CLAIM NO: FL-2020-000018

IN THE HIGH COURT OF JUSTICE
BUSINESS AND PROPERTY COURTS
COMMERCIAL COURT (QBD)
FINANCIAL LIST
FINANCIAL MARKETS TEST CASE SCHEME

BETWEEN

THE FINANCIAL CONDUCT AUTHORITY

Claimant

-and-

(1) ARCH INSURANCE (UK) LIMITED

(2) ARGENTA SYNDICATE MANAGEMENT LIMITED

(3) ECCLESIASTICAL INSURANCE OFFICE PLC

(4) HISCOX INSURANCE COMPANY LIMITED

(5) QBE UK LIMITED

(6) MS AMLIN UNDERWRITING LIMITED

(7) ROYAL & SUN ALLIANCE INSURANCE PLC

(8) ZURICH INSURANCE PLC

Defendants

AGREED FACTS – DOCUMENT 2

COVID-19 DISEASE

INTRODUCTION

1. The purpose of this document is to explain some of the basic characteristics of the coronavirus disease ("**COVID-19**"). The note reflects the parties' understanding of the position as at June 2020. The proposed agreed facts have been sourced from publicly available information which is referenced throughout. Therefore, whilst it is agreed that the references to publicly available material have been accurately reflected in this document, the parties make no admissions as to their correctness going beyond proceedings regarding the wordings relevant to these proceedings.

SECTION 1: BACKGROUND TO CORONAVIRUSES

2. Coronaviruses are a large family of viruses that are known to cause illness ranging from the common cold to more severe diseases.[1]

3. A virus that is transmitted from an animal to a human is known as a zoonotic virus. There have been two zoonotic coronaviruses that have emerged in the last twenty years, namely the Severe Acute Respiratory Syndrome ("**SARS-CoV-1**"), which caused an outbreak in 2003, and the Middle East Respiratory Syndrome ("**MERS-CoV**"), which caused an outbreak in 2012.[2]

SECTION 2: THE EMERGENCE OF SARS-COV-2

4. On 31 December 2019, the World Health Organization ("**WHO**") was informed of a cluster of cases of pneumonia of unknown cause detected in Wuhan City, Hubei Province, China.[3]

5. On 12 January 2020, it was announced that a novel coronavirus had been identified in samples obtained from cases and that initial analysis of virus genetic sequences suggested that this was the cause of the outbreak. This virus was named severe acute respiratory syndrome coronavirus 2 (**SARS-CoV-2**) and the associated disease is COVID-19.[4]

SECTION 3: CLINICAL CHARACTERISTICS OF COVID-19

6. Symptoms associated with the disease COVID-19 vary in severity from having no symptoms at all (being asymptomatic or pre-symptomatic) to having fever, cough, sore throat, general weakness and fatigue and muscular pain and in the most severe cases, severe pneumonia, acute respiratory distress syndrome, sepsis and septic shock, all

[1] WHO, "Q&A on coronaviruses", https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/q-a-coronaviruses **[AF-2 Bundle, p.1]**
[2] European Centre for Disease Prevention and Control, "Coronaviruses", https://www.ecdc.europa.eu/en/covid-19/latest-evidence/coronaviruses **[AF-2 Bundle, p.2]**
[3] Public Health England Guidance: "COVID-19: epidemiology, virology and clinical features", "1. Epidemiology", https://www.gov.uk/government/publications/wuhan-novel-coronavirus-background-information/wuhan-novel-coronavirus-epidemiology-virology-and-clinical-features **[AF-2 Bundle, p.6]**
[4] Public Health England Guidance: "COVID-19: epidemiology, virology and clinical features", "1. Epidemiology", https://www.gov.uk/government/publications/wuhan-novel-coronavirus-background-information/wuhan-novel-coronavirus-epidemiology-virology-and-clinical-features **[AF-2 Bundle, p.6]**

potentially leading to death. Common symptoms such as having fever, cough, sore throat, general weakness, fatigue, muscular pain and pneumonia are not unique to COVID-19 and may be symptoms of infection with a virus or pathogen other than SARS-CoV-2. Reports show that clinical deterioration in people infected with SARS-CoV-2 can occur rapidly, often during the second week of disease.[5]

7. The WHO reports that most people infected with SARS-CoV-2 will experience mild to moderate respiratory illness and recover without requiring special treatment. Older people, and those with underlying medical problems like cardiovascular disease, diabetes, chronic respiratory disease, and cancer are more likely to develop serious illness.[6]

8. Public Health England ("**PHE**") identifies the most common symptoms of COVID-19 as a new continuous cough, high temperature and a loss of, or change to, your sense of smell or taste. Some people may also experience muscle aches, tiredness and shortness of breath.[7]

9. Accurately estimating the case-fatality risk of those infected with SARS-CoV-2 is difficult. An article published on the centres for disease control and prevention website entitled "Case-Fatality Risk Estimates for COVID-19 Calculated by Using a Lag Time for Fatality" provides a case-fatality risk estimate within a broad range of 0.25-3%.[8] There may, however, be other studies which identify a different case-fatality rate for COVID-19.

SECTION 4: THE REPRODUCTION NUMBER OF SARS-COV-2

10. The reproduction number is the average number of secondary infections produced by 1 infected person (the "R" number).[9]

11. An R number of 1 means that on average every person who is infected will infect 1 other person, meaning the total number of new infections is stable. If R is 2, on average, each infected person infects 2 more people. If R is 0.5 then on average for each 2 infected people, there will be only 1 new infection. If R is greater than 1 the epidemic is growing, if R is less than 1 the epidemic is shrinking.[10]

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[5] European Centre for Disease Prevention and Control, "Q&A on COVID-19", https://www.ecdc.europa.eu/en/covid-19/questions-answers **[AF-2 Bundle, p.9]**

[6] WHO, Coronavirus, https://www.who.int/health-topics/coronavirus#tab=tab_1 **[AF-2 Bundle, p.16]**

[7] Public Health England: "Coronavirus (COVID-19) - what you need to know", https://publichealthmatters.blog.gov.uk/2020/01/23/wuhan-novel-coronavirus-what-you-need-to-know/. **[AF-2 Bundle, p.19]**

[8] Centres for Disease Control and Protection (**CDC**), "Case-Fatality Risk Estimates for COVID-19 Calculated by Using a Lag Time for Fatality", https://wwwnc.cdc.gov/eid/article/26/6/20-0320_article **[AF-2 Bundle, p.23]**

[9] UK Government Guidance, "The R number in the UK", https://www.gov.uk/guidance/the-r-number-in-the-uk **[AF-2 Bundle, p.27]**

[10] UK Government Guidance, "The R number in the UK", https://www.gov.uk/guidance/the-r-number-in-the-uk **[AF-2 Bundle, p.27]**

12. Absent mitigating measures, the mean R_0 number for SARS-CoV-2 (defined as average number of new infections generated by an infectious person in a totally naive population) has been estimated in an article published in the Journal of Travel Medicine to be 3.28 with a median of 2.79.[11]

SECTION 5: MODES OF TRANSMISSION

Symptomatic transmission

13. The WHO explains that people can catch SARS-CoV-2 from others who have the virus. SARS-CoV-2 spreads primarily from person to person through small droplets from the nose or mouth, which are expelled when a person with COVID-19 coughs, sneezes or speaks. These droplets are relatively heavy, do not travel far and quickly sink to the ground.[12]

14. People can become infected with SARS-CoV-2 if they breathe in or ingest these droplets from a person infected with the virus. These droplets can land on objects and surfaces around the person such as tables, doorknobs and handrails. People can become infected by touching these objects or surfaces, then touching their eyes, nose or mouth.[13]

15. Experimental studies show that the environmental stability of SARS-CoV-2 is:

    15.1 up to 3 hours in the air post aerosolisation;

    15.2 up to 4 hours on copper;

    15.3 up to 24 hours on cardboard; and

    15.4 up to 2–3 days on plastic and stainless steel, albeit with significantly decreased concentration.[14]

16. A recent publication also showed that the virus was more stable on smooth surfaces, with detection of infective virus on surgical mask material for up to 7 days.[15]

17. However, the amount of viable virus declines over time and may not always be present in sufficient quantity to cause infection.

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[11] Liu et al, "The reproductive number of COVID-19 is higher compared to SARS coronavirus", 13 February 2020, https://academic.oup.com/jtm/article/27/2/taaa021/5735319 **[AF-2 Bundle, p.31]**

[12] WHO, "Q&A on coronaviruses (COVID-19)", "How does COVID-19 spread?", https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/q-a-coronaviruses **[AF-2 Bundle, p.35]**

[13] WHO, "Q&A on coronaviruses (COVID-19)", "How does COVID-19 spread?", https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/q-a-coronaviruses **[AF-2 Bundle, p.36]**

[14] European Centre for Disease Prevention and Control, "Coronaviruses", https://www.ecdc.europa.eu/en/covid-19/latest-evidence/coronaviruses **[AF-2 Bundle, p.3]**

[15] European Centre for Disease Prevention and Control, "Coronaviruses", https://www.ecdc.europa.eu/en/covid-19/latest-evidence/coronaviruses **[AF-2 Bundle, p.3]**

18. A recent study by retired virologists from the US Army and the US Food and Drug Administration has shown that the virus may be inactivated by UV sunlight.[16] The FCA can agree this as a general point set out in the referenced article, but does not admit the extent or details of such inactivation, which it does not consider necessary for the test case.

Pre-symptomatic and asymptomatic transmission

19. The incubation period for SARS-CoV-2 (i.e. the time between exposure to the virus and onset of symptoms) is currently estimated to be between one and 14 days.[17]

20. The infectious period for SARS-CoV-2 may begin one to two days before symptoms appear, but people are likely most infectious during the symptomatic period, even if symptoms are mild and very non-specific. The infectious period is now estimated to last for 7-12 days in moderate cases and up to two weeks on average in severe cases.[18]

21. There is also some evidence suggesting that transmission can occur from a person that is infected even two days before showing symptoms; however, uncertainties remain about the effect of transmission through asymptomatic and pre-symptomatic persons.[19] Recent modelling suggests that asymptomatic individuals who, though not exhibiting symptoms, carry and can transmit the disease, might be major drivers for the growth of the COVID-19 pandemic.[20] Although transmission from asymptomatic carriers has been reported, the risk of transmission from pre-symptomatic or symptomatic patients is considered to be higher.[21] Transmission of SARS-Cov-2 through asymptomatic and pre-symptomatic individuals remains the subject of ongoing research.

22. It is generally accepted that a large proportion of persons infected with SARS-CoV-2 are asymptomatic. A recent scientific study found that asymptomatic persons accounted for approximately 40% to 45% of COVID-19 carriers.[22] The study refers to the *Diamond Princess* cruise ship which experienced an outbreak of COVID-19 on board, and notes that at the time of testing 46.5% of those returning positive results were asymptomatic.

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[16] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7300806/pdf/PHP-9999-na.pdf **[AF-2 Bundle, p.37, 39]**
[17] European Centre for Disease Prevention and Control, "Q&A on COVID-19", https://www.ecdc.europa.eu/en/covid-19/questions-answers **[AF-2 Bundle, p.8]**
[18] European Centre for Disease Prevention and Control, "Q&A on COVID-19", https://www.ecdc.europa.eu/en/covid-19/questions-answers **[AF-2 Bundle, p.8]**
[19] European Centre for Disease Prevention and Control, "Q&A on COVID-19", https://www.ecdc.europa.eu/en/covid-19/questions-answers **[AF-2 Bundle, p.8]**
[20] European Centre for Disease Prevention and Control, "Transmission of COVID-19", https://www.ecdc.europa.eu/en/covid-19/latest-evidence/transmission **[AF-2 Bundle, p.63]**
[21] European Centre for Disease Prevention and Control, "Transmission of COVID-19", https://www.ecdc.europa.eu/en/covid-19/latest-evidence/transmission **[AF-2 Bundle, p.63]**
[22] Daniel Oran and Eric Topol, 'Prevalence of Asymptomatic SARS-CoV-2 Infection', Annals of Internal Medicine, 3 June 2020 https://www.acpjournals.org/doi/10.7326/M20-3012 **[AF-2 Bundle, p.66]**

World Health Organization

< Go back to all Coronavirus disease 2019 Q&As

Q&A on coronaviruses (COVID-19)

17 April 2020 | Q&A

What is a coronavirus?

Coronaviruses are a large family of viruses which may cause illness in animals or humans. In humans, several coronaviruses are known to cause respiratory infections ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). The most recently discovered coronavirus causes coronavirus disease COVID-19.

What is COVID-19?

What are the symptoms of COVID-19?

What should I do if I have COVID-19 symptoms and when should I seek medical care?

How does COVID-19 spread?

European Centre for Disease Prevention and Control

Coronaviruses

General background

Coronaviruses (CoV) have been identified as human pathogens since the 1960s. They infect humans as well as a variety of animals, including birds and mammals.

Illness in humans is mostly respiratory or gastrointestinal infections, while symptoms can range from common cold to those of more severe lower respiratory infections [1]. Viral shedding occurs via these respiratory and digestive systems and transmission can occur through different routes: fomites, airborne or faecal-oral.

Coronaviruses are enveloped positive stranded RNA viruses in the order of *Nidovirales* [2]. With their characteristic surface, the virions have a crown-like appearance under the electron microscope, which is why the viruses are named after the Latin word corona, meaning 'crown' or 'halo'. The subfamily *Orthocoronavirinae* of the family *Coronaviridae* is further classified into four CoV genera: *Alpha-, Beta-, Delta-* and *Gammacoronavirus*. *Betacoronavirus* genus is further separated in five subgenera (*Embecovirus*, *Hibecovirus*, *Merbecovirus*, *Nobecovirus* and *Sarbecovirus*).

To date, seven coronaviruses have been shown to infect humans. Common human coronaviruses *Betacoronavirus* HCoV-OC43 and HCoV-HKU1 as well as *Alphacoronavirus* HCoV-229E cause common colds but also severe lower respiratory tract infections in the youngest and oldest age groups, while *Alphacoronavirus* HCoV-NL63 is considered to be an important cause of (pseudo) croup and bronchiolitis in children [3]. A broad range of coronaviruses are found in bats, which might play a crucial role in the virus evolution of *Alpha-* and *Betacoronavirus* lineages in particular. However, other animal species can also act as an intermediate host and animal reservoir.

In the last twenty years, two zoonotic coronaviruses have emerged SARS-CoV discovered in 2002, and belonging to *Betacoronavirus*, subgenus *Sarbecovirus*, and MERS-CoV discovered in 2012, and belonging to *Betacoronavirus*, subgenus *Merbecovirus*).Both have caused human outbreaks, the Severe Acute Respiratory Syndrome (SARS) in 2003 and the Middle East Respiratory Syndrome (MERS) since 2012. In late 2019, a third novel coronavirus initially related to a cluster of pneumonia cases in Wuhan, China, was identified and named as SARS-CoV-2. This new coronavirus is closely related to SARS-CoV and genetically clusters within *Betacoronavirus* subgenus *Sarbecovirus* [4,5]. Based on a modelling study, SARS-CoV-2 could become the fifth endemic human coronavirus [6].

SARS-CoV-2 virus evolution

Over 35 000 genome sequences have been deposited in the GISAID EpiCoV database as of 29 May 2020 (www.gisaid.org (http://www.gisaid.org/)). A meta-analysis of different estimates of the time to the last common ancestor of the virus indicates that the pandemic started sometime between 6 October and 11 December 2019 [7]. The original animal reservoir of the virus was most likely bats, and an intermediate animal host could have been involved in the transmission to humans [8-11]. From the genomic evidence it is unlikely that the virus is a product of in-vitro manipulation, passaging in cell-culture, or that it is of synthetic origin [12,13].

There are several proposed nomenclature systems for assigning a label to SARS-CoV-2 strains based on their genetic characteristics; including the GISAID [14], Nextstrain [15] and Pangolin [16] nomenclatures. The GISAID and Nextstrain nomenclatures use the term clades for their assigned labels while the Pangolin nomenclature, which has higher level of resolution than the other two, uses the term lineages.

There is currently very limited 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 or transmissibility. The frequency of the variant of the virus that carries a substitution from aspartate to glycine at position 614 in the spike glycoprotein has increased in the GISAID sequence database over time and with sequences reported from all parts of the world. Some preliminary reports based on the genomic data suggested that this mutation could affect the transmissibility of the virus [17,18], but there is still no supporting evidence to strengthen this hypothesis [19].

Mutations in the receptor-binding domain of the spike glycoprotein are of interest as they may affect infectivity and host-specificity [20]. Some mutations in this domain have been reported [21], but these have so far been rare and are not present in any of the major SARS-CoV-2 clades. Other mutations that could be of potential interest are those that have occurred independently several times, but preliminary findings show that none of these mutations provide any fitness advantage [22].

Mutations in primer binding sites for published reverse transcription polymerase chain reaction (RT-PCR) detection assays have so far been rare. These mutations are shown in the ECDC Primerscan tool [23].

SARS-CoV-2 virus seasonality

The transmission dynamic of SARS-CoV-2 depends on a number of factors, including the timing and extent of implementation of control measures, duration of host immunity to SARS-CoV-2, cross-immunity between SARS-CoV-2 and other human coronaviruses, and the strength of seasonal forcing on transmission. Analyses of the early phase of the pandemic suggested that temperature, and relative and absolute humidity were associated with transmission intensity of SARS-CoV-2 [24-29]. These studies suggested that cold and dry weather conditions could favour the transmission of SARS-CoV-2.

SARS-CoV-2 might display seasonal patterns similar to those of other human coronaviruses with peak incidence in winter months. However, it remains to be seen if weather factors, such as higher temperature, higher humidity or more UV, will supress the transmissibility of SARS-CoV-2 during summer months in temperate regions of the northern hemisphere. Modelling of the SARS-CoV-2 transmission dynamic using known characteristics of other human coronaviruses suggests that a possible decrease during the summer would not prevent substantial outbreaks if no control measures are in place [6].

Population immunity might be a more important determinant of transmission while climate would affect the timing and extent of transmission, at least at the early phase of the pandemic. Once the virus is established in human populations, climatic factors will then likely define the seasonality of endemic cycles by latitude [30].

SARS-CoV-2 survival in the environment

Recent publications have evaluated the survival of SARS-CoV-2 on different surfaces. The environmental stability of viable SARS-CoV-2 is up to 3 hours in the air post aerosolisation, up to 4 hours on copper, up to 24 hours on cardboard, and up to 2–3 days on plastic and stainless steel, albeit with significantly decreased titres [31]. These findings are comparable with the results obtained for environmental stability of SARS-CoV-1. However, as these are results from experimental studies, they do not directly translate to fomite infectivity in the real life situations [31].

The virus has been shown to be more stable on smooth surfaces, with detection of infective virus on surgical mask material for up to 7 days [32]. In vitro tests showed that in transport medium, the virus is stable at 4 degrees Celsius (C) but sensitive at higher temperatures. At 4 degrees C, the virus was stable up to 14 days, but inactivated after 5 minutes at 70 degrees C [32]. In addition, with the exception of a 5-min incubation with hand soap, no infectious virus could be detected after a 5-min incubation at room temperature (22°C), in contact with the usual disinfectants such as household bleach, 70% ethanol etc.[32].

Various levels of environmental contamination have been described in rooms of COVID-19 patients. No air samples were positive in these studies, but one sample from an air exhaust outlet was positive indicating, according to the authors, that virus particles may be displaced by air and deposited on surfaces [33,34].

In a study of environmental contamination in a Chinese hospital during the COVID-19 outbreak, SARS-CoV-2 was detected in environmental samples from intensive care units (ICU) dedicated to COVID-19 care, a COVID-19-dedicated obstetric isolation ward, and a COVID-19-dedicated isolation ward [35]. SARS-CoV-2 was also detected on objects such as the self-service printers used by patients to self-print the results of their exams, desktop keyboards and doorknobs [35]. Virus was detected most commonly on gloves (15.4% of samples) but rarely on eye protection devices (1.7%) [35]. This evidence indicates that fomites may play a role in transmission of SARS-CoV-2 but the relative importance of this route of transmission compared to direct exposure to respiratory droplets is still unclear.

Currently there are no data on the survival of SARS-CoV-2 in seawater, but a dilution effect will contribute to decreasing the viral load and salinity may contribute to viral inactivation, as it occurs with similar viruses. Survival of the novel coronavirus is expected to be higher in the untreated water of rivers, lakes and freshwater pools, in comparison with survival in swimming pools and the sea as the presence of viral inhibitors such as salinity and chlorine is less expected, and if present, the concentration is expected to be lower[36,37].

Viral RNA of SARS-CoV-2 has been detected by quantitative RT-PCR methodology in wastewater in a number countries, including Belgium, the Netherlands, Sweden, and the United States [38-41]. These RNA fragments are assumed to originate from symptomatic, pre-symptomatic or asymptomatic individuals that shed the virus into the wastewater. Positive test results from wastewater were obtained after the diagnosis of a COVID-19 patient in the community of the catchment area of a sewer treatment plant [38]. More recently, COVID-19 RNA was identified in wastewater prior to the first diagnosis of a COVID-19 patient in the community of the catchment area [38]. Whether these RNA fragments constitute infectious virus particles that would result in faecal-oral transmission has not been documented to date. The risk of viable virus may not be high since wastewater originating directly from households contains detergents and soap, which would quickly inactivate SARS-CoV-2. Moreover, once the wastewater reaches the sewer treatment plant, the purification processes are designed to inactivate any remaining pathogens, such as bacteria and viruses. The remaining water effluent is discharged and sewage sludge is discharged or processed (see below). Internationally, no drinking water source, even from reclaimed water, has detected SARS-CoV-2 and WHO considers the risk of drinking water contamination small [42].

References

Supporting document: List of references ▸ (https://www.ecdc.europa.eu/sites/default/files/documents/References-DiseaseBackground-COVID-19-2020-06-11.pdf)

Coronavirus (/en/search?f%5B0%5D=diseases%3A2943) | COVID-19 (/en/search?f%5B0%5D=diseases%3A2942) | Public health threat (/en/search?f%5B0%5D=public_health_areas%3A1583)

Page last updated 11 Jun 2020

GOV.UK

1. Home (https://www.gov.uk/)
2. Coronavirus (COVID-19) (https://www.gov.uk/coronavirus-taxon)
3. COVID-19: background information (https://www.gov.uk/government/publications/wuhan-novel-coronavirus-background-information)

1. Public Health England (https://www.gov.uk/government/organisations/public-health-england)

Guidance

COVID-19: epidemiology, virology and clinical features

Updated 1 July 2020

Contents

This publication is available at https://www.gov.uk/government/publications/wuhan-novel-coronavirus-background-information/wuhan-novel-coronavirus-epidemiology-virology-and-clinical-features

Latest updates to this information

1 July 2020: updated with latest global case numbers.

1. Epidemiology

On 31 December 2019, the World Health Organization (WHO) was informed of a cluster of cases of pneumonia of unknown cause (http://www.who.int/csr/don/05-january-2020-pneumonia-of-unkown-cause-china/en/) detected in Wuhan City, Hubei Province, China.

On 12 January 2020 (http://www.who.int/csr/don/12-january-2020-novel-coronavirus-china/en/), it was announced that a novel coronavirus had been identified in samples obtained from cases and that initial analysis of virus genetic sequences suggested that this was the cause of the outbreak. This virus is referred to as SARS-CoV-2 (https://www.biorxiv.org/content/10.1101/2020.02.07.937862v1), and the associated disease as COVID-19.

As of 1 July 2020 (10:00am CET), over 10.4 million cases have been diagnosed globally with more than 511,000 fatalities. In the 14 days to 1 July, more than 2.3 million cases were reported (European Centre for Disease Prevention and Control, situation update worldwide (https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases)).

The WHO coronavirus dashboard (https://who.sprinklr.com/) has country by country information. WHO also publishes a daily international situation report (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/).

