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 Ebolavirus 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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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. 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.

**Transmissibility** – How does it spread from one host to another? How easily is it spread? ........................................... 4

SARS-CoV-2 is passed easily between humans, primarily through close contact and aerosol transmission. At least six variants (Delta, Gamma, Alpha, Beta, Kappa, Eta) have higher transmission rates than wild-type SARS-CoV-2. COVID-19 vaccines reduce transmission rates by approximately 54% (range of 38-66%). The amount of infectious virus emitted from an infective 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. Infection risk is particularly high indoors, while outdoor transmission is rare. Household transmission is rapid, and household contacts spread infection more than casual community contacts. Superspreading events (SSEs) appear common in SARS-CoV-2 transmission and may be crucial for controlling spread.

**Incubation Period** – How long after infection do symptoms appear? Are people infectious during this time? .......... 6

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. The average time between symptom onset in successive cases (i.e., the serial interval) is approximately 5 days. Individuals can shed virus for several weeks, though it is not necessarily infectious. We need to know the incubation duration and length of infectivity in different patient populations.

**Acute Clinical Presentation** – What are the initial signs and symptoms of an infected person? ................................. 7

Most symptomatic cases are mild, but severe disease can be found in any age group. Older individuals and those with underlying conditions are at higher risk of serious illness and death, as are men. Fever is most often the first symptom. The B.1.617.2 (Delta) and B.1.1.7 (Alpha) variants are associated with increased hospitalization and mortality. Approximately 33% of individuals will remain asymptomatic after SARS-CoV-2 infection. COVID-19 is more severe than seasonal influenza, evidenced by higher ICU admission and mortality rates. In the US, 29-34% of hospitalized patients required ICU admission, and 12.6-13.6% died from COVID-19. Adults >60 years old and those with comorbidities are at elevated risk of hospitalization and death. Minority populations are disproportionately affected by COVID-19, independent of underlying conditions. Children are susceptible to COVID-19, though generally show milder symptoms or no symptoms. We need to know the impact of new SARS-CoV-2 variants on presentation and disease severity.

**Chronic Clinical Presentation** – What are the long-term symptoms of COVID-19 infection? ........................................... 8

COVID-19 symptoms persist for weeks to months after initial onset in up to 73% of those infected. Researchers are identifying methods to diagnose patients with chronic COVID-19 (PASC) early. We need to know the rate of PASC and chronic symptoms in different patient populations.

**Protective Immunity** – How long does the immune response provide protection from reinfection? ......................... 9

Recovered individuals appear protected against reinfection for at least several months. Reinfecion is rare, though novel variants may increase reinfection frequency. Immune responses persist in most patients for >6 months. Convalescent patients are expected to have long-lasting protection against SARS-CoV-2, especially after vaccination. The impact of emerging SARS-CoV-2 variants on protective immunity and reinfection risk is unclear. Reinfecion with SARS-CoV-2 is possible but appears rare, though the true frequency is unknown. In patients recovered from natural infection, one dose of an mRNA vaccine increases protective immunity, but the benefits of a second dose are unclear. In uninfected individuals, two doses of mRNA vaccines show clear benefits.
We need to know the frequency and severity of reinfection, as well as the protective effects of immune components.

**Clinical Diagnosis – Are there tools to diagnose infected individuals? When during infection are they effective?**

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. Validated serological (antibody) assays are being used to help determine who has been exposed to SARS-CoV-2.

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

**Medical Treatments – Are there effective treatments?**

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.

We need clear, randomized trials for treatment efficacy in patients with both severe and mild/moderate illness.

**Vaccines – Are there effective 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).

“Breakthrough” infections are rare and associated with milder illness, but more common in those with comorbidities.

We need to understand the long-term impact of SARS-CoV-2 variants on vaccine efficacy and the need for boosters.

**Non-pharmaceutical Interventions (NPIs) – Are public health control measures effective at reducing spread?**

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.

Research is needed to plan the path to SARS-CoV-2 elimination via pharmaceutical and non-pharmaceutical interventions.

Lifting NPIs before widespread vaccine uptake is predicted to increase COVID-19 cases and deaths.

We need to understand the magnitude of measures necessary to limit spread of new SARS-CoV-2 variants.

**Environmental Stability – How long does the agent live in the environment?**

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.

Viable SARS-CoV-2 and/or RNA can be recovered from contaminated surfaces; however, survivability varies.

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

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

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.

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

**Decontamination – What are effective methods to kill the agent in the environment?**

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.

We need additional SARS-CoV-2 decontamination studies, particularly with regard to indoor aerosol transmission.

**PPE – What PPE is effective, and who should be using it?**

Face masks appear effective at reducing infections from SARS-CoV-2. Healthcare workers are at high risk of acquiring COVID-19, even with recommended PPE.

We need to continue assessing PPE effectiveness with specific regard to SARS-CoV-2 instead of surrogates.

**Forensics – Natural vs intentional use? Tests to be used for attribution.**

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

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

**Genomics – How does the disease agent compare to previous strains?**

Current evidence suggests that SARS-CoV-2 accumulates mutations at a similar rate as other coronaviruses.

We need to identify differences in transmissibility or severity caused by different SARS-CoV-2 mutations and variants.

**Forecasting – What forecasting models and methods exist?**

Several platforms provide digital dashboards summarizing the current status of the pandemic in US states and counties.

The US 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.

Additional forecasting efforts are designed to assess the effects of interventions such as social distancing and vaccination.

We need to know how different vaccine uptake rates will affect the epidemic in the US and neighboring countries.
## 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.

- The UK has initiated a human challenge study to determine the intranasal infectious dose of “wild-type” SARS-CoV-2, where wild-type is defined hereafter as the original or comparator SARS-CoV-2 strain in a particular study (e.g., Wuhan-1).
- There is no preferential animal model for SARS-CoV-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.

### Non-human primates

- In cynomolgus macaques, the median dose required to induce SARS-CoV-2 seropositivity (wild-type virus) was 52 TCID$_{50}$ (approximately 36.4 PFU) via the inhalation route. The median dose needed to induce fever was 256 TCID$_{50}$ (approximately 179.2 PFU) via the inhalation route. This also suggests that symptom severity may be dose dependent.
- Approximately 700,000 plaque-forming units (PFU) of the novel coronavirus SARS-CoV-2 infected cynomolgus macaques via combination intranasal and intratracheal exposure (10$^6$ TCID$_{50}$ total dose).
- Rhesus and cynomolgus macaques showed mild to moderate clinical infections at doses of 4.75x10$^5$ PFU (delivered through several routes), while marmosets developed mild infections when exposed to 1x10$^5$ PFU intranasally.
- Rhesus macaques infected with 2,600,000 TCID$_{50}$ of SARS-CoV-2 by the intranasal, intratracheal, oral and ocular routes combined recapitulate moderate human disease. A small study infected Rhesus macaques via ocular inoculation (1x10$^5$ TCID$_{50}$), resulting in mild infection; however, gastric inoculation did not result in infection (same dose), suggesting a limited role of gastric transmission. Interpretation is limited due to the small scale.
- African green monkeys replicate aspects of human disease, including severe pathological symptoms (exposed to 500,000 PFU via intranasal and intratracheal routes), mild clinical symptoms (aerosol exposures between 5,000 - 16,000 PFU), and acute respiratory distress syndrome (ARDS), with small particle aerosol exposure doses as low as 2,000 PFU.
- Aerosol exposure of three primate species (African green monkeys, cynomolgus macaques, and rhesus macaques) via a Collison nebulizer resulted in mild clinical disease in all animals with doses between 28,700 and 48,600 PFU.

