Coronaviruses

Outbreak Report

The What's New section is updated by 7:00 p.m. ET every Monday, Wednesday, and Friday (last updated September 23, 2020). Items remain for 1 week, and the most recent items are presented first. The material in the rest of the comprehensive Outbreak Report is updated by 8:00 p.m. ET every Wednesday (last updated September 23, 2020), including the incorporation of What's New content from the previous week.

What's New

Specific Shoreland travel recommendations are now available for individual countries on their respective Destinations page and in Report Builder (sample shown below). Each recommendation is based on aggregate national data (daily cases per 100,000), available medical care, testing positivity rates (when available), and access to testing.

The Shoreland recommendation levels are:

- All persons should avoid nonessential travel to this country.
- Healthy younger persons should avoid nonessential travel to this country if consistent masking and careful physical distancing are not possible. Vulnerable persons should avoid all nonessential travel to this country.
- Healthy younger persons should consider avoiding nonessential travel to this country if consistent masking and careful physical distancing are not possible. Vulnerable persons should consider avoiding all nonessential travel to this country.
- No recommendation against travel to this country is in place.

Because some cities or regions may have higher or lower risk within an individual country, over the coming weeks, cities/regions with risk higher than the national average will be specified on each Destination page. The Shoreland travel recommendations will be updated every Tuesday evening.

Following positive Phase 2 trial data (yet to be published), Ad26.COV2.S (Johnson & Johnson/Janssen) has entered a Phase 3 trial with a planned enrollment of 60,000 subjects at 215 locations across the U.S., Argentina, Brazil, Chile, Colombia, Mexico, Peru, and South Africa. Ad26.COV2.S will be administered as 1 dose to subjects aged ≥ 18 years, including a significant enrollment of subjects aged 60 years. A parallel Phase 3 trial using a 2-dose series will occur in multiple countries in collaboration with the U.K. Preliminary trial results are not expected for at least 2 months; if the vaccine is proven safe and effective, earliest availability is expected to be in early 2021. The U.S., Canada, and E.U. have advanced-purchase agreements in place for approximately 238 million doses. Ad26.CoV.S may be stored at -20°C (-4°F) for up to 2 years or at 2-8°C (36-46°F) for up to 3 months, unlike mRNA vaccines, which are unstable; some (e.g., BNT162b2 [Pfizer/BioNTech]) must be stored at -70°C (-94°F).

A propensity score-adjusted analysis was conducted on all veterans with rheumatological conditions in the U.S. Veterans Health Administration clinical administrative database, and no association was found with a preventive effect against SARS-CoV-2 infection. Each patient on chronic treatment with HCQ (n = 10,703) was matched to 2 patients who were not receiving HCQ (control, n = 21,406). No significant difference in the incidence of active SARS-CoV-2 infections (0.3% vs. 0.4%) exists between the 2 groups. Among patients who developed active SARS-CoV-2 infection, no difference in hospital admission, intensive care requirement, or mortality associated with SARS-CoV-2 was identified. Overall mortality was lower in the HCQ group (odds ratio = 0.70).

In the U.S., health department staff from 2 counties in North Carolina conducted contact tracing during June-July 2020. They reached 77% to 99% of new COVID-19 cases within a median of 3 to 4 days from specimen collection, but 35% to 48% of these COVID-19 cases reported no contacts. The proportion without identified contacts is similar to reports from Maryland and New Jersey, which found that 50% to 52% of COVID-19 cases reported no contacts.

During the first several months of the COVID-19 pandemic, persons in older age groups had the highest incidence. In the U.S. during June-August 2020, persons aged 20-29 years had the highest COVID-19 incidence (> 20% of all confirmed cases). The percentage of positive SARS-CoV-2 tests in adults aged 20-39 years preceded increases in adults aged ≥ 60 years by 4 to 15 days and likely contributed to transmission.

A U.S. cohort study of 1641 COVID-19 adult patients who were hospitalized found an association in mortality risk with elevated red blood cell distribution width (RDW) and increasing RDW during the hospital course.

In Canada, daily new COVID-19 cases have been steadily increasing since August 16, 2020. As of September 23, daily new cases have reached approximately 1,100; daily case numbers peaked at 1,900 on May 1 and decreased to a nadir of approximately 170 on June 26.

A small study from a hospital in Rome, Italy supports the continuation of face-mask use after COVID-19 lockdowns to contain SARS-CoV-2 droplet spread. Four male patients with COVID-19 hospitalized in double rooms were studied (2 patients in each room). In one room, the patients wore surgical masks; in the other room, the patients did not. Environmental samples were tested for SARS-CoV-2 RNA after 5 hours. Samples were PCR-positive (from the headboard and sides of the beds) in the room where patients did not wear surgical masks. In the other room, all samples tested negative.

