures offer to risk groups?

Even if two physical distancing approaches give rise to a comparable reduction in transmission, one may be more effective in reducing cases in risk groups, such as the elderly or those with underlying conditions.

What we know: certain groups, for example, those aged 65 years and over, are more at risk of developing severe disease or dying. Homes for the care of the elderly should therefore remain subject to control measures.

What we need: little is known about the relative effectiveness of various control measures in protecting risk groups. As additional data is gathered over time on the age and co-morbidity of cases, it will be possible to assess how interventions affect transmission, morbidity and mortality.

What is the preparedness for de-escalation?

De-escalation of measures carries the risk of a rapid upsurge in transmission, which may remain unobserved until newly infected cases present with symptoms (at least 10 days). Before considering the lifting of any intervention measures, Member States should assess whether sufficient surveillance and monitoring systems are in place to assess the epidemiological consequences [158]. While data on hospital occupancy may inform the decision to tentatively reduce the stringency of control measures, they should not be used alone to assess whether transmission is becoming re-established. Real-time data on behaviour and mobility (based on telecommunication data) will give the first indication of the extent to which people have returned to their regular routines and contact rates with other people.

In short, de-escalation of measures in any EU/EEA Member State would need to be carefully planned and conducted, in order to avoid a swift return to high levels of transmission. The situation may become increasingly challenging when the initial periods of physical distancing measures are extended over the coming months, and social unrest or non-compliance may emerge. The importance of supporting populations in terms of mental health, protection of vulnerable groups, provision of food and essential medicines, etc. should be emphasised. Please refer to the <u>guidance on community engagement</u> [129] for more details.

6 Research needs

Age-stratified serological studies are a critical priority in order to understand the extent of infection at population level and assess potential pre-existing immunity in the population. Serological studies should assess the true attack rate and the duration of COVID-19 immunity, and explore the levels of population immunity at different stages of the epidemic. Such studies require sensitive and reliable serological tests, which are currently under development but necessitate validation. Study protocols are currently being developed and should be conducted in a harmonised manner across the EU/EEA.

Studies on the most affected populations or risk groups are yielding important information to inform public health measures and improve case management for the prevention of severe and fatal outcomes. In particular, the following issues require urgent attention:

- risk factors for development of severe COVID-19 (e.g. smoking, medications, co-morbidities) should be identified, to allow targeted interventions to protect the most vulnerable;
- the role of children in transmitting the virus;
- the proportion of asymptomatic cases and their role in transmission;
- information on how long a COVID-19 patient remains infective, how long antibodies protect from re-infection, and what evidence is required before an infected, and subsequently recovered, person can go back to his/her normal life and work;
- the relative efficiency and relevance of the different modes of transmissions (e.g. droplets, airborne, surfaces, or faecal-oral);
- public health relevance and mode of potential indoor transmission through ventilation systems in hospitals, offices and buildings, ships and airplanes;
- molecular studies to shed more light on disease dynamics and viral evolution and spread;
- indirect impact of COVID-19 pandemic on healthcare systems performance (e.g. delays, disruptions), other diseases (excess morbidity and mortality from e.g. cardiovascular disease, cancer), uptake of routine immunisations, vulnerable groups (health inequities), empirical usage of antibiotics and other medications (e.g. chloroquine), shortages of medical treatments and substances and potential consequences;
- identification of long-term sequelae of COVID-19 in particular among patients who have undergone mechanical ventilation.

Several clinical trials for medicines and vaccines are currently recruiting participants and require funding and harmonised approaches. To boost global preparedness, prevention and containment of the virus, the European Commission has allocated EUR 232 million to different sectors [194]. This includes EUR 48.5 million to 18 projects funded through a COVID-19 specific EU Research and Innovation Programme [195]. National governments are also supporting significant research activity to enhance understanding of disease progression and options for mitigation at national level, and a number of international donors are also making significant research contributions at global level. ECDC collaborates, or will be collaborating, in relevant EU projects to ensure coherence and synergies, but it is important that researchers apply internationally agreed protocols, share data on open access platforms and commit to the early communication of emerging results to ensure that all can benefit from the developing science around COVID-19 [196].

An assessment of the use and effectiveness of PPE in various settings would provide more evidence regarding the prevention of transmission in healthcare settings and in particular shed light on how best to protect healthcare workers. To overcome shortages, re-usable and user-friendly PPE should be developed as soon as possible, and methods for the safe disinfection of PPE should be standardised.

Finally, modelling studies assessing the effectiveness of interventions and policies to delay disease transmission could be of vital importance in supporting decision-making and ensuring hospital capacity.

7 Limitations

This assessment is undertaken based on information available to ECDC at the time of publication. There is substantial uncertainty regarding the epidemiological characteristics of COVID-19. There is limited epidemiological and clinical information on the cases of COVID-19 identified so far (e.g. efficiency of different modes of transmission, proportion of mild and asymptomatic cases, transmission during incubation and recovery period, effectiveness of treatment regimes, risk factors for severe illness other than age, effective preventive measures). Given these limitations, ECDC will revise the current risk assessment as soon as more information becomes available.

8 Source and date of request

ECDC internal decision, 6 April 2020

9 Consulted experts

ECDC experts (in alphabetic order): Cornelia Adlhoch, Natalia Alberska, Barbara Albiger, Leonidas Alexakis, Agoritsa Baka, Eeva Broberg, Sergio Brusin, Nick Bundle, Mike Catchpole, Orlando Cenciarelli, Scott Chiossi, Edoardo Colzani, Angelo D'Ambrosio, Stefania De Angelis, Tarik Derrough, Dragoslav Domanovic, Erika Duffell, Lisa Ferland, Emilie Finch, Tjede Funk, Joana Haussig, Ole Heuer, Helen Johnson, Irina Jovel Quinonez Dalmau, Tommi Karki, Pete Kinross, John Kinsman, Csaba Kodmon, Vicky Lefevre, Katrin Leitmeyer, Felix Lötsch, Angeliki Melidou, Grazina Mirinaviciute, Otilia Mårdh, Howard Needham, Teymur Noori, Pasi Penttinen, Anastasia Pharris, Diamantis Plachouras, Senia Rosales-Klintz, Emmanuel Robesyn, Jan Semenza, Ettore Severi, Gianfranco Spiteri, Marc Struelens, Bertrand Sudre, Carl Suetens, Lars Söderblom, Svetla Tsolova, Marius Vochin, Ariana Wijermans.

Disclaimer

ECDC issues this risk assessment document based on an internal decision and in accordance with Article 10 of Decision No 1082/13/EC and Article 7(1) of Regulation (EC) No 851/2004 establishing a European centre for disease prevention and control (ECDC). In the framework of ECDC's mandate, the specific purpose of an ECDC risk assessment is to present different options on a certain matter. The responsibility on the choice of which option to pursue and which actions to take, including the adoption of mandatory rules or guidelines, lies exclusively with the EU/EEA Member States. In its activities, ECDC strives to ensure its independence, high scientific quality, transparency and efficiency.

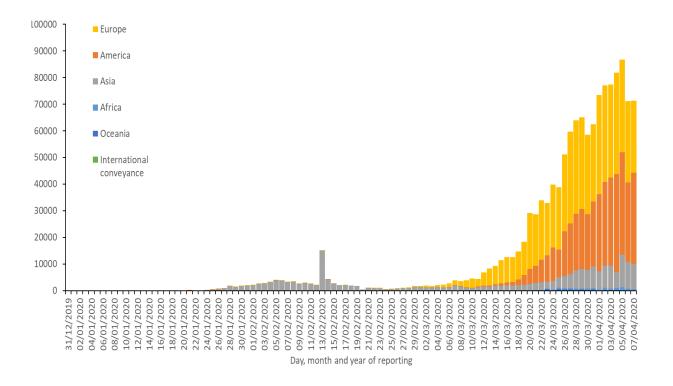
This report was written with the coordination and assistance of an Internal Response Team at the European Centre for Disease Prevention and Control. All data published in this risk assessment are correct to the best of our knowledge at the time of publication. Maps and figures published do not represent a statement on the part of ECDC or its partners on the legal or border status of the countries and territories shown.