The total number of confirmed cases in the UK (https://www.gov.uk/guidance/coronavirus-covid-19-information-for-the-public) is published by the Department of Health and Social Care, and is available in a visual dashboard (https://coronavirus.data.gov.uk/).

2. Virology

Coronaviruses are a large family of viruses with some causing less severe disease, such as the common cold, and others causing more severe disease, such as Middle East respiratory syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) coronaviruses.

2.1 Nomenclature and characterisation

On 11 February, WHO (https://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020) named the syndrome caused by this novel coronavirus COVID-19 (https://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020) (Coronavirus Disease 2019) using its best practice guidance (https://www.who.int/topics/infectious_diseases/naming-new-diseases/en/).

The Coronavirus Study Group (CSG) of the International Committee on Taxonomy of Viruses (https://www.biorxiv.org/content/10.1101/2020.02.07.937862v1) designated the aetiological agent 'severe acute respiratory syndrome coronavirus 2' (SARS-CoV-2). Characterisation of SARS-CoV-2 is ongoing. The virus belongs to a group of genetically related coronaviruses that includes SARS-CoV and viruses isolated from bat populations. MERS-CoV also belongs to this group but is less closely related.

3. Transmission

The source of the outbreak has yet to be determined. A zoonotic source to the outbreak has not been identified yet, but investigations are ongoing.

According to current evidence, SARS-CoV-2 is primarily transmitted between people through respiratory droplets and contact routes. Airborne transmission is possible in specific settings in which procedures or support treatments that generate aerosols are performed.

At the moment, human-to-human transmission is occurring extensively. Hence, precautions to prevent human-to-human transmission are appropriate for both suspected and confirmed cases (see infection prevention and control guidance (https://www.gov.uk/government/publications/wuhan-novel-coronavirus-infection-prevention-and-control)).

In addition to respiratory secretions, SARS-CoV-2 has been detected in blood, faeces and urine.

4. Clinical features

COVID-19 presents with a range of symptoms of varying severity. Asymptomatic infection also occurs often although frequency is not defined.

More common symptoms are fever, a new and continuous cough, shortness of breath, fatigue, loss of appetite, anosmia (loss of smell) and ageusia (loss of taste). Non-specific symptoms include shortness of breath, fatigue, loss of appetite, myalgia, sore throat, headache, nasal congestion, diarrhoea, nausea and vomiting.

Atypical symptoms, such as delirium and reduced mobility, can present in older and immunocompromised people, often in the absence of a fever.

Of people who develop symptoms, current data indicate that 40% have mild symptoms without hypoxia (problems with the level of oxygen in the blood) or pneumonia, 40% have moderate symptoms and non-severe pneumonia, 15% have significant disease including severe pneumonia, and 5% experience critical disease with life-threatening complications.

Critical disease includes acute respiratory distress syndrome (ARDS), sepsis, septic shock, cardiac disease, thromboembolic events, such as pulmonary embolism and multi-organ failure.

Evidence is growing that the longer-term consequences of more severe complications associated with the inflammatory response may be considerable in those who experience critical and life-threatening illness. Rare neurological and psychiatric complications, which can also occur in patients without respiratory symptoms, include stroke, meningo-encephalitis, delirium, encephalopathy, anxiety, depression and sleep disturbances.

Risk of severe disease and death is higher in people who are older, male, from deprived areas or from certain non-white ethnicities. Certain underlying health conditions (https://www.gov.uk/government/publications/staying-alert-and-safe-social-distancing/staying-alert-and-safe-social-distancing#clinically-vulnerable-people), as well as obesity, increase risk in adults.

Infants and children generally appear to experience milder symptoms than adults and further evidence is needed about the association between underlying conditions and risk of COVID-19 disease in children. A rare presentation of multisystem inflammatory syndrome temporarily associated with COVID-19 in children and adolescents (https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19) has been noted.

Public Health England has issued guidance on the investigation and initial clinical management of possible cases (https://www.gov.uk/government/publications/wuhan-novel-coronavirus-initial-investigation-of-possible-cases).

4.1 Reference for section 4

WHO Clinical management of COVID-19 (https://www.who.int/publications/i/item/clinical-management-of-covid-19), published 27 May 2020.

European Centre for Disease Prevention and Control

Q & A on COVID-19

Questions and answers

1. What is SARS-CoV-2? What is COVID-19?

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is the name given to the 2019 novel coronavirus. COVID-19 is the name given to the disease associated with the virus. SARS-CoV-2 is a new strain of coronavirus that has not been previously identified in humans.

(/en/publications-data/covid-19-what-we-know)
Data
Video on COVID-19: What we know
Video - 1 Mar 2020

2. Where do coronaviruses come from?

Coronaviruses are viruses that circulate among animals with some of them also known to infect humans.

Bats are considered natural hosts of these viruses yet several other species of animals are also known to act as sources. For instance, Middle East Respiratory Syndrome Coronavirus (MERS-CoV) is transmitted to humans from camels, and Severe Acute Respiratory Syndrome Coronavirus-1 (SARS-CoV-1) is transmitted to humans from civet cats. More information on coronaviruses can be found in the disease background of COVID-19.

(/en/covid-19/latest-evidence)
Latest evidence on COVID-19

3. Is this virus comparable to SARS or to the seasonal flu?

The novel coronavirus detected in China in 2019 is closely related genetically to the SARS-CoV-1 virus. SARS emerged at the end of 2002 in China, and it caused more than 8 000 cases in 33 countries over a period of eight months. Around one in ten of the people who developed SARS died.

As of 24 April 2020, the COVID-19 outbreak had caused over 2 668 000 cases worldwide since the first case was reported in China in January 2020. Of these, more than 190 000 are known to have died.

See the situation updates for the latest available information.

(/en/cases-2019-ncov-eueea)
COVID-19 situation update for the EU/EEA and the UK, as of 3 July 2020

(/en/geographical-distribution-2019-ncov-cases)
COVID-19 situation update worldwide, as of 3 July 2020

While the viruses that cause both COVID-19 and seasonal influenza are transmitted from person-to-person and may cause similar symptoms, the two viruses are very different and do not behave in the same way.

ECDC estimates that between 15 000 and 75 000 people die prematurely due to causes associated with seasonal influenza infection each year in the EU, the UK, Norway, Iceland and Liechtenstein. This is approximately 1 in every 1 000 people who are infected. Despite the relatively low mortality rate for seasonal influenza, many people die from the disease due to the large number of people who contract it each year. The concern about COVID-19 is that, unlike influenza, there is no vaccine and no specific treatment for the disease. It also appears to be more transmissible than seasonal influenza. As it is a new virus, nobody has prior immunity, which means that the entire human population is potentially susceptible to SARS-CoV-2 infection.

4. What is the mode of transmission? How (easily) does it spread?

While animals are believed to be the original source, the virus spread is now from person to person (human-to-human transmission). There is not enough epidemiological information at this time to determine how easily this virus spreads between people, but it is currently estimated that, on average, one infected person will infect between two and three other people.

The virus seems to be transmitted mainly via small respiratory droplets through sneezing, coughing, or when people interact with each other for some time in close proximity (usually less than one metre). These droplets can then be inhaled, or they can land on surfaces that others may come into contact with, who can then get infected when they touch their nose, mouth or eyes. The virus can survive on different surfaces from several hours (copper, cardboard) up to a few days (plastic and stainless steel). However, the amount of viable virus declines over time and may not always be present in sufficient numbers to cause infection.

The incubation period for COVID-19 (i.e. the time between exposure to the virus and onset of symptoms) is currently estimated to be between one and 14 days.

We know that the virus can be transmitted when people who are infected show symptoms such as coughing. There is also some evidence suggesting that transmission can occur from a person that is infected even two days before showing symptoms; however, uncertainties remain about the effect of transmission by asymptomatic persons.

5. When is a person infectious?

The infectious period may begin one to two days before symptoms appear, but people are likely most infectious during the symptomatic period, even if symptoms are mild and very non-specific. The infectious period is now estimated to last for 7-12 days in moderate cases and up to two weeks on average in severe cases.

6. How severe is COVID-19 infection?

Preliminary data from the EU/EEA (from the countries with available data) show that around 20-30% of diagnosed COVID-19 cases are hospitalised and 4% have severe illness. Hospitalisation rates are higher for those aged 60 years and above, and for those with other underlying health conditions.

Medical information

1. What are the symptoms of COVID-19 infection

Symptoms of COVID-19 vary in severity from having no symptoms at all (being asymptomatic) to having fever, cough, sore throat, general weakness and fatigue and muscular pain and in the most severe cases, severe pneumonia, acute respiratory distress syndrome, sepsis and septic shock, all potentially leading to death. Reports show that clinical deterioration can occur rapidly, often during the second week of disease.

Recently, anosmia – loss of the sense of smell – (and in some cases the loss of the sense of taste) have been reported as a symptom of a COVID-19 infection. There is already evidence from South Korea, China and Italy that patients with confirmed SARS-CoV-2 infection have developed anosmia/hyposmia, in some cases in the absence of any other symptoms.

2. Are some people more at risk than others?

Elderly people above 70 years of age and those with underlying health conditions (e.g. hypertension, diabetes, cardiovascular disease, chronic respiratory disease and cancer) are considered to be more at risk of developing severe symptoms. Men in these groups also appear to be at a slightly higher risk than females.

See links to national guidelines on the treatment of patients with serious and life threatening conditions during COVID-19 under external resources (https://www.ecdc.europa.eu/en/novel-coronavirus-china/sources-updated)

3. Are children also at risk of infection and what is their potential role in transmission?

Children make up a very small proportion of reported COVID-19 cases, with about 1% of all cases reported being under 10 years, and 4% aged 10-19 years. Children appear as likely to be infected as adults, but they have a much lower risk than adults of developing symptoms or severe disease. There is still some uncertainty about the extent to which asymptomatic or mildly symptomatic children transmit disease.

4. What is the risk of infection in pregnant women and neonates?

There is limited scientific evidence on the severity of illness in pregnant women after COVID-19 infection. It seems that pregnant women appear to experience similar clinical manifestations as non-pregnant women who have progressed to COVID-19 pneumonia and to date (as of 25 March), there have been no maternal deaths, no pregnancy losses and only one stillbirth reported. No current evidence suggests that infection with COVID-19 during pregnancy has a negative effect on the foetus. At present, there is no evidence of transmission of COVID-19 from mother to baby during pregnancy and only one confirmed COVID-19 neonatal case has been reported to date.

ECDC will continue to monitor the emerging scientific literature on this question, and suggests that all pregnant women follow the same general precautions for the prevention of COVID-19, including regular handwashing, avoiding individuals who are sick, and self-isolating in case of any symptoms, while consulting a healthcare provider by telephone for advice.

5. Is there a treatment for the COVID-19 disease?

There is no specific treatment or vaccine for this disease.

Healthcare providers are mostly using a symptomatic approach, meaning they treat the symptoms rather than target the virus, and provide supportive care (e.g. oxygen therapy, fluid management) for infected persons, which can be highly effective.

In severe and critically ill patients, a number of drugs are being tried to target the virus, but the use of these need to be more carefully assessed in randomised controlled trials. Several clinical trials are ongoing to assess their effectiveness but results are not yet available.

As this is a new virus, no vaccine is currently available. Although work on a vaccine has already started by several research groups and pharmaceutical companies worldwide, it may be many months or even more than a year before a vaccine has been tested and is ready for use in humans.

6. When should I be tested for COVID-19?

Current advice for testing depends on the stage of the outbreak in the country or area where you live. Testing approaches will be adapted to the situation at national and local level. National authorities may decide to test only subgroups of suspected cases based on the national capacity to test, the availability of necessary equipment for testing, the level of community transmission of COVID-19, or other criteria.

As a resource conscious approach, ECDC has suggested that national authorities may consider prioritising testing in the following groups:

- hospitalised patients with severe respiratory infections;
- symptomatic healthcare staff including those with mild symptoms;
- cases with acute respiratory infections in hospital or long-term care facilities;
- patients with acute respiratory infections or influenza-like illness in certain outpatient clinics or hospitals;
- elderly people with underlying chronic medical conditions such as lung disease, cancer, heart failure, cerebrovascular disease, renal disease, liver disease, diabetes, and immunocompromising conditions.

7. Where can I get tested?

If you are feeling ill with COVID-19 symptoms (such as fever, cough, difficulty breathing, muscle pain or general weakness), it is recommended that you contact your local healthcare services online or by telephone. If your healthcare provider believes there is a need for a laboratory test for the virus that causes COVID-19, he/she will inform you of the procedure to follow and advise where and how the test can be performed.

8. Do persons suffering from pollen allergy or allergies in general have a higher risk to develop severe disease when having COVID-19?

A large proportion of the population (up to 15-20%) reports seasonal symptoms related to pollen, the most common of which include itchy eyes, nasal congestion, runny nose and sometimes wheezing and skin rash. All these symptoms are usually referred to as hay fever, pollen allergy or more appropriately allergic rhinitis. Allergic rhinitis is commonly associated with allergic asthma in children and adults.

Allergies, including mild allergic asthma, have not been identified as a major risk factor for SARS-CoV-2 infection or for a more unfavourable outcome in the studies available so far. Moderate to severe asthma on the other hand, where patients need treatment daily, is included in the chronic lung conditions that predispose to severe disease.

Children and adults on maintenance medication for allergies (e.g. leukotriene inhibitors, inhaled corticosteroids and/or bronchodilators) need to continue their treatment as prescribed by their doctor and should not discontinue their medication due to fears of COVID-19. If they develop symptoms compatible with COVID-19, they will need to self-isolate, inform their doctor and monitor their health as everyone else. If progressive difficulty breathing develops, they should seek prompt medical assistance.

9. How can we differentiate between hay fever/pollen allergy related respiratory symptoms and COVID-19 infection?

Many people with COVID-19 have mild, flu-like symptoms (see above question 1), which are rather common and need to be distinguished from similar symptoms caused by common cold viruses and from allergic symptoms during springtime.

The following table presents a comparison of the most common symptoms of all three conditions according to their reported frequency.

It is good to bear in mind that the definitive diagnosis of COVID-19 is not clinical, but through laboratory testing of a sample from the nose or mouth.

Table: comparison of common symptoms between common cold, hay fever and COVID-19

Illness	Common cold	Hay fever (pollen allergy)	COVID-19
Fever	± Sometimes usually <38.5°C	No	+++ Yes, (maybe high grade)
Cough	+ Sometimes	± Sometimes	+++ Yes, persistent dry cough
Runny/stuffy nose	++ Yes	+++ Yes	± Sometimes
Sneezing	++ Yes	+++ Yes	± Sometimes
Headache	+ Yes	+ Yes	+++ Yes
Myalgia	No	No	++ Yes
Anosmia (loss of smell)	± Sometimes	± Sometimes	± Sometimes
Conjunctivitis	± Sometimes, depends on the virus	+++ Yes	++ Yes
Skin rash	No	++ Yes	No
Fatigue	± Sometimes	± Sometimes	+++ Yes
Difficulty breathing	No	± Sometimes, esp. if allergic asthma	++ Yes, in moderate to severe cases accounting for about 20% of infected
N/V/D	No	No	± Sometimes
Relieved by antihistamines	+ Antihistamines are included in OTC cold medications to relieve runny nose	+++ Yes	No

Table: comparison of common symptoms between common cold, hay fever and COVID-19

10. Should people who suffer from pollen allergy self-isolate if they develop typical hay fever symptoms?

No, there is no more reason for people suffering from pollen allergy to self-isolate if they develop their typical hay-fever symptoms than for anyone else. They should continue following the general guidance for physical distancing and seek medical advice if their symptoms get worse, if they develop fever or progressive difficulty breathing.

Prevention

1. How can I avoid getting infected?

The virus enters your body via your eyes, nose and/or mouth, so it is important to avoid touching your face with unwashed hands.

Washing of hands with soap and water for at least 20 seconds, or cleaning hands thoroughly with alcohol-based solutions, gels or tissues is recommended in all settings. It is also recommended to stay one metre or more away from people infected with COVID-19 who are showing symptoms, to reduce the risk of infection through respiratory droplets.

(/en/publications-data/video-covid-19-how-wash-your-hands)
Data
Video on COVID-19: How to wash your hands?
Video - 20 Mar 2020

(/en/publications-data/video-covid-19-5-ways-help-prevent-spread)
Data
Video on COVID-19: 5 ways to help prevent the spread
Video - 16 Mar 2020

2. How can I avoid infecting others?

- Cough or sneeze into your elbow or use a tissue. If you use a tissue, dispose of it carefully after a single use
- Wash your hands with soap and water for at least 20 seconds.
- Stay one metre or more away from people to reduce the risk of spreading the virus through respiratory droplets.

If you feel unwell, stay at home. If you develop any symptoms suggestive of COVID-19, you should immediately call your healthcare provider for advice.

3. What is physical distancing and why and how should I do it?

Physical distancing aims to reduce physical contact between potentially infected people and healthy people, or between population groups with high rates of transmission and others with low or no level of transmission. The objective of this is to decrease or interrupt the spread of COVID-19.

Note that the term 'physical distancing' means the same thing as the widely used term 'social distancing', but it more accurately describes what is intended, namely that people keep *physically* apart. It is possible that physical distancing measures will have to be implemented over an extended period, and their success depends partially on ensuring that people maintain *social* contact – from a distance – with friends, family and colleagues. Internet-based communications and the phone are therefore key tools for ensuring a successful physical distancing strategy.

On a personal level, you can perform physical distancing measures by:

- Voluntarily self-isolating if you know you have the virus that causes COVID-19, or if you have suggestive respiratory symptoms, or if you belong to a high-risk group (i.e. you are aged 70 years or more, or you have an underlying health condition).

Many countries in the EU/EEA and the UK have installed quarantine and social/physical distancing as measures to prevent the further spread of the virus.

These measures can include:

- The full or partial closure of educational institutions and workplaces;
- Limiting the number of visitors and limiting 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 buildings or residential areas;
- Internal or external border closures;
- Stay-at-home restrictions for entire regions or countries.

(/en/publications-data/video-covid-19-why-social-distancing-important)
Data
Video on COVID-19: Why social distancing is important
Video - 18 Mar 2020

(/en/publications-data/video-covid-19-stay-home-importance-social-distancing)
Data
Video on COVID-19: Stay at home! The importance of social distancing
Video - 17 Mar 2020

4. What should I do if I develop symptoms of COVID-19?

Follow the guidelines of the public health authorities in your area on the steps to take or call the local COVID-19 helpline.

5. Are face masks effective in protecting against COVID-19?

If you are infected, the use of surgical face masks may reduce the risk of you infecting other people. On the other hand there is *no evidence* that face masks will effectively prevent you from becoming infected with the virus. In fact, it is possible that the use of face masks may even increase the risk of infection due to a false sense of security and increased contact between hands, mouth and eyes while wearing them. The inappropriate use of masks also may increase the risk of infection.

6. Is there a vaccine against the virus?

There are currently no vaccines against human coronaviruses, including the virus that causes COVID-19. This is why it is very important to prevent infection and to take measures to contain further spread of the virus.

7. How long will it take to develop a vaccine?

The development of vaccines take time. Several pharmaceutical companies and research laboratories are working on vaccine candidates. It will, however, take many months or even years before any vaccine can be widely used, as it needs to undergo extensive testing in clinical trials to determine its safety and efficacy. These clinical trials are an essential precursor to regulatory approval and usually take place in three phases. The first, involving a few dozen healthy volunteers, tests the vaccine for safety, monitoring for adverse effects. The second, involving several hundred people, usually in a part of the world badly affected by the disease, looks at how effective the vaccine is in the field, and the third does the same in several thousand people.

8. Am I protected against COVID-19 if I had the influenza vaccine this year?

Influenza and the virus that causes COVID-19 are two very different viruses and the seasonal influenza vaccine will not protect against COVID-19.

What is the current situation in the EU regarding COVID-19?

1. What is the situation in Europe at the moment?

The COVID-19 pandemic is posing an unprecedented threat to the EU/EEA countries and the UK, which have been experiencing widespread transmission of the virus in the community for several weeks. In addition, there has been an increasing number of reports of COVID-19 outbreaks in long-term care homes across Europe with high associated mortality, highlighting the extreme vulnerability of the elderly in this setting.

The absence of an effective treatment or a vaccine combined with an exponential growth in infections from late February led many countries to implement non-pharmaceutical interventions such as “stay-at-home” policies (recommended or enforced), jointly with other community and physical distancing measures such as the cancellation of mass gatherings, closure of educational institutions and public spaces.

2. How are countries in the EU/EEA and the UK responding to COVID-19?

The outbreak of COVID-19 in the EU/EEA and the UK has evolved dramatically, and many countries have moved to a scenario of sustained community transmission with large numbers of cases infected. The rapid escalation of cases in countries such as Italy and Spain has placed an enormous pressure on the healthcare system and this has been a major challenge for local services. All countries in the EU have responded to the emerging situation through implementation of a comprehensive package of measures including surveillance, testing, case management and strategies to mitigate the impact of the pandemic such as physical distancing measures.[

3. How prepared is Europe for COVID-19?

The outbreak of COVID-19 has evolved dramatically in the EU/EEA and the UK. The rapid escalation of cases in several countries has placed enormous pressure on healthcare systems, and presented a major challenge for local services. All countries in the EU have responded to the emerging situation. The situation continues to evolve and lessons are still being learnt and countries are working hard to adapt their response to the ever changing situation.

4. What is the EU doing?

The European Centre for Disease Prevention and Control (ECDC) is in continuous contact with the European Commission and the World Health Organization (WHO) regarding the assessment of this outbreak.

To inform the European Commission and the public health authorities in Member States of the ongoing situation, ECDC publishes daily updates and continuously assesses the risk for EU citizens. ECDC and WHO develop technical guidance to support countries in their response. The European Commission is ensuring the coordination of risk management activities at EU level.

(/en/cases-2019-ncov-eueea)
COVID-19 situation update for the EU/EEA and the UK, as of 3 July 2020 ›

(/en/geographical-distribution-2019-ncov-cases)
COVID-19 situation update worldwide, as of 3 July 2020 ›

(https://qap.ecdc.europa.eu/public/extensions/COVID-19/COVID-19.html)
Situation dashboard - COVID-19 cases in Europe and worldwide

The European Commission is organising regular coordination meetings between the Ministers of the Member States and providing some support for overcoming the equipment and supplies shortages that are being felt in many countries.

5. When can we return to normal?

The stay-at-home and physical distancing measures that have been imposed throughout the EU/EEA and the UK are highly disruptive to society, both economically and socially, and there is very wide agreement that they should be lifted as soon as it is safe to do so. However, lifting the measures too early or too quickly carries the risk of a rapid return to high infection rates, and this could overwhelm the health system while causing high levels of illness and many deaths. The Joint European Roadmap towards lifting COVID-19 containment measures addresses this issue by providing the framework for an economic and social recovery plan for the EU alongside a set of public health principles that are aimed at minimising the risk of a resurgence in the number of cases. Should a resurgence occur, the stay-at-home and physical distancing measures may need to be put in place again.

It is increasingly recognised that we will be living with COVID-19 for many months, or even years. This disease will continue to affect our lives for some time to come, and we all need to prepare mentally for that.

6. Am I at risk of contracting COVID-19 infection in the EU?

This outbreak is evolving rapidly. ECDC is continuously assessing the risk for EU citizens and the risk assessment is changing accordingly. As this is a new virus, most people do not have any immunity that can safeguard against infection.

You can find the latest information in the daily situation update and the regular ECDC risk assessment.

(/en/current-risk-assessment-novel-coronavirus-situation)
Risk assessment on COVID-19, 11 June 2020 ›

(/en/cases-2019-ncov-eueea)
COVID-19 situation update for the EU/EEA and the UK, as of 3 July 2020 ›

(/en/geographical-distribution-2019-ncov-cases)
COVID-19 situation update worldwide, as of 3 July 2020 ›

(https://qap.ecdc.europa.eu/public/extensions/COVID-19/COVID-19.html)
Situation dashboard - COVID-19 cases in Europe and worldwide

7. How many people have been infected in the EU/EEA?

COVID-19 is spreading rapidly worldwide, and the number of cases in Europe is increasing exponentially in many affected areas.