### Rodents and other animal models

- The SARS-CoV-2 median infectious dose in Golden Syrian hamsters via the intranasal route was experimentally estimated at 5 TCID$_{50}$ (~3.5 PFU). Low-dose intranasal inoculation of ferrets (2,000 PFU) and Golden Syrian hamsters (1,800 PFU) with SARS-CoV-2 resulted in mild clinical symptoms, the production of infectious virus, and seroconversion.
- 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.
- Golden Syrian hamsters exposed to 80,000 TCID$_{50}$ (~56,000 PFU) via the intranasal route developed clinical symptoms reminiscent of mild human infections. Golden Syrian hamsters infected with 100,000 PFU intranasally exhibited mild clinical symptoms and developed neutralizing antibodies, and were also capable of infecting individuals in separate cages.
- Transgenic (hACE2) mice became infected after timed aerosol exposure (36 TCID$_{50}$/minute) to between 900 and 1080 TCID$_{50}$ (~630-756 PFU). All mice (4/4) exposed for 25-30 minutes became infected, while no mice (0/8) became infected after exposure for 0-20 minutes (up to 720 TCID$_{50}$, ~504 PFU). This paper has methodological caveats (e.g., particle size).
- Ferrets infected with 316,000 TCID$_{50}$ or 600,000 TCID$_{50}$ of SARS-CoV-2 by the intranasal route show similar symptoms to human disease. In a separate 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$^4$ PFU became infected.
- 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.

### 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"); 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.
- Modeling aerosol exposures from 5 case studies suggests the inhalation ID$_{50}$ for SARS-CoV-2 is approximately 361-2,000 viral particles, which is approximately 250-1,400 PFU.

### Related Coronaviruses

- Humans exposed intranasally to ~70 PFU of seasonal coronavirus 229E developed infections with a plausible intranasal ID$_{50}$ of 10 TCID$_{50}$ (~7 PFU). 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?
- Does the SARS-CoV-2 infectious dose in humans differ by viral variant?
SARS-CoV-2 is passed easily between humans, primarily through close contact and aerosol transmission.\(^{29-32}\)

- As of 12/7/2021, COVID-19 has caused at least 266,915,820 infections and 5,281,883 deaths globally.\(^{33}\) In the US, 49,002,475 cases and 785,655 deaths\(^{33}\) have been confirmed. Cases\(^{34}\) and fatalities are underestimated.\(^{35-38}\)
- SARS-CoV-2 can spread via aerosol or “airborne” transmission\(^{39}\) beyond 6 ft in certain situations\(^{40}\) (i.e. enclosed spaces with inadequate ventilation).\(^{41}\) The risk of infection from fomites\(^{42}\) is believed to be low.\(^{43}\) Vertical transmission is rare.\(^{44}\) Hospital transmission follows community incidence\(^{45}\) and may involve superspreading events.\(^{46}\)

**At least six variants (Delta, Gamma, Alpha, Beta, Kappa, Eta) have higher transmission rates than wild-type SARS-CoV-2.**\(^{47}\)

- The Delta (B.1.617.2) variant is highly transmissible, with an estimated \(R_0\) of 5-9.\(^{47-48}\) This is far higher than wild-type SARS-CoV-2 (\(R_0 = 2.2\) to 3.1).\(^{49-53}\) As of 12/7/2021, the Delta variant (and subvariantsAY.1, AY.2, and AY.3) account for more than 99.5% of newly sequenced cases in the US.\(^{54}\) Low vaccination rates facilitate COVID-19 transmission.\(^{55}\)
- The Delta variant may lead to higher viral load compared to wild-type virus or other variants.\(^{56}\) The viral load in vaccinated cases with Delta variant was similar to infected, unvaccinated cases (via RNA copies\(^{57-58}\) and infectious virus\(^{59}\)). However, preliminary studies suggest vaccinated cases with breakthrough infections have less infectious virus than unvaccinated individuals, despite similar viral RNA levels, during a period of Delta variant prevalence.\(^{60}\)
- As of 12/7/2021, the effective reproduction number (\(R_e\)) was 1.47 for South Africa nationally, where the Delta variant is dominant, but 1.93 in the Gauteng province, which is dominated by the novel Omicron variant, suggesting a transmission advantage.\(^{61}\)
- Early analyses show that \(R_0\) is above 2 in most provinces in South Africa, coincident with an increase in the prevalence of the Omicron variant.\(^{62-63}\)

**COVID-19 vaccines reduce transmission rates by approximately 54% (range of 38-66%).**\(^{64}\)

- Vaccination provides protection by reducing viral load\(^{65}\) and transmission.\(^{66-67}\) However, vaccinated index cases transmitted the Delta variant to 25% of household members in one study (38% for unvaccinated index cases).\(^{68}\)
- The amount of infectious virus emitted from an infectious individual is unclear but appears highly variable.\(^{69}\)
  - Breath may emit 10^5-10^7 genome copies per hour.\(^{69}\) Individual emission rates vary substantially\(^{70-71}\) and with activity.\(^{72}\)
  - Higher viral loads in COVID-19 patients result in higher secondary attack rates,\(^{73}\) with a rate of 12% with viral loads below 10^6 genome copies/mL (nasopharyngeal swab), and 24% with viral loads more than 10^10 viral genome copies/mL.\(^{74}\)
- Asymptomatic or pre-symptomatic individuals can transmit SARS-CoV-2\(^{75}\) and play a large role in new case growth.\(^{76}\)
  - Individuals are infectious 1-3 days prior to symptom onset.\(^{77-78}\) Pre-\(^{79-84}\) or asymptomatic\(^{85-87}\) patients can transmit SARS-CoV-2.\(^{88}\) Most transmission occurs prior to\(^{89}\) and within 5 days of symptom onset,\(^{90-91}\) as seen in case studies\(^{92}\) and models.\(^{93}\)
  - Asymptomatic cases transmit less often than symptomatic ones,\(^{94-96}\) causing 66%-83%/97 fewer cases, due to lower viral loads.\(^{98}\) The likelihood of symptoms in secondary cases increases with severity of symptoms in the primary or index case.\(^{99}\)
- **Infection risk is particularly high indoors,**\(^{100}\) while outdoor transmission is rare.\(^{100}\)
  - SARS-CoV-2 may be spread by conversation and exhalation\(^{101-104}\) in indoor areas such as restaurants\(^{105-106}\) and offices.\(^{107}\) Clusters are often associated with large indoor gatherings,\(^{108-109}\) including bars,\(^{110}\) restaurants,\(^{111}\) and gyms.\(^{112-113}\)
- **Household transmission is rapid,**\(^{114}\) and household contacts spread infection more than casual community contacts.\(^{115}\)
  - The secondary attack rate of SARS-CoV-2 is 24% on average,\(^{116}\) but has been increasing over time.\(^{117}\)
  - Within households, children were infected as often as adults when community transmission was high.\(^{118}\)
  - The household secondary attack rate for the Alpha variant was 77.8% in one study, compared to 42.5% for non-Alpha and non-Delta variant viruses.\(^{119}\) The Delta variant has household attack rates 70% higher than the Alpha variant.\(^{120}\)
  - One observational study found asymptomatic individuals transmitted COVID-19 to household members half as often as symptomatic individuals.\(^{121}\)
- **Superspreading events (SSEs) appear common in SARS-CoV-2 transmission and may be crucial for controlling spread.**
  - Most new infections come from a few infectious individuals (overdispersion parameter \(k = 0.2-0.5).\(^{122-127}\)
  - In France, modeling suggests that reducing transmission in 20-29 year-olds can reduce transmission in other age groups.\(^{128}\)
- **Rates of transmission on public transit are plausible but appear low,**\(^{129}\) particularly on airplanes.\(^{130}\)
  - Transmission on airplanes is plausible\(^{131-135}\) despite screenings.\(^{136-137}\) Leaving middle seats open may reduce exposure.\(^{138}\) As of October 2020, only 5 of 20 major airlines maintained seat distancing, and as of April 2021, no airline enforces this distancing. Outbreaks have also been linked to trains\(^{139}\) and buses.\(^{140}\)
- **Infection in children is underestimated,**\(^{141-144}\) and children of any age can acquire and transmit infection.\(^{145}\) There is some evidence that younger children (<10-15) are less susceptible\(^{146-147}\) and less infectious\(^{148}\) than older children and adults.\(^{149-150}\)
  - Children seem to transmit SARS-CoV-2 less often than adults\(^{148}\) though few studies have addressed this directly.\(^{149}\) Children appear to have lower concentrations of viral RNA\(^{89}\) and infectious virus than adults.\(^{150}\)
  - Transmission in schools is generally low,\(^{151-155}\) follows community incidence\(^{156-158}\) and can be mitigated.\(^{159}\)

**What do we need to know?**

- What is the impact of the Omicron (B.1.1.529) variant on human-human transmissibility, particularly vis-à-vis Delta? Will it eventually outcompete Delta and become the next dominant strain?
Animals can transmit SARS-CoV-2 to humans, but the potential role of long-term reservoir species is unknown. Current evidence suggests a direct jump from bats to humans is plausible. We need to know the best animal model for replicating human infection by various exposure routes. SARS-CoV-2 is closely related to other coronaviruses circulating in bats in Southeast Asia. Previous coronaviruses have passed through unknown. SARS-CoV-2 not yet recorded in other human or animal sequences.

