COVID-19: Epidemiology, virology, and prevention

Author:Kenneth McIntosh, MDSection Editor:Martin S Hirsch, MDDeputy Editor:Allyson Bloom, MD

INTRODUCTION

Coronaviruses are important human and animal pathogens. At the end of 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei Province of China. It rapidly spread, resulting in an epidemic throughout China, followed by a global pandemic. In February 2020, the World Health Organization designated the disease COVID-19, which stands for coronavirus disease 2019 [1]. The virus that causes COVID-19 is designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); previously, it was referred to as 2019-nCoV.

Understanding of COVID-19 is evolving. Interim guidance has been issued by the World Health Organization and by the United States Centers for Disease Control and Prevention [2,3]. Links to these and other related society guidelines are found elsewhere. (See 'Society guideline links' below.)

This topic will discuss the virology, epidemiology, and prevention of COVID-19. The clinical features and diagnosis of COVID-19 are discussed in detail elsewhere. (See "COVID-19: Clinical features".)

The management of COVID-19 is also discussed in detail elsewhere:

VIROLOGY

Coronavirus virology — Coronaviruses are enveloped positive-stranded RNA viruses. Full-genome sequencing and phylogenic analysis indicated that the coronavirus that causes COVID-19 is a betacoronavirus in the same subgenus as the severe acute respiratory syndrome (SARS) virus (as well as several bat coronaviruses), but in a different clade. The Coronavirus Study Group of the International Committee on Taxonomy of Viruses has proposed that this virus be designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [4]. The Middle East respiratory syndrome (MERS) virus, another betacoronavirus, appears more distantly related [5,6]. The closest RNA sequence similarity is to two bat coronaviruses, and it appears likely that bats are the primary source; whether COVID-19 virus is transmitted directly from bats or through some other mechanism (eg, through an intermediate host) is unknown [7]. (See "Coronaviruses", section on 'Virology'.)

The host receptor for SARS-CoV-2 cell entry is the same as for SARS-CoV, the angiotensin-converting enzyme 2 (ACE2) [8]. SARS-CoV-2 binds to ACE2 through the receptor-binding domain of its spike protein (figure 1). The cellular protease TMPRSS2

also appears important for SARS-CoV-2 cell entry [9].

Variants of concern — Like other viruses, SARS-CoV-2 evolves over time. Most mutations in the SARS-CoV-2 genome have no impact on viral function. Certain variants have garnered widespread attention because of their rapid emergence within populations and evidence for transmission or clinical implications; these are considered variants of concern (table 1). Each variant has several designations based on the nomenclature used by distinct phylogenetic classification systems; the World Health Organization (WHO) has also designated labels for notable variants based on the Greek alphabet [10].

Early in the pandemic, a study that monitored amino acid changes in the spike protein of SARS-CoV-2 included in a large sequence database identified a D614G (glycine for aspartic acid) substitution that became the dominant polymorphism globally over time [11]. In animal and in vitro studies, viruses bearing the G614 polymorphism demonstrate higher levels of infectious virus in the respiratory tract, enhanced binding to ACE-2, and increased replication and transmissibility compared with the D614 polymorphism [12,13]. The G614 variant does not appear to be associated with a higher risk of hospitalization [11] or to impact anti-spike antibody binding [14]. It is now present in most circulating SARS-CoV-2 lineages, including the variants of concern listed below.

In the United States, the proportions of circulating viruses that are variants of concern are detailed on the CDC website.

Alpha (B.1.1.7 lineage) — This variant, also known as 20I/501Y.V1, was first identified in the United Kingdom in late 2020 and was temporally associated with an increase in regional infections (table 1) [15-17]. This variant contains more than a dozen mutations compared with other circulating strains, with several within the spike protein. It has subsequently been identified in other countries, including the United States [18].

Several studies had indicated that Alpha is approximately 50 to 75 percent more transmissible than previously circulating strains and was associated with higher secondary attack rates (eg, 13 versus 10 percent) [15,19-22]. The underlying mechanism for the increased transmissibility is uncertain. Some studies have suggested that Alpha is associated with a higher median viral RNA level in respiratory secretions compared with wild-type strains, and some have also suggested that viral RNA may be detectable in respiratory specimens for longer [23-25]. Whether these findings are associated with increased transmission and which mutations contribute are under investigation. One of the mutations in the Alpha variant, N501Y, is in the receptor-binding domain of the spike protein and increased SARS-CoV-2 infectivity in a mouse model [26]. Another spike protein mutation in the variant, P618H, abuts the furin-cleavage site, which is thought to have a role in SARS-CoV-2 cell entry.

Some [27,28], but not all, studies [24] suggest that the Alpha variant may also be associated with greater disease severity. Thus far, there is no evidence that the Alpha variant is associated with clinically significant immune escape. Several studies indicate

that serum from COVID-19 vaccine recipients maintains neutralizing activity against the Alpha variant, and some vaccines maintain efficacy against the variant [29-32]. These data are discussed elsewhere. (See "COVID-19: Vaccines to prevent SARS-CoV-2 infection", section on 'Immunogenicity, efficacy, and safety of select vaccines'.)

However, ongoing genomic analysis of the Alpha variants circulating in the United Kingdom has identified another mutation in the spike protein, E484K, in some sequences [22]. This mutation is present in the Beta (B.1351) and Gamma (P.1) variants, and some studies have suggested that it is associated with immune escape, as discussed below.

Another mutation in this variant is a deletion in the spike protein at amino acids 69-70 (del 69-70). Some SARS-CoV-2 molecular tests are unable to detect the S gene (which encodes the spike protein) target when this deletion is present. These tests would still be able to detect viral RNA since they employ more than one gene target and thus would not result in false-negative results. Nevertheless, S gene target failure has been used as a marker to detect the Alpha variant, with the caveat that del 69-70 has also been reported in other variants [31].

Delta (B.1.617.2 lineage) — This lineage, also known as 20A/S:478K, was first identified in India in December 2020 and has become the most prevalent variant there and in several other countries, including the United States and United Kingdom (table 1).

Data suggest that the Delta variant is highly transmissible, more so than Alpha. In reports from the United Kingdom, the proportion of SARS-CoV-2 infections caused by Delta rose as that caused by Alpha declined, and the secondary household infection rate associated with Delta infection was 13.6 percent compared with 9.0 percent for Alpha [33]. In another report of a small outbreak in the United States, the household attack rate associated with the Delta variant was 53 percent [34]. An unpublished study of an outbreak in China suggested that initial respiratory tract viral RNA levels are about 1000 times higher with Delta than were observed with ancestral virus circulating during the first phase of the pandemic.

Reports have also suggested that infection with Delta is associated with a higher risk of hospitalization than Alpha [33,35].

Several studies suggest that vaccine effectiveness is slightly attenuated against symptomatic infection with Delta but remains high against severe disease and hospitalization. These data are discussed elsewhere. (See "COVID-19: Vaccines to prevent SARS-CoV-2 infection", section on 'Immunogenicity, efficacy, and safety of select vaccines'.)

Others

●**Beta (B.1.351 lineage)** – This variant, also known as 20H/501Y.V2, was identified in

South Africa in late 2020 (table 1) [36]. It is phylogenetically distinct from B.1.1.7 but shares several mutations, including the spike protein mutation N501Y. Surveillance data in South Africa indicate that this variant rapidly became the dominant strain, suggesting that it also has the potential for increased transmissibility. It has subsequently been identified in other countries, including the United States.

