Coronavirus disease 2019 (COVID-19): Epidemiology, virology, and prevention

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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 an increasing number of cases in other countries throughout the world. 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 and "Coronavirus disease 2019 (COVID-19): Clinical features and diagnosis", section on 'Society guideline links'.)

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 "Coronavirus disease 2019 (COVID-19): Clinical features and diagnosis".)

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

- (See "Coronavirus disease 2019 (COVID-19): Outpatient management in adults".)
- (See "Coronavirus disease 2019 (COVID-19): Management in hospitalized adults".)
- (See "Coronavirus disease 2019 (COVID-19): Infection control in health care and home settings".)
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Issues related to COVID-19 in pregnant women and children are discussed elsewhere:

- (See "Coronavirus disease 2019 (COVID-19): Pregnancy issues".)
- (See "Coronavirus disease 2019 (COVID-19): Considerations in children" and "Coronavirus disease 2019 (COVID-19): Multisystem inflammatory syndrome in children".)

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

Common cold coronaviruses, severe acute respiratory syndrome (SARS) coronavirus, and Middle East respiratory syndrome (MERS) coronavirus are discussed separately. (See "Coronaviruses" and "Severe acute respiratory syndrome (SARS)" and "Middle East respiratory syndrome coronavirus: Virology, pathogenesis, and epidemiology".)

VIROLOGY

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 structure of the receptor-binding gene region is very similar to that of the SARS coronavirus, and the virus has been shown to use the same receptor, the angiotensin-converting enzyme 2 (ACE2), for cell entry [4]. 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) [5].

The Middle East respiratory syndrome (MERS) virus, another betacoronavirus, appears more distantly related [6,7]. 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 [8]. (See "Coronaviruses", section on 'Viral serotypes'.)

In a phylogenetic analysis of 103 strains of SARS-CoV-2 from China, two different types of SARS-CoV-2 were identified, designated type L (accounting for 70 percent of the strains) and type S (accounting for 30 percent) [9]. The L type predominated during the early days of the epidemic in China, but accounted for a lower proportion of strains outside of Wuhan than in Wuhan. The clinical implications of these findings are uncertain.

EPIDEMIOLOGY

Geographic distribution — Globally, more than six 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, except for Antarctica.

In the United States, COVID-19 has been reported in all 50 states, Washington DC, and at least four territories [10]. The cumulative incidence varies by state and likely depends on a number of factors, including population density and demographics, extent of testing and reporting, and timing of mitigation strategies. In the United States, outbreaks in long-term care facilities and homeless shelters have emphasized the risk of exposure and infection in congregate settings [11-13]. (See 'Risk of transmission' below.)

Transmission — Understanding of the transmission risk is incomplete. Epidemiologic investigation in Wuhan at the beginning of the outbreak identified an initial association with a seafood market that sold live animals, where most patients had worked or visited and which was subsequently closed for disinfection [14]. However, as the outbreak progressed, person-to-person spread became the main mode of transmission.

Person-to-person

Route of person-to-person transmission — Direct person-to-person transmission is the primary means of transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is thought to occur through close-range contact, mainly via respiratory droplets; virus released in the respiratory secretions when a person with infection coughs, sneezes, or talks can infect another person if it makes direct contact with the mucous membranes; infection can also occur if a person touches an infected surface and then touches his or her eyes, nose, or mouth. Droplets typically do not travel more than six feet (about two meters).

Whether SARS-CoV-2 can be transmitted through the airborne route (through particles smaller than droplets that remain in the air over time and distance) under natural conditions has been a controversial issue. One letter to the editor described a study in which SARS-CoV-2 grown in tissue culture remained viable in experimentally generated aerosols for at least three hours [15]; some studies have identified viral RNA in ventilation systems and in air samples of hospital rooms of patients with COVID-19, but cultures for viable virus were not performed in these studies [16-18]. Other 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 [19-21]. However, the direct relevance of these findings to the epidemiology of COVID-19 and their clinical implications are unclear. Long-range airborne transmission of SARS-CoV-2 has not clearly been documented [22], and 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 [23,24]. Reflecting the current uncertainty regarding 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

"Coronavirus disease 2019 (COVID-19): Infection control in health care and home settings", section on 'Patients with suspected or confirmed COVID-19'.)

