COVID-19: Epidemiology, virology, and prevention

Author: Kenneth McIntosh, MD
Section Editor: Martin S Hirsch, MD
Deputy Editor: Allyson Bloom, MD

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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.

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" and "COVID-19: Diagnosis".)

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

- (See "COVID-19: Management in hospitalized adults".)
- (See "COVID-19: Management of adults with acute illness in the outpatient setting".)
- (See "COVID-19: Infection prevention for persons with SARS-CoV-2 infection".)

Issues related to COVID-19 in pregnant women and children are discussed elsewhere:

- (See "COVID-19: Overview of pregnancy issues".)

- (See "COVID-19: Clinical manifestations and diagnosis in children" and "COVID-19: Multisystem inflammatory syndrome in children (MIS-C) clinical features, evaluation, and diagnosis".)

See specific topic reviews for details on complications of COVID-19 and issues related to COVID-19 in other patient populations.

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) [2]. The Middle East respiratory syndrome (MERS) virus, another betacoronavirus, appears more distantly related [3,4]. 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 [5]. (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) [6]. SARS-CoV-2 binds to ACE2 through the receptor-binding domain of its spike protein (figure 1). The cellular serine protease TMPRSS2 also appears important for SARS-CoV-2 cell entry [7].

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 [8].

Omicron (B.1.1.529) and its sublineages — The Omicron variant was first reported from Botswana and very soon thereafter from South Africa in November 2021 (table 1). In South Africa, it was associated with an increase in regional infections, and it was promptly identified in multiple other countries, where it was similarly associated with sharp increases in reported

infections [9-12]. Subsequently, Omicron sublineages with increasingly greater replication advantages emerged, replacing the previous predominant sublineage. The original Omicron variant was sublineage BA.1, followed by sublineage BA.2, which in turn was supplanted by BA.4 and BA.5 [13]. Other Omicron sublineages, such as BQ.1, BQ.11, BF.7, BA.2.75, XBB, XBB.1, and XBB.1.5, which evolved from various previously circulating sublineages, have been increasing in prevalence worldwide. Each sublineage differs from the others by at least one mutation in the spike protein (except for BA.4 and BA.5, which have identical spike proteins) [14].

In the United States, the proportion of variants circulating in different regions of the country can be found on the CDC variant tracker website.

Several Omicron sublineages have a replication advantage over the Delta variant and evade infection- and vaccine-induced humoral immunity to a greater extent than prior variants. They also appear to be associated with less severe disease than other variants:

- **Replication advantage** – The emergence of each predominant Omicron sublineage (BA.1, then BA.2, then BA.4, BA.5, then BQ.11 and XBB and its derivatives XBB.1 and XBB.1.5) has been associated with local increases in SARS-CoV-2 infections, suggesting a replication advantage over the prior prevailing variant or sublineage. Omicron (specifically the BA.1 sublineage) has also been associated with a higher secondary attack rate compared with Delta (in one study, 25 versus 19 percent) [15]. Another study of household contacts of patients with Omicron BA.1 infection suggested a secondary attack rate of 53 percent, which varied by vaccination status of the index patient and use of preventive measures in the household [16]. Data on secondary attack rates of other Omicron sublineages are lacking.

  The replication advantage may be related, in part, to immune escape by Omicron sublineages, as discussed below. Whether Omicron sublineages are inherently more transmissible than the variants that precede them is uncertain. Immune escape as well as increased affinity for the ACE2 receptor are proposed explanations for the replication advantage of the XBB.1.5 subvariant and its predecessors [17].