This lineage contains another mutation in the spike protein, E484K, which has the potential to impact immunity from prior infection or vaccination. In a study that assessed the impact of spike protein mutations on neutralization by antibodies in convalescent plasma, E484K on average reduced neutralization to the greatest extent compared with other mutations (with some plasma samples, the reduction was >10-fold), although the impact varied between individual samples and over time among samples from the same individual [37]. In another report, introduction of the B.1.351 lineage spike protein into a viral construct attenuated neutralizing activity of convalescent plasma, with 48 percent of the plasma samples losing neutralizing activity; most plasma specimens still maintained non-neutralizing antibody binding to the Beta spike protein [38]. Plasma from recipients of the mRNA COVID-19 vaccines appears to maintain neutralizing activity against the Beta variant, but at lower titers than against wild-type virus [30,39]. The clinical implications of these reductions in neutralizing activity are uncertain given that the precise immunologic correlates of immunity have not been elucidated, but it seems likely that mRNA COVID-19 vaccine-induced immunity will still be protective against the Beta variant. Preliminary reports of trials evaluating other vaccine candidates suggest that they retain efficacy in South Africa, although the magnitude of protection may be lower there compared with locations where Beta is not prevalent [40,41]. These data are discussed elsewhere. (See "COVID-19: Vaccines to prevent SARS-CoV-2 infection", section on 'Immunogenicity, efficacy, and safety of select vaccines'.)

●**Gamma (P.1 lineage)** – This variant, also known as 20J/501Y.V3, was first identified in Japan in four travelers from Brazil and was later reported to account for 42 percent of 31 sequenced specimens in the Amazonas state of Brazil in December 2020 (table 1) [42]. It has subsequently been identified in other countries, including the United States. It has several mutations, including three in the spike protein receptor-binding domain, N501Y, E484K, and K417T, which raise concern about the potential for increased transmissibility and an impact on immunity [43].

●**Epsilon (B.1.427 and B.1.429 lineages)** – These related variants are also collectively referred to as 20C/S452R or CAL.20C (table 1). In October 2020, only four global cases were identified, all in Southern California; by January 2021, the variant accounted for 35 percent of viral samples sequenced in California and had been identified in other countries [44]. The variants contain several spike protein mutations, including L452R, which is associated with increased cell entry and reduced susceptibility to neutralization by convalescent and vaccine recipient plasma in vitro [45]. However, some evidence suggests that the reduced susceptibility to neutralization of B.1.429 is modest compared with that of Beta [46]. The variants are also associated with a twofold higher viral RNA level on nasal swabs compared with wild-type virus.

EPIDEMIOLOGY

Geographic distribution and case counts — Globally, over 200 million confirmed cases of COVID-19 have been reported. Updated case counts in English can be found on the World Health Organization and European Centre for Disease Prevention and Control websites. An interactive map highlighting confirmed cases throughout the world can be found here.

Since the first reports of cases from Wuhan, a city in the Hubei Province of China, at the end of 2019, cases have been reported in all continents.

The reported case counts underestimate the overall burden of COVID-19, as only a fraction of acute infections are diagnosed and reported. Seroprevalence surveys in the United States and Europe have suggested that after accounting for potential false positives or negatives, the rate of prior exposure to SARS-CoV-2, as reflected by seropositivity, exceeds the incidence of reported cases by approximately 10-fold or more [47-49].

Transmission — Person-to-person spread is the main mode of SARS-CoV-2 transmission.

Person-to-person

Route of person-to-person transmission — Direct person-to-person respiratory transmission is the primary means of transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [50]. It is thought to occur mainly through close-range contact (ie, within approximately six feet or two meters) via respiratory particles; virus released in the respiratory secretions when a person with infection coughs, sneezes, or talks can infect another person if it is inhaled or makes direct contact with the mucous membranes. Infection might also occur if a person's hands are contaminated by these secretions or by touching contaminated surfaces and then they touch their eyes, nose, or mouth, although contaminated surfaces are not thought to be a major route of transmission.

SARS-CoV-2 can also be transmitted longer distances through the airborne route (through inhalation of particles that remain in the air over time and distance), but the extent to which this mode of transmission has contributed to the pandemic is uncertain [51-54]. Scattered reports of SARS-CoV-2 outbreaks (eg, in a restaurant, on a bus) have highlighted the potential for longer distance airborne transmission in enclosed, poorly ventilated spaces [55-57]. Experimental studies have also supported the feasibility of airborne transmission. As examples, studies using specialized imaging to visualize respiratory exhalations have suggested that respiratory droplets may get aerosolized or carried in a gas cloud and have horizontal trajectories beyond six feet (two meters) with speaking, coughing, or sneezing [58-60]. Other studies have identified viral RNA in ventilation systems and in air samples of hospital rooms of patients with

COVID-19, including patients with mild infection [61-65]; attempts to find viable virus in air and surface specimens in health care settings have only rarely been successful [64-68]. Nevertheless, the overall transmission and secondary attack rates of SARS-CoV-2 suggest that long-range airborne transmission is not a primary mode [53,54]. Furthermore, in a few reports of health care workers exposed to patients with undiagnosed infection while using only contact and droplet precautions, no secondary infections were identified despite the absence of airborne precautions [69,70]. Reflecting the current uncertainty regarding the relative contribution of different transmission mechanisms, recommendations on airborne precautions in the health care setting vary by location; airborne precautions are universally recommended when aerosol-generating procedures are performed. This is discussed in detail elsewhere. (See "COVID-19: Infection control for persons with SARS-CoV-2 infection", section on 'Aerosol-generating procedures/treatments'.)

SARS-CoV-2 has been detected in non-respiratory specimens, including stool, blood, ocular secretions, and semen, but the role of these sites in transmission is uncertain [71-78]. In particular, several reports have described detection of SARS-CoV-2 RNA from stool specimens, even after viral RNA could no longer be detected from upper respiratory specimens [74,75], and replicative virus has been cultured from stool in rare cases [72,79]. Scattered reports of clusters in a residential building and in a dense urban community with poor sanitation have suggested the possibility of transmission through aerosolization of virus from sewage drainage [80,81]. However, according to a joint WHO-China report, transmission through the fecal-oral route did not appear to be a significant factor in the spread of infection [82].

Detection of SARS-CoV-2 RNA in blood has also been reported in some but not all studies that have tested for it [71,72,75,83,84]. However, the likelihood of bloodborne transmission (eg, through blood products or needlesticks) appears low; respiratory viruses are generally not transmitted through the bloodborne route, and transfusion-transmitted infection has not been reported for SARS-CoV-2 or for the related Middle East respiratory syndrome coronavirus (MERS-CoV) or SARS-CoV [85]. (See "Blood donor screening: Laboratory testing", section on 'Emerging infectious disease agents'.)

There is also no evidence that SARS-CoV-2 can be transmitted through contact with non-mucous membrane sites (eg, abraded skin).

The risk of vertical transmission of SARS-CoV-2 is discussed elsewhere. (See "COVID-19: Pregnancy issues and antenatal care", section on 'Frequency of congenital infection'.)

