DHS SCIENCE AND TECHNOLOGY

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

Annual Report

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

Homeland Security

Science and Technology

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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SARS-COV-2 – Master Question List

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FOREWORD

The Department of Homeland Security's (DHS) Science and Technology Directorate (S&T) developed the following "Master Question List" (MQL) that quickly summarizes what is known and what additional information is needed to address such fundamental questions as, "What is the infectious dose?" and "How long does the virus persist in the environment?" This 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 the need to review scientific reports, and to prevent duplication of efforts by highlighting and coordinating research.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a member of the coronavirus family and is the causative agent of Coronavirus Disease 2019 (COVID-19). Members of the coronavirus family cause a variety of diseases from head or chest colds to more severe and rare diseases such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). Like other respiratory viruses, coronaviruses spread quickly through droplets expelled when an individual breathes, coughs, sneezes, or speaks. As SARS-CoV-2 continues to spread through populations, genetic changes can accumulate over time and form distinct evolutionary lineages or variants with differing mutation rates, transmissibility, vaccine efficacy, and pathogenicity.

KEY UPDATES

- COVID-19 has caused at least 774,075,242 infections and 7,012,986 deaths globally.[1] In the United States, 1,169,666 deaths have been confirmed.[2]
- The Omicron variant accounts for 100% of new cases in the U.S., with subvariant JN.1 being the most prevalent, projected to account for 85.7% of cases.[3]
- There is no evidence that JN.1, which is closely related to the BA.2.86 subvariant, causes more severe disease and currently available vaccines are expected to be effective against this new subvariant.[4]
- Omicron variants result in less frequent and less severe COVID-19 lung damage compared to previous variants and a lower affinity for the lower respiratory tract.[5-6]
- Prolonged symptoms (≥ 3 months post-infection) were more common with pre-Omicron infections than with Omicron variants.[7-9]
- The U.S. Food and Drug Administration (FDA) authorized use of the updated mRNA vaccines, called the "2023-2024 Formula" from Moderna and Pfizer. They have a monovalent (single) component corresponding to the Omicron variant XBB.1.5. The FDA made a similar ruling for Novavax's protein vaccine 2023-2024 Formula, which contains the spike protein from Omicron variant XBB.1.5.[10]

Major Findings by Topic	
Topic	**Overview of Current Knowledge**
INFECTIOUS DOSE	In a human challenge study (36 adults between 18-29 years), an intranasal dose of 10 median tissue culture infectious dose ($TCID_{50}$) (~7 plaque forming units [PFU]) of wild-type virus successfully infected 53% of healthy volunteers, with 89% developing mild/moderate symptoms. Decreased threshold for infectivity has been modeled in newer variants, suggesting SARS-CoV-2 infection can occur from 500 virus copies of wild-type, 300 virus copies of Delta variant, and 100 virus copies of Omicron variant. Particle size exposure may be a relevant factor influencing transmission risk based on different activities influencing exhaled particle sizes.
TRANSMISSIBILITY	As of 1/22/2024, COVID-19 has caused at least 774,075,242 infections and 7,012,986 deaths globally. In the United States 1,169,666 deaths have been confirmed. Cases and fatalities are likely underestimated. As of 1/22/2024, the Omicron variant accounts for 100% of new cases in the U.S., with subvariant JN.1 being the most prevalent. SARS-CoV-2 is transmitted easily between humans, primarily through close contact (either direct or within 6 feet) and aerosol transmission. Within households, the two main risk factors include higher viral loads in the index patient and sharing a room with an infectious patient. There is substantial variation of transmission among individuals. Pre- or asymptomatic patients can transmit SARS-CoV-2 one to three days prior to symptom onset.
HOST RANGE	SARS-CoV-2 is closely related to other coronaviruses circulating in Southeast Asia bat populations. Previous coronaviruses have passed through an intermediate mammal host before infecting humans, but the presence or identity of the SARS-CoV-2 intermediate host remains unknown. Several animal species are susceptible to SARS-CoV-2 infection at varying degrees. Receptor binding studies of Omicron with the ACE2 receptors of mammalian hosts showed that this variant binds to the ACE2 receptor of 122 other mammals better than human ACE2, with rat (*Rattus rattus*) ACE2 displaying the strongest interaction, indicating that the host range of this variant may increase.
INCUBATION PERIOD	The incubation period for Omicron variants is approximately 3.4 days, while previous variants displayed incubation periods between 4 and 7 days. Incubating individuals can transmit disease for several days before symptom onset. Some individuals never develop symptoms but can still transmit disease. It is estimated that most individuals are no longer infectious beyond 10 days after symptom onset. Individuals can shed virus for several weeks, though it is not necessarily infectious. A large comparison across variants shows the mean incubation period for wild-type virus at 4.61 days; Alpha at 4.96, Beta and Gamma at 5.18; Delta at 4.43; and Omicron at 3.61 days with the incubation period increasing with age and in females.
ACUTE CLINICAL PRESENTATION	Most symptomatic COVID-19 cases are mild. Fever, cough, and shortness of breath are generally the most common symptoms, followed by malaise, and fatigue. Chills, muscle pain, joint pain, sore throat, gastrointestinal symptoms, neurological symptoms, and dermatological symptoms also occur. Adults >60 years old and those with comorbidities are at elevated risk of hospitalization and death. Children are susceptible to SARS-CoV-2, though generally show milder or no symptoms. Minority populations are disproportionately affected by COVID-19. Omicron variants result in less frequent and less severe COVID-19 lung damage compared to previous variants.
CHRONIC CLINICAL PRESENTATION	COVID-19 symptoms commonly persist for weeks to months after initial onset. Long-term symptoms such as fatigue, smell/taste disorders, and neurological impairment may affect the ability to return to work. In a cohort of COVID-19 patients, 39% reported symptoms 7-9 months after initial infection, with fatigue, loss of taste or smell, shortness of breath, and headache as the most common chronic symptoms. Prolonged symptoms (≥ 3 months post-infection) were more common during pre-Omicron than with Omicron variants.
PROTECTIVE IMMUNITY	Recovered and vaccinated individuals appear protected against reinfection for several months; however, the duration of protection is variable and depends on the individual and the variants circulating at the time.

Major Findings by Topic	
Topic	**Overview of Current Knowledge**
	While protection against reinfection wanes over a couple months, especially as new variants circulate, protection against serious disease or hospitalization remains high, with hybrid immunity providing the highest magnitude and duration of protection.
CLINICAL DIAGNOSIS	Diagnosis of COVID-19 is based on symptoms consistent with COVID-19, polymerase chain reaction (PCR)-based testing, and/or the presence of SARS-CoV-2 antigen in individuals (detected by enzyme-linked immunosorbent assay [ELISA]). Screening solely by temperature or other symptoms is unreliable. Asymptomatic individuals without COVID-19 symptoms can be diagnosed with SARS-CoV-2 infection by the same tests. In children, viral loads from saliva correlated better with clinical outcomes than viral loads from nasopharyngeal swabs, which may also be true for adults, as saliva tests consistently yield less false-negative results.
MEDICAL TREATMENTS	Detailed, real-time COVID-19 treatment recommendations are provided by the U.S. Centers for Disease Control and Prevention (CDC), the World Health Organization (WHO), the U.S. National Institutes of Health (NIH), Infectious Disease Society of America, and British Medical Journal in regularly updated guidance documents based on ongoing analysis of evidence from clinical trials. For hospitalized, critically ill patients on mechanical ventilation or extracorporeal membrane oxygenation (with organ failure and ARDS), dexamethasone is strongly recommended; if unavailable, use of alternative corticosteroids (hydrocortisone, methylprednisolone, prednisone) is recommended. The WHO strongly recommends against convalescent plasma use for non-severe COVID-19 patients but can be used in severe patients in clinical research settings.
VACCINES	Safe and effective COVID-19 vaccines are currently available through three manufacturers in the U.S., including mRNA vaccines developed by Pfizer-BioNTech and Moderna, and a protein subunit vaccine by Novavax. Vaccines are monitored for effectiveness against new virus variants and this data is used for the development of updated vaccines and boosters, and for national vaccine policy decision making. In September 2023, the FDA authorized use of the updated mRNA vaccines, called the "2023-2024 Formula" from Moderna and Pfizer. The 2023-2024 Formula mRNA vaccines are for individuals 6 months and older. They have a monovalent (single) component corresponding to the Omicron variant XBB.1.5, and use of the prior vaccines is no longer authorized. In October 2023, the FDA made a similar ruling for Novavax's protein vaccine 2023-2024 Formula, which contains the spike protein from Omicron variant XBB.1.5, for individuals 12 years and older.
NON-PHARMACEUTICAL INTERVENTIONS	Broad-scale control measures such as stay-at-home orders and widespread face mask use effectively reduced transmission early in the pandemic, though the enhanced transmissibility of the Omicron variant has limited the effectiveness of some measures. The combined use of multiple non-pharmaceutical interventions (NPIs) is far more effective than the singular use of any one NPI individually.
ENVIRONMENTAL STABILITY	SARS-CoV-2 can survive on surfaces from hours to weeks 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 considered to be common. 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.
DECONTAMINATION	Soap and water, as well as common alcohol and chlorine-based cleaners, hand sanitizers, and disinfectants are effective at inactivating SARS-CoV-2 on hands and surfaces. Several methods exist for decontaminating N95 respirators and other personal protective equipment (PPE). Increased resistance to ethanol was demonstrated by Alpha, Beta, Delta, and Omicron variants; however, all strains were inactivated by 35% ethanol after 15 seconds.
PERSONAL PROTECTIVE EQUIPMENT	Face masks (medical and non-medical) are effective at reducing infections from SARS-CoV-2. Mask fit is a critical component of effectiveness, in addition to filter efficiency. Healthcare workers are at elevated risk of acquiring COVID-19, even with recommended PPE.
GENOMICS	Current evidence suggests that SARS-CoV-2 accumulates mutations at a rate similar to other coronaviruses.

Major Findings by Topic	
Topic	**Overview of Current Knowledge**
	As of 1/22/2024, Omicron variant lineage JN.1 has become most prevalent and is predicted to make up 85.7% of infections. The S:L455S spike mutation in JN.1 variants has been associated with enhanced immune evasion when compared to BA.2.86 and HV.1 variants. Currently, Omicron variants XBB.1.5, XBB.1.16, EG.5, BA.2.86, and JN.1 are listed as variants of interest (VOIs); and DV.7, XBB, XBB.1.9.1, XBB.1.9.2, and XBB.2.3 are listed as variants under monitoring (VUMs) by the WHO.
FORECASTING	Several platforms provide digital dashboards summarizing the current state of the pandemic in U.S. states and counties. The CDC no longer provides forecasts of COVID-19 cases, as too many observations were falling outside of forecast intervals (i.e., forecast accuracy was generally low). Innovative approaches may be needed to forecast COVID-19 re-emergence after elimination or during periods of low incidence. There are efforts aimed at forecasting important SARS-CoV-2 mutations to predict emerging variants and their characteristics.