- **Immune evasion** – Omicron variants may escape humoral immunity and are associated with a higher risk of reinfection in individuals previously infected with a different strain. In a study evaluating national surveillance data from South Africa, the ratio of reinfections (repeat positive test at least 90 days after an earlier positive test) to primary infections was higher during the beginning of the case surge associated with the Omicron BA.1 variant compared with the surges associated with the Beta and Delta variants (0.25 versus 0.12 and 0.09) [18]. Similar findings were reported from a case-control study from Qatar, in

which a history of prior infection was associated with an 85 to 90 percent lower risk of infection with Alpha, Delta, or Beta variants, but only a 56 percent lower risk with Omicron BA.1 [19]. These observations are further supported by findings from several laboratories, in which sera from individuals with prior infection or prior vaccination did not neutralize Omicron as well as other variants; in some cases, neutralizing activity against Omicron was undetectable in convalescent as well as post-vaccination sera [20-22]. Similarly, compared with Omicron BA.1, sublineages BA.2.12.1, BA.4, and BA.5 are not as well recognized by antibodies elicited by BA.1 or BA.2 infection or vaccination [23-25]. However, prior infection with one Omicron subvariant may still provide some protection against subsequent infection with certain other subvariants, even if in vitro studies suggest low antibody cross-reactivity [26-28]. As an example, the risk of reinfection with BA.4 and BA.5 was lower following BA.1 or BA.2 infection than following infection with a pre-Omicron variant [26,27]. The impact of Omicron on vaccine-induced immunity is discussed elsewhere. (See "COVID-19: Vaccines".)

Other data suggest that Omicron sublineages escape binding by bamlanivimab-etesevimab, casirivimab-imdevimab, and regdanvimab (a monoclonal antibody therapy available outside the United States), and thus these monoclonal antibodies are expected to be ineffective when these sublineages are circulating (table 1) [24,29-31]. Sotrovimab appears to bind to Omicron BA.1, but not to BA.2, BA.2.12.1, BA.4, or BA.5 [24,32]. Bebtelovimab and cilgavimab (a component of tixagevimab-cilgavimab) retain activity against these Omicron sublineages. However, emerging Omicron sublineages appear to escape neutralization by one or both of these monoclonal antibodies [33]. In particular, bebtelovimab and tixagevimab-cilgavimab activity against BQ.1, BQ.1.1, and XBB (and its derivatives XBB.1 and XBB.1.5) is greatly reduced [34].

- **Severity of disease** – Observational data from multiple studies suggest that the risk of severe disease or death with Omicron infection is lower than with prior variants of concern [35-42]. An analysis from England estimated that the risk of hospital admission or death with Omicron was approximately one-third that with Delta, adjusted for age, sex, vaccination status, and prior infection [38]. Evidence also suggests that the risk of severe disease with BA.4 and BA.5 is comparable to that with earlier Omicron sublineages [14,43,44].

  Even if the individual risk for severe disease with Omicron is lower than with prior variants, the high number of associated cases can still result in a cumulative excess of COVID-19-associated hospitalizations and deaths compared with other variants [45,46].

The reduced risk for severe disease may reflect partial protection conferred by prior infection or vaccination. However, animal studies that show lower viral levels in lung tissue and milder clinical features (eg, less weight loss) with Omicron compared with other variants provide further support that Omicron infection may be intrinsically less severe [47-49].

- **Impact on diagnostic testing** – This is discussed in detail elsewhere. (See "COVID-19: Diagnosis", section on 'Impact of SARS-CoV-2 mutations/variants on test accuracy'.)

Others

- **Alpha (B.1.1.7 lineage)** – This variant was first identified in the United Kingdom in late 2020 and subsequently became the globally dominant variant until the emergence of the Delta variant (table 1) [50-52]. Alpha was approximately 50 to 75 percent more transmissible than previously circulating strains [50,53-56]. Some [57,58], but not all, studies [59] suggested that the Alpha variant was associated with greater disease severity.

- **Beta (B.1.351 lineage)** – This variant, also known as 20H/501Y.V2, was identified and predominated in South Africa in late 2020 (table 1) [60]. Although it was subsequently identified in other countries, including the United States, it did not become a globally dominant variant. The main concern with Beta variant was immune evasion: convalescent and post-vaccination plasma did not neutralize viral constructs with Beta spike protein as well as those with wild-type spike protein [61-64].

- **Gamma (P.1 lineage)** – This variant, also known as 20J/501Y.V3, was first identified in Japan in December 2020 and was prevalent in Brazil (table 1) [65]. Although it was subsequently identified in other countries, including the United States, it did not become a globally dominant variant. Several mutations in the variant raised concern about increased transmissibility and an impact on immunity [66].