See the ECDC daily situation update for the latest available numbers.

(/en/cases-2019-ncov-eueea)
COVID-19 situation update for the EU/EEA and the UK, as of 3 July 2020 ›

8. How long will this outbreak last? When will we see the peak?

As greater evidence emerges regarding the nature of the virus and the effectiveness of measures used to control the outbreak, predictions relating to the future course of COVID-19 will become more reliable.

9. Should schools and day care centres be closed?

The evidence we have to date indicates that COVID-19 does not cause serious illness in children – not nearly as much as it does for adults. However, they can still be infected, though the extent to which children play a role in the transmission of the virus to others is still uncertain. Therefore, as one of several measures to limit the possible spread of the virus, most EU/EEA countries and the UK have closed some or all schools and day care centres. However, school closures may have an impact on availability of healthcare staff and other essential services, due to the need for having to care for their children when not in school, which needs to be taken into consideration (e.g. some countries only maintain schooling for these children of staff in a critical role). Also, if grandparents are asked to care for the children, the benefits of lower transmission between children might be offset by transmission into a more vulnerable population group.

Following a reduction in the virus transmission, several countries (e.g., Austria, Denmark, Germany, Italy, Norway, Slovenia) have now started to ease some of the measures they have had in place, including by re-opening primary schools and day care centres. If the virus starts to spread again once these measures are lifted, it is possible that schools may have to be closed again for a period of time.

10. Where can I learn more about the situation and the guidelines from my country?

Each EU/EEA country and the UK have dedicated websites with information for the public on COVID-19 and on the national situation.

Consult with your national authorities to get advice tailored for your setting.

(/en/COVID-19/national-sources)
National information resources on COVID-19 ›

COVID-19 and travel

1. What are the travel restrictions in the European Union?

Travel has been shown to facilitate the spread of COVID-19 from affected to unaffected areas. Travel and trade restrictions during a public health event of international concern (PHEIC) are regulated under the International Health Regulations (IHR), part III.

On 16 March, in an effort to slow the spread of the coronavirus, the European Union leaders agreed to a temporary restriction on non-essential travel from third countries into the EU area by closing its borders for the next 30 days staring on 17 March 2020. On 8 April, the Commission invited Member States and non-EU Schengen countries to extend the temporary restrictions on non-essential travel to the EU until 15 May. The temporary travel restriction foresees exemptions for nationals of all EU Member States and Schengen Associated States (Iceland, Liechtenstein, Norway and Switzerland; whilst UK nationals are still to be treated in the same way as EU citizens until end 2020), for the purposes of returning to their homes. Exceptions are also foreseen for travellers with an essential function or need.

In addition, most EU countries have also applied national borders closure and/or border checks and travel and transport restrictions or bans within their national borders and between different regions as a measure to slow the spread. See the measures implemented by EU Member States.

Mobility measures implemented or announced by Member States (https://ec.europa.eu/transport/coronavirus-response_en)

Many EU countries have also encouraged their citizens to return home (with recommendations for 14 days self-quarantine upon return) but also recommended that travellers avoid non-essential travels to areas with transmission of COVID-19.

2. What precautions should I take if I need to travel?

Travellers should adhere to strict hygiene measures, wash hands with soap and water regularly, and/or use alcohol-based hand sanitisers. Touching the face with unwashed hands should be avoided. Travellers should avoid contact with sick persons, in particular those with respiratory symptoms and fever. It should be emphasised that older people and those with underlying health conditions should take these precautionary measures very seriously. Travellers who develop any symptoms during or after travel should self-isolate; those developing acute respiratory symptoms within 14 days upon return should be advised to seek immediate medical advice, ideally by phone first to their national healthcare provider.

3. What is the risk of infection when travelling by plane?

The risk of being infected on an airplane cannot be excluded, but is currently considered to be low for an individual traveller. The risk of being infected in an airport is similar to that of any other place where many people gather. If it is established that a COVID-19 case has been on an airplane, other passengers who were at risk (as defined by how near they were seated to the infected passenger) will be contacted by public health authorities. Should you have questions about a flight you have taken, please contact your local health authority for advice.

The European Union Aviation Safety Agency (EASA) has recommended measures to be taken by national authorities, such as thorough disinfecting and cleaning of aircraft after each flight serving high-risk destinations. EASA also recommended that airlines operating on all routes step up the frequency of cleaning, disinfect as a preventative measure and ensure full disinfection of any aircraft which has carried a passenger who was suspected or confirmed as being infected with COVID-19. Airport operators should similarly disinfect terminals regularly.

4. Why are people not being checked for COVID-19 at the airport when arriving from areas of local or community transmission?

There is evidence that checking people at the airport by reading their skin temperature (known as entry screening) is not very effective in preventing the spread of the virus, especially when people do not have symptoms. It is generally considered more useful to provide those arriving at airports with clear information explaining what to do if they develop symptoms after arrival.

COVID-19 and sport

1. What is the risk of getting COVID-19 while exercising?

Exercising poses a potential risk from SARS-CoV-2 infection to athletes and coaches. This is particularly an issue in settings where athletes train in groups, engage in contact sports, share equipment or use common areas, including locker rooms. Community and individual-level recreational sport activities could also potentially heighten the risk of spreading coronavirus. Transmission could occur through person-to-person contact, exposure to a common source, or aerosols/droplets from an infected individual. Nevertheless, in light of the benefits of regular physical activity to physical and mental health it is important to remain active during the COVID-19 pandemic while respecting physical distancing and personal hygiene recommendations.

COVID-19 and postal packages

1. What is the risk of getting COVID-19 from packages delivered through the postal system?

A recent study published by The New England Journal of Medicine (NEJM) reported that the causal agent of COVID-19 (SARS-CoV-2) is able to persist for up to 24 hours on cardboard, in experimental settings (e.g. controlled relative humidity and temperature). In practice however there is no evidence of the infection ever being transmitted through contaminated packages that are exposed to different environmental conditions and temperatures.

2. Are people working in the supply chain including logistics, control services, retail, etc. at risk of getting COVID-19 by handling packages? What measures can be taken to reduce the risk of getting infected in this type of work setting?

People working in the supply chain, including logistics, control services, retail, etc. are not at greater risk of getting COVID-19 as a result of managing and handling packages. ECDC does not recommend any special measures at the supply chain over and above those addressed to the general public: frequent and thorough hand washing and use of alcohol-based hand disinfectants, keeping a distance from other employees, and not working if showing signs of respiratory symptoms.

3. Are couriers at risk of getting COVID-19 by handling packages? What measures can be taken to reduce the risk of getting infected in this type of work setting?

People working as couriers are not at greater risk of getting COVID-19 as a result of managing and handling packages. Couriers delivering packages at homes are advised to keep a distance from the customer, use alcohol-based hand disinfectant frequently (and always before and after contact with a customer), and avoid working if showing signs of respiratory symptoms.

COVID-19 and cash

1. What is the risk of coins and banknotes to be contaminated with SARS-CoV-2?

Like any other object, coins and banknotes can be potentially contaminated with SARS-CoV-2. A study by van Doremalen et al. published by The New England Journal of Medicine reported that the environmental stability of the causal agent of COVID-19 (i.e. SARS-CoV-2) is up to four hours on copper, up to 24 hours on cardboard, and up to two to three days on stainless steel, albeit with significantly decreased titres. A pre-printed publication by Chin et al. describes detectable levels of infectious virus recovered from banknotes up to two days after inoculation and up to four days on stainless steel. These findings resulted from experiments in a controlled environment and should be interpreted with caution when translated to a real-life environment. In summary, it is possible that SARS-CoV-2 survives on banknotes and coins in real-life conditions; depending on the material properties end environmental conditions, contamination may persist for a variable period of time.

2. What is the risk of getting COVID-19 from coins and banknotes?

There is currently no evidence to confirm or rule out that SARS-CoV-2 can be transmitted through coins or banknotes. Just like doorknobs and handrails in public places, coins and banknotes are touched by a large number of people. Thorough hand washing with soap and water or use of alcohol-based hand sanitisers – especially before eating, drinking or smoking – and avoidance of touching the face, eyes and mouth is recommended after physical contact with frequently touched objects, including banknotes and coins.

COVID-19 and food

1. What is the risk of COVID-19 infection from food products imported from affected areas?

There has been no report of transmission of COVID-19 via food, and therefore there is no evidence that food items imported into the European Union in accordance with the applicable animal and public health regulations pose a risk for the health of EU citizens in relation to COVID-19. The main mode of transmission is from person to person.

COVID-19 and animals

1. What is the risk of COVID-19 infection from animals or animal products imported from affected areas?

There is no evidence that any of the animals or animal products authorised for entry into the European Union pose a risk to the health of EU citizens as a result of the presence of COVID-19.

2. What is the risk of COVID-19 infection from contact with pets and other animals in the EU?

Current research links COVID-19 to certain types of bat as the original source, but does not exclude the involvement of other animals. Several types of coronaviruses can infect animals and can be transmitted to other animals and people. There is no evidence that companion animals (e.g. dogs or cats) pose a risk of infection to humans, however there have been reports of pet dogs and pet cats that have had positive swabs. It appears likely that they were infected by their owners or some other person who had COVID-19. As a general precaution, it is always wise to observe basic principles of hygiene when in contact with animals.

Coronavirus (/en/search?f%5B0%5D=diseases%3A2943) | COVID-19 (/en/search?f%5B0%5D=diseases%3A2942) | Public health threat (/en/search?f%5B0%5D=public_health_areas%3A1583) | Scientific advice (/en/search?f%5B0%5D=public_health_areas%3A1592)

Page last updated 24 Apr 2020

All updates on the outbreak

(/en/publications-data/rapid-risk-assessment-resurgence-reported-cases-covid-19)

Publication

Rapid Risk Assessment: Resurgence of reported cases of COVID 19 in the EU/EEA, the UK and EU candidate and potential candidate countries ›

Risk assessment - 2 Jul 2020

(/en/publications-data/download-todays-data-geographic-distribution-covid-19-cases-worldwide)
Data
Download today's data on the geographic distribution of COVID-19 cases worldwide
Table - 3 Jul 2020

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World Health Organization

There is a current outbreak of Coronavirus (COVID-19) disease Find out more →

Coronavirus

Overview More

Coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus.

Most people infected with the COVID-19 virus will experience mild to moderate respiratory illness and recover without requiring special treatment. Older people, and those with underlying medical problems like cardiovascular disease, diabetes, chronic respiratory disease, and cancer are more likely to develop serious illness.

The best way to prevent and slow down transmission is be well informed about the COVID-19 virus, the disease it causes and how it spreads. Protect yourself and others from infection by washing your hands or using an alcohol based rub frequently and not touching your face.

The COVID-19 virus spreads primarily through droplets of saliva or discharge from the nose when an infected person coughs or sneezes, so it's important that you also practice respiratory etiquette (for example, by coughing into a flexed elbow).

At this time, there are no specific vaccines or treatments for COVID-19. However, there are many ongoing clinical trials evaluating potential treatments. WHO will continue to provide updated information as soon as clinical findings become available.

Stay informed:

- Protect yourself: advice for the public
- Myth busters
- Questions and answers
- Situation reports
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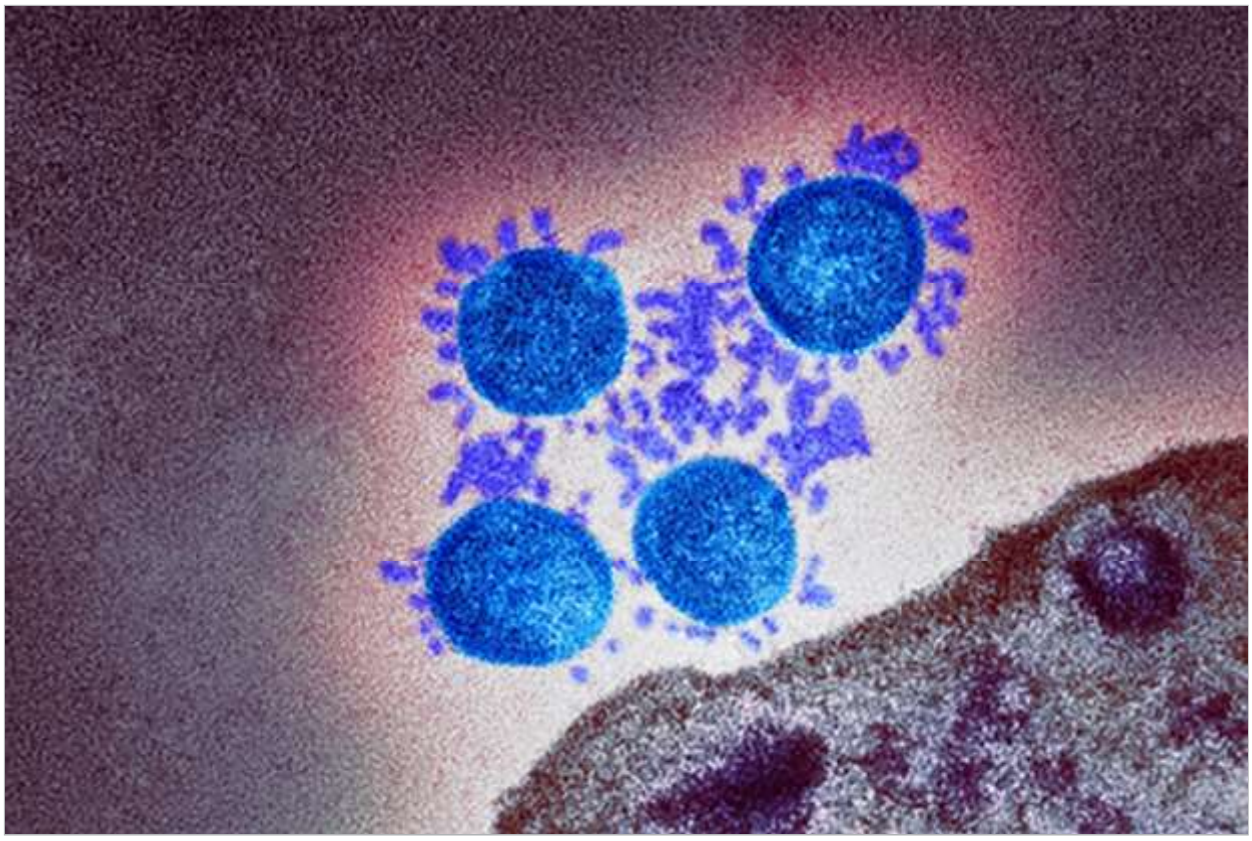
Coronavirus (COVID-19) - what you need to know

Blog Editor, 23 January 2020 - Coronavirus (COVID-19), Global health, Health Protection



Coloured transmission electron micrograph (TEM) of a SARS-CoV-2 coronavirus particle isolated from a UK case of the disease Covid-19.

Updated 3 July 2020

On Monday 11th May, the Government set out a roadmap for how and when the UK will adjust its response to the COVID-19 crisis.

In this blog we'll answer some of the questions many people have. We'll update this blog as new information becomes available.

Please note we cannot answer any questions that relate to individual health concerns.

What is coronavirus and should I be concerned?

A coronavirus is a type of virus. As a group, coronaviruses are common across the world.

Generally, coronavirus can cause more severe symptoms in people with weakened immune systems, older people, and those with long term conditions like diabetes, cancer and chronic lung disease.

What are the signs and symptoms of this new virus?

The most common symptoms of this new coronavirus (COVID-19) are:

- a new continuous cough
- high temperature
- a loss of, or change to, your sense of smell or taste.

Some people may also experience muscle aches, tiredness and shortness of breath.

How does this new coronavirus spread?

The main route of transmission is from cough and sneeze droplets. These droplets fall on people in the vicinity and can be directly inhaled or picked up on the hands and transferred when someone touches their face.

How long any respiratory virus survives will depend on a number of factors; for example:

- what surface the virus is on
- whether it is exposed to sunlight
- differences in temperature and humidity
- exposure to cleaning products

Under most circumstances, the amount of infectious virus on any contaminated surfaces is likely to have decreased significantly by 24 hours, and even more so by 48 hours.

Am I allowed to leave my house?

From 4 July, new changes on lockdown measures, announced by the Prime Minister on 23 June, come into place. All the information on this can be found in the full guidance.

The measures that have been eased mean you can now meet in groups of up to two households (your support bubble counts as one household) in any location, indoors or outdoors. You can see different households at different times and you can stay overnight in another household – but it is still important that family and friends meeting up keep their distance, and stay two metres apart.

More shops and public venues will start to open, you can go out to eat in a restaurant, grab a drink at your local pub, stay at a hotel or campsite, visit a library, attend a place of worship, get your haircut and go to an outdoor playground or an outdoor gym.

What can I do to make sure I don't catch coronavirus?

Here are our top 5 tips to make sure you and your family can stay safe while getting on with day to day activities:

1. Keep your distance from people outside your household and try and stay two metres apart at all times.
2. Continue to wash your hands well and regularly for 20 seconds, use sanitiser when outside your home and avoid touching your face.
3. Avoid crowded spaces and plan ahead when you can to avoid travelling on public transport at peak times.
4. Wearing a face covering is now compulsory on public transport and, if you can, wear one in other enclosed public spaces, such as shops. Read our advice on how to wear and make your own face covering at home.
5. And if you go to the pub, have fun but be sensible; show respect for others, follow the advice, and don't do anything that puts you or other people at risk.

How many cases do we have in the UK?

As of 9am 2 July, there have been 9,914,663 tests, with 252,084 tests on 1 July. 283,757 people have tested positive. As of 5pm on 1 July, of those tested positive for coronavirus, across all settings, 43,995 have sadly died.

We will update these figures daily.

How do I apply for a coronavirus test?

As part of the government's 5-pillar strategy for coronavirus testing (https://www.gov.uk/government/publications/coronavirus-covid-19-scaling-up-testing-programmes), people who have coronavirus-like symptoms are being tested to see if they currently have the virus.

You can ask for a test:

- for yourself, if you have coronavirus symptoms now (a high temperature, a new, continuous cough, or a loss or change to your sense of smell or taste)
- for someone you live with, if they have coronavirus symptoms

You can also apply for a test if you have a clinical referral from NHS 111 online.

What is NHS Test and Trace?

The NHS test and trace service:

- ensures that anyone who develops symptoms of coronavirus (COVID-19) can quickly be tested to find out if they have the virus, and also includes targeted asymptomatic testing of NHS and social care staff and care home residents
- helps trace close recent contacts of anyone who tests positive for coronavirus and, if necessary, notifies them that they must self-isolate at home to help stop the spread of the virus

We are introducing this service to help return life more to normal, in a way that is safe and protects our NHS and social care. The service will allow us to trace the spread of the virus and isolate new infections and play a vital role in giving us early warning if the virus is increasing again, locally or nationally.

Can I travel abroad?

The Foreign & Commonwealth Office (FCO) advises British people against all non-essential travel worldwide. This applies for an indefinite period (https://www.gov.uk/government/news/foreign-office-steps-up-plans-to-bring-home-britons-stranded-overseas) due to unprecedented international border closures and other restrictions. All countries may restrict travel without notice.

If your travel is essential, see the guidance on international travel (https://www.gov.uk/guidance/coronavirus-covid-19-essential-international-travel-guidance).

When you return, you must follow the rules for entering the UK (https://www.gov.uk/uk-border-control). You must:

- provide your journey and contact details (https://www.gov.uk/provide-journey-contact-details-before-travel-uk) up to 48 hours before you're due to arrive in the UK
- not leave the place you're staying for the first 14 days you're in the UK except in very limited situations (known as 'self-isolating'). See the guidance for England (https://www.gov.uk/government/publications/coronavirus-covid-19-how-to-self-isolate-when-you-travel-to-the-uk/coronavirus-covid-19-how-to-self-isolate-when-you-travel-to-the-uk), Scotland (https://www.gov.scot/publications/coronavirus-covid-19-public-health-checks-at-borders/pages/overview/), Wales (https://gov.wales/how-self-isolate-when-you-travel-wales-coronavirus-covid-19) and Northern Ireland (https://www.nidirect.gov.uk/articles/coronavirus-covid-19-travel-advice)

Read the Foreign & Commonwealth Office's travel advice page for more information.

Is hand sanitiser effective?

The best way to protect yourself from infections like coronavirus is to regularly wash your hands with soap and water. If soap or water aren't available and your hands are visibly clean, then sanitiser gel can be used. But proper hand washing is the most effective method and this should be your first choice.

Should people wear face masks to protect themselves from infection?

Face masks play a very important role in clinical settings, such as hospitals but there's very little evidence of widespread benefit from their use outside of these clinical settings. Facemasks must be worn correctly, changed frequently, removed properly and disposed of safely in order to be effective.

Should I wear a face covering?

Face coverings offer minimal benefit to the wearer, but may help you protect others and reduce the spread of the disease if you are suffering from coronavirus but not showing any symptoms.

Consider wearing a face covering if you have to use public transport to get to work, or are visiting a busy enclosed space where you can't social distance such as a crowded shop.

From 15 June, face coverings will be required while using public transport in England.

See our guidance for instructions on making your own face covering at home.

How do we know if the virus is evolving?

PHE has used whole genome sequencing to sequence the viral genome from the first two positive cases in this country and has made the sequence available to the scientific community. Our findings are consistent with viral genomes sequenced in China, and we are not seeing changes that suggest the virus has evolved in the last month.

What advice have professional groups being given?

We have produced a range of advice for health professionals and other organisations such as schools and businesses. This is all available on gov.uk

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Case-Fatality Risk Estimates for COVID-19 Calculated by Using a Lag Time for Fatality

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DOI: https://doi.org/10.3201/eid2606.200320

We estimated the case-fatality risk for coronavirus disease cases in China (3.5%); China, excluding Hubei Province (0.8%); 82 countries, territories, and areas (4.2%); and on a cruise ship (0.6%). Lower estimates might be closest to the true value, but a broad range of 0.25%–3.0% probably should be considered.

The coronavirus disease (COVID-19) is spreading globally; as of March 5, 2020, cases were reported in China and 85 other countries, territories, and areas (*1*). Disease severity is a particularly crucial parameter for understanding this new disease (*2*), but accurately estimating the case-fatality risk is difficult because milder cases are not being diagnosed and death is delayed.

We used data from the World Health Organization (WHO) (*1*) to calculate crude estimates of the case-fatality risk on March 5, 2020, for 4 populations: China; China, excluding Hubei Province; a group of 82 countries, territories, and areas; and passengers and crew of a cruise ship (Table 1). However, given the critical need to consider time lags to death when calculating case-fatality risk (*3*), we used time lags from a recent study from China (*4*). Yang et al. (*4*) reported that the median time from symptom onset to radiological confirmation of pneumonia was 5 days (interquartile range [IQR] 3–7 days); from symptom onset to intensive care unit (ICU) admission was 11 days (IQR 7–14 days); and from ICU admission to death was 7 days (IQR 3–11 days). Therefore, a median of 13 days passed from pneumonia confirmation to death ([11–5] + 7 = 13).

For our calculation, we assumed that the day of radiological confirmation of pneumonia approximately equated to the reporting date for laboratory-confirmed cases of COVID-19 to WHO. We obtained cumulative COVID-19 case counts reported by WHO on February 21 (*5*), which was 13 days before March 5, the date we used for calculating the crude case-fatality risk. Our approach is broadly comparable to a study that used earlier data to estimate the median time delay of 13 days from illness onset to death (*6*).

By using the number of cumulative cases on February 21 as the denominator for the adjusted case-fatality risk (aCFR), we assumed that half of the additional cumulative reported deaths on March 5 could be matched with cases reported on February 21. We acknowledge our approach is fairly simplistic and that it can be superseded when higher quality cohort-based analyses become available.