Annex 1. ECDC latest publications on COVID-19 (1 February 2020 – 8 April 2020)

- Guidance for discharge and ending isolation in the context of widespread community transmission of COVID-19 first update. 8 April 2020
- Strategies for the surveillance of COVID-19. 8 April 2020.
- <u>Using face masks in the community Reducing COVID-19 transmission from potentially asymptomatic or pre-symptomatic people through the use of face masks. 8 April 2020.</u>
- An overview of the rapid test situation for COVID-19 diagnosis in the EU/EEA. 1 April 2020.
- Infection prevention and control and preparedness for COVID-19 in healthcare settings second update, 31
 March 2020.
- Infection prevention and control in the household management of people with suspected or confirmed coronavirus disease (COVID-19). 31 March 2020
- <u>Contact tracing: Public health management of persons, including healthcare workers, having had contact with COVID-19 cases in the European Union first update. 31 March 2020.</u>
- Cloth masks and mask sterilisation as options in case of shortage of surgical masks and respirators. 26
 March 2020.
- <u>Disinfection of environments in healthcare and non-healthcare settings potentially contaminated with SARS-CoV-2. 26 March 2020.</u>
- Rapid risk assessment: Novel coronavirus disease 2019 (COVID-19) pandemic: increased transmission in the EU/EEA and the UK seventh update. 25 Mar 2020.
- Considerations related to the safe handling of bodies of deceased persons with suspected or confirmed COVID-19. ECDC. Stockholm. 23 March 2020.
- Coronavirus disease 2019 (COVID-19) and supply of substances of human origin in the EU/EEA. ECDC.
 Stockholm. 23 March 2020.
- Guidance for health system contingency planning during widespread transmission of SARS-CoV-2 with high impact on healthcare services. 17 March 2020.
- Rapid risk assessment: Novel coronavirus disease 2019 (COVID-19) pandemic: increased transmission in the EU/EEA and the UK sixth update. 25 Mar 2020.
- <u>Considerations relating to social distancing measures in response to COVID-19 second update. 23 March</u> 2020.
- Novel coronavirus (SARS-CoV-2) Discharge criteria for confirmed COVID-19 cases. 10 March 2020.
- Resource estimation for contact tracing, quarantine and monitoring activities for COVID-19 cases in the EU/EEA. 2 March 2020.
- Rapid risk assessment: Outbreak of novel coronavirus disease 2019 (COVID-19): increased transmission globally fifth update. 2 March 2020Guidance for wearing and removing personal protective equipment in healthcare settings for the care of patients with suspected or confirmed COVID-19. 28 February 2020.
- <u>Checklist for hospitals preparing for the reception and care of coronavirus 2019 (COVID-19) patients. 26</u> February 2020.
- <u>Interim guidance for environmental cleaning in non-healthcare facilities exposed to SARS-CoV-2. 18</u>
 February 2020.
- <u>Guidelines for the use of non-pharmaceutical measures to delay and mitigate the impact of 2019-nCoV. 10</u>
 February 2020.
- Personal protective equipment (PPE) needs in healthcare settings for the care of patients with suspected or confirmed novel coronavirus (2019-nCoV). 7 February 2020.

Annex 2. Global epidemic curve

Figure 1. Distribution by continent of COVID-19 cases reported in accordance with the applied case definitions in the affected countries, as of 7 April 2020



Annex 3. Time distribution of 14-day incidence of reported COVID-19

Figure 3A. 14-day incidence of reported COVID-19 cases in Hubei Province (China), Italy and Northern Europe, 7 April 2020

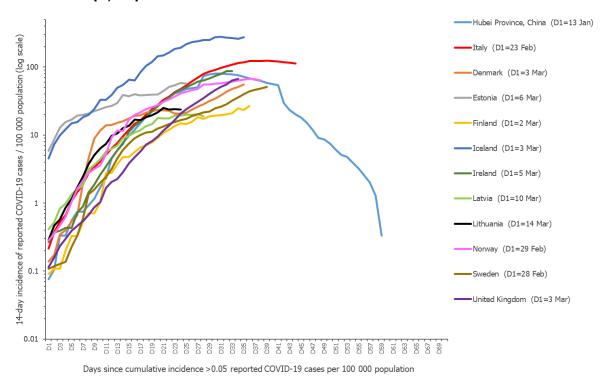


Figure 3B. 14-day incidence of reported COVID-19 cases in Hubei Province (China) and Southern Europe, 7 April 2020

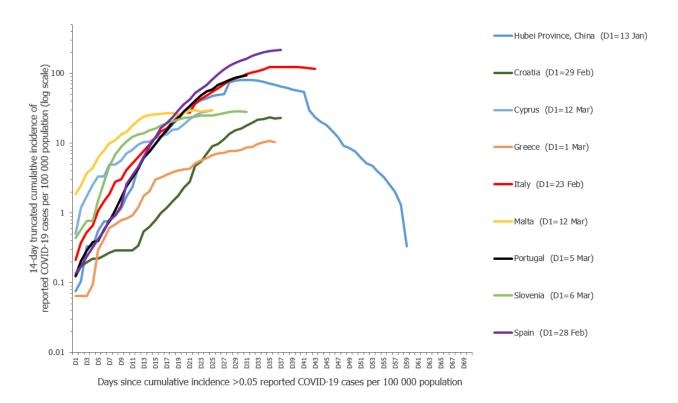


Figure 3C. 14-day incidence of reported COVID-19 cases in Hubei Province (China), Italy and Eastern Europe, 7 April 2020

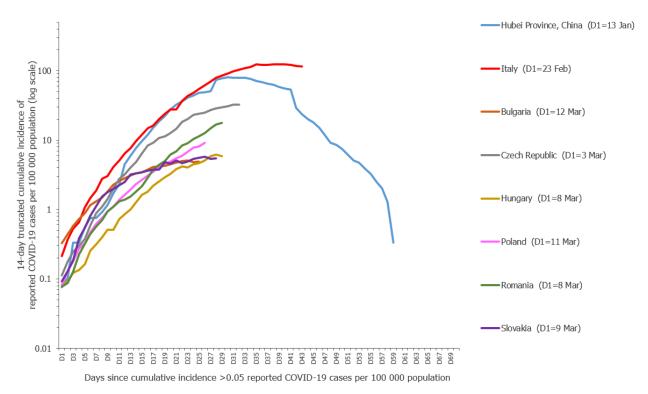
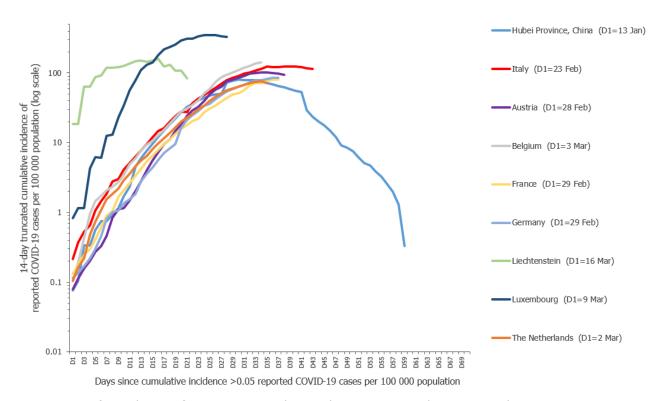
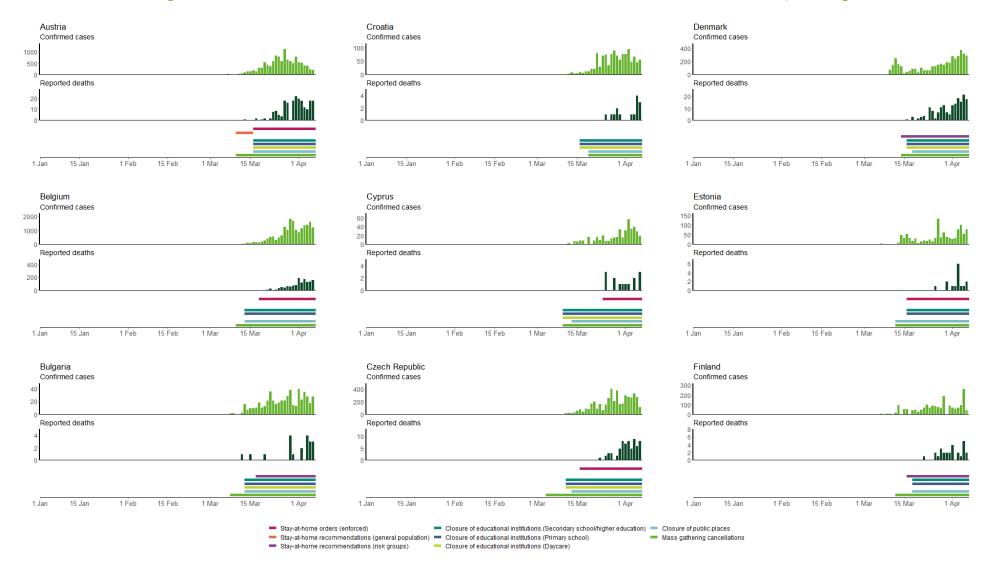


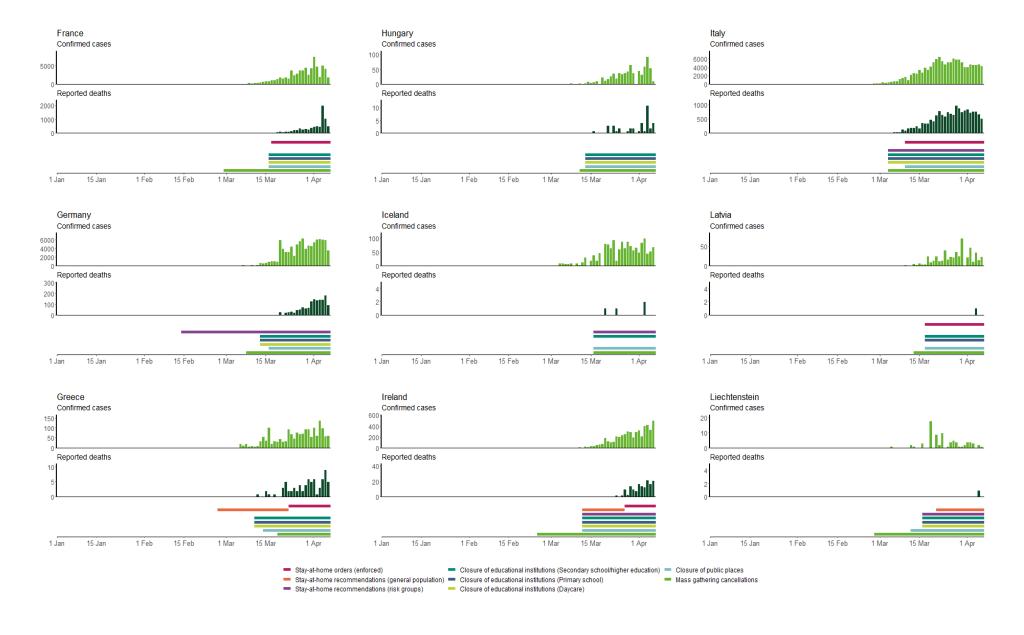
Figure 3D. 14-day incidence of reported COVID-19 cases in Hubei Province (China), Italy and Western Europe, 7 April 2020

