DHS SCIENCE AND TECHNOLOGY

Master Question List for COVID-19 (caused by SARS-CoV-2)

Quarterly Report
April 2022

For comments or questions related to the contents of this document, please contact the DHS S&T Hazard Awareness & Characterization Technology Center at HACTechnologyCenter@hq.dhs.gov.
FOREWORD

The Department of Homeland Security (DHS) is paying close attention to the evolving Coronavirus Infectious Disease (COVID-19) situation in order to protect our nation. DHS is working very closely with the Centers for Disease Control and Prevention (CDC), other federal agencies, and public health officials to implement public health control measures related to travelers and materials crossing our borders from the affected regions.

Based on the response to a similar product generated in 2014 in response to the Ebola virus outbreak in West Africa, the DHS Science and Technology Directorate (DHS S&T) developed the following “master question list” that quickly summarizes what is known, what additional information is needed, and who may be working to address such fundamental questions as, “What is the infectious dose?” and “How long does the virus persist in the environment?” The Master Question List (MQL) is intended to quickly present the current state of available information to government decision makers in the operational response to COVID-19 and allow structured and scientifically guided discussions across the federal government without burdening them with the need to review scientific reports, and to prevent duplication of efforts by highlighting and coordinating research.

The information contained in the following table has been assembled and evaluated by experts from publicly available sources to include reports and articles found in scientific and technical journals, selected sources on the internet, and various media reports. It is intended to serve as a “quick reference” tool and should not be regarded as comprehensive source of information, nor as necessarily representing the official policies, either expressed or implied, of the DHS or the U.S. Government. DHS does not endorse any products or commercial services mentioned in this document. All sources of the information provided are cited so that individual users of this document may independently evaluate the source of that information and its suitability for any particular use. This document is a “living document” that will be updated as needed when new information becomes available.

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<th>Topic</th>
<th>Overview of Current Knowledge</th>
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<tr>
<td>INFECTIOUS DOSE</td>
<td>In a human challenge study (36 adults between 18-29 years), an intranasal dose of 10 TCID$_{50}$ (~7 PFU) of wild-type virus successfully infected 53% of healthy volunteers, with 89% developing mild-moderate symptoms. Infectious virus was shed from contagious individuals for up to 10 days after inoculation and began within 24 hours (earliest sampled timepoint). There is no preferential animal model for SARS-CoV-2 as clinical signs, recovery, and transmission vary between species.</td>
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<tr>
<td>TRANSMISSIBILITY</td>
<td>SARS-CoV-2 is transmitted easily between humans, primarily through close contact (either direct or within 6 feet) and aerosol transmission. COVID-19 vaccines reduce transmission rates by approximately 54% (range of 38-66%). Individuals are infectious 1-3 days prior to symptom onset. Pre- or asymptomatic patients can transmit SARS-CoV-2. Most transmission occurs prior to and within 5 days of symptom onset. In a study of 38 adult volunteers, researchers found median SARS-CoV-2 aerosol emission rates of 4,200; 6,600; and 4,800 RNA genome copies per hour for breathing, talking, and singing, respectively. A second study found breathing may emit 10$^5$-$10^7$ genome copies per hour. There is substantial variation among individuals and higher emission rates closer to symptom onset.</td>
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<tr>
<td>HOST RANGE</td>
<td>SARS-CoV-2 is closely related to other coronaviruses circulating in Southeast Asia bat populations. Previous coronaviruses have passed through an intermediate mammal host before infecting humans, but the presence or identity of the SARS-CoV-2 intermediate host remains unknown. A direct jump from bats to humans is plausible based on current evidence. Several animal species are susceptible to SARS-CoV-2 infection at varying degrees. These species include, but are not limited to bat, hamster, mink, deer, rats, rabbits, voles, dogs, cats, and large wild cats. Farm animals are generally not susceptible to SARS-CoV-2 infection.</td>
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<tr>
<td>INCUBATION PERIOD</td>
<td>On average, symptoms develop 5 days after exposure with a range of 2-14 days. Incubating individuals can transmit disease for several days before symptom onset. Some individuals never develop symptoms but can still transmit disease. It is estimated that most individuals are no longer infectious beyond 10 days after symptom onset. Individuals can shed virus for several weeks, though it is not necessarily infectious. In a small human study (n=12 transmission pairs) the average time between symptom onset in two successive cases (i.e., the serial interval) of the Omicron variant was 2.9 days, which is faster than wild-type SARS-CoV-2.</td>
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<tr>
<td>ACUTE CLINICAL PRESENTATION</td>
<td>Most symptomatic COVID-19 cases are mild (81%). Fever, cough, and shortness of breath are generally the most common symptoms, followed by malaise, fatigue, and sputum/secretion. Chills, muscle pain, skeletal pain, sore throat, gastrointestinal symptoms, neurological symptoms, delirium, and dermatological symptoms also occur. COVID-19 is more severe than seasonal influenza. Adults &gt;60 years old and those with comorbidities are at elevated risk of hospitalization and death. Children are susceptible to SARS-CoV-2 though generally show milder or no symptoms. Minority populations are disproportionately affected by COVID-19.</td>
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<tr>
<td>CHRONIC CLINICAL PRESENTATION</td>
<td>COVID-19 symptoms commonly persist for weeks to months after initial onset in up to 73% of those infected. Long-term symptoms such as fatigue, smell/taste disorders, and neurological impairment may affect the ability to return to work. In a cohort of COVID-19 patients, 39% reported symptoms 7-9 months after initial infection, with fatigue, loss of taste or smell, shortness of breath, and headache as most common chronic symptoms. One year after ICU admission for COVID-19, lingering physical (74% of 246 ICU patients), mental (26%), and cognitive (16%) symptoms were common, with 58% of patients experiencing issues with returning fully to work.</td>
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<tr>
<td>PROTECTIVE IMMUNITY</td>
<td>Recovered individuals appear protected against reinfection for 3-6 months. Reinfection is rare, though the true frequency is unknown and novel variants may increase reinfection frequency. Immune responses persist in most patients for &gt;6 months. Current vaccines (from AstraZeneca and Pfizer/BioNTech in this study) provide protection against mutant variants of SARS-CoV-2, with neutralization ability against Delta (B.1.617.2) and Kappa (B.1.617.1) variants comparable to Alpha (B.1.1.7) and Gamma (P.1) variants, and higher than neutralization of the Beta (B.1.351) variant.</td>
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</table>
**Clinical Diagnosis**

Diagnosis of COVID-19 is based on symptoms consistent with COVID-19, PCR-based testing, and/or the presence of SARS-CoV-2 antigen in individuals (detected by ELISA). Screening solely by temperature or other symptoms is unreliable.

The timing of diagnostic PCR tests impacts results. The false-negative rate for RT-PCR tests is lowest between 7 and 9 days after exposure, and PCR tests are more likely to give false-negative results before symptoms begin (within 4 days of exposure) and more than 14 days after exposure.

Asymptomatic individuals without COVID-19 symptoms can be diagnosed with SARS-CoV-2 infection by the same tests.

In children, viral loads from saliva correlated better with clinical outcomes than viral loads from nasopharyngeal swabs. This may also be true for adults, as saliva tests consistently yield less false-negative results.

**Medical Treatments**

For hospitalized, critically ill patients, dexamethasone is strongly recommended; if dexamethasone is unavailable, the use of alternative corticosteroids (hydrocortisone, methylprednisolone, prednisone) is recommended.

WHO now recommends the use of baricitinib (anti-inflammatory) combination with corticosteroids for severe or critical COVID-19 patients, and conditionally recommends the use of sotrovimab (monoclonal antibody) in patients with non-severe COVID-19 but at elevated risk of hospitalization.

FDA has issued emergency approval of Evusheld, a monoclonal antibody treatment for pre-exposure prophylaxis for adults and children over the age of 12 years old at greater risk of severe disease.

Experimental studies in vitro have shown Evusheld continues to show neutralization activity against BA.2 (Omicron), but BA.2 easily evades other monoclonal antibodies. Paxlovid, molnupiravir, and remdesivir (all are nucleoside analogs) remain highly effective against both BA.1 and BA.2 (Omicron subvariants).

**Vaccines**

Three safe and effective vaccines are currently being administered in the US, with two under FDA EUA (Moderna and Johnson and Johnson/Janssen) and one with full FDA approval (Pfizer/BioNTech). All three vaccines have been approved for use as booster doses, and each can serve as a booster regardless of the initial vaccination type.

In the US, both Pfizer/BioNTech and Moderna vaccine efficacy has been estimated at 88% overall, with 80% efficacy two weeks after the first dose, rising to 90% or more two weeks after the second dose. Booster efficacy for Moderna and Pfizer-BioNTech ranges from 89.8-95.2%.

A third dose of an mRNA vaccine was 82% effective at reducing emergency department or urgent care visits during the U.S. Omicron wave, and 90% effective at reducing hospitalizations. Patients who receive a booster vaccination are 66% less likely to develop a symptomatic infection from the SARS-CoV-2 Omicron variant compared to un-boosted individuals.

**Non-Pharmaceutical Interventions**

Broad-scale control measures such as stay-at-home orders and widespread face mask use effectively reduce transmission.

Individual behaviors (e.g., face masks, social distancing) have been associated with reduced risk of COVID-19 infection.

Particular focus should be placed on minimizing large gatherings where superspreading events are more likely.

**Environmental Stability**

SARS-CoV-2 can survive on surfaces from hours to days and is stable in air for at least several hours, depending on the presence of UV light, temperature, and humidity. Transmission via contaminated surfaces is not thought to be common.

In the absence of sunlight, SARS-CoV-2 can persist for up to 4 weeks. Stability of SARS-CoV-2 RNA in clinical samples depends on temperature and transport medium. There is currently no evidence that SARS-CoV-2 is transmitted to people through food or food packaging.

SARS-CoV-2 stability in sewage and human wastewater remains unknown.

**Decontamination**

Soap and water, as well as common alcohol and chlorine-based cleaners, hand sanitizers, and disinfectants are effective at inactivating SARS-CoV-2 on hands and surfaces.

Several methods exist for decontaminating N95 respirators and other PPE.

**Personal Protective Equipment**

Face masks (medical and non-medical) are effective at reducing infections from SARS-CoV-2. Healthcare workers are at elevated risk of acquiring COVID-19, even with recommended PPE.
<table>
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<tr>
<th>FORENSICS</th>
<th>Current evidence supports the natural emergence of SARS-CoV-2 via a bat and possible intermediate mammal species. Based on phylogenetic analysis, SARS-CoV-2 most likely emerged from <em>Rhinolophus</em> (horseshoe) bats living in China, Laos, Myanmar, Vietnam, or another Southeast Asian country. The molecular sequence of the SARS-CoV-2 furin cleavage site is novel among coronaviruses and contributes to the increased number of potential intermediate hosts for this specific virus.</th>
</tr>
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</table>
| GENOMICS | Current evidence suggests that SARS-CoV-2 accumulates mutations at a rate similar to other coronaviruses. The estimated mutation rate for SARS-CoV-2 is $6 \times 10^{-4}$ changes at each nucleotide per year (or $3 \times 10^{-6}$ nucleotide mutations per replication cycle). This value is considered a medium or moderate level for RNA viruses. While this frequency appears moderate, rapid emergence of numerous variants is related to the wide transmissibility. Immunosuppressed patients are a possible source of viral variants due to prolonged virus replication within a single host.  
*Omicron* (B.1.1.529) – Detected on November 26, 2021, in South Africa and/or Botswana, the SARS-CoV-2 Omicron variant includes 21 unique mutations in the Spike gene with 14 shared Spike mutations with other variants of concern.  
*Omicron subvariant BA.2* - Cases are rising in Europe with 2x increase in cases over the last month and in the US, cases have increased to over 50% of all sequenced cases in the last month and account for 72% of all U.S. cases. |
| FORECASTING | Several platforms provide digital dashboards summarizing the current status of the pandemic in U.S. states and counties. The U.S. CDC provides ensemble forecasts of cases and deaths based on the average of many participating groups. Ensemble forecasts generally show better predictive accuracy than individual forecast models. Innovative approaches may be needed to forecast COVID-19 re-emergence after elimination or during periods of low incidence. Several characteristics of SARS-CoV-2 mutations, such as their prevalence and relationship to immune escape, may enable forecasting which mutations are likely to show up in future variants of concern months before their emergence. |
Infectious Dose – How much agent will make a healthy individual ill?

What do we know?

The current best estimate of the human infectious dose of SARS-CoV-2 comes from primate research, with 36-179 viral particles (plaque-forming units, PFU) necessary to cause infection via the inhalation route.