Viral shedding and period of infectiousness — The precise interval during which an individual with SARS-CoV-2 infection can transmit infection to others is uncertain. The potential to transmit SARS-CoV-2 begins prior to the development of symptoms and is highest early in the course of illness; the risk of transmission decreases thereafter. Transmission after 7 to 10 days of illness is unlikely, particularly for otherwise immunocompetent patients with nonsevere infection.

●Period of greatest infectiousness – Infected individuals are more likely to be contagious in the earlier stages of illness when viral RNA levels from upper respiratory specimens are the highest [86-91]. One modeling study, in which the mean serial interval between the onset of symptoms among 77 transmission pairs in China was 5.8 days, estimated that infectiousness peaked between two days before and one day after symptom onset and declined within seven days [89]. In another study that evaluated over 2500 close contacts of 100 patients with COVID-19 in Taiwan, all of the 22 secondary cases had their first exposure to the index case within six days of symptom onset; there were no infections documented in the 850 contacts whose exposure was after this interval [92].

●Prolonged viral RNA detection does not indicate prolonged infectiousness – The duration of viral RNA shedding is variable and may increase with age and the severity of illness [75,88,93-99]. In a review of 28 studies, the pooled median duration of viral RNA detection in respiratory specimens was 18 days following the onset of symptoms; in some individuals, viral RNA was detected from the respiratory tract several months after the initial infection [98]. Detectable viral RNA, however, does not necessarily indicate the presence of infectious virus, and there appears to be a threshold of viral RNA level below which infectiousness is unlikely.

As an example, in a study of nine patients with mild COVID-19, infectious virus was not detected from respiratory specimens when the viral RNA level was <106 copies/mL [88]. In other studies, infectious virus has only been detected in respiratory specimens with high concentrations of viral RNA. Such high viral RNA concentrations are reflected by lower numbers of reverse transcriptase polymerase chain reaction (RT-PCR) amplification cycles necessary for detection. Depending on the study, the cycle threshold (Ct) for specimen culture positivity may vary from <24 to ≤32 [100,101]. According to information from the United States Centers for Disease Control and Prevention (CDC), by three days after clinical recovery, if viral RNA is still detectable in upper respiratory specimens, the RNA concentrations are generally at or below the levels at which replication-competent virus can be reliably isolated; additionally, isolation of infectious virus from upper respiratory specimens more than 10 days after illness onset has only rarely been documented in patients who had nonsevere infection and whose symptoms have resolved [88,100-105]. Except for sporadic reports of reinfection, infectious virus has not been isolated from respiratory specimens of immunocompetent patients who have a repeat positive RNA test following clinical improvement and initial viral RNA clearance, and in studies evaluating such patients, secondary infections in their close contacts have not been documented despite opportunities for transmission [106,107]. (See 'Risk of reinfection' below.)

Occasional reports have described isolation of infectious virus from respiratory specimens for several months following symptom onset in immunocompromised patients [108-112]. Prolonged shedding of virus in fecal specimens has also been described [79]. Further data are needed to understand the frequency and clinical significance of these findings.

The relevance of virus and viral RNA detection to duration of infection control precautions is discussed elsewhere. (See "COVID-19: Infection control for persons with SARS-CoV-2 infection", section on 'Discontinuation of precautions'.)

Risk of transmission depends on exposure type — The risk of transmission from an individual with SARS-CoV-2 infection varies by the type and duration of exposure, use of preventive measures, and likely individual factors (eg, the amount of virus in respiratory secretions) [113]. Many individuals do not transmit SARS-CoV-2 to anyone else, and epidemiologic data suggest that the minority of index cases result in the majority of secondary infections [114-116].

The risk of transmission after contact with an individual with COVID-19 increases with the closeness and duration of contact and appears highest with prolonged contact in indoor settings. Thus, most secondary infections have been described in the following settings:

●Among household contacts [117,118]. One systematic review of 54 studies evaluated secondary infection rates among household or family contacts of index patients with COVID-19 [118]. Among 77,758 contacts in Asia, Europe, the United States, and Australia, the estimated pooled household secondary infection rate was 17 percent, with substantial variability across studies (range 4 to 45 percent). Within households, spouses or significant others have the highest secondary infection rates [117]. Nevertheless, children and adolescents can also serve as index cases for secondary household infections [119-121]. (See "COVID-19: Clinical manifestations and diagnosis in children", section on 'Do children transmit SARS-CoV-2 to others?'.)

A large seroprevalence survey from Spain also highlighted the greater risk of infection with household compared with non-household exposures [122]. The rate of detectable antibodies to SARS-CoV-2 was 31 to 37 percent (depending on the serologic assay used) among individuals who reported having a household member with confirmed COVID-19, compared with rates of 10 to 14 percent among those who reported a co-worker, non-household family member, or friend with confirmed COVID-19.

These studies were performed prior to the prevalence of more transmissible variants, with which higher secondary attack rates have been reported. (See 'Variants of concern' above.)

●In health care settings when personal protective equipment was not used (including hospitals [123] and long-term care facilities [124]).

●In other congregate settings where individuals are residing or working in close quarters (eg, cruise ships [125], homeless shelters [126,127], detention facilities [128,129], college dormitories [130], and food processing facilities [131,132]).

Although transmission rates are highest in household and congregate settings,

frequently reported clusters of cases after social or work gatherings also highlight the risk of transmission through close, non-household social contact [56,133-135]. As an example, epidemiologic analysis of a cluster of cases in the state of Illinois showed probable transmission through two family gatherings at which communal food was consumed, embraces were shared, and extended face-to-face conversations were exchanged with symptomatic individuals who were later confirmed to have COVID-19 [133]. Going to restaurants and other drinking or eating establishments has also been associated with a higher likelihood of infection, likely because of the difficulty with mask-wearing and distancing in such settings [136,137]. (See 'Wearing masks in the community' below.)

Superspreading events, in which large clusters of infections can been traced back to a single index case, are thought to be major drivers of the pandemic [113,114,138]. They have been mainly described following prolonged group exposure in an enclosed, usually crowded, indoor space. As an example, in an outbreak among a choir group, 33 confirmed and 20 probable cases were identified among 61 members who attended a practice session with a symptomatic index case [56]. This outbreak also highlighted the possibility of a high transmission risk through singing in close proximity.

Variable amounts of virus in respiratory secretions may contribute to the variable risk of transmission from different individuals. In an observational study that included 282 individuals with COVID-19 who had undergone respiratory tract viral RNA quantification as part of a trial and 753 of their close contacts, transmission was identified from only 32 percent of index patients [139]. Higher respiratory tract RNA levels (taken at a median of four days after symptom onset) were independently associated with higher secondary attack rates.

Traveling with an individual with COVID-19 is also a high-risk exposure [140-142], as it generally results in close contact for a prolonged period. One study reported a 62 percent attack rate among passengers who shared a business class cabin with the index case during a 10-hour flight; almost all of the infected individuals (11 of 12) had been seated within six feet (two meters) of the index case [141]. An analysis from China looked at the risk among individuals who traveled by train and were exposed within three rows to individuals later confirmed to have COVID-19 [142]. The study identified 2334 primary and 234 secondary cases for an overall attack rate 0.32 percent. The risk of secondary infection was highest (3.5 percent) for individuals in seats adjacent to the index patient, and higher for those seated in the same row than for those in front or behind. The risk also increased over time of travel. This study could not account for the possibility that individuals seated next to one another could have been from the same household or shared other exposures.