Infectious Dose – How much agent will make a healthy individual ill?

What do we know?

The human infectious dose is estimated to be 10 $TCID_{50}$ (~7 PFU) for wild-type SARS-CoV-2 (originating strain) delivered intranasally in a human challenge study (36 adults between 18-29 years). Healthy volunteers (53%) were successfully infected with 89% developing mild-to-moderate symptoms.[11] Infectious virus was shed from contagious individuals for 10 days after inoculation, and could be detected as early as 24 hours post-infection.[11]

- While there is a likely dose-infection relationship, there is no significant link between dose and severity in humans.[12]
- There is no preferential animal model for SARS-CoV-2 as clinical signs, recovery, and transmission vary between species.[13]
- Transgenic models may represent extreme conditions with unnatural gene expression patterns and rapid lethality, as the random integration strategy used to insert additional angiotensin-converting enzyme 2 (ACE2) copies is largely stochastic.[14]

An estimate of the human infectious dose of SARS-CoV-2 from primate research is 36-179 viral particles (PFU) necessary to cause infection via the inhalation route.

Non-Human Primates (NHP)

- Several NHP species (rhesus macaques, African green monkeys, cynomolgus macaques) are able to replicate aspects of human SARS-CoV-2 infection[15] from mild[16] to severe illness,[17] including acute respiratory distress syndrome (ARDS).[18]
- In cynomolgus macaques, the median dose required to induce wild-type SARS-CoV-2 seropositivity was 52 $TCID_{50}$ (approximately 36.4 PFU) via the inhalation route.[19] The median dose needed to induce fever was 256 $TCID_{50}$ (approximately 179.2 PFU) via the inhalation route,[19] which also suggests that symptom severity may be dose-dependent in macaques,[19] although severity is not necessarily dependent upon viral load.[20]
- Larger doses of SARS-CoV-2 have been shown to infect NHPs via the inhalation route[15-18, 21] or its surrogates (intranasal, intratracheal, combination routes)[17, 19, 21-22] and the ocular route.[23] Intragastric exposure does not appear to result in NHP infection.[23]

Rodents and Other Animal Models

- Many rodent models are modified to express human airway cells,[24] and the infectious dose of SARS-CoV-2 in these models is estimated at 4 x 10^3 $TCID_{50}$.[25] Golden Syrian hamsters and ferrets can replicate COVID-19 symptoms observed in humans[26-29] and are able to transmit to animals in separate cages without direct contact.[28, 30]
- In hamsters, higher infectivity at low doses of the Alpha variant of SARS-CoV-2 compared to wild-type virus suggests a mechanism for increased variant transmissibility.[31]
- Infection of golden Syrian hamsters with the Alpha variant administered by inhalation at two different particle sizes (1.3 µm or 5.2 µm) determined a significantly lower ID_{50} of 0.3 $TCID_{50}$ (0.2 PFU) for small particle aerosol exposure versus 11.5 $TCID_{50}$ (8.05 PFU) for large particle exposure, suggesting exhaled particle size due to various activities is a relevant factor influencing transmission risk.[32]
- One in six ferrets exposed intranasally to 10^2 PFU became infected, while 12 out of 12 animals exposed to >10^4 PFU became infected.[33]
- A median lethal dose (LD_{50}) of 10^4 PFU was calculated for K18-hACE2 mice.[12]
- SARS-CoV-2 Omicron B.1.1.529 was shown to infect C57BL/6 mice (10^5 $TCID_{50}$/mouse intranasal exposure dose) and cause changes in the lungs. A mutation in the spike protein was critical for this adaptation.[34]

Modeling Estimates

- The infectious dose of a pathogen can be estimated by the amount of genetic material passed between infector and infectee (called "bottleneck" size);[35] 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.[36] Bottleneck size is estimated to be 1-8 among households[37] and ~1,000 in a well-traced outbreak of Delta variant in Guangzhou.[38]
- Modeling aerosol exposures from five case studies suggests the inhalation median infectious dose (ID_{50}) for SARS-CoV-2 is approximately 361-2,000 viral particles, which is approximately 250-1,400 PFU.[39]
- Decreased threshold for infectivity has been modeled in newer variants. SARS-CoV-2 infection can occur from 500 virus copies of wild-type, 300 virus copies of Delta variant, and 100 virus copies of Omicron variant.[40]

What do we need to know?

- How does the infectious dose vary among the different routes of transmission for humans?

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

What do we know?

SARS-CoV-2 is passed easily between humans, primarily through close contact and airborne transmission.[41-44]

- As of 1/22/2024, COVID-19 has caused at least 768,654,968 infections and 6,953,483 deaths globally.[1] In the United States, 1,169,666 deaths have been confirmed.[2] Cases and fatalities are likely underestimated.[45-51]
- SARS-CoV-2 can spread via aerosol or "airborne" transmission[52] beyond six feet in certain situations[53] (i.e., enclosed spaces with inadequate ventilation).[54] The risk of infection from fomites[55] is believed to be low,[56] potentially due to mucins in saliva and mucus.[57] Vertical transmission is rare.[58-59] Hospital transmission follows community incidence[60] and may involve superspreading events.[61]

Several variants (Delta, Gamma, Alpha, Beta, Kappa, Eta, Omicron) have higher transmission than wild-type SARS-CoV-2.[62]

- As of 1/22/2024, the Omicron variant accounts for 100% of new cases in the U.S., and the JN.1 subvariant is predominant with 85.7% of new cases.[3]
- Omicron variants do not have higher viral loads than the Delta variant;[63-65] however, they replicate faster in human bronchial tissue, but slower in deeper lung tissues, explaining its higher transmissibility but lower disease severity than prior variants.[66]
- Measurements of transmission for those ≥ age 75 were estimated to be 1.45 times higher during the Omicron period than the Delta period.[67]
- Elevated infection risk from Omicron subvariants is partly due to their enhanced ability to evade the human immune response, even in vaccinated and previously infected individuals.[68-74]

COVID-19 vaccines reduce transmission rates.[75] Booster vaccinations significantly reduced infections from both Delta and Omicron variants.[76-77]

- Studies in household transmission showed that cases with children had higher odds of transmission within the household during outbreaks with Omicron variants.[78-79] Overall, there was reduced infectiousness in primary cases and reduced susceptibility in contacts when both were vaccinated.[78] Within households, the two main risk factors include higher viral loads in the index patient and sharing a room with an infectious patient which increased the odds of transmission by 40% and 199% respectively.[80]

The amount of infectious virus emitted from an infectious individual is unclear but appears highly variable.

- In a small study (n=38), researchers found median SARS-CoV-2 aerosol emission rates of 70, 110, and 80 RNA genome copies per minute for breathing, talking, and singing, respectively, with substantial variation among individuals and higher emission rates closer to symptom onset.[81]
- In a study of 25 patients infected with Omicron, 40% exhaled detectable virus, with 11 patients exhaling between 4.4-5.8 x 10^7 genome copies per hour.[82] In a separate study, 85% of exhaled particles containing virus were in the fine range (<5µm), with talking and singing producing more particles (844 and 1,094 per minute, respectively) and a greater proportion of fine particles (93.1% and 83.2%, respectively) compared to breathing (65 particles per minute, 54.2% <5µm).[83]
- Higher viral loads in COVID-19 patients result in higher secondary attack rates,[84] 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.[85] Mask, air, hand, and surface viral loads are more associated with nasal viral load than throat.[86]

Asymptomatic or pre-symptomatic individuals can transmit SARS-CoV-2[87] and play a large role in new case growth.[88]

- Individuals are infectious 1-3 days prior to symptom onset.[89-90] Pre-[91-96] or asymptomatic[97-99] patients can transmit SARS-CoV-2.[100] Most transmission occurs prior to[101] and within 5 days of symptom onset,[102-103] as seen in case studies[104] and models.[105] In samples collected from exhaled air from three individuals, infectiousness was determined to be greatest when the individual was near symptom onset, or if they were singing.[106]
- In a case series of 622 index patients infected with the Omicron variant, half of the 455 secondary cases were due to transmission before symptom onset of the index patient (only symptomatic cases were examined in the study).[107]
- Asymptomatic cases transmit less often than symptomatic ones,[108-110] causing 66-83%[101, 111-112] fewer cases. The likelihood of symptoms in secondary cases increases with severity of symptoms in the primary case.[103]

Infection risk is particularly high indoors,[113] while outdoor transmission is rare.[114]

- SARS-CoV-2 may be spread by conversation and exhalation[115-118] in indoor areas such as restaurants[119-120] or offices.[121] Clusters are often associated with large indoor gatherings,[122-123] including bars,[124] restaurants,[125] and gyms.[126-127]
- Transmission dynamics for different modes of public transport vary; subways are estimated to pose the greatest risk, with an average reproduction number 2.0-fold higher than high speed trains and 1.4-fold higher than buses.[128]

Superspreading events appear common in SARS-CoV-2 transmission and may be crucial for controlling spread.

- Most new infections originate from a few infectious individuals (overdispersion parameter k = 0.2-0.5).[129-134]
- Individuals vary greatly in their estimated infectivity. Importantly, this variation is not entirely due to the number of viral genome copies estimated by nasal or saliva samples,[68] which suggests that there may be host-specific indicators of infectiousness, and superspreading potential that could identify individuals at high risk of onward transmission.[68]

What do we need to know?

- What are the transmission rates of Omicron in different environments among varying ages and vaccination status?
- What is the relationship between detectable SARS-CoV-2 RNA in breath samples and contagiousness?[135]

Host Range – How many species does it infect? Can it transfer from species to species?

What do we know?