- **Delta (B.1.617.2 lineage)** — This lineage was first identified in India in December 2020 and had since been the most prevalent variant worldwide until emergence of the Omicron variant (table 1). Compared with the Alpha variant, the Delta variant was more transmissible [67,68] and was associated with a higher risk of severe disease and hospitalization [67,69-71]. 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", section on 'Immunogenicity, efficacy, and safety of select vaccines'.)

EPIDEMIOLOGY

Geographic distribution and case counts — 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. Globally, over 500 million confirmed cases of COVID-19 have been reported. An interactive map highlighting confirmed cases throughout the world can be found here.

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 [72-75]. One study that used multiple data sources, including databases on case counts, COVID-19-related deaths, and seroprevalence, estimated that by November 2021, over 3 billion individuals, or 44 percent of the world's population, had been infected with SARS-CoV-2 at least once [76]. Approximately one-third of the total cases were estimated to have occurred in South Asia (including India).

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) [77]. 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 [78-81]. 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 [82-85]. Experimental studies have also supported the feasibility of airborne transmission [86-88]. 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 [89-93]; attempts to find viable virus in air and

surface specimens in health care settings have only rarely been successful [92-96]. Nevertheless, the overall transmission and secondary attack rates of SARS-CoV-2 suggest that long-range airborne transmission is not a primary mode [80,81]. 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 [97,98]. 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 prevention 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 [99-106]. 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 [102,103], and replicative virus has been cultured from stool in rare cases [100,107]. 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 [108,109]. 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 [110].

Detection of SARS-CoV-2 RNA in blood has also been reported in some but not all studies that have tested for it [99,100,103,111,112]. 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 [113]. (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: Overview of pregnancy issues", section on 'Risk of vertical transmission'.)

Viral shedding and period of infectiousness — 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 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 within the first 7 to 10 days of infection, when viral RNA levels from upper respiratory specimens are the highest and infectious virus is most likely detectable [114-122]. This is supported by data evaluating the duration of transmission risk. 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 [117]. 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 [123].

  Most of these data were collected during the first year of the pandemic. Subsequent data on the Omicron variant suggest that the peak of viral RNA and greatest likelihood of infectious virus shedding may occur slightly later, at three to six days after symptom onset [124,125]. Nevertheless, the median duration that infectious Omicron virus was detectable in nasal specimens ranged from three to five days following diagnosis, and infectious virus was rarely detected more than 10 days after symptom onset, suggesting that transmission after this period remains unlikely with Omicron [126,127].

- **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 [103,116,128-134]. 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 [133]. 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 $<10^6$ copies/mL [116]. 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 [135,136]. 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 [116,135-140].

Occasional reports have described isolation of infectious virus from respiratory specimens for several months following symptom onset in immunocompromised patients [141-145]. Prolonged shedding of virus in fecal specimens has also been described [107]. 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 prevention 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) [146]. 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 [147-149].

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 [150-153]. In a systematic review of 87 studies published through June 2021 that included over 1.2 million household contacts of individuals with SARS-CoV-2 infection in 30 countries, the overall secondary household attack rate was 18.9 percent (95% CI 16.2-22), although there was substantial heterogeneity across studies [153]. However, the attack rate increased over time with the emergence of more transmissible variants. As an example, in a subsequent systematic review of 58 studies published from June 2021 to March 2022, the secondary household attack rate during circulation of different variants was 36 percent (95% CI 33-39) for the Alpha variant, 29.7 percent (95% CI 23-37) for Delta, and 43 percent (95% CI 35-50) for Omicron. During Omicron prevalence, vaccination status of either the index case or household contact was not associated with a statistically significant difference in secondary attack rate [154]. However, other potential features that could impact household transmission rates (such as isolation from other household members) were not accounted for. (See 'Omicron (B.1.1.529) and its sublineages' above.)

  Within households, spouses or significant others have the highest secondary infection rates [150]. Nevertheless, children and adolescents can also serve as index cases for

secondary household infections [155-157]. (See "COVID-19: Clinical manifestations and diagnosis in children", section on 'Transmission'.)