The risk of transmission in outdoor settings appears to be substantially lower than indoors, although data are limited [143]. Nevertheless, close contact with an individual with COVID-19 remains a risk outdoors.

The risk of transmission with more indirect contact (eg, passing someone with infection

on the street, handling items that were previously handled by someone with infection) is not well established and is likely very low. However, many individuals with COVID-19 do not report having had a specific close contact with COVID-19 in the weeks prior to diagnosis [144].

The risk of transmission from children with COVID-19 is discussed in detail elsewhere. (See "COVID-19: Clinical manifestations and diagnosis in children", section on 'Do children transmit SARS-CoV-2 to others?'.)

Asymptomatic or presymptomatic transmission — Transmission of SARS-CoV-2 from individuals with infection but no symptoms (including those who later developed symptoms and thus were considered presymptomatic) has been well documented [145-151].

The biologic basis for this is supported by a study of a SARS-CoV-2 outbreak in a long-term care facility, in which infectious virus was cultured from RT-PCR-positive upper respiratory tract specimens in presymptomatic and asymptomatic patients as early as six days prior to the development of typical symptoms [152]. The levels and duration of viral RNA in the upper respiratory tract of asymptomatic patients are also similar to those of symptomatic patients [153].

The risk of transmission from an individual who is asymptomatic appears less than that from one who is symptomatic [118,120,154-157]. As an example, in an analysis of 628 COVID-19 cases and 3790 close contacts in Singapore, the risk of secondary infection was 3.85 times higher among contacts of a symptomatic individual compared with contacts of an asymptomatic individual [158]. Similarly, in an analysis of American passengers on a cruise ship that experienced a large SARS-CoV-2 outbreak, SARS-CoV-2 infection was diagnosed in 63 percent of those who shared a cabin with an individual with asymptomatic infection, compared with 81 percent of those who shared a cabin with a symptomatic individual and 18 percent of those without a cabin mate [156].

Nevertheless, asymptomatic or presymptomatic individuals are less likely to isolate themselves from other people, and the extent to which transmission from such individuals contributes to the pandemic is uncertain. A CDC modeling study estimated that 59 percent of transmission could be attributed to individuals without symptoms: 35 percent from presymptomatic individuals, and 24 percent from those who remained asymptomatic [159]. This estimate was based on several assumptions, including that 30 percent of infected individuals never develop symptoms and are 75 percent as infectious as those who do.

Environmental contamination — Virus present on contaminated surfaces may be another source of infection if susceptible individuals touch these surfaces and then transfer infectious virus to mucous membranes in the mouth, eyes, or nose. The frequency and relative importance of this type of transmission are uncertain, although contaminated surfaces are not thought to be a major source of transmission. It may be more likely a potential source of infection in settings where there is heavy viral

contamination (eg, in an infected individual's household or in health care settings).

Extensive SARS-CoV-2 RNA contamination of environmental surfaces in hospital rooms and residential areas of patients with COVID-19 has been described [61,160,161]. In a study from Singapore, viral RNA was detected on nearly all surfaces tested (handles, light switches, bed and handrails, interior doors and windows, toilet bowl, sink basin) in the airborne infection isolation room of a patient with symptomatic mild COVID-19 prior to routine cleaning [61]. Viral RNA was not detected on similar surfaces in the rooms of two other symptomatic patients following routine cleaning (with sodium dichloroisocyanurate). Of note, viral RNA detection does not necessarily indicate the presence of infectious virus [88].

It is unknown how long SARS-CoV-2 can persist on surfaces [162-164]; other coronaviruses have been tested and may survive on inanimate surfaces for up to six to nine days without disinfection. In a study evaluating the survival of viruses dried on a plastic surface at room temperature, a specimen containing SARS-CoV (a virus closely related to SARS-CoV-2) had detectable infectivity at six but not nine days [163]. However, in a systematic review of similar studies, various disinfectants (including ethanol at concentrations between 62 and 71%) inactivated a number of coronaviruses related to SARS-CoV-2 within one minute [162]. Simulated sunlight has also been shown to inactivate SARS-CoV-2 over the course of 15 to 20 minutes in experimental conditions, with higher levels of ultraviolet-B (UVB) light associated with more rapid inactivation [165]. Based on data concerning other coronaviruses, duration of viral persistence on surfaces also likely depends on the ambient temperature, relative humidity, and the size of the initial inoculum [166].

These data highlight the importance of environmental disinfection in the home and health care setting. (See "COVID-19: Infection control for persons with SARS-CoV-2 infection", section on 'Environmental disinfection'.)

Risk of animal contact — SARS-CoV-2 infection is thought to have originally been transmitted to humans from an animal host, but the ongoing risk of transmission through animal contact is uncertain. There is no evidence suggesting animals (including domesticated animals) are a major source of infection in humans.

SARS-CoV-2 infection has been described in animals in both natural and experimental settings. There have been rare reports of animals with SARS-CoV-2 infection (including asymptomatic infections in dogs and symptomatic infections in felines) following close contact with a human with COVID-19 [167-170]. Moreover, asymptomatic, experimentally infected domestic cats may transmit SARS-CoV-2 to cats they are caged with [171]. The risk of infection may vary by species. In one study evaluating infection in animals after intranasal viral inoculation, SARS-CoV-2 replicated efficiently in ferrets and cats; viral replication was also detected in dogs, but they appeared to be less susceptible overall to experimental infection [172]. Pigs and poultry were not susceptible to infection. Mink appear highly susceptible to SARS-CoV-2; outbreaks on mink farms have been reported in Europe and the United States, and in this setting, suspected

cases of mink to human transmission have been described, including cases with SARS-CoV-2 variants that appear less susceptible to neutralizing antibodies to wild-type virus [173-175]. In view of these findings, mink on farms in both the Netherlands and Denmark have been, or are being, culled.

Given the uncertainty regarding the transmission risk and the apparent susceptibility of some animals to SARS-CoV-2 infection, the United States CDC recommends that pets be kept away from other animals or people outside of the household and that people with confirmed or suspected COVID-19 try to avoid close contact with household pets, as they should with human household members, for the duration of their self-isolation period. There have been no reports of domesticated animals (other than mink) transmitting SARS-CoV-2 infection to humans.

Immune responses following infection — SARS-CoV-2-specific antibodies and cell-mediated responses are induced following infection. Evidence suggests that some of these responses are protective and can be detected for at least a year following infection.

●Humoral immunity – Following infection with SARS-CoV-2, the majority of patients develop detectable serum antibodies to the receptor-binding domain of the viral spike protein and associated neutralizing activity [87,88]. However, the magnitude of antibody response may be associated with severity of disease, and patients with mild infection may not mount detectable neutralizing antibodies [176,177]. When neutralizing antibodies are elicited, they generally decline over several months after infection, although studies have reported detectable neutralizing activity up to 12 months [178-181]. In one study of 121 convalescent plasma donors with initial spike-binding titers ≥1:80, titers declined slightly over five months but remained ≥1:80 in the vast majority, and neutralizing titers correlated with the binding titers [182]. Other studies have also identified spike- and receptor-binding domain memory B cells that increased over the few months after infection as well as spike protein-specific plasma cells, and these findings suggest the potential for a long-term memory humoral response [178,180,181,183].

Neutralizing activity has been associated with protection from subsequent infection [184]. Detectable binding antibodies, which generally correlate with neutralizing activity, are also associated with a reduced risk of SARS-CoV-2 reinfection [185-188]. (See 'Risk of reinfection' below.)