SARS-CoV-2 is closely related to other coronaviruses circulating in bats in Southeast Asia. Previous coronaviruses have passed through an intermediate mammal host before infecting humans, but presence or identity of the SARS-CoV-2 intermediate host is unknown.[136-139] Bat coronaviruses with >95% identity to SARS-CoV-2 have been identified in bat species;[140-141] however, whether a direct jump from bats to humans occurred is unknown.[142]

- SARS-CoV-2 does not appear to cause productive infection in horseshoe bats,[143] big brown bats,[144] or fruit bats;[145] however, transient infection may occur.
- Receptor binding studies of Omicron with the ACE2 receptors of mammalian hosts showed that this variant binds to the ACE2 receptor of 122 other mammals better than human ACE2, with rat (*Rattus rattus*) ACE2 displaying the strongest interaction, indicating that the host range of this variant may increase.[146]
- One study found that rabbit and hare ACE2 receptors had enhanced binding affinity to Omicron BA.4/5 and its subvariants when compared to wild-type.[147] Others found that Beluga and dolphin ACE2 receptors allowed cell entry of wild-type as well as Delta B.1.617.2 and Omicron BA.1 strains.[148] Another group tested the interactions of the spike domain of several SARS-CoV-2 variants with the ACE2 receptors from 18 different animal species and found that Omicron spike proteins had a decreased affinity for ACE2 receptors from horses, donkeys, pigs, dogs, cats, pangolins, American pikas, and Rhinolophus sinicus bats (Chinese horseshoe bat) when compared to wild-type.[149]

Several animal species are susceptible to SARS-CoV-2 infection.[150]

- White-tailed deer are susceptible to SARS-CoV-2 and can transmit the virus to other deer.[151-153] Deer in four U.S. states were found to have SARS-CoV-2 antibodies,[154] and recent evidence epidemiologically links deer-to-human transmission.[155]
- SARS-CoV-2 cases in mink on U.S. farms show high mortality rates.[156-157] High reinfection levels in farmed mink likely contributed to the detection of virus with several additional mutations compared to wild-type virus.[158-159] Infected mink have been linked to human infections.[139, 157, 160-161] Humans and mink are able to transmit infectious virus back and forth.[161] Aerosol concentrations of viral RNA on mink farms can be high, leading to occupational exposure risks.[162]
- Domestic cats are susceptible to infection with SARS-CoV-2,[163-165] and can transmit virus to other cats via droplet or short-distance aerosol.[163] Stray and domestic cats were found to be seropositive at low frequencies (1.6% to 7.1%);[166-168] and evidence exists of household human-to-cat transmission,[169-170] and to veterinarians.[171]
- Dogs exposed to SARS-CoV-2 produce anti-SARS-CoV-2 antibodies,[172-173] but exhibit no clinical symptoms.[163, 174]
- Retrospective genome-wide studies on mammalian SARS-CoV-2 strains indicate most transmission events involved minks, and rarely involved cats, dogs, or deer.[175]
- A literature review by the European Food Safety Authority noted that cats, ferrets, mink, hamsters, carnivores, great apes, and white-tailed deer are the highest at risk for SARS-CoV-2 infection and transmission.[176] White-tailed deer, Syrian hamsters, and mink are considered the only known wildlife reservoir currently.[177]
- Farmed poultry (ducks,[163, 178] chickens,[145, 163 178]pigs,[163] turkey,[178] geese,[178] and quail,[178]) are generally not susceptible to SARS-CoV-2. Sheep and cattle can be infected with SARS-CoV-2, but have limited transmission potential.[179-181] A serology survey of 612 sheep and goats, belonging to 24 different farms, found that 23 were ELISA positive (17 sheep, 6 goats) with only 1 having a neutralizing antibody titer.[182] The overall risk of human-to-animal transmission in commercial breeding/livestock operations appears to be low.[183]
- Other susceptible species include puma, snow leopard, fishing cat, binturong, coatimundi, lynx, tiger, lion, hippopotamus,[142] black-tailed marmoset, giant anteater, cougar, Indian leopard, spotted hyena, Asian small-clawed otter, manatee, and mule deer.[184-185]
- Rats in New York City were found to be serologically positive (16.5%) and Sprague Dawley rats were susceptible to Alpha, Delta, and Omicron variants.[186]
- Research studies have shown that invertebrates, birds, reptiles, and amphibians are not susceptible.[187]

There is currently no single animal model to study the full spectrum of COVID-19 phenotypes in humans, although several models allow the study of SARS-CoV-2 induced respiratory disease.[188]

- Several NHPs are susceptible to infection with SARS-CoV-2 including cynomolgus macaques,[22] African green monkeys,[17] rhesus macaques,[189] and pigtail macaques.[190]
- Golden Syrian hamsters,[139] ferrets,[28, 30, 145, 163] deer mice,[191] rabbits,[192] and raccoon dogs[193] are susceptible to infection and can be experimentally infected with SARS-CoV-2 via intranasal exposure.
- Bank voles (*Myodes glareolus*) seroconvert after exposure, but are asymptomatic and do not transmit infection to others.[194]

What do we need to know?

We need to know the best animal model for replicating human infection by various exposure routes.

- What is the intermediate host(s) (if any)?
- Can SARS-CoV-2 circulate in animal reservoir populations, potentially leading to future spillover events?
- Will ACE2 receptor binding specificity lead to different SARS-CoV-2 variants in different animal populations?

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

What do we know?

On average, symptoms develop 3-4 days after exposure to Omicron variants. Incubating individuals can transmit disease for several days before symptom onset. Some individuals never develop symptoms but can still transmit disease.[195]

- The incubation period for Omicron variants is approximately 3.4 days, while previous variants displayed incubation periods between 4 and 7 days.[196] Few infected individuals show symptoms sooner than 2 days after exposure.[197]
- There is evidence that younger (<14) and older (>75) individuals have longer COVID-19 incubation periods, creating a U-shaped relationship between incubation period length and patient age.[198]
- Individuals can test positive for COVID-19 even if they lack clinical symptoms.[91, 97, 199-200] Individuals can be infectious while asymptomatic,[91, 199, 201-202] and asymptomatic and pre-symptomatic individuals have similar amounts of virus in the nose and throat compared to symptomatic patients.[90, 203-204] Asymptomatic infections have been reported more often in Omicron cases than previous variants.[196]
- 19% of individuals undergoing a 7-day quarantine after a COVID-19 contact were at risk of developing COVID-19,[205] which indicates that quarantines of less than 14 days carries risk of disease and transmission, and that care should be taken after a shortened quarantine period (e.g., wearing a mask, distancing).[205]

Gradual shortening in incubation period, serial interval (time between successive cases), and generation time in association with newer variants and the general progression of the pandemic has been reported.[206-207]

- A large comparison across variants shows the mean incubation period for wild-type at 4.61 days; Alpha at 4.96, Beta and Gamma at 5.18; at Delta 4.43; and Omicron 3.61 days with the incubation period increasing with age and in females.[208]
- The generation time (time between infection events in a chain of transmission) for SARS-CoV-2 is estimated as 4-5 days.[209] The serial intervals for Alpha, Delta, and Omicron BA.1 are 3.47, 3.59, and 3.21 days, respectively, and the mean generation times for each strain are 4.35, 3.65, and 2.99 days, respectively.[206]

It is estimated that most individuals are no longer infectious beyond 10 days after symptom onset.[210]

- A systematic review of published studies on SARS-CoV-1, SARS-CoV-2, and MERS-CoV found none that reported isolation of infectious virus from COVID-19 patients beyond 9 days from symptom onset, despite high viral loads by genetic tests.[211]
- Asymptomatic and mild cases had a median conversion time from positive to negative RT-PCR for SARS-CoV-2 Omicron BA.2.2 of 7 days. Those involving individuals with major comorbidities or ≥ age 60 had a median conversion time of 9 days.[212]
- Among 53 healthcare workers infected with the Omicron variant, rates of viral culture positivity – a surrogate for the probability of shedding infectious virus – were 83%, 52%, 13.5%, and 8% at 5, 7, 10, and 14 days after initially testing positive, respectively; in 19% of cases, patients shed infectious virus after their symptoms stopped.[213]
- In a small study of 11 Omicron cases, individuals were not infectious (estimated by tissue culture infectivity of collected samples) beyond 8 days after symptom onset.[214]
- In a small (n=14) sample of young, healthy, vaccinated patients, rapid COVID-19 antigen test results were plausible surrogates for the infectiousness of collected samples, with those testing negative shedding non-infectious samples.[215]

Individuals can shed virus for several weeks, though it is not necessarily infectious.

- The median duration of viral RNA shedding by nasopharyngeal swab in patients over age 13 with positive SARS-CoV-2 infection was seven days. There was no significant difference in mean duration of shedding in symptomatic and asymptomatic individuals.[216]
- Omicron variants have a shorter incubation period and decreased prevalence of symptoms compared to Delta, but the viral loads associated with each and the extent of their contribution to symptom severity remains disputed.[65, 196]
- Viral loads tend to peak about 3 days after symptom onset for Omicron, suggesting that detection of viral RNA 2 days before symptom onset could be observed, and detection as soon as 1 day post infection may be possible.[217]
- Viral RNA shedding in nasopharyngeal and fecal samples have been reported for up to 21 and 14 days, respectively, yet none of these samples contained viable SARS-CoV-2.[218]

What do we need to know?

We need to know the incubation duration and length of infectivity in different patient populations.

- How soon can asymptomatic patients transmit infection after exposure?
- Does the incubation period correlate with disease severity or exposure dose?

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 appear in any age group. Older individuals and those with underlying conditions[219] are at higher risk of serious illness and death, as are men.[220]

- Most symptomatic COVID-19 cases are mild (81%).[221] COVID-19 causes a wide range of symptoms including fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, and diarrhea.[222]
- Multisystem Inflammatory Syndrome in Adults (MIS-A) is a rare condition that may develop days to weeks after SARS-CoV-2 infection where inflammation occurs in the heart, gastrointestinal tract, skin or brain.[223]

The Omicron variant and subvariants are less likely to result in hospitalization or death than the Delta variant.[224]

- The Omicron variant has a significantly higher replication in human bronchi compared to wild-type and Delta variants, potentially increasing infectious particles released by breathing and speaking, explaining its rapid forward transmissibility.[66]
- In a retrospective cohort study, the Omicron variant resulted in a 59% lower likelihood of hospitalization or death than the Delta variant,[224] though elevated case counts resulted in greater absolute hospitalizations,[225] and estimating variant severity with population-level data is difficult.[226]
- Omicron variants result in less frequent and less severe COVID-19 lung damage compared to previous variants[6] and a lower affinity for the lower respiratory tract.[5]

COVID-19 is more severe than seasonal influenza,[227] evidenced by higher intensive care unit (ICU) admission[228] and mortality rates.[229]

In the U.S., 29-34% of hospitalized patients required ICU admission, and 12.6-13.6% died from COVID-19.[230-231]

- Higher SARS-CoV-2 RNA loads at admission have been linked to greater risk of death,[232-235] though this is not universal.[236]
- High viral loads (reverse transcription polymerase chain reaction [RT-PCR] cycle threshold value <28) are associated with symptom severity 6 months after illness onset.[237]
- COVID-19 also causes pneumonia,[238] cardiac injury,[239] kidney damage,[240-241] pancreatitis,[242] arrhythmia, sepsis, stroke,[243-244] respiratory complications,[245] and shock.[200, 246-248] SARS-CoV-2 weakens blood vessels in the lungs[249] and is associated with hyperactive platelets,[250] leading to ARDS.[251-252] Clotting affects multiple organs[253] and is present in 15-27% of cases.[254]
- Low oxygen saturation and shallow breathing upon hospital admission are associated with elevated mortality risk.[255]
- The risk of severe COVID-19 may be influenced by the environment, as in one study where elevated ozone (10x greater than acceptable concentrations) predisposed mice to severe illness by upregulating cellular entry proteins (e.g., *Tmprss2*).[256]

Adults >60 years old[257] and those with comorbidities[258-259] are at elevated risk of hospitalization[260] and death.[199, 248]