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 [25-30]. 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 [28,29], and live virus has been cultured from stool in rare cases [26,31]. Although it would be difficult to confirm, fecal-oral transmission has not been clinically described, and according to a joint WHO-China report, did not appear to be a significant factor in the spread of infection [32].

Detection of SARS-CoV-2 RNA in blood has also been reported in some but not all studies that have tested for it [25,26,29,33]. 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 [34]. (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).

Viral shedding and period of infectivity — The precise interval during which an individual with COVID-19 is infectious is uncertain. It appears that SARS-CoV-2 can be transmitted prior to the development of symptoms and throughout the course of illness, particularly early in the course. However, most data informing this issue are from studies evaluating viral RNA detection from respiratory and other specimens; detection of viral RNA does not necessarily indicate the presence of infectious virus, and thus prolonged viral RNA detection following the resolution of illness does not necessarily indicate infectiousness.

Largely indirect data suggest that infected individuals are more likely to be infectious in the earlier stages of infection. Viral RNA levels from upper respiratory specimens appear to be higher soon after symptom onset compared with later in the illness [35-39]. Additionally, in a study of nine patients with mild COVID-19, infectious virus was isolated from naso/oropharyngeal and sputum specimens during the first eight days of illness, but not after this interval, despite continued high viral RNA levels at these sites [37]. One modeling study, based on the timing of infection among 77 transmission pairs in China (with a mean serial interval of 5.8 days between the onset of symptoms in each pair) and assumptions about incubation period, suggested that infectiousness started 2.3 days prior to symptom onset, peaked 0.7 days before symptom onset, and declined within seven days; however, most patients were isolated following symptom onset, which would reduce the risk of transmission later in illness regardless of infectiousness [38]. 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 [40].

Transmission of SARS-CoV-2 from asymptomatic individuals (or individuals within the incubation period) has also been well documented [41-47]. 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 reverse transcription polymerase chain reaction (RT-PCR)-positive upper respiratory tract specimens in presymptomatic and asymptomatic patients as early as six days prior to the development of typical symptoms [48]. However, the extent to which asymptomatic or presymptomatic transmission occurs and how much it contributes to the pandemic remain unknown. In an analysis of 157 locally acquired COVID-19 cases in Singapore, transmission during the incubation period was estimated to account for 6.4 percent; in such cases, the exposures occurred one to three days prior to symptom development [49]. Large-scale serologic screening may be able to provide a better sense of the scope of asymptomatic infections and inform epidemiologic analysis; several serologic tests for SARS-CoV-2 have been granted emergency use authorization by the US Food and Drug Administration (FDA) [50,51].

How long a person remains infectious is also uncertain, but available data suggest that prolonged viral RNA shedding after symptom resolution is not clearly associated with prolonged infectiousness. The duration of viral RNA shedding is variable; there appears to be a wide range, which may depend on severity of illness [29,37,52-54]. In one study of 21 patients with mild illness (no hypoxia), 90 percent had repeated negative viral RNA tests on nasopharyngeal swabs by 10 days after the onset of symptoms; tests were positive for longer in patients with more severe illness [52]. In contrast, in another study of 56 patients with mild to moderate illness (none required intensive care), the median duration of viral

RNA shedding from naso- or oropharyngeal specimens was 24 days, and the longest was 42 days [55].

However, as mentioned above, detectable viral RNA does not always correlate with isolation of infectious virus, and there may be a threshold of viral RNA level below which infectivity is unlikely. In the study of nine patients with mild COVID-19 described above, infectious virus was not detected from respiratory specimens when the viral RNA level was $<10^6$ copies/mL [37]. In another study, infectious virus was only detected on stored respiratory specimens that had a high concentration of viral RNA (RT-PCR positive at cycle threshold [Ct] <24) [56]. According to information from the United States Centers for Disease Control and Prevention (CDC), when patients continue to have detectable viral RNA in upper respiratory samples following clinical recovery, by three days after recovery, 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 nine days after illness onset has not yet been documented [56,57]. Infectious virus has also not been isolated from respiratory specimens of patients who have a repeat positive RNA test following clinical improvement and initial viral clearance [58]. (See 'Immunity and risk of reinfection' below.)