●Cell-mediated immunity – Studies have also identified SARS-CoV-2-specific CD4 and CD8 T cell responses in patients who had recovered from COVID-19 and in individuals who had received an investigational COVID-19 vaccine, which suggest the potential for a durable T cell immune response [178,183,189,190].

●Protective immune response after infection or vaccination in primate studies – Animal studies have suggested that the immune response to infection may offer some protection against reinfection, at least in the short term [191-194]. In one study of nine

rhesus macaques experimentally infected with SARS-CoV-2, all animals developed neutralizing antibodies; upon rechallenge with the same viral dose 35 days later, all had anamnestic immune responses and, on nasal swab, had lower viral RNA levels and more rapid viral RNA decline compared with the initial challenge and with challenged naïve control animals [191]. Studies evaluating COVID-19 vaccine candidates in macaques have also suggested that immune responses to vaccination result in lower levels or more rapid clearance of viral RNA in respiratory tract specimens following viral challenge compared with unvaccinated controls [192,193,195-197]. Immunity in humans following vaccination is discussed in detail elsewhere. (See "COVID-19: Vaccines to prevent SARS-CoV-2 infection", section on 'Immunogenicity, efficacy, and safety of select vaccines'.)

Antibodies that neutralize SARS-CoV-2 and SARS-CoV-2-reactive CD4 T cells have been identified in some individuals without known exposure to SARS-CoV-2, and some of these appear to be cross-reactive with antigens from common cold coronaviruses [190,198-200]. Whether these pre-existing immune responses impact the risk or the severity of COVID-19 and whether they will influence COVID-19 vaccine responses remain unknown.

Risk of reinfection — The short-term risk of reinfection (eg, within the first several months after initial infection) is low. Prior infection reduces the risk of infection in the subsequent six to seven months by 80 to 85 percent [187,201].

An observational study from Denmark attempted to evaluate the risk of reinfection by analyzing the risk of a positive PCR test during the second COVID-19 surge (September to December 2020) among individuals who had undergone PCR testing during the first COVID-19 surge (February to June 2020) [201]. Of 11,068 individuals with a positive PCR test during the first surge, 72 tested positive during the second surge (0.65 percent), compared with 16,819 of 514,271 individuals (3.27 percent) who had tested negative during the first surge; the estimated "protective effect" of previous infection was approximately 80 percent. Age greater than 65 years was associated with a higher rate of testing positive in both surges.

These results are consistent with those from other observational studies that suggest a lower rate of SARS-CoV-2 PCR positivity among individuals with detectable antibodies against the virus [185-188]. In a study of health care workers in the United Kingdom who underwent intermittent PCR and antibody testing, the 8278 participants with evidence of prior infection had an 84 percent lower rate of subsequent infection (as determined by PCR positivity) over seven months compared with the 17,383 participants who had no prior infection (8 versus 57 cases per 100,000 days; incidence rate ratio 0.16) [187]. In another study, reinfection among individuals who were seropositive at baseline was associated with lower titers of anti-spike IgG and lower rates of detectable neutralizing activity [188]. (See 'Immune responses following infection' above.)

Reinfection with variants of concern (such as B.1.351, which is less susceptible to

neutralizing antibodies generated against wild-type virus) has been documented following infection with wild-type virus, but the overall risk of reinfection with such variants is uncertain [202,203]. (See 'Variants of concern' above.)

Simply having a positive SARS-CoV-2 viral test after recovery does not necessarily indicate reinfection; sequencing that demonstrates a different strain at the time of presumptive reinfection is necessary to make the distinction between reinfection and prolonged or intermittent viral RNA shedding following an initial infection. (See "COVID-19: Diagnosis", section on 'Diagnosis of reinfection'.)

Sporadic cases of confirmed reinfection using sequencing data have been described throughout the world [204-212]. In some of these cases, the second infection was asymptomatic or milder than the first, raising the possibility that immunity from an initial infection might attenuate the severity of a reinfection even if it does not prevent it. However, not all cases of purported reinfection have been less severe than the initial infection, and at least one fatal reinfection has been reported in a patient undergoing B cell-depleting therapy and chemotherapy [208].

These cases contrast with prior reports of positive PCR tests in patients with laboratory-confirmed COVID-19 following clinical improvement and negative results on two consecutive tests [213-216]. In these earlier cases, positive tests usually occurred shortly after the negative tests and were usually not associated with worsening symptoms. In a study of 108 patients with a repeat positive RNA test after previously testing negative and being cleared from isolation, infectious virus could not be isolated in cell culture and there were no newly confirmed cases among close contacts exposed during the period of the repeat positive test [106]. Thus, many individuals who have repeat positive PCR tests soon after infection have ongoing viral RNA shedding rather than reinfection. (See 'Viral shedding and period of infectiousness' above.)

PREVENTION

Infection control in the health care setting — In locations where community transmission is widespread, preventive strategies for all individuals in a health care setting are warranted to reduce potential exposures. Additional measures are warranted for patients with suspected or confirmed COVID-19. Infection control in the health care setting is discussed in detail elsewhere. (See "COVID-19: Infection control for persons with SARS-CoV-2 infection", section on 'Infection control in the health care setting'.)

Personal preventive measures — If community transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is present, residents are generally encouraged to practice social distancing by avoiding crowds and maintaining a distance of six feet (two meters) from others when in public [217]. In particular, individuals should avoid close contact with ill individuals. Individuals are also encouraged to wear masks when out in public. These and other general public health measures are discussed elsewhere. (See 'Wearing masks in the community' below and 'Social/physical distancing' below and 'Other public health measures' below.)

The following general measures are additionally recommended to reduce transmission of infection:

●Diligent hand washing, particularly after touching surfaces in public. Use of hand sanitizer that contains at least 60% alcohol is a reasonable alternative if the hands are not visibly dirty. The importance of hand hygiene was illustrated by a study in which mucus specimens inoculated with cultured SARS-CoV-2 virus were applied to human skin collected from autopsy [218]. SARS-CoV-2 remained viable on the skin for about nine hours but was completely inactivated within 15 seconds of exposure to 80% alcohol.

●Respiratory hygiene (eg, covering the cough or sneeze).

●Avoiding touching the face (in particular eyes, nose, and mouth). The American Academy of Ophthalmology suggests that people not wear contact lenses, because they make people touch their eyes more frequently [219].

●Cleaning and disinfecting objects and surfaces that are frequently touched. The United States Centers for Disease Control and Prevention (CDC) has issued guidance on disinfection in the home setting; a list of Environmental Protection Agency-registered products can be found here.

●Ensure adequate ventilation of indoor spaces. This includes opening windows and doors, placing fans in front of windows to exhaust air to the outside, running heating/air conditioning fans continuously, and using portable high-efficiency particulate air (HEPA) filtration systems [220,221].

These measures should be followed by all individuals when there is community transmission of SARS-CoV-2 but should be emphasized for older adults and individuals with chronic medical conditions, in particular.

The CDC has included recommended measures to prevent spread in the community on its website [217].