- In health care settings when personal protective equipment was not used (including hospitals [158] and long-term care facilities [159]).

- In other congregate settings where individuals are residing or working in close quarters (eg, cruise ships [160], homeless shelters [161,162], detention facilities [163,164], college dormitories [165], and food processing facilities [166,167]).

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 [84,168-170]. 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 [168]. 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 [171,172]. (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 [146,147,173]. 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 [84]. 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 [174]. 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 [175-178], 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 [176]. 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 [177]. 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 [179]. 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 [180].

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 'Transmission'.)

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 [181-187].

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 [188]. The levels and duration of viral RNA in the upper respiratory tract of asymptomatic patients are also similar to those of symptomatic patients [189].

The risk of transmission from an individual who is asymptomatic appears less than that from one who is symptomatic [151,156,190-193]. 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 [194]. 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 [192].

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 [195]. 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.

Incubation period — The time from exposure to infection is discussed in detail elsewhere. (See "COVID-19: Clinical features", section on 'Incubation period'.)

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 [89,196,197]. 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 [89]. 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 [116].

It is unknown how long SARS-CoV-2 can persist on surfaces [198-200]; 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 [199]. 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 [198]. 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 [201]. 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 [202].

These data highlight the importance of environmental disinfection in the home and health care setting. (See "COVID-19: Infection prevention 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 [203-206]. Moreover, asymptomatic, experimentally infected domestic cats may transmit SARS-CoV-2 to cats they are caged with [207]. 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 [208]. 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 [209-211]. In view of these findings, mink on farms in both the Netherlands and Denmark have been, or are being, culled. Hamster-to-human transmission resulting in a large cluster of human cases has also been described [212].

Immune responses following infection — Protective SARS-CoV-2-specific antibodies and cell-mediated responses are induced following infection. Evidence suggests that some of these responses 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 [115,116]. However, the magnitude of antibody response may be associated with severity of disease, and patients with mild infection may not mount detectable neutralizing antibodies [213,214]. When neutralizing antibodies are

elicited, they generally decline over several months after infection, although studies have reported detectable neutralizing activity up to 12 months [215-221]. 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 [215,217,218,222]. Although detectable antibodies and neutralizing activity have been associated with protection from subsequent infection [223-227], humoral responses after infection with one variant do not necessarily provide strong protection against other variants. (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 COVID-19 vaccination, which suggest the potential for a durable T cell immune response [215,222,228,229].

Immune responses following vaccination are discussed in detail elsewhere. (See "COVID-19: Vaccines", section on 'Immunogenicity, efficacy, and safety of select vaccines'.)

Risk of reinfection — Prior to emergence of the Omicron variant, the short-term risk of reinfection (eg, within the first several months after initial infection) was low. Prior infection reduced the risk of infection in the subsequent six to nine months by at least 80 to 85 percent [226,230-233]. Several other studies had estimated the risk of reinfection as less than 1 percent over that time frame [234-238]. However, the risk of reinfection with Omicron variant in individuals previously infected with other variants is higher; the risk of reinfection with certain Omicron sublineages after prior infection with a different Omicron sublineage is uncertain but also likely higher than earlier reinfection estimates, given evidence of immune evasion [26]. (See 'Omicron (B.1.1.529) and its sublineages' above.)

Some studies suggest that reinfections are milder than initial infections. As an example, in a study from Qatar, the odds of severe disease among 1304 individuals with reinfection was 0.12 compared with age-, sex-, and infection date-matched individuals with an initial infection [239]; there were no cases of critical illness or death among the reinfection group (compared with 28 and 7, respectively, in the initial infection group). However, reinfections that were more severe than the initial infection as well as fatal reinfections have been reported [238,240,241].

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' and '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 prevention for persons with SARS-CoV-2 infection", section on 'Infection prevention in the health care setting'.)

Personal preventive measures — In the setting of community transmission of SARS-CoV-2, the following general measures are recommended to prevent infection [242]:

- Hand washing and respiratory hygiene (eg, covering the cough or sneeze). Use of hand sanitizer that contains at least 60% alcohol is a reasonable alternative to hand washing if the hands are not visibly dirty. In one study, SARS-CoV-2 remained viable on the skin for about nine hours but was completely inactivated within 15 seconds of exposure to 80% alcohol [243].