- Cardiovascular disease,[261] obesity,[262-264] hypertension,[265] diabetes,[266-267] cancer,[268] down syndrome,[269] and respiratory conditions increase the case fatality rate (CFR).[199, 248] Kidney disease,[270] dialysis,[271] and lack of physical activity[272] may increase disease severity.
- Estimates of the age-specific infection fatality rate were identified in a large meta-analysis using data publicly disseminated prior to September 18, 2020: 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%.[273] Provisional death counts through April 15, 2023 indicate that rate of death from COVID-19 for 85 and older are 360 times higher than 18-29 year-olds.[274]

Minority populations are disproportionately affected by COVID-19[275] and appears to be linked to underlying conditions.[276]

- Minority ethnic populations[277] acquire SARS-CoV-2 infection at higher rates,[278-281] are hospitalized,[282-283] and die disproportionately.[284-285] Hispanic and Black COVID-19 patients tend to die at younger ages.[286]
- Pregnant women with COVID-19 have higher mortality rates compared to those without;[287] the proportion of pregnant patients with severe COVID-19 increased after the introduction of the Delta variant.[288]
- Individuals with physical or intellectual disabilities are at greater risk of poor COVID-19 outcomes, including mortality, ICU admission, and lengthy hospital stays.[289]

Children are susceptible to COVID-19,[290] though generally show milder[291-292] or no symptoms.[293]

- Children appear primed to mount early, effective immune responses to SARS-CoV-2. Studies have found that pediatric airway immune cells have a stronger interferon response compared to adult cells and that infants and young children have more durable antibody responses, which help to explain their lower rates of severe disease and death compared to adults.[294-296]
- Children (21% to 28% <19 years old) may be asymptomatic.[292, 297-298] Most symptomatic children show mild or moderate symptoms.[298-299] Severe disease in infants[300-302] is more likely in those with complex medical histories.[303-304]
- MIS in Children (MIS-C) is a rare inflammatory condition, occurring in 1 of approximately 3,000 to 4,000 children that had COVID-19 early in the pandemic. Symptoms generally appear 2-6 weeks after infection and can occur when children had no or few symptoms of COVID-19.[305]

What do we need to know?

We need to know the impact of new SARS-CoV-2 variants on presentation and disease severity.

- What therapeutics can be used as treatments?[306]
- What treatments reduce transmissibility of SARS-CoV-2 and improve outcomes for immunocompromised?[307-308]

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

What do we know?

Long COVID is a multisystemic illness, sometimes referred to as Post-Acute Sequelae of COVID-19 (PASC),[309] long-haul COVID, post-COVID-19 conditions, or chronic COVID where symptoms linger for weeks, months, or years after initial diagnosis of COVID-19.[310] The incidence is estimated at 10-30% for non-hospitalized cases, 50-70% for hospitalized cases, and 10-12% for vaccinated cases.[311]

- Over 203 symptoms were reported by long COVID patients in a large (n=3,762) survey.[312] SARS-CoV-2 infection appears to exacerbate underlying conditions, with symptoms ranging from vascular and cardiac issues,[313-314] central nervous system and demyelination issues,[315] and sex-specific reproductive complications.[316-318] Long-term symptoms such as fatigue,[319-321] smell/taste disorders,[320, 322-323] neurological impairment,[312] and dyspnea, difficulties with concentration, and finding correct words during speech[321] may affect the ability to return to work.[312]
- Vaccination reduces the odds of hospitalization and number of symptoms within the first week of illness, and reduced symptoms lasting ≥28 days following the second dose, suggesting a reduced risk of long COVID.[324-326]

The Omicron variant has lower odds of causing long COVID in patients compared to prior variants.[7-9]

- Prolonged symptoms (≥ 3 months post-infection) were more common during pre-Delta variants at 28.4% than with Delta variants at 21.7% or Omicron variants at 16%.[326] Another study found similar rates of long COVID with 10-17% incidence for Omicron variants and 35% with pre-Omicron infection.[8]

Researchers are identifying methods to diagnose patients with long COVID 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 4 weeks post-infection compared to those without neurological symptoms, suggesting that corneal microscopy could be a potential rapid objective test when evaluating long COVID patients.[327]
- 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.[328]
- 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.[328]
- Different antibody levels correspond to different manifestations of PASC (e.g., neurological, respiratory, gastrointestinal), suggesting that patient risk may be assessed for both PASC risk and presentation.[329]
- One year after ICU admission for COVID-19, lingering physical (74% of 246 ICU patients), mental (26%), and cognitive (16%) symptoms were common, with 58% of patients experiencing issues returning fully to work.[330]
- The incidence rate of pediatric long COVID is still uncertain. Due to small study sizes and inconsistent collection and analysis methods, the reported incidence rate can vary from approximately 25% to <5%. Additionally, the correlation between pediatric long COVID and medical history, including mental health, is not well established.[331]

Accurate correlations behind the mechanisms of long COVID are difficult to determine as it affects many organs and systems within our body. However, the main mechanisms found so far have involved viral persistence, hypercoagulopathy, immune dysregulation, autoimmunity, hyperinflammation, or a combination of these.[332]

- Risk factors potentially include obesity,[333] age,[334] female sex,[335] type 2 diabetes, Epstein-Barr Virus reactivation, presence of specific autoantibodies, connective tissue disorders, attention deficit hyperactivity disorder, chronic urticaria and allergic rhinitis, and other autoimmune conditions; although no identified preexisting conditions have been identified in a third of long COVID cases.[311] T cell and antibody responses did not differ between individuals with acute or chronic COVID-19 nine months post-infection,[336] suggesting that differences in immune response are not the only cause of long COVID.
- The importance of initial symptom severity for subsequent development of long COVID is unclear, with some studies showing high risk in mildly ill patients,[337] while others show higher risk in severely ill patients.[338]
- A study determined that age, sex, and vaccination status could not be used to predict the development of long COVID.[7]
- Most current evidence recommends maintaining a vaccination schedule for SARS-CoV-2 to prevent long COVID in breakthrough cases. Although, some studies found conflicting correlation between vaccinations and long COVID cases; overall vaccinations did not change or exacerbate symptoms in long COVID patients, therefore it's still recommended to receive boosters.[339]

What do we need to know?

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

- What is the mechanism[340] and clinical implication of long COVID?[341-343]
- How prevalent are chronic symptoms in children or individuals over 60?[344]
- Does previous diagnosis of COVID-19 confer complications during pregnancy after viral clearance?
- What latent pathogens are potentially reactivated in long COVID?[345]

Protective Immunity – How long does the immune response provide protection from reinfection or severe disease?

What do we know?

Recovered and vaccinated individuals appear protected against reinfection for several months; however, the duration of protection is variable and depends on the individual and the variants circulating at the time.

- Protective immunity, or the level of protection, is often measured and reported on as one of three different outcomes: 1) protection from reinfection; 2) reinfection but protection from symptomatic disease (asymptomatic); and 3) reinfection but protection from severe disease, including hospitalization and death.[346]
- Predicting protective immunity can be complex due to the heterogenicity of immune responses. The duration and level of protective immunity can vary greatly from person to person depending on age, sex, medical history, prior infection or exposure to SARS-CoV-2, vaccination, circulating variants, and individual humoral and cellular responses.[347]
- Neutralizing antibody levels have been shown to correlate with protective immunity from COVID-19.[348]
- Neutralizing antibody responses are present within 8-19 days after symptom onset[349] and can persist for many months.[61, 350-351] Some unvaccinated individuals have no detectible neutralizing antibody activity after infection.[352] Individuals with more severe infections developed higher neutralizing antibody levels that persisted longer.[352-353] Others have found higher total immunoglobulin (Ig) levels, and symptom severity could be used to predict protective immunity.[354]
- Immunocompromised individuals typically have a weaker response to immunization, leading to lower levels of protective immunity and a greater likelihood of reinfection, especially if new variants are circulating.[355]
- Vaccine-derived immunity is robust in pregnant and lactating women.[356] Antibodies are transferred to neonates by the placenta[357] and through breast milk,[358] if the woman gets vaccinated during pregnancy[359] or recovers from a natural infection[360] during pregnancy.[361]

While protection against reinfection wanes over a couple months, especially as new variants circulate, protection against serious disease or hospitalization remains high, with hybrid immunity providing the highest magnitude and duration of protection.[347, 362-363] Even with mild to no symptoms, individuals are able to spread the virus during a reinfection.[364]

- In a large metadata review of 26 studies before and during the Omicron wave, prior infection led to a 25% reduction in reinfection and a 75% reduction in severe disease or hospitalization at the 12 month time point. Hybrid immunity led to a 42% reduction in reinfection and a 97% reduction in serious disease or hospitalization projected to last up to at least 12 months.[362]
- In a 2023 review of protective immunity in 65 studies from 19 countries over 2.5 years, excluding hybrid immunity (vaccination plus recovery from natural infection), data showed that immunity from previous infection was highly protective against reinfection from earlier variants such as Alpha and Delta (82%) and only moderately protective against reinfection with Omicron (45%). While reinfection can still occur, the protection from infection via acquired immunity reduces the risk of severe disease from any variant by 88.9%, and reduces the risk of hospitalization or death from any variant by 78% for over 10 months.[346]

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

- SARS-CoV-2 mutations can reduce responses to serum from vaccinated patients.[365]
- Neutralization of the Omicron variant has been observed in groups with 3-4 antigenic exposures such as 2 vaccinations plus booster[366-370] or convalescent plus 2 vaccinations.[366, 370-371] However, the significant antigenic shift of Omicron compared to earlier variants causes a substantial reduction in protective immunity, both in naturally infected and vaccinated people.[372]
- Neutralizing antibodies rapidly decline by Day 91, with differences between Omicron sublineages.[373] Preliminary evidence suggests BA.2.10.1 and BA.2.75 recombinant, XBB, is the most antibody-evasive variant identified.[374]
- Vaccinated patients with prior infection before vaccination had a higher antibody and B cell response and faster increase in antibodies by Day 7 than those who did not have a prior infection, suggesting a benefit in hybrid humoral immunity.[375] Longer lasting immunity was identified following two doses of vaccine regardless of prior infection.[375]
- Vaccination followed by breakthrough infection with BA.1 produces neutralizing antibodies to earlier variants,[376-377] but can be evaded by variants BA.4/5,[378-380] and breakthrough infections with BA.2 have shown protective neutralizing antibodies.[381]
- Long-term analysis of healthcare workers found that triple vaccinated, SARS-CoV-2 naïve individuals showed increased B cell and T cell recall and cross-neutralizing antibodies against previous variants following infection with Omicron, but immunity against Omicron itself was dampened.[382]
- Patient serum from individuals infected with non-Omicron variants exhibited poor neutralization ability against the Omicron variant, suggesting low protective immunity against Omicron from infection with prior variants.[383]

What do we need to know?

We need to know the frequency and severity of reinfection, as well as the protective effects of immune components.