Wearing masks in the community

When to wear a mask — Local guidelines on mask-wearing depend on the level of community transmission and vaccination rates. The World Health Organization (WHO) recommends mask-wearing as part of a comprehensive approach to reducing SARS-CoV-2 transmission in either indoor or outdoor settings where there is widespread transmission and social distancing is difficult as well as indoor settings with poor ventilation (regardless of ability to distance) [222]. In the United States, the CDC advises unvaccinated individuals to wear masks when in public and around other individuals outside their household. The CDC has also issued a mandate requiring masks for all individuals on public transportation (including taxis and ride-shares) and at

transportation hubs (eg, airports, bus or ferry terminals, railway stations, seaports) [223]. Recommendations on mask-wearing for individuals who have been vaccinated are discussed elsewhere. (See "COVID-19: Vaccines to prevent SARS-CoV-2 infection", section on 'Post-vaccine public health precautions'.)

Individuals who are caring for individuals with suspected or documented COVID-19 at home should also wear a mask when in the same room as that person. Precautions for individuals with suspected or documented COVID-19 and their caretakers are discussed in detail elsewhere. (See "COVID-19: Infection control for persons with SARS-CoV-2 infection", section on 'Isolation at home'.)

Type of masks — In the United States, cloth masks and disposable masks (eg, commercially available surgical masks) are recommended for community use [224]. The CDC specifies that the mask recommendation does not include N95 respirators, which should be reserved for health care workers. Cloth masks should be made with several layers of tightly woven fabric [225,226]. All masks should fit snugly over the face without gaps. Strategies to improve mask fit include using a mask with an adjustable nose bridge, wearing a cloth mask over a disposable mask, knotting the ear loops of a disposable mask to cinch the sides of the mask and secure it against the face, using masks with ties rather than ear loops, and using a mask brace [227]. Masks should not have exhalation valves. The CDC notes that the importance of fit and filtration likely increases in situations where the risk of exposure is high (eg, prolonged close contact indoors with people outside the household). Some individuals may opt to wear KN95 respirators, which are intended to have a very high filtration efficacy when fit tightly against the face and are available commercially. However, people should be aware that many marketed KN95 respirators do not meet the advertised filtration standards; if used, KN95 respirators that have been granted emergency use authorization by the US Food and Drug Administration (FDA) should be chosen [228]. Detailed information on the types of recommended masks can be found on the CDC website.

The WHO also recommends non-medical masks for most individuals and has issued standards for the ideal composition of a cloth mask to optimize fluid resistance and filtration efficiency [229]. However, it recommends that medical masks be used by individuals at risk for severe COVID-19 (eg, individuals >60 years old or with high-risk underlying conditions) when in public settings where distancing is not feasible and by any household members of individuals with suspected or confirmed COVID-19 when in the same room [222]. In certain European countries, medical masks (including respirators, such as N95 masks) are recommended in certain indoor public settings, including on public transportation and in stores [230].

When advising patients on the use of masks, clinicians should counsel them to avoid touching the eyes, nose, and mouth when putting on or removing the mask, to practice hand hygiene before and after handling the mask, and to launder cloth masks routinely. Clinicians should also emphasize that the mask does not diminish the importance of other preventive measures, such as social distancing and hand hygiene. Patients can also be counseled that masks have not been associated with impairment in gas

exchange, including among patients with underlying lung disease [231,232].

Rationale — The rationale for wearing masks in the community is primarily to contain secretions of and prevent transmission from individuals with infection, including those who have asymptomatic or presymptomatic infection. Masks can also reduce exposure to SARS-CoV-2 for the wearer.

●Source control – Several studies support the use of masks to provide source control and reduce transmission in the community [225,233-240]. In a retrospective study of 124 patients with confirmed COVID-19 and their families in Beijing, China, secondary transmission occurred in 41 families; use of masks by family members (including the index patient) prior to illness onset in the index patient was independently associated with a reduced risk of infection [233]. The type of mask used (medical or cloth) was not specified. In a case report of two hair stylists with COVID-19 who worked while symptomatic prior to the diagnosis but wore face coverings, there were no subsequent COVID-19 diagnoses among 139 clients with close contact, all of whom were also wearing face coverings; both medical masks and cloth face coverings were used [241]. In epidemiologic studies, government-issued mask mandates and high rates of self-reported mask wearing have each been associated with decreased community incidence rates and, in some cases, decreased COVID-19 hospitalization rates [240,242-244]. Although limited by assumptions and estimates, modeling studies have also suggested that high adoption of mask-wearing by the general public can reduce transmission, even if masks are only moderately effective in containing infectious respiratory secretions [245,246].

●Prevent exposure – Mask-wearing in the community may also be associated with protection for the wearer [247-249]. In a report of 382 service members who were surveyed about personal preventive strategies in the setting of a SARS-CoV-2 outbreak on a United States Navy aircraft carrier, self-report of wearing a face cover was independently associated with a lower likelihood of infection (odds ratio [OR] 0.3), as were avoiding common areas (OR 0.6) and observing social distancing (OR 0.5) [247]. In a retrospective analysis of 1060 individuals identified by contact tracing following clusters of infections in Thailand, wearing a mask all the time was associated with a lower odds of infection compared with not wearing a mask; there was no significant association between wearing a mask some of the time and infection rate [248]. A randomized trial from Denmark did not identify a decreased rate of infection among individuals who were provided with surgical masks and advised to wear them when outside of the house for a month (1.8 versus 2.1 percent among individuals who were not given masks or the recommendation) [250]; however, clear conclusions about mask efficacy cannot be made from this study because of a low rate of community transmission during the time of the study and other limitations.

Mask-wearing has also been hypothesized to reduce the viral inoculum, even if it doesn't eliminate exposure, and thereby reduce the risk of severe illness [251,252].

●Filtration efficacy – Filtering facepiece respirators (FFR) have the highest filtration

efficacy. In the United States, the prototypical FFR is the N95 respirator, which filters at least 95 percent of 0.3 micrometer particles. Medical masks have lower filtration efficacy, which depends on how closely the mask lies against the face. In one study, medical masks with ties versus ear loops filtered 72 and 38 percent of particles, respectively (approximately 0.02 to 3.00 micrometers) [253]. Other strategies to improve the fit of a medical mask, such as using a cloth mask over it or knotting the ear loops to eliminate gaps, also appear to increase filtration efficacy [254]. Studies on the filtration efficacy of fabrics suggest that certain fabrics (eg, tea towel fabric [termed dish towel fabric in the United States], cotton-polypropylene blends), particularly when double-layered, can approach the filtration efficacy of medical masks [225,255-257]. In an experimental model, universal masking with a three-ply cotton mask was shown to substantially reduce aerosol exposure [221]. Tight-weave fabric, two or more layers, and a tight fit are essential for adequate filtration.

Despite the variability in filtration efficacy of different masks (respirators, medical masks, cloth masks) in experimental settings, data on clinical efficacy differences in preventing transmission of SARS-CoV-2 are lacking.

Other face protection — Although eye protection is recommended in health care settings, the role of face shields or goggles in addition to masks to further reduce the risk of infection in the community is uncertain [258,259]. Although one study suggested that the proportion of hospitalized patients with COVID-19 who used eyeglasses daily was lower than that estimated for the general population, eyeglasses are generally considered insufficient for eye protection [260]. (See "COVID-19: Infection control for persons with SARS-CoV-2 infection", section on 'Type of PPE'.)