The case-fatality risks, when adjusted for a 13-day lag time from reporting to death, were 3.5% in China; 0.8% in China, excluding Hubei Province; 4.2% in the group of 82 countries, territories, and areas; and 0.6% for the cruise ship (Table). Our result for China, excluding Hubei Province, is similar to a previous estimate of 0.9% (95% CI 0.6%–1.3%) by using a time-delay adjusted case-fatality risk for the same area (K. Mizumoto and G. Chowell, unpub. data; https://www.medrxiv.org/content/10.1101/2020.02.19.20025163v1).

Table. Crude and adjusted estimates of case-fatality risk for COVID-19 in 4 populations*

Location	Cumulative deaths†	Cumulative confirmed cases†	Crude CFR, %	Adjusted deaths‡	Adjusted cumulative confirmed cases‡	Adjusted CFR, % (95% CI)§
China¶	3,015	80,565	3.74	2,627	75,569	3.48 (3.35–3.61)
China, excluding Hubei Province#	113	13,099	0.86	104	12,907	0.81 (0.67–0.98)
82 countries, territories, and areas**	27	2,285	1.18	15	354	4.24 (2.58–6.87)
Cruise ship	6	706	0.85	4	634	0.63 (0.25–1.61)

*CFR, case-fatality risk; COVID-19, coronavirus disease.
†Calculated by using data on laboratory-confirmed COVID-19 cases reported by the World Health Organization on March 5, 2020 (*1*).
‡Calculated by using cumulative confirmed cases as of February 21, 2020.
§Calculated using OpenEpi v3 (http://www.openepi.com) by using the Score (Wilson) method.
¶Includes Hong Kong, Macau, and Taiwan.
#We excluded Hubei Province because COVID-19 appears to have originated in this province and cases might have been missed because of shortages of appropriate diagnostic tests or health system overload.
**Includes 82 countries, territories, and areas outside of China and reporting cases on March 5, 2020; excludes areas with >500 cases (i.e., Italy, Iran, and South Korea) because of the possibility of uncontrolled spread and missed diagnoses in these localities.

Of our results, the least generalizable might be the result for China, which could be elevated because of undiagnosed mild cases, initial shortages of test kits, and elevated risk for death due to initial high demands on the healthcare system in Wuhan. The aCFR for the group of 82 countries, territories, and areas also might be affected by missed mild cases if some of the areas had undetected transmission. In terms of undiagnosed mild cases, the aCFR for the cruise ship population likely is the most accurate even though the 95% CI is broad. In addition, the aCFR for the cruise ship had a higher denominator due to inclusion of asymptomatic test-positive cases. Among 3,711 crew and passengers, 255 asymptomatic cases were identified (*7*); some of these persons subsequently might have developed symptoms. Thus, the aCFR for the cruise ship partially could reflect an infection-fatality risk. Also of note, 2,165 persons on the cruise ship were ≥60 years of age (*7*), and data from China indicates a much higher case-fatality risk among this age group (*8*); thus, a higher case-fatality risk might be expected in the cruise ship population than in other communities sampled. Considering these issues of generalizability, the aCFR of 0.8% for China, excluding Hubei Province, might be most accurate.

Nevertheless, given the residual uncertainties, health sector decision-makers and disease modelers probably should consider a broad range of 0.25%–3.0% for COVID-19 case-fatality risk estimates. The higher values could be more appropriate in resource poor settings where the quality of hospital and intensive care might be constrained. Higher values might also be appropriate in high-income countries with limited surge capacity in hospital services because elevated case-fatality risks could be seen at the peak of local epidemics. Because COVID-19 is expected to further spread globally, ongoing work using country-specific cohorts will be needed to more robustly clarify the case-fatality risk of this new disease.

This report was done as part of work for the New Zealand Ministry of Health (contract and funding support pending at the time of submission).

About the Author

Dr. Wilson is a professor of public health at the University of Otago, New Zealand. He has a long-standing research interest in historical and contemporary pandemics.

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Serial Interval of COVID-19 among Publicly Reported Confirmed Cases

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We estimate the distribution of serial intervals for 468 confirmed cases of coronavirus disease reported in China as of February 8, 2020. The mean interval was 3.96 days (95% CI 3.53–4.39 days), SD 4.75 days (95% CI 4.46–5.07 days); 12.6% of case reports indicated presymptomatic transmission.

DOI: https://doi.org/10.3201/eid2606.200357

Key aspects of the transmission dynamics of coronavirus disease (COVID-19) remain unclear (*1*). The serial interval of COVID-19 is defined as the time duration between a primary case-patient (infector) having symptom onset and a secondary case-patient (infectee) having symptom onset (*2*). The distribution of COVID-19 serial intervals is a critical input for determining the basic reproduction number (R_0) and the extent of interventions required to control an epidemic (*3*).

To obtain reliable estimates of the serial interval, we obtained data on 468 COVID-19 transmission events reported in mainland China outside of Hubei Province during January 21–February 8, 2020. Each report consists of a probable date of symptom onset for both the infector and infectee, as well as the probable locations of infection for both case-patients. The data include only confirmed cases compiled from online reports from 18 provincial centers for disease control and prevention (https://github.com/MeyersLabUTexas/COVID-19).

Fifty-nine of the 468 reports indicate that the infectee had symptoms earlier than the infector. Thus, presymptomatic transmission might be occurring. Given these negative-valued serial intervals, COVID-19 serial intervals seem to resemble a normal distribution more than the commonly assumed gamma or Weibull distributions (*4*,*5*), which are limited to positive values (Appendix, https://wwwnc.cdc.gov/EID/article/26/7/20-0357-App1.pdf). We estimate a mean serial interval for COVID-19 of 3.96 (95% CI 3.53–4.39) days, with an SD of 4.75 (95% CI 4.46–5.07) days (Figure), which is considerably lower than reported mean serial intervals of 8.4 days for severe acute respiratory syndrome (*5*) to 14.6 days (*6*) for Middle East respiratory syndrome. The mean serial interval is slightly but not significantly longer when the index case is imported (4.06 [95% CI 3.55–4.57] days) versus locally infected (3.66 [95% CI 2.84–4.47] days), but slightly shorter when the secondary transmission occurs within the household (4.03 [95% CI 3.12–4.94] days) versus outside the household (4.56 [95% CI 3.85–5.27] days). Combining these findings with published estimates for the early exponential growth rate COVID-19 in Wuhan (*7*), we estimate an R_0 of 1.32 (95% CI 1.16–1.48) (*5*), which is lower than published estimates that assume a mean serial interval exceeding 7 days (*7*,*8*).

These estimates reflect reported symptom onset dates for 752 case-patients from 93 cities in China, who range in age from 1 to 90 years (mean 45.2 years, SD 17.21 years). Recent analyses of putative COVID-19 infector–infectee pairs from several countries have indicated average serial intervals of 4.0 days (95% CI 3.1–4.9 days; n = 28; unpub. data, H. Nishiura et al., unpub. data, https://doi.org/10.1101/2020.02.03.20019497), 4.4 days (95% CI 2.9–6.7 days, n = 21; S. Zhao et al., unpub. data, https://doi.org/10.1101/2020.02.21.20026559], and 7.5 days (95% CI 5.3–19, n = 6; *8*). Whereas none of these studies report negative serial intervals in which the infectee had symptoms before the infector, 12.6% of the serial intervals in our sample were negative.

[1]These first authors contributed equally to this article.

GOV.UK

1. Home (https://www.gov.uk/)
2. Coronavirus (COVID-19) (https://www.gov.uk/coronavirus-taxon)

Guidance

The R number and growth rate in the UK

The latest reproduction number (R) and growth rate of coronavirus (COVID-19) in the UK.

Published 15 May 2020
Last updated 3 July 2020 — see all updates

From:
Government Office for Science (https://www.gov.uk/government/organisations/government-office-for-science) and Scientific Advisory Group for Emergencies (https://www.gov.uk/government/organisations/scientific-advisory-group-for-emergencies)

Contents

Latest R number and growth rate

Last updated on Friday 3 July 2020.

Latest R number range for the UK *0.7-0.9*

Latest growth rate range for the UK *-6% to -0%* per day

Latest by NHS England regions

These are the latest R and growth rate estimates by NHS England regions. The values are shown as a range, the most likely true values are somewhere towards the middle of this range.

Region	R	Growth rate % per day
England	0.8-0.9	-5 to -2
East of England	0.7-0.9	-5 to 0
London	0.8-1.1	-4 to +2
Midlands	0.8-1.0	-4 to 0
North East and Yorkshire	0.8-1.0	-5 to 0
North West	0.7-0.9	-4 to 0

Region	R	Growth rate % per day
South East	0.7-1.0	-5 to 0
South West	0.7-1.0	-7 to +2

Latest for devolved administrations

The latest ranges for values in the devolved administrations are published on their respective websites:

- Northern Ireland R number (https://www.health-ni.gov.uk/news/r-number-covid-19)
- Scotland R number (https://www.gov.scot/publications/?term=modelling&cat=filter&topics=Coronavirus%20in%20Scotland&publicationTypes=research-and-analysis&page=1)
- Wales R number (https://gov.wales/advice-coronavirus-technical-advisory-cell)
- Wales R number (Welsh version) (https://llyw.cymru/y-gell-cyngor-technegol)

What is R?

The reproduction number (R) is the average number of secondary infections produced by 1 infected person.

An R number of 1 means that on average every person who is infected will infect 1 other person, meaning the total number of new infections is stable. If R is 2, on average, each infected person infects 2 more people. If R is 0.5 then on average for each 2 infected people, there will be only 1 new infection. If R is greater than 1 the epidemic is growing, if R is less than 1 the epidemic is shrinking.

R can change over time. For example, it falls when there is a reduction in the number of contacts between people, which reduces transmission.

What is a growth rate?

The growth rate reflects how quickly the number of infections are changing day by day It is an approximation of the change of number infections each day. If the growth rate is greater than zero (+ positive), then the disease will grow. If the growth rate is less than zero (- negative) then the disease will shrink.

The size of the growth rate indicates the speed of change. A growth rate of +5% will grow faster than one with a growth rate of +1%. Likewise, a disease with a growth rate of -4% will be shrinking faster than a disease with growth rate of -1%. Further technical information on growth rate can be found on Plus magazine (https://plus.maths.org/content/epidemic-growth-rate).

How are growth rates different to R estimates?

R does not tell us how quickly an epidemic is changing. Different diseases with the same R can give epidemics that grow at very different speeds. For instance, two diseases, both with R=2, could have very different lengths of time for one infected individuals to infect two other people; one disease might take years, while the other might take days.

The growth rate provides us with information on the size and speed of change, whereas the R value only gives us information on the direction of change.

To calculate R, information on the time taken between each generation of infections is needed. That is how long it takes for one set of people in an infected group to infect a new set of people in the next group. This can depend on several different biological, social, and behavioural factors. The growth rate does not depend on the “generation time” and so requires fewer assumptions to estimate.

Neither one measure, R nor growth rate, is better than the other but each provide information that is useful in monitoring the spread of a disease.

The R estimate and growth rates are not the only important measures of the epidemic. Both should be considered alongside other measures of the spread of disease, such as the number of people currently infected. If R equals 1 with 100,000 people currently infected, it is a very different situation to R equals 1 with 1,000 people currently infected. The number of people currently infected with coronavirus (COVID-19) (https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases) – and so able to pass the virus on – is therefore very important.

Estimates of the growth rates and R are currently updated on a weekly basis. However, as the numbers of cases decrease, these metrics will become less helpful indicators and other measures need to be considered. These include the number of new cases of the disease identified during a specified time period (incidence), and the proportion of the population with the disease at a given point in time (prevalence), and these will become more important to monitor.

How are R and growth rates estimated?

Individual modelling groups use a range of data to estimate growth rates and R values including:

- epidemiological data such as hospital admissions, ICU admissions and deaths – it generally takes 2 to 3 weeks for changes in the spread of disease to be reflected in the estimates due to the time delay between initial infection and the need for hospital care
- contact pattern surveys that gather information on behaviour – these can be quicker (with a lag of around a week) but can be open to bias as they often rely on self-reported behaviour and make assumptions about how the information collected relates to the spread of disease.
- household infection surveys where swabs are performed on individuals. These can provide estimates of how many people are infected. Longitudinal surveys (where samples are repeatedly taken from the same people) allow a more direct estimate of the growth in infection rates

Different modelling groups use different data sources to estimate these values using mathematical models that simulate the spread of infections. Some may even use all these sources of information to adjust their models to better reflect the real-world situation. There is uncertainty in all these data sources so estimates can vary between different models, so we do not rely on just one model; evidence from several models is considered, discussed, combined, and the growth rate and R are then presented as ranges. The most likely true values are somewhere towards the middle of these ranges.

Who estimates the R and growth rates?

The growth rate and R are estimated by several independent modelling groups based in universities and Public Health England (PHE). The modelling groups discuss their individual R estimates at the Science Pandemic Influenza Modelling group (SPI-M) - a subgroup of SAGE. Attendees compare the different estimates of each and SPI-M collectively agrees a range for which the values are very likely to be within.

Limitations of R

R is an average value that can vary in different parts of the country, communities, and subsections of the population. It cannot be measured directly so there is always uncertainty around its exact value. This becomes even more of a problem when calculating R using small numbers of cases, either due to lower infection rates or smaller geographical areas. This uncertainty may be due to variability in the underlying data, leading to a wider range for R and more frequent changes in the estimates.

Even when the overall UK R estimate is below 1, some regions may have R estimates that include ranges that exceed 1, for example from 0.7 to 1.1; this does not necessarily mean the epidemic is increasing in that region, just that the uncertainty means it cannot be ruled out. It is also possible that an outbreak in one specific place could result in an R above 1 for the whole region.

Estimates of R for geographies smaller than regional level are less reliable and it is more appropriate to identify local hotspots through, for example, monitoring numbers of cases, hospitalisations, and deaths.

Limitations of growth rates

The growth rate is an average value that can vary. When case numbers are low, uncertainty increases. This could happen when only a very small proportion of people are infected, or the geographical area considered has a very small population. A smaller number of cases means that variability in the underlying data makes it difficult to estimate the growth rate; there will be a wider range given for growth rate and frequent changes in the estimates. This will happen for both R and the growth rate; however, the growth rate requires fewer assumptions about the disease when it is calculated than R.

Even when the overall UK growth rate estimate is negative (below 0), some regions may have growth rate estimates that include ranges that are positive (above 0), for example from -4% to +1%; this does not necessarily mean the epidemic is increasing in that region, just that the uncertainty means it cannot be ruled out. It is also possible that an outbreak in one specific place could result in a positive (above 0) growth rate for the whole region.

Published 15 May 2020
Last updated 3 July 2020 + show all updates

1. 3 July 2020
   The R number range for the UK is 0.7-0.9 and the growth rate range is -6% to -0% as of 3 July 2020.
2. 25 June 2020
   The R number range for the UK is 0.7-0.9 and the growth rate range is -4% to -2% as of 25 June 2020.
3. 19 June 2020
   The R number range for the UK is 0.7-0.9 and the growth rate range is -4% to -2% as of 19 June 2020.
4. 12 June 2020
   The R number range for the UK is 0.7-0.9 as of 12 June 2020.
5. 5 June 2020
   The R number range for the UK is 0.7-0.9 as of 5 June 2020.
6. 29 May 2020
   The R number range for the UK is 0.7-0.9 as of 29 May 2020.
7. 22 May 2020
   The R number range for the UK is 0.7-1.0 as of 22 May 2020.
8. 15 May 2020
   First published.

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Journal of Travel Medicine
International Society of Travel Medicine
Established 1991
Promoting healthy travel worldwide
Journal of Travel Medicine, 2020, 1–4
doi: 10.1093/jtm/taaa021
Advance Access Publication Date: 00 Month 0000
Research Letter

Research Letter

The reproductive number of COVID-19 is higher compared to SARS coronavirus

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Teaser: Our review found the average R_0 for COVID-19 to be 3.28, which exceeds WHO estimates from 1.4 to 2.5.

Key words: Coronavirus, Wuhan, China, SARS, Public health emergency of international concern, COVID-19, Epidemic potential, R_0

Introduction

In Wuhan, China, a novel and alarmingly contagious primary atypical (viral) pneumonia broke out in December 2019. It has since been identified as a zoonotic coronavirus, similar to SARS coronavirus and MERS coronavirus and named COVID-19. As of 8 February 2020, 33 738 confirmed cases and 811 deaths have been reported in China.

Here we review the basic reproduction number (R_0) of the COVID-19 virus. R_0 is an indication of the transmissibility of a virus, representing the average number of new infections generated by an infectious person in a totally naïve population. For $R_0 > 1$, the number infected is likely to increase, and for $R_0 < 1$, transmission is likely to die out. The basic reproduction number is a central concept in infectious disease epidemiology, indicating the risk of an infectious agent with respect to epidemic spread.

Methods and Results

PubMed, bioRxiv and Google Scholar were accessed to search for eligible studies. The term 'coronavirus & basic reproduction number' was used. The time period covered was from 1 January 2020 to 7 February 2020. For this time period, we identified 12 studies which estimated the basic reproductive number for COVID-19 from China and overseas. Table 1 shows that the estimates ranged from 1.4 to 6.49, with a mean of 3.28, a median of 2.79 and interquartile range (IQR) of 1.16.

The first studies initially reported estimates of R_0 with lower values. Estimations subsequently increased and then again returned in the most recent estimates to the levels initially reported (Figure 1). A closer look reveals that the estimation method used played a role.

The two studies using stochastic methods to estimate R_0, reported a range of 2.2–2.68 with an average of 2.44.[1, 9] The six studies using mathematical methods to estimate R_0 produced a range from 1.5 to 6.49, with an average of 4.2.[2, 4–6, 8, 10] The three studies using statistical methods such as exponential growth estimated an R_0 ranging from 2.2 to 3.58, with an average of 2.67.[3, 7, 11]

Discussion

Our review found the average R_0 to be 3.28 and median to be 2.79, which exceed WHO estimates from 1.4 to 2.5. The studies using stochastic and statistical methods for deriving R_0 provide estimates that are reasonably comparable. However, the studies using mathematical methods produce estimates that are, on average, higher. Some of the mathematically derived estimates fall within the range produced the statistical and stochastic estimates. It is important to further assess the reason for the higher R_0 values estimated by some the mathematical studies. For example, modelling assumptions may have played a role. In more recent studies, R_0 seems to have stabilized at around 2–3. R_0 estimations produced at later stages can be expected to be more reliable, as they build upon more case data and include the effect of awareness and intervention. It is worthy to note that the WHO point estimates are consistently below all published estimates, although the higher end of the WHO range includes the lower end of the estimates reviewed here.

R_0 estimates for SARS have been reported to range between 2 and 5, which is within the range of the mean R_0 for COVID-19 found in this review. Due to similarities of both pathogen and region of exposure, this is expected. On the other hand,

Table 1. Published estimates of R_0 for 2019-nCoV

Study (study year)	Location	Study date	Methods	Approaches	R_0 estimates (average)	95% CI
Joseph *et al.*[1]	Wuhan	31 December 2019–28 January 2020	Stochastic Markov Chain Monte Carlo methods (MCMC)	MCMC methods with Gibbs sampling and non-informative flat prior, using posterior distribution	2.68	2.47–2.86
Shen *et al.*[2]	Hubei province	12–22 January 2020	Mathematical model, dynamic compartmental model with population divided into five compartments: susceptible individuals, asymptomatic individuals during the incubation period, infectious individuals with symptoms, isolated individuals with treatment and recovered individuals	$R_0 = \beta/\alpha$ β = mean person-to-person transmission rate/day in the absence of control interventions, using nonlinear least squares method to get its point estimate α = isolation rate = 6	6.49	6.31–6.66
Liu *et al.*[3]	China and overseas	23 January 2020	Statistical exponential Growth, using SARS generation time = 8.4 days, SD = 3.8 days	Applies Poisson regression to fit the exponential growth rate $R_0 = 1/M(-r)$ M = moment generating function of the generation time distribution r = fitted exponential growth rate	2.90	2.32–3.63
Liu *et al.*[3]	China and overseas	23 January 2020	Statistical maximum likelihood estimation, using SARS generation time = 8.4 days, SD = 3.8 days	Maximize log-likelihood to estimate R_0 by using surveillance data during a disease epidemic, and assuming the secondary case is Poisson distribution with expected value R_0	2.92	2.28–3.67
Read *et al.*[4]	China	1–22 January 2020	Mathematical transmission model assuming latent period = 4 days and near to the incubation period	Assumes daily time increments with Poisson-distribution and apply a deterministic SEIR metapopulation transmission model, transmission rate = 1.94, infectious period =1.61 days	3.11	2.39–4.13
Majumder *et al.*[5]	Wuhan	8 December 2019 and 26 January 2020	Mathematical Incidence Decay and Exponential Adjustment (IDEA) model	Adopted mean serial interval lengths from SARS and MERS ranging from 6 to 10 days to fit the IDEA model,	2.0–3.1 (2.55)	/
WHO	China	18 January 2020	/	/	1.4–2.5 (1.95)	/
Cao *et al.*[6]	China	23 January 2020	Mathematical model including compartments Susceptible-Exposed-Infectious-Recovered-Death-Cumulative (SEIRDC)	$R = K\ 2\ (L \times D) + K(L + D) + 1$ L = average latent period = 7, D = average latent infectious period = 9, K = logarithmic growth rate of the case counts	4.08	/
Zhao *et al.*[7]	China	10–24 January 2020	Statistical exponential growth model method adopting serial interval from SARS (mean = 8.4 days, SD = 3.8 days) and MERS (mean = 7.6 days, SD = 3.4 days)	Corresponding to 8-fold increase in the reporting rate $R_0 = 1/M(-r)$ r =intrinsic growth rate M = moment generating function	2.24	1.96–2.55

(continued)

Table 1. Continued

Study (study year)	Location	Study date	Methods	Approaches	R_0 estimates (average)	95% CI
Zhao *et al.*[7]	China	10–24 January 2020	Statistical exponential growth model method adopting serial interval from SARS (mean = 8.4 days, SD = 3.8 days) and MERS (mean = 7.6 days, SD = 3.4 days)	Corresponding to 2-fold increase in the reporting rate $R_0 = 1/M(-r)$ r =intrinsic growth rate M = moment generating function	3.58	2.89–4.39
Imai (2020)[8]	Wuhan	January 18, 2020	Mathematical model, computational modelling of potential epidemic trajectories	Assume SARS-like levels of case-to-case variability in the numbers of secondary cases and a SARS-like generation time with 8.4 days, and set number of cases caused by zoonotic exposure and assumed total number of cases to estimate R_0 values for best-case, median and worst-case	1.5–3.5 (2.5)	/
Julien and Althaus[9]	China and overseas	18 January 2020	Stochastic simulations of early outbreak trajectories	Stochastic simulations of early outbreak trajectories were performed that are consistent with the epidemiological findings to date	2.2	
Tang *et al.*[10]	China	22 January 2020	Mathematical SEIR-type epidemiological model incorporates appropriate compartments corresponding to interventions	Method-based method and Likelihood-based method	6.47	5.71–7.23
Qun Li *et al.*[11]	China	22 January 2020	Statistical exponential growth model	Mean incubation period = 5.2 days, mean serial interval = 7.5 days	2.2	1.4–3.9
Averaged					3.28	

CI, Confidence interval.