- How long does protective immunity last for children compared to adults?
- What is the probability of reinfection, particularly with SARS-CoV-2 variants?
- Is infection with the Omicron variant more likely to lead to protection against future variants?

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

What do we know?

Diagnosis of COVID-19 is based on symptoms consistent with COVID-19 and 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 1/22/2024, the FDA has granted Emergency Use Authorization (EUA) for 304 molecular tests and sample collection devices, 83 antibody and other immune response tests and 65 antigen tests.[384]
- Multiplex PCR assays able to detect influenza A, influenza B, respiratory syncytial virus and SARS-CoV-2 have been developed for rapid differential diagnosis of respiratory viruses.[385]
- Serology tests allow health care professionals to identify individuals who have developed an adaptive immune response to SARS-CoV-2, but the tests should not be used to diagnose or exclude acute COVID-19 infection.[386]
- The FDA granted EUA to a non-invasive, non-diagnostic device based on machine learning algorithms that screens for biomarkers of SARS-CoV-2 infection in asymptomatic individuals older than 5 years.[387]
- 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.[388] Low viral loads can lead to false-negative RT-PCR tests.[389]
- 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.[390] After 10 days, alternative testing methods (e.g., lower respiratory samples) may be necessary.[390]
- 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.[391] The FDA has now approved the InspectIR COVID-19 breathalyzer that uses gas chromatography-mass spectrometry to detect SARS-CoV-2.[392]
- Pooled nasal and throat swabs show high diagnostic accuracy, while saliva, nasal swabs, and throat swabs all showed lower accuracy.[393] However, homogenization of saliva samples prior to RNA extraction increases diagnostic accuracy, with results comparable to nasopharyngeal swabs.[394] The detection of Omicron-infected patients from saliva by PCR testing was comparable to nasopharyngeal swabs.[395]
- In a study using household testing, children (age 0-19 years old) tested positive at a lower frequency than adults and may be under-detecting when compared to the serological data.[396] Another study found that 90% of children had negative nasopharyngeal RT-PCR tests but seroconverted 6 weeks later.[397]
- Symptom-based screening at airports was ineffective at detecting cases (9 identified out of 766,044 passengers screened),[398] and intensive screening on a U.S. military base during mandatory quarantine produced positive PCR test results for 19 out of 189 seropositive and 1079 out of 2247 seronegative participants.[399]
- Infrared temperature readings may be misleading when used at the entrance of buildings with low outdoor temperatures.[400]
- Foam swabs lead to more accurate diagnostic tests than polyester swabs for collecting patient samples, though polyester swabs are adequate to be used in case of a shortage in foam swabs.[401]
- Immunological indicators,[246, 365, 402-411] blood glucose levels,[365] oxygen levels,[412] and bilirubin levels[413] may help identify future severe cases, and tools for diagnosing severe infections[414-416] and predicting mortality[417] exist.
- Self- or caregiver-taken diagnostic swabs could be as accurate as those taken by healthcare workers in some instances.[418]
- Wearable technology may be able to detect COVID-19 days before symptoms begin.[419-420]
- Aerosol detection devices are capable of identifying SARS-CoV-2 in the air (minimum of approximately 6,000 particles).[421] Improvements to aerosol sampling protocols (e.g., use of fetal calf serum during elution, using polytetrafluoroethylene filters instead of glass fiber) may lower the limit of detection to 10-50 genome copies/m^3.[422]
- 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.[423]

Validated serological (antibody) assays are being used to help determine who has been exposed to SARS-CoV-2.[424]

- Meta-analysis suggests that lateral flow immunoassays (LFIA) are less accurate than ELISA or chemiluminescent methods, but that the target of serological studies (e.g., IgG or IgM) does not affect accuracy.[425]
- LFIA testing showed lower accuracy in pregnant women than other patient cohorts.[426]

What do we need to know?

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

- What is the relationship between disease severity and the timing of positive serological assays?
- Are certain subpopulations (e.g., those with blood cancers)[427] more likely to show false-negative tests?

Medical Treatments – Are there effective treatments?

What do we know?

Detailed, real-time COVID-19 treatment recommendations are provided by the U.S. Centers for Disease Control and Prevention (CDC),[428] the WHO,[429-430] the U.S. National Institutes of Health,[431] Infectious Disease Society of America,[432] and British Medical Journal[433] in regularly updated guidance documents based on ongoing analysis of evidence from clinical trials.

- A list of all current FDA approved, or FDA EUA authorized products for medical treatment of COVID-19 can be found at the FDA COVID-19 website.[434]
- Most people present with mild symptoms and the most common medical treatments are over the counter medicines such as acetaminophen (Tylenol) or ibuprofen (Motrin, Advil) to treat the symptoms of fever and discomfort.[428, 435] Aspirin can also be used for pain and fever, and has shown an association with reduced risk of mortality in hospitalized patients.[436]
- Paxlovid (nirmatrelvir co-administered with ritonavir). For patients with non-severe illness at highest risk of hospitalization, the WHO[437] and the CDC[428] recommends use of Paxlovid as the best choice for most eligible patients.[438] Paxlovid is an oral antiviral approved by the FDA for the treatment of mild-to-moderate COVID-19 in adults and children (≥12 years old),[439-440] and can be used for treatment outside of the hospital.[441] Treatment should be started as soon as possible, within 5 days of the start of symptoms.[428] This treatment showed an 89% reduction in risk of hospitalization and death in high-risk individuals.[442] A clinical trial of Paxlovid found non-significant reduction (51%) for either vaccinated or unvaccinated patients without other health risks, suggesting limited benefits for those at low hospitalization risk.[443]
- Veklury (remdesivir) may be considered for patients at high risk of severe disease.[444] It is an antiviral drug that can be used for treatment in or out of the hospital,[441] and should be started as soon as possible but no later than 7 days from the start of symptoms.[428] The WHO notes the conditional recommendation for use of remdesivir in patients with severe COVID-19, and conditional recommendation against use of remdesivir in patients with mild to moderate COVID-19.[441, 445]
- Lagevrio (molnupiravir) is an oral antiviral that shows a 30% reduction in hospitalization and death,[446-447] and an increase in viral clearance, but no effect on symptom duration.[448] Due to the potential side effects, which may include cancer and birth defects, the FDA has approved an EUA in mild-to-moderate cases in adults ≥18 years old, when no other FDA approved drugs are available.[434, 449-451]
- Actemra (tocilizumab) is an immunosuppressive drug which is FDA EUA approved for certain children and young adults with severe acute COVID-19.[452-453]
- The WHO recommends FDA approved Olumiant (baricitinib)[434, 454] as an alternative to interleukin-6 (IL-6) blockers, with corticosteroids for severe or critical COVID-19 patients.[455] Baricitinib combined with standard of care reduced all-cause mortality.[456] Additionally, they recommend that IL-6 blockers can be combined with the baricitinib and corticosteroids for severe or critical COVID-19.[445]
- Additional immune modulators are available for the treatment of COVID-19 in certain cases through the FDA EUA, including Kineret (anakinra) as well as Gohibic (vilobelimab).[434]
- For hospitalized, critically ill patients on mechanical ventilation or extracorporeal membrane oxygenation (with organ failure and ARDS), dexamethasone is strongly recommended; if unavailable, use of alternative corticosteroids (hydrocortisone, methylprednisolone, prednisone) is recommended.[350, 457-462] Methylprednisolone may increase duration of viral shedding.[463]
- The WHO strongly recommends against convalescent plasma use for non-severe COVID-19 patients, but can be used in severe patients in clinical research settings.[464]
- Treatment with anticoagulants can lead to decreased morbidity or mortality in certain hospitalized patients that have complications from COVID-19, such as pulmonary embolism, ischemic stroke, deep vein thrombosis, myocardial infarction, etc. A therapeutic dose (full dose) has been shown to be more effective than a prophylactic (low dose) approach.[465]
- Prior use of statins,[466-467] renin-angiotensin-aldosterone system inhibitors,[468] anticoagulants,[469] non-steroidal anti-inflammatory drugs (NSAIDs),[470] and angiotensin-converting-enzyme (ACE) inhibitors[471] do not appear to elevate COVID-19 risk.[472]

Prompt treatment for acute COVID-19 improves survivability in immunocompromised individuals.

- A recent study found treatment with molnupiravir or nirmatrelvir-ritonavir within 30 days of diagnosis improved patient recovery in immunocompromised patients with SARS-CoV-2.[473]
- A 2023 large meta-data review shows treatment with convalescent plasma is associated with decreased risk of mortality in immunocompromised patients infected with COVID-19.[474]

What do we need to know?

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

- What treatment, or combination of treatments, is most effective for different disease severities and patient demographics?
- What is the efficacy of transmission-blocking peptides[475] and nasal sprays in humans?[476]
- Are inflammation inhibitors effective at improving the outcome of COVID-19 associated hyperinflammation?[477]

Vaccines – Are there effective vaccines?

What do we know?

Safe and effective COVID-19 vaccines are currently available through three manufacturers in the U.S., including mRNA vaccines developed by Pfizer-BioNTech and Moderna, and a protein subunit vaccine by Novavax.[10] Vaccines are monitored for effectiveness against new virus variants and this data is used for the development of updated vaccines and boosters, and for national vaccine policy decision making.[478]