- Vaccination. (See "COVID-19: Vaccines", section on 'Dose and interval'.)

- Ensuring 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 [244,245].

- If symptoms suggestive of COVID-19 (table 2) occur, staying home away from others and getting tested for SARS-CoV-2. (See "COVID-19: Diagnosis", section on 'Diagnostic approach'.)

- Avoiding close contact with individuals who have or may have COVID-19. If levels of community transmission are high, avoiding crowds and close contact with other people outside of the household is also advised to reduce the risk of exposure. (See 'Social/physical distancing' below.)

  Precautions following known exposure are discussed elsewhere. (See 'Post-exposure management' below.)

- Wearing masks, depending on the level of community transmission and the individual risk for severe infection. (See 'Wearing masks in the community' below.)

These preventive measures are recommended for all individuals in locations where SARS-CoV-2 is circulating and are particularly emphasized for individuals who have immunocompromising conditions and are at higher risk for severe infection.

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) [246]. In the United States, the CDC recommendations on masking depend on the estimated COVID-19 community levels, which reflect a combined measure of local case counts, new COVID-19 hospital admissions, and the percent of staffed inpatient beds occupied by patients with COVID-19 [247]. In locations with low community levels, the CDC suggests that mask wearing be optional; at medium levels, it advises individuals who are immunocompromised or otherwise at risk for severe disease to consider masking in public and advises their close contacts to wear masks; at high levels, the CDC recommends that all individuals wear masks in indoor public settings. All masking recommendations assume that strategies to achieve and maintain high rates of vaccination, including booster doses, are ongoing. The CDC also recommends that all individuals wear masks on public transportation (including taxis and ride-shares) and at transportation hubs (eg, airports, bus or ferry terminals, railway stations, seaports) [248]. Masking is also recommended for all persons who have suspected or documented COVID-19 or exposure to SARS-CoV-2, regardless of community level. Precautions for individuals with infection or exposure are discussed in detail elsewhere. (See "COVID-19: Infection prevention for persons with SARS-CoV-2 infection", section on 'Isolation at home' and 'Testing and masking precautions' below.)

Type of masks — In the United States, the CDC recommends that, in locations or situations where masks are recommended, individuals wear the mask with the highest filtration efficacy that fits well and that one can wear reliably over the mouth and nose [249]. When fit tightly around the face, respirators (eg, N95) have the highest filtration efficacy, followed by disposable medical masks. In general, cloth masks have the lowest filtration efficacy, although cloth masks made of several layers of tightly woven fabric can approach the filtration efficacy of medical masks [250,251]. The importance of filtration efficacy increases in situations in which the risk of exposure is high (eg, prolonged close contact indoors or in vehicles with people outside the

household, particularly if other people are unmasked) or for individuals who are at risk for severe COVID-19. Ultimately, however, consistent and correct use is the most important aspect of mask use, as incorrect use or poor fit diminishes the value of high filtration efficacy of the material. 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 medical 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 [252]. Respirators and masks should not have exhalation valves. For individuals who opt to wear a respirator, KN95 and KF94 are advertised as meeting high filtration standards in China and South Korea, respectively, and are alternatives to the N95 respirator. People should be aware, however, that many marketed KN95 and KF94 respirators do not meet the advertised filtration standards; if used, KN95 or KF94 respirators that have been independently assessed for filtration efficiency should be chosen [253]. Detailed information on the types of recommended masks can be found on the CDC website.

The WHO also recommends medical or nonmedical masks (including homemade multilayered masks) for most individuals and has issued standards for the ideal composition of a cloth mask to optimize fluid resistance and filtration efficiency [254]. However, it specifically recommends medical masks for individuals with symptoms consistent with COVID-19, for 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 for household contacts of individuals with suspected or confirmed COVID-19 when in the same room [246]. 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 [255].

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 [256,257].

Rationale — The primary objective for wearing masks in the community is to prevent transmission from individuals with infection by containing their respiratory secretions. Masks can also reduce exposure to SARS-CoV-2 for the wearer.