- In a human challenge study (36 adults between 18-29 years), an intranasal dose of 10 TCID50 (~7 PFU) of wild-type SARS-CoV-2 (originating strain) successfully infected 53% of healthy volunteers, with 89% developing mild-moderate symptoms.\(^1\) Infectious virus was shed from contagious individuals for up to 10 days after inoculation, and could be detected as early as 24 hours post infection.\(^1\)

- There is no preferential animal model for SARS-CoV-2\(^2\) as clinical signs, recovery, and transmission vary between species. Transgenic models may represent extreme conditions with unnatural gene expression patterns and rapid lethality, as the random integration strategy used to insert additional ACE2 copies is largely stochastic.\(^3\)

**Non-human primates**

- In cynomolgus macaques, the median dose required to induce SARS-CoV-2 seropositivity (wild-type virus) was 52 TCID50 (approximately 36.4 PFU) via the inhalation route.\(^4\) The median dose needed to induce fever was 256 TCID50 (approximately 179.2 PFU) via the inhalation route.\(^4\) This also suggests that symptom severity may be dose dependent.\(^4\)

- Larger doses of SARS-CoV-2 have been shown to infect non-human primates (NHPs) via the inhalation route\(^5\-\(^7\) or its surrogates (intranasal, intratracheal, combination routes)\(^8\-\(^9\) and the ocular route.\(^10\) Intragastric exposure does not appear to result in NHP infection.\(^11\)

- Several NHP species (Rhesus macaques, African green monkeys, Cynomolgus macaques) are able to replicate aspects of human COVID-19 infection,\(^10\) from mild\(^6\) to severe illness,\(^9\) including acute respiratory distress syndrome (ARDS).\(^5\)

**Rodents and other animal models**

- The infectious dose of SARS-CoV-2 in rodent models has been estimated as low as 4x10^3 TCID50,\(^12\) though many rodent models are modified to express human airway cells (e.g., ACE2).\(^13\) Several rodent species (Golden Syrian hamsters,\(^14\) ferrets\(^15\-\(^16\)) are able to replicate COVID-19 symptoms seen in humans.\(^17\) Some experimentally infected rodents (Golden Syrian hamsters,\(^18\) ferrets\(^15\)) are able to transmit to animals in separate cages without direct contact.

- The Alpha (B.1.1.7) variant of SARS-CoV-2 was better able to infect hamsters when introduced at low doses compared to earlier, wild-type virus, suggesting a potential mechanism for increased variant transmissibility.\(^19\)

- In a ferret study, 1 in 6 individuals exposed to 10^2 PFU via the intranasal route became infected, while 12 out of 12 individuals exposed to >10^6 PFU became infected.\(^20\)

- While the infectious dose is unknown, Syrian hamsters exposed to soiled bedding of SARS-CoV-2 infected hamsters for 48 hours showed clinical evidence of infection (weight loss) as well as viral shedding, demonstrating fomite transmission.\(^21\)

**Modeling estimates**

- The infectious dose of a pathogen can be estimated by the amount of genetic material passed between an infector and infectee (called “bottleneck” size);\(^22\) using epidemiological data, sequencing data, and statistics, the average “bottleneck” size for SARS-CoV-2 has been estimated as ~1,200 viral particles, though exposure routes were not possible to identify.\(^23\)

**Related Coronaviruses**

- Humans exposed intranasally to ~70 PFU of seasonal coronavirus 229E developed infections,\(^25\) with a plausible intranasal ID50 of 10 TCID50 (~7 PFU).\(^26\-\(^27\) The inhalation infectious dose of seasonal coronavirus 229E is unknown in humans.

What do we need to know?

We need to know the infectious dose for humans by all possible exposure routes in order to inform models, develop diagnostics and countermeasures, and inform disinfection efforts.

- What is the ratio of virus particles/virions to PFU for SARS-CoV-2?
SARS-CoV-2 is passed easily between humans, primarily through close contact and aerosol transmission. Asymptomatic or pre-symptomatic individuals can transmit SARS-CoV-2 and play a large role in new case growth. We need to know the relative contribution of different routes of transmission and the effect of new variants. Rates of transmission within public transit are unclear but appear low, particularly on airplanes. SARS-CoV-2 is passed easily between humans, primarily through close contact and aerosol transmission. Superspreading events (SSEs) appear common in SARS-CoV-2 transmission and may be crucial for controlling spread. COVID-19 vaccines reduce transmission rates by approximately 54% (range of 38-66%). Low vaccination rates facilitate COVID-19 transmission. Booster vaccinations significantly reduced infections from both Delta and Omicron variants. The amount of infectious virus emitted from an infectious individual is unclear but appears highly variable. Asymptomatic or pre-symptomatic individuals can transmit SARS-CoV-2 and play a large role in new case growth. What do we know? What do we need to know?
We need to know the best animal model for replicating human infection by various exposure routes.

- What is the intermediate host(s) (if any)?
- Which animal species can transmit SARS-CoV-2 to humans?
- Can SARS-CoV-2 circulate in animal reservoir populations, potentially leading to future spillover events?
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<th>What do we know?</th>
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<tr>
<td><strong>Incubation Period – How long after infection do symptoms appear? Are people infectious during this time?</strong></td>
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<tr>
<td><strong>On average, symptoms develop 5 days after exposure with a range of 2-14 days. Incubating individuals can transmit disease for several days before symptom onset. Some individuals never develop symptoms but can still transmit disease.</strong></td>
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<tr>
<td>- By general consensus, the incubation period of COVID-19 is between 5 and 6 days. Fewer than 2.5% of infected individuals show symptoms sooner than 2 days after exposure. However, more recent estimates using different models calculate a longer incubation period, between 7 and 8 days. This could mean that 5-10% of individuals undergoing a 14-day quarantine are still infectious at the end.</td>
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<td>- There is evidence that younger (&lt;14) and older (&gt;75) individuals have longer COVID-19 incubation periods, creating a U-shaped relationship between incubation period length and patient age, while adolescent and young adult populations (15-24 years old) have been estimated at ~2 days.</td>
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<tr>
<td>- Individuals can test positive for COVID-19 even if they lack clinical symptoms. Individuals can be infectious while asymptomatic and pre-symptomatic individuals have similar amounts of virus in the nose and throat compared to symptomatic patients.</td>
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<td>- Peak infectiousness may be during the incubation period, one day before symptoms develop. Infectious virus has been cultured in patients up to 6 days before the development of symptoms.</td>
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<td>- Of individuals quarantining after a COVID-19 contact in the home, 81% of those testing negative on day 7 also tested negative on day 14; 19% of individuals undergoing a 7-day quarantine, then, were at risk of developing and potentially transmitting COVID-19. The percentage of individuals at risk declined to 7% for those still asymptomatic and test-negative 10 days after contact. This indicates that quarantines of less than 14 days still carry some risk of disease and transmission, and that care should be taken after completing a shortened quarantine period (e.g., wearing a mask, distancing).</td>
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<tr>
<td>- Some SARS-CoV-2 variants have a shorter incubation period. Recent estimates of the SARS-CoV-2 serial interval ranged from 2.7 to 3.2 days. There is some evidence that the Delta variant spreads faster than prior virus lineages, predicting a shorter incubation period (~3 days) than the original, wild-type SARS-CoV-2 virus (~5 days).</td>
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<tr>
<td>- In a small study (n=12 transmission pairs) the average time between symptom onset in two successive cases (i.e., the serial interval) of the Omicron variant was 2.9 days, which is faster than for wild-type virus.</td>
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<tr>
<td>- It is estimated that most individuals are no longer infectious beyond 10 days after symptom onset. A systematic review of published studies on SARS-CoV-1, SARS-CoV-2, and MERS-CoV found none that reported isolation of infectious virus from COVID-19 patients beyond 9 days from symptom onset, despite high viral loads by genetic tests. While the amount of virus needed to infect another individual is unknown, mild-moderate COVID-19 cases appear to be infectious for no longer than 10 days after symptom onset, while severely ill or immunocompromised patients may be infectious for 20-70 days after symptom onset; individuals can also transmit infection before symptoms appear.</td>
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<tr>
<td>- Asymptomatic individuals are estimated to be infectious for between 5.7 and 9.5 days. The average time between symptom onset in successive cases (i.e., the serial interval) is approximately 5 days. On average, there are approximately 4.2 to 7.5 days between symptom onset in successive cases of a single transmission chain (i.e., the serial interval). The generation time (time between infection events in a chain of transmission) for SARS-CoV-2 is estimated as 4-5 days.</td>
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<td>- Individuals can shed virus for several weeks, though it is not necessarily infectious. Children are estimated to shed virus for 15 days on average, with asymptomatic individuals shedding virus for less time (11 days) than symptomatic individuals (17 days).</td>
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<tr>
<td>- Viral RNA loads in the upper respiratory tract tend to peak within a few days of symptom onset and become undetectable approximately two weeks after symptoms begin. The duration of the infectious period is unknown, though patients can test positive for SARS-CoV-2 viral RNA for extended periods of time, particularly in stool samples.</td>
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<thead>
<tr>
<th>What do we need to know?</th>
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<tbody>
<tr>
<td><strong>We need to know the incubation duration and length of infectivity in different patient populations.</strong></td>
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<tr>
<td>- What is the average infectious period during which individuals can transmit the disease?</td>
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<td>- How soon can asymptomatic patients transmit infection after exposure?</td>
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<tr>
<td>- Does the incubation period correlate with disease severity or exposure dose?</td>
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<tr>
<td>- Do novel SARS-CoV-2 variants alter the incubation period of COVID-19? Do they affect the generation time or serial interval?</td>
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**Acute Clinical Presentation – What are the initial signs and symptoms of an infected person?**

**What do we know?**

<table>
<thead>
<tr>
<th>Symptom</th>
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<tr>
<td><strong>Most symptomatic cases are mild, but severe disease can appear in any age group.</strong> Older individuals and those with underlying conditions are at higher risk of serious illness and death, as are men.</td>
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<tr>
<td><strong>Most symptomatic COVID-19 cases are mild (81%).</strong> Fever, cough, shortness of breath, sore throat, gastrointestinal symptoms, neurological symptoms, delirium, and dermatological symptoms also occur. While fever is the most common early symptom, many individuals do not exhibit fever at all.</td>
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<tr>
<td><strong>Headaches are common, may persist for weeks, and may be associated with shorter disease duration.</strong> Gastrointestinal symptoms (particularly abdominal pain) may be associated with increased risk of severe disease. Loss of taste or smell (anosmia) is predictive of COVID-19, occurring in 28% of pediatric COVID-19 cases.</td>
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<tr>
<td><strong>Adults experiencing post-acute COVID-19 multisystem inflammatory syndrome (MIS-A) may be underdiagnosed.</strong> The Omicron variant and subvariants are less likely to result in hospitalization or death than previous variants.</td>
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<tr>
<td><strong>The proportion of asymptomatic infections among confirmed COVID-19 cases may be as high as 40%</strong>, evidenced by higher ICU admission and mortality rates. <strong>COVID-19 is more severe than seasonal influenza</strong>, evidenced by higher ICU admission and mortality rates. <strong>The Omicron variant appears to replicate better in human bronchi than prior variants</strong>, potentially explaining its rapid forward transmissibility.</td>
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<tr>
<td><strong>In a retrospective cohort study, the Omicron variant resulted in a 59% lower likelihood of hospitalization or death than the Delta variant</strong>, though elevated case counts resulted in greater absolute hospitalizations, and estimating variant severity with population-level data is difficult.</td>
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<tr>
<td><strong>Approximately 33% of individuals will remain asymptomatic after SARS-CoV-2 infection.</strong> Modeling and seroprevalence studies, however, suggest the asymptomatic ratio is much higher (&gt;80%). When asymptomatic individuals do transmit, those they infect are more likely to develop asymptomatic COVID-19.</td>
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<tr>
<td><strong>COVID-19 is more severe than seasonal influenza</strong>, evidenced by higher ICU admission and mortality rates. In the U.S., 29-34% of hospitalized patients required ICU admission, and 12.6-13.6% died from COVID-19.</td>
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<td><strong>Higher SARS-CoV-2 RNA loads at admission have been linked to greater risk of death</strong>, though this not universal. High viral loads (RT-PCR cycle threshold value &lt;28) are associated with symptom severity six months after illness onset.</td>
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<tr>
<td><strong>COVID-19 also causes pneumonia, cardiac injury, kidney damage, pancreatitis, arrhythmia, sepsis, stroke, respiratory complications, and shock.</strong> SARS-CoV-2 weakens blood vessels in the lung and is associated with hyperactive platelets, leading to ARDS. Clotting affects multiple organs and is present in 15-27% of cases.</td>
</tr>
<tr>
<td><strong>Higher SARS-CoV-2 RNA loads at admission have been linked to greater risk of death</strong>, though this not universal. Low oxygen saturation and shallow breathing upon hospital admission are associated with elevated mortality risk.</td>
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<tr>
<td><strong>The risk of severe COVID-19 may be influenced by the environment</strong>, as in one study where elevated ozone (10x greater than acceptable concentrations) predisposed mice to severe illness by upregulating cellular entry proteins.</td>
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<tr>
<td><strong>Adults &gt;60 years old and those with comorbidities are at elevated risk of hospitalization and death.</strong> Cardiovascular disease, obesity, hypertension, diabetes, cancer, down syndrome, and respiratory conditions increase the CFR. Kidney disease, dialysis, and lack of physical activity may increase disease severity. Estimates of the age-specific infection fatality rate were identified in a large meta-analysis: 0-34 years = 0.004%; 35-44 years = 0.068%; 45-54 years = 0.23%; 55-64 years = 0.75%; 65-74 years = 2.5%; 75-84 years = 8.5%; 85 and older = 28.3%.</td>
</tr>
<tr>
<td><strong>Minority populations are disproportionately affected by COVID-19</strong>, and appears to be linked to underlying conditions. Minority ethnic populations acquire SARS-CoV-2 infection at higher rates and are hospitalized and die disproportionately. Hispanic and Black COVID-19 patients tend to die at younger ages. Pregnant women with COVID-19 have higher mortality rates compared to those without. The proportion of pregnant patients with severe COVID-19 increased after the introduction of the Delta variant.</td>
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<tr>
<td><strong>Individuals with physical or intellectual disabilities are at greater risk of poor COVID-19 outcomes</strong>, including mortality, ICU admission, and lengthy hospital stays.</td>
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<tr>
<td><strong>Children are susceptible to COVID-19</strong>, though generally show milder or no symptoms. Children appear primed to mount early, effective immune (particularly interferon) responses to SARS-CoV-2, which may help to explain their lower rates of severe disease and death compared to adults.</td>
</tr>
<tr>
<td><strong>21% to 28% of children (&lt;19 years old) may be asymptomatic.</strong> Most symptomatic children show mild or moderate symptoms. Severe disease in children and infants is more likely in those with complex medical histories. A rare inflammatory condition in children (MIS-C) is linked to COVID-19 infection, though the prevalence is unknown. Children with any initial symptoms can develop MIS-C, though non-white children are overrepresented.</td>
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**What do we need to know?**

- We need to know the impact of new SARS-CoV-2 variants on presentation and disease severity.
- What are the pathogenic pathways of SARS-CoV-2 infection in children, and why are their illnesses typically mild?
- Are associations between COVID-19 severity and fine particulate matter (PM2.5) caused by the particulates themselves or conditions associated with living in areas with more air pollution?
### Chronic Clinical Presentation – What are the long-term symptoms of COVID-19 infection?