- As of the CDC's final tracking update on 5/11/2023, 230.64 million in the U.S. were fully vaccinated against wild-type SARS-CoV-2, and 56.5 million have received one of the updated bivalent boosters.[479]
- The CDC maintains a detailed summary table of all U.S. COVID-19 vaccine manufacturers and dosing schedules based on age group, vaccination history, and health status.[480]
- Current guidelines consider a person 'up to date' on their vaccinations when an adult or child over 5 years old has had at least 1 updated COVID-19 vaccine, or when a child 6 months to 4 years old has had the manufacturer's recommended dosage for their vaccine, including at least 1 updated vaccine.[10, 480]
- In September 2023, the FDA authorized use of the updated mRNA vaccines, called the "2023-2024 Formula" from Moderna[481] and Pfizer.[482] The 2023-2024 Formula mRNA vaccines are for individuals 6 months and older. They have a monovalent (single) component corresponding to the Omicron variant XBB.1.5, and use of the bivalent vaccines is no longer authorized.[483-484] In October 2023, the FDA made a similar ruling for Novavax's protein vaccine 2023-2024 Formula, which contains the spike protein from Omicron variant XBB.1.5, for individuals 12 years of age and older.[485]
- In June 2023, the FDA's VRBPAC met to review safety, efficacy, and immunogenicity of all vaccines in conjunction with circulating strains to provide guidance for the composition and schedule of vaccinations in 2023-2024. The committee unanimously voted that a monovalent COVID-19 vaccine with an XBB-lineage of the Omicron variant (XBB.1.5 is recommended) should be used for all vaccinations starting in fall 2023.[486-487]
- While the efficacies of the initial 2021 monovalent vaccines from Pfizer and Moderna were high (91.3%[488] and 94.1%[489] respectively) and consistent across age,[490] race, ethnicity, and sex,[489] protection from the monovalent vaccines dropped to 20-25% once Omicron became the prominent circulating strain. Introducing bivalent vaccines or boosters raised the efficacy against symptomatic COVID-19 to 59-73%,[491-492] thereby changing the vaccination strategy going forward. In late 2023, updated vaccines were developed, which targeted the Omicron variant XBB.1.5 for better protection against circulating variants.[483]
- As of September 2023, the Pfizer and Moderna bivalent vaccines and initial vaccines are no longer authorized for use in the U.S., and have been replaced by the 2023-2024 formulas.[484, 493-494]
- The CDC prepared a summary table of all U.S. COVID-19 vaccine manufacturers and dosing schedules per age group.[480]
- Vaccination has provided robust protection from infection,[495-498] and vaccinated individuals generally experience milder symptoms than unvaccinated individuals.[499]
- Vaccination is safe and efficacious in pregnant women, with no increase in risk of adverse pregnancy or fetal or neonatal outcomes. Vaccination during pregnancy provides protection through placental transfer, as well as through breastmilk.[359]
- **Pfizer/BioNTech** – mRNA vaccine named Comirnaty.[500] The updated 2023-2024 formula is authorized by the FDA for use in individuals 6 months of age and older.[482]
  - Depending on vaccination history, children 6 months to 4 years old receive up to 3 doses of the updated 2023-2024 formula vaccine, and individuals 5 years and older receive up to 1 dose of the updated 2023-2024 formula vaccine (full detailed vaccination schedule provided in reference).[480]
- **Moderna** – mRNA vaccine named Spikevax or Elasomeran.[501, 502-503] The updated 2023-2024 formula is authorized by the FDA for use in individuals 6 months of age and older.[481]
  - Depending on vaccination history, children 6 months to 4 years old receive up to 2 doses of the updated 2023-2024 formula vaccine, and individuals 5 years and older receive up to 1 dose of the updated 2023-2024 formula vaccine (full detailed vaccination schedule provided in reference).[480]
- **Novavax –** a protein subunit-based vaccine named Covovax, or Nuvaxovid depending on location.[504] The updated 2023-2024 formula is authorized by the FDA for individuals 12 years of age and older.[485] This vaccine is the first protein-based COVID-19 vaccine available in the U.S.[505] The vaccine is given as 2 shots, 8 weeks apart, and is recommended as a 2-dose primary series for unvaccinated individuals 12 and older.[506]
- **Johnson & Johnson/Janssen** (Discontinued) – adenovirus vaccine[507] named Janssen COVID-19 vaccine. Authorized through a FDA EUA from Feb 27, 2021 through June 1, 2023, no longer in use in the U.S.[508]

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.

- What are the correlates between neutralizing antibody levels and vaccine-induced efficacy in humans?
- How protective are vaccines in those taking immunosuppressants[509] or with autoimmune disorders?

Non-Pharmaceutical Intervention (NPI) – 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 reduced transmission early in the pandemic, though the enhanced transmissibility of the Omicron variant has limited the effectiveness of some measures. The combined use of multiple NPIs is far more effective than the singular use of any one NPI individually.[510-511]

- Social distancing and other policies quickly reduced spread of early pandemic SARS-CoV-2 throughout China,[512-517] Europe,[518-519] and the U.S.[520-521] Delaying control measures increases outbreak duration,[522] cases,[523] mortality,[524] and effective viral population size.[525]
- U.S. states[526] with mask mandates had lower case growth rates and higher likelihoods of controlling transmission[527] and shelter-in-place orders[528] and restaurant and bar closures were associated with large reductions in exponential growth rate of cases.[529] At the start of the pandemic, mobility reductions in the U.S. were associated with reductions in COVID-19 case growth.[530-531] Social distancing and reductions in both non-essential visits to stores and overall movement distance led to lower transmission rates.[532]
- Reducing capacity at crowded indoor locations,[533] increasing indoor air flow rates,[534] adding portable air cleaners,[535] and wearing masks may reduce indoor transmission.[536] Aerosol infection risk is not uniform in indoor environments, and can be greatly impacted by patterns of ventilation.[537]
- 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.[538] Similarly, targeting NPIs at those in high-risk occupations may help reduce COVID-19 burden.[539]
- Layered control strategies in Shanghai were overwhelmed during a period of new Omicron variant cases in early 2021; only after a city-wide lockdown did transmission rates fall substantially.[540] Similarly, regular testing, isolation, case investigation, contact tracing, and quarantine at a U.S. university was insufficient to stop a large outbreak of the Omicron variant, despite substantial levels of vaccination among students.[541] Researchers have proposed an Omicron variant model to provide insights to coordinate NPIs and vaccination.[542]

Individual behaviors (e.g., face masks, social distancing) have been associated with reduced risk of COVID-19 infection.[543-544]

- 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.[545] The efficacy of masks depends largely on the type of mask, the way it is worn, and the overall fit.[546] A large analysis across 56 countries found that mask wearing reduced the mean transmission rate by 19%.[547] In a study of K-12 school districts across nine states, those with universal masking policies reported 3.6 times fewer secondary infections than those with optional masking policies.[548]
- A cross-sectional online survey found NPIs such as using sanitizer, quarantine, and isolation can decrease incidence and mortality of COVID-19.[549]
- 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.[550]

Particular focus should be placed on minimizing large gatherings where superspreading events are more likely.[551-552]

- Large retrospective studies showed that reductions in COVID-19 transmission were noted approximately 1 week after policies that reduced contact in large groups, such as workplace and school closures, cancelling large public events and restricting private gatherings, were put in place.[553] Re-opening restaurants in the U.S. was associated with significantly higher mortality 61-100 days after relaxation of restrictions in a largely unvaccinated population.[554]
- Reducing community prevalence, increasing ventilation,[555] and universal testing can reduce spread in schools.[556] As children are estimated to be less susceptible to SARS-CoV-2 infection, school closures are relatively ineffective NPIs,[557] though there is some evidence they were impactful at the national level.[558-559]

NPIs should be implemented in conjunction with vaccination [560-561]

- NPIs and vaccines work synergistically to reduce disease burden, and both are needed when vaccine coverage rates are low.[562-563] Early in the pandemic, NPIs were responsible for a 35% reduction in transmission, while vaccinations were responsible for a 38% reduction in transmission; however, when NPIs were combined with vaccination it resulted in a 53% reduction in transmission.[564]
- 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.[565]
- Researchers have proposed an Omicron variant model to provide insights to coordinate NPIs and vaccination, where NPIs become more important to control transmission as the vaccine efficacy is reduced due to the emergence of new variants.[542, 564, 566]

What do we need to know?

We need to understand the magnitude of measures necessary to limit spread of new 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 variants display differences in environmental stability.

- Variants Alpha, Beta, Delta, and Omicron subvariants BA.1 and BA.2 have higher environmental stability on human skin and plastic (13 and 141 hours, respectively) compared to wild-type, with greatest stability recorded in Omicron.[68]

The stability of SARS-CoV-2 in biological fluids of animals was measured.

- SARS-CoV-2 is stable for up to 1 day in the saliva of cats, sheep, and white-tailed deer regardless of the environmental conditions. It can remain infectious for up to 6 days in feces and 15 days in fecal suspension of white-tailed deer, whereas the virus is rather unstable in cat and sheep feces. The longest survival of SARS-CoV-2 was in the urine of cats, sheep, and white-tailed deer.[567]
- Side-by-side comparison of different SARS-CoV-2 strains showed that the Alpha, Delta, and Omicron variants were less stable than the wild-type strain in white-tailed deer fecal suspension.[567]

SARS-CoV-2 can survive on surfaces from hours to days and is stable in air for at least several hours, depending on UV light, temperature, and humidity.[568] However, transmission via contaminated surfaces is not considered to be common.

- 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).[569] Persistence is reduced with warmer temperatures (37°C), and enhanced at colder temperatures (4°C).[570]
- SARS-CoV-2 survives longer at 22°C on non-porous material surfaces, such as stainless steel, plastic, and glass (half-lives of 5-9 hours, up to 3 days, and as short as 4 min), than on porous material surfaces, such as paper and fabric (half-lives of 1-5 hours, up to 2 days, and as short as 13 min).[571]
- Infectious virus can be recovered from a surgical mask after 7 days (22°C, 65% RH)[572] and other PPE for at least 72 hours at 22°C.[573] However, a 2023 study showed that infectious virus could not be recovered from N95 or surgical masks after 1 hour (28°C, 80% RH), and no infectious virus is transferred to artificial skin from masks contaminated via aerosol.[574]

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 surfaces for at least 28 days (20°C; 50% RH); higher temperatures greatly reduce the environmental stability of SARS-CoV-2.[575] This value is longer than other stability estimates,[572, 575-576] potentially due to a fluid matrix with more protein to simulate human respiratory fluid and a higher inoculation dose.[575] 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.[577]
- 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),[576] retaining infectivity for up to 16 hours in appropriate conditions (23°C, 53% RH, no sunlight).[578]

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

- 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).[579] In dark conditions, the half-life of aerosolized SARS-CoV-2 is approximately 86 minutes in simulated saliva.[579] Humidity alone had no significant impact on aerosolized virus survival.[579]

There is currently no evidence that SARS-CoV-2 is transmitted to people through food or food packaging.[580-581]

- SARS-CoV-2 can persist for at least 2 weeks at refrigerated temperatures (4°C),[572, 582] and the spike G614 variant remains infectious at 4°C for over 30 days.[583] SARS-CoV-2 maintains infectivity for at least 30 days when inoculated on frozen foods and stored at -20°C.[583] Infectious SARS-CoV-2 has been found on frozen food packaging, but has not been linked to actual infections.[584] Several outbreaks have a hypothesized food origin.[585]
- Studies have shown that cold-chain transportation and salt were risk factors that could prolong SARS-CoV-2 viability due to the low freezing point of seawater, which slows the rate of freezing and thawing of the virus and effectively maintains the structural integrity. This suggests that when transporting seafood and other goods that may contain seawater, the outer packaging of the goods should be properly washed in advance to reduce the presence of salt ions, which may reduce the risk of virus transmission from food sources.[586-587]

SARS-CoV-2-contaminated wastewater may cause infections,[588-589] particularly in areas of poor waste management, and via landfill leachate, in which the virus may be transmitted to humans from pollution.[590]

- 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.[591] 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.[592-593]

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.

- Are certain SARS-CoV-2 variants more or less stable on surfaces or in aerosols?
- What is the transmission process from surfaces that results in infection?

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

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.