Social/physical distancing — In locations where there is community transmission of SARS-CoV-2 (including throughout the United States), individuals are advised to practice social or physical distancing in both indoor and outdoor spaces by maintaining a minimum distance from other people outside their household. The optimal distance is uncertain; in the United States, the CDC recommends a minimum distance of six feet (two meters), whereas the WHO recommends a minimum distance of three feet (one meter). The rationale is to minimize close-range contact with an individual with infection, which is thought to be the primary risk of exposure to SARS-CoV-2. (See 'Route of person-to-person transmission' above.)

Physical distancing is likely independently associated with a reduced risk of SARS-CoV-2 transmission [237,261-263]. In a meta-analysis of observational studies evaluating the relationship between physical distance and transmission of SARS-CoV-2, SARS-CoV, and Middle East respiratory syndrome coronavirus (MERS-CoV), proximity and risk of infection were closely associated, and the infection rate was higher with contact within three feet (one meter) compared with contact beyond that distance (12.8 versus 2.6 percent) [237]. A distance more than six feet (two meters) was associated with further reduction in transmission.

Screening in high-risk settings — Screening for SARS-CoV-2 infection with serial viral

testing is recommended in long-term care facilities to quickly identify cases so that infected individuals can be isolated, contacts can be quarantined, and outbreaks can be prevented [264,265] (see "COVID-19: Management in nursing homes", section on 'Screening and testing'). Similar strategies have been employed in other congregate environments, such as college campuses [266]. Some have proposed more widespread use of serial testing as a measure to slow community transmission [267,268].

Both nucleic acid amplification tests (NAATs) and antigen tests have been used for serial screening. Although antigen tests are generally less sensitive than NAAT, modelling studies have suggested that if the frequency of testing is high enough, tests with lower sensitivity can be successfully used to reduce cumulative infection rates [269,270]. Accessibility and fast turnaround time are also important features of a useful screening test. (See "COVID-19: Diagnosis", section on 'Specific diagnostic techniques'.)

Testing-based screening strategies have the advantage of identifying asymptomatic or presymptomatic infections. Several studies have highlighted the limitations of symptom-based screening methods because of the high proportion of asymptomatic cases [271,272]. (See "COVID-19: Clinical features", section on 'Asymptomatic infections'.)

Other public health measures — On January 30, 2020, the WHO declared the COVID-19 outbreak a public health emergency of international concern and, in March 2020, began to characterize it as a pandemic in order to emphasize the gravity of the situation and urge all countries to take action in detecting infection and preventing spread. Throughout the world, countries have employed various nonpharmaceutical interventions to reduce transmission. In addition to personal preventive measures (eg, masks, hand hygiene, respiratory etiquette, and environmental disinfection), transmission reduction strategies include:

●Social/physical distancing orders

●Stay-at-home orders

●School, venue, and nonessential business closure

●Bans on public gatherings

●Travel restriction with exit and/or entry screening

●Aggressive case identification and isolation (separating individuals with infection from others)

●Contact tracing and quarantine (separating individuals who have been exposed from others)

These measures have been associated with reductions in the incidence of SARS-CoV-2

infection over time, with epidemiologic studies showing reductions in cases, and in some situations, COVID-19-related deaths following implementation of these mitigation measures [273-281].

For countries where incidence has declined and relaxation of transmission reduction measures is being considered, the WHO has issued interim guidance on implementation, which includes a step-wise approach that is adjusted according to local circumstances and prioritizes protecting vulnerable populations; it recommends that personal preventive measures be maintained and that public health efforts to detect cases for isolation and to identify contacts for quarantine be strengthened [282,283].

Specific recommendations on global travel are available on the WHO website.

Recommendations on international and domestic travel in the United States are found on the CDC website [284,285]. Because the risk of travel changes rapidly and recommendations on restricting activity and testing after travel vary by state, individuals should consult country- and state-specific guidance prior to travel.

Post-exposure management — In areas where SARS-CoV-2 is prevalent, all residents should be encouraged to stay alert for symptoms and practice appropriate preventive measures to reduce the risk of infection. (See 'Personal preventive measures' above.)

Testing and quarantine — Testing and quarantine are strategies to quickly identify secondary infections in an exposed individual and reduce the risk of that individual exposing others before an infection is recognized. In the United States, CDC suggestions on testing and quarantine following an exposure in the community depend on the vaccination status and history of infection. The following measures are recommended for those who have had close contact with a person with suspected or confirmed SARS-CoV-2 infection in the community (including during the 48 hours prior to that patient developing symptoms and regardless of whether the individuals involved were wearing masks) [286]:

●For unvaccinated individuals:

•Daily monitoring for fever, cough, or dyspnea for 14 days. Individuals who develop such signs or symptoms should stay home and maintain distance from other individuals, including those in their household, if they are not doing so already (as below), and contact their medical providers. (See "COVID-19: Outpatient evaluation and management of acute illness in adults", section on 'Management and counseling for all outpatients'.)

•Self-quarantine at home, with maintenance of at least six feet (two meters) from others at all times. In particular, they should avoid contact with individuals at high risk for severe illness. (See "COVID-19: Clinical features", section on 'Risk factors for severe illness'.)

The preferred quarantine period is 14 days following the date of the last exposure (so long as the individual remains asymptomatic) and is based on the incubation period for SARS-CoV-2 infection. (See "COVID-19: Clinical features", section on 'Incubation period'.)

However, the CDC acknowledges that shorter durations of quarantine may ameliorate the associated community burdens and adherence challenges in exchange for a slightly increased risk of post-quarantine transmission [287]. Thus, it notes that acceptable alternatives are:

-A seven-day quarantine period, provided that the individual remained asymptomatic throughout and has a negative NAAT or antigen SARS-CoV-2 test within 48 hours of the planned end of quarantine

-A 10-day quarantine period, provided that the individual remained asymptomatic throughout

These intervals were based on modeling performed by the CDC that suggested median post-quarantine transmission rates of 4 percent (range 2.3 to 8.6) for the 7-day quarantine with negative NAAT and 1.4 percent (range 0.1 to 10.6) for the 10-day quarantine, compared with 0.1 percent (range 0 to 3.0) for the 14-day quarantine. In another study of individuals who had household exposure to SARS-CoV-2 and underwent daily symptom monitoring and polymerase chain reaction (PCR) testing, there was an 81 percent probability that those who were asymptomatic with negative testing through day 7 would remain so through day 14 [288].

If quarantine periods shorter than 14 days are used, individuals should be counseled to continue symptom monitoring and maintain strict adherence to other prevention efforts within and outside of the household (eg, mask wearing, physical distancing) for a full 14 days.

For household members of an individual with COVID-19 who cannot physically separate themselves (eg, maintain physical distance, sleep in a separate room, use a separate bathroom) from that person, the quarantine period begins once the isolation period of the individual with COVID-19 is complete.

•Testing (ideally five to seven days following exposure) is also recommended following close contact to promptly identify new infections [289]. However, a negative test performed earlier after exposure should not be used to reduce the quarantine period to shorter than seven days. (See "COVID-19: Diagnosis", section on 'Select asymptomatic individuals'.)

●For vaccinated individuals: Fully vaccinated individuals are exempted from the self-quarantine suggestions above but should get tested 3 to 5 days following exposure and wear a mask in public for 14 days or until the test is negative [290]. They should also continue to self-monitor for fever and symptoms for 14 days following exposure and

undergo evaluation if features of COVID-19 develop.