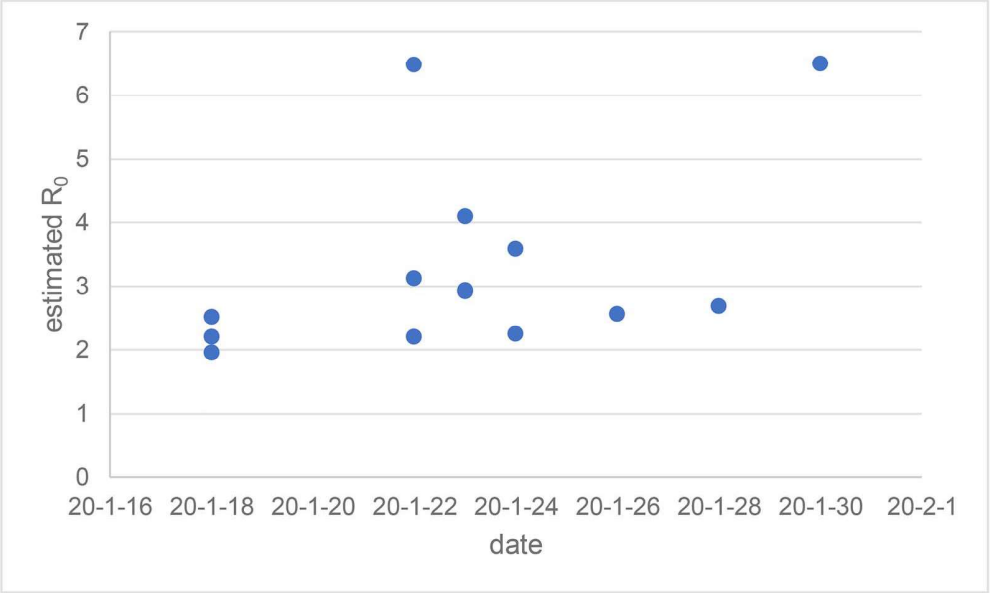

Figure 1. Timeline of the R_0 estimates for the 2019-nCoV virus in China

despite the heightened public awareness and impressively strong interventional response, the COVID-19 is already more widespread than SARS, indicating it may be more transmissible.

Conclusions

This review found that the estimated mean R_0 for COVID-19 is around 3.28, with a median of 2.79 and IQR of 1.16, which is considerably higher than the WHO estimate at 1.95. These estimates of R_0 depend on the estimation method used as well as the validity of the underlying assumptions. Due to insufficient data and short onset time, current estimates of R_0 for COVID-19 are possibly biased. However, as more data are accumulated, estimation error can be expected to decrease and a clearer picture should form. Based on these considerations, R_0 for COVID-19 is expected to be around 2–3, which is broadly consistent with the WHO estimate.

Author contributions

J.R. and A.W.S. had the idea, and Y.L. did the literature search and created the table and figure. Y.L. and A.W.S. wrote the first draft; A.A.G. drafted the final manuscript. All authors contributed to the final manuscript.

Conflict of interest

None declared.

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Q&A on coronaviruses (COVID-19)

17 April 2020 | Q&A

People can catch COVID-19 from others who have the virus. The disease spreads primarily from person to person through small droplets from the nose or mouth, which are expelled when a person with COVID-19 coughs, sneezes, or speaks. These droplets are relatively heavy, do not travel far and quickly sink to the ground. People can catch COVID-19 if they breathe in these droplets from a person infected with the virus. This is why it is important to stay at least 1 meter) away from others. These droplets can land on objects and surfaces around the person such as tables,

doorknobs and handrails. People can become infected-by touching these objects or surfaces, then touching their eyes, nose or mouth. This is why it is important to wash your hands regularly with soap and water or clean with alcohol-based hand rub.

WHO is assessing ongoing research on the ways that COVID-19 is spread and will continue to share updated findings.

Can COVID-19 be caught from a person who has no symptoms?

How can we protect others and ourselves if we don't know who is infected?

What should I do if I have come in close contact with someone who has COVID-19?

What does it mean to self-isolate?

What should I do if I have no symptoms, but I think I have been exposed to COVID-19? What does it mean to self-quarantine?

What is the difference between self-isolation, self-quarantine and distancing?

Can children or adolescents catch COVID-19?

What can I do to protect myself and prevent the spread of disease?

Is there a vaccine, drug or treatment for COVID-19?

Does WHO recommend wearing medical masks to prevent the spread of COVID-19?

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Article type : Rapid Communication

Rapid Communication

Estimated Inactivation of Coronaviruses by Solar Radiation

With Special Reference to COVID-19

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/PHP.13293

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Keywords: SARS-CoV-2, COVID-19, coronaviruses, Influenza, virus inactivation, solar radiation, photobiology, UV radiation, antiviral effect.

ABSTRACT

Using a model developed for estimating solar inactivation of viruses of biodefense concerns, we calculated the expected inactivation of SARS-CoV-2 virus, cause of COVID-19 pandemic, by artificial UVC and by solar ultraviolet radiation in several cities of the world during different times of the year. The UV sensitivity estimated here for SARS-CoV-2 is compared with those reported for other ssRNA viruses, including influenza A virus. The results indicate that SARS-CoV-2 aerosolized from infected patients and deposited on surfaces could remain infectious outdoors for considerable time during the winter in many temperate-zone cities, with continued risk for re-aerosolization and human infection. Conversely, the presented data indicate that SARS-CoV-2 should be inactivated relatively fast (faster than influenza A) during summer in many populous cities of the world, indicating that sunlight should have a role in the occurrence, spread rate, and duration of coronavirus pandemics.

INTRODUCTION

The current (2019-2020) COVID-19 world pandemic is caused by a member of the *Coronaviridae* family [Reviewed in (1)]. Coronaviruses have a lipid-containing envelope with the genome consisting of a single-stranded, positive-sense RNA genome that is not segmented (2-5). Coronaviruses have the largest genomes of all ssRNA viruses which will become of relevance latter

in this work. In the absence of pandemics, coronaviruses cause about 15-20% of all upper respiratory infections in humans (6). Previous pandemics like Severe Acute Respiratory Syndrome (caused by SARS-CoV during 2002-2003), and Middle East Respiratory Syndrome (caused by MERS-CoV during 2012) indicate that pandemics caused by coronaviruses should be expected to occur with frequency (7-8). Additional coronaviruses are known to cause disease in animals closely associated to humans like cat and dog, rat and mouse, cow, swine, chicken and turkey (6).

Although clusters of infected family members and medical workers have confirmed direct, person-to-person transmission (9), the rapid expansion of COVID-19, that progressed unquenched even after quarantine of nearly one third of the world population and major social distancing measures, suggests that an environmental component (with the virus remaining infectious outside the host) plays a role in disease transmission. Of relevance here is the amount of infectious virus present in the aerosolized droplets produced by COVID-19 symptomatic patients or non-symptomatic carriers. This amount is not well established for coronaviruses, but it has been reported that nasal secretions contain up to 10^7 infectious influenza viral particles per ml (10), from which aerosolized droplets generated by coughing, sneezing, and talking can contain several hundred infectious virions (11). These micro droplets can reach distances of 12.5 meters (over 40 feet, [12]). SARS-CoV has been reported to persist on contaminated surfaces with risk of disease transmission for up to 96 h (13) and other coronaviruses for up to 9 days (14). SARS-CoV-2 persisted viable from 3 hours to 3 days depending on the type of surface on which it was deposited (15). Influenza virus was readily re-aerosolized by sweeping floors without much loss in infectivity (16). It must be assumed that SARS-CoV-2 will be re-aerosolized in a similar manner.

Three main physical factors generally considered with a potential effect on virus persistence outdoors, include temperature, humidity, and the contribution of sunlight. The survival of influenza virus, a member of the *Orthomyxoviridae* family, also with ssRNA and a lipid–containing envelope, only varied up to 9% when the relative humidity changed between 50% and 70% (17). Rather extreme changes in relative humidity between 15% and 90% varied survival of influenza 12.5–fold [1.1 Log_{10}, (18)]. In these studies, virus survival was even less influenced by changes in temperature. A recent study where virus infectivity was corrected by aerosol losses and natural decay, demonstrated that aerosolized influenza A virus remained equally infectious at all relative humidity

tested, ranging from 23% to 98% (19). In agreement with the relatively small effect of humidity and temperature on influenza virus inactivation, epidemiological studies concluded that the mortality increase in winter was largely independent of temperature and humidity (20-21).

If the limited role of relative humidity and temperature (within the range encountered in the environment) reported for influenza A parallels that for SARS-CoV-2 then, the effect of artificial and natural UV radiation on SARS-CoV-2 inactivation should be preeminent. The preeminent effect indoors of germicidal UV (UVC, 254nm) radiation is clearly confirmed by a report whereby inactivation of air-borne virions by UV radiation virtually prevented the spread of influenza among patients in a veterans hospital, during the same time that an epidemic of influenza ravaged similar patients in nearby non-irradiated rooms (22).

There are published reports indicating that very high doses of UVC are effective for inactivating SARS-CoV-2 or SARS-CoV that had been added to different blood products or remaining in virus culture medium (23-28) but there is no data on the viral sensitivity to UVC in UV-transparent liquids or in absence of protective substances, as needed to estimate UVC sensitivity. Nor is there information for UVC inactivation of the virus suspended in aerosols or deposited on surfaces as needed for environmental risk assessment.

Ultraviolet radiation in sunlight is the primary virucidal agent in the environment (29-31). This notion is supported by the correlation found in Brazil between increased influenza incidence in hospital admission records and solar UV-blocking by smoke during the burning season (32). The reports on influenza A warrant the present study to estimate UV sensitivity of SARS-CoV-2 and its possible role in the COVID-19 pandemic.

The purpose of this study was two-fold, i) to estimate the sensitivity of SARS-CoV-2 to inactivation by germicidal UV (UVC) and ii) to predict the inactivation of the virus by the UVB in sunlight for various populous cities of the world at different times of the year. These goals were achieved by utilizing a model developed for biodefense purposes for estimating solar UVB inactivation of dangerous viruses (30). This methodology has been validated with Ebola and Lassa viruses (33). The model has also been used to estimate inactivation of influenza viruses at various times in numerous locations in the U.S. and globally (34).

Estimation of the time required for inactivation of 90% and 99% of infectious virus reported

here should be useful in evaluating the persistence of SARS-CoV-2 in environments exposed to solar radiation.

MATERIALS AND METHODS

We estimated SARS-CoV-2 virus UV (254 nm) sensitivity and inactivation at different U.S. and global locations by an approach originally developed to predict the survival of viruses of interest in biodefense (30) and later employed to estimate persistence of influenza A virus (34)

SARS-CO V2 virus UV_{254} sensitivity. The UVC sensitivity is reported here as D_{37} which corresponds to the UV fluence that produces, on average, one lethal hit to the virus, resulting in 37% survival. D_{37} equals the reciprocal of the slope on the semi-logarithmic graph of viral survival versus dose and can be calculated by dividing the fluence that results in 1 Log_{10} reduction of virus load by 2.3 (the natural logarithmic base). A lower value of D_{37} indicates a higher sensitivity to inactivation by UV radiation. Comparison of a virus of unknown UVC sensitivity to that of other viruses of similar genomic structure allows an estimate to be determined (30). An important part of the method is the fact that UVC sensitivities of viruses depends proportionally on genome size, especially with single-stranded RNA or DNA, i.e., the larger the genome "target", the more sensitive (and lower D_{37}). This results in the product of the genome size and the D_{37}, defined as size normalized sensitivity (SnS), being relatively constant for a given type of viral genome (30) and it is used in this study to compare viruses with ssRNA genomes. This approach has been used successfully to estimate the UVC sensitivities of Ebola and Lassa viruses, later confirmed experimentally in the laboratory (33), thus validating the method.

Solar intensity at different locations and times of year. Solar UVB flux measured by the USDA UV-B Monitoring and Research Program (35) have been used in the development and testing of the method (30). Maximum daily solar UVB fluence values for the selected locations at specific times of year have been presented in a previous article predicting the inactivation of influenza A by solar UVB (34). Those daily solar flux values were normalized using a virucidal action spectrum to 254 nm equivalent levels (30). Whereas the total UV_{254} equivalent fluence per full day was previously used in the influenza A inactivation study (34), the flux values at solar noon are preferable and are used here because they are essentially constant during two hours (36, 37). It has been previously

determined that 35% of the total daily UVB occurs in the two-hour period (120 minutes) around solar noon (37). Thus 35% of the total daily UVB fluence divided by 120 minutes yields the noontime UVB flux (in J/m^2/min) at the locations and times of the year presented in Tables 2 and 3. It should be noted that the solar UVB flux used in the present study assumed no atmospheric influence, whether by haze, clouds, or air pollution. Also, there was no correction for an increase in the solar virucidal effect due to the elevation of the urban sites (38).

RESULTS

UVC sensitivity of SARS-CoV-2

<Table 1>

In Table 1 we compare the genomic and UV_{254} characteristics of SARS-CoV-2 (causing COVID-19) with those of other coronaviruses and viruses that have similar nucleic acid composition. The first three coronaviruses cause disease in humans. Studies with MHV and EtoV have found similar values for D_{37}s (36,39). Therefore, a reasonable estimate for the D_{37}s for the SARSs and MERS-CoV viruses would be 3.0 J/m^2. Comparison with other ssRNA viruses yields a similar D_{37} value. Since the influenza A genomes are 2.2 times shorter than those of the coronaviruses, it is further reasonable that the coronaviruses (larger UV targets) would be at least twice as sensitive to UVC; the reciprocal ratio of the genome sizes times the D_{37} for the influenza viruses yields an estimated D_{37} for SARS-CoV-2 of 4.7 J/m^2. When a similar comparison is done with the viruses of the other ssRNA families in Table 1, the median value for the SARS-CoV-2 D_{37} was 5.0 J/m2. The D_{37} value of 3.0 J/m2 was used in the following calculations because it follows from values derived directly from members of the same *Coronaviridae* family; D_{10} (6.9 J/m^2) was used as it represents 10% survival (90% inactivation).

It may be useful to estimate the solar exposure for 99% virus inactivation (1% survival) or for even lower levels of survival. Because the material in aerosols created by COVID-19 patients and carriers may shield the virus from the UV as has been shown in laboratory experiments with viruses in culture medium, the virus survival curves indicate that the virus apparently becomes less UV sensitive (33,

36, 40-42). This resulted in a change of slope of approximately 4-fold in experiments with Ebola and Lassa viruses and affected several percent of the virus population (33, 42). Therefore, for survival beyond 10%, a UV fluence of 4 times the chosen D_{10} (28 J/m^2) was assumed. This value was used to estimate the solar exposure needed for 99% inactivation. Assuming that the survival curve maintains that 4-fold greater UV resistance at lower survival levels, 99.9% inactivation (disinfection level) would require 56 J/m^2; sterilization level inactivation (10^{-6} survival) would require 140 J/m^2.

Estimated time for inactivation of SARS-Co V-2 virus

<Table 2>

Table 2 shows reported solar virucidal flux at solar noon together with the estimated minutes of sunlight exposure needed at various populous North American metropolitan areas to inactivate 90% of SARS-CoV-2. The (+) sign in Table 2 indicates that 99% of SARS-CoV-2 may be inactivated within the two hours period around solar noon during summer in most US cities located south of Latitude 43^{o}N. Also 99% of the virus will be inactivated during two hours midday in several cities south of latitude 35^{o}N in Fall, but only Miami and Houston will receive enough solar radiation to inactivate 99% of the virus in spring. During winter, most cities will not receive enough solar radiation to produce 90% viral inactivation during 2-hours midday exposure (underlined values in Table 2).

<Table 3>

Table 3 presents germicidal solar flux values and resulting inactivation of SARS-CoV-2 for populous metropolitan areas on other continents. The values in Tables 2 and 3 clearly illustrate that SARS-CoV-2 in environments exposed to sunlight will be differentially inactivated in different cities and at different times of the year. For example, at winter solstice (December, in the northern hemisphere), just at the beginning of the COVID-19 pandemic, virus exposed to full midday sunlight would be reduced by at least 90% (1 Log_{10}) during 22 minutes in Mexico City, and will be receiving enough germicidal solar flux to inactivate 99% of virus as indicated by (+) in Table 3. A 90% inactivation of SARS-CoV-2 in December should have taken considerably longer time in Shanghai (99 min), and Cairo (86 min). Nearly full virus persistence should occur in winter (December) in the European cities listed in Table 3 (where COVID-19 was severe). Of course, the same trend applies to the

Southern Hemisphere where winter begins in June and 90% of SARS-CoV-2 should be inactivated in 41 min in Sao Pablo (Brazil), but not within the 2 hours solar noon period in Buenos Aires (Argentina) or Sydney (Australia) in the incoming winter season.

DISCUSSION

The transmission of viral infections and evolution of pandemics are a multi-factorial process involving, among others, properties of the viral agent, health condition of the host and available health care, viral inactivation in the environment, social dynamics and political decisions. It is well known that there is direct transmission of infectious virions by inhalation of contaminated aerosols exhaled, coughed, or sneezed from infected persons, allowing for little time and opportunity for environmental viral inactivation, unless the virions settle on some surface. Although direct (person-to-person) transmission is important between nearby individuals (9), it is remarkable that the COVID-19 pandemic progressed at a sustained rate even after one-third of the world population was in quarantine or in-house lock-down (51). The rapid progression of the COVID-19 pandemic, in spite of greatly hindered direct transmission, supports elucidating the relevance of indirect infection through aerosolized virus, contact with contaminated surfaces and other fomites, and the inactivation thereof.

Changes in relative humidity and ambient temperature have been reported as having a rather limited effect on environmental virus survival and disease transmission (17-21). In contrast, UVC radiation has considerable virucidal effect (22). The methodology employed in the present study has been used previously to estimate the UVC sensitivity of Lassa virus and other viruses of relevance in biodefense (30). A close agreement was obtained between UVC D_{37} values predicted for Lassa virus (member of the Arenavirus family) (13 J/m^2, Table 4 in Ref 30) and measured years later in the laboratory (16 J/m^2) (33). These results suggest that the accuracy of the methodology used here to estimate the UV sensitivity of the SARS-CoV-2 virus from data obtained for members of the same family may be within 20%.

The relevance of sunlight in viral inactivation contrasts with and is supported by the i) long-term persistence in darkness of smallpox (an Orthopoxivirus) in scabs and surfaces (52), ii) with laboratory results were pathogenic viruses in the dark survived for much longer times (T_{37} [time to

37% survival)]between 15 and 43 hours for the different viruses studied) (53), and iii) with the rapid inactivation of vaccinia virus exposed to direct sunlight or simulated solar UVB (42).

The solar germicidal flux shown in Tables 2 and 3 allows estimating SARS-CoV-2 inactivation outdoors for the cities presented, as well as for almost any other location of which latitude is known, from sun exposure under clear skies. Modeling of viruses suspended in the atmosphere indicates that the diffuse (scatter) component of sunlight may still have approximately 50% of the virucidal efficacy exerted by direct solar radiation (38, 54). These findings demonstrate that viral inactivation by sunlight continues outdoors (albeit at half the rate or less) even in the shade or in polluted air or partially cloudy days.

Although the solar zenith angle at a given location is the same at the spring and fall equinoxes, the solar UV radiation received in the northern hemisphere was generally greater in the fall than in the spring, except for the location furthest south, Hawaii (latitude 19.5 ^{o}N). Data for Alexandra, New Zealand, in the southern hemisphere where the seasons are reversed, demonstrated the same trend with spring UVB radiation being lower than fall UV radiation (data not shown). This differential solar germicidal fluence between spring and summer has been previously discussed (30).

Data for the COVID-19 pandemics from the World Health Organization and from Johns Hopkins' Center for Systems Science and Engineering (as of May 7, 2020) indicates that of the 30 countries with highest infections per million inhabitants, 28 were north of the Tropic of Cancer (the two exceptions being Qatar and Mayotte) (55). Any correlation between solar flux during December-March 2019/20, (when COVID-19 was in expansion) and infection rate is limited by inaccuracy and availability of testing, different numbers of infected travelers, as well as vast differences on each country demographics and response. However, the statistical data [as of May 7 2020 (55)] suggest that COVID-19 may have progressed differently in countries at northern latitudes where it was winter and sun exposure was limited at the onset of the pandemic, than in countries in the southern latitudes where summer sunlight was abundant.

Considering that SARS-Co V-2 is three-times more sensitive to UV than influenza A (as presented in Table 1 and discussed in RESULTS) it should be inferred that sunlight should have an effect on coronaviruses transmission at least similar to that previously established for the evolution of influenza epidemics (22,32) If we accept a possible virucidal role of sunlight during coronavirus

pandemics, then forcing people to remain indoors may have increased (or assured) contagion of COVID-19 among same house-hold dwellers and among patients and personnel inside the same hospital or geriatric facilities. In contrast, healthy people outdoors receiving sunlight could have been exposed to lower viral dose with more chances for mounting an efficient immune response. This argument supports considering the results of two opposed containment approaches to deal with the COVID-19 crisis.

Almost all countries and territories affected with COVID-19 have closed their borders, mandated the use of masks and promoted social distancing. By 26 March, 2020, 1.7 billion people worldwide were under some form of lock-down, which increased to 3.9 billion people by the first week of April, amounting to more than half of the world's population (56). Schools, universities and colleges have closed either on a nationwide or local basis in 177 countries, affecting approximately 98.6 per cent of the world's student population (57). In addition to these measures, some countries (for example: Italy, Spain, the UK, Peru, Chile, Argentina and Rep South Africa) implemented nation-wide strict quarantine and in-house lock-down measures, often enforced by police, that decreased the time individuals could spent outdoors thus preventing potential exposure to sunlight. Most countries (like USA, Finland, and Brazil) implemented regional less stringent lock-down measures at varying degrees. A third group of countries (for example: Sweden, Belorussia, Nicaragua, Uruguay, Indonesia, South Korea and Namibia) did not mandate lock-downs that prevented healthy individuals to remain outdoors with potential exposure to sunlight (58). These "unlock" countries have not enforced any strict lock-downs but have rather implemented large-scale social distancing, face mask wearing measures and/or instituted quarantine mainly for travelers and infected patients (58).

Analyzing the value (if any) of whole-population quarantine or in-house lock-down of healthy individuals is beyond the scope of the present work. However, the freely available epidemiological data (as of May 29, 2020 [55]) demonstrates that lock-down measures preventing healthy individuals from remaining outdoors have not resulted in an obvious and statistically significant difference on infections per million inhabitants when compared to countries where healthy individuals were free to stay outdoors, with potential exposure to sunlight radiation. If lock-down of healthy citizens may not be determinant as these statistics suggest, then the potential role of being outside exposed to direct

or scattered sunlight in COVID-19 pandemic should not be underestimated.

CONCLUSION

The data presented estimates the sensitivity to UVC (254nm) of the SARS-CoV-2 virus with a D_{37} of 3.0 J/m^2, corresponding to 90% inactivation (D_{10}) after a dose of 7 J/m^2. Inactivation of 99% viral load (D_1) was estimated to be 28 J/m^2 (4x D_{10}) due to the biphasic nature of the virus inactivation curve found for other viruses shielded by culture media and other components that accompany virus infections.

90% or more of SARS-CoV-2 virus will be inactivated after being exposed for ≒11-34 minutes of midday sunlight in most US and world cities during summer. In contrast, the virus will persist infectious for a day or more in winter (December-March), with risk of re-aerosolization and transmission in most of these cities.

Although latitude, population size, public health and control measures vastly vary among countries, the viral persistence estimated here for cities at northern latitudes where COVID-19 expanded rapidly during winter 2019-2020 and relatively higher viral inactivation in more southern latitudes receiving high solar radiation during the same period, suggests an environmental role for sunlight in the COVID-19 pandemic.

Acknowledgements-The authors appreciate the encouragement to initiate this study received from Ms. Jessica Seigel (journalist, New York University).