- **Source control and transmission reduction** – Multiple observational studies support the use of masks to provide source control and reduce transmission in the community [250,258-269]. 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 [265,270-272]; lifting of universal mask mandates has conversely been associated with increased case rates [273]. In a meta-analysis of six observational studies, mask-wearing was associated with a 53 percent reduction in the incidence of COVID-19 [267]. 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 [274,275].

Nevertheless, efficacy of masks has been difficult to demonstrate consistently in clinical trials. In a meta-analysis of six trials that did not demonstrate reductions in laboratory-confirmed influenza or SARS-CoV-2 infection with wearing medical masks in the community (risk ratio [RR] 1.01, 95% CI 0.72 to 1.42), only two of those trials evaluated SARS-CoV-2 transmission [276]. One of those was a cluster-randomized trial in Bangladesh, in which villages that received free masks as well as behavioral and social interventions to promote masks had increased mask use (40 versus 14 percent in control villages) and, among those who received medical masks, an associated 11 percent relative reduction in SARS-CoV-2 seroprevalence that was not statistically significant (adjusted RR 0.89, 95% CI 0.78-1.01) [277]. The other trial, from Denmark, is discussed below.

- **Prevent exposure** – Mask-wearing in the community may protect the wearer; in several observational studies, consistent mask wearing, particularly with medical masks or respirators, has been associated with a lower risk of infection [278-281]. 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) [278]. 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 [279]. In contrast, 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) [282]. However, the low rate of community transmission (as reflected by the low overall infection rate) may have made it difficult to detect a meaningful difference.

- **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) [283]. 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 [284]. 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 [250,285-287]. In an experimental model, universal masking with a three-ply cotton mask was shown to substantially reduce aerosol exposure [245]. 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 [288,289]. Data are mixed on whether wearing eyeglasses daily is associated with reduced risk of infection [290,291]; eyeglasses are generally considered insufficient for eye protection. (See "COVID-19: Infection prevention for persons with SARS-CoV-2 infection", section on 'Type of PPE'.)

Social/physical distancing — In locations where there are high levels of community transmission of SARS-CoV-2, 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; 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 [262,292-294]. 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) [262]. A distance more than six feet (two meters) was associated with further reduction in transmission.

Screening in selected high-risk settings — Testing asymptomatic individuals without known exposure is not routinely warranted, although the practice may be useful in high-risk congregate settings, such as long-term care facilities, shelters, and correctional facilities, when community transmission of SARS-CoV-2 is prevalent.

- **Serial testing in congregate settings** – Screening for SARS-CoV-2 infection with serial viral testing can quickly identify cases so that infected individuals can be isolated, contacts can be quarantined, and outbreaks can be prevented [295,296]. 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 [297,298]. Accessibility and fast turnaround time are also important features of a useful screening test. (See "COVID-19: Diagnosis", section on 'For other screening purposes'.)

- **Testing prior to group events** – Rapid testing with antigen tests prior to events (and only allowing individuals who test negative to enter) has been proposed as a strategy to reduce the risk of outbreaks. This is discussed in detail elsewhere. (See "COVID-19: Diagnosis", section on 'Antigen testing'.)

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 [299,300]. (See "COVID-19: Clinical features", section on 'Asymptomatic infections'.)

Other public health measures — Throughout the world, countries have employed various nonpharmaceutical interventions to reduce transmission. In addition to personal preventive measures (vaccination, hand and respiratory hygiene, ventilation, masking), transmission reduction strategies have included:

- 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 [267,301-309].

Implementation of these measures varies widely by country as well as over time, depending on regional rates of infection. 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 [310,311]. Because the risk of travel changes rapidly and recommendations on restricting activity and testing after travel vary, individuals should consult country- and state-specific guidance prior to travel.

Vaccines — Vaccines to prevent SARS-CoV-2 infection are considered the most promising approach for curbing the pandemic [312]. COVID-19 vaccines are discussed in detail elsewhere. (See "COVID-19: Vaccines".)