Humans and mink are able to transmit infectious virus back and forth, potentially facilitating development of new variants. Rabbits are susceptible to SARS-CoV-2 via the intranasal route (dose = 10^4-10^6 TCID50) and develop asymptomatic infections, though several non-human primates are also susceptible to infection with SARS-CoV-2 including cynomolgus macaques, African green monkeys, Rhesus macaques, and pigtail macaques. Raccoon dogs (mammals related to foxes) are susceptible to COVID-19 (10^5 intranasal exposure dose) and were shown to transmit infectious virus back and forth, potentially facilitating development of new variants. Aerosol concentrations of SARS-CoV-2 RNA on mink farms can be high, leading to occupational exposure risks. Approximately 16% of mink on a farm in Poland tested positive for SARS-CoV-2 infection, and those mink harbored a unique genotype of SARS-CoV-2 not yet recorded in other human or animal sequences.

In Spain, feral populations of American mink have been found with SARS-CoV-2 RNA, suggesting a potential reservoir. Infected mink in the US have been linked to human infections. SARS-CoV-2 cases in mink on US farms show high mortality rates, and farms have implemented strict biosecurity measures. Mink presumed to have escaped from commercial farms in Utah have been found in the wild with detectable SARS-CoV-2 antibody levels, providing a plausible pathway to disease establishment in wild mink, though confirmation of SARS-CoV-2 in wild mink has not been established.

In Italy, approximately 3-6% of domestic dogs and cats showed detectable neutralizing antibodies to SARS-CoV-2, though no evidence exists of transmission from dogs or cats to humans. Wild cats (tigers and lions) can be infected with SARS-CoV-2, although their ability to spread to humans is unknown. Studies have confirmed that human keepers transmitted SARS-CoV-2 to tigers and lions at the Bronx Zoo. Captive gorillas have tested positive for SARS-CoV-2, and experience mild symptoms (cough, congestion). Farm animals (ducks, chickens, pigs, turkey, geese, and cattle) are generally not susceptible to SARS-CoV-2. Sheep can be infected with SARS-CoV-2 but have limited transmission potential. Dogs exposed to SARS-CoV-2 produced anti-SARS-CoV-2 antibodies but exhibited no clinical symptoms. Hyenas can be infected with SARS-CoV-2 but it is unclear if they can transmit the virus to other animals or humans.

In Italy, approximately 3-6% of domestic dogs and cats showed detectable neutralizing antibodies to SARS-CoV-2, though no evidence exists of transmission from dogs or cats to humans. What do we need to know? We need to know the best animal model for replicating human infection by various exposure routes. 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?
### Incubation Period – How long after infection do symptoms appear? Are people infectious during this time?

**What do we know?**

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<tr>
<th>Description</th>
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<tr>
<td>On average, symptoms develop 5 days after exposure with a range of 2-14 days.</td>
<td>Incubating individuals can transmit disease for several days before symptom onset. Some individuals never develop symptoms but can still transmit disease.</td>
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<td>By general consensus, the incubation period of COVID-19 is between 5(^2)(^{209}) and 6(^2)(^{210}) 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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<td>Individuals can test positive for COVID-19 even if they lack clinical symptoms.</td>
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<td>Individuals can be infectious while asymptomatic and 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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<td>Asymptomatic individuals are estimated to be infectious for between 5.7(^2)(^{227}) and 9.5 days.</td>
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**The average time between symptom onset in successive cases (i.e., the serial interval) is approximately 5 days.**

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<td>On average, there are approximately 4(^2)(^{24}) to 7.5(^2)(^{20}) days between symptom onset in successive cases of a single transmission chain (i.e., the serial interval). Recent estimates of the SARS-CoV-2 serial interval ranged from 2.7 to 3.2 days, regardless of the dominance of the Alpha variant in the UK.</td>
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<td>The serial interval of COVID-19 has declined substantially over time as a result of increased case isolation, meaning individuals tend to transmit virus for less time.</td>
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<td>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>There is some evidence that the Delta variant spreads faster than prior virus lineages (e.g., time between successive cases of 2.9 vs 5.7 days, respectively).</td>
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**Individuals can shed virus for several weeks, though it is not necessarily infectious.**

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<td>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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<td>Asymptomatic and mildly ill patients who test positive for SARS-CoV-2 take less time to test negative than severely ill patients.</td>
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<td>Patients infected by asymptomatic or young (&lt;20 years old) individuals may take longer to develop symptoms than those infected by other groups of individuals.</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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<td>Patients being released from the hospital may still exhale detectable levels of SARS-CoV-2 RNA (~7,000 genome copies per hour), though the infectivity of these patients is unknown.</td>
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**What do we need to know?**

- What is the average incubation period during which individuals can transmit the disease?
- How soon can asymptomatic patients transmit infection after exposure?
- Does the incubation period correlate with disease severity or exposure dose?
- Do novel SARS-CoV-2 variants alter the incubation period of COVID-19? Do they affect the generation time or serial interval?
**Acute Clinical Presentation – What are the initial signs and symptoms of an infected person?**

What do we know?

Most symptomatic cases are mild, but severe disease can be found in any age group. Older individuals and those with underlying conditions are at higher risk of serious illness and death, as are men. Fever is most often the first symptom.

- Most symptomatic COVID-19 cases are mild (81%). Fever, cough, shortness of breath are generally the most common symptoms, followed by malaise, fatigue, and sputum/secretion. Chill, muscle pain, skeletal pain, 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.
- Headaches are common, may persist for weeks, and may be associated with shorter disease duration. 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.
- Adults experiencing post-acute COVID-19 multisystem inflammatory syndrome (MIS-A) may be underdiagnosed.
- Inherited genetic factors may contribute to COVID-19 disease severity in humans (e.g., prenylation of OAS1 gene is protective against severe COVID-19, but the frequency of this event is genetically biased).

The B.1.617.2 (Delta) and B.1.1.7 (Alpha) variants are associated with increased hospitalization and mortality.

- In the US, 29-34% of hospitalized patients required ICU admission, and 12.6-13.6% died from COVID-19.
- Approximately 33% of individuals will remain asymptomatic after SARS-CoV-2 infection. Modeling and seroprevalence studies, however, suggest the asymptomatic ratio is much higher (>80%).
- When asymptomatic individuals do transmit, those they infect are more likely to develop asymptomatic COVID-19.

COVID-19 is more severe than seasonal influenza, evidenced by higher ICU admission, hospitalization, and mortality rates.

In the US, 29-34% of hospitalized patients required ICU admission, and 12.6-13.6% died from COVID-19.