One study reported a patient with critical COVID-19 from whom replicative virus was isolated from the stool 28 days following symptom onset; further data are needed to understand the frequency and clinical significance of this finding [31].

The relevance of viral RNA detection to duration of infection control precautions is discussed elsewhere. (See "Coronavirus disease 2019 (COVID-19): Infection control in health care and home settings", section on 'Discontinuation of precautions'.)

Risk of transmission — 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). Most secondary infections have been described among household contacts, in congregate or health care settings when personal protective equipment was not used (including hospitals [59] and long-term care facilities [11]), and in closed settings (eg, cruise ships [60]). However, reported clusters of cases after social or work gatherings also highlight the risk of transmission through close, non-household contact.

Contact tracing in the early stages of epidemics at various locations suggested that most secondary infections were among household contacts, with a secondary attack rate of up to 15 percent [32,61-64]; some studies have suggested even higher household infection rates [46,65,66]. According to a joint WHO-China report, the rate of secondary COVID-19 in various locations ranged from 1 to 5 percent among tens of thousands of close contacts of confirmed patients in China; most of these occurred within households, with an in-household secondary attack rate of 3 to 10 percent [32]. In the United States, the symptomatic secondary attack rate was 0.45 percent among 445 close contacts of 10 confirmed patients; among household members, the rate was 10.5 percent [61]. In a similar study in Korea, the rates were comparable, with secondary infections in 0.55 percent of all contacts and 7.6 percent of family members [62].

Clusters of cases have also been reported following family, work, or social gatherings where close, personal contact can occur [67,68]. 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 [67]. A report of an outbreak among a choir group, with 33 confirmed and 20 probable cases identified among 61 members who attended a practice session, raised the possibility of a high transmission risk through singing in close proximity [69].

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 low.

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 remain unclear. It may be more likely to be 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 contamination of environmental surfaces in hospital rooms of patients with COVID-19 has been described [16,70]. 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 [16]. 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 [37].

It is unknown how long SARS-CoV-2 can persist on surfaces [15,71,72]; 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 [72]. 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 [71]. 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 [73]. 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 [74].

These data highlight the importance of environmental disinfection in the home and health care setting. (See "Coronavirus disease 2019 (COVID-19): Infection control in health care and home settings", section on 'Environmental disinfection'.)

Uncertain 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 cats) following close contact with a human with COVID-19 [75,76]. Moreover, asymptomatic, experimentally infected domestic cats may transmit SARS-CoV-2 to cats they are caged with [77]. 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 [78]. Pigs and poultry were not susceptible to infection.

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 transmitting SARS-CoV-2 infection to humans.

Immunity and risk of reinfection — Antibodies to the virus are induced in those who have become infected. Preliminary evidence suggests that some of these antibodies are protective, but this remains to be definitively established. Moreover, it is unknown whether all infected patients mount a protective immune response and how long any protective effect will last.

Data on protective immunity following COVID-19 are emerging [36,37,79]. A case series evaluating convalescent plasma for treatment of COVID-19 identified neutralizing activity in plasma of recovered patients that appeared to be transferred to recipients following plasma infusion [79]. Similarly, in another study of 23 patients who recovered from COVID-19, antibodies to the receptor-binding domain of the spike protein and the nucleocapsid protein were detected by enzyme-linked immunosorbent assay (ELISA) in most patients by 14 days following the onset of symptoms; ELISA antibody titers correlated with neutralizing activity [36]. Animal studies have suggested that the immune response to infection may offer some protection against reinfection, at least in the short term. 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 [80]. Studies evaluating SARS-CoV-2 vaccine candidates in macaques have also suggested that immune responses to vaccination result in lower levels of viral RNA in respiratory tract specimens following viral challenge compared with unvaccinated controls [81,82].