In a hospital in Gainesville, Florida (U.S.), air samples in the rooms of 2 COVID-19 patients were obtained, one ready for discharge with a negative PCR, the other newly admitted. Samples were tested with RT-qPCR, virus culture, and genome sequencing. Air samples collected 2 to 4.8 m (6-16 ft) away from the newly admitted patient contained viable SARS-CoV-2, whereas air samples from the other patient's room tested negative. The air sample genome sequences were identical to that from the newly admitted patient, suggesting that in the absence of aerosol-generating procedures, patients with acute respiratory symptoms of COVID-19 can produce infectious aerosols.

Contact tracing was conducted on international passengers arriving to or departing from Greece from February 26 through March 9, 2020. This included persons sitting less than 2 m (6 ft) apart for more than 15 minutes, including passengers seated 2 seats around the index case, all crew members, and persons who had close contact with the index case. Among 18 international flights with 2,224 passengers and 110 crew members investigated, identified cases included 21 index cases and 891 contact-traced cases, including 6 index cases who were symptomatic during the flight. Two COVID-19 index cases were associated with 4 passengers and 1 crew member that developed laboratory-confirmed infection (3 symptomatic and 2 asymptomatic).

Two passengers and 2 flight attendants with COVID-19 were identified to have traveled on the same flight March 9-10 from Boston, Massachusetts (U.S.) to Hong Kong. The genomic sequences of their viruses were identical, unique, and belong to clade G–not previously identified in Hong Kong–suggesting that the 2 passengers were infected in North America and transmitted the virus during air travel.

During March 1-2, a traveler (probable index case, symptomatic) flew from London, U.K. to Hanoi, Vietnam and was subsequently confirmed to have COVID-19. An additional 15 COVID-19 cases were identified among passengers (n = 14) and crew (n = 1). Twelve of the 16 confirmed COVID-19 cases (75%) were passengers seated in business class with the probable index case (attack rate 62%). Proximity in seating is associated with increased infection risk (risk ratio = 7.3).

One more clinical trial (n = 1,483) on HCQ (once weekly or twice weekly as preexposure prophylaxis for COVID-19) has preliminarily announced that no significant reduction exists in COVID-19 incidence compared to a placebo.

Hong Kong presents a localized and well-monitored environment for contact tracing. Contact-tracing data from 1,038 SARS-CoV-2 cases in Hong Kong between January 23 and April 28, 2020, identified 4 to 7 superspreading events across 51 clusters (n = 309 cases) and estimated that 19% of cases seeded 80% of all local transmission. Transmission in social settings was eventually associated with more secondary cases than in households (when controlling for age).

Information regarding close-contact exposure has been enhanced in several locations in the Outbreak Report to clarify that contact with a symptomatic or asymptomatic COVID-19 case (outside of health care settings) includes any amount of direct physical or face-to-face contact of less than 2 m (6 ft) for more than 15 minutes, irrespective of whether the COVID-19 case or the contact was wearing a mask.

The U.S. CDC has reverted to the previous COVID-19 diagnostic testing guidelines to emphasize that all close contacts (symptomatic and asymptomatic) of a confirmed COVID-19 case (symptomatic or asymptomatic) should be tested. Persons should self-isolate/self-quarantine at home for 14 days and stay separated from other household members, even if the test result is negative. Asymptomatic persons who attended a high-risk event/gathering or returned from an area experiencing high levels of COVID-19 should self-quarantine for 14 days and may be considered for testing by their provider or local health authorities.

In Europe, the current 365,000 weekly COVID-19 cases exceed those reported during the initial peak in March. Over half of European countries (including France, Germany, Italy, Spain, and the U.K.) have reported more than a 10% increase in the past 2 weeks. Persons aged 25-49 years account for most cases.

The Canada-U.S. and the Mexico-U.S. land borders will be closed to nonessential travel until October 21, 2020. Areas of high transmission in Wales entered an indefinite lockdown on September 22; only those traveling for work or education will be allowed to enter or leave affected areas. Six districts in Madrid, Spain, affecting approximately 850,000 people, entered a partial lockdown on September 21, restricting movement between the districts. Access to public areas in affected districts are restricted and shops are required to close by 10:00 p.m.

Weekly Epidemiologic Summary

This section provides a global epidemiologic summary (updated every Wednesday by 7:00 p.m. ET). For more current data, see the comprehensive table on the Cases by Country page and/or the Destination pages of individual countries (updated every

Monday, Wednesday, and Friday by 5:00 p.m. ET).