- While a 4-5 log (99.99-99.999%) reduction in viral titer is often used as a metric of effective decontamination,[594-595] achieving this level of reduction is dependent on methodological issues like the initial viral stock concentration.
- A systematic review identified sunlight, UV light, ethanol, hydrogen peroxide, and hypochlorite as methods to reduce surface contamination.[568] Selected studies found positive results favoring photo-irradiation as a decontamination method, but the best dosimetry, safety, and efficiency of light as a tool for decontamination are variable and related to initial viral load, radiant exposure, surface characteristic, relative humidity, light equipment model, distance from irradiation, and wavelength.[596]
- Vaporized hydrogen peroxide (VHP) can inactivate SARS-CoV-2 on non-porous surfaces within 5 min.[597]
- Chlorine bleach (1%, 2%), 70% ethanol, and 0.05% chlorhexidine are effective against live virus in laboratory tests.[572] Chlorous acid ($HClO_2$) can exert sufficient disinfection effects against SARS-CoV-2 D614G, Delta and Omicron variants even in the presence of proteins.[598]
- Twice-daily cleaning with sodium dichloroisocyanurate decontaminated surfaces in COVID-19 patient hospital rooms.[599] Regular disinfection of hospital rooms (with benzalkonium wipes) can reduce the presence of SARS-CoV-2 on surfaces.[600]
- Heat, soap, and ethanol were also able to decontaminate SARS-CoV-2 variants (Alpha and Beta) on various surfaces.[601] Increased resistance to ethanol was demonstrated by Alpha, Beta, Delta, and Omicron strains; however, all strains were completely inactivated by 35% ethanol after 15 seconds.[68]
- Steam heat can provide high levels of decontamination (>3 log reduction) for transit-related materials contaminated with SARS-CoV-2 using a commercially available steam generator with a manageable exposure time of 2-5 seconds.[602]
- Mass public transit systems treated with Natural Protective Shield 360°, a self-decontaminating coating, showed 100% reduction of SARS-CoV-2 for up to 20 days post-application.[603]
- Concentrations of 10-20 mg/mL ZnO-NP-45 (Zinc Oxide Nanoparticles) can inactivate Delta and Omicron SARS-CoV-2 variants by a factor of more than 10^6.[604]
- The U.S. Environmental Protection Agency has released a list of SARS-CoV-2 disinfectants that are considered effective against all strains and variants of SARS-CoV-2.[605]

Several methods exist for decontaminating N95 respirators[606] and other PPE.

- Researchers have identified three methods capable of decontaminating N95 respirators while maintaining physical integrity: UV radiation, heating to 70°C, and VHP.[607-608] Dry heat and UV decontamination can also be used under certain conditions.[609] Ethanol (70%) was associated with loss of physical integrity.[607]
- Germicidal UVC decontamination methods for N95s was successful when both sides were irradiated yielding a 3.5 log reduction and can be scaled for large-scale decontamination efforts.[610]
- Several decontamination methods, including VHP, UVC,[611] moist heat,[612] and dry heat[613] are capable of decontaminating N95 respirators for 2-15 cycles without loss of fit or filtration efficiency. Overall wear time and number of uses are the primary contributors to functional degradation.[614]
- Shape and structure of specific N95 models impact the efficacy of UVC decontamination methods.[615]
- A thermal inactivation model for SARS-CoV-2 provides estimates of infectivity reduction based on time and temperature.[616]
- Medical mask material inoculated with SARS-CoV-2 was treated with light-activated methylene blue (MB) then exposed to white light, which inactivated SARS-CoV-2 in 5 minutes.[617] Pretreatment of mask material with MB successfully disinfected masks following virus inoculation and subsequent light exposure.[617]

Air filtration and purification systems may reduce concentration of airborne SARS-CoV-2.

- High efficiency particulate air (HEPA) filtration systems have consistently outperformed other methods of air purification.[618]
- UV light combined with a fibrous filter was ~100% efficient at removing aerosolized 0.1-2.5 µm particles of SARS-CoV-2.[619] Various materials like ozone, hydrogen peroxide, alcohol, and titanium dioxide were described in these studies to disinfect places contaminated by SARS-CoV-2.[620]
- Air purification via photoelectrochemical oxidation utilizes reactive oxygen species to inactivate viruses, bacteria, and molds. Although untested with SARS-CoV-2, Molekule air purification technology is approximately 99% effective at inactivating M2 bacteriophage virus, which is smaller than SARS-CoV-2.[621]

What do we need to know?

We need additional SARS-CoV-2 decontamination studies, particularly regarding indoor aerosol transmission.

- Does contamination with human fluids/waste alter disinfectant efficacy profiles?
- How do different testing methods and standards affect decontamination efficacy estimates?
- Are specific decontamination methods needed for different SARS-CoV-2 variants?

Personal Protective Equipment (PPE) – What PPE is effective, and who should be using it?

What do we know?

Recommended PPE for healthcare workers caring for patients with COVID-19 includes respirator (N95 or higher), face shield or goggles, gown, and clean gloves, combined with regular hand hygiene.[622]

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

- Contacts with healthcare workers tend to transmit COVID-19 more often than other casual contacts.[623] Risk of COVID-19 infection was higher when healthcare workers were exposed to an infected coworker than when exposed to patients.[624]
- 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.[625]
- Aerosolized SARS-CoV-2 pulled through N95 and surgical masks had no detectible infectivity after 1 hour. Artificial skin contact transferred viral RNA but not infectious virus.[574]
- Healthcare worker self-infection during doffing of PPE positively correlated with length of shift and number of positive COVID-19 patients in the ward.[626]
- Respirators (National Institute for Occupational Safety and Health [NIOSH]-certified N95 or higher) are recommended for those working with potential aerosols,[627] though procedure type is not the only factor influencing risk of aerosol generation in hospitals.[628] Additional protection (powered air purifying respirator [PAPR] with hood), should be considered for high-risk procedures.[629]
- In a meta-analysis, N95 respirators were found to be beneficial for reducing the occurrence of SARS-CoV-2 infection in a health care setting, while use of medical or surgical masks in both health care and community settings also reduced risk of infection but to a lesser degree.[630] N95 respirators were associated with up to 80% reductions in SARS-CoV-1 infections.[630-631]
- 85% of tested N95 respirators passed fit tests after at least five cycles of standard donning/doffing and dry heat decontamination,[632] though extended use has previously been associated with fit failures.[633]
- 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.[634]

A recent meta-analysis compared protection from COVID-19 infection across N95, surgical, and non-medical masks worn with high compliance versus low compliance/no mask. Overall increased protection was shown for an uninfected individual wearing any type of mask with high compliance, with greatest protection from N95 masks, then surgical, then non-medical masks.[630]

- As of September 27, 2022, the CDC recommends that individuals with symptoms, a positive test, caring for someone who has COVID-19, or recent exposure should wear a mask, as well as individuals using indoor public transportation.[635-638]
- The CDC maintains a list of NIOSH-tested facemasks,[639] and also maintains a list of single-use and reusable masks that meet updated ASTM F3502-21 standards.[640]
- 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).[641]
- Surgical face masks, respirators, and homemade face masks may prevent transmission of coronaviruses from infectious individuals to other individuals.[642-644] Surgical masks were associated with a reduction of approximately 48% in the amount of seasonal coronavirus expressed as fine aerosol particles (<5 µm) and 77% in coarse aerosols (>5 µm), though the majority of viral RNA was exhaled in fine aerosol particles.[644-645] 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.[646]

Mask fit is another critical component of effectiveness,[647] in addition to filter efficiency.

- Fit modifications are recommended if warranted, such as knotting ear loops, tucking in sides of mask, and double-masking.[648] Wearing a plastic brace around the sides of the mask blocked ≥95% of aerosols produced by coughing compared to ≥56% in unmodified masks.[648]
- The CDC recommends masks without exhalation vents or valves,[649-650] as these can allow particles to pass through unfiltered.[651]
- A 4-mm hole in an N-95 mask demonstrated up to a 10% increase in 1-4 mm particles passing into the mask.[652]
- When properly fitted, surgical masks provide infection control at the source, whereas N95s and PAPRs provide respiratory protection.[652]

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?[653]
- What is the risk of COVID-19 to those collecting nasopharyngeal swabs?[654]
- Should decontamination methods be optimized for individual makes/models of PPE?

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

What do we know?

While ancestral SARS-CoV-2 accumulates mutations at a similar rate as other coronaviruses, variants possess genomes that accrue at approximately two mutations per month.

- Molecular clock models indicate that variant emergence has been driven by a substitution rate increase of approximately 4-fold the background phylogenetic rate estimate.[655] A novel near-neutral balanced selection theory has been proposed to explain the genomic substitution rate of SARS-CoV-2 which leads to a molecular clock feature.[656]
- The estimated mutation rate for SARS-CoV-2 is 6 x 10^{-4} nucleotides per genome, per year.[657] Another group reviewed literature and found the rate of evolution to be from 10^{-3} to 10^{-4} substitutions per site per year but varied among variants.[658] Yet another group reviewed literature and found the mutation rate to be from 1×10^{-6} to 2×10^{-6} mutations per nucleotide per replication cycle, but was estimated to acquire about 2 evolutionary changes per month or 2×10^{-6} per site per day.[177]
- More than 6 million SARS-CoV-2 genomes were analyzed to identify mutations associated with virus transmissibility, which include mutations in spike, nucleocapsid, and nonstructural proteins.[659]

While several named variants have emerged since the beginning of the SARS-CoV-2 pandemic, discussion of pre-Omicron variants are no longer included in this section.

- **Omicron (B.1.1.529)** – First detected on November 26, 2021 in South Africa and Botswana, the Omicron variant includes 21 unique mutations in the spike gene with 14 shared with other prior variants.[660] The location of many of these mutations may play a role in ACE2 binding and antibody recognition.[660] The risk of severe outcomes is greatly reduced in patients infected with Omicron versus Delta strains.[661, 662] In March 2023, the WHO noted that over 98% of available sequences since February 2022 were Omicron, which prompted changing the variant tracking system to track Omicron variants independently.[663] It is estimated that ~99% of sequenced strains in the U.S. since March 2023 have been Omicron variants.[3, 664]
- **Omicron BA.4** and **BA.5 –** Omicron variants first detected in April 2022; these two sublineages outcompeted BA.2 and BA.2.12.1.[665] BA.5 has shown a transmission advantage over prior Omicron variants, lower neutralizing antibody titers compared to BA.1, and reduced neutralization activity to sotrovimab and casirivimab/imdevimab.[666] Further analysis of subvariants of BA.4/5 suggest they continue to evolve to escape neutralizing antibodies.[667]
- **XBB –** Omicron BA.2.10.1 and BA.2.75 recombinant, XBB, is highly immune evasive.[73-74, 374] XBB.1.5 has a mutation that increases receptor binding affinity and infectivity.[668] XBB.1.5 and XBB.1.9 predominated worldwide in February 2023. XBB.1.16 emerged from XBB.1.5.[664] XBB.1.16 has a reproductive number 1.13 fold higher than XBB.1.5.[664]
- **Eris (EG.5)** – Omicron variant lineage that includes sublineages EG.5.1, EG.5.1.1, and EG.5.2. First reported by the WHO in February 2023 and listed as a variant under monitoring (VUM) in July 2023 and a variant of interest (VOI) in August 2023. Descendent of XBB.1.9.2. Has the same spike amino acid profile as XBB.1.5, but EG.5 has a F456L mutation and EG.5.1 has another mutation of Q52H.[669-670]
- **Fornax (FL.1.5.1)** – Omicron variant lineage that was one of the most common variants next to Eris in the U.S. in the late summer and fall of 2023. However, only ~7% of sequences collected in the U.S. in November 2023 were found to be this lineage.[3]
- **JN.1** – As of 1/22/2024, Omicron variant lineage JN.1 has become most prevalent and is predicted to make up 85.7% of infections.[3] The S:L455S spike mutation in JN.1 variants has been associated with enhanced immune evasion when compared to BA.2.86 and HV.1 variants.[671]
- Currently, Omicron variants XBB.1.5, XBB.1.16, EG.5, BA.2.86, and JN.1 are listed as VOIs and DV.7, XBB, XBB.1.9.1, XBB.1.9.2, and XBB.2.3 are listed as VUMs by the WHO.[672]

What do we need to know?