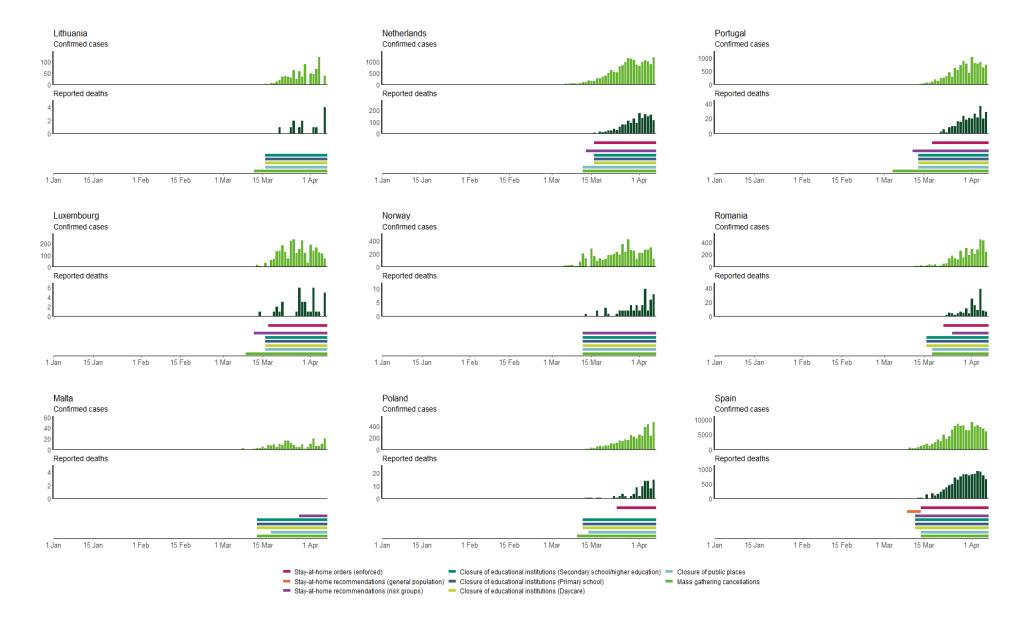


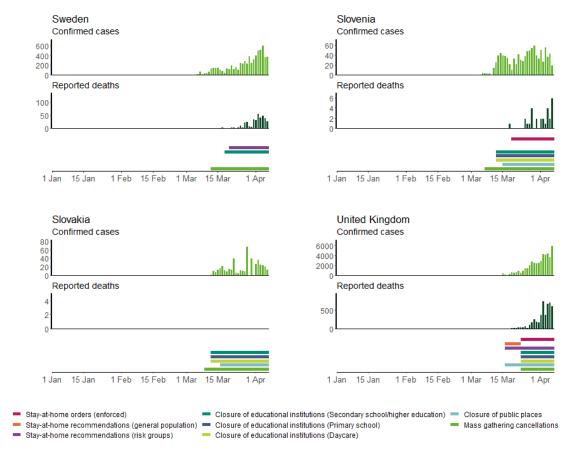
Key: Data as of 7 April 2020. If a country reported an incidence >0.05 cases/ 100 000 population AND <5 cases in the previous 14 days, D1 is the most recent day with ≥ 5 cases in the previous 14 days. The assignment of countries to geographical regions of Europe according to the United Nations geoscheme are for statistical convenience, and does not imply any assumption regarding political or other affiliation of countries or territories (https://unstats.un.org/unsd/methodology/m49). The 'flattening of the curve' observed for Hubei Province at day 30 (D30) coincides with a change in the Chinese case definition on 14 February.

Annex 4. Response measures in EU/EEA countries and the UK, 3 April 2020*









^{*} The data on response measures are based on information available from official public sources as of Friday 3 April 2020 at 18:00 and may not capture measures being taken by countries that are not reported on publicly available websites. The situation is evolving rapidly and this represents a snapshot of the measures that countries in the EU/EEA and the UK have reported to date.

The response measures displayed are national measures, reported on official public websites. Response measures collected include: mass gathering cancellations (for specific events or a ban on gatherings of a particular size); closure of public spaces (including restaurants, entertainment venues, non-essential shops and so on); closure of educational institutions (including day-care or nursery, primary schools, and secondary schools and higher education); stay-at-home recommendations for risk groups or vulnerable populations (such as the elderly, people with underlying health conditions, physically disabled people etc.); stay-at-home recommendations for the general population (which are voluntary or not enforced); and stay-at-home orders for the general population (these are enforced and also referred to as 'lockdown').

The data on response measures has several limitations. Firstly, there is substantial heterogeneity in physical distancing policies and their implementation between countries. For instance, the level of enforcement of measures may vary between countries and there may be specific rules and exceptions to the measures, making interpretation of the data challenging. The measures displayed in these figures are measures reported at national level and it should be noted that due to the evolution of the outbreak in certain regions, regional or local measures often preceded national ones. The exact dates of introduction were often available from official sources but delays in their implementation may have occurred. Additionally, availability of public data from official government sources varies among countries. For some countries, data are no longer available on official websites concerning measures that are no longer in force, which may result in the data for more recent measures being more complete.

Annex 5. Scenarios to describe progression of COVID-19 outbreaks

The following five scenarios, adapted from ECDC's strategic analysis, are used to describe the possible progression of the COVID-19 outbreak in EU/EEA countries.

Scenario 0 describes a situation with no reported cases in the country and multiple introductions and/or community transmission elsewhere in Europe. At this stage, the main objective for public health measures should be to enable rapid detection and isolation of individual cases to prevent domestic transmission chains, and to prepare for the response once cases are detected in the country.

Scenario 1 describes a situation with multiple introductions but limited local transmission in the country. Despite the introductions, there is no apparent sustained transmission (only second generation cases observed or transmission within sporadic contained clusters with known epidemiological links). In this situation, the objective is containment of the outbreak, by blocking transmission opportunities through early detection of imported and locally-transmitted COVID-19 cases in order to try to avoid, or at least delay, the spread of infection and the associated burden on healthcare systems. Delaying the start of local transmission will allow the current influenza season to end, freeing up some healthcare capacity.

Scenario 2 describes a situation with an increasing number of introductions and more widespread reports of localised human-to-human transmission in the country (more than two generations of cases outside of sporadic clusters with known epidemiological links). In this situation, the objective is still to contain, where practical, and otherwise slow down the transmission of the infection. This will increase the time available for development, production and distribution of PPE and effective therapeutic options, and would play a crucial role in reducing the burden on the healthcare system and other sectors, particularly if wider transmission of COVID-19 is delayed beyond the ongoing influenza season. A reduced burden would also allow for more time to increase laboratory capacity and surge capacity in healthcare services. All these measures will facilitate effective treatment of infected patients [44]. Rapid collection and analysis of epidemiological and virological data will facilitate the targeting of measures in this scenario and later.

Scenario 3 describes a situation with localised outbreaks which start to merge, becoming indistinct. In this scenario, there is sustained human-to-human transmission in the country (more than two generations of cases outside of sporadic clusters with known epidemiological links) and an increasing pressure on healthcare systems. The objective at this stage is to mitigate the impact of the outbreak by decreasing the burden on healthcare systems and to protect populations at risk of severe disease. At the same time, operational research should guide the development of better and more efficient diagnostic and treatment options.

Scenario 4 describes a situation with widespread sustained transmission where healthcare systems are overburdened due to a large demand for emergency healthcare services, a strained ICU capacity, overworked healthcare workers and reduced staff availability due to illness, lack of PPE and lack of diagnostic testing capacity. The objective at this stage is still to mitigate the impact of the outbreak, decrease the burden on healthcare services, protect populations at risk of severe disease and reduce excess mortality.