- Almost all (99.5%) US deaths from COVID-19 in May and June 2021 have occurred in unvaccinated individuals.
- Higher SARS-CoV-2 RNA loads at initial screening or upon admission are linked to a higher risk of death.
- High viral loads (RT-PCR cycle threshold value <28) are associated with symptom severity six months after illness onset.
- COVID-19 also causes pneumonia, cardiac injury, kidney damage, pancreatitis, arrhythmia, sepsis, stroke, respiratory complications, and shock.
- 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.
- Low oxygen saturation and shallow breathing upon hospital admission are associated with elevated mortality risk.
- Adults >60 years old and those with comorbidities are at elevated risk of hospitalization and death.
- Cardiovascular disease, obesity, hypertension, diabetes, cancer, down syndrome, and respiratory conditions increase the CFR.
- Kidney disease, dialysis, and loss 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%.
- Minority populations are disproportionately affected by COVID-19, and appears to be linked to underlying conditions.
- Black, Asian, and Minority Ethnic populations acquire SARS-CoV-2 infection at higher rates, are hospitalized and die disproportionately.
- Hispanic and Black COVID-19 patients tend to die at younger ages than white patients.
- Social vulnerability is associated with higher COVID-19 risk.
- 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.

**Children are susceptible to COVID-19, 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.
- 21% to 28% of children (<19 years old) may be asymptomatic. Most symptomatic children show mild or moderate symptoms. Severe disease in children 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.
- A small (n=181) cohort study found children (5-13 years old) developed asymptomatic COVID-19 more often than adults (46% vs. 13%).
- A larger (n=1,236) observational cohort study found asymptomatic illness declined with increasing age (52% for those 0-4 years old; 50% for 5-11 year-olds; 45% for 12-17-year-olds; 12% for those 18 and older).

**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\(^{157}\) to months\(^{158}\) after initial onset\(^{159}\) in up to 73% of those infected.\(^{360}\)

- The US NIH has defined the effects of “long-haul” COVID-19 as Post-Acute Sequelae of SARS-CoV-2 infection (PASC).\(^{361}\)
- Estimates of the prevalence of PASC range from 5-10% of COVID-19 patients,\(^{352-354}\) with obesity,\(^{364}\) age, female sex,\(^{365}\) and number of initial symptoms increasing risk.\(^{366-367}\)
- Hospital readmission rates are 9-29% of COVID-19 patients.\(^{368-370}\)
- The importance of initial symptom severity for subsequent development of PASC is unclear, with some studies showing high risk in mildly ill patients\(^ {373}\) while others show higher risk in severely ill patients.\(^ {372}\)
- Long-term symptoms such as fatigue,\(^ {373}\) smell/taste disorders,\(^ {374-375}\) and neurological impairment\(^ {376}\) may affect the ability to return to work.\(^ {376}\)
- Approximately 8% of mildly ill individuals had disrupted work schedules 8 months after initial illness.\(^ {377}\)
- 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.\(^ {378}\)
- 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.\(^ {379}\)
- Over 203 symptoms were reported by long-haul COVID (PASC) patients in a large (n=3,762) survey.\(^ {380}\)
- 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.\(^ {381}\)
- 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,\(^ {382-383}\) CNS and demyelination issues,\(^ {384}\) and sex specific reproductive complications.\(^ {385-387}\)
- T cell and antibody responses did not differ between individuals with acute or chronic COVID-19 nine months post-infection,\(^ {388}\) 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 1 year after initial diagnosis were positive, with no fatalities and 2 hospital readmissions (thought to be unrelated to MIS-C).\(^ {389}\)
- Women, individuals with comorbidities, and those older than 40 were more likely to report COVID-19 symptoms lasting longer than two months.\(^ {390}\)
- Vaccination reduces the odds of individuals reporting COVID-19 symptoms for longer than 28 days.\(^ {381}\)

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.\(^ {391}\)
- 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.\(^ {392}\)
- 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.\(^ {392}\)

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,\(^ {393}\) and clinical implication of chronic COVID syndrome (PASC).\(^ {394-395}\)
- 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?
Recovered individuals appear protected against reinfection for at least several months. Reinfection is rare, though novel variants may increase reinfection frequency. Immune responses persist in most patients for ~6 months.

- Infection with SARS-CoV-2 provides robust protection against reinfection for at least 3–6 months. In a study from Italy (n=6,000), prior COVID-19 infection reduced the likelihood of subsequent infection by 94.6%.

- Protective immunity from vaccines may take longer to develop in patients undergoing active cancer treatment.

- Rhesus macaques exposed to wild-type SARS-CoV-2 (WA1/2020 strain) were protected against secondary challenge by the same strain 35 days later, but protection (quantified by viral loads after secondary challenge) was reduced when faced with the B.1.351 (Beta) or B.1.1.7 (Alpha) variants. These results suggest that natural SARS-CoV-2 infection may provide incomplete protection from reinfection with different SARS-CoV-2 variants.

Convalescent patients are expected to have long-lasting protection against SARS-CoV-2, especially after vaccination. Convalescent plasma from those infected with Gamma (P.1) or Beta (B.1.351) variants showed reduced neutralization of the Delta (B.1.617.2) variant, suggesting elevated potential for reinfection. Additionally, serum from vaccinated individuals (AstraZeneca or Pfizer/BioNTech vaccines) had lower neutralization of the Delta variant compared to wild-type virus.

- 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.

- Convalescent plasma from previously infected individuals (e.g., Moderna, Pfizer/BioNTech) results in a large increase in the body’s ability to neutralize wild-type and variant SARS-CoV-2.

- Infection with SARS-CoV-2 provides robust protection against reinfection for at least 3-6 months. In a study from Italy (n=6,000), prior COVID-19 infection reduced the likelihood of subsequent infection by 94.6%.

- Protective immunity from vaccines may take longer to develop in patients undergoing active cancer treatment.

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

- Convalescent plasma from those infected with Gamma (P.1) or Beta (B.1.351) variants showed reduced neutralization of the Delta (B.1.617.2) variant, suggesting elevated potential for reinfection. Additionally, serum from vaccinated individuals (AstraZeneca or Pfizer/BioNTech vaccines) had lower neutralization of the Delta variant compared to wild-type virus. Current vaccines (from AstraZeneca and Pfizer/BioNTech in this study) provide protection against novel Variants of Concern (VOCs), 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.

- After one dose of an mRNA vaccine, only 10% of individual serum showed any ability to neutralize the Delta variant, though this increased to 95% after the second dose.

- Vaccination provides greater protection from the Delta variant than prior infection with non-Delta SARS-CoV-2.

- 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).

- SARS-CoV-2 mutations can reduce responses to serum from vaccinated patients, though data from Moderna suggest a robust immune response to the Alpha (B.1.1.7) variant, and a lower response to the Beta (B.1.351) variant.

- T cells of individuals infected with non-variant SARS-CoV-2 were able to recognize and respond to three SARS-CoV-2 variants (B.1.1.7, B.1.351, and P.1), though the overall contribution to long-term immunity is not yet clear.

- The Lambda (C.37) variant may be more resistant to antibodies than wild-type virus.

- 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. Titers remain elevated among individuals that recovered from natural infections prior to vaccination.

Reinfection with SARS-CoV-2 is possible but appears rare, though the true frequency is unknown.

- Infection with COVID-19 appears to provide at least an 83% reduction in the risk of reinfection for at least 5 months, and reinfection was plausibly identified in 44 out of 6,600 COVID-19 patients.

- Possible reinfections were found in 4.8% of patients in one retrospective study, though some of these could represent lingering viral shedding. Only 2.4% of patients developed symptomatic COVID-19 >90 days after initial infection.

- Reinfection with the Delta variant was 46% more likely than with the Alpha variant, with the highest risk seen more than six months after initial infection. However, reinfections in this study were rare overall (1.2%).

In patients recovered from natural infection, one dose of an mRNA vaccine increases protective immunity, but the benefits of a second dose are unclear. In uninfected individuals, two doses of mRNA vaccines show clear benefits.

What do we need to know?

- How long does protective immunity last for children compared to adults?

- What is the probability of reinfection, particularly with SARS-CoV-2 variants?