Cumulative case numbers for COVID-19, caused by SARS-CoV-2, are as follows:

- Cases/deaths worldwide: 31.9 million/978,100 in more than 210 countries
- Cases/deaths in Latin America: 8.8 million/327,000
- Cases/deaths in the U.S.: 7.1 million/205,000
- Cases/deaths in Europe: 4.5 million/218,000
- Cases/deaths reported from China since March 3: 5,000 of 85,300 cumulative cases/4,600
- Transmission aboard large ships: more than 5,700 cases aboard more than 100 ships

Globally, the 7-day rolling average of daily new cases has increased to more than 287,000; a record number of more than 323,100 cases was reported on September 18. The 7-day rolling average of daily new deaths has plateaued at approximately 5,000 since September 14; daily new deaths peaked at more than 10,000 on April 29 and decreased to a nadir of approximately 1,200 on May 25. Weekly case numbers are currently highest in Asia and Latin America, representing approximately 35% and 23% of the total cases reported globally over the past 7 days, respectively. Cumulative case numbers are respectively highest in the U.S., India, Brazil, Russia, and Colombia. In terms of COVID-19 cases per million population per day (7-day rolling average), the following countries now have the highest incidence: Aruba (686), Montenegro (472), Andorra (449), Israel (439), Bahrain (402), Argentina (274), Spain (242), Costa Rica (240), Guam (223), Puerto Rico (221). Significant numbers of daily cases are being reported in countries with previously controlled outbreaks, including France, Israel, the Netherlands, Spain, and the U.K. As of September 13, the 14-day incidence reported in the E.U./E.E.A. and the U.K. was 76 per 100,000 population compared to 66 per 100,000 as of September 9, representing an increase of 15%. The rate has been increasing for 56 consecutive days. The 14-day incidence in Austria, Belgium, Croatia, Czech Republic, Denmark, Estonia, France, Hungary, Ireland, Luxembourg, Malta, the Netherlands, Norway, Portugal, Romania, Slovakia, Slovenia, Spain, and the U.K. have all increased compared to the previous 7 days. Due to summer holidaymakers, significantly increased numbers of daily cases (7-day average) were reported in the past week in countries with previously controlled outbreaks, including Spain (> 11,300), France (> 10,400), the U.K, (> 4,500), Germany (1,700), and Italy (> 1,500). All these countries have experienced their highest daily case counts since early May.

More than 276,500 daily cases were reported on September 22 in India (> 80,300 cases; > 1,000 deaths), the U.S. (> 35,600 cases; > 960 deaths), Brazil (> 35,200 cases; > 800 deaths), Argentina (> 12,000 cases; 470 deaths), Spain (> 10,700 cases; > 240 deaths), and in 156 other countries. In examining trends globally, 32 countries have daily cases (7-day rolling average) that are high (≥ 4 cases per 10,000 population) and staying high, including France, India, Russia, Spain, the U.K., and the U.S.; Brazil has high but decreasing cases; 25 countries have low (less than 4 cases per 100,000 population) but increasing cases, including Canada, Germany, Iran, and Sweden; and 59 countries have low and staying low cases, including Australia, China, Hong Kong, Italy, Japan, Mexico, Pakistan, Singapore, South Africa, and South Korea. In the U.S., current hospitalizations (28,900) are at the lowest number since June 23 (> 30,200 hospitalized). Daily new cases increased to approximately 41,100 per day over the past 7 days after an exponential increase over 6 weeks to a peak of more than 78,400 on July 24, followed by a steady decrease to approximately 25,500 on September 7. The initial peak of more than 36,000 occurred on April 24, followed by a plateau of approximately 20,000 per day (with minor fluctuations) for many weeks. Over the past 14 days, 14 states have had consistent downward trends and 30 states have had increasing case numbers; of these, 18 states have had consistently increasing numbers of daily cases for the past week based on a 7-day rolling average. Seven states have had their highest number of daily new cases ever over the past 7 days. Nationally, daily death numbers in the U.S. have plateaued at approximately 800 per day since September 1. A peak of approximately 2,800 occurred on April 22, followed by a decrease to a nadir of approximately 280 on June 28 and an increase to approximately 1,800 on July 30.

Asia and Latin America represented 35% and 23% of the total cases reported globally over the past 7 days, respectively, followed by Europe (18%), North America (15%), the Middle East (6%), and Africa (3%). In Africa, more than 1.4 million cases and more than 34,400 deaths were reported in 56 countries from February 25 through September 23, mainly in South Africa (> 663,200 cases; > 16,100 deaths), Morocco (> 107,700 cases; > 1,900 deaths), and Egypt (> 102,200 cases; > 5,800 deaths); total cases and deaths increased by approximately 4% during September 17-23. Approximately 48% of the cases reported in Africa during September 17-23 were reported in Morocco and South Africa. In Latin America, more than 8.8 million cases and more than 327,800 deaths were reported in all 27 countries from February 26 through September 23, mainly in Brazil (> 4.6 million cases; > 138,400 deaths), Colombia (> 777,500 cases; > 24,500 deaths), and Peru (> 776,500 cases; > 31,500 deaths); total cases increased by approximately 6% and deaths increased by approximately