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

SARS-CoV-2 vaccine, which suggest the potential for a durable T cell immune response [83,84].

Some studies have reported positive RT-PCR tests for SARS-CoV-2 in patients with laboratory-confirmed COVID-19 following clinical improvement and negative results on two consecutive tests [85-87]. However, these positive tests occurred shortly after the negative tests, were not associated with worsening symptoms, may not represent infectious virus, and likely did not reflect reinfection. Specifically, in a report from the Korea Centers for Disease Control and Prevention of patients with COVID-19 who had a repeat positive RNA test after being previously cleared from isolation, infectious virus could not be isolated in cell culture in any of the 108 patients tested [58]. Among 790 contacts, there were no newly confirmed cases that were traced to exposure during the period of the repeat positive test.

As above, the FDA has granted emergency use authorization for tests that identify antibodies against SARS-CoV-2 in serum or plasma [51]. Should evidence confirm that the presence of these antibodies reflects a protective immune response, serologic screening will be an important tool to understand population immunity and distinguish individuals who are at lower risk for reinfection.

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 "Coronavirus disease 2019 (COVID-19): Infection control in health care and home settings", 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 should be encouraged to practice social distancing by staying home as much as possible and maintaining six feet (two meters) distance from others when they have to leave home. In particular, individuals should avoid crowds and close contact with ill individuals. Many countries also encourage individuals to wear masks when out in public. (See '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 percent alcohol is a reasonable alternative if the hands are not visibly dirty.
- 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 [88].
- Cleaning and disinfecting objects and surfaces that are frequently touched. The CDC has issued guidance on disinfection in the home setting; a list of Environmental Protection Agency-registered products can be found here.

These measures should be followed by all individuals, but should be emphasized for older adults and individuals with chronic medical conditions, in particular.

For people without respiratory symptoms, the WHO does not recommend wearing a medical mask in the community, since it does not decrease the importance of other general measures to prevent infection and may result in unnecessary cost and supply problems; the WHO also emphasizes that medical masks should be prioritized for health care workers [89]. Recommendations on use of masks by healthy members of the community vary by country [90].

In the United States, the CDC updated its recommendations in early April to advise individuals to wear a cloth face covering (eg, homemade masks or bandanas) when in public settings where social distancing is difficult to achieve, especially in areas with substantial community transmission [91]. Individuals should be counseled to avoid touching the eyes, nose, and mouth when removing the covering, practice hand hygiene after handling it, and launder it routinely. Clinicians should emphasize that the face covering does not diminish the importance of other preventive measures, such as social distancing and hand hygiene. The rationale for the face covering is primarily to contain secretions of and prevent transmission from individuals who have asymptomatic or presymptomatic infection.

The CDC also reiterates that the face covering recommendation does not include medical masks, which should be reserved for health care workers.

Individuals who develop an acute respiratory illness (eg, with fever and/or respiratory symptoms) should be encouraged to self-isolate at home (away from other individuals and pets in the household) for the duration of the illness and wear a face cover if they have to be around other people. Some may warrant evaluation for COVID-19. Individuals who are caring for patients with suspected or documented COVID-19 at home should also wear a face cover when in the same room as that patient (if the patient cannot wear a face cover). (See "Coronavirus disease 2019 (COVID-19): Clinical features and diagnosis", section on 'Clinical suspicion and criteria for testing' and "Coronavirus disease 2019 (COVID-19): Infection control in health care and home settings", section on 'Isolation at home'.)

The use of face covers/masks to provide source control and reduce transmission in the community is supported by indirect evidence [92-96]. 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 [92]. The type of mask used (medical or cloth) was not specified. In another study that included 17 patients with common cold coronavirus infections, use of a medical mask eliminated detectable viral RNA in droplet and aerosol particles collected from exhaled breath (although viral RNA was only detected in 30 and 40 percent of such specimens when patients were not wearing masks) [93]. Studies on the filtration efficacy of fabrics suggest that certain fabrics (eg, tea towel fabric [termed dish towel fabric in the United States]), particularly when double-layered, can approach the filtration efficacy of medical masks [94].