- What is the impact of the Omicron variant on antibody response and T-cell immunity?
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 12/7/2021 the FDA has granted Emergency Use Authorization for 421 test and sample collection devices, including 293 molecular tests and sample collection devices, 90 antibody, and 38 antigen tests. There are 66 authorized molecular tests for home-collected samples with one prescription at-home molecular test, three prescription at-home antigen tests, nine OTC at-home antigen tests, and three OTC molecular tests.
- The US FDA released guidance on the impact of SARS-CoV-2 mutations on diagnostic tests. The FDA has also issued guidance on interpreting serological test result performance in light of background COVID-19 prevalence.
- The US FDA granted Emergency Use Authorization 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.
- 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. Low viral loads can lead to false-negative RT-PCR tests.
- 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. After 10 days, alternative testing methods (e.g., lower respiratory samples) may be necessary.
- A smartphone app (COVID Symptom Study) in the US and UK has been used by researchers to predict the need for respiratory support and provide data on PASC (“long-haul” COVID-19) symptoms.
- 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. 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.
- 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. However, homogenization of saliva samples prior to RNA extraction increases diagnostic accuracy, with results comparable to nasopharyngeal swabs.
- Researchers have demonstrated the utility of disposable, bio-functional strips for SARS-CoV-2 identification.
- In children, viral loads from saliva correlated better with clinical outcomes than viral loads from nasopharyngeal swabs.
- 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.
- New diagnostic methods involving CRISPR, exhaled breath condensate, and the microbiome are being developed.
- Symptom-based screening at airports was ineffective at detecting cases (9 identified out of 766,044 passengers screened) and intensive screening on a US military base during mandatory quarantine did not identify any COVID-19 cases.
- Infrared temperature readings may be misleading when used at the entrance of buildings with low outdoor temperatures.
- 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.
- Immunological indicators blood glucose levels, oxygen levels and bilirubin levels may help identify future severe cases, and tools for diagnosing severe infections and predicting mortality exist.
- A high-throughput assay for screening asymptomatic individuals has received US Emergency Use Authorization.
- Self- or caregiver-taken diagnostic swabs could be as accurate as those taken by healthcare workers in some instances.
- Wearable technology may be able to detect COVID-19 days before symptoms begin, and several attempts to create mobile applications for disease notification are underway.
- Aerosol detection devices are capable of identifying SARS-CoV-2 in the air (minimum of approximately 6,000 particles). 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.
- 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.

What do we need to know?

- What do we need to know?

What do we need to know?

- What do we need to know?

What do we need to know?

- What do we need to know?
### Medical Treatments – Are there effective treatments?

**What do we know?**

**COVID-19 treatment recommendations are provided by the WHO,493 NIH,494 Infectious Disease Society of America (IDSA),495 and British Medical Journal (BMJ).496 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.497,500 Methylprednisolone may increase the duration of viral shedding.504
- For hospitalized patients, it is recommended that convalescent plasma treatment only proceed in a clinical trial, as benefits are not uniformly reported.505-512 Convalescent plasma is more beneficial when given early in treatment with high SARS-CoV-2 antibody titers513 or when patients were treated with near-sourced plasma (donor within 150 miles of recipient).524 though the treatment fails to show benefits in large, randomized trials.525
- For any subset of patients, there is a strong recommendation against the use of hydroxychloroquine or hydroxychloroquine plus azithromycin516 and lopinavir/ritonavir517-522 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.501
- WHO guidance includes a strong recommendation for the use of tocilizumab or sarilumab in patients with severe or critical COVID-19.521 A large meta-analysis found that 28-day all-cause mortality was lower in patients receiving IL-6 inhibitor (e.g., tocilizumab, sarilumab) treatment, with significant clinical improvement in those patients also receiving corticosteroids.523 The effects were most beneficial in patients not on invasive mechanical ventilation.523
- The US FDA has granted EUA for sotrovimab, a monoclonal antibody treatment for those at risk of severe disease.524
- The US FDA has approved Remdesivir in hospitalized patients ≥12 years.494,525-526 There is a conditional recommendation in hospitalized, severe patients.527-529
- In the US, for hospitalized patients on supplemental oxygen but not mechanical ventilation, there is a conditional recommendation of 5-day course of Remdesivir vs. 10-day course.530
- In the US, in hospitalized patients not on supplemental oxygen, there is a conditional recommendation against the routine use of Remdesivir.530 though it may be considered for patients at high risk of severe disease.531
- The WHO and BMJ, however, recommend against Remdesivir use in patients of any severity.496,532 and recent results from the Discovery trial found no clinical benefit from Remdesivir plus standard of care when given to hospitalized patients for longer than 7 days, and those requiring supplemental oxygen (compared to standard of care alone).533
- For hospitalized patients, treatment with Remdesivir, baricitinib, or corticosteroids is recommended only in clinical trials.530 Baricitinib in addition to standard of care reduced all-cause mortality in patients.534
- Regeneron’s REGEN-COV treatment (casirivimab / imdevimab) is recommended for use in non-hospitalized patients,535 and has EUA for those at high risk of developing severe disease.536
- Therapeutic heparin in moderate COVID-19 patients with high D-dimer levels showed decreased mortality after 28 days.537

**Clinical trial updates**

- Interim results of Paxlovid (with co-administration of ritonavir) showed an 89% reduction in the risk of hospitalization and death in high-risk individuals when administered within 3 days of symptom onset, with similar results in those given the drug within 5 days of symptom onset.538
- Phase III clinical trial results of a single dose of REGEN-COV have been shown to reduce COVID-19 acquisition by 81.6%, with protection lasting up to 8 months after injection.539
- Two clinical trials of the long-lasting antibody AZD7442 determined a risk reduction of symptomatic disease of 83%, with no severe disease or deaths. As a treatment, there was an 88% reduced risk of severe illness and death when administered within 3 days of symptom onset.540
- Clinical trials to assess early fluvoxamine treatment to high-risk outpatients found reduced risk of hospitalization.541
- Clinical trials for molnupiravir have shown a 30% reduction in hospitalization and death,542-543 however, the potential side effects are not well understood, but may include potential for cancer and birth defects.
- Preliminary results suggest high doses of anticoagulants may reduce rates of mechanical ventilation for mild-moderate COVID-19.544 The WHO recommends a standard dosing level545 as high doses of anticoagulants were not more effective at improving outcomes for critically ill patients.546-547

**Common treatment medications for existing disease pre-COVID-19 diagnosis**

- Prior use of statins,548-549 RAAS inhibitors,550 anticoagulants,551 NSAIDs,552 and ACE inhibitors553 do not appear to elevate COVID-19 risk, and potential benefits of aspirin use require assessment in a clinical trial.554

**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 peptides555 and nasal sprays in humans556

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Updated 12/7/2021

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### Vaccines – Are there effective vaccines?

**What do we know?**

Three safe and effective vaccines are currently being administered in the US, with two under FDA EUA (Moderna 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.