References

- European Centre for Disease Prevention and Control (ECDC). COVID-19. Stockholm: ECDC; 2020 [cited 1 March 2020]. Available from: https://www.ecdc.europa.eu/en/novel-coronavirus-china
- World Health Organization (WHO). Coronavirus disease (COVID-19) outbreak. Geneva: WHO; [1 March 2020]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019
- 3. Dipartimento della Protezione Civile. COVID-19 Italia Monitoraggio della situazione. [7 April 2020]. Available from: https://opendatadpc.maps.arcgis.com/apps/opsdashboard/index.html#/b0c68bce2cce478eaac82fe38d4138b1
- 4. Goberno De España. Situación de COVID-19 en España: Basada en la notificación diaria de casos agregados de COVID-19 al Ministerio de Sanidad [Actualizado a 6 de abril de 2020 a las 20:00 horas]. Madrid: Ministerio de Sanidad; [7 April 2020]. Available from: https://covid19.isciii.es/
- 5. Folkhälsomyndigheten (FHM). Antal fall av covid-19 i Sverige. Stockholm: FHM; [7 April 2020]. Available from: https://experience.arcgis.com/experience/09f821667ce64bf7be6f9f87457ed9aa
- 6. ANSA. Nel Bergamasco 600 morti in Rsa.: ANSA; [6 April 2020]. Available from: https://www.ansa.it/sito/notizie/topnews/2020/03/28/nel-bergamasco-600-morti-in-rsa_01194197-6d88-427e-8dcc-7859a311751d.html
- 7. Santé Publique France. COVID-19: point épidémiologique du 2 avril 2020. Paris: Santé Publique France; [6 April, 2020]. Available from: https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-et-infections-respiratoires/infection-a-coronavirus/documents/bulletin-national/covid-19-point-epidemiologique-du-2-avril-2020
- 8. RTL Nieuws. Nieuwe cijfers verpleeghuizen: vermoedelijk meer doden door corona: RTL Nieuws; [6 April 2020]. Available from: https://www.rtlnieuws.nl/nieuws/nederland/artikel/5080506/verpleeghuis-corona-patient
- VRT NWS. 20-tal woonzorgcentra getroffen door grotere corona-uitbraak: VRT NWS; [6 April 2020]. Available from: https://www.vrt.be/vrtnws/nl/2020/04/05/20-tal-woonzorgcentra-getroffen-door-grotere-corona-uitbraak/
- Robert Koch Institut (RKI). Coronavirus Disease 2019 (COVID-19) Daily Situation Report of the Robert Koch Institute Berlin: RKI; 2020 [6 April 2020]. Available from:
 https://www.rki.de/DE/Content/InfAZ/N/Neuartiges Coronavirus/Situationsberichte/2020-04-06-en.pdf?

 blob=publicationFile
- 11. Folkhälsomyndigheten (FHM). Veckorapport om covid-19, vecka 13. Stockholm: FHM; [6 April 2020]. Available from: https://www.folkhalsomyndigheten.se/globalassets/statistik-uppfoljning/smittsamma-sjukdomar/veckorapporter-covid-19/2020/covid-19-veckorapport-vecka-13-2020 final.pdf
- 12. Svenska Dagbladet (SvD). Corona på äldreboenden i stora delar av landet. [7 April 2020]. Available from: https://www.svd.se/corona-pa-aldreboenden-i-stora-delar-av-landet
- 13. European monitoring of excess mortality for public health action (euroMOMO). Mortality monitoring in Europe [6 April 2020]. European mortality bulletin week 13, 2020. Available from: https://www.euromomo.eu/
- 14. European Centre for Disease Prevention and Control (ECDC). Event background COVID-19. Stockholm: ECDC; [1 March 2020]. Available from: https://www.ecdc.europa.eu/en/novel-coronavirus/event-background-2019
- 15. European Centre for Disease Prevention and Control (ECDC). Situation update worldwide. Stockholm: ECDC; [1 March 2020]. Available from: https://www.ecdc.europa.eu/en/qeographical-distribution-2019-ncov-cases
- 16. World Health Organization (WHO). Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). Geneva: WHO; 2020 [1 March 2020]. Available from: https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf
- 17. European Centre for Disease Prevention and Control (ECDC). Novel coronavirus disease 2019 (COVID-19) pandemic: increased transmission in the EU/EEA and the UK sixth update 12 March 2020. Stockholm: ECDC; 2020. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/RRA-sixth-update-Outbreak-of-novel-coronavirus-disease-2019-COVID-19.pdf
- Chen J, Fan H, Zhang L, Huang B, Zhu M, Zhou Y, et al. Retrospective Analysis of Clinical Features in 101 Death Cases with COVID-19. medRxiv. 9 March 2020. 20033068.
- 19. Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) United States, February 12–March 16, 2020. MMWR Morb Mortal Wkly Rep 2020;69:343-346. DOI: http://dx.doi.org/10.15585/mmwr.mm6912e2
- 20. Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, et al. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. JAMA. 2020.
- 21. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet. 9 March 2020.
- 22. Kujawski SA, Wong KK, Collins JP, Epstein L, Killerby ME, Midgley CM, et al. First 12 patients with coronavirus disease 2019 (COVID-19) in the United States. medRxiv.9 March 2020. 20032896.
- 23. Liu Y, Gayle AA, Wilder-Smith A, Rocklöv J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. Journal of Travel Medicine. 2020;27(2).
- 24. Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. Annals of Internal Medicine. 2020.
- Chinese Center for Disease Control and Prevention. Epidemic update and risk assessment of 2019 Novel Coronavirus. [29 February 2020]. Available from: http://www.chinacdc.cn/yyrdgz/202001/P020200128523354919292.pdf

- 26. Backer JA, Klinkenberg D, Wallinga J. Incubation period of 2019 novel coronavirus (2019-nCoV) infections among travellers from Wuhan, China, 20–28 January 2020. Eurosurveillance. 2020;25(5).
- 27. Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, et al. Virological assessment of hospitalized patients with COVID-2019. Nature. 1 April 2020.
- 28. Liu Y, Yan L-M, Wan L, Xiang T-X, Le A, Liu J-M, et al. Viral dynamics in mild and severe cases of COVID-19. The Lancet Infectious Diseases. 19 March 2020.
- 29. To KK-W, Tsang OT-Y, Leung W-S, Tam AR, Wu T-C, Lung DC, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. The Lancet Infectious Diseases. 23 March 2020.
- 30. Cai J, Xu J, Lin D, Yang z, Xu L, Qu Z, et al. A Case Series of children with 2019 novel coronavirus infection: clinical and epidemiological features. Clinical Infectious Diseases. 2020.
- 31. Chang L, Yan Y, Wang L. Coronavirus Disease 2019: Coronaviruses and Blood Safety. Transfusion Medicine Reviews. 21 February 2020.
- 32. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet. 15 February 2020;395(10223):497-506.
- 33. Peng L, Liu J, Xu W, Luo Q, Deng K, Lin B, et al. 2019 Novel Coronavirus can be detected in urine, blood, anal swabs and oropharyngeal swabs samples. medRxiv. 21 February 2020. 20026179.
- 34. European Centre for Disease Prevention and Control (ECDC). Coronavirus disease 2019 (COVID-19) pandemic: increased transmission in the EU/EEA and the UK seventh update, 25 March 2020. Stockholm: ECDC; 2020 [6 April 2020]. Available from: https://www.ecdc.europa.eu/en/publications-data/rapid-risk-assessment-coronavirus-disease-2019-covid-19-pandemic#no-link
- 35. Ministry of Health, Labour and Welfare, Japan. Coronavirus disease 2019 (COVID-19) situation within and outside the country 2020 [updated 10 March 2020]. Available from: https://www.mhlw.qo.jp/stf/seisakunitsuite/bunya/newpage 00032.html
- 36. Mizumoto K, Kagaya K, Zarebski A, Chowell G. Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. Eurosurveillance. 2020;25(10):2000180.
- 37. Ki M. Epidemiologic characteristics of early cases with 2019 novel coronavirus (2019-nCoV) disease in Korea. Epidemiol Health. 2020;42(0):e2020007-0.
- 38. Dong XC, Li JM, Bai JY, Liu ZQ, Zhou PH, Gao L, et al. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. Zhonghua liu xing bing xue za zhi = Zhonghua liuxingbingxue zazhi. 18 February 2020 Medline;41(2):145-51.
- 39. Luo S-H, Liu W, Liu Z-J, Zheng X-Y, Hong C-X, Liu Z-R, et al. A confirmed asymptomatic carrier of 2019 novel coronavirus (SARS-CoV-2). Chinese Medical Journal. 9000; [published ahead of print]
- 40. Cereda D, Tirani M, Rovida F, Demicheli V, Ajelli M, Poletti P, et al. The early phase of the COVID-19 outbreak in Lombardy, Italy 2020. Available from: https://arxiv.org/abs/2003.09320v1
- 41. Aguilar JB, Faust JS, Westafer LM, Gutierrez JB. Investigating the Impact of Asymptomatic Carriers on COVID-19 Transmission. medRxiv. 18 March 2020. 20037994.
- Wei WE, Li Z, Chiew CJ, Yong SE, Toh MP, VJ. L. Presymptomatic Transmission of SARS-CoV-2 Singapore, January 23–March 16, 2020. ePub: 1 April 2020. MMWR Morb Mortal Wkly Rep. 2020. doi: http://dx.doi.org/10.15585/mmwr.mm6914e1
- 43. Ganyani T, Kremer C, Chen D, Torneri A, Faes C, Wallinga J, et al. Estimating the generation interval for COVID-19 based on symptom onset data. medRxiv. 5 March 2020: 20031815.
- 44. Chang L, Zhao L, Gong H, Wang Lunan, Wang L. Severe acute respiratory syndrome coronavirus 2 RNA detected in blood donations. Emerg Infect Dis. 2020 Jul [7 April 2020] Available from: https://doi.org/10.3201/eid2607.200839
- 45. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020.
- 46. Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? The Lancet. 13 March 2020.
- 47. International Council of Nurses. High proportion of healthcare workers with COVID-19 in Italy is a stark warning to the world: protecting nurses and their colleagues must be the number one priority [cited 5 April 2020]. Available from: https://www.icn.ch/news/high-proportion-healthcare-workers-covid-19-italy-stark-warning-world-protecting-nurses-and
- 48. Ministerio de Sanidad Espana. Informe sobre la situación de COVID-19 en España. Informe COVID-19 nº 20. 3 de abril 2020. Available from: https://www.isciii.es/QueHacemos/Servicios/VigilanciaSaludPublicaRENAVE/EnfermedadesTransmisibles/Paginas/InformesCOVID-19.aspx
- 49. Kluytmans M, Buiting A, Pas S, Bentvelsen R, van den Bijllaardt W, van Oudheusden A, et al. SARS-CoV-2 infection in 86 healthcare workers in two Dutch hospitals in March 2020. medRxiv. 23 March 2020. 20041913.
- 50. Min L, Peng H, Huiguo L, Xiaojiang W, Fajiu L, Chen Shi C, et al. Clinical characteristics of 30 medical workers infected with new coronavirus pneumonia. Chin J Tuberc Respir Dis,. (2020,43: epub ahead of print.)
- 51. Mizumoto K, Omori R, Nishiura H. Age specificity of cases and attack rate of novel coronavirus disease (COVID-19). medRxiv. 9 March 2020. 20033142.
- 52. Bi Q, Wu Y, Mei S, Ye C, Zou X, Zhang Z, et al. Epidemiology and Transmission of COVID-19 in Shenzhen China: Analysis of 391 cases and 1,286 of their close contacts. medRxiv. 3 March 2020. 20028423.