#### What do we know?

**COVID-19 symptoms commonly persist for weeks**[^32] **to months**[^33] **after initial onset**[^34] **in up to 73% of those infected.**[^35]

- The U.S. NIH has defined the effects of “long-haul” COVID-19 as Post-Acute Sequelae of SARS-CoV-2 infection (PASC).[^36]
- Estimates of the prevalence of PASC range from 5-10% of COVID-19 patients,[^37][^38] with obesity[^39], age, female sex[^40], and number of initial symptoms increasing risk.[^41][^42]
- Hospital readmission rates are 9-29% of COVID-19 patients.[^43][^44][^45]
- The importance of initial symptom severity for subsequent development of PASC is unclear, with some studies showing high risk in mildly ill patients[^46] while others show higher risk in severely ill patients.[^47]
- Long-term symptoms such as fatigue,[^48] smell/taste disorders,[^49][^50] and neurological impairment[^51] may affect the ability to return to work.[^51]
- Approximately 8% of mildly ill individuals had disrupted work schedules 8 months after initial illness.[^52]
- In a cohort of 410 COVID-19 patients, 39% reported symptoms 7-9 months after initial infection, with fatigue, loss of taste or smell, dyspnea (shortness of breath), and headache the most common chronic symptoms.[^53]
- In a smaller study (n=96), 77% of patients reported ongoing symptoms 12 months after initial infection, with the most common symptoms being reduced exercise capacity, fatigue, dyspnea, and difficulties with concentration, finding correct words during speech, and sleep.[^54]
- Over 203 symptoms were reported by long-haul COVID (PASC) patients in a large (n=3,762) survey.[^55]
- In the UK, individuals vaccinated with the Pfizer/BioNTech, AstraZeneca, or Moderna vaccines had a 50% lower chance of experiencing COVID-19 symptoms lasting more than one month, compared to unvaccinated individuals.[^55]
- Long-term sequelae of SARS-CoV-2 infection appear to be linked to pre-existing conditions. Underlying auto-immune or internal complications observed following COVID-19 may be attributed to viral infection stimulating a broad immune response exacerbating underlying conditions, with symptoms ranging from vascular and cardiac issues,[^56][^57] CNS and demyelination issues,[^58] and sex specific reproductive complications.[^59][^61]
- T cell and antibody responses did not differ between individuals with acute or chronic COVID-19 nine months post-infection,[^62] suggesting that differences in immune response are not the only cause of chronic COVID-19 (PASC).
- In a small cohort (n=86) of pediatric patients with MIS-C, long-term outcomes at one year after initial diagnosis were positive, with no fatalities and two hospital readmissions (thought to be unrelated to MIS-C).[^63]
- Women, individuals with comorbidities, and those older than 40 were more likely to report COVID-19 symptoms lasting longer than two months.[^64]
- Vaccination reduces the odds of individuals reporting COVID-19 symptoms for longer than 28 days.[^65]

**Researchers are identifying methods to diagnose patients with chronic COVID-19 (PASC) early.**

- Corneal scans in 40 patients who had recovered from acute COVID-19 showed greater corneal nerve fiber damage in those who reported neurological symptoms up to four weeks post-infection compared to those without neurological symptoms, suggesting that corneal microscopy could be a potential rapid objective test when evaluating long-haul COVID patients.[^65]
- Researchers examined plasma and isolated peripheral blood mononuclear cells from 224 healthy and sick individuals (including 121 with PASC symptoms) and, using bioinformatics to analyze cytokines, were able to discriminate between severe disease and PASC.[^66]
- PASC patients may be differentiated from severe COVID-19 patients by the type and persistence of monocytes and SARS-CoV-2 proteins (e.g., S1) in the body.[^66]
- Several factors were found to increase individual likelihood of developing PASC, including initial SARS-CoV-2 viral load, early development of auto-antibodies, type 2 diabetes, and potential reactivation of Epstein-Barr Virus.[^67] Different antibody levels corresponded to different manifestations of PASC (e.g., neurological, respiratory, gastrointestinal), suggesting that patient risk may be assessed for both PASC risk and presentation.[^67]
- One year after ICU admission for COVID-19, lingering physical (74% of 246 ICU patients), mental (26%), and cognitive (16%) symptoms were common, with 58% of patients experiencing issues returning fully to work.[^68]

#### What do we need to know?

**We need to know the rate of PASC and chronic symptoms in different patient populations.**

- We need to understand the frequency, mechanism,[^69] and clinical implication of chronic COVID syndrome (PASC).[^70][^71]
- How many symptoms are linked to chronic COVID-19?
- How prevalent are chronic symptoms in children or individuals over 60?
- Do variants change the risk of PASC?
- Does previous diagnosis of COVID-19 confer complications during pregnancy after viral clearance?
### Protective Immunity – How does the immune response provide protection from reinfection?

**What do we know?**

<table>
<thead>
<tr>
<th>Recovered individuals appear protected against reinfection for at least several months. Immune responses persist in most patients for &gt;6 months.</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Infection with SARS-CoV-2 provides robust protection against reinfection for at least 3-6 months.(^{35, 372})</td>
</tr>
<tr>
<td>• Vaccine-derived immunity is robust in pregnant and lactating women,(^{373}) with evidence that antibodies are transferred to neonates by the placenta(^{374}) and through breast milk.(^{375})</td>
</tr>
<tr>
<td>• Neutralizing antibody responses are present within 8-19 days after symptom onset(^{376-377}) and can persist for many months.(^{378})</td>
</tr>
<tr>
<td>• In a study among 60,000 cancer patients, those that received active cancer treatment within 6 months showed 58% vaccine effectiveness, while those without active cancer treatment for 6 months showed 85% efficacy.(^{380})</td>
</tr>
<tr>
<td>• Rhesus macaques infected with wild-type SARS-CoV-2 (WA1/2020 strain) were protected against secondary homologous challenge 35 days later, but heterologous protection (challenge with a different strain) was reduced(^{381}) suggesting natural SARS-CoV-2 infection provides incomplete protection from reinfection with different SARS-CoV-2 variants.</td>
</tr>
<tr>
<td>• Administration of a fourth dose of either the Pfizer or Moderna vaccine was given four months after a third dose (booster). No serious side effects were observed, and both vaccines generated a 9-10 fold increase in IgG and neutralizing antibodies.(^{382})</td>
</tr>
</tbody>
</table>

**Convalescent patients are expected to have long-lasting protection against SARS-CoV-2, especially after vaccination.\(^{383-384}\)**

| • Multiple components of the human immune response to SARS-CoV-2, including circulating antibodies, memory B cells, and memory T cells, are detectable for at least 6-8 months after infection regardless of initial symptom severity.\(^{385}\) |
| • Bone marrow plasma cells (BMPC) are generated by natural infection and vaccination and persist for several months, suggesting a lasting humoral immune response to SARS-CoV-2 infection.\(^{386}\) |

**The impact of emerging SARS-CoV-2 variants on protective immunity and reinfection risk is unclear.**

| • Current vaccines (from AstraZeneca and Pfizer/BioNTech in this study) provide protection against variants, with neutralization ability against Delta (B.1.617.2) and Kappa (B.1.617.1) variants comparable to Alpha (B.1.1.7) and Gamma (P.1) variants, and higher than neutralization of the Beta (B.1.351) variant.\(^{387}\) |
| • The Moderna vaccine appeared to induce greater antibody responses than the Pfizer/BioNTech vaccine, shown by higher antibody titers (3836 units/mL vs. 1444 units/mL).\(^{388}\) |
| • SARS-CoV-2 mutations can reduce responses to serum from vaccinated patients.\(^{389}\) |
| • T cells of individuals infected with wild-type SARS-CoV-2 were able to recognize and respond to three SARS-CoV-2 variants (Alpha, Beta, and Gamma), though the overall contribution to long-term immunity is not yet clear.\(^{390}\) A small cohort study (n=52) in England found that increased IL-2 secreting T cells following exposure confers protection in individuals with COVID-19 contacts, and that this T cell subset is cross-reactive to the nucleocapsid of 3 different coronaviruses.\(^{391}\) |
| • Antibody titers in individuals who only received the Pfizer vaccine begin to wane after 2+ months (reduced to 20% after 4 months), but still confer protection from severe symptoms.\(^{392}\) Titers remain elevated among individuals that recovered from natural infections prior to vaccination.\(^{392-393}\) |
| • A study compared sera neutralization of the Omicron variant from a variety of vaccinated (Pfizer or Moderna)/recovered patients (convalescent, 2 dose vaccinated; vaccinated plus booster; etc.).\(^{394}\) Neutralization of the Omicron variant only occurred in groups with 3-4 antigenic exposures (e.g., 2 vaccinations plus booster, convalescent plus 2 vaccinations).\(^{394}\) Sera from unvaccinated convalescent patients showed 73% no neutralization against Omicron. |

**Reinfection with a homologous SARS-CoV-2 strain is possible, though the true frequency is unclear.**

| • Infection with COVID-19 appears to provide at least an 83% reduction in the risk of reinfection for at least 5 months,\(^{395-397}\) and reinfection was plausibly identified in 44 out of 6,600 COVID-19 patients.\(^{398}\) |
| • Possible reinfections were found in 4.8% of patients in one retrospective study, though some of these could represent lingering viral shedding.\(^{399}\) Only 2.4% of patients developed symptomatic COVID-19 >90 days after initial infection.\(^{399}\) |
| • One study estimated that the SARS-CoV-2 reinfection rate in the UK was approximately 3.62 per 1,000 primary infections during the dominance of wild-type and Alpha variant virus.\(^{400}\) During this period, the risk of hospitalization and death were substantially lower for reininfected individuals compared to those with primary infections.\(^{400}\) |
| • Patient serum from individuals infected with non-Omicron variants exhibited poor neutralization ability against the Omicron variant, suggesting low protective immunity against Omicron from infection with prior variants.\(^{401}\) |

**What do we need to know?**

<table>
<thead>
<tr>
<th>We need to know the frequency and severity of reinfection, as well as the protective effects of immune components.</th>
</tr>
</thead>
<tbody>
<tr>
<td>• How long does protective immunity last for children compared to adults?</td>
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<tr>
<td>• What is the probability of reinfection, particularly with SARS-CoV-2 variants?</td>
</tr>
<tr>
<td>• What is the impact of the Omicron variant on antibody response and T-cell immunity?</td>
</tr>
<tr>
<td>• Is infection with the Omicron variant more likely to lead to protection against future variants?</td>
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</tbody>
</table>
Clinical Diagnosis – Are there tools to diagnose infected individuals? When during infection are they effective?

What do we know?

Diagnosis of COVID-19 is based on symptoms consistent with COVID-19, PCR-based testing of active cases, and/or the presence of SARS-CoV-2 antibodies in individuals. Screening solely by temperature or other symptoms is unreliable.