- **As of 12/7/2021**, 199.3 million people in the US are considered fully vaccinated, and 47.0 million have received boosters.
- 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.
- After 2 doses, the Pfizer/BioNTech vaccine is highly effective against the B.1.617.2 (Delta) variant (88% reduction in symptomatic disease), though protection against the Delta variant is low after only a single dose.
- There is evidence of reduced vaccine efficacy against infection from both Israel and the United States compared to earlier in the pandemic. Across all approved US vaccines, efficacy against preventing infection declined from approximately 91% to approximately 66% before and after the predominance of the Delta variant.
- In Los Angeles, vaccinated individuals were 29 times less likely to be hospitalized after COVID-19 infection, despite the predominance of the Delta variant. Similarly, unvaccinated teenagers (12-17 years-old) were 10.1 times more likely to be hospitalized from COVID-19 than vaccinated teenagers.
- The duration of vaccine-derived immunity is unclear, but vaccine-derived antibodies persist for at least 6 months (Moderna vaccine), though neutralization ability is dependent on viral variant (with the Moderna vaccine showing the lowest neutralization ability against the Beta variant).
- Initial evidence from Israel suggests that booster shots for the Pfizer/BioNTech vaccine reduces the risk of infection and severe disease.
- Third doses (boosters) of Pfizer/BioNTech and Moderna vaccines are allowed by the US FDA for all adults ≥18 years old if they are 6 months after the completion of their full series.
- Booster efficacy for Moderna and Pfizer-BioNTech ranges from 89.8-95.2%.
- Initial evidence from a small (n=900) survey found that vaccines may reduce symptom severity in approximately half of those with PASC, though the effects were not consistent across symptom types (e.g., fatigue, muscle pain).
- mRNA vaccines have been associated with elevated (but low) risk of certain blood clots and myocarditis/pericarditis.
- Vaccination of family members provides a protective effect for those remaining unvaccinated, substantially reducing infection risk, with increasing fractions of vaccinated family members increasing the protective effect.
- 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.
- **Pfizer/BioNTech** – mRNA vaccine named BNT162b2 (Comirnaty). US FDA approval and WHO EUL.
  - This vaccine is given as 2 shots, 21 days apart. 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. The US FDA granted EUA for use in 12-15 year-olds, and initial data shows high protective efficacy in 5-11 year-olds.
  - As of October 29, 2021, 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 µg versus the 30 µg dose for people 12 years or older.
- **Moderna** – mRNA vaccine named mRNA-1273. US EUA, approved in Canada and European Union, WHO EUL.
  - The vaccine is given as 2 shots, 28 days apart. Trials with adolescents (12-17 years old) show protective efficacy.
  - The vaccine showed 94.1% efficacy, 14 days after the second dose, consistent across age, race, ethnicity, and sex. Trials with reduced doses show high neutralizing responses, potentially expanding vaccine availability.
- **Johnson and Johnson/Janssen** – adenovirus vaccine named Janssen COVID-19 vaccine. US EUA, approved in EU.
  - This vaccine is given as a single shot to adults 18 and older.
  - In clinical trials, the vaccine was 77-85% effective at preventing severe and critical COVID-19 14-28 days post infection, and 67% effective at preventing moderate to severe COVID-19. Initial evidence shows efficacy against the Delta variant. Associated with a rare clotting disorder and an elevated risk of Guillain-Barré syndrome.

**“Breakthrough” infections are rare and associated with milder illness, but more common in those with comorbidities.**

- Vaccination has provided robust protection from infection, evidenced by low rates of “breakthrough” infections. Individuals generally experience milder symptoms than unvaccinated individuals, and most hospitalizations have occurred in individuals older than 65 and those with underlying conditions.
- SARS-CoV-2 variants of concern result in significantly more breakthrough infections than non-variant SARS-CoV-2.
- Reductions in circulating neutralizing antibody concentrations were associated with breakthrough infections in vaccinated healthcare workers in Israel, though breakthrough infections can also occur when neutralizing antibody levels are high.

**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?
- What are the correlates between neutralizing antibody levels and vaccine-induced efficacy in humans?
- 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 US. Delaying control measures increases outbreak duration 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 US was associated with significantly higher mortality 61-100 days after relaxation of restrictions. However, this study was conducted using a largely unvaccinated population.
- US counties with mask mandates had lower case growth rates and higher likelihoods of controlling transmission than neighboring counties lacking mask mandates. Modeling shows that slight increases in mask adherence (e.g., from 75% to 90% of individuals) can dramatically reduce simulated infections.
- In the US, shelter-in-place orders (SIPOs) and restaurant and bar 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 US 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.
- Individuals in the US who were more active (e.g., store visits) and spent Thanksgiving of 2020 away from home were more likely to test positive for SARS-CoV-2 than those with lower activity or who remained at home.
- 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 inhibit 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 polices 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 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.

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?
Environmental Stability – How long does the agent live in the environment?

**What do we know?**

- 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.\(^6\)\(^7\) 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.\(^5\)\(^7\)
- 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 non-porous surfaces, with cooler, less humid environments facilitating survival (stainless steel, ABS plastic, and nitrile rubber; indoors only; simulated saliva matrix).\(^6\)\(^7\) Persistence is reduced with warmer temperatures (37°C), and enhanced at colder temperatures (4°C).\(^6\)\(^8\)
- 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.\(^6\)\(^9\) At 22°C, SARS-CoV-2 was shown to be detectable (via plaque assay) on paper currency for up to 24 hours, on clothing for up to 4 hours, and on skin for up to 96 hours.\(^6\)\(^7\)
- SARS-CoV-2 was found to be stable across pH 3-10 on several surfaces at 22°C.\(^6\)\(^8\) 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.\(^6\)\(^8\)
- SARS-CoV-2 can persist on plastic and metal surfaces for up to 3 days (21-23°C, 40% RH)\(^6\)\(^8\) and infectious virus can be recovered from a surgical mask after 7 days (22°C, 65% RH)\(^6\)\(^8\) and other PPE for at least 72 hours at 22°C.\(^6\)\(^2\)
- 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.\(^6\)\(^3\)
- 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.\(^6\)\(^4\) However, other human fluids – particularly blood – enhanced SARS-CoV-2 stability on surfaces across a variety of temperature and humidity treatments.\(^6\)\(^5\)

**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.\(^6\)\(^6\) This value is longer than other stability estimates,\(^6\)\(^8\)\(^6\)\(^8\)\(^6\) potentially due to a fluid matrix with more protein to simulate human respiratory fluid and a higher inoculation dose.\(^6\)\(^8\) 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.\(^6\)\(^8\)
- 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.\(^6\)\(^9\)
- Organic material (e.g., feces) can enhance the ability of SARS-CoV-2 to transfer between surfaces.\(^6\)\(^0\)

**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.\(^6\)\(^1\) Due to evaporation, hot, dry conditions increase the aerosol risk, though cold, humid conditions facilitate droplet spread.\(^6\)\(^2\)
- 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).\(^6\)\(^3\) In dark conditions, the half-life of aerosolized SARS-CoV-2 is approximately 86 minutes in simulated saliva.\(^6\)\(^3\) Humidity alone had no significant impact on aerosolized virus survival.\(^6\)\(^3\)
- 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),\(^6\)\(^1\) retaining infectivity for up to 16 hours in appropriate conditions (23°C, 53% RH, no sunlight).\(^6\)\(^4\)

**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,\(^6\)\(^5\) while use of phosphate buffered saline (PBS, 18-25°C) resulted in sample instability.\(^6\)\(^6\)
- There is currently no evidence that SARS-CoV-2 is transmitted to people through food or food packaging.\(^6\)\(^7\)\(^6\)\(^8\)
- SARS-CoV-2 can persist for at least two weeks at refrigerated temperatures (4°C).\(^6\)\(^7\)\(^6\)\(^9\) SARS-CoV-2 maintains infectivity for at least 21 days when inoculated on frozen foods and stored below -20°C.\(^7\)\(^0\) Infectious SARS-CoV-2 has been found on frozen food packaging, but has not been linked to actual infections.\(^7\)\(^1\) Several outbreaks have a hypothesized food origin.\(^7\)\(^2\)

**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.\(^7\)\(^0\) 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.\(^7\)\(^0\)

**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?\(^7\)\(^0\)-\(^7\)\(^6\)
- Are certain SARS-CoV-2 variants (e.g., Delta) more or less stable on surfaces or in aerosols?
We need additional SARS-CoV-2 decontamination studies, particularly regarding indoor aerosol transmission.

What do we know?

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.
- 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.
- Heat, soap, and ethanol were also able to decontaminate SARS-CoV-2 variants (B.1.1.7 and B.1.351) on various surfaces.
- While a 4-5 log (99.99-99.999%) reduction in 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 antiseptics 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, which do not emit ozone, are being trialed at 4 UK hospitals due to their efficacy in reducing concentrations of a surrogate virus (M2 phase).
- 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; Phi6, 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.
- Peracetic 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. Dry heat and UV decontamination can also be used under certain conditions.
- 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. Devices capable of decontaminating 80,000 masks per day have been granted Emergency Use Authorization from the FDA.
- Canadian hospitals have shown blanket heating cabinets can sterilize reusable and N95 masks with wet or dry heat using a temperature of 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 US FDA has issued guidance for bioburden reduction systems using dry heat to decontaminate certain respirators. Shape and structure of specific N95 models impact the efficacy of UVC decontamination methods.
- A thermal inactivation model for SARS-CoV-2 provides estimates of infectivity reduction based on time and temperature.