Monoclonal antibodies ineffective for pre-exposure prophylaxis — COVID-19 vaccination is the optimal method of pre-exposure prophylaxis. The monoclonal antibody combination of tixagevimab-cilgavimab had previously been an effective option for pre-exposure prophylaxis in certain individuals expected to have suboptimal protection from vaccination or unable to receive vaccination [313-316]. However, it is not expected to be effective against certain Omicron subvariants (including BQ.1/BQ.1.1, and XBB and its derivatives XBB.1 and XBB.1.5) (table 1), which accounted for over 90 percent of circulating variants in the United States as of January 2023. The US Food and Drug Administration (FDA) adjusted the emergency use authorization (EUA) for tixagevimab-cilgavimab to be contingent on the prevalence of resistant variants being less than 90 percent; thus, it is no longer authorized in the United States [317].

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 masking precautions — Throughout the pandemic, identifying secondary infection in an exposed individual and reducing the risk of that individual exposing others

before an infection is recognized have been consistent goals of preventive efforts.

In the United States, the Centers for Disease Control and Prevention (CDC) suggests the following for all individuals, regardless of vaccination history, 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) [318]:

- Wear well-fitting masks or respirators whenever around other people indoors for 10 days following exposure (day 0 is the day of exposure). Exposed individuals should avoid places where they cannot mask and should avoid contact, if possible, with other individuals at risk for severe infection.

- Test for SARS-CoV-2 at least five full days following exposure (eg, on day 6) to identify new infections promptly [319]. Because the Omicron subvariants may have a shorter incubation period than earlier variants, testing as early as four days after exposure may be helpful to identify infections sooner. Individuals with a history of SARS-CoV-2 infection in the prior 30 days do not need to test if they are asymptomatic; those with infection in the prior 30 to 90 days should undergo antigen testing rather than NAAT. (See "COVID-19: Diagnosis", section on 'Selected asymptomatic individuals' and "COVID-19: Diagnosis", section on 'Diagnosis of reinfection'.)

- Monitor for fever, cough, upper respiratory symptoms, and any other symptoms consistent with COVID-19 (table 2) following the exposure. Individuals who develop such signs or symptoms should get tested for SARS-CoV-2. While awaiting results, they should stay home, continue to mask, and maintain distance from other individuals, including those in their household. (See "COVID-19: Diagnosis", section on 'Symptomatic patients'.)

- Anyone who tests positive likely has SARS-CoV-2 infection and should self-isolate. (See "COVID-19: Infection prevention for persons with SARS-CoV-2 infection", section on 'Isolation at home'.)

Recommendations on post-exposure precautions are intended to balance the risk of infection over time (which is based in part on the incubation period for SARS-CoV-2) with the community burdens and adherence challenges associated with strategies to avoid ongoing exposure. As the impact of infection on individuals and health care systems has declined over the course of the pandemic along with rising rates of immunity and expanded therapeutic options, these recommendations have evolved from a 14-day post-exposure quarantine (ie, staying at home, away from others, for the duration of the incubation period) to shorter quarantine periods, to

relying on masking to mitigate potential transmission. There are limited data informing the risk of transmission with these various approaches.

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

Limited role for post-exposure prophylaxis — In the United States, the Food and Drug Administration (FDA) had issued an emergency use authorization (EUA) to use the monoclonal antibody combinations casirivimab-imdevimab or bamlanivimab-etesevimab to prevent SARS-CoV-2 infection in select individuals over 12 years of age [320,321]. However, these combinations do not neutralize the Omicron subvariants and thus are likely ineffective for post-exposure prophylaxis in regions where these variants predominate, which is the case throughout the United States. (See 'Omicron (B.1.1.529) and its sublineages' above.)

Thus, we defer using post-exposure prophylaxis with monoclonal antibodies during the Omicron subvariant surges. If other variants emerge that are susceptible to casirivimab-imdevimab or bamlanivimab-etesevimab, post-exposure prophylaxis may be useful for individuals who are at high risk for progression (table 3) and are either unvaccinated or expected to have suboptimal immune response to vaccination (table 4).