- As of 4/5/2022 the FDA has granted Emergency Use Authorization (EUA) for 425 test and sample collection devices, including 293 molecular tests and sample collection devices, 84 antibody, and 48 antigen tests.402 There are 74 authorized molecular tests for home-collected samples with 1 prescription at-home molecular test, two prescription at-home antigen tests, 15 OTC at-home antigen tests, and three OTC molecular tests.403
- The U.S. FDA released guidance on the impact of SARS-CoV-2 mutations on diagnostic tests.403 The FDA has also issued guidance on interpreting serological test result performance in light of background COVID-19 prevalence.404
- The U.S. FDA granted EUA to a non-invasive, non-diagnostic device based on machine learning algorithms that screens for biomarkers of SARS-CoV-2 infection in asymptomatic individuals older than 5 years.405
- The timing of diagnostic PCR tests impacts results. The false-negative rate for RT-PCR tests is lowest between 7 and 9 days after exposure, and PCR tests are more likely to give false-negative results before symptoms begin (within 4 days of exposure) and more than 14 days after exposure.406 Low viral loads can lead to false-negative RT-PCR tests.407
- The duration of PCR-detectable viral samples is longer in the lower respiratory tract than the upper respiratory tract; nasopharyngeal sampling is most effective (89%) between 0 and 4 days after symptom onset but falls significantly (to 54%) by 10 to 14 days.408 After 10 days, alternative testing methods (e.g., lower respiratory samples) may be necessary.408
- Trained dogs show high accuracy for SARS-CoV-2 detection (sensitivity = 0.88, specificity = 0.99), and could be used to identify individuals needing confirmation via rapid antigen or molecular testing.409 With training, dogs are able to recognize odors (volatile organic compounds) from infected individuals even if they’re asymptomatic; this work is also supporting development of organic semi-conducting sensors to detect COVID-19 volatile organic compounds.410
- While nasopharyngeal swabs are the gold standard for COVID-19 diagnosis, pooled nasal and throat swabs also show high diagnostic accuracy, while saliva, nasal swabs, and throat swabs all showed lower accuracy.411 However, homogenization of saliva samples prior to RNA extraction increases diagnostic accuracy, with results comparable to nasopharyngeal swabs.412
- Researchers have demonstrated the utility of disposable, bio-functional strips for SARS-CoV-2 identification.413
- In children, viral loads from saliva correlated better with clinical outcomes than viral loads from nasopharyngeal swabs.414
- Rapid tests based on RT-PCR or standard laboratory nucleic acid amplification tests (NAATs) are preferred over rapid isothermal NAATs in symptomatic individuals to reduce the chance of false-positives.415
- New diagnostic methods involving CRISPR,416 exhaled breath condensate,417-418 and the microbiome419 are being developed.
- Symptom-based screening at airports was ineffective at detecting cases (9 identified out of 766,044 passengers screened),420 and intensive screening on a U.S. military base during mandatory quarantine did not identify any COVID-19 cases.421
- Infrared temperature readings may be misleading when used at the entrance of buildings with low outdoor temperatures.422
- Foam swabs lead to more accurate diagnostic tests than polyester swabs for collecting patient samples, though polyester swabs are good enough to be used in case of a shortage in foam swabs.423
- Immunological indicators424-435 blood glucose levels,436 oxygen levels,437 and bilirubin levels438 may help identify future severe cases,439 and tools for diagnosing severe infections439-441 and predicting mortality442 exist.
- A high-throughput assay for screening asymptomatic individuals has received U.S. EUA.443-444
- Self- or caregiver-taken diagnostic swabs could be as accurate as those taken by healthcare workers in some instances.445
- Wearable technology may be able to detect COVID-19 days before symptoms begin,446-447 and several attempts to create mobile applications for disease notification are underway.448-449
- Aerosol detection devices are capable of identifying SARS-CoV-2 in the air (minimum of approximately 6,000 particles).450 Improvements to aerosol sampling protocols (e.g., use of fetal calf serum during elution, using PTFE filters instead of glass fiber) may lower the limit of detection to 10-50 genome copies/mL.451
- Patients with long-term or chronic COVID-19 appear to have auto-antibodies not present in patients who have recovered, sparking interest in developing a diagnostic blood test to identify the proteins.452

Validated serological (antibody) assays are being used to help determine who has been exposed to SARS-CoV-2.453

- Meta-analysis suggests that lateral flow immunoassays (LFIA) are less accurate than ELISA or chemiluminescent methods (CLIA), but that the target of serological studies (e.g., IgG or IgM) does not affect accuracy.454
- LFIA testing showed lower accuracy in pregnant women than other patient cohorts.455

What do we need to know?

We need to identify additional factors that affect the accuracy of serological or PCR-based diagnostic tests.

- What is the relationship between disease severity and the timing of positive serological assays?
- Are certain subpopulations (e.g., those with blood cancers) more likely to show false-negative tests?
- How likely are children of different ages to test positive via RT-PCR?
### Medical Treatments – Are there effective treatments?

#### What do we know?

**COVID-19 treatment recommendations are provided by the WHO, NIH, Infectious Disease Society of America (IDSA), and British Medical Journal (BMJ), based on ongoing analysis of evidence from clinical trials.**

**Treatment recommendations**
- For hospitalized, critically ill patients on mechanical ventilation or ECMO (with organ failure and ARDS), dexamethasone is strongly recommended; if dexamethasone is unavailable, the use of alternative corticosteroids (hydrocortisone, methylprednisolone, prednisone) is recommended. Methyprednisolone may increase the duration of viral shedding.
- A recent update to the living guideline for COVID-19 treatment from the WHO strongly recommends against administering convalescent plasma to non-severe COVID-19 patients but can be used in severe patients in clinical research settings only. Convalescent plasma is more beneficial when given early in treatment with high SARS-CoV-2 antibody titers or when patients were treated with near-sourced plasma (donor within 150 miles of recipient), though the treatment fails to show benefits in large, randomized trials.
- For any subset of patients, there is a strong recommendation against the use of hydroxychloroquine or hydroxychloroquine plus azithromycin and lopinavir/ritonavir due to lack of observed benefit.
- For hospitalized patients with non-severe illness, SpO2 ≥94%, and no supplemental oxygen, there is a conditional recommendation against the use of glucocorticoids.
- In the U.S., in hospitalized patients not on supplemental oxygen, there is a conditional recommendation against the routine use of Remdesivir, though it may be considered for patients at high risk of severe disease.
- The WHO and BMJ, however, recommend against Remdesivir use in patients of any severity and recent results from the Discovery trial found no clinical benefit from Remdesivir plus standard of care when given to hospitalized patients, those with symptoms for longer than 7 days, and those requiring supplemental oxygen compared to standard of care alone.
- For hospitalized patients, treatment with Remdesivir, baricitinib, or corticosteroids is recommended only in clinical trials.
- WHO now recommends the use of baricitinib as an alternative to IL-6 blockers, in combination with corticosteroids for severe or critical COVID-19 patients, and also conditionally recommends the use of sotrovimab in patients with non-severe COVID-19 but at high risk of hospitalization.
- Regeneron’s REGEN-COV treatment (casirivimab/imdevimab) is recommended for use in non-hospitalized patients and has EUA for those at high risk of developing severe disease. The use of REGEN-COV is not authorized in regions with known Omicron variant infections, as this treatment is not effective against this strain.
- FDA has issued emergency approval of Evusheld, a monoclonal antibody treatment for pre-exposure prophylaxis for adults and children over the age of 12 years old at greater risk of severe disease. The treatment is tixagevimab copackaged with cilgavimab.
- Experimental studies in vitro have shown Evusheld continues to show neutralization activity against BA.2, but BA.2 easily evades other monoclonal antibodies. Paxlovid, molnupiravir, and remdesivir remain effective against both BA.1 and BA.2.

**Clinical trial updates**
- The FDA issued an EUA for Paxlovid co-administered with ritonavir for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (≥12 years old). As this treatment showed an 89% reduction in the risk of hospitalization and death in high-risk individuals when administered within 5 days of symptom onset.
- Two clinical trials of the antibody AZD7442 determined a risk reduction of symptomatic disease at 83%. As a treatment, there was an 88% reduced risk of severe illness and death when administered within 3 days of symptom onset.
- Clinical trials to assess early fluvoxamine treatment to high-risk outpatients found reduced risk of hospitalization.
- Clinical trials for molnupiravir have shown a 30% reduction in hospitalization and death, and showed an increase in viral clearance, but does not affect symptomatic duration. The potential side effects of molnupiravir are not well understood, but may include potential for cancer and birth defects. The FDA as approved an EUA for molnupiravir in mild to moderate cases of COVID-19, though no other FDA approved drugs are available.
- Preliminary results suggest high doses of anticoagulants may reduce rates of mechanical ventilation for mild-moderate COVID-19. The WHO recommends a standard dosing level as high doses of anticoagulants were not more effective at improving outcomes for critically ill patients.

**Common treatment medications for existing disease pre-COVID-19 diagnosis**
- Prior use of statins, RAAS inhibitors, anticoagulants, NSAIDs, and ACE inhibitors do not appear to elevate COVID-19 risk, and potential benefits of aspirin use require assessment in a clinical trial.

#### What do we need to know?

**We need clear, randomized trials for treatment efficacy in patients with both severe and mild/moderate illness.**
- What treatment, or combination of treatments, is most effective for different disease severities and patient demographics?
- What is the efficacy of transmission-blocking peptides and nasal sprays in humans?
Three safe and effective vaccines are currently being administered in the U.S.,510 with two under FDA EUA (Moderna and Johnson and Johnson/Janssen) and one with full FDA approval (Pfizer/BioNTech). All three vaccines have been approved for use as booster doses, and each can serve as a booster regardless of the initial vaccination type.489

- As of 5/4/2022, 219.9 million people in the U.S. are considered fully vaccinated, and 100.9 million have received boosters.511-512
- In the U.S., both Pfizer/BioNTech and Moderna vaccine efficacy has been estimated at 88% overall,513 with 80% efficacy two weeks after the first dose, rising to 90% or more two weeks after the second dose.514
- In Los Angeles, vaccinated individuals were 29 times less likely to be hospitalized after COVID-19 infection.515 Similarly, unvaccinated teenagers (12-17 years-old) were 10.1 times more likely to be hospitalized than vaccinated ones.516
- The duration of vaccine-derived immunity is unclear, but vaccine-derived antibodies persist for at least 6 months (Moderna vaccine),517 though neutralization is dependent on viral variant.518 Initial evidence from Israel suggests that booster shots for the Pfizer/BioNTech vaccine reduces the risk of infection and severe disease.519
- Third doses (boosters) of Pfizer/BioNTech and Moderna vaccines are allowed by the U.S. FDA for all adults ≥18 years old if they are 6 months after the completion of their full series.520
- Booster efficacy for Moderna and Pfizer-BioNTech ranges from 89.8-95.2%,519-520 A third dose of an mRNA vaccine was 82% effective at reducing emergency department or urgent care visits during the U.S. Omicron wave, and 90% effective at reducing hospitalizations.521 Fourth doses of Moderna and Pfizer-BioNTech have proven safe and immunogenic and offers 30% efficacy against all SARS-CoV-2 strains.521
- Compared to the D614G variant, second doses of the Moderna mRNA vaccine elicited weaker neutralizing antibody responses against the Omicron variant, though a third (booster) dose substantially elevated antibody responses.522
- A study of 1.3 million households in Israel found the secondary attack rate for SARS-CoV-2 was lower in households where the index case was vaccinated. Unvaccinated children of vaccinated household members had a 41% reduced risk of infection.523
- In a study of individuals with prior SARS-CoV-2 infection, reinfection rates were 2.34 times higher in those who were unvaccinated (i.e., natural immunity only) compared to those who were subsequently vaccinated.383

### Pfizer/BioNTech – mRNA vaccine named BNT162b2 (Comirnaty).59 U.S. FDA approval524 and WHO EUL.525
- This vaccine is given as 2 shots, 21 days apart.526 Six months after the first doses were administered, efficacy was 91.3% in terms of preventing symptomatic COVID-19, and >95% in terms of preventing severe COVID-19.527 The U.S. FDA granted EUA for use in 12-15 year-olds,528 and initial data shows high protective efficacy in 5-11 year-olds.527
- The FDA approved the use of the Pfizer vaccine in 5-11 year-olds, given as a two-dose regimen, three weeks apart. The dose is 10 ug versus the 30 ug dose for people 12 years or older,529 and are now approved as a third dose booster.530
- As of December 23, 2021, Pfizer announced their vaccine is safe and efficacious in 6 month to 5-year-old children.527
- Three doses of the Pfizer vaccine increases antibody titer 25-fold against wild-type virus compared to 2 vaccine doses.531

### Moderna – mRNA vaccine named mRNA-1273,532 U.S. EUA,533 approved in Canada534 and European Union,535 WHO EUL.536
- The vaccine is given as 2 shots, 28 days apart.537 Trials with adolescents (12-17 years old) show protective efficacy.538
- The vaccine showed 94.1% efficacy, 14 days after the second dose,539 consistent across age,540 race, ethnicity, and sex.539 Trials with reduced doses show high neutralizing responses, potentially expanding vaccine availability.540
- Receiving a booster from Moderna increases neutralizing antibody titers against the Omicron variant by 37-fold.540

### Johnson and Johnson/Janssen – adenovirus vaccine541 named Janssen COVID-19 vaccine. U.S. EUA,528 approved in EU535
- This vaccine is given as a single shot to adults 18 and older.528
- In clinical trials, the vaccine was 77.85% effective at preventing severe and critical COVID-19 14-28 days post injection, and 67% effective at preventing moderate to severe COVID-19.528 Initial evidence shows efficacy against the Delta variant.7 Associated with a rare clotting disorder542 and an elevated risk of Guillain-Barré syndrome.528
- Vaccination has provided robust protection from infection,544-545 evidenced by low rates of “breakthrough” infections.546 Vaccinated individuals generally experience milder symptoms than unvaccinated individuals,547-548 and most hospitalizations have occurred in individuals older than 65549 and those with underlying conditions.550
- Patients who receive a booster vaccination are 66% less likely to develop a symptomatic Omicron infection compared to unboosted individuals. 551

#### What do we need to know?

- We need to understand the long-term impact of SARS-CoV-2 variants on vaccine efficacy and the need for boosters.
- Does vaccination of individuals with post-acute sequelae of SARS-CoV-2 infection affect their long-term symptoms? A recent study has found that COVID vaccination (whether with Pfizer, Moderna or Johnson and Johnson vaccine) is not associated with improvement with post-acute sequelae of COVID (PASC).552
- What are the correlates between neutralizing antibody levels and vaccine-induced efficacy in humans?553
- How protective are vaccines in those taking immunosuppressants or with autoimmune disorders?
Non-pharmaceutical Interventions (NPIs) – Are public health control measures effective at reducing spread?