- 53. Istituto Superiore di Sanità. Sorveglianza Integrata COVID-19 in Italia. [27 February 2020]. Available from: https://www.iss.it/documents/20126/0/Infografica 09marzo.pdf/
- 54. Zheng F, Liao C, Fan Q-h, Chen H-b, Zhao X-g, Xie Z-g, et al. Clinical Characteristics of Children with Coronavirus Disease 2019 in Hubei, China. Current Medical Science. 24 March 2020.
- 55. Virtual Pediatric Systems. COVID-19 Data: North American Pediatric ICUs. [6 April 2020]. Available from: https://www.myvps.org/
- 56. The Connexion. Covid-19: 16-year-old first minor to die in France [updated 27 March 2020]. Available from: https://www.connexionfrance.com/French-news/Covid-19-16-year-old-Julie-Alliot-first-minor-to-die-in-France-of-coronavirus-after-mild-cough
- 57. Euronews. Two COVID-19 infected children, aged 12 and 13, die in Belgium and UK. [updated 1 April 2020]. Available from: https://www.euronews.com/2020/03/31/coronavirus-doctors-devastated-as-covid-19-claims-life-of-12-year-old-girl-in-belgium
- 58. Hamilton County Health Department (Tenessee). Health Department Announces First COVID-19 Related Pediatric Death of Hamilton County Resident, 1 April 2020 [cited 6 April 2020]. Available from: http://health.hamiltontn.org/Portals/14/AllServices/CommunicableDiseases/COVID-19/Press%20release_new%20data_4-1-20_rev3.pdf
- 59. Illinois Department of Public Health. Public Health Officials Announce the First Death of an Infant with Coronavirus Disease. 28th March 2020 [6 April 2020]. Available from: http://dph.illinois.gov/news/public-health-officials-announce-first-death-infant-coronavirus-disease
- 60. Ministry of Health, Panama. Comunicado No. 23, 23 March 2020. [6 April 2020]. Available from: http://www.minsa.gob.pa/noticia/comunicado-ndeg-23
- 61. Pan X, Chen D, Xia Y, Wu X, Li T, Ou X, et al. Asymptomatic cases in a family cluster with SARS-CoV-2 infection. The Lancet Infectious Diseases. 19 February 2020.
- 62. Kam K-q, Yung CF, Cui L, Lin Tzer Pin R, Mak TM, Maiwald M, et al. A Well Infant with Coronavirus Disease 2019 (COVID-19) with High Viral Load. Clinical Infectious Diseases. 2020.
- 63. Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, et al. SARS-CoV-2 Infection in Children. New England Journal of Medicine. 2020.
- 64. Tang A, Tong ZD, Wang HL, Dai YX, Li KF, Liu JN, et al. Detection of Novel Coronavirus by RT-PCR in Stool Specimen from Asymptomatic Child, China. Emerging Infectious Diseases. 2020 Jun 17;26(6).
- 65. Feng Kai, Yun Yongxing, Wang Xianfeng, al. e. CT image characteristics analysis of 15 cases of children with new coronavirus infection [J/OL]. [Pre-published online]. 2020 [cited 22 March 2020]. Available from: http://rs.yiigle.com/yufabiao/1181979.htm
- 66. Wang Duan JX, Xie Feng, et al. Clinical analysis of 31 cases of new coronavirus infection in children in six provinces (autonomous regions) of northern China in 2019 [J/OL]. [Internet pre-publishing]. Chinese Journal of Pediatrics. Available from: http://rs.yiigle.com/yufabiao/1183296.htm
- 67. Ji L-N, Chao S, Wang Y-J, Li X-J, Mu X-D, Lin M-G, et al. Clinical features of pediatric patients with COVID-19: a report of two family cluster cases. World Journal of Pediatrics. 16 March 2020.
- 68. Park JY, Han MS, Park KU, Kim JY, Choi EH. First Pediatric Case of Coronavirus Disease 2019 in Korea. J Korean Med Sci. 2020 3;35(11).
- 69. Liao X, Yang H, Kong J, H Yang. Chest CT Findings in a Pregnant Patient with 2019 Novel Coronavirus Disease. [7 April 2020]. Available from: http://balkanmedicaljournal.org/uploads/pdf BMJ 2196.pdf
- 70. Liu H, Liu F, Li J, Zhang T, Wang D, Lan W. Clinical and CT imaging features of the COVID-19 pneumonia: Focus on pregnant women and children. Journal of Infection. 21 March 2020.
- 71. Chen S, Liao E, Shao Y. Clinical analysis of pregnant women with 2019 novel coronavirus pneumonia. Journal of Medical Virology. In press. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.25789
- 72. Mullins E, Evans D, Viner RM, O'Brien P, Morris E. Coronavirus in pregnancy and delivery: rapid review. Ultrasound in Obstetrics & Gynecology. medRxiv. Available from: https://www.medrxiv.org/content/10.1101/2020.03.06.20032144v1
- 73. Karimi-Zarchi M, Neamatzadeh H, Dastgheib SA, Abbasi H, Mirjalili SR, Behforouz A, et al. Vertical Transmission of Coronavirus Disease 19 (COVID-19) from Infected Pregnant Mothers to Neonates: A Review. Fetal and Pediatric Pathology. 2020:1-5.
- 74. Liu D, Li L, Wu X, Zheng D, Wang J, Yang L, et al. Pregnancy and Perinatal Outcomes of Women With Coronavirus Disease (COVID-19) Pneumonia: A Preliminary Analysis. American Journal of Roentgenology. 2020:1-6.
- 75. Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. The Lancet. 7 March 2020;395(10226):809-15.
- 76. Li Y, Zhao R, Zheng S, Chen X, Wang J, Sheng X, et al. Lack of Vertical Transmission of Severe Acute Respiratory Syndrome Coronavirus 2, China. Emerging Infectious Diseases. 2020 Jun 17;26(6).
- 77. Zeng L, Xia S, Yuan W, Yan K, Xiao F, Shao J, et al. Neonatal Early-Onset Infection With SARS-CoV-2 in 33 Neonates Born to Mothers With COVID-19 in Wuhan, China. JAMA Pediatrics. 2020.
- 78. Alonso Díaz C, López Maestro M, Moral Pumarega MT, Flores Antón B, Pallás Alonso C. Primer caso de infección neonatal por SARS-CoV-2 en España. Anales de Pediatría. 31 March 2020.
- 79. Zambrano LI, Fuentes-Barahona IC, Bejarano-Torres DA, Bustillo C, Gonzales G, Vallecillo-Chinchilla G, et al. A pregnant woman with COVID-19 in Central America. Travel Medicine and Infectious Disease. 25 March 2020:101639.