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

Managing asymptomatic individuals with potential exposure — In areas where SARS-CoV-2 is prevalent, all residents should be encouraged to stay alert for symptoms and practice social distancing by staying home as much as possible and maintaining six feet (two meters) distance from others when they have to leave the home.

In the United States, the CDC suggests this approach for all residents [97]. For those returning from international travel (including cruise ship travel) and those who have had close contact with a patient with suspected or confirmed COVID-19 (including during the 48 hours prior to that patient developing symptoms), the CDC also suggests [97,98]:

- Self-quarantine at home for 14 days following the last exposure, with maintenance of at least six feet (two meters) from others at all times.
- Avoiding contact with individuals at high risk for severe illness (unless they are household members with the same exposure). (See "Coronavirus disease 2019 (COVID-19): Clinical features and diagnosis", section on 'Risk factors for severe illness'.)
- Twice-daily temperature checks with monitoring for fever, cough, or dyspnea. If they develop such clinical manifestations, they should continue to stay at home away from other household members and contact their medical providers. (See "Coronavirus disease 2019 (COVID-19): Outpatient management in adults", section on 'Management and counseling for all outpatients'.)

For asymptomatic individuals who are critical infrastructure workers, the CDC has provided guidance on returning to work during the 14-day post-exposure period with symptom and temperature monitoring, mask use, social distancing, and workspace disinfection [99].

Management of health care workers with a documented exposure is discussed in detail elsewhere. (See "Coronavirus disease 2019 (COVID-19): Infection control in health care and home settings", section on 'Return to work for health care workers'.)

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, hand hygiene, respiratory etiquette and face covers, 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 [100-104], although the relative contribution of each is difficult to assess, as most countries have employed a combination of interventions. As an example, in an epidemiologic study in Wuhan, a number of these interventions (implementation of travel restrictions in and around Wuhan with home quarantine and compulsory mask-wearing in public, followed by centralized quarantine for all cases and contacts, followed by proactive symptom screening for all residents) were associated with progressive reductions in the incidence of confirmed cases in Wuhan and a decrease in the effective reproduction number (ie, the average number of secondary cases for each case in a population made up of both susceptible and nonsusceptible individuals) from >3 prior to the interventions to 0.3 after them [100]. In another study from China, cities in which combined control measures were preemptively implemented prior to identification of COVID-19 cases recorded 33 percent fewer laboratory-confirmed cases during the first week of the outbreak compared with cities that implemented control measures later [101]. In a study from the United States evaluating incident cases in bordering counties in Illinois, which issued a stay-at-home order, and Iowa, which did not, the counties in Iowa experienced a more rapid increase in cases following implementation of the order in Illinois, estimated to result in 217 excess cases after one month [102].

Physical distancing is likely independently associated with a reduced risk of transmission. 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) [105]. A distance more than six feet (two meters) was associated with further reduction in transmission.

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 [106,107].

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

In the United States, the CDC currently recommends that individuals avoid all nonessential international travel and nonessential travel from some domestic locations [108]. Because the risk of travel changes rapidly, travelers should check United States government websites for restrictions.

Investigational approaches

Vaccines — Numerous vaccine candidates are being evaluated for prevention of COVID-19 [83,109]. These include various types of vaccines, including nucleic acid-based (mRNA and DNA) vaccines, viral-vector vaccines, and inactivated or recombinant protein vaccines [110]. The different vaccine platforms vary in their potential safety and immunogenicity, speed and cost of manufacturing, and other features important for meeting global demand.

There is also interest in Bacille-Calmette-Guerin (BCG) immunization for prevention of COVID-19, and clinical trials are underway to evaluate its use among health care workers [111]. Studies have suggested that, although its primary purpose is prevention of tuberculosis, BCG immunization induces a nonspecific immune response that may have protective effects against non-mycobacterial, including viral, infections [112,113]. Any impact of BCG immunization on COVID-19 is unknown. The WHO recommends BCG vaccination not be used for prevention or lessening the severity of COVID-19, pending further data [114].