What do we need to know?

- Does contamination with human fluids/waste alter disinfectant efficacy profiles?
- We need to understand how different testing methods and standards affect decontamination efficacy estimates.
- Are specific decontamination methods needed for different SARS-CoV-2 variants (e.g., Delta)?
# PPE – What PPE is effective, and who should be using it?

## What do we know?

**Face masks appear effective at reducing infections from SARS-CoV-2. Healthcare workers are at high 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. Universal masking policies also reduced the rate of new healthcare worker infections.

- 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, EUFFP2 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 Emergency Use Authorization. On May 7, 2020, the FDA rescinded a number of KN95 models that no longer meet the FDA 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 SARS-CoV-2 infection 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.**

- Effective February 1, 2021, the CDC requires all passengers on public transit to wear facemasks. The CDC recommends masks without exhalation vents or valves, as these can allow particles to pass through unfiltered.

- The US 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.

- Face masks (surgical and cotton) reduced the amount of SARS-CoV-2 shed by approximately 48% in fine aerosols (<5μm) and 77% in coarse aerosols (>5μm), 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 health care 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?

**We need to continue assessing PPE effectiveness with specific regard to SARS-CoV-2 instead of surrogates.**

- 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.

- How do SARS-CoV-2 variants affect the need for (and efficacy of) PPE?

- Should decontamination methods be optimized for individual makes/models of PPE?
REQUIRED INFORMATION FOR EFFECTIVE INFECTIOUS DISEASE OUTBREAK RESPONSE
SARS-CoV-2 (COVID-19)
Updated 12/7/2021

<table>
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<tr>
<th>Forensics – Natural vs intentional use? Tests to be used for attribution.</th>
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<tr>
<td><strong>What do we know?</strong></td>
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<tr>
<td>Current evidence supports the natural emergence of SARS-CoV-2 via a bat and possible intermediate mammal species.</td>
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<tr>
<td>• The WHO and others have called for more research into SARS-CoV-2 origins.783</td>
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<tr>
<td>• 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.163 Current sampling of pangolin viruses does not implicate them as an intermediate to human SARS-CoV-2.163</td>
</tr>
<tr>
<td>• 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.784</td>
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<tr>
<td>• 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.785-786</td>
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<tr>
<td>• 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.787 The rest of the genome is more closely related to other bat coronaviruses.787</td>
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<tr>
<td>• 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.788</td>
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<tr>
<td>• 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.789 Additional work is needed to confirm the role of this mutation, as well as to identify other mutations that enabled a jump to humans.</td>
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<tr>
<td>• 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).790</td>
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<tr>
<td>• A novel bat coronavirus (RmYN02) has been identified in China with an insertion between the S1/S2 cleavage site of the Spike protein, demonstrating that such insertions can occur naturally.791</td>
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<td>• 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.792 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.792</td>
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<tr>
<td>• 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.793 Additional whole-genome sequencing in humans would help to confirm this finding.</td>
</tr>
<tr>
<td>• 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.”786 Both scenarios are consistent with the observed genetic changes found in all known SARS-CoV-2 isolates.</td>
</tr>
<tr>
<td>• Bats are not the only reservoir of SARS-like coronaviruses.794</td>
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<tr>
<td>• 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.786, 794-796 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.</td>
</tr>
<tr>
<td>• Additionally, “[…] SARS-CoV-2 is not derived from any previously used virus backbone,” reducing the likelihood of laboratory origination,786 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.”786</td>
</tr>
<tr>
<td>• 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.797</td>
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<tr>
<td>• A report claiming a laboratory origin of SARS-CoV-2798 has been heavily disputed by scientists at Johns Hopkins University, who have extensive education ties in China.799</td>
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<table>
<thead>
<tr>
<th><strong>What do we need to know?</strong></th>
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<tbody>
<tr>
<td>We need to know whether there was an intermediate host species between bats and humans.</td>
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<tr>
<td>• What tests for attribution exist for coronavirus emergence?</td>
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<tr>
<td>• What is the identity of the intermediate species if it exists?</td>
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<tr>
<td>• Are there closely related coronaviruses in bats or other animals with the novel PRRA cleavage site found in SARS-CoV-2?</td>
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REQUIRED INFORMATION FOR EFFECTIVE INFECTIOUS DISEASE OUTBREAK RESPONSE  SARS-CoV-2 (COVID-19)

Updated 12/7/2021

Genomics – How does the disease agent compare to previous strains?

What do we know?

Current evidence suggests that SARS-CoV-2 accumulates mutations at a similar rate as other coronaviruses.

- The estimated mutation rate for SARS-CoV-2 is 6x10^{-4} nucleotides per genome per year.800
- The US 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 US, the Delta is currently the only VOC.801
- Immunosuppressed patients are a possible source of viral variants due to prolonged virus replication within a single host.802
- The WHO has applied different names to major SARS-CoV-2 variants using Greek letters.521

- **B.1.1.7 (20V/S01Y.V1) (VOC202012/01) (Alpha)** - The B.1.1.7 variant (Alpha) is associated with a 50-75% higher transmission rate than wild-type virus,803-804 potentially due to higher patient viral loads,805-807 higher rates of symptomatic illness,808 and a longer infectious period.821 Contains several Spike protein mutations (H69-70 deletion, N501Y, N493K).809
- There are currently no concerns relating to the efficacy of the Pfizer/BioNTech810-811 or Moderna vaccines,812 and the AstraZeneca/Oxford vaccine appears to show efficacy against B.1.1.7 (though lower than efficacy against non-variant SARS-CoV-2).813
- Serum from patients with non-B.1.1.7 variant SARS-CoV-2 can neutralize B.1.1.7 virus.814
- The E484K mutation has appeared independently in several individuals with the B.1.1.7 variant in the UK815 and US.816

- **B.1.617.2 (Delta)** - Variant of concern817 initially identified in India in January 2021, containing several mutations of concern (E484Q and L452R).818 The variant has been documented in California and the UK.819 Initial research suggests that this variant is more transmissible820 and more virulent821 than non-variant SARS-CoV-2.
- Resists neutralization by certain monoclonal antibodies417,822 and is more resistant to vaccine-derived antibodies than non-variant SARS-CoV-2; serum from patients given mRNA vaccines was able to neutralize the B.1.617.1 (Kappa) lineage.823
- B.1.617.2 has 13 sub-lineages; 4 are being monitored in the US: AY.1, AY.2, AY.3, AY.3.1.824 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.825 This mutation affects class I antibody binding826-827 and reduces affinity to ACE2 but provides stability to ACE2 binding in the presence of the E484K mutation.828-829
- As of October 21, 2021, the UK has identified a Delta subvariant (B.1.617.2.4.2; AY.4.2) as a Variant Under Investigation due to the moderate increase of cases with a secondary attack rate of 12.4%.829

- **B.1.351 (20H/S01Y.V2) (Beta)** - First identified in South Africa in December 2020830 with notable mutations N501Y, E484K, and K417N.831 This variant is resistant to neutralization from convalescent plasma and vaccine recipient sera.881 Preliminary studies from Moderna,820 Johnson and Johnson,852 AstraZeneca,835 and Novavax834 suggest a lower vaccine response to this variant, though the Pfizer/BioNTech vaccine appears to generate neutralizing ability in laboratory835 and human trials.852
- Convalescent serum from patients with B.1.351 infection shows high neutralization ability against wild-type virus.836
- The B.1.351 variant is partially resistant to the monoclonal antibody casirivimab and is fully resistant to bamlanivimab.837