In a trial performed before the emergence of the Omicron variant, administration of casirivimab-imdevimab to household contacts of individuals with SARS-CoV-2 infection (within 96 hours of the index case's positive test) reduced the risk of symptomatic COVID-19 (1.5 versus 7.8 percent with placebo, adjusted OR 0.17, 95% CI 0.09-0.33) and the risk of any SARS-CoV-2 infection (4.8 versus 14.2 percent with placebo, adjusted OR 0.31, 95% CI 0.21-0.46) [322]. The efficacy of bamlanivimab-etesevimab was extrapolated from an earlier trial of nursing home residents and staff, in which bamlanivimab alone reduced the risk of subsequent COVID-19 [323]. Casirivimab-imdevimab and bamlanivimab-etesevimab are expected to retain activity against the Delta variant but, as above, not the Omicron variant.

We recommend against using other agents for post-exposure prophylaxis outside a clinical trial. Specifically, another monoclonal antibody combination, tixagevimab-cilgavimab is not authorized for post-exposure prophylaxis and, in an unpublished trial, did not result in a significant reduction in COVID-19 rates compared with placebo when given within eight days of exposure [313].

Data from placebo-controlled randomized trials indicate that hydroxychloroquine is not effective in preventing infection [323-328]; the World Health Organization specifically recommends against using hydroxychloroquine to prevent COVID-19 [329]. Ivermectin has also been proposed as a potential prophylactic agent, but it has only been evaluated in low-quality

unpublished studies [330], 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 [331].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: COVID-19 – Index of guideline topics".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: COVID-19 overview (The Basics)" and "Patient education: COVID-19 vaccines (The Basics)" and "Patient education: COVID-19 and pregnancy (The Basics)" and "Patient education: COVID-19 and children (The Basics)" and "Patient education: Long COVID (The Basics)")

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 500 million confirmed cases worldwide. An interactive map highlighting confirmed cases throughout the world can be found here. (See 'Epidemiology' above.)

- **Variants of concern** – Several variants of SARS-CoV-2 have emerged that are notable because of the potential for increased transmissibility (table 1). Omicron variant sublineages are associated with a higher risk of reinfection in individuals previously infected with other variants and breakthrough infection in vaccinated individuals, but they are also associated with less severe disease. (See 'Variants of concern' above.)

- **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 over longer distances, particularly in enclosed, poorly ventilated spaces. (See 'Route of person-to-person transmission' above and 'Environmental contamination' above.)

  SARS-CoV-2 has been detected in non-respiratory specimens, including stool, but the role of these sites in transmission is uncertain. (See 'Route of person-to-person transmission' above.)

- **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. (See 'Viral shedding and period of infectiousness' above.)

- **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. (See 'Immune responses following infection' above and 'Risk of reinfection' above.)

- **Personal preventive measures** – In settings where there is community transmission of SARS-CoV-2, personal measures to reduce the risk of transmission include vaccination, hand and respiratory hygiene, improving indoor ventilation and avoiding poorly ventilated crowded areas, being vigilant for signs and symptoms of COVID-19, and avoiding close contact with ill individuals. In the United States, recommendations on mask-wearing depend on the COVID-19 community levels. (See 'Personal preventive measures' above and 'Wearing masks in the community' above and 'Social/physical distancing' above and 'Other public health measures' above.)

- **Post-exposure precautions** – Individuals who have close contact with someone known or suspected to have COVID-19 should monitor for symptoms, wear well-fitting masks whenever around other people, and get tested for SARS-CoV-2. (See 'Post-exposure management' above.)

- **Vaccines** – COVID-19 vaccines are an essential element of prevention and are discussed in detail elsewhere. (See "COVID-19: Vaccines".)

- **Monoclonal antibodies not effective for pre-exposure prophylaxis** – In the United States, the monoclonal antibody combination tixagevimab-cilgavimab had previously received emergency use authorization (EUA) for pre-exposure prophylaxis in individuals who are expected to have suboptimal response to vaccination; however, tixagevimab-cilgavimab is not expected to be effective against the most prevalent Omicron subvariants and thus is no longer authorized. (See 'Monoclonal antibodies ineffective for pre-exposure prophylaxis' above.)

- **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. Links to these guidelines can be found elsewhere. (See 'Society guideline links' above.)

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