Post-exposure prophylaxis — Clinical trials are also being conducted in the United States and elsewhere to evaluate the safety and efficacy of post-exposure drug prophylaxis against COVID-19 [115,116]. No agent is known to be effective in preventing infection; we recommend that post-exposure prophylaxis not be attempted outside a clinical trial.

Hydroxychloroquine was one candidate agent for post-exposure prophylaxis, but available data suggest it is not effective in preventing infection. In a double-blind trial, 821 individuals were randomly assigned to hydroxychloroquine or placebo folate tablets within four days of a household or occupational exposure to SARS-CoV-2, which was defined as contact within six feet for more than 10 minutes without an eye shield; most were also not wearing a medical mask [117]. Hydroxychloroquine did not reduce the rate of the combined outcome of polymerase chain reaction (PCR)-confirmed COVID-19 or consistent symptoms within 14 days (11.8 versus 14.3 percent with placebo, difference -2.4 percentage points, 95% CI -7.0 to 2.2); there were also no differences in the separate rates of PCR-confirmed or presumed cases. Side effects were reported in 40.1 percent of hydroxychloroquine-treated versus 16.8 percent of placebo-treated subjects. Loss to follow-up in about 11 percent, a greater rate of treatment discontinuation in the hydroxychloroquine group, and use of self-reported symptoms as a proxy for incident COVID-19 reduce confidence in the findings; nevertheless, the study did not demonstrate a role for hydroxychloroquine for prevention of COVID-19.

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: Coronavirus disease 2019 (COVID-19) – International and government guidelines for general care" and "Society guideline links: Coronavirus disease 2019 (COVID-19) – Guidelines for specialty care" and "Society guideline links: Coronavirus disease 2019 (COVID-19) – Resources for patients".)

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: Coronavirus disease 2019 (COVID-19) overview (The Basics)" and "Patient education: Coronavirus disease 2019 (COVID-19) and pregnancy (The Basics)" and "Patient education: Coronavirus disease 2019 (COVID-19) and children (The Basics)")

SUMMARY AND RECOMMENDATIONS

- In late 2019, a novel coronavirus, now designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified as the cause of an outbreak of acute respiratory illness in Wuhan, a city in China. In February 2020, the World Health Organization (WHO) designated the disease COVID-19, which stands for coronavirus disease 2019. (See 'Introduction' above and "Coronavirus disease 2019 (COVID-19): Clinical features and diagnosis", section on 'Introduction'.)

- Since the first reports of COVID-19, infection has spread to include more than six million confirmed cases worldwide, prompting the WHO to declare a public health emergency in late January 2020 and characterize it as a pandemic in March 2020. (See 'Epidemiology' above.)

- Direct person-to-person transmission is the primary means of SARS-CoV-2 transmission. It is thought to occur through close-range contact, mainly via respiratory droplets. Virus on heavily contaminated surfaces (eg, in an infected individual's household or in health care settings) 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 extent to which airborne transmission (through particles smaller than droplets that remain in the air over time and distance) contributes to spread of SARS-CoV-2 has been a controversial issue. (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.)

- Individuals with SARS-CoV-2 infection appear more likely to be infectious in the earlier stages of infection (including prior to the development of symptoms). How long a person remains infectious is uncertain, but data suggest that prolonged viral RNA shedding after symptom resolution is not clearly associated with prolonged infectiousness. Isolation of infectious virus from upper respiratory specimens more than nine days after illness onset has not yet been documented. (See 'Viral shedding and period of infectivity' above.)

- Infection appears to induce protective antibodies. However, it is as yet unknown whether all infected patients mount a protective immune response and how long any protective effect will last. (See 'Immunity and risk of reinfection' above.)

- To reduce the risk of transmission in the community, individuals should be advised to wash hands diligently, practice respiratory hygiene (eg, cover their cough), and avoid crowds and close contact with ill individuals, if possible. Social distancing is recommended in locations that have community transmission. In some locations, face coverings are advised in public settings. (See 'Personal preventive measures' above.)

- We recommend that post-exposure prophylaxis not be attempted outside a clinical trial (**Grade 1B**).

- Interim 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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