What do we know?

**Broad-scale control measures such as stay-at-home orders and widespread face mask use effectively reduce transmission.**
- Social distancing and other policies quickly reduced spread throughout China, Europe, and the U.S. Delays in implementation increase outbreak duration and mortality, and effective viral population size.
- Reductions in transmission appear 6-9 days after the implementation of NPIs, and increased transmission is visible 14-20 days after NPIs are lifted. Re-opening restaurants in the U.S. was associated with significantly higher mortality 61-100 days after relaxation of restrictions. However, this study was conducted using a largely unvaccinated population.
- U.S. states with mask mandates had lower case growth rates and higher likelihoods of controlling transmission. Modeling shows that slight increases in mask adherence (e.g., from 75% to 90% of individuals) can dramatically reduce simulated infections.
- In the U.S., shelter-in-place orders and restaurant closures were associated with large reductions in exponential growth rate of cases. Limiting gatherings to fewer than 10 people, closing schools and universities, and closing non-essential businesses also reduced SARS-CoV-2 transmission.
- Mobility reductions in the U.S. have been associated with reductions in COVID-19 case growth. Social distancing and reductions in both non-essential visits to stores and overall movement distance led to lower transmission rates.
- Reducing capacity at crowded indoor locations increasing indoor air flow rates, adding portable air cleaners, and wearing masks may reduce indoor transmission. Aerosol infection risk is not uniform in indoor environments, and can be greatly impacted by patterns of ventilation.
- NPIs and societal aid focused on populations at highest risk of infection, such as those living or working in crowded environments, are more effective than NPIs that assume equal risk of infection and transmission across subpopulations. Similarly, targeting NPIs at those in high-risk occupations may help reduce COVID-19 burden.

**Individual behaviors (e.g., face masks, social distancing) have been associated with reduced risk of COVID-19 infection.**
- Face masks inhibited transmission by both reducing the number of exhaled particles from infectious individuals, as well as reducing the number of inhaled particles when worn by uninfected individuals. The safety efficacy of masks depends largely on the type of mask, the way it is worn, and the overall fit.
- Always wearing masks, maintaining physical distance >1m, and frequently washing hands were all associated with reduced risk of COVID-19 infection in individuals who had direct contact with infected individuals.
- Restricting transmission in large urban areas is critical; they can serve as sources of infection for more distant regions.
- Policies implemented at the state level affect SARS-CoV-2 transmission, as states with a greater number of preventative policies showed lower COVID-19 case growth rates than those with less preventative action.

**Particular focus should be placed on minimizing large gatherings where superspreading events are more likely.**
- Eliminating superspreading events can result in slower case growth while easing broadly restrictive interventions. Focusing interventions on high-risk activities or locations (e.g., gyms, bars, and restaurants) may help reduce transmission.
- Reducing community prevalence, increasing ventilation, and universal testing can reduce spread in schools.
- As children are estimated to be less susceptible to SARS-CoV-2 infection, school closures are relatively ineffective NPIs. Modeling shows that masks and increased ventilation, along with portable air purifiers, are effective at reducing infection risk in classrooms.
- Across 177 countries, healthcare capacity or preparedness metrics were not associated with country-specific infection fatality rates (IFRs). Rather, age-structure, gross domestic product per capita, and body mass index were stronger predictors of IFR at the country-level.

**Research is needed to plan the path to SARS-CoV-2 elimination via pharmaceutical and non-pharmaceutical interventions.**
- Travel restrictions may be effective in certain conditions, such as when countries have low incidence themselves. Travel restrictions, though, are only effective at reducing the importation of novel variants if effectively implemented in a short time window; quarantines for travelers may be more broadly effective at reducing variant importation risk.
- Mobility data are useful proxies for pathogen transmission rate, but only early in epidemics before more complex behaviors and NPIs emerge.
- The level of NPI implementation in a country is related to its ability to export SARS-CoV-2 cases to neighboring countries.

**Lifting NPIs before widespread vaccine uptake is predicted to increase COVID-19 cases and deaths.**
- Modeling suggests that NPIs will need to be in place for 6-12 months after the initiation of vaccination campaigns. NPIs and vaccines work synergistically to reduce disease burden, and both are needed when vaccine coverage rates are low.
- Modeling shows that NPIs can reduce the likelihood of vaccine-resistant variant emergence, as the simulated emergence of vaccine-resistant strains was highest when vaccination levels were high (60%) but transmission was uncontrolled.

What do we need to know?

**We need to understand the magnitude of measures necessary to limit spread of new SARS-CoV-2 variants.**
- What NPIs are effective at reducing transmission from common SARS-CoV-2 variants?
- How does NPI effectiveness change over time as a result of changes in adherence or behavior?
SARS-CoV-2 can survive on surfaces from hours to days and is stable in air for at least several hours, depending on the presence of UV light, temperature, and humidity.\(^{622}\) Transmission via contaminated surfaces is not thought to be common.

- Given limited evidence of fomite transmission, guidance on cleaning and disinfecting surfaces continues to evolve.\(^{613}\) Viable SARS-CoV-2 and/or RNA can be recovered from contaminated surfaces; however, survivability varies.

- Both temperature and humidity contribute to SARS-CoV-2 survival on nonporous surfaces, with cooler, less humid environments facilitating survival (stainless steel, ABS plastic, and nitrile rubber; indoors only; simulated saliva matrix).\(^{614}\) Persistence is reduced with warmer temperatures (37°C), and enhanced at colder temperatures (4°C).\(^{615}\)

- SARS-CoV-2 was shown to be stable up to 7 days (25-27°C, 35% RH) on smooth surfaces, to include plastic, stainless steel, glass, ceramics, wood, latex gloves, and surgical masks.\(^{616}\) It is important to realize that SARS-CoV-2 detection by various methods does not confirm the presence of live virus, with a recent study finding no live virus on banknotes.\(^{615}\)

- SARS-CoV-2 was found to be stable across pH 3-10 on several surfaces at 22°C.\(^{617}\) After 3 hours (22°C, 65% RH), no infectious virus was detected on printing and tissue papers; on day 2, none was found on treated wood and cloth; on day 4, none was found on glass or banknote; on day 7, none was found on stainless steel or plastic.\(^{617}\)

- SARS-CoV-2 can persist on plastic and metal surfaces for up to 3 days (21-23°C, 40% RH)\(^{618}\) and infectious virus can be recovered from a surgical mask after 7 days (22°C, 65% RH)\(^{617}\) and other PPE for at least 72 hours at 22°C.\(^{619}\)

- In indoor environments, infectious virus persisted on cloth for up to 1 day, on steel and concrete for up to 3 days, and on nitrile, Tyvek, N95 respirators, Styrofoam, cardboard, rubber, and glass for up to 4 days.\(^{620}\)

- SARS-CoV-2 stability on surfaces may be inhibited by human fluids, as the virus persisted for only 1.5-3.3 hours in liquid nasal mucus on non-porous surfaces and 1.5-5.8 hours in liquid sputum on non-porous surfaces.\(^{621}\) However, other human fluids—particularly blood—enhanced SARS-CoV-2 stability on surfaces across a variety of temperature and humidity treatments.\(^{622}\)

**In the absence of sunlight, SARS-CoV-2 can persist on surfaces for weeks.**

- In the absence of sunlight, infectious SARS-CoV-2 can remain on non-porous (e.g., glass, vinyl) surfaces for at least 28 days at 20°C and 50% RH; higher temperatures greatly reduce the environmental stability of SARS-CoV-2.\(^{623}\) This value is longer than other stability estimates,\(^{617, 618}\) potentially due to a fluid matrix with more protein to simulate human respiratory fluid and a higher inoculation dose.\(^{623}\) In simulated saliva on stainless steel surfaces, SARS-CoV-2 shows negligible decay over 60 minutes in darkness, but loses 90% of infectivity every 6.8-12.8 minutes, depending on simulated UVB radiation.\(^{624}\)

- The Department of Homeland Security (DHS) developed a data-based model for SARS-CoV-2 decay on inert surfaces (stainless steel, ABS plastic and nitrile rubber) at varying temperature and relative humidity, also considering UV light.\(^{625}\)

- Organic material (e.g., feces) can enhance the ability of SARS-CoV-2 to transfer between surfaces.\(^{626}\)

**SARS-CoV-2 survival in the air is highly dependent on the presence of UV light and temperature.**

- DHS has developed a tool for estimating the decay of airborne SARS-CoV-2 in different environmental conditions.\(^{627}\) Due to evaporation, hot, dry conditions increase the aerosol risk, though cold, humid conditions facilitate droplet spread.\(^{628}\)

- Experimental studies using SARS-CoV-2 aerosols found that simulated sunlight rapidly inactivates the virus, with 90% reductions in infectious concentration after 6 minutes in high-intensity sunlight (similar to mid-June) and 19 minutes in low-intensity sunlight (similar to early March or October).\(^{629}\) In dark conditions, the half-life of aerosolized SARS-CoV-2 is approximately 86 minutes in simulated saliva.\(^{629}\) Humidity alone had no significant impact on aerosolized virus survival.\(^{629}\)

- SARS-CoV-2 was shown to have an aerosol half-life of 2.7 hours (without sunlight, particles <5 μm, tested at 21-23°C and 65% RH),\(^{618}\) retaining infectivity for up to 16 hours in appropriate conditions (23°C, 53% RH, no sunlight).\(^{630}\)

**Stability of SARS-CoV-2 RNA in clinical samples depends on temperature and transport medium.**

- RNA in clinical samples collected in viral transport medium is stable at 18-25°C or 2-8°C for up to 21 days without impacting real-time RT-PCR results,\(^{631}\) while use of phosphate buffered saline (PBS, 18-25°C) resulted in sample instability.\(^{632}\)

**There is currently no evidence that SARS-CoV-2 is transmitted to people through food or food packaging.**\(^{633-634}\)

- SARS-CoV-2 can persist for at least two weeks at refrigerated temperatures (4°C).\(^{617, 635}\) SARS-CoV-2 maintains infectivity for at least 21 days when inoculated on frozen foods and stored below -20°C.\(^{636}\) Infectious SARS-CoV-2 has been found on frozen food packaging, but has not been linked to actual infections.\(^{637}\) Several outbreaks have a hypothesized food origin.\(^{638}\)

**SARS-CoV-2 stability in sewage and human wastewater remains unknown.**

- Surrogate studies of human and animal coronaviruses suggest wastewater is not conducive to long-term virus survival, as coronaviruses undergo spontaneous and progressive inactivation because of temperature and organic or microbial pollution.\(^{639}\) SARS-CoV-2 RNA was found in untreated liquid and solid waste systems (infectious virus was not quantified), though typical treatment effectively eliminated viral RNA from effluent.\(^{640}\)

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**What do we need to know?**

**We need to quantify the duration of viable SARS-CoV-2 on surfaces, not simply the presence of RNA.**

- Can SARS-CoV-2-contaminated wastewater cause infections?\(^{641, 642}\)

- Are certain SARS-CoV-2 variants more or less stable on surfaces or in aerosols?
Soap and water, as well as common alcohol and chlorine-based cleaners, hand sanitizers, and disinfectants are effective at inactivating SARS-CoV-2 on hands and surfaces.