- **P.1 (20J/S01Y.V3) (Gamma)** - First identified in Brazil,838 contains various mutations including K417N, E484K, and N501Y.839
- The variant is estimated to be 1.7-2.4 times more transmissible than non-variant SARS-CoV-2.839
- Prior infection with non-variant SARS-CoV-2 is estimated to provide only 54-79% protection against infection with the P.1 variant,839 potentially explaining the resurgence of COVID-19 in Manaus, Brazil after a large initial epidemic.840-841
- Partially resistant to the monoclonal antibody casirivimab and is fully resistant to bamlanivimab.837
- Appears 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.842
- Preliminary analysis suggests this variant leads to increased mortality in younger individuals, specifically those aged 20-29.843
- The H655V mutation, which was seen in early human isolates, is associated with resistance to human antibodies.844 and has arisen in experimental animal models of SARS-CoV-2 infection.845-846 Experimental studies in mink found increased viral cell entry, transmission, and host susceptibility with this mutation.846

- **C.37 (Lambda)** - In vitro studies suggest two single mutations (T76I, L452Q) make the Lambda variant more infectious than wild-type virus, while a deletion mutation (RSYLPGD246-253N) increases antibody resistance.847

- **B.1.429 (Epsilon) ([CAL.20C [20C/S:452R]] [GH/452R.V1 [B.1.429+B.1.427]])** - L452R mutation located on the Spike protein was first reported in Denmark848 and has increased in prevalence in California.850 The B.1.429 lineage is more transmissible and leads to more severe disease than non-variant SARS-CoV-2,851 and is partially resistant to antibodies.852-853

- **B.1.621 (Mu)** - Includes B.1.621.1. Mutations of note in Spike: E484K, N501Y, D614G, P681H. Prevalence is increasing in Colombia and Ecuador; present in the US.84 Preliminary studies suggest that the Mu variant is highly resistant to convalescent patient sera and severe from those vaccinated with the Pfizer/BioNTech Vaccine.854-855

- **B.1.1.529 (Omicron)** – Detected on November 26, 2021, in South Africa, the SARS-CoV-2 Omicron variant includes 21 unique mutations in the Spike gene with 14 shared Spike mutations with other variants of concern.856 Many of these mutations are located in the RBD and NTD and may play a role in ACE2 binding and antibody recognition.856 More work is needed to determine what, if any, effects these changes may play in transmission dynamics.

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?857

CLEARED FOR PUBLIC RELEASE 18
Forecasting – What forecasting models and methods exist?

What do we know?

Several platforms provide digital dashboards summarizing the current status of the pandemic in US states and counties.

- The US CDC maintains a dashboard of state-level COVID-19 vaccination data for first and second doses.858
- Hospital IQ has a dashboard that forecasts hospital and ICU admissions for each county in the US.859
- 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.860
- 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.861
- 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.862

The US CDC provides ensemble forecasts of cases and deaths based on the average of many participating groups.863 Ensemble forecasts generally show better predictive accuracy than individual forecast models.864

- Columbia University Model: Spatially explicit SEIR model incorporating contact rate reductions due to social distancing. Estimates total cases and risk of healthcare overrun.865
- 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.866 Also provides global forecasts.867
- 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.868
- Google/Harvard University: Time-series machine learning model that makes assumptions about which non-pharmaceutical interventions will be in place in the future.869
- 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.870

Additional forecasting efforts are designed to assess the effects of interventions such as social distancing and vaccination.

- Massachusetts Institute of Technology: Mechanistic SEIR model that forecasts cases, hospitalizations, and deaths.871 Also includes estimates of intervention measures, allows users to project based on different intervention scenarios.872
- 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.872
- Shen et al. estimate US COVID-19 cases under different scenarios of vaccine efficacy, studying the continued need for non-pharmaceutical interventions such as face masks and physical distancing.873
- In a modeling study, vaccination strategies prioritizing adults >60 years old minimized mortality, while those prioritizing adults 20-49 years old minimized disease incidence.874
- Prioritizing vaccines for elderly individuals with high COVID-19 mortality maximizes life-years saved by vaccination,875 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.876
- CovidSim: SEIR model allow users to simulate effects of future intervention policies at state and national levels (US only).877
- Covasim: Agent-based model for testing effects of intervention measures, also available as Python library.878
- 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 US.879
- Vaccination is most effective at reducing new infections before local peaks in incidence.880
- Researchers use a rolling window analysis incorporating uncertainty in the generation time distribution to estimate time-varying transmission rates in US states (the effective reproduction number, R\text{e}_0 or R\text{e}_1).881
- Accounting for superspreading in forecast models can increase model accuracy and precision,882 while incorporating memory effects (e.g., the duration of individual infectiousness) can also increase forecast model fit to data.883
- Wastewater may be useful in forecasting local SARS-CoV-2 prevalence884 and early identification of variant spread.885
- US counties experiencing larger historical influenza outbreaks also saw higher COVID-19 transmission rates, suggesting common features at the county level that contribute to the spread of respiratory diseases, and accounting for these features increased the accuracy of 1-week-ahead COVID-19 forecasts.886

What do we need to know?

We need to know how different vaccine uptake rates will affect the epidemic in the US and neighboring countries.

- How will spillover and movement between countries affect local COVID-19 resurgence after initial vaccine distribution?
- Does modeling support giving initial vaccine doses to as many people as possible despite reduced efficacy?887
Table 1. Definitions of commonly used acronyms

<table>
<thead>
<tr>
<th>Acronym/Term</th>
<th>Definition</th>
<th>Description</th>
</tr>
</thead>
<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>
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<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), exposed (E), 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>
</tbody>
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%X Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants that result in increased transmissibility and partial evasion of neutralizing antibodies have recently emerged. Whether natural immunity induced by the original SARS-CoV-2 WA1/2020 strain protects against re-challenge with these SARS-CoV-2 variants remains a critical unresolved question. In this study, we show that natural immunity induced by the WA1/2020 strain leads to partial but incomplete protection against the SARS-CoV-2 variants B.1.1.7 (alpha) and B.1.351 (beta) in rhesus macaques. We challenged rhesus macaques with B.1.1.7 and B.1.351 and showed that infection with these variants resulted in high viral replication in the upper and lower respiratory tract. We then infected rhesus macaques with the WA1/2020 strain and re-challenged them on day 35 with the WA1/2020, B.1.1.7, or B.1.351 variants. Natural immunity to WA1/2020 led to robust protection against re-infection with WA1/2020 but only partial protection against re-challenge with B.1.351. An intermediate degree of protection was observed in rhesus macaques against re-challenge with B.1.1.7. These data demonstrate partial but incomplete protective efficacy of natural immunity induced by WA1/2020 against SARS-CoV-2 variants of concern. Our findings have important implications for both vaccination and public health strategies in the context of emerging SARS-CoV-2 variants of concern. SARS-CoV-2 WA1/2020 infection of rhesus macaques partially protects against re-infection with SARS-CoV-2 variants.

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REQUIRED INFORMATION FOR EFFECTIVE INFECTIOUS DISEASE OUTBREAK RESPONSE

SARS-CoV-2 (COVID-19)

Updated 12/7/2021

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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
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**Required Information for Effective Infectious Disease Outbreak Response**

**SARS-CoV-2 (COVID-19)**

Updated 12/7/2021

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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. SARS-CoV-2 variants with multiple amino acid mutations in the spike protein are emerging in different parts of the world, raising concerns regarding their possible impact on human immune response and vaccine efficacy against the virus. Recently, a variant named lineage B.1.1.7 was detected and shown to be rapidly spreading across the UK since November 2020. As surveillance for these SARS-CoV-2 variants of concern (VOCs) becomes critical, we have investigated the use of environmental surveillance (ES) for the rapid detection and quantification of B.1.1.7 viruses in sewage as a way of monitoring its expansion that is 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 >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 >95% in January 2021, in agreement with increasing SARS-CoV-2 infections associated with B.1.1.7 viruses.

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