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

- What are the mechanisms driving the resistance of variants to neutralization by the immune system?
- How do variants affect the likelihood of reinfection or coinfection?
- How prevalent are coinfections with multiple strains, and what is their clinical progression?[673]

Forecasting – What forecasting models and methods exist?

What do we know?

Digital dashboards summarizing the status of the pandemic in the U.S. and counties are available. Ensemble forecasts generally show better predictive accuracy than individual forecast models.[674]

- COVID Act Now: State and county-level dashboard showing trends in three metrics related to COVID-19 risk.[675]
- Maps and dashboards depicting COVID-19 infection rates do not necessarily increase likelihood of adhering to NPIs; additional information is needed to influence perceptions of individual risk.[676]
- The CDC National SARS-CoV-2 Genomic Surveillance system collects sequence data to rapidly identify variants and make short term predictions on variant prevalence using Nowcast.[3]
- Several groups have evaluated wastewater to determine the relationships between SARS-CoV-2 in wastewater and COVID-19 clinical cases and hospitalizations.[677-680] Wastewater may be useful in forecasting local SARS-CoV-2 prevalence[681-682] and early identification of variant spread.[683-684]
- Researchers use a rolling window analysis incorporating uncertainty in the generation time distribution to estimate time-varying transmission rates in U.S. states (the effective reproduction number, R_{eff} or R_t).[685]
- A two-parameter Weibull-distribution applied to case data and swab-testing rates can be used to predict infection rates.[686]
- CA Notify: California's Google Apple Exposure Notification system data was used in short-term forecasting models of local caseloads.[687]
- Deep learning models, such as Long Short-Term Memory (LSTM) and Gated Recurrent Unit, have been used to predict case progression with varying degrees of success due to the investigated region, social diversity, and population size.[688-689]

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

- U.S. COVID-19 cases could be estimated under different scenarios of vaccine efficacy and need for NPIs such as face masks and physical distancing.[690]
- The Johns Hopkins University Infectious Disease Dynamics Lab used modeling to rapidly assess the impact of different interventions.[691]
- Covasim: Agent-based model for testing effects of intervention measures, also available as Python library.[692]
- Accounting for superspreading in forecast models can increase model accuracy and precision,[693] while incorporating memory effects (e.g., the duration of individual infectiousness) can also increase forecast model fit to data.[694]
- An agent-based and extended SEIR model was developed to forecast future waves in Japan that considered vaccination, virus mutation, government policies, and PCR test results.[695]
- A Markov-switching model using global surveillance data was proposed to determine necessary policy changes and predict variants.[696]
- An automatic regressive integrated moving average model with mask wearing and vaccination variables included was used to predict case growth rates.[697]
- A group used a Bayesian latent variable model to predict short term trends in cases and hospitalizations regionally in Wisconsin.[698] A two-component model was developed to forecast healthcare demands using a mathematical epidemiology model that fed into a clinical pathway model.[699]
- SARS-CoV-2 co-infection or interaction with another pathogen may be important for future risk modeling.[700] New modeling approaches may be needed to forecast COVID-19 re-emergence after elimination or during periods of low incidence.[701]

There are efforts aimed at forecasting important SARS-CoV-2 mutations to predict emerging variants and their characteristics.

- Characteristics of SARS-CoV-2 mutations (e.g., prevalence, receptor binding ability, relationship to immune escape) may enable forecasting which mutations are likely to show up in future variants months before their emergence.[702-704]
- Improved prediction models correctly projected Omicron BA.4 and BA.5 to become predominant variants.[705]
- The CoVigator tool was developed to collect genomic data, process/denotate variants, and highlight findings as a way to track variant emergence.[706]
- Baseline genomic surveillance programs have been implemented to provide early detection of variants. Belgium added SARS-CoV-2 to their severe acute respiratory infections sampling and detected Omicron (BA.1, BA.2, BA.4 and BA.5) and Delta (B.1.617.2) variants 2 weeks prior to the start of epidemic growth.[707]

What do we need to know?

- How will different vaccine uptake rates, spillover, and movement between countries affect local resurgence?
- To what extent does waning immunity, changes in human behavior, and seasonal changes affect COVID-19 transmission rates with Omicron variants?
- How accurate are/were the model predictions? Which factors in the model systems should be used during future waves/pandemics?

Table 1. Definitions of Commonly Used Acronyms

Acronym/Term	Definition	Description
ACE2	Angiotensin-Converting Enzyme 2	Acts as a receptor for SARS-CoV-1 and SARS-CoV-2, allowing entry into human cells.
Airborne transmission	Aerosolization of infectious particles	Aerosolized particles can spread for long distances (e.g., between hospital rooms via heating, ventilation, and air conditioning [HVAC systems]). Particles generally <5 µm.
ARDS	Acute Respiratory Distress Syndrome	Leakage of fluid into the lungs that inhibits respiration and leads to death.
Attack rate	Proportion of "at-risk" individuals who develop infection	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.
CDC	Centers for Disease Control and Prevention	N/A
CFR	Case Fatality Rate	Number of deaths divided by confirmed patients.
CoV	Coronavirus	Virus typified by crown-like structures when viewed under electron microscope.
COVID-19	Coronavirus Disease 19	Official name for the disease caused by the SARS-CoV-2 virus.
DHS S&T	U.S. Department of Homeland Security's Science and Technology Directorate	N/A
DNA	Deoxyribonucleic Acid	Molecule that encodes genetic information.
ELISA	Enzyme-Linked Immunosorbent Assay	Method for serological testing of antibodies.
EPA	U.S. Environmental Protection Agency	N/A
EUA	Emergency Use Authorization	N/A
FDA	U.S. Food and Drug Administration	N/A
Fomite	Inanimate vector of disease	Surfaces such as hospital beds, doorknobs, healthcare worker gowns, and faucets.
HEPA	High Efficiency Particulate Air	An efficiency standard for air filters.
HVAC	Heating, Ventilation, and Air Conditioning	N/A
ICU	Intensive Care Unit	N/A
ID_{50}	Median Infectious Dose	The dose necessary to infect 50% of the target population. Generally, assumes typical, healthy, adult individuals.
Ig	Immunoglobulin	Proteins of the immune system that can act as antibodies.
IL-6	Interleukin-6	A cell signaling protein that can act ither as pro- or anti-inflammatory.
Incubation period	Time between infection and symptom onset	Time between infection and onset of symptoms typically establishes guidelines for isolating patients before transmission is possible.
Infectious period	Length of time an individual can transmit infection to others	Reducing the infectious period is a key method of reducing overall transmission; hospitalization, isolation, and quarantine are all effective methods.
Intranasal	Agent deposited into external nares of subject	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.

Acronym/Term	Definition	Description
LD_{50}	Median Lethal Dose	The dose necessary to be lethal in 50% of the target population. Generally, assumes typical, healthy, adult individuals.
MERS	Middle East Respiratory Syndrome	Coronavirus with over 2,000 cases in regional outbreak since 2012.
MIS	Multisystem Inflammatory Syndrome	A rare but serious condition that is associated with inflammation of several organ systems due to SARS-CoV-2 infection.
MQL	Master Question List	N/A
mRNA	Messenger RNA	Molecule that encodes protein sequences.
Mutation	Change in SARS-CoV-2 genome relative to early pandemic or reference strain	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.
NHP	Non-Human Primate	N/A
NIH	National Institutes of Health	N/A
NIOSH	National Institute for Occupational Safety and Health	N/A
Non-variant SARS-CoV-2	"Wild-type" or comparator strain or variant in any comparison of novel or emerging variants	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."
NPI	Non-Pharmaceutical Intervention	Public health control measures designed to reduce transmission, such as social distancing, movement restrictions, and face mask requirements.
PAPR	Powered Air Purifying Respirator	Devices that are battery-powered and pass air through filters to provide clear air to the user.
PASC	Post-Acute Sequelae of SARS-CoV-2 Infection	Term used to encompass symptoms experienced for weeks to months after a primary infection with SARS-CoV-2.
PCR	Polymerase Chain Reaction	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.
PFU	Plaque Forming Unit	Measurement of the number of infectious virus particles as determined by plaque forming assay. A measurement of sample infectivity.
PPE	Personal Protective Equipment	Gowns, masks, gloves, and any other measures used to prevent spread between individuals.
R_0	Basic reproduction number	A measure of transmissibility. Specifically, the average number of new infections caused by a typical infectious individual in a wholly susceptible population.
RBD	Receptor Binding Domain	Protein domain used by virus to gain entry into host cells by recognizing specific host cell receptors (e.g., ACE2).
RNA	Ribonucleic Acid	Genetic material for some viruses. Also, the intermediate between DNA and protein.
SARS	Severe Acute Respiratory Syndrome	Coronavirus with over 8,000 cases in global 2002-2003 outbreak.

Acronym/Term	Definition	Description
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2	Official name for the virus previously known as 2019-nCoV.
SEIR	Susceptible, Exposed, Infected, and Resistant	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.
Serial interval	Length of time between symptom onset of successive cases in a transmission chain	The serial interval can be used to estimate R_0, and is useful for estimating the rate of outbreak spread.
$TCID_{50}$	Median Tissue Culture Infectious Dose	The number of infectious units that will infect 50% of tissue culture monolayers. A measurement of sample infectivity.
Transgenic	Genetically modified	In this case, animal models modified to be more susceptible to MERS and/or SARS by adding proteins or receptors necessary for infection.
UK	United Kingdom	N/A
Variant	SARS-CoV-2 lineage with shared collection of mutations	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.
Vertical transmission	Transmission from mother to fetus	Generally understood as intrauterine transmission via blood or placenta; not the same as transmission during or after birth.
VHP	Vaporized Hydrogen Peroxide	An antimicrobial vapor used to decontaminate enclosed areas.
WHO	World Health Organization	N/A
Wild-type	Original SARS-CoV-2 strains	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.”

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