- 80. 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. Archives of Pathology & Laboratory Medicine. In press. Available from: https://www.archivesofpathology.org/doi/10.5858/arpa.2020-0901-SA
- 81. Bundesamt für Gesundheit BAG. Neues Coronavirus: Situation Schweiz und International [6 April 2020]. Available from: https://www.bag.admin.ch/bag/de/home/krankheiten/ausbrueche-epidemien-pandemien/aktuelle-ausbrueche-epidemien/novel-cov/situation-schweiz-und-international.html#-1222424946
- 82. Rijksinstituut voor Volksgezondheid en Milieu (RIVM). Data nieuwe coronavirus (COVID-19) in Nederland [6 April 2020]. Available from: https://www.rivm.nl/actuele-informatie-over-coronavirus/data
- 83. Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. The Lancet Oncology. 1 March 2020;21(3):335-7.
- 84. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet. 15 February 2020;395(10223):507-13.
- 85. Chow N, Fleming-Dutra K, Gierke R, Hall A, Hughes M, Pilishvili T, et al. Preliminary Estimates of the Prevalence of Selected Underlying Health Conditions Among Patients with Coronavirus Disease 2019 United States, February 12–March 28, 2020. MMWR Morb Mortal Wkly Rep 2020;69:382–386 [cited 6 April 2020]. Available from: http://dx.doi.org/10.15585/mmwr.mm6913e2external
- 86. Li F. Structure, Function, and Evolution of Coronavirus Spike Proteins. Annual Review of Virology. 2016;3(1):237-61.
- 87. Ou J, Zhou Z, Zhang J, Lan W, Zhao S, Wu J, et al. RBD mutations from circulating SARS-CoV-2 strains enhance the structural stability and human ACE2 affinity of the spike protein. bioRxiv. 15 March 2020.991844.
- 88. European Centre for Disease Prevention and Control (ECDC). primerscan.ecdc.europa.eu. Stockholm: ECDC; [7 April 2020]. Available from: https://primerscan.ecdc.europa.eu/?assay=Overview
- 89. European Centre for Disease Prevention and Control (ECDC). Disease background of COVID-19. Stockholm: ECDC; [1 March 2020]. Available from: https://www.ecdc.europa.eu/en/2019-ncov-background-disease
- European Medicines Agency (EMA). Update on treatments and vaccines against COVID-19 under development. [5 April 2020]. Available from: https://www.ema.europa.eu/en/news/update-treatments-vaccines-against-covid-19-under-development
- 91. Ferguson NM, Laydon D, Nedjati-Gilani G, Imai N, Ainslie K, Baguelin M, et al. Impact of non-pharmaceutical interventions (NPIs) to reduce COVID19 mortality and healthcare demand: Imperial College; 2020 [updated 16 March 2020; cited 23 March, 2020]. Available from: https://www.imperial.ac.uk/media/imperial-college/medicine/sph/ide/gida-fellowships/Imperial-College-COVID19-NPI-modelling-16-03-2020.pdf
- 92. Woelfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Mueller MA, et al. Clinical presentation and virological assessment of hospitalized cases of coronavirus disease 2019 in a travel-associated transmission cluster. medRxiv. 5 March 2020. 20030502.
- 93. Zhao J, Yuan Q, Wang H, Liu W, Liao X, Su Y, et al. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. medRxiv. 2 March 2020. 20030189.
- 94. Okba NMA, Muller MA, Li W, Wang C, GeurtsvanKessel CH, Corman VM, et al. SARS-CoV-2 specific antibody responses in COVID-19 patients. medRxiv. 18 March 2020. 20038059.
- 95. Liu W, Liu L, Kou G, Zheng Y, Ding Y, Ni W, et al. Evaluation of Nucleocapsid and Spike Protein-based ELISAs for detecting antibodies against SARS-CoV-2. medRxiv. 16 March 2020. 20035014.
- Long Q-x, Deng H-j, Chen J, Hu J, Liu B-z, Liao P, et al. Antibody responses to SARS-CoV-2 in COVID-19 patients: the perspective application of serological tests in clinical practice. medRxiv. 18 March 2020. 20038018.
- 97. Wan WY, Lim SH, Seng EH. Cross-reaction of sera from COVID-19 patients with SARS-CoV assays. medRxiv. 17 March 2020. 20034454.
- 98. Bao L, Deng W, Gao H, Xiao C, Liu J, Xue J, et al. Reinfection could not occur in SARS-CoV-2 infected rhesus macaques. bioRxiv. 13 March 2020. 990226.
- 99. European Medicines Agency (EMA). EMA provides recommendations on compassionate use of remdesivir for COVID-19. [5 April 2020]. Available from: https://www.ema.europa.eu/en/news/ema-provides-recommendations-compassionate-use-remdesivir-covid-19
- 100. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. New England Journal of Medicine. 2020.
- 101. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. BioScience Trends. 2020;14(1):72-3.
- 102. Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. International Journal of Antimicrobial Agents. 20 March 2020. 105949.
- 103. Molina JM, Delaugerre C, Goff JL, Mela-Lima B, Ponscarme D, Goldwirt L, et al. No Evidence of Rapid Antiviral Clearance or Clinical Benefit with the Combination of Hydroxychloroquine and Azithromycin in Patients with Severe COVID-19 Infection. Médecine et Maladies Infectieuses. 30 March 2020.
- 104. World Health Organization (WHO). Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected Interim guidance (13 March 2020). Geneva: WHO; [17 January 2020]. Available from: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected

- 105. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. JAMA. 2020.
- 106. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, et al. The feasibility of convalescent plasma therapy in severe COVID-19 patients: a pilot study. medRxiv. 16 March 2020. 20036145.
- 107. U.S. Food & Drug Administration (FDA). Investigational COVID-19 Convalescent Plasma Emergency INDs: FDA; [6 April 2020]. Available from: https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds
- 108. European Medicines Agency (EMA). EMA gives advice on the use of non-steroidal anti-inflammatories for COVID-19. [cited 23 March 2020]. Available from: https://www.ema.europa.eu/en/news/ema-gives-advice-use-non-steroidal-anti-inflammatories-covid-19
- 109. European Medicines Agency (EMA). EMA advises continued use of medicines for hypertension, heart or kidney disease during COVID-19 pandemic. [5 April 2020]. Available from: https://www.ema.europa.eu/en/news/ema-advises-continued-use-medicines-hypertension-heart-kidney-disease-during-covid-19-pandemic
- 110. European Centre for Disease Prevention and Control (ECDC). Operational tool on rapid risk assessment methodology. Stockholm: ECDC; 2019 [6 April 2020]. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/operational-tool-rapid-risk-assessment-methodology-ecdc-2019.pdf
- 111. European Centre for Disease Prevention and Control (ECDC). Guidelines for the use of non-pharmaceutical measures to delay and mitigate the impact of 2019-nCoV. Stockholm: ECDC; 2020 [6 April 2020]. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/novel-coronavirus-guidelines-non-pharmaceutical-measures 0.pdf
- 112. European Centre for Disease Prevention and Control (ECDC). Outbreak of novel coronavirus disease 2019 (COVID-19): increased transmission globally fifth update, 2 March 2020. Stockholm: ECDC; [6 April 2020]. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/RRA-outbreak-novel-coronavirus-disease-2019-increase-transmission-globally-COVID-19.pdf
- 113. Davies A, Thompson K-A, Giri K, Kafatos G, Walker J, Bennett A. Testing the Efficacy of Homemade Masks: Would They Protect in an Influenza Pandemic? Disaster Medicine and Public Health Preparedness. 2013;7(4):413-8.
- 114. Rengasamy S, Eimer B, Shaffer RE. Simple Respiratory Protection—Evaluation of the Filtration Performance of Cloth Masks and Common Fabric Materials Against 20–1000 nm Size Particles. The Annals of Occupational Hygiene. 2010;54(7):789-98.
- 115. European Centre for Disease Prevention and Control (ECDC). Using face masks in the community. Stockholm: ECDC; 2020 [8 April 2020]. Available from: https://www.ecdc.europa.eu/en/publications-data/using-face-masks-community-reducing-covid-19-transmission
- 116. European Centre for Disease Prevention and Control (ECDC). Infection prevention and control in the household management of people with suspected or confirmed coronavirus disease (COVID-19). Stockholm: ECDC; [6 April 2020]. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/Home-care-of-COVID-19-patients-2020-03-31.pdf
- 117. European Centre for Disease Prevention and Control (ECDC). Resource estimation for contact tracing, quarantine and monitoring activities for COVID-19 cases in the EU/EEA Stockholm: ECDC; 2020. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/COVID-19-resources-for-contact-tracing-2-March-2020 0.pdf
- 118. COVID-19 Community Mobility Reports [6 April 2020]. Available from: https://www.google.com/covid19/mobility/
- 119. Jarvis C, van Zandvoort K, Gimma A, Prem K, Klepac P, Rubin G, et al. Impact of physical distance measures on transmission in the UK. 1 April 2020. medRxiv. Available from: https://www.medrxiv.org/content/10.1101/2020.03.31.20049023v1
- 120. Karako K, Song P, Chen Y, Tang W. Analysis of COVID-19 infection spread in Japan based on stochastic transition model. BioScience Trends. 2020.
- 121. Flaxman, S., Mishra, S., & Gandy, A. (2020). Estimating the number of infections and the impact of nonpharmaceutical interventions on COVID-19 in 11 European countries. Imperial College COVID-19 Response Team, 30. Available from https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/covid-19/report-13-europe-npi-impact/
- 122. Milne G, Xie S. The Effectiveness of Social Distancing in Mitigating COVID-19 Spread: a modelling analysis. Perth: University of Western Australia, 21 March 2020. medRxiv. Available from: https://www.medrxiv.org/content/10.1101/2020.03.20.20040055v1
- 123. Prem K, Liu Y, Russell T, Kucharski A, Eggo R, Davies N. The effect of control strategies to reduce social mixing on outcomes of the COVID-19 epidemic in Wuhan, China: a modelling study. Lancet Public Health. 25 March 2020.
- 124. Flaxman S, Mishra S, Gandy A, Unwin H, Coupland H, Mellan T, et al. Estimating the number of infections and the impact of non-pharmaceutical interventions on COVID-19 in 11 European countries London: Imperial Colleage London; [6 April 2020]. Available from: https://spiral.imperial.ac.uk:8443/handle/10044/1/77731
- 125. Liu P, Beeler P, Chakrabarty RK. COVID-19 Progression Timeline and Effectiveness of Response-to-Spread Interventions across the United States. medRxiv. 17 March 2020. 20037770.
- 126. Sjödin H, Wilder-Smith A, Osman S, Farooq Z, Rocklöv J. Only strict quarantine measures can curb the coronavirus disease (COVID-19) outbreak in Italy, 2020. Eurosurveillance. 2020;25(13):2000280.