●For individuals with a recent history of infection: Individuals who had documented SARS-CoV-2 infection within the three months prior to the exposure are exempted from these self-quarantine and testing recommendations [291]. (See "COVID-19: Diagnosis", section on 'Symptomatic patients'.)

Management of health care workers with a documented exposure is discussed in detail elsewhere. (See "COVID-19: Infection control for persons with SARS-CoV-2 infection".)

Post-exposure prophylaxis for select individuals — In the United States, the FDA has issued an emergency use authorization (EUA) to use the monoclonal antibody casirivimab-imdevimab to prevent SARS-CoV-2 infection in select individuals over 12 years of age who have had close contact with an individual with infection or who are at high risk of exposure to individuals with infection in an institutional setting [292]. If casirivimab-imdevimab is available, we suggest this approach to post-exposure prophylaxis for the following individuals, who meet the criteria for use according to the EUA:

●Those who are at high risk for progression to severe COVID-19 based on age or underlying conditions, as outlined in the table (table 2)

and

●Those who are expected to have an inadequate immune response to COVID-19 vaccination (eg, patients who have immunocompromising conditions or are taking immunosuppressive agents) or who have not been fully vaccinated (ie, have not received a complete vaccine series by at least two weeks prior)

The dose for post-exposure prophylaxis is casirivimab-imdevimab 600 mg-600 mg as a subcutaneous injection or intravenous infusion given once as soon as possible following exposure; we suggest not casirivimab-imdevimab if the exposure was more than 96 hours previously. For those who are expected to have an inadequate immune response to vaccination and have ongoing exposure to SARS-CoV-2, subsequent doses of casirivimab-imdevimab 300 mg-300 mg can be given every four weeks for the duration of the exposure.

Individuals in the community should continue to follow post-exposure quarantine and testing suggestions, as discussed above, regardless of monoclonal antibody receipt (see 'Testing and quarantine' above). We recommend future COVID-19 vaccination for those who have not yet received it; the CDC has suggested that individuals wait 90 days after receiving a monoclonal antibody before vaccination to avoid potential interference with the vaccine response [293].

The use of casirivimab-imdevimab as post-exposure prophylaxis is supported by the results of a double-blind, randomized trial, which has not yet been published but was

presented to the US FDA [292]. Among 1500 participants who had a household contact with SARS-CoV-2, receipt of casirivimab-imdevimab within 96 hours of the index case's positive test reduced the risk of symptomatic COVID-19 (1 versus 8 percent with placebo, adjusted OR 0.17, p <0.0001) and the risk of any SARS-CoV-2 infection (5 versus 14 percent with placebo, adjusted OR 0.31, p <0.0001). Mutations in the Delta variant are not expected to impact the antiviral activity of casirivimab-imdevimab.

In this trial and others assessing casirivimab-imdevimab for treatment of COVID-19, injection site reactions occurred in approximately 4 to 12 percent and were nonsevere. Infusion-related reactions (eg, flushing, pyrexia, shortness of breath) occurred very rarely and at doses higher than authorized doses.

The concept of using monoclonal antibodies as prevention is further supported by a randomized trial of nursing home residents and staff, among whom bamlanivimab reduced the risk of overall and symptomatic SARS-CoV-2 infection over eight weeks; however, bamlanivimab is not clinically available, as the prevalence of resistant viral variants diminished its utility [294].

We recommend against using other agents for prophylaxis outside a clinical trial.

Data from placebo-controlled randomized trials indicate that hydroxychloroquine is not effective in preventing infection [295-300]; the World Health Organization specifically recommends against using hydroxychloroquine to prevent COVID-19 [301]. Ivermectin has also been proposed as a potential prophylactic agent, but it has only been evaluated in low-quality unpublished studies [302], and clinical evidence supporting its use is lacking. Furthermore, although ivermectin has demonstrated activity against SARS-CoV-2 in vitro, plasma levels high enough for antiviral activity cannot be achieved with safe drug doses [303].

Vaccines — Vaccines to prevent SARS-CoV-2 infection are considered the most promising approach for curbing the pandemic [304]. COVID-19 vaccines are discussed in detail elsewhere. (See "COVID-19: Vaccines to prevent SARS-CoV-2 infection".)

SUMMARY AND RECOMMENDATIONS

●Burden of disease – Since the first reports of coronavirus disease 2019 (COVID-19) and identification of the novel coronavirus that causes it, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), infection has spread to include more than 200 million confirmed cases worldwide. An interactive map highlighting confirmed cases throughout the world can be found here.

●Variants of concern – Several variants of SARS-CoV-2 have emerged that are notable because of the potential for increased transmissibility (table 1). Possible immune escape is another concern for some recently isolated variants.

●Modes of transmission – Direct person-to-person transmission is the primary means of

SARS-CoV-2 transmission. It is thought to occur mainly through close-range contact via respiratory particles; virus released in respiratory secretions when a person with infection coughs, sneezes, or talks can infect another person if it is inhaled or makes direct contact with the mucous membranes. SARS-CoV-2 can also be transmitted longer distances, particularly in enclosed, poorly ventilated spaces.

SARS-CoV-2 has been detected in non-respiratory specimens, including stool, but the role of these sites in transmission is uncertain.

●Period of infectiousness – Individuals with SARS-CoV-2 infection are most infectious in the earlier stages of infection (starting a few days prior to the development of symptoms). Transmission after 7 to 10 days of illness is unlikely, particularly for otherwise immunocompetent patients with nonsevere infection. Prolonged viral RNA shedding after symptom resolution is not clearly associated with prolonged infectiousness.

●Immune response and risk of reinfection – Infection induces a protective immune response for at least six to eight months. However, it is unclear how long the protective effect lasts beyond that period. The risk of reinfection within the first several months after initial infection is low.

●Personal preventive measures – In settings where there is community transmission of SARS-CoV-2, personal measures to reduce the risk of transmission include mask-wearing in public, diligent hand washing, respiratory hygiene, physical distancing, and avoiding crowds and close contact with ill individuals. Masks should have multiple layers, cover the nose and mouth, and fit snugly against the face.

●Quarantine – Unvaccinated individuals who have close contact with someone with known or suspected COVID-19 should monitor for symptoms and self-quarantine (ie, stay at home, physically distanced from others). The preferred quarantine period is 14 days; shorter quarantine periods of 7 days (following a negative viral test within 48 hours) or 10 days are acceptable alternatives, although they are associated with a higher risk of post-quarantine transmission.

●Post-exposure prophylaxis – Administration of the monoclonal antibody casirivimab-imdevimab within 96 hours of exposure to SARS-CoV-2 can reduce the risk of infection. We suggest post-exposure prophylaxis with casirivimab-imdevimab in individuals who meet all of the following criteria (Grade 2B)

•They had close contact with an individual with infection or have a high risk of exposure to individuals with infection in an institutional setting.

•They are at high risk for progression to severe COVID-19 based on age or underlying conditions (table 2).

•They are expected to have an inadequate immune response to COVID-19 vaccination

or they are not fully vaccinated.

●Vaccines – Vaccines to prevent SARS-CoV-2 infection are considered the most promising approach for curbing the pandemic. COVID-19 vaccines are discussed in detail elsewhere.

●Public health guidance - Guidance has been issued by the WHO and the United States Centers for Disease Control and Prevention (CDC), as well as other expert organizations. These are updated on an ongoing basis.
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