- A systematic review identified sunlight, UV light, ethanol, hydrogen peroxide, and hypochlorite as methods to reduce surface contamination. However, the levels of decontamination necessary to affect transmission per se are still unknown.
- Alcohol-based hand rubs are effective at inactivating SARS-CoV-2.
- Chlorine bleach (1%, 2%), 70% ethanol and 0.05% chlorhexidine are effective against live virus in lab tests. Disinfection using 1% sodium hypochlorite dispersed by cold fogging significantly reduces the amount of disinfectant used without compromising inactivation.
- EPA has released a list of SARS-CoV-2 disinfectants that have been found effective against SARS-CoV-2 specifically.
- Twice-daily cleaning with sodium dichloroisocyanurate decontaminated surfaces in COVID-19 patient hospital rooms.
- Regular disinfection of hospital rooms (with benzalkonium wipes) can reduce the presence of SARS-CoV-2 on surfaces, though contamination is widespread without regular cleaning. Chlorhexidine digluconate may be ineffective.
- Heat, soap, and ethanol were also able to decontaminate SARS-CoV-2 variants (Alpha and Beta) on various surfaces.
- While a 4-5 log (99.99-99.999%) reduction in viral titer is often used as a metric of effective decontamination, achieving this level of reduction is dependent on methodological issues like the initial viral stock concentration.
- Oral antiseptic rinses used for dentistry containing povidone-iodine (PVP-I) are effective decontaminants of SARS-CoV-2, completely inactivating SARS-CoV-2 at concentrations above 0.5% in lab tests (for 15-30 s).
- A mouth-spray previously investigated for the cold-causing coronavirus 229E (ColdZyme®) effectively inactivated SARS-CoV-2 in vitro; additional tests are necessary to determine any clinical benefit.
- Indoor air filters based on non-thermal plasma or reactive oxygen species may be effective at reducing circulating SARS-CoV-2 concentrations, estimated by reductions in surrogate virus, though additional testing on live SARS-CoV-2 virus is needed.
- Indoor air filtration devices based on hydroxyl radical cascades, which do not emit ozone, are being trialed at 4 UK hospitals due to their efficacy in reducing concentrations of a surrogate virus (M2 phage).
- In tests with a surrogate virus (Phi6 phage), a modified version of the Joint Biological Agent Decontamination System (JBADS) was effective at decontaminating military aircrafts in approximately three hours using high heat and humidity; however, may be less stable than SARS-CoV-2 on surfaces, and therefore may not be the best surrogate.
- Aquila Bioscience has developed a spray decontamination technique to pair with its existing alcohol- and chemical-free wipe; these products may be used to capture SARS-CoV-2 on skin, surfaces, and washable masks via high-affinity binding.
- Percacetic acid dry fogging inactivated SARS-CoV-2 on stainless steel coupons, simulating whole-room fumigation.
- Initial research suggests that SARS-CoV-2 can be inactivated within 1 minute on pure copper and copper-coated surfaces.
- Widespread surface decontamination (e.g., streets) may not be necessary due to lack of documented fomite transmission.

Several methods exist for decontaminating N95 respirators and other PPE.

- Researchers have identified three methods capable of decontaminating N95 respirators while maintaining physical integrity: UV radiation, heating to 70°C, and vaporized hydrogen peroxide (VHP). Ethanol (70%) was associated with loss of physical integrity.
- Germicidal UVC decontamination methods for N95s was successful when both sides were irradiated for a minimum of 120 seconds at 1.3 Joules/cm² (yielding a 3.5 log reduction) and can be scaled for large-scale decontamination efforts.
- Hydrogen peroxide vapor (VHP) can repeatedly decontaminate N95 respirators.
- Canadian hospitals have shown blanket heating cabinets can sterilize reusable and N95 masks with wet or dry heat using a temperature ≥70°C without functional changes to mask integrity.
- Respirator decontamination methods such as VHP appear to maintain filtration efficiency after repeated cycles. Several decontamination methods, including VHP, moist heat, and UVC, are capable of decontaminating N95 respirators for 10-20 cycles without loss of fit or filtration efficiency. Stacking respirators may increase decontamination rates without compromising efficiency. Repeated wet and dry heat sterilization methods do not alter N95 quantitative fit capacity, but rather overall wear time and number of uses are the primary contributors to functional degradation.
- The U.S. FDA has issued guidance for bioburden reduction systems using dry heat to decontaminate certain respirators.
- A thermal inactivation model for SARS-CoV-2 provides estimates of infectivity reduction based on time and temperature.
Face masks appear effective at reducing infections from SARS-CoV-2. Healthcare workers are at elevated risk of acquiring COVID-19, even with recommended PPE.
- Contacts with healthcare workers tend to transmit COVID-19 more often than other casual contacts. Hospital-acquired infection rates fell after introduction of comprehensive infection control measures, including expanded testing and use of PPE for all patient contacts.
- A modeling study suggests that healthcare workers are primarily at risk from droplet and inhalation exposure (compared to contact with fomites), with greater risk while in closer proximity to patients.
- The WHO considers face shields as inferior to masks and respirators for control of droplet transmission. WHO indicates healthcare workers should wear clean long-sleeve gowns and gloves. PPE that covers all skin may reduce exposure.
- Respirators (NIOSH-certified N95, EUFPP2 or equivalent) are recommended for those working with potential aerosols, though procedure type is not the only factor influencing risk of aerosol generation in hospitals. Additional protection (Powered Air Purifying Respirator (PAPR) with hood), should be considered for high-risk procedures.
- KN95 respirators are, under certain conditions, approved for use under FDA EUA. On May 7, 2020, the FDA rescinded a number of KN95 models that no longer meet the EUA criteria and are no longer authorized.
- 85% of tested N95 respirators passed fit tests after at least five cycles of standard donning/doffing and dry heat decontamination, though extended use has previously been associated with fit failures previously.
- While several observational studies have linked a lack of eye protection to COVID-19 in healthcare workers, the presence of other protective measures or PPE was not controlled, resulting in a need for additional research.
- Mathematical modeling suggests that mask efficacy depends heavily on the aerosol concentration of SARS-CoV-2, with higher efficacy in situations with lower aerosol concentrations; pairing mask use with other interventions that reduce aerosol concentrations, such as increasing ventilation, can greatly reduce transmission risk.
- Healthcare workers exposed to aerosol-generating procedures (AGPs) without wearing respirators or eye protection became infected with SARS-CoV-2 during periods of time with universal face mask use, suggesting AGPs do not dramatically increase infection risk as long as other precautions (i.e., masks) are in use.

Non-medical masks may be effective at slowing transmission, though data specific to SARS-CoV-2 are sparse.
- As of April 27, 2022, the CDC recommends that individuals with symptoms, a positive test, or recent exposure wear a mask as well as individuals using indoor public transportation. The CDC recommends masks without exhalation vents or valves, as these can allow particles to pass through unfiltered.
- The U.S. CDC maintains a list of NIOSH-tested facemasks with estimates of minimum and maximum filter efficiency, and also maintains a list of single-use and reusable masks that meet updated ATSM F3502-21 standards. Mask fit is another critical component of effectiveness, in addition to filter efficiency.
- Face masks (surgical and cotton) reduced the amount of SARS-CoV-2 shed by approximately 48% in fine aerosols (<5um) and 77% in coarse aerosols (>5um), though the majority of viral RNA was exhaled in fine aerosol particles.
- In a prospective cohort study in the U.S., the secondary attack rate of SARS-CoV-2 was higher when at least one person was not wearing a face mask compared to when both individuals were wearing a mask (25.6% vs. 12.5%, respectively).
- Secondary attack rates were lower when contacts wore masks and the emitter did not (10%) than when the emitter wore a mask and the contacts did not (29.1%). This contrasts previous findings.
- Infected individuals wearing facemasks in the home before the onset of symptoms reduced household transmission rates.
- In a meta-analysis, N95 respirators were found to be beneficial for reducing the occurrence of respiratory illness in healthcare professionals including influenza, though surgical masks were similarly effective for influenza.
- N95 respirators were associated with up to 80% reductions in SARS-CoV-1 infections.
- Surgical face masks, respirators, and homemade face masks may prevent transmission of coronaviruses from infectious individuals to other individuals. Surgical masks were associated with a significant reduction in the amount of seasonal coronavirus expressed as aerosol particles (<5 μm). Homemade masks reduce overall flow from breathing and coughing (63-86% reduction) but also generate leakage jets facing downward and backward from the wearer's face.
- Some non-standard materials may be able to filter out >90% of simulant particles >0.3μm, while other materials (e.g., T-shirt, vacuum cleaner bag, towels) appear to have lower filtration efficacy (~35-62%).
- Neck fleeces (gaiters) commonly worn by runners may increase the frequency of small aerosol particles, compared to wearing no mask at all. Cotton T-shirt masks appear ineffective at reducing emitted particles when individuals talk, breathe, sneeze, or cough, with those made of single layers increasing emitted particles during these activities. Smaller aerosol particles (e.g., <0.1μm) are more difficult to filter for most respirators and face masks.

What do we need to know?
- Can mask efficacy be predicted from material composition?
- What is the efficacy of combining multiple facemasks compared with single multilayered masks?
- Very few studies have been conducted to assess the risk of COVID-19 to those collecting nasopharyngeal swabs.
- Should decontamination methods be optimized for individual makes/models of PPE?
Forensics – Natural vs intentional use? Tests to be used for attribution.

What do we know?

Current evidence supports the natural emergence of SARS-CoV-2 via a bat and possible intermediate mammal species.

- The WHO and others have called for more research into SARS-CoV-2 origins.717
- Analysis of SARS-CoV-2 and related SARS-like coronaviruses suggests that SARS-CoV-2 jumped directly from bats to humans, without the influence of an intermediate ‘mixing’ host.140 Current sampling of pangolin viruses does not implicate them as an intermediate to human SARS-CoV-2.140
- Based on phylogenetic analysis, SARS-CoV-2 most likely emerged from Rhinolophus (horseshoe) bats living in China, Laos, Myanmar, Vietnam, or another Southeast Asian country.718
- Genomic analysis suggests that SARS-CoV-2 is a natural variant and is unlikely to be human-derived or otherwise created by “recombination” with other circulating strains of coronavirus.719-720
- The SARS-CoV-2 Spike protein, which mediates entry into host cells and is a major determinant of host range, is very similar to the SARS-CoV-1 Spike protein.721 The rest of the genome is more closely related to other bat coronaviruses.721
- Ancestors of SARS-CoV-2 underwent diversifying selection in bats, making host jumps to other mammals, including humans, feasible even without the presence of an intermediate species.722
- At least one mutation in the SARS-CoV-2 genome (A1114G; T372A) shows evidence of increased viral replication in human lung cells, and appears to have undergone positive selection that potentially enabled infection in humans.723 Additional work is needed to confirm the role of this mutation, as well as to identify other mutations that enabled a jump to humans.
- A key difference between SARS-CoV-2 and other beta-coronaviruses is the presence of a polybasic furin cleavage site in the Spike protein (insertion of a PRRA amino acid sequence between S1 and S2).724
- SARS-CoV-2 possesses a unique S1/S2 furin cleavage site unknown elsewhere in nature. Comparing genomes of multiple coronaviruses using machine-learning has identified key genomic signatures shared among high case fatality rate coronaviruses (SARS-CoV-1, SARS-CoV-2, MERS) and animal counterparts.726 These data further suggest that SARS-CoV-2 emergence is the result of natural emergence and that there is a potential for future zoonotic transmission of additional pathogenic strains to humans.726
- Deletion mutants were identified at low levels in human clinical samples, suggesting that the PRRA furin cleavage site alone is not fully responsible for human infection, but does confer a fitness advantage in the human host.727 Additional whole-genome sequencing in humans would help to confirm this finding.
- Genomic data support at least two plausible origins of SARS-CoV-2: (i) natural selection in a non-human animal host prior to zoonotic transfer, and (ii) natural selection in humans following zoonotic transfer.772 Both scenarios are consistent with the observed genetic changes found in all known SARS-CoV-2 isolates.
- Bats are not the only reservoir of SARS-like coronaviruses.728
- There are multiple studies showing that the SARS-CoV-2 S protein receptor binding domain, the portion of the protein responsible for binding the human receptor ACE2, was acquired through recombination between coronaviruses from pangolins and bats.138-139, 720, 728 These studies suggest that pangolins may have played an intermediate role in the adaptation of SARS-CoV-2 to be able to bind to the human ACE2 receptor. Additional research is needed.
- Additionally, “[…] SARS-CoV-2 is not derived from any previously used virus backbone,” reducing the likelihood of laboratory origination,726 and “[…] genomic evidence does not support the idea that SARS-CoV-2 is a laboratory construct, [though] it is currently impossible to prove or disprove the other theories of its origin.”720
- Work with other coronaviruses has indicated that heparan sulfate dependence can be an indicator of prior cell passage, due to a mutation in the previous furin enzyme recognition motif.729

What do we need to know?

We need to know whether there was an intermediate host species between bats and humans.

- What tests for attribution exist for coronavirus emergence?
- What is the identity of the intermediate species if it exists?
- Are there closely related coronaviruses in bats or other animals with the novel PRRA cleavage site found in SARS-CoV-2?
We need to identify differences in transmissibility or severity caused by different SARS-CoV-2 mutations and variants.

What do we know?