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Table 1. UVC Sensitivity of SARS-CoV-2 and Selected Viruses[a]

Virus Family	**Genome**	**Size[b] (Knt)**	**Measured[c] D_{37} (J/m^2)**	**SNS[d] (J/m^2.Knt)**	**Predicted D_{37} (J/m^2)**	**References**
Coronaviridae						
SARS-CoV-2	ssRNA+	29.8		89	3.0	
SARS-CoV	ssRNA+	29.7		89	3.0	
MERS	ssRNA+	30.1		89	3.0	
MHV	ssRNA+	31.6	2.9	91		(36)
EToV	ssRNA+	28.5	3.1	88		(39)
Togaviridae						
SINV	ssRNA+	11.7	19	220		(43)
VEEV	ssRNA+	11.4	23	260		(44)
SFV	ssRNA+	13.0	7.2	94		(39)
Paramyxiviridae						
NDV	ssRNA-	15.2	11-13.5	170-210		(45,46)
MeV	ssRNA-	15.9	8.8-10.9	140-170		(47)
Orthomyxoviridae						
FLUAV	ssRNA-	13.6				
Melbourne H1N1			10.2	139		(48)
NIB-4 H3N2-3			11	150		(40)
NIB-6 H1N1			9.6	131		(40)
ISAV	ssRNA-	14.5	4.8	70		(49)
Rhabdoviridae						
RABV	ssRNA-	11.9	4.3	51		(39)

[a] Selected viruses of different genetic Families having ssRNA as the genome

[b] Size of the genome expressed as thousands of nucleotide bases (Knt).

[c] UVC fluence that causes one lethal event per virus on average, resulting in 37% survival.

[d] Size-normalized sensitivity defined as the product of the D_{37} and the genome size in thousands of bases is relatively constant for a given genome type, but can be vastly different for different genomic types. If the size and genome type is known for an untested virus, the D_{37} can be predicted from the SNS.

Table 2. Calculated maximum[1] virucidal (254-nm equivalent[2]) UV flux during two-hour period around solar noon for populous metropolitan areas in North America at specified times of year. Effectiveness estimated for inactivation of SARS-CoV-2 virus.

Metropolitan area	Latitude	Solar virucidal UV flux ($J/m^2_{254}{}^2/min$)[3]/ ***Time for*** 90% ***Infectivity reduction (min)***[4]			
		Summer Solstice	Equinox		Winter Solstice
			Spring	Fall	
Miami, FL	25.8 °N	0.51/***14*** + [5]	0.34/***20*** +	0.41/***17*** +	0.13/***53***
Houston, TX	29.8 °N	0.44/***16*** +	0.25/***28*** +	0.33/***21*** +	0.08/***86***
Dallas, TX	32.8 °N	0.39/***18*** +	0.20/***34***	0.28/***25*** +	0.06/***115***
Phoenix, AZ	33.4 °N	0.39/***18*** +	0.19/***36***	0.26/***27*** +	0.05/***138*** [6]
Atlanta, GA	33.7 °N	0.39/***18*** +	0.18/***38***	0.26/***27*** +	0.05/***138***
Los Angeles, CA	34.1 °N	0.38/***18*** +	0.18/***38***	0.26/***27*** +	0.05/***138***
San Francisco, CA	37.7 °N	0.34/***20*** +	0.13/***53***	0.20/***34***	0.03/***230***
Washington, D.C.	38.9 °N	0.33/***21*** +	0.12/***57***	0.19/***36***	0.02/>***300***
Philadelphia, PA	39.9 °N	0.32/***22*** +	0.11/***63***	0.18/***38***	0.02/>***300***
New York City, NY	40.7 °N	0.32/***22*** +	0.10/***69***	0.17/***41***	0.02/>***300***
Chicago, IL	41.9 °N	0.31/***22*** +	0.10/***69***	0.16/***43***	0.01/***>300***
Boston, MA	42.3 °N	0.30/***23*** +	0.09/***77***	0.15/***46***	0.01/***>300***
Detroit, MI	42.3 °N	0.30/***23*** +	0.09/***77***	0.15/***46***	0.01/***>300***
Toronto, Ontario	43.6 °N	0.29/***24***	0.08/***86***	0.14/***49***	0.01/***>300***

Minneapolis, MN	45.0 °N	0.28/***25***	0.07/***99***	0.13/***53***	0.01/***>300***
Seattle, WA	47.6 °N	0.26/***27***	0.06/***115***	0.11/***63***	0.01/***>300***

1. Maximum solar exposure with no clouds, haze, air pollution or shadows to reduce exposure, independent of site elevation.
2. Obtained using the virus inactivation action spectrum normalized to unity at 254nm (30).
3. Methodology: Maximum daily solar UVB fluence values for the selected locations at specific times of year have been represented in Tables 1 and 2 in the previous article on predicted Influenza inactivation by solar UVB (34). 35% of the total daily UVB fluence divided by 120 minutes yields the noontime UVB flux in J/m^2/min at the locations and times in Tables 2 and 3.
4. The UVB fluence D_{10} to inactivate SARS-CoV-2 90% (10% survival) was estimated as 6.9 J/m^2.
5. Under ideal conditions, solar UV could inactivate SARS-CoV-2 99% (1% survival) during 2-hour period around solar noon. Four times the D_{10} was chosen to account for the likely biphasic inactivation due to protective elements surrounding the virus.
6. Underlined values indicate solar UVB is likely not enough to inactivate SARS-CoV-2 90% (10% survival) during two-hour period around solar noon.

Table 3. Calculated maximum[1] virucidal (254-nm equivalent[2]) UV flux for two-hour period around solar noon for selected major world cities at specified times of year:

Effectiveness estimated for inactivation of SARS-CoV-2 virus.

City	Latitude	Solar virucidal UV flux ($J/m^2_{254}{}^2/min$)[3]/ ***Time for*** 90% ***Infectivity reduction (min)***[4]			
		Summer Solstice**	Equinox		Winter Solstice**
			Spring	Fall	
Central and South America					
Bogota, Colombia	4.6 °N	0.64[7]/***11***+[5]	0.64/***11***+	0.64/***11***+	0.64/***11***+
Mexico City, Mexico	19.5 °N	0.64/***11***+	0.62/***11***+	0.62/***11***+	0.31/***22***+
São Paulo, Brasil	23.3 °S	0.55/***13***+	0.40/***17***+	0.48/***14***+	0.17/***41***
Buenos Aires, Argentina	34.6 °S	0.37/***19***+	0.17/***41***	0.24/***29***	0.04/***172***[6]
Europe					
Barcelona, Spain	41.4 °N	0.31/***22***+	0.10/**69**	0.16/**43**	0.01/**>300**
Paris, France	48.9 °N	0.25/***28***+	0.05/**138**[6]	0.10/**69**	0.00/**>300**
London, UK	51.5 °N	0.23/***30***	0.04/**173**	0.09/**77**	0.00/**>300**
Moscow, Russia	55.7 °N	0.20/***34***	0.03/**230**	0.07/**99**	0.00/**>300**

Middle East					
Baghdad, Iraq	33.3 ^{o}N	0.39/**18**+	0.19/**36**	0.26/**27**+	0.05/**138**
Tehran, Iran	35.7 ^{o}N	0.36/**19**+	0.16/**43**	0.23/**30**	0.04/**172**
Istanbul, Turkey	41.0 ^{o}N	0.31/**22**+	0.10/**69**	0.16/**43**	0.02/**>300**
Africa					
Kinshasa, Congo	4.3 ^{o}S	0.64/**11**+	0.64/**11**+	0.64/**11**+	0.64/**11**+
Lagos, Nigeria	6.4 ^{o}N	0.64/**11**+	0.64/**11**+	0.64/**11**+	0.64/**11**+
Khartum, Sudan	15.6 ^{o}N	0.64/**11**+	0.64/**11**+	0.64/**11**+	0.32/**22**+
Cairo, Egypt	30.0 ^{o}N	0.43/**16**+	0.25/**28**+	0.32/**22**+	0.08/**86**
Asia					
Mumbai (Bombay), India	19.0 ^{o}N	0.64/**11**+	0.62/**11**+	0.62/**11**+	0.32/**22**+
Shanghai, China	31.2 ^{o}N	0.42/**16**+	0.22/**31**	0.31/**22**+	0.07/**99**
Seoul, Republic of Korea	33.5 ^{o}N	0.38/**18**+	0.19/**36**	0.26/**27+**	0.05/***138***
Tokyo, Japan	35.7 ^{o}N	0.36/**20**+	0.16/**43**	0.23/**30**	0.04/***172***
Australia					

Sydney, Australia	33.9 °S	0.38/**18**+	0.18/**38**	0.26/**27**+	0.05/***138***

1. Maximum solar exposure with no clouds, haze, air pollution or shadows to reduce exposure, independent of site elevation.
2. Obtained using the virus inactivation action spectrum normalized to unity at 254nm (30).
3. Methodology: Maximum daily solar UVB fluence values for the selected locations at specific times of year have been represented in Tables 1 and 2 in the previous article on predicted Influenza inactivation by solar UVB (34). 35% of the total daily UVB fluence divided by 120 minutes yields the noontime UVB flux in J/m^2/min at the locations and times in Tables 2 and 3.
4. The UVB fluence D_{10} to inactivate SARS-CoV-2 90% (10% survival) was estimated as 6.9 J/m^2.

5. Under ideal conditions, solar UV could inactivate SARS-CoV-2 99% (1% survival) during 2-hour period around solar noon. Four times the D_{10} was chosen to account for the likely biphasic inactivation due to protective elements surrounding the virus.

6. Underlined values indicate solar UVB is likely not enough to inactivate SARS-CoV-2 90% (10% survival) during two-hour period around solar noon.
7. Flux values above 0.62 are likely underestimates. Therefore, the time for 90% and 99% inactivation are possibly overestimates.

European Centre for Disease Prevention and Control

Transmission of COVID-19

Viral shedding

Over the course of the infection, the RNA of 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 in mild cases [118], and for longer periods in more severe cases, peaking in the second week after infection [111,118]. Prolonged viral RNA shedding has been reported from nasopharyngeal swabs (up to 63 days among adult patients)[119] and in faeces (more than one month after infection in paediatric patients) [120].

Late viral RNA clearance (≥15 days after illness onset), is associated with male sex, old age, hypertension, delayed admission to hospital, severe illness at admission, invasive mechanical ventilation, and corticosteroid treatment [121].

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. Viral load can however be a potentially useful marker for assessing disease severity and prognosis: a recent study indicated that viral loads in severe cases were up to 60 times higher than in mild cases [111].

In terms of viral load profile, SARS-CoV-2 is similar to that of influenza, which peaks at around the time of symptom onset [122,123], but contrasts with that of SARS-CoV, which peaks at around 10 days after symptom onset, and that of MERS-CoV which peaks at the second week after symptom onset. Older age has also been associated with higher viral loads [123]. The high viral load close to symptom onset suggests that SARS-CoV-2 can be easily transmissible at an early stage of infection [52].

Viral RNA has been detected in faeces [120] [124], whole blood [125,126], serum [76,127], saliva [76,127], nasopharyngeal specimens [128], urine [129]; ocular fluid [129,130], breastmilk [74] and in placental or foetal membrane samples [131]. A correlation has been suggested between the isolation of viable virus and the initial viral load (i.e. cycle threshold [Ct]) [132].

Data from Germany show that in symptomatic children, initial SARS-CoV-2 viral loads at diagnosis are comparable to those in adults [118], and that symptomatic children of all ages shed infectious virus in early acute illness [133]. In this study, also infectious virus isolation success was comparable to that of adults. The youngest patient from whom SARS-CoV-2 was isolated was a seven-day old neonate. In another non peer-reviewed publication, it was also shown that there is no significant difference between viral loads in persons 1-20 years of age in comparison to adults 21-100 years of age [134].

Virus and substances of human origin (SoHO)

There were so far no reports of transmission of COVID-19 through substances of human origin (SoHO). More evidence is needed to assess the importance of recent findings of viral RNA in seminal fluid [135] and breast milk [74] for the safety of their donation, since the infectivity of detectable RNA in breast milk and seminal fluid has not been proven. Three organisations in reproductive medicine have jointly issued a statement on the resumption of fertility treatment that had been discontinued in March [136]. Recommendations in the first update of the ECDC's technical document on the safety of SoHO supply in EU/EEA remain valid [137].

The collection and clinical use of convalescent plasma for the treatment of COVID-19 patients is ongoing in the EU/EEA and the USA within clinical studies or as an emergency compassionate use. In EU/EEA Members States, these activities are carried out according to EC guidance developed in collaboration with ECDC, national competent authorities and other stakeholders [138]. The early studies showed that convalescent plasma infusion to COVID-19 patients is safe and effective [139,140]. As of 29 May 17 674 units of convalescent plasma have been infused to COVID-19 patients in the USA [141].

Role of asymptomatic and pre-symptomatic individuals

Asymptomatic infection at time of laboratory confirmation has been reported from many settings [52,142-147]. Some of these cases developed some symptoms at a later stage of infection [148,149]. In a recent review, the proportion of positive cases that remained asymptomatic was estimated at 16%, with a range from 6 to 41% [150]. In another systematic review, the pooled proportion of asymptomatic cases at time of testing was 25% [151]. A majority of these cases developed symptoms later on, with only 8.4% of the cases remaining asymptomatic throughout the follow-up period [151]. There are also reports of asymptomatic cases with laboratory-confirmed viral shedding in respiratory and gastrointestinal samples [148,152,153]. Similar viral loads in asymptomatic versus symptomatic cases have been reported, indicating the potential of virus transmission from asymptomatic patients [154].

Asymptomatic transmission (i.e. when the infector has no symptoms throughout the course of the disease), is difficult to quantify. Available data, mainly derived from observational studies, vary in quality and seem to be prone to publication bias [151,155]. Mathematical modelling studies (not peer-reviewed) have suggested that asymptomatic individuals might be major drivers for the growth of the COVID-19 pandemic [156,157].
Although transmission from asymptomatic carriers has been reported [158,159], 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 [127].
Pre-symptomatic transmission (i.e. when the infector develops symptoms after transmitting the virus to another person) has been reported [147,160,161]. Exposure of secondary cases occurred 1–3 days before the source patient developed symptoms [161]. 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, respectively [162]. Pre-symptomatic transmission was deemed likely based on a shorter serial interval of COVID-19 (4.0 to 4.6 days) than the mean incubation period (five days) [163].

Major uncertainties remain with regard to the influence of pre-symptomatic transmission on the overall transmission dynamics of the pandemic because the evidence on transmission from asymptomatic cases from case reports is suboptimal.

Transmission risks in different settings

Currently available evidence indicates that COVID-19 may be transmitted from person to person through several different routes. In the scoping review published by La Rosa et al [164], the human coronaviruses primary transmission mode is person-to-person contact through respiratory droplets generated by breathing, sneezing, coughing, etc., as well as contact (direct contact with an infected subject or indirect contact, trough hand-mediated transfer of the virus from contaminated fomites to the mouth, nose, or eyes). Infection is understood to be mainly transmitted via large respiratory droplets containing the SARS-CoV-2 virus. Transmission through aerosols has also been implicated but the relative role of large droplets and aerosols is still unclear. Indirect transmission through fomites that have been contaminated by respiratory secretions is considered possible, although, so far, transmission through fomites has not been documented.

Evidence on SARS-CoV-2 transmission is available from a recent animal study on ferrets, which are considered suitable animal models for human respiratory infections, that assessed transmission in an experimental setting [165]. The findings suggest that direct transmission occurs between the animals, and the virus can be shed through multiple routes with rapid transmission to naive hosts in close contact with the infected hosts. The evidence for airborne transmission is considered less robust than the evidence for direct contact transmission between infected animals and naïve animals.

Transmission in children and in school

Children most likely contract COVID-19 in their households or through contact with infected family members, particularly in countries where school closures and strict physical distancing has been implemented [49,54,166,167]. In a publication from Italy, exposure to SARS-CoV-2 from an unknown source or from a source outside the child's family accounted for 55% of the cases of infection [46], while in another Italian cohort, contact with a SARS-CoV-2 infected person outside the family was rarely reported and 67.3% (113/168) of children had at least one parent who tested positive for SARS-CoV-2 infection [47]. Two studies on household transmission estimated the household secondary attack rate (SAR) to be 16.3% [168] and 13.8% [169]. Age-stratified analysis showed that the SAR in children was 4.7% compared with 17.1% in adults (≥ 20 years of age) [168], and that the odds of infection in children was 0.26 times (95%CI 0.13-0.54) of that among the elderly (≥ 60 years of age) [169].

Child-to-adult transmission appears to be uncommon. There are few case reports, with poorly documented data, describing a paediatric case as potential source of infection for adults [120,170].

Crowded and confined indoor spaces

Several outbreak investigation reports have shown that COVID-19 transmission can be particularly effective in crowded, confined indoor spaces such as workplaces including factories, churches, restaurants, ski resorts, shopping centres, worker dormitories, cruise ships and vehicles, or events occurring indoor such as, parties, and dance classes, [171]. They indicated that transmission can be linked with specific activities, such as singing in a choir [172] or religious services that may be characterised by increased production of respiratory droplets through loud speech and singing.
In a study of 318 outbreaks in China, transmission in all cases except one occurred in indoor spaces [173]. The only case of outdoor transmission identified in this study involved two persons. However, outdoor events have also been implicated in the spread of COVID-19, typically those associated with crowding such as carnival celebrations [174] and football matches [175] suggesting a risk of transmission linked to crowding even at outdoor events. However, exposure in crowded indoor spaces is also very common during such events.

The duration that people stay in indoor settings appears also to be associated with the attack rate. For example, in a 2.5 hour choir practice in Washington, US, there were 32 confirmed and 20 probable secondary COVID-19 cases among 61 participants (85.2%)[172].
An epidemiological investigation at a call centre in South Korea showed an attack rate of 43.5% among 216 employees on the 9th floor of the call centre indicating high transmission in crowded indoor workplace environment [176]. Most of the infected employees were sitting at the same side of the 9th floor which suggests the influence of proximity, but there was no obvious relation of risk of transmission and distance from the index case on this side of the 9th floor. The authors also conclude that the duration of contact played the most important role in spreading of COVID-19, since the cases were limited almost exclusively to the 9th floor despite interaction with colleagues in other settings (such as the elevators and lobby).
It is not possible to disentangle in these reports the role of physical proximity and direct contact through handshaking, or indirect transmission through contaminated objects and surfaces or longer distance transmission through aerosols. However, they illustrate the risk of transmission in crowded indoor settings and the importance of bundled prevention measures.
A systematic review and meta-analysis of 172 observational studies both in healthcare settings and the community, that looked into the effect of distance from the source patient and the use of respiratory and eye protection in the risk of transmission of SARS-CoV, MERS-CoV and SARS-CoV-2, concluded that physical distancing of at least one metre, use of face masks and eye protection were associated with a much lower risk of transmission [177]. Distances of two metres provided an even larger protective effect and the use of respirators was found to be more protective than medical masks in this review.
In a restaurant outbreak of 10 cases in three families in Guangzhou, China, transmission was attributed to the spread of respiratory droplets carrying SARS-CoV-2 by the airflow generated by the air-conditioning [128].
Similarly, two other outbreaks from China in January 2020 attribute air conditioning systems using a re-circulating mode as a likely aid to transmission [178].

Schools

In the investigation of the first outbreak in France, one infected child attended three different schools while symptomatic and despite 112 contacts identified (including children and teachers), no symptomatic secondary cases were detected [179]. In a recent study from New South Wales, Australia, 863 close contacts of 18 COVID-19 cases (9 students and 9 staff) from 15 schools (10 high schools and 5 primary schools) were tested. Of these 863 close contacts, only two students have been identified as secondary cases. The secondary case in high school was presumed to have been infected following close contact with two student cases. The other secondary case was presumed to have been infected by a teacher who was a case. The investigation found no evidence of children infecting teachers [180].

Sports

Sporting events pose a potential risk from SARS-CoV-2 infection to athletes, coaches and spectators alike [181-184]. This is particularly an issue in certain settings where athletes train in groups, engage in contact sports, share equipment or use common areas, including locker rooms. Moreover, community and individual-level recreational sport activities could also potentially heightened risk of spreading the coronavirus. Transmission could occur through person-to-person contact, exposure to a common-source or aerosols/droplets from an infected individual.

Whether physical exertion per se increases the risk of infections to the athlete is controversial. It has been speculated that vigorous exercise can temporarily suppress the immune function but this assertion has been questioned [185]. The return to vigorous exercise during convalescence has raised the concern of cardiac complications [183] but an association with SARS-CoV-2 infections has not been documented to date. In light of the benefits of regular physical activity to physical and mental health it is important to remain active during the COVID-19 pandemic while respecting the physical distancing and personal hygiene recommendations [186].

Neither waterborne transmission of SARS-CoV-2 virus in humans, nor occurrence of SARS-CoV-2 virus in the seawater environment has been proven to date. Scientists from the Spanish National Research Council (CSIC) have released a report on the current state of knowledge about the transmission of the novel coronavirus in recreational areas used for bathing and other aquatic activities [36,37]. The report reviews the available scientific literature to give a

series of recommendations. According to the CSIC findings, infection by SARS-CoV-2 through contact with water under usual bathing conditions is very unlikely during recreational activities.

References

Supporting document: List of references ▸ (https://www.ecdc.europa.eu/sites/default/files/documents/References-DiseaseBackground-COVID-19-2020-06-11.pdf)

Coronavirus (/en/search?f%5B0%5D=diseases%3A2943) | COVID-19 (/en/search?f%5B0%5D=diseases%3A2942) | Public health threat (/en/search?f%5B0%5D=public_health_areas%3A1583)

Page last updated 11 Jun 2020

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Prevalence of Asymptomatic SARS-CoV-2 Infection

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A Narrative Review

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https://doi.org/10.7326/M20-3012

Eligible for CME Point-of-Care

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread rapidly throughout the world since the first cases of coronavirus disease 2019 (COVID-19) were observed in December 2019 in Wuhan, China. It has been suspected that infected persons who remain asymptomatic play a significant role in the ongoing pandemic, but their relative number and effect ha been uncertain. The authors sought to review and synthesize the available evidence on asymptomatic SARS-CoV-2 infection. Asymptomatic persons seem to account for approximately 40% to 45% of SARS-CoV-2 infections, and they can transmit the virus to others for an extended period, perhaps longer than 14 days. Asymptomatic infection may be associated with subclinical lung abnormalities, as detected by computed tomography. Because of the high risk for silent spread by asymptomatic persons, it is imperative that

testing programs include those without symptoms. To supplement conventional diagnostic testing, which is constrained by capacity, cost, and its one-off nature, innovative tactics for public health surveillance, such as crowdsourcing digital wearable data and monitoring sewage sludge, might be helpful.

Key Summary Points

The likelihood that approximately 40% to 45% of those infected with SARS-CoV-2 will remain asymptomatic suggests that the virus might have greater potential than previously estimated to spread silently and deeply through human populations.

Asymptomatic persons can transmit SARS-CoV-2 to others for an extended period, perhaps longer than 14 days.

The absence of COVID-19 symptoms in persons infected with SARS-CoV-2 might not necessarily imply an absence of harm. More research is needed to determine the significance of subclinical lung changes visible on computed tomography scans.

The focus of testing programs for SARS-CoV-2 should be substantially broadened to include persons who do not have symptoms of COVID-19.

In the early months of the coronavirus disease 2019 (COVID-19) pandemic, an iconic image has been the “proned” patient in intensive care, gasping for breath, in imminent need of artificial ventilation. This is the deadly face of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which as of

26 May 2020 had claimed more than 348 000 lives worldwide (1). But it is not the only face, because SARS-CoV-2 now seems to have a dual nature: tragically lethal in some persons and surprisingly benign in others.

Since February 2020 (2, 3), there have been reports of persons who were infected with SARS-CoV-2 but did not develop symptoms of COVID-19. In some cases (4, 5), the viral load of such asymptomatic persons has been equal to that of symptomatic persons, suggesting similar potential for viral transmission. The prevalence of asymptomatic SARS-CoV-2 infection, however, has remained uncertain. We sought to review and synthesize the available evidence on testing for SARS-CoV-2 infection, carried out by real-time reverse transcriptase polymerase chain reaction using nasopharyngeal swabs in all studies that specified the method of testing.

Most data from the 16 cohorts in this narrative review are not the output of large, carefully designed studies with randomly selected, representative samples. They do not generally purport to depict anything more than certain circumscribed cohorts at specific moments in time. We have not attempted to pool them for the purposes of statistical analysis. When viewed as a collection, though—as a kind of mosaic or patchwork—these data may yield potentially valuable insights into SARS-CoV-2 incidence and the highly variable effect of infection.

The difficulty of distinguishing asymptomatic persons from those who are merely presymptomatic is a stumbling block. To be clear, the asymptomatic individual is infected with SARS-CoV-2 but will never develop symptoms of COVID-19. In contrast, the presymptomatic individual is similarly infected

but eventually will develop symptoms. The simple solution to this conundrum is longitudinal testing—that is, repeated observations of the individual over time. Unfortunately, only 5 of our cohorts include longitudinal data. We must therefore acknowledge the possibility that some of the proportions of asymptomatic persons are lower than reported.

Methods

From 19 April through 26 May 2020, using the keywords *COVID-19*, *SARS-CoV-2*, *symptoms*, and *asymptomatic*, we periodically searched the published medical literature using the PubMed service maintained by the U.S. National Library of Medicine of the National Institutes of Health. We also searched for unpublished manuscripts using the bioRxiv and medRxiv services operated by Cold Spring Harbor Laboratory. In addition, we searched for news reports using Google and monitored relevant information shared on Twitter.

Cohorts

Iceland

In the largest cohort in our set (6), researchers in Iceland used the following 2 methods to screen the general population for SARS-CoV-2 infection: an open invitation for interested parties to register online then provide biosamples at a Reykjavik location, and a text message sent to "randomly chosen Icelanders between the ages 20 and 70 years" inviting them to

participate in the same manner as the first group (Table)<(7–19)>. In all, 13 080 persons volunteered for the screening, 100 (0.8%) of whom tested positive for SARS-CoV-2. All who tested positive were aged 10 years or older. None of the 848 children younger than 10 years in the sample tested positive. Among those with positive results, 43 (43%) had no symptoms of COVID-19 at the time of testing. As the researchers note, though, "symptoms almost certainly developed later in some of them" (6).

Table. Summary of SARS-CoV-2 Testing Studies

Table. Summary of SARS-CoV-2 Testing Studies

Cohort	Tested, *n*	SARS-CoV-2 Positive, *n* (%)	Positive but Asymptomatic, *n* (%)	Notes*
Iceland residents (6)	13 080	100 (0.8)	43 (43.0)	R
Vo', Italy, residents (7)	5155	102 (2.0)	43 (42.2)	R, L
Diamond Princess cruise ship passengers and crew (8)	3711	712 (19.2)	331 (46.5)	–
Boston homeless shelter occupants (9)	408	147 (36.0)	129 (87.8)	–
New York City obstetric patients (11)	214	33 (15.4)	29 (87.9)	L
U.S.S. *Theodore Roosevelt* aircraft carrier crew (12)	4954	856 (17.3)	~500 (58.4)	E
Japanese citizens evacuated from Wuhan, China (2)	565	13 (2.3)	4 (30.8)	L
Greek citizens evacuated from the United Kingdom, Spain, and Turkey (14)†	783	40 (5.1)	35 (87.5)	L
Charles de Gaulle aircraft carrier crew (13)	1760	1046 (59.4)	~500 (47.8)	E
Los Angeles homeless shelter occupants (10)	178	43 (24.2)	27 (62.8)	–
King County, Washington, nursing facility residents (15)	76	48 (63.2)	3 (6.3)	L
Arkansas, North Carolina, Ohio, and Virginia inmates (16)	4693	3277 (69.8)	3146 (96.0)	–
New Jersey university and hospital employees (17)	829	41 (4.9)	27 (65.9)	–
Indiana residents (18)	4611	78 (1.7)	35 (44.8)	R
Argentine cruise ship passengers and crew (19)	217	128 (59.0)	104 (81.3)	–
San Francisco residents (29)	4160	74 (1.8)	39 (52.7)	–

E = estimated from incomplete source data; L = longitudinal data collected; R = representative sample.
* A dash indicates that the study did not have a representative sample, collected no longitudinal data, and did not require estimation of missing data.
† Clarified via e-mail communication with coauthor.

Vo', Italy

At the beginning and end of a 14-day lockdown imposed by authorities in the northern Italian town of Vo' (7), researchers collected nasopharyngeal swabs from 2812 residents during the first sampling effort and 2343 during the second; this represented 85.9% and 71.5%, respectively, of the entire population. In the first group, 30 (41.1%) of 73 persons who tested positive for SARS-CoV-2 had no symptoms. In the second, 13 (44.8%) of 29 who tested positive were asymptomatic. According to the researchers, in the roughly 2-week period between the sampling efforts, none of the asymptomatic

persons developed any symptoms of COVID-19. In addition, through contact tracing, they confirmed that several new cases of SARS-CoV-2 infection that appeared during the second sampling had been caused by exposure to asymptomatic persons. In Vo' during the 14-day period studied, young children seemed to play no role in the transmission of SARS-CoV-2: "No infections were detected in either survey in 234 tested children ranging from 0 to 10 years, despite some of them living in the same household as infected people" (7).

Diamond Princess

On 3 February 2020, the *Diamond Princess* cruise ship returned to Yokohama, Japan, for quarantine (8), having transferred an ill passenger to shore in Hong Kong on 25 January who later tested positive for SARS-CoV-2. As of 16 March, 712 (19.2%) of 3711 passengers and crew had tested positive. At the time of testing, 331 (46.5%) of those with positive results were asymptomatic. Although the latter infected persons reported no symptoms, some actually had subclinical changes in their lungs. When computed tomography scans for 76 of these persons were examined, 54% showe opacities (20).

An independent statistical modeling analysis (21) based on data available as of 21 February claimed to estimate—with "a Bayesian framework using Hamiltonian Monte Carlo algorithm"—the proportion of asymptomatic persons on the *Diamond Princess*; it arrived at a figure of 17.9%. Considering, though, that data for asymptomatic persons were available only

for 15 through 20 February and that the actual proportions of asymptomatic persons among those tested on these dates were 56.7%, 54.3%, 70.7%, 73.9%, 86.1%, and 46.2%, this estimate seems puzzling. In a separate news account (22), one of the coauthors of this analysis was reported to have estimated that "40% of the general population might be able to be infected [with SARS-CoV-2] without showing any signs."

Boston Homeless Shelter

After a cluster of 15 COVID-19 cases was identified over 5 days at a large homeless shelter in Boston, Massachusetts, the infected persons were removed from the shelter, and all occupants were subsequently tested over a 2-day period (9). Among 408 occupants, 147 (36.0%) tested positive for SARS-CoV-2, of whom 129 (87.8%) were asymptomatic (23). The researchers concluded that "front-door symptom screening in homeless shelter settings will likely miss a substantial number of COVID-19 cases in this high-risk population" (9).

Los Angeles Homeless Shelter

On 28 March, an initial case of COVID-19 was diagnosed with a positive test result at a homeless shelter in downtown Los Angeles, California (10). After a cluster of symptomatic persons was identified early in the week of 20 April, the shelter was closed to new occupants and testing was started for current occupants. As of 22 April, 43 (24.2%) of 178 completed tests were positive for

SARS-CoV-2 and 27 (63.8%) of the persons who tested positive were asymptomatic.

New York City Obstetric Patients

Between 22 March and 4 April 2020, women who delivered infants at 2 New York City hospitals were tested for SARS-CoV-2 (11). Among 214 patients, 33 (15.4%) tested positive, 29 (87.9%) of whom were asymptomatic. The researchers note that "fever developed in 3 (10%) before postpartum discharge (median length of stay, 2 days)" (11). Two of those patients, though, were presumed to have endomyometritis, for which they were treated with antibiotics.

U.S.S. *Theodore Roosevelt*

The first case of SARS-CoV-2 infection aboard the American aircraft carrier U.S.S. *Theodore Roosevelt* was diagnosed on 22 March 2020 (24). As of 24 April, 4954 crew members had been tested for the virus; 856 (17.3%) tested positive (12). According to a news report, about 60% of those with pos results were asymptomatic (25). After an extended period of isolation, many of these asymptomatic persons continued to test positive for SARS-CoV-2. An internal U.S. Navy document stated, "Results of out-testing portions of the [*Theodore Roosevelt*] crew following 14 days of quarantine leads us to reevaluate our assessment of how the virus can remain active in an asymptomatic host" (26).

Charles de Gaulle Aircraft Carrier

On 8 April 2020, crew members aboard the French naval vessel *Charles de Gaulle* first began showing symptoms of COVID-19, 24 days after last having had contact with those outside the ship while docked on 15 March (27). On 10 April, 50 crew members received positive test results for SARS-CoV-2. The entire crew of 1760 was subsequently tested. As of 18 April, 1046 (59.4%) had tested positive, and of these, nearly 50% were asymptomatic (13).

Japanese Citizens Evacuated From Wuhan, China

As of 6 February 2020, a total of 565 Japanese citizens had been repatriated from Wuhan, China, on charter flights. Thirteen (2.3%) tested positive for SARS-CoV-2, of whom 4 (30.8%) were asymptomatic. As of 6 March, none of the latter persons had developed COVID-19 symptoms (2).

Greek Citizens Evacuated From Spain, Turkey, and the United Kingdom

From 20 through 25 March 2020, a total of 783 Greek citizens were repatriated from Spain, Turkey, and the United Kingdom on 7 flights. Forty (5.1%) tested positive for SARS-CoV-2 (14). At the time of testing, 39 (97.5%) were asymptomatic. At follow-up about 2 weeks later, 35 (87.5%) had remained asymptomatic (Lytras T. Personal communication.).

Nursing Facility Residents in King County, Washington

On 1 March 2020, a staff member who had worked at a 116-bed skilled-nursing facility in King County, Washington, on 26 and 28 February tested positive for SARS-CoV-2 (15). On 13 March, 76 (92.6%) of the facility's 82 current residents were tested; 23 (30.3%) tested positive. At the time of testing, 12 (52.2%) of the latter persons were asymptomatic. On 19 and 20 March, 49 residents were retested, including those who had previously received negative results and those who had tested positive but were asymptomatic or had atypical symptoms. In this second round of testing, 24 residents (49.0%) had positive results. Of these, 15 (63.5%) were asymptomatic. After a median of 4 days of follow-up, 24 (88.9%) of the 27 asymptomatic persons developed symptoms of COVID-19.

The researchers note, "More than half of residents with positive test results were asymptomatic at the time of testing and most likely contributed to transmission. Infection-control strategies focused solely on symptomatic residents were not sufficient to prevent transmission after SARS-CoV-2 introduction into this facility" (15).

Inmates in Arkansas, North Carolina, Ohio, and Virgin

Widespread outbreaks of COVID-19 in the correctional facilities of several states have led to large-scale screening programs. According to research by Reuters journalists (16), as of 25 April 2020, SARS-CoV-2 test results that include data on symptom status were available for 4693 inmates in the state prison systems of Arkansas, North Carolina, Ohio, and Virginia. Among

these inmates, 3277 (69.8%) tested positive, of whom 3146 (96%) had no symptoms at the time of testing.

Rutgers University Students and Employees

From 24 March through 7 April 2020, researchers recruited 829 students and employees at Rutgers University and 2 affiliated hospitals for SARS-CoV-2 testing (17); 546 were health care workers. In total, 41 (4.9%) tested positive. Among health care workers, 40 (7.3%) tested positive, compared with 1 (0.4%) of those in other fields. Of all who tested positive, 27 (65.9%) reported no symptoms when they were tested.

Indiana Residents

From 25 April through 1 May 2020, the Indiana State Department of Health and the Indiana University Richard M. Fairbanks School of Public Health tested 4611 residents of Indiana for SARS-CoV-2 (18, 28). "This number includes more than 3,600 people who were randomly selected and an additional 900 volunteers recruited through outreach to the African American and Hispanic communities to more accurately represent state demographics" (28). In total, 78 (1.7%) tested positive; 35 (44.8%) of these persons were asymptomatic.

Argentine Cruise Ship Passengers and Crew

In mid-March 2020, a cruise ship departed Ushuaia, Argentina, for a planned 21-day expedition (19). After the emergence of a febrile passenger on the eighth day of the cruise, the ship's itinerary was altered, and it eventually docked at Montevideo, Uruguay, on the 13th day. All 217 passengers and crew members were tested; 128 (59.0%) tested positive, of whom 104 (81.3%) were asymptomatic.

San Francisco Residents

During 4 days in late April 2020, "4,160 adults and children, including more than half of the residents in the 16 square blocks that make up San Francisco Census Tract 229.01" in the Mission District, were tested (29). Seventy-four (1.8%) tested positive, of whom 39 (52.7%) were asymptomatic.

Discussion

Despite concerns about distinguishing asymptomatic from presymptomatic persons, data from 4 of 5 of the cohorts with longitudinal reporting suggest that a small fraction of asymptomatic persons may eventually develop symptoms. In the Italian and Japanese cohorts, 0% of asymptomatic persons became symptomatic. In the Greek and New York cohorts, 10.3% of asymptomatic persons became symptomatic. In the New York cohort, the figure might be as low as 3.4% because of the presumed diagnosis of endomyometritis in 2 of the 3 women who developed fevers. The observation period in this cohort, however, was extremely brief: a median of 2 days.

The King County cohort—in a skilled-nursing facility—is an outlier. Of 27 initially asymptomatic residents, 24 (88.9%) eventually developed symptoms and were therefore recategorized as having been presymptomatic. These persons were presumably much older and had more comorbid conditions than those in the other 4 longitudinal cohorts. In addition, they resided together in a single facility, which might have allowed for repeated exposures to infected persons. More research is needed to ascertain the effect of age and environmental factors on the natural history of COVID-19.

The Vo' cohort seems to confirm that asymptomatic persons can indeed transmit SARS-CoV-2 to others, and the experience aboard the U.S.S. *Theodore Roosevelt* suggests that they might be able to transmit the virus to others for longer than 14 days. These worrisome findings could explain, in part, the rapid spread of the virus around the globe. Persons who do not feel or look ill are likely to have far more interaction with others than those who have symptoms. If asymptomatic transmission is indeed common, testing only those with symptoms would seem to be folly.

The finding that 54% of the 76 asymptomatic persons on the *Diamond Princess* who were examined by computed tomography appeared to h significant subclinical abnormalities in their lungs is disturbing. Further research will be required to confirm this potentially important finding, taking into account possible confounding factors, including the age of passengers aboard the *Diamond Princess*. If confirmed, this finding suggests that the absence of symptoms might not necessarily mean the absence of harm. The subclinical nature of the finding raises the possibility that SARS-

CoV-2 infection causes subtle deficits in lung function that might not be immediately apparent.

Does the relatively high proportion (60.5%) of asymptomatic cases on the U.S.S. *Theodore Roosevelt*—whose crew members, presumably, are mostly in their 20s and 30s—suggest that asymptomatic infection is more likely in younger persons? Perhaps, but it must be noted that the proportion of asymptomatic infection (47.8%) on the *Charles de Gaulle* aircraft carrier seems to be only marginally higher than average. A case series from Wuhan, China, from 24 December 2019 to 24 February 2020 included data for "78 patients from 26 cluster cases of exposure to the Hunan seafood market or close contact with other patients with COVID-19" (30). Asymptomatic patients "were younger (median [interquartile range] age, 37 [26-45] years vs 56 [34-63] years; $P < .001$), and had a higher proportion of women (22 [66.7%] women vs 14 [31.%] [*sic*] women; $P = .002$)."

As noted earlier, the data and studies reviewed here are imperfect in many ways. The ideal study of asymptomatic SARS-CoV-2 infection has yet to be done. What might that study look like? Most important, it must includ large, representative sample of the general population, similar to the U serosurvey for which the National Institutes of Health is currently recruiting (31). In contrast to the narrowly defined cohorts here, it will be illuminating to have data that accurately reflect the population at large. In addition, longitudinal data must be collected over a sufficiently long time to distinguish between asymptomatic and presymptomatic cases.

Closed cohorts, such as cruise ships, aircraft carriers, and correctional facilities, offer both advantages and disadvantages. Because the likelihood of viral exposure is so much greater than in other settings, the "treatment" that participants receive may be close to uniform. As a result, we may learn more about the average incidence of asymptomatic infection. But the confined environment—which ensures frequent, overlapping interaction between participants—makes it challenging to accurately trace contacts and elucidate the chain of viral transmission.

On the basis of the 3 cohorts with representative samples—Iceland and Indiana, with data gathered through random selection of participants, and Vo', with data for nearly all residents—the asymptomatic infection rate may be as high as 40% to 45%. A conservative estimate would be 30% or higher to account for the presymptomatic admixture that has thus far not been adequately quantified. In any case, these high rates are not aligned with current testing programs that have predominantly focused on symptomatic cases. Beyond expanding testing to those without symptoms or known exposure, our inability to recognize carriers might make necessary the broad adoption of preventive strategies, such as masks.

The 96% rate of asymptomatic infection among thousands of inmates in 4 state prison systems is remarkable. Without any longitudinal data, we cannot estimate the number of presymptomatic cases. If the missing data prove to be similar to the Italian, Japanese, Greek, and New York cohorts, though, the vast majority of these persons will remain asymptomatic. Why,

then, might the asymptomatic infection rate in this setting be so anomalously high?

One plausible factor could be cross-immunity imparted by the betacoronaviruses HCoV-OC43 and HCoV-HKU1, which has been proposed as a mitigating factor in the spread of SARS-CoV-2 (32). According to the U.S. Centers for Disease Control and Prevention, HCoV-HKU1 was active across the United States from late November 2019 through mid-February 2020 (33). In a locked-down congregate setting like a prison, it seems possible that contagious respiratory viruses could spread rapidly, so it would be interesting to do a serosurvey for antibodies to these betacoronaviruses. Still, 96% is very high. It would be prudent to review the source data carefully for errors.

What individual differences might account for why 2 persons of the same age, sex, and health status, for example, have idiosyncratic responses to SARS-CoV-2 infection? Why does one come through with nary a symptom, while the other lies near death in intensive care? At the moment, we simply do not know. If ever there were a need for precision medicine—for dee and thoroughly understanding the multitudinous "-omics" that shape us—this is it. Perhaps there will be not just 1 therapy or vaccine for SARS-CoV-2 but versions that are individualized to maximize their efficacy.

In countries like the United States that have been hardest hit by the SARS-CoV-2 pandemic, it has been apparent for some time that the amount of testing must be significantly and rapidly increased—perhaps by an order of magnitude or more. With this new knowledge that a large proportion of

those infected with SARS-CoV-2 have no symptoms, the urgency for more testing becomes even greater.

In a perfect world, perhaps using simple, accurate, inexpensive technology that is still on the drawing board (34), we would test each person every day for SARS-CoV-2. Until that is possible, innovative surveillance tactics might provide useful data for public health officials. Self-monitoring with internet-connected thermometers and smart watches that monitor heart rate, then crowdsourcing the resulting data, has been shown to accurately predict the incidence of influenza-like illness as reported by the California Department of Public Health and the Centers for Disease Control and Prevention (35–37). Similarly, monitoring sewage sludge provided "SARS-CoV-2 RNA concentrations [that] were a seven-day leading indicator ahead of compiled COVID-19 testing data and led local hospital admissions data by three days" (38).

The early data that we have assembled on the prevalence of asymptomatic SARS-CoV-2 infection suggest that this is a significant factor in the rapid progression of the COVID-19 pandemic. Medical practice and public h measures should be modified to address this challenge.

This article was published at Annals.org on 3 June 2020.

Comments

16 Comments

SIGN IN TO SUBMIT A COMMENT

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July 2020

Proportion of Asymptomatic SARS-COV-2 Carriers: The Challenge of Stepping Twice into the Same River

To the Editor,

In a recent narrative review, Oran and Topol (1) aimed to determine the prevalence of asymptomatic SARS-CoV-2 infection. They concluded that asymptomatic persons seem to account for 40% to 45% of the infections.

What moves us to seek the proportion? Assuming that it is feasible to anticipate the scale of tricky asymptomatic carriers according to accessible symptomatic cases. Detecting and isolating these persons will prevent them from spreading the virus. This demand ignited the passion. In fact, only adopt the inferred proportion to predict existing asymptomatic carriers might fail at a greater than expected rate.

To a large extent, the relative proportion of asymptomatic carriers and presymptomatic patients reflects the capacity of active detection, intensity of RT-PCR testing and the scope of coverage. Meanwhile, different pandemic phases are the most important heterogeneous factor in determining the true number of asymptomatic carriers.

At the beginning of the outbreak, nucleic acid testing resources were extremely limited. Close contact tracking could incidentally catch only a small number of asymptomatic carriers (2). The overall initial data (1% asymptomatic) mirrored the dilemma (3). Evacuated citizens from the epicenters were convenient samples which could partially represent the internal situations.

As community outbreaks continued to spread, a wider range of the population exposed to the virus. With the gradual improvement of nucleic acid testing capacity, widespread testing was carried out in enclosed environments. As expected, poorly quantified presymptomatic admixture disturbed ou asymptomatic carrier. Only longitudinal studies with a long enough follow-up period could effec distinguish them. In addition, the demographic characteristics of these samples—cruise ships, nursing facilities (mainly for the elderly), obstetrics (women of childbearing age) and aircraft carriers (healthy young male dominated)—had a significant impact on the proportion of asymptomatic carriers.

When the exponential growth of cases had been successfully reversed by lockdown and social distancing, longitudinal serial testing data showed the falling asymptomatic infection rates tracked the declining general population infection curve (4).

At the remission period, substantially all community outbreaks had been contained. New cases persisted to tend to zero. Mass indiscriminate RT-PCR testing was employed to identify hidden asymptomatic

carriers to completely interrupt chains of transmission. The results indicated the proportion of asymptomatic carriers diminished dramatically (5).

In the setting of coexisting global pandemic and local remission, it is wise to rethink about the evidence dynamically and comprehensively rather than stick to the rigid proportion.

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Andrew N. Cohen, Bruce Kessel • Center for Research on Aquatic Bioinvasions • 2 July 2020

Problems with review: false positives; inadequate longitudinal study; overly narr symptom definitions; poor evidence of asymptomatic transmission

Oran and Topol have not responded to our comments submitted earlier (June 7) nor to some critical comments submitted by others. We write so that four key criticisms are not missed.

The authors concluded that 40-45% of individuaCenter for Research on Aquatic Bioinvasions, Richmond CA, USA; John A. Burns School of Medicine, University of Hawaii, Honolulu HI, USAls infected with SARS-CoV-2 are asymptomatic, in the sense of never developing symptoms. The authors state, and we agree, that evidence for the asymptomatic ratio in the general population must be based on (a) cohorts that are representative of the general population, and (b) longitudinal studies that are capable of distinguishing individuals that never develop symptoms from those who are simply presymptomatic at the time of testing. Of the 16 studies covered in the review only three, according to the authors, are of representative

cohorts, and of these only one is longitudinal: the study conducted in Vo', Italy (1). Accordingly, we will focus on the Vo' study.

We previously commented, based on the authors' summary of the Vo' study, that even a low false positive rate could produce enough false positives to account for all of the individuals reported as infected and asymptomatic. We have now examined the data set posted with the Vo' preprint (1), and can provide more detail. At total of 5,220 tests were administered to 2,900 residents, with 131 positive results on samples from 80 residents. 35 residents were classified as both infected and asymptomatic; of these, 25 tested positive only once. With the reported test numbers, a false positive rate of only 0.5% would produce 25 false positive results. Since the median false positive rate in 43 external quality assessments of similar viral diagnostic tests was 2.3% (2), 25 of the 35 residents reported as infected and asymptomatic could easily have been uninfected individuals who received false positive test results.

We, along with Cevik et al. and Hyde, raised concerns about the inadequacy of the longitudinal studies reviewed. A fully adequate longitudinal study would check for symptoms over the entire period of time in which symptoms could potentially appear. Since an individual can test positive near the beginning of the incubation period, an effective longitudinal study should monitor for symptoms over a period that includes the time from the first positive test to either the first negative test or to the length of the maximum incubation period after the first positive test, whichever comes first. The maximum incubation period for COVID-19 isn't known, but the best fit model indicates that it is over 14 days (3).

The authors inaccurately characterized the length of time that the Vo' study monitored symptoms. They stated that tests were conducted "at the beginning and end of a 14-day lockdown" and referred to "the roughly 2-week period between the sampling efforts." In responding Cevik et al. the authors described the Vo' study as a "longitudinal…study, complete over 14 days…none of the subjects who were asymptomatic at the beginning of the study had developed symptoms by the end." These statements appear to suggest that symptoms were monitored over 14 or nearly 14 days. However, the Vo' data set shows that 10 of the 35 residents reported as infected and asymptomatic were not tested again after their initial positive test, and thus were not monitored longitudinally at all. Another 9 of the 35 residents weren't monitored until they received a negative test result or until 14 days after their first positi
Thus a majority of the 35 residents—even assuming they were all infected—may have been presymptomatic rather than asymptomatic.

Cevik et al. and Hyde argued that the studies reviewed did not consider all relevant symptoms when distinguishing asymptomatic individuals, and we agree. The World Health Organization (WHO) lists 10 symptoms of COVID-19 (4), but the Vo' study classified residents as symptomatic only if they had fever or cough or were hospitalized. Consider one symptom listed by WHO that the Vo' study did not ask about: the loss of taste or smell. Based on the prevalence of this symptom in individuals that tested positive for COVID-19 but did not have fever or cough (5), 8 or 9 of the 35 Vo' residents reported as infected and asymptomatic would be expected to have this symptom.

Cevik et al., Hyde, and Halperin argued, and we agree, that the evidence for asymptomatic transmission cited by the authors is too weak to support the authors' conclusions that there is a "high risk" of spread by asymptomatic individuals, that "asymptomatic individuals can transmit SARS-CoV-2 to others for an extended period", and that transmission by asymptomatic individuals is a "significant factor in the rapid progression of the COVID-19 pandemic." The authors defended these statements by referring to the Vo' study, which suggested that two individuals may have been infected by contacts that the study identified as asymptomatic and infected, since in each case contact tracing failed to identify an alternative source of infection. However, the strength of that argument depends on how thorough and effective the contact tracing was, which in this study failed to identify any possible source of infection in 25% of the cases traced. Also, as discussed earlier, the individuals identified by the study as potential asymptomatic sources might have been uninfected false positives, or infected but not asymptomatic. These two suggested cases thus seem an inadequate basis for the authors' statements about the risk and significance of asymptomatic transmission.

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Disclosures:

No conflicts of interest.

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Could the MMR Vaccine Offer Cross-protection for Covid-19?

Dear Editor,

We have read with enthusiasm the article by Daniel et al.,[1] describing the prevalence of asymptomatic SARS-CoV-2 infection. It draws our attention the interesting finding of the inmates in Arkansas, North

Carolina, Ohio and Virginia, in whom 96% of the positively tested patients were asymptomatic. As the authors proposed that this high rate could be due to cross immunity by the betacoronaviruses HCoV-OC43 and HCoV-HKU1 or could be error in data collection, yet, we think that this high rate is related to the compulsory vaccines given to the inmates.

Given the available data of children being less affected by COVID-19 with significantly lower mortality and no severe cases in 6-10 age range [2], we thought that a childhood vaccine may be also responsible for cross-protection against COVID-19 [3], with Measles, Mumps and Rubella (MMR) vaccine high in the list as a booster dose is scheduled around the age of six.

Measles vaccine was used as a vector for other Coronaviruses such as Severe Acute Respiratory Syndrome Corona Virus (SARS-Co-V) and also in the Middle East Respiratory Syndrome Coronavirus (MERS-Co-V) where it was able to induce multifunctional T cell response in a mouse model [4].

Interestingly, Italy suffered from measles outbreaks in the last couple of years. Physicians in Italy have one of the lowest rates of measles vaccination which may be the cause for such high infections among physicians there [5].

Preliminary data from our assessment of titres for vaccine-preventable diseases in patients with COVID-19 showed high titres with Measles and variable results with Rubella (data not published yet) hence we started the first study for prevention of COVID-19 with Measles, Mumps and Rubella vaccine in Healthcare workers [NCT04357028].

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Wynn Bear, Mingzi Wu • International WYNNBEAR Advanced Innovation, China/US • 29 June 2020

Binary Star Social Systems for SARS-CoV-2

Although truth can be gleaned from lively debates and consensus is usually formed in the midst of discussions and arguments, we preferred 40-45% asymptomatic case rate since some of the comments represent the past, the author's conclusion representative now, more ongoing conclusions will on behalf of the future.

With continuous mutation of the virus, only current data and models will be more conducive to the current work. The author even suggested that this is the early data that they have assembled and therefore manifests that public health measures should be modified to address this challenge. Actually, this unprecedented pandemic calls for unprecedented measures to achieve its ultimate defeat is too much(RE.1).

This is a novel intervention measure be called binary star social systems for symptomatic transmission, pre-symptomatic transmission, and asymptomatic transmission, in which the whole society is divided into two or more subsystems. They are respectively with a swappable model for lockdown and free to get adequately both in economic and social benefits and isolating the virus. The details of the swappable model had been as a Letter submitted to Science (shown in RE.2)

Along with the continuous progress of cognition to SARS-CoV-2, more and more specialist have realized that effective drugs and vaccines will be unable to rely on for a long time, and the use of creative non-pharmaceutical interventions and alternative approaches with reliable means would be a long-term task.

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N.Belgin Akilli, Ramazan Koylu • Konya Resarch and Education Hospital • 23 June 2020

40-45% Asymptomatic case rate may not reflect reality.

Dear Editor,

The world is facing a problem that's very rare to date. Since its diagnosis in December 2019 8,860,331 people have been infected worldwide and 465,740 people have died (22 June 2020) (1). Many issues related to this disease are waiting to be clarified. Oran and Topol analyzed 16 studies on patients with positive diagnosis for Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by reverse transcriptase polymerase chain reaction (RT-PCR), and suggested that the disease may be asymptomatic in 40-45% (2). Even thought he evidence level of the studies is low, we think that a remarkable point that may affectt he daily functioning of health institution sand public health professionals in pandemic conditions is mentioned.

However, the point we want to emphasize is that the sensitivity of RT-PCR may be low due to factors such as suboptimal clinical sampling and variability in viral load and sensitivity of the manufacturer test kit (3). False negativite rate for SARS-CoV-2 was reported between 2-29% (3). In a study of 205 patients, RT-PCR sensitivity was 93% for bronchoalveolaer lavage, 72% for sputum, and 63% for nasal swabs and 32% for throat (4). This value is uncertain for asymptomatic patients. Woloshin et al. stated that determining the test sensitivity in asymptomatic individuals is an urgent priority, and even in a highly sensitive test, negative results cannot exclude the infection if the probability of pretesting is high (5). We think that the rate of asymptomatic individuals in the society may be higher due to the lack of gold standard for the diagnosis of coronavirus disease 2019 (COVID-19).

Despite the World Health Organization's report on the contamination of asymptomatic COVID 19 cases causing confusion, we believe that asymptomatic COVID 19 cases may be more than expected in the community and that public health policies for controlling infection should be developed accordingly.

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Eric Topol, Daniel Oran • Scripps Translational Science Institute • 23 June 2020

Author's Response to Han and Li

None of the sources cited by Han and Li present data that were collected from representative samples. In contrast, three of the studies that we have included in our review are the result of representative samples, and one of these has the added benefit of longitudinal data from a 14-day period. We were impressed by the narrow range reported in these studies for the proportion of asymptomatic infected persons: between 42.2% and 44.8%. However, in the absence of longitudinal data for two of these studies, and the resulting uncertainty concerning the possible admixture of presymptomatic persons, we have suggested that 30% is a conservative estimate.

We agree with Han and Li that carefully designed studies will be required to determine accurately the prevalence of asymptomatic SARS-CoV-2 infection in human populations.

Dongsheng Han, Jinming Li • National Center for Clinical Laboratories, Beijing Hospital, National Center of Gerontology; Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, P.R. China • 16 June 2020

Proportion of asymptomatic SARS-COV-2 infections: need convincing answers

The existence of a substantial but unclear number of asymptomatic SARS-COV-2 patients worldwide has raised concerns among global public health authorities. This narrative review concluded that the proportion of asymptomatic patients might account for approximately 40% to 45% of SARS-CoV-2 infections based on results of 16 cohort studies from different sources. Unfortunately, however, this article did not include any of the studies from China.

In fact, in China, the detection of asymptomatic infection is a core task for combating COVID-19 spread. Based on the studies in China that have been peer-reviewed and officially published, we found that the proportion of asymptomatic infection was no more than 20% (from 6% to 15.8%), much lower than the reported proportion (40% to 45%) in this narrative review.

These studies in China were based on different populations, including hospitalized contacts of COVID-19 patients (Wuhan City in Hubei province: 12.2%, 34/279) [1], all infected people tracked throughout (Shenzhen City in Guangdong province: 6%, 25/391 [2]; Anqing city in Anhui province: 9.6%, 8/83 [asymptomatic infections in childhood cases across China (12.9%, 94/731) [4] and Wuhan city in Hubei province (15.8%, 27/171) [5]. However, due to the differences in the study setting and the included populations of all the studies, including the 16 cohorts in this narrative review, the inferred proportion of asymptomatic SARS-CoV-2 infection, whether 20% or 40%, may not be accurate. The true proportion needs to be answered by more carefully designed studies in the future.

Nevertheless, in the context of the current research, we think that this article should supplement the knowledge we provide here in order to give readers a more objective understanding of the proportion of asymptomatic infections.

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Disclosures:

there is no any conflicts of interest

Daniel Oran, Eric topal • Scripps Translational Science Institute • 15 June 2020

Authors' response to Zoë Hyde

The study cited by Hyde about the U.S.S. Theodore Roosevelt, which reported an asymptomatic proportion of 18.5%, included just 382 (27%) of the 1,417 crew members. The researchers describe this as a "convenience sample of persons who might have had a higher likelihood of exposure."

The fact that 18.5% of this unrepresentative 27% were asymptomatic does not tell us anything about the remaining 73%.

Daniel Oran, Eric Topal • Scripps Translational Science Institute • 15 June 2020

Authors' response to Daniel T. Halperin

In our view, Halperin does not fairly characterize the evidence of asymptomatic transmission presented by Lavezzo et al. concerning their research in Vo', Italy. The authors state, "The presence of a significant number of asymptomatic SARS-CoV-2 infections raises questions about their ability to transmit the virus. To address this issue, we conducted an extensive contact tracing analysis of the 8 new infections."Then, after describing the various contacts of the infected individuals, the authors conclude, "These results suggest that asymptomatic infections may play a key role in the transmission of SARS-CoV-2."

This is the complete sentence in the final paragraph of our review from which Halperin quotes: "The early data that we have assembled on the prevalence of asymptomatic SARS-CoV-2 infection suggest that this is a significant factor in the rapid progression of the COVID-19 pandemic."From our perspective, it appears that Halperin has inferred a far more extreme interpretation than our actual words are meant to convey. We stress that the data are early, not definitive. We describe them as suggestive, not conclusive.

We believe that our review accurately portrays the source material that we have collected. Our review is a beginning, though, not an end. In the months and years to come, we expect that far more will be learned about asymptomatic SARS-CoV-2 infection. We are eager to see what research teams around the world will contribute to this important area.

Daniel T. Halperin • Adjunct Full Professor, Gillings School of Global Public Health, University of North Carolina, Chapel Hill • 10 June 2020

A Very Useful, also Highly Problematic Review Article

Comment: This review is commendably useful for estimating the PROPORTION of SARS-CoV-2 carriers who are asymptomatic. However, the additional conclusion that “asymptomatic SARS-CoV-2 infection…is a significant factor in the rapid progression of COVID-19” appears to be utterly unsubstantiated (and surprising, considering this journal’s normally rigorous peer review standards). Regarding the authors’ assertion, in the abstract, that “asymptomatic persons…can transmit the virus,” only two data are presented to support this: 1) Citing an Italian study, they claim (my CAPS for emphasis) that the Italian authors: “CONFIRMED several new cases of SARS-CoV-2 infection had been caused by exposure to asymptomatic persons.” However, the (non-peer-reviewed) online paper cited merely mentions that 2 (or at most 3) of 8 persons studied “MAY have become infected from an asymptomatic carrier.” (E.g., “Subject 5 reported meeting an asymptomatic infected individual before the lockdown…”) Note the same study reported that “No infections were detected in…234 tested children [under age 11], despite…living in same household as infected people,” consistent with other evidence that children are much less likely become infected, and even if infected are typically asymptomatic (as opposed to presymptomat carriers 2) (www.washingtonpost.com/opinions/2020/05/29/case-reopening-schools-this-fall/).

The only other evidence cited by Oran and Topal for the role of asymptomatic transmission is from one of the other 16 cohort studies they reviewed, regarding which they conclude: “More than half of [infected nursing facility] residents…were ASYMPTOMATIC at the time of testing and MOST LIKELY contributed to transmission.” In fact, the cited 3) NEJM paper explains that “7 days after their positive test, 24 of 27 asymptomatic residents (89%) had onset of symptoms and were RECATEGORIZED as presymptomatic.” Apparently Oran and Topal have confused here the very same issue (asymptomatic vs presymptomatic transmission) that they attempt to clarify at the onset of their own paper, re “To be clear, the asymptomatic individual…will NEVER develop symptoms.” I petition the journal editors to retract this paper, or at least to request that the authors modify their (perhaps unintentional but clearly misleading) conclusion regarding the contagiousness of asymptomatic SARS-CoV-2 carriers. Surely any objective

expert or meticulous reader would also wonder whether the paper's conclusion, that asymptomatic carriers in point of fact are significant drivers of COVID-19 at the population level, is sufficiently substantiated by the "data" cited by the authors (i.e., that two or three persons in Italy reporting having had contact with asymptomatic carriers MAY thereby have become infected). This article and in particular its unsubstantiated conclusion has already been widely cited and therefore requires immediate correction.

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Daniel P. Oran and Eric J. Topol • Scripps Translational Science Institute • 11 June 2020

Authors' Response to Cevik, Bogoch, Carson et al

We are puzzled by your critique. In the opening paragraphs of our review, we clearly state that m these studies are cross-sectional in nature, taking care to label in our table the minority of longitudinal studies. We also clearly explain the ambiguity surrounding asymptomatic versus presymptomatic status.

In our opinion, the unpublished "systematic review" preprint that you refer to, which appeared after our article was published and has not been subject to peer review, fails to adequately address the compelling data that it includes (as did we) from Vo, Italy. Not only is that a large representative sample with longitudinal data, but its findings are supported by other groups that we included. In the study, completed over 14 days, the researchers concluded that the proportion of asymptomatic individuals was 43%. In addition, none of the subjects who were asymptomatic at the beginning of the study had developed symptoms by the end.

In the midst of a global pandemic, we believed that it would be valuable to collect all the currently available data on an ill-defined phenotype and address an important issue: whether a sizable proportion of those infected with SARS-CoV-2 will have no symptoms. As of late May 2020, when we completed our review, which was just five months after the appearance of the first cases of COVID-19, much of that data was in rough and fragmentary form. We think that we faithfully and accurately reported what we found.

Journalism has been described as a first draft of history. In a similar way, our narrative review, which has collected the earliest available evidence, is a first draft of science. In the months and years ahead, new evidence — ideally, from well-designed, large-scale studies with representative samples — will appear, adding greater detail and clarity to our knowledge.

We share your perspective that significant gaps remain in what we know about crucial aspects of COVID-19, including the details and frequency of SARS-CoV-2 transmission by infected individuals who have no symptoms, and the harm to the lungs and possibly other parts of the body that might be associated with asymptomatic infection.

We are unaware of any other pathogen that can cause asymptomatic infection in a significant minority of patients — whether that is 20% or 40% — while also having a serious potential of taking lives. We look forward to collaborating with all interested investigators to expand our knowledge of SARS-CoV-2 and COVID-19.

Zoë Hyde • Western Australian Centre for Health and Ageing, Medical School, University of Western Australia, Perth, Australia • 11 June 2020

Comment on: Prevalence of Asymptomatic SARS-CoV-2 Infection: A Narrative Review

To the Editor: In their recent review, Oran and Topol (1) aimed to determine the prevalence of asymptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and concluded 40-45% of infected persons likely remain symptom-free.

Although the authors attempted to distinguish between pre-symptomatic cases (i.e., those yet t symptoms) and those who are truly asymptomatic, they base their conclusions on only three studies, two of which are cross-sectional. Furthermore, the remaining longitudinal study considered symptomatic persons to be those with fever or cough, which is an extremely limited definition.

At least two high-quality longitudinal studies were published during the period the authors searched the literature, both reporting a considerably lower prevalence. In a study of 100 laboratory-confirmed index cases and 2,761 close contacts in Taiwan, 22 secondary cases were identified, of which only 4 (18%) were asymptomatic during 14 days of follow-up (2). Following an outbreak in a call centre in Korea, 1,143 people were tested and 97 were found to be infected with SARS-CoV-2. Of these, 4 were pre-symptomatic and 4 (1.9%) remained asymptomatic during a 14-day monitoring period (3). These findings more likely

represent the prevalence of asymptomatic infection, given the rigorous testing, contact tracing, and monitoring strategy employed in both settings.

The authors also noted an apparent high proportion of asymptomatic cases (58.4%) among crew members of the U.S.S. Theodore Roosevelt. However, in a serological study of crew and associated personnel published subsequently, only 18.5% were found to be asymptomatic (4). Oran and Topol (1) also draw attention to the persistent test positivity of crew members, writing that asymptomatic persons "might be able to transmit the virus to others for longer than 14 days." This thankfully now seems unlikely. While shedding of viral RNA may occur for a month or more, infectious virus was never cultured after the 11th day of illness in patients in Singapore (5). Thus, with the exception of immunocompromised persons and severely ill patients, infectivity is unlikely to persist beyond the second week of illness.

Nonetheless, the authors' suggestion that widespread mask use may be necessary is wise. The infectious period begins approximately two days before symptom onset, and pre-symptomatic transmission accounts for a substantial fraction of cases (5). While the authors rightly call for policy changes to minimise the risk of silent transmission, their apparent overestimate of asymptomatic infection risks creating the perception that SARS-CoV-2 is less virulent than in reality.

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Muge Cevik, Isaac I Bogoch, Gail Carson, Eric D'Ortenzio, Krutika Kuppalli • on behalf of the CORRE Network (International COVID-19 Rapid Evidence Reviews Group) • 10 June 2020

A problematic interpretation of a narrative review containing a dearth of poor-quality evidence resulting in an overestimate of asymptomatic infections, which might

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misinform policy response.

There is a clear need to better understand the contribution of asymptomatic SARS-CoV-2 infections (those with no symptoms at all throughout the infection) in driving the current pandemic. However, there are caveats that in our opinion are pertinent when interpreting the reported findings of this review, including the lack of a clear definition of asymptomatic infection and selective inclusion of cross-sectional studies.

In addition, there is a problematic interpretation of a narrative review containing a dearth of poor-quality evidence resulting in an overestimate of asymptomatic infections, which might misinform policy response. Of the 16 reports included in this review, four defined symptoms of COVID-19 as fever and respiratory symptoms, three had no clear symptom definition, and six were media articles proving no information about symptoms. Respiratory symptoms or fever do not cover the spectrum of COVID-19 presentations, and many individuals with non-specific or mild symptoms are misclassified as being asymptomatic. For instance, Gudbjartsson et al. reported that approximately half of the participants in their population screening had rhinorrhoea and cough despite inquiring for those not to participate (1).

Second, cross-sectional studies cannot determine who will remain asymptomatic throughout their infection (2). For example, a study of 359 COVID-19 cases in Guangzhou found that 71 (86%) later developed symptoms (3). Oran and Topal include 9/16 cross-sectional reports, but describe them as cohorts, so it is unclear whether some patients might have developed symptoms later on. Only one report included other symptoms (malaise, rhinorrhoea, sore throat etc.) and followed individuals, with 89% of patients developing symptoms later (4).

Third, none of the studies cited included contact tracing; therefore, we cannot comment on asymptomatic transmission based on included studies. In contrast to the author's conclusions, recent studies assessing longitudinal characteristics of viral load and transmission have found truly asymptomatic patients have significantly lower viral loads than those who develop symptoms and transmit to fewer secondary cases (5).

Finally, a systematic review addressed the same question using a robust methodology, excluded of the studies that Oran and Topol included and conclude that 15-20% of SARS-CoV-2 infected p remain asymptomatic (2). There remains an immediate need to fill knowledge gaps on COVID-19; however, efforts must coalesce to conducting systematic reviews using robust and transparent methodologies, to avoid selective reporting and to provide a balanced synthesis of evidence. Academic groups should join forces to coordinate efforts, share the burden to deliver timely robust systematic reviews, avoid duplication and improve quality.

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Len Geiger • Alpha-1 Lungs Disease Advocate • 8 June 2020

WHO Statement

I'd like to see the authors' response to The World Health Organization's recent statement, "Asymptomatic spread of coronavirus is 'very rare.'" It seems to me that a "minimum of 30%" and "very rare" are difficult to equate and border on being mutually exclusive statements.

CNBC article on the subject: https://www.cnbc.com/2020/06/08/asymptomatic-coronavirus-patients-arent-spreading-new-infections-who-says.html

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Andrew N. Cohen, Bruce Kessel • Center for Research on Aquatic Bioinvasions, Richmond CA, USA; John A. Burns School of Medicine, University of Hawaii, Honolulu HI, USA • 7 June 2020

Analysis should address test specificity/sensitivity, and adequate assessment of asymptomatic status

Oran and Topol reviewed 16 studies that provide data on asymptomatic individuals who tested positive for SARS-CoV-2 by RT-PCR, and based on three representative studies concluded that 40-45% of infected individuals are asymptomatic. From this they drew several policy recommendations. However, their calculations did not take into account the tests' sensitivity or specificity. We found 20 studies that reported false negative rates of 0-52% (i.e. sensitivities of 48-100%) in SARS-CoV-2 RT-PCR tests (1). Though these tests typically have 100% analytical specificity, there are no data yet on their clinical specificity, which includes false positives due to contamination and other human error. In a review of 37 large external quality assessments of RT-PCR viral assays conducted in 2004-2019, false positive rates ranged from <0.6-8.1% (1).

The three representative studies cited by Oran and Topol had positivity rates of 0.8-2.0%; with a false negative rate of 0-52%, false positive rates of 0.3-0.9% would yield enough false positives to account for all the asymptomatic infected individuals reported. In other words, they may not actually have been infected. They also may not have been asymptomatic. Oran and Topol noted that asymptomatic individuals—those who are infected but never develop symptoms—must be distinguished from presymptomatic individuals. This requires checking for symptoms over the period of time in which symptoms could potentially appear, that is, over the maximum reported incubation period starting from the individual's date of infection (if known) or diagnosis. Oran and Topal acknowledged that longitudinal observations were made in only 5 of the 16 studies they reviewed. However, in 4 of those 5 studies the actual or median observation periods were 2 days (obstetric patients), 7 days (nursing home), 0 to about 14 days (Italy), and about 14 days (Greek evacuees), while the maximum incubation period for COVID-19 is reported as more than 14 days (2).

In the three representative studies specifically, there was either no effort to determine symptoms over time (Iceland, Indiana) or an insufficient effort (Italy). We want to be clear that we do not here argue that there are no asymptomatic carriers of SARS-CoV-2. Rather, we suggest that the data reviewed does not support the review's conclusion that a large proportion of infected individuals are asymptomatic.

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Dr. Charles Bens • CEO Health at Work • 7 June 2020

Nearly Half of Coronavirus Spread May Be Traced to People Without Symptoms

This article raises many questions, but provides very few answers. Why get you not explore the A Theory of priorities for nutrient use, the existing level of vitamin D3, the negative impact of sugar consumption on white blood cell strength or the overall strength of the immune system measured by the Bens Immune Biomarker Test? Previous Coronavirus exposure many have allowed the COVID-19 virus to think this person has immunity, if so why were lungs still damaged?

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