- 127. DiGiovanni C, Conley J, Chiu D, Zaborski J. Factors Influencing Compliance with Quarantine in Toronto During the 2003 SARS Outbreak. Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science. 2004;2(4):265-72.
- 128. Barbera J, Macintyre A, Gostin L. Large-Scale Quarantine Following Biological Terrorism in the United States Scientific Examination, Logistic and Legal Limits, and Possible Consequences. JAMA. 2001;286(21):2711-7.
- 129. European Centre for Disease Prevention and Control (ECDC). Guidance on community engagement for public health events caused by communicable disease threats in the EU/EEA. Stockholm: ECDC; 2020 [5 April 2020]. Available from: https://www.ecdc.europa.eu/en/publications-data/guidance-community-engagement-public-health-events-caused-communicable-disease
- 130. The Guardian. 'Everything will be all right': message of hope spreads in Italy. 12 March 2020.
- 131. Anderson R, Heesterbeek H, Klinkenberg D, Hollingswort T. How will country-based mitigation measures influence the course of the COVID-19 epidemic? Lancet. 6 March 2020.
- 132. European Centre for Disease Prevention and Control (ECDC). Community and institutional public health emergency preparedness synergies enablers and barriers. Case studies on acute gastroenteritis in two EU/EEA Member States. Stockholm: ECDC; 2019 [6 April 2020]. Available from: https://www.ecdc.europa.eu/en/publications-data/community-and-institutional-public-health-emergency-preparedness-synergies
- 133. Brooks SK, Webster RK, Smith LE, Woodland L, Wessely S, Greenberg N, et al. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. The Lancet. 14 March 2020;395(10227):912-20.
- 134. DiGiovanni C CJ, Chiu D, Zaborski J. Factors Influencing Compliance with Quarantine in Toronto During the 2003 SARS Outbreak. Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science. 2004;2(4):265-72.
- 135. Dickerson D. Seven tips to manage your mental health and well-being during the COVID-19 outbreak. Nature; 26 March 2020. Available from: https://www.nature.com/articles/d41586-020-00933-5
- 136. Liu K. How I faced my coronavirus anxiety. Science. 2020;367(6484):1398.
- 137. Public Health England (PHE). Guidance on social distancing for everyone in the UK: Updated 20 March 2020 [5 April 2020]. Available from: https://www.gov.uk/government/publications/covid-19-guidance-on-social-distancing-for-everyone-in-the-uk-and-protecting-older-people-and-vulnerable-adults
- 138. Unadkat S, Farquhar M. Doctors' wellbeing: self-care during the covid-19 pandemic. BMJ. 2020;368:m1150.
- 139. Sprang G, Silman M. Posttraumatic Stress Disorder in Parents and Youth After Health-Related Disasters. Disaster Medicine and Public Health Preparedness. 2013;7(1):105-10.
- 140. TVNZ. Jacinda Ardern says Easter Bunny an essential worker, but warns it 'might not get everywhere this year'. Aukland [6 April 2020]. Available from: https://www.tvnz.co.nz/one-news/new-zealand/jacinda-ardern-says-easter-bunny-essential-worker-but-warns-might-not-get-everywhere-year
- 141. Greenberg N, Docherty M, Gnanapragasam S, Wessely S. Managing mental health challenges faced by healthcare workers during Covid-19 pandemic. BMJ. 2020;368:m1211.
- 142. European Centre for Disease Prevention and Control (ECDC). Guidance for health system contingency planning during widespread transmission of SARS-CoV-2 with high impact on healthcare services. Stockholm: ECDC; [6 April 2020]. Available from: https://www.ecdc.europa.eu/en/publications-data/guidance-health-system-contingency-planning-during-widespread-transmission-sars
- 143. Istituto Superiore di Sanità. Sorveglianza Integrata COVID-19 in Italia: AGGIORNAMENTO 22 marzo 2020 [cited 23 March 2020]. Available from: https://www.epicentro.iss.it/coronavirus/bollettino/Infografica 22marzo%20ITA.pdf
- 144. Klompas M, Morris CA, Sinclair J, Pearson M, Shenoy ES. Universal Masking in Hospitals in the Covid-19 Era. New England Journal of Medicine. 2020.
- 145. European Centre for Disease Prevention and Control (ECDC). Infection prevention and control and preparedness for COVID-19 in healthcare settings: Second update 31 March 2020. ECDC: Stockholm; 2020. [7 April 2020]. Available from: https://www.ecdc.europa.eu/en/publications-data/infection-prevention-and-control-and-preparedness-covid-19-healthcare-settings
- 146. European Centre for Disease Prevention and Control (ECDC). Personal protective equipment (PPE) needs in healthcare settings for the care of patients with suspected or confirmed novel coronavirus (2019-nCoV) 2020 [6 April 2020]. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/novel-coronavirus-personal-protective-equipment-needs-healthcare-settings.pdf
- 147. European Centre for Disease Prevention and Control (ECDC). Guidance for wearing and removing personal protective equipment in healthcare settings for the care of patients with suspected or confirmed COVID-19. Stockholm: ECDC; 2020 [8 March 2020]. Available from: https://www.ecdc.europa.eu/en/publications-data/guidance-wearing-and-removing-personal-protective-equipment-healthcare-settings
- 148. World Health Organization (WHO). Rational use of personal protective equipment for coronavirus disease 2019 (COVID-19): Interim guidance 27 February 2020. Geneva: WHO; 2020 [March 11 2020]. Available from: https://apps.who.int/iris/bitstream/handle/10665/331215/WHO-2019-nCov-IPCPPE use-2020.1-eng.pdf
- 149. World Health Organization (WHO). Infection prevention and control My 5 Moments for Hand Hygiene. Geneva: WHO; [1 March 2020]. Available from: https://www.who.int/infection-prevention/campaigns/clean-hands/5moments/en/

- 150. Lai S, Ruktanonchai NW, Zhou L, Prosper O, Luo W, Floyd JR, et al. Effect of non-pharmaceutical interventions for containing the COVID-19 outbreak: an observational and modelling study. medRxiv. 3 March 2020. 20029843.
- 151. World Health Organization (WHO). Non-pharmaceutical public health measures for mitigating the risk and impact of epidemic and pandemic influenza. Geneva: WHO; 2019 [1 March 2020]. Available from: https://apps.who.int/iris/bitstream/handle/10665/329438/9789241516839-eng.pdf?ua=1
- 152. World Health Organization (WHO). Home care for patients with suspected novel coronavirus (nCoV) infection presenting with mild symptoms and management of contacts. Interim guidance. Geneva: WHO; 2020 [updated January 2020, April 2020]. Available from: https://www.who.int/publications-detail/home-care-for-patients-with-suspected-novel-coronavirus-(ncov)-infection-presenting-with-mild-symptoms-and-management-of-contacts
- 153. European Centre for Disease Prevention and Control (ECDC). Guidance for discharge and ending isolation in the context of widespread community transmission of COVID-19 first update. [in press]. Stockholm: ECDC; 2020 [8 April 2020]. Available from: https://www.ecdc.europa.eu/en/publications-data/covid-19-guidance-discharge-and-ending-isolation
- 154. Centers for Disease Control and Prevention (CDC). Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease 2019 (COVID-19) 2020 [updated 25 February 2020; cited 1 March 2020]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html
- 155. Gossner O. "Group Testing against COVID-19," Working Papers 2020-02, Center for Research in Economics and Statistics. 2020 [5 April 2020]. Available from: https://ideas.repec.org/p/crs/wpaper/2020-02.html
- 156. Sinnott-Armstrong N, Klein D, Hickey B. Evaluation of Group Testing for SARS-CoV-2 RNA. medRxiv. 27 March 2020. 20043968.
- 157. World Health Organization (WHO). Population-based age-stratified seroepidemiological investigation protocol for COVID-19 virus infection Geneva: WHO; 2020 [6 April 2020]. Available from:

 https://www.who.int/publications-detail/population-based-age-stratified-seroepidemiological-investigation-protocol-for-covid-19-virus-infection
- 158. European Centre for Disease Prevention and Control (ECDC). Strategies for the surveillance of COVID-19, ECDC 2020 [in press]. Stockholm: ECDC; [8 April 2020]. Available from: https://www.ecdc.europa.eu/en/publications-data/strategies-surveillance-covid-19
- 159. World Health Organization (WHO). Laboratory testing for coronavirus disease 2019 (COVID-19) in suspected human cases: Interim guidance 19 March 2020. Geneva: WHO; 2020 [11 March 2020]. Available from: https://www.who.int/publications-detail/laboratory-testing-for-2019-novel-coronavirus-in-suspected-human-cases-20200117
- 160. European Centre for Disease Prevention and Control (ECDC). Laboratory support for COVID-19 in the EU/EEA. Stockholm: ECDC; [5 April 2020]. Available from: https://www.ecdc.europa.eu/en/novel-coronavirus/laboratory-support
- 161. European Commission (EC). COVID-19: EU recommendations for testing strategies. [6 April 2020]. Available from: https://ec.europa.eu/info/files/covid19 eu recommendations on testing strategies v2.pdf
- 162. World Health Organization (WHO). Laboratory testing strategy recommendations for COVID-19; Interim guidance 21 March 2020 Geneva: WHO; [6 April 2020]. Available from: https://apps.who.int/iris/bitstream/handle/10665/331509/WHO-COVID-19-lab_testing-2020.1-eng.pdf
- 163. World Health Organization (WHO). Coronavirus disease 2019 (COVID-19) Situation Report 62. Geneva: WHO; 2020 [23 March 2020]. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200322-sitrep-62-covid-19.pdf?sfvrsn=f7764c46 2
- 164. European Centre for Disease Prevention and Control (ECDC). Contact tracing: Public health management of persons, including healthcare workers, having had contact with COVID-19 cases in the European Union first update. Stockholm: ECDC; [8 April 2020]. Available from: https://www.ecdc.europa.eu/en/publications-data/contact-tracing-public-health-management-persons-including-healthcare-workers
- 165. World Health Organization (WHO). Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). Geneva: WHO; 2020 [6 April 2020]. Available from: https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf
- 166. Chen W, Wang Q, Li YQ, Yu HL, Xia YY, Zhang ML, et al. Early containment strategies and core measures for prevention and control of novel coronavirus pneumonia in China. Zhonghua yu fang yi xue za zhi [Chinese Journal of Preventive Medicine]. 2020;54(3):1.
- 167. Choe YJ. Coronavirus disease-19: Summary of 2,370 Contact Investigations of the First 30 Cases in the Republic of Korea. medRxiv. 15 March 2020. 20036350.
- 168. Ng Y, Li Z, Chua YX, Chaw WL, Zhao Z, Er B, et al. Evaluation of the effectiveness of surveillance and containment measures for the first 100 patients with COVID-19 in Singapore-January 2–February 29, 2020.
- 169. Bi Q, Wu Y, Mei S, Ye C, Zou X, Zhang Z, et al. Epidemiology and Transmission of COVID-19 in Shenzhen China: Analysis of 391 cases and 1,286 of their close contacts. medRxiv. 2020.
- 170. World Health Organization (WHO). About Go.Data Geneva: WHO; [7 April 2020]. Available from: https://www.who.int/godata/about
- 171. CNA938. Singapore launches TraceTogether mobile app to boost COVID-19 contact tracing efforts: CNA; 2020 [cited 23 March 2020]. Available from: https://www.channelnewsasia.com/news/singapore/covid19-trace-together-mobile-app-contact-tracing-coronavirus-12560616?fbclid=IwAR2apNBUi2CEME6coD0S_HuhU3i0WiOUDCq9h_6H2XMYPbueDa0rBumPvRM

- 172. Iceland Review. Icelanders Can Download App to Help With Coronavirus Contact Tracing. [7 April 2020]. Available from: https://www.icelandreview.com/sci-tech/icelanders-can-download-app-to-help-with-coronavirus-contact-tracing/
- 173. Ferretti L, Wymant C, Kendall M, Zhao L, Nurtay A, Abeler-Dörner L, et al. Quantifying SARS-CoV-2 transmission suggests epidemic control with digital contact tracing. Science. 2020:eabb6936.
- 174. Helse- og omsorgsdepartementet. Forskrift om digital smittesporing og epidemikontroll i anledning utbrudd av Covid-19. Oslo 2020 [6 April 2020]. Available from:

 https://www.regjeringen.no/contentassets/116076d9a39b473a97d97474048e1fb0/kgl.-res.-27.-mars-digital-smittesporing.pdf
- 175. TheJournal.ie. Covid-19: HSE says contact tracing app could be rolled out 'in the next 10 days': The Journal.ie; 2020 [6 April 2020]. Available from: https://www.thejournal.ie/coronavirus-contact-tracing-app-5061145-Mar2020/
- 176. Die Bundesregierung. Kontaktketten digital identifizieren: Die Bundesregierung; [6 April 2020]. Available from: https://www.bundesregierung.de/breg-de/themen/coronavirus/corona-app-1738516
- 177. Politico. Europe cracks code for coronavirus warning app: Politico; 2020 [6 April 2020]. Available from: https://www.politico.eu/pro/europe-cracks-code-for-coronavirus-warning-app/?utm source=POLITICO.EU&utm campaign=b2706a749e-EMAIL CAMPAIGN 2020 04 01 09 05&utm medium=email&utm term=0 10959edeb5-b2706a749e-190588771
- 178. European Centre for Disease Prevention and Control (ECDC). Laboratory support by specialised laboratories in the EU/EEA. Stockholm: ECDC; 2020 [updated 8 February 2020, 1 March, 2020]. Available from: https://www.ecdc.europa.eu/en/novel-coronavirus/laboratory-support
- 179. Fomsgaard AS, Rosenstierne MW. An alternative workflow for molecular detection of SARS-CoV-2 escape from the NA extraction kit-shortage. medRxiv. 27 March 2020. 20044495.
- 180. Gossner O, Gollier C. A temporary coronavirus testing fix: Use each kit on 50 people at a time: The Washington Post; 21 March 2020 [5 April 2020]. Available from: https://www.washingtonpost.com/outlook/2020/03/31/coronavirus-testing-groups/
- 181. World Health Organization (WHO). Guidance for laboratories shipping specimens to WHO reference laboratories that provide confirmatory testing for COVID-19 virus: Interim guidance, 31 March 2020. Geneva: ECDC; [5 April 2020]. Available from: https://apps.who.int/iris/bitstream/handle/10665/331639/WHO-2019-nCoV-laboratory_shipment-2020.3-eng.pdf
- 182. World Health Organization (WHO). Laboratory biosafety guidance related to coronavirus disease 2019 (COVID-19); Interim guidance 12 February 2020. Geneva: WHO; [11 March 2020]. Available from: https://apps.who.int/iris/bitstream/handle/10665/331138/WHO-WPE-GIH-2020.1-enq.pdf
- 183. World Health Organization (WHO). Operational considerations for COVID-19 surveillance using GISRS: Interim gudiance 26 March 2020. Geneva: WHO; [5 April 2020]. Available from: https://apps.who.int/iris/bitstream/handle/10665/331589/WHO-2019-nCoV-Leveraging GISRS-2020.1-eng.pdf
- 184. Amanat F, Nguyen T, Chromikova V, Strohmeier S, Stadlbauer D, Javier A, et al. A serological assay to detect SARS-CoV-2 seroconversion in humans. medRxiv. 17 March 2020. 20037713.
- 185. World Health Organization (WHO). Coronavirus disease (COVID-19) technical guidance: Early investigations protocols. Geneva: WHO; [5 April 2020]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/early-investigations
- 186. European Centre for Disease Prevention and Control (ECDC). An overview of the rapid test situation for COVID-19 diagnosis in the EU/EEA. 1 April 2020. Stockholm: ECDC; [5 April 2020]. Available from: https://www.ecdc.europa.eu/en/publications-data/overview-rapid-test-situation-covid-19-diagnosis-eueea#no-link
- 187. World Health Organization (WHO). Medical Product Alert N°3/2020: Falsified medical products, including in vitro diagnostics, that claim to prevent, detect, treat or cure COVID-19. Geneva: WHO; [5 April 2020]. Available from: https://www.who.int/news-room/detail/31-03-2020-medical-product-alert-n-3-2020
- 188. Liu P, Beeler P, Chakrabarty R. COVID-19 Progression Timeline and Effectiveness of Response-to-Spread Interventions across the United States. medRxiv. 2020.
- 189. Townsend M, Kassam A. "UK's Covid-19 lockdown could crumble as frustration grows, police warn." Observer. 2020.
- 190. Davies N, Kucharski A, Eggo R, Edmunds W. The effect of non-pharmaceutical interventions on COVID-19 cases, deaths and demand for hospital services in the UK: a modelling study. 2020. Available from: https://www.medrxiv.org/content/10.1101/2020.03.20.20040055v1
- 191. Russell T, Hellewell J, Abbott S, Jarvis C, van Zandvoort K, CMMID nCov working group, et al. Using a delay-adjusted case fatality ratio to estimate under-reporting. (This study has not yet been peer reviewed.) [7 April 2020]. Available from: https://cmmid.github.io/topics/covid19/severity/global cfr estimates.html
- 192. Alqahtani JS, Oyelade T, Aldhahir AM, Alghamdi SM, Almehmadi M, Alqahtani AS, et al. Prevalence, Severity and Mortality associated with COPD and Smoking in patients with COVID-19: A Rapid Systematic Review and Meta-Analysis. medRxiv. 25 March 2020. 20043745.
- 193. Jarvis CI, Van Zandvoort K, Gimma A, Prem K, Klepac P, Rubin GJ, et al. Quantifying the impact of physical distance measures on the transmission of COVID-19 in the UK. medRxiv. 31 March 2020. 20049023.
- 194. European Commission (EC). The EU's Response to COVID-19: European Commission; 2020 [11 March 2020]. Available from: https://ec.europa.eu/commission/presscorner/detail/en/qanda_20_307

- 195. European Commission (EC). Emergency coronavirus research: Commission selects 18th project to develop rapid diagnostics. [7 April 2020]. Available from: https://ec.europa.eu/info/news/emergency-coronavirus-research-commission-selects-18th-project-develop-rapid-diagnostics-2020-mar-31 en&pk campaign=whatsnew newsletter
- 31 en&pk campaign=whatsnew newsletter

 196. Dye C, Bartolomeos K, Moorthy V, Kieny P. Data sharing in public health emergencies: a call to researchers. Bull World Health Organ 2016;94:158. [6 April 2020]. Available from: https://www.who.int/bulletin/volumes/94/3/16-170860.pdf