- The estimated mutation rate for SARS-CoV-2 is $6 \times 10^{-4}$ nucleotides per genome, per year.\textsuperscript{730}
- The U.S. CDC has updated language to discuss “variants being monitored” (VBM) as opposed to “variant of interest” (VOI), maintaining the classification of “variant of concern” (VOC), in the U.S., Omicron (including subvariants) is currently the only VOC.\textsuperscript{731}
- Immunosuppressed patients are a possible source of viral variants due to prolonged virus replication within a single host.\textsuperscript{732}
- B.1.1.7 (20I/S01Y.V1) (VOC202012/01) (Alpha) - The B.1.1.7 variant (Alpha) is associated with 50-75% higher transmission than wild-type virus.\textsuperscript{733-734} Contains several Spike protein mutations (HV 69-70 deletion, N501Y, N493K).\textsuperscript{735}
- There are currently no concerns relating to the efficacy of the Pfizer/BioNTech\textsuperscript{736-737} or Moderna vaccines,\textsuperscript{738} and the AstraZeneca/Oxford vaccine appears to show efficacy against B.1.1.7 (though lower than efficacy against wild-type SARS-CoV-2).\textsuperscript{739}
- The E484K mutation has appeared independently in several individuals with the B.1.1.7 variant in the UK and U.S.\textsuperscript{740}
- B.1.617.2 (Delta) - Variant being monitored\textsuperscript{742} initially identified in India in January 2021, containing several mutations of concern (E484Q and L452R).\textsuperscript{743}
- Resists neutralization by certain monoclonal antibodies\textsuperscript{744-745} and is more resistant to vaccine-derived antibodies than wild-type SARS-CoV-2; serum from patients given mRNA vaccines was able to neutralize the B.1.617.1 (Kappa) lineage.\textsuperscript{746}
- B.1.617.2 has 13 sub-lineages; 4 are being monitored as VBMs in the U.S.: AY.1, AY.2, AY.3, AY.3.1.\textsuperscript{747} AY.1 and AY.2 possess a mutation of concern at K417N that is also present in B.1.351 (Beta) and P.1 (Gamma) variants.\textsuperscript{748} This mutation affects class I antibody binding\textsuperscript{749-750} and reduces affinity to ACE2 but provides stability to ACE2 binding in the presence of the E484K mutation.\textsuperscript{750-751}
- As of October 21, 2021, the UK has identified a Delta variant (B.1.617.2.4.2; AY.4.2) as a VOC due to the moderate increase of cases with a secondary attack rate of 12.4%.\textsuperscript{752}
- B.1.351 (20H/S01Y.V2) (Beta) - Identified in South Africa in December 2020\textsuperscript{753} with mutations N501Y, E484K, and K417N.\textsuperscript{754}
- Beta resistant to neutralization from convalescent plasma and vaccine recipient sera.\textsuperscript{620} Preliminary studies from Moderna,\textsuperscript{755} Johnson and Johnson,\textsuperscript{756} AstraZeneca,\textsuperscript{757} and Novavax\textsuperscript{758} suggest a lower vaccine response, though the Pfizer/BioNTech vaccine appears neutralizing in laboratory settings\textsuperscript{759} and human trials.\textsuperscript{760}
- Convalescent serum from patients with B.1.351 infection shows high neutralization ability against wild-type virus.\textsuperscript{759}
- The B.1.351 variant is partially resistant to the monoclonal antibody casirivimab and is fully resistant to bamlanivimab.\textsuperscript{744}
- P.1 (20J/S01Y.V3) (Gamma) - First identified in Brazil;\textsuperscript{760} contains K417N, E484K, and N501Y mutations.\textsuperscript{760}
- The variant is estimated to be 1.7-2.4 times more transmissible than wild-type SARS-CoV-2.\textsuperscript{761}
- Prior SARS-CoV-2 infection is estimated to provide 54-79% protection against infection.\textsuperscript{761}
- Less resistant to neutralization than the B.1.351 variant despite three critical shared mutations (E484K, K417N/T, and N501Y), suggesting RBD mutations are not the only factor influencing variant immune escape.\textsuperscript{762}
- The H655Y mutation is associated with reduced neutralization,\textsuperscript{763} and has arisen in experimental animal models.\textsuperscript{764-765}
- Experimental studies in mink found increased viral cell entry, transmission, and host susceptibility with this mutation.\textsuperscript{765}
- C.37 (Lambda variant) - In vitro studies suggest two single mutations (T76I, L452Q) make the Lambda variant more infectious than wild-type virus, while a deletion mutation (RSYLTPGD246-253N) increases antibody resistance.\textsuperscript{766}
- B.1.429 (Epsilon) ([CAL.20C (20C/S:452R]) [GH/452R.V1 (B.1.429+B.1.427)]) - L452R\textsuperscript{767} mutation located on the Spike protein was first reported in Denmark\textsuperscript{768} and has increased in prevalence in California.\textsuperscript{769} The B.1.429 lineage is more transmissible and leads to more severe disease than wild-type SARS-CoV-2.\textsuperscript{770} and is partially resistant to antibodies.\textsuperscript{771-772}
- B.1.621 (Mu) - Includes B.1.621.1. Mutations of note in Spike: E484K, N501Y, D614G, P681H. Preliminary studies suggest the Mu variant is resistant to convalescent patient sera and sera from those vaccinated with the Pfizer/BioNTech vaccine.\textsuperscript{773-774}
- B.1.529 (Omicron) - Detected on November 26, 2021 in South Africa and/or Botswana, the Omicron variant includes 21 unique mutations in the Spike gene with 14 shared with other VOIs.\textsuperscript{775} Many of these mutations are located in the RBD and NTD and may play a role in ACE2 binding and antibody recognition.\textsuperscript{775} More work is needed.
- The risk of severe outcomes is greatly reduced in patients infected with Omicron versus previous Delta strains.\textsuperscript{776}
- Omicron sublineage BA.2 cases are rising in Europe with a 100% increase over the last month. In the U.S., cases have increased to over 50% of all sequenced cases in the last month and account for 72% of all U.S. cases,\textsuperscript{777} with an 80% growth rate in the UK over BA.1.\textsuperscript{778}
- BA.2 has additional mutations in the Spike protein that may be responsible for the increased transmissibility. More research is needed.\textsuperscript{779}

What do we need to know?

- We need to identify differences in transmissibility or severity caused by different SARS-CoV-2 mutations and variants.
- What are the mechanisms driving the resistance of variants to neutralization by the immune system?
- How do variants affect the likelihood of reinfection or coinfection?
- How prevalent are coinfections with multiple strains, and what is their clinical progression?\textsuperscript{780}
### Forecasting – What forecasting models and methods exist?

<table>
<thead>
<tr>
<th>What do we know?</th>
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<tbody>
<tr>
<td>Several platforms provide digital dashboards summarizing the current status of the pandemic in U.S. states and counties.</td>
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<tr>
<td><strong>The U.S. CDC maintains a dashboard of state-level COVID-19 vaccination data for first and second doses.</strong></td>
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<td><strong>Hospital IQ has a dashboard that forecasts hospital and ICU admissions for each county in the U.S.</strong></td>
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<td><strong>COVID Act Now: State and county-level dashboard focused on re-opening strategies, showing trends in four metrics related to COVID-19 risk. Fundamentally uses an SEIR model fit to observed data.</strong></td>
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<td><strong>The National Association of County and City Health Officials (NACCHO) provides a dashboard with estimates of county-specific test positivity rates as well as mortality incidence for different racial groups.</strong></td>
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<td><strong>Maps and dashboards depicting COVID-19 infection rates do not necessarily increase likelihood of adhering to non-pharmaceutical interventions; additional information is needed to influence perceptions of individual risk.</strong></td>
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<td><strong>The U.S. CDC provides ensemble forecasts of cases and deaths based on the average of many participating groups.</strong></td>
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<td><strong>Ensemble forecasts generally show better predictive accuracy than individual forecast models.</strong></td>
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<td><strong>Columbia University Model: Spatially explicit SEIR model incorporating contact rate reductions due to social distancing. Estimates total cases and risk of healthcare overrun.</strong></td>
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<tr>
<td><strong>Institute of Health Metrics and Evaluation (IHME): Mechanistic SEIR model combined with curve-fitting techniques to forecast cases, hospital resource use, and deaths at the state and country level. Also provides global forecasts.</strong></td>
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<tr>
<td><strong>Los Alamos National Laboratory: Forecasts of state-level cases and deaths based on statistical growth model fit to reported data. Implicitly accounts for effects of social distancing and other control measures.</strong></td>
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<tr>
<td><strong>Google/Harvard University: Time-series machine learning model that makes assumptions about which non-pharmaceutical interventions will be in place in the future.</strong></td>
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<td><strong>Northeastern University: Spatially explicit, agent-based epidemic model used to forecast fatalities, hospital resource use, and the cumulative attack rate for unmitigated and mitigated scenarios.</strong></td>
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<td><strong>Additional forecasting efforts are designed to assess the effects of interventions such as social distancing and vaccination.</strong></td>
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<tr>
<td><strong>Massachusetts Institute of Technology: Mechanistic SEIR model that forecasts cases, hospitalizations, and deaths. Also includes estimates of intervention measures, allows users to project based on different intervention scenarios.</strong></td>
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<tr>
<td><strong>MITRE: Dashboards for COVID-19 forecasts and decision support tools, including regional comparisons and intervention planning. Uses combinations of SEIR models and curve-fitting approaches.</strong></td>
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<tr>
<td><strong>Shen et al. estimate U.S. COVID-19 cases under different scenarios of vaccine efficacy, studying the continued need for non-pharmaceutical interventions such as face masks and physical distancing.</strong></td>
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<td><strong>In a modeling study, vaccination strategies prioritizing adults &gt;60 years old minimized mortality, while those prioritizing adults 20-49 years old minimized disease incidence.</strong></td>
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<td><strong>Prioritizing vaccines for elderly individuals with high COVID-19 mortality maximizes life-years saved by vaccination; though prioritization of older or younger individuals for initial vaccine distribution may depend on the stage of the pandemic in a location. Vaccination focused on interrupting transmission (prioritizing younger individuals) may reduce mortality more than prioritizing vulnerable groups when vaccine campaign initiation is delayed.</strong></td>
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<tr>
<td><strong>CovidSim: SEIR model allow users to simulate effects of future intervention policies at state and national levels (U.S. only).</strong></td>
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<tr>
<td><strong>Covasim: Agent-based model for testing effects of intervention measures, also available as Python library.</strong></td>
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<tr>
<td><strong>University of Georgia: Statistical models used to estimate the current number of symptomatic and incubating individuals, beyond what is reported (e.g., “nowcasts”). Available at the state and national level for the U.S..</strong></td>
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<td><strong>Vaccination is most effective at reducing new infections before local peaks in incidence.</strong></td>
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<td><strong>Researchers use a rolling window analysis incorporating uncertainty in the generation time distribution to estimate time-varying transmission rates in U.S. states (the effective reproduction number, R&lt;sub&gt;eff&lt;/sub&gt; or R&lt;sub&gt;t&lt;/sub&gt;).</strong></td>
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<td><strong>Accounting for superspreading in forecast models can increase model accuracy and precision, while incorporating memory effects (e.g., the duration of individual infectiousness) can also increase forecast model fit to data.</strong></td>
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<tr>
<td><strong>Wastewater may be useful in forecasting local SARS-CoV-2 prevalence and early identification of variant spread.</strong></td>
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<td><strong>New approaches may be needed to forecast COVID-19 re-emergence after elimination or during periods of low incidence.</strong></td>
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<tr>
<td><strong>Several characteristics of SARS-CoV-2 mutations, such as their prevalence and relationship to immune escape, may enable forecasting which mutations are likely to show up in future variants of concern months before their emergence.</strong></td>
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### What do we need to know?

| We need to know how different vaccine uptake rates will affect the epidemic in the U.S. and neighboring countries. |
| **How will spillover and movement between countries affect local COVID-19 resurgence after initial vaccine distribution?** |
| **What are likely scenarios for the post-vaccination phase of COVID-19? Endemicity? Seasonal peaks in children?** |
### Table 1. Definitions of commonly used acronyms

<table>
<thead>
<tr>
<th>Acronym/Term</th>
<th>Definition</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACE2</td>
<td>Angiotensin-converting enzyme 2</td>
<td>Acts as a receptor for SARS-CoV and SARS-CoV-2, allowing entry into human cells</td>
</tr>
<tr>
<td>Airborne transmission</td>
<td>Aerosolization of infectious particles</td>
<td>Aerosolized particles can spread for long distances (e.g., between hospital rooms via HVAC systems). Particles generally &lt;5 μm</td>
</tr>
<tr>
<td>ARDS</td>
<td>Acute respiratory distress syndrome</td>
<td>Leakage of fluid into the lungs which inhibits respiration and leads to death</td>
</tr>
<tr>
<td>Attack rate</td>
<td>Proportion of “at-risk” individuals who develop infection</td>
<td>Defined in terms of “at-risk” population such as schools or households, defines the proportion of individuals in those populations who become infected after contact with an infectious individual</td>
</tr>
<tr>
<td>CCV</td>
<td>Canine coronavirus</td>
<td>Canine coronavirus</td>
</tr>
<tr>
<td>CFR</td>
<td>Case Fatality Rate</td>
<td>Number of deaths divided by confirmed patients</td>
</tr>
<tr>
<td>CoV</td>
<td>Coronavirus</td>
<td>Virus typified by crown-like structures when viewed under electron microscope</td>
</tr>
<tr>
<td>COVID-19</td>
<td>Coronavirus disease 19</td>
<td>Official name for the disease caused by the SARS-CoV-2 virus.</td>
</tr>
<tr>
<td>Droplet transmission</td>
<td>Sneezing, coughing</td>
<td>Transmission via droplets requires relatively close contact (e.g., within 6 feet)</td>
</tr>
<tr>
<td>ELISA</td>
<td>Enzyme-linked immunosorbent assay</td>
<td>Method for serological testing of antibodies</td>
</tr>
<tr>
<td>Fomite</td>
<td>Inanimate vector of disease</td>
<td>Surfaces such as hospital beds, doorknobs, healthcare worker gowns, faucets, etc.</td>
</tr>
<tr>
<td>HCW</td>
<td>Healthcare worker</td>
<td>Doctors, nurses, technicians dealing with patients or samples</td>
</tr>
<tr>
<td>Incubation period</td>
<td>Time between infection and symptom onset</td>
<td>Time between infection and onset of symptoms typically establishes guidelines for isolating patients before transmission is possible</td>
</tr>
<tr>
<td>Infectious period</td>
<td>Length of time an individual can transmit infection to others</td>
<td>Reducing the infectious period is a key method of reducing overall transmission; hospitalization, isolation, and quarantine are all effective methods</td>
</tr>
<tr>
<td>Intranasal</td>
<td>Agent deposited into external nares of subject</td>
<td>Simulates inhalation exposure by depositing liquid solution of pathogen/virus into the nose of a test animal, where it is then taken up by the respiratory system</td>
</tr>
<tr>
<td>MERS</td>
<td>Middle East Respiratory Syndrome</td>
<td>Coronavirus with over 2,000 cases in regional outbreak since 2012</td>
</tr>
<tr>
<td>MHV</td>
<td>Mouse hepatitis virus</td>
<td>Coronavirus surrogate</td>
</tr>
<tr>
<td>Mutation</td>
<td>Change in SARS-CoV-2 genome relative to original or reference strain</td>
<td>Mutations are alterations (e.g., insertions, deletions, transpositions) in the RNA genome of SARS-CoV-2 that may or may not affect viral function. Mutations are often defined by the change in amino acid encoded by a sequence at a particular location. For instance, the N501Y mutation changes the 501st amino acid from an asparagine (N) to a tyrosine (Y). SARS-CoV-2 variants are usually comprised of multiple mutations, and mutations can arise in distinct SARS-CoV-2 variants</td>
</tr>
<tr>
<td>Non-variant SARS-CoV-2</td>
<td>“Original” or comparator strain or variant in any comparison of novel or emerging variants</td>
<td>Used to indicate a comparison between a new or emerging variant (such as B.1.1.7) and an older strain or variant of SARS-CoV-2 (e.g., WA-1). There is no single “non-variant” SARS-CoV-2 virus. See also “wild-type.”</td>
</tr>
<tr>
<td>Acronym/Term</td>
<td>Definition</td>
<td>Description</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Nosocomial</td>
<td>Healthcare- or hospital-associated infections</td>
<td>Characteristic of SARS and MERS outbreaks, lead to refinement of infection control procedures</td>
</tr>
<tr>
<td>NPI</td>
<td>Non-pharmaceutical intervention</td>
<td>Public health control measures designed to reduce transmission, such as social distancing, movement restrictions, and face mask requirements</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
<td>PCR (or real-time [RT] or quantitative [Q] PCR) is a method of increasing the amount of genetic material in a sample, which is then used for diagnostic testing to confirm the presence of SARS-CoV-2</td>
</tr>
<tr>
<td>PFU</td>
<td>Plaque forming unit</td>
<td>Measurement of the number of infectious virus particles as determined by plaque forming assay. A measurement of sample infectivity</td>
</tr>
<tr>
<td>PPE</td>
<td>Personal protective equipment</td>
<td>Gowns, masks, gloves, and any other measures used to prevent spread between individuals</td>
</tr>
<tr>
<td>RBD</td>
<td>Receptor binding domain</td>
<td>Protein domain used by virus to gain entry into host cells by recognizing specific host cell receptors (e.g., ACE2)</td>
</tr>
<tr>
<td>R₀</td>
<td>Basic reproduction number</td>
<td>A measure of transmissibility. Specifically, the average number of new infections caused by a typical infectious individual in a wholly susceptible population</td>
</tr>
<tr>
<td>SAR</td>
<td>Secondary attack rate</td>
<td>The proportion of contacts infected with COVID-19 after interactions with a primary or index case, often in a household, school, or community setting</td>
</tr>
<tr>
<td>SARS</td>
<td>Severe Acute Respiratory Syndrome</td>
<td>Coronavirus with over 8,000 cases in global 2002-2003 outbreak</td>
</tr>
<tr>
<td>SARS-CoV-2</td>
<td>Severe acute respiratory syndrome coronavirus 2</td>
<td>Official name for the virus previously known as 2019-nCoV</td>
</tr>
<tr>
<td>SEIR</td>
<td>Susceptible (S), exposed (E), infected (I), and resistant (R)</td>
<td>A type of modeling that incorporates the flow of people between the following states: susceptible (S), exposed (E), infected (I), and resistant (R), and is being used for SARS-CoV-2 forecasting</td>
</tr>
<tr>
<td>Serial interval</td>
<td>Length of time between symptom onset of successive cases in a transmission chain</td>
<td>The serial interval can be used to estimate R₀ and is useful for estimating the rate of outbreak spread</td>
</tr>
<tr>
<td>SIR</td>
<td>Susceptible (S), infected (I), and resistant (R)</td>
<td>A type of modeling that incorporates the flow of people between the following states: susceptible (S), infected (I), and resistant (R), and is being used for SARS-CoV-2 forecasting</td>
</tr>
<tr>
<td>TCID₅₀</td>
<td>50% Tissue Culture Infectious Dose</td>
<td>The number of infectious units which will infect 50% of tissue culture monolayers. A measurement of sample infectivity</td>
</tr>
<tr>
<td>Transgenic</td>
<td>Genetically modified</td>
<td>In this case, animal models modified to be more susceptible to MERS and/or SARS by adding proteins or receptors necessary for infection</td>
</tr>
<tr>
<td>Variant</td>
<td>SARS-CoV-2 lineage with shared collection of mutations</td>
<td>Variants are used to designate distinct SARS-CoV-2 lineages that share any number of mutations. For instance, the B.1.1.7 variant is characterized by an HV 69-70 deletion, N501Y mutation, and N493K mutation.</td>
</tr>
<tr>
<td>Vertical transmission</td>
<td>Transmission from mother to fetus</td>
<td>Generally understood as intrauterine transmission via blood or placenta. Not the same as transmission during or after birth</td>
</tr>
<tr>
<td>Wild-type</td>
<td>Original SARS-CoV-2 strains</td>
<td>Generally considered to be early SARS-CoV-2 strains spreading from Wuhan, China to other locations, before the emergence of newer variants of interest or concern (e.g., Alpha, Delta). See also “non-variant.”</td>
</tr>
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</table>
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REQUIRED INFORMATION FOR EFFECTIVE INFECTIOUS DISEASE OUTBREAK RESPONSE

SARS-CoV-2 (COVID-19)

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https://royalsocietypublishing.org/doi/abs/10.1098/rspa.2020.0584 %X By modelling the evaporation and settling of droplets emitted during respiratory releases and using previous measurements of droplet size distributions and SARS-CoV-2 viral load, estimates of the evolution of the liquid mass and the number of viral copies suspended were performed as a function of time from the release. The settling times of a droplet cloud and its suspended viral dose are significantly affected by the droplet composition. The aerosol (defined as droplets smaller than 5 μm) resulting from 30 s of continued speech has O(1 h) settling time and a viable viral dose an order-of-magnitude higher than in a short cough. The time-of-flight to reach 2 m is only a few seconds resulting in a viral dose above the minimum required for infection, implying that physical distancing in the absence of ventilation is not sufficient to provide safety for long exposure times. The suspended aerosol emitted by continuous speaking for 1 h in a poorly ventilated room gives 0.1–11% infection risk for initial viral loads of 10^8–10^{10} copies ml^{-1}, respectively, decreasing to 0.03–3% for 10 air changes per hour by ventilation. The present results provide quantitative estimates useful for the development of physical distancing and ventilation controls.


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severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused fast-spreading outbreaks
globally. Intrinsically, this variant has greater transmissibility than its predecessors, but this capacity has
been amplified in some circumstances to tragic effect by a combination of human behavior and local
immunity. What are the extrinsic factors that help or hinder the rapid dissemination of variants?
Kraemer et al. explored the invasion dynamics of B.1.1.7. in fine detail, from its location of origin in Kent,
UK, to its heterogenous spread around the country. A combination of mobile phone and virus data
including more than 17,000 genomes shows how distinct phases of dispersal were related to intensity of
mobility and the timing of lockdowns. As the local outbreaks grew, importation from the London source
area become less important. Had B.1.1.7. emerged at a slightly different time of year, its impact might
have been different. —CA Disentangling the factors that contribute to the rapid spread of virus variants
is essential for understanding their epidemiological consequences. Understanding the causes and
consequences of the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants
of concern is crucial to pandemic control yet difficult to achieve because they arise in the
context of variable human behavior and immunity. We investigated the spatiotemporal invasion dynamics
of
lineage B.1.1.7 by jointly analyzing UK human mobility, virus genomes, and community-based polymerase chain reaction data. We identified a multistage spatial invasion process in which early B.1.1.7 growth rates were associated with mobility and asymmetric lineage export from a dominant source location, enhancing the effects of B.1.1.7’s increased intrinsic transmissibility. We further explored how B.1.1.7 spread was shaped by nonpharmaceutical interventions and spatial variation in previous attack rates. Our findings show that careful accounting of the behavioral and epidemiological context within which variants of concern emerge is necessary to interpret correctly their observed relative growth rates.


Epidemiological data about SARS-CoV-2 indicate that the virus is not transmitted uniformly in the population. The transmission tends to be more effective in select settings that involve exposure to relatively high viral dose, such as in crowded indoor settings, assisted living facilities, prisons or food processing plants. To explore the effect on infection dynamics, we describe a new mathematical model where transmission can occur (i) in the community at large, characterized by low-dose exposure and mostly mild disease, and (ii) in so-called transmission hot zones, characterized by high-dose exposure that can be associated with more severe disease. The model yields different types of epidemiological dynamics, depending on the relative importance of hot zone and community transmission. Interesting dynamics occur if the rate of virus release/deposition from severely infected people is larger than that of mildly infected individuals. Under this assumption, we find that successful infection spread can hinge upon high-dose hot zone transmission, yet the majority of infections are predicted to occur in the community at large with mild disease. In this regime, residual hot zone transmission can account for continued virus spread during community lockdowns, and the suppression of hot zones after community interventions are relaxed can cause a prolonged lack of infection resurgence following the reopening of society. This gives rise to the notion that targeted interventions specifically reducing virus transmission in the hot zones have the potential to suppress overall infection spread, including in the community at large. Epidemiological trends in the USA and Europe are interpreted in light of this model.


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%X Prolonged school closure has been adopted worldwide to control COVID-19. Indeed, UN Educational, Scientific and Cultural Organization figures show that two-thirds of an academic year was lost on average worldwide due to COVID-19 school closures. Such pre-emptive implementation was predicated on the premise that school children are a core group for COVID-19 transmission. Using surveillance data from the Chinese cities of Shenzhen and Anqing together, we inferred that compared with the elderly aged 60 and over, children aged 18 and under and adults aged 19–59 were 75% and 32% less susceptible to infection, respectively. Using transmission models parametrized with synthetic contact matrices for 177 jurisdictions around the world, we showed that the lower susceptibility of school children substantially limited the effectiveness of school closure in reducing COVID-19 transmissibility. Our results, together with recent findings that clinical severity of COVID-19 in children is lower, suggest that school closure may not be ideal as a sustained, primary intervention for controlling COVID-19. This article is part of the theme issue ‘Data science approach to infectious disease surveillance’.


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independent on the investigation of identified clinical cases. Next-generation sequencing analysis of amplicons synthesized from sewage concentrates revealed the presence of B.1.1.7 mutations in viral sequences, first identified in a sample collected in London on 10 November 2020 and shown to rapidly increase in frequency to $\geq 95\%$ in January 2021, in agreement with clinical data over the same period. We show that ES can provide an early warning of VOCs becoming prevalent in the population and that, as well as B.1.1.7, our method can detect VOCs B.1.351 and P.1, first identified in South Africa and Brazil, respectively, and other viruses carrying critical spike mutation E484K, known to have an effect on virus antigenicity. Although we did not detect such mutation in viral RNAs from sewage, we did detect mutations at amino acids 478, 490, and 494, located close to amino acid 484 in the spike protein structure and known to also have an effect on antigenicity. IMPORTANCE The recent appearance and growth of new SARS-CoV-2 variants represent a major challenge for the control of the COVID-19 pandemic. These variants of concern contain mutations affecting antigenicity, which raises concerns on their possible impact on human immune response to the virus and vaccine efficacy against them. Here, we show how environmental surveillance for SARS-CoV-2 can be used to help us understand virus transmission patterns and provide an early warning of variants becoming prevalent in the population. We describe the detection and quantification of variant B.1.1.7, first identified in southeast England in sewage samples from London (UK) before widespread transmission of this variant was obvious from clinical cases. Variant B.1.1.7 was first detected in a sample from early November 2020, with the frequency of B.1.1.7 mutations detected in sewage rapidly increasing to $\geq 95\%$ in January 2021, in agreement with increasing SARS-CoV-2 infections associated with B.1.1.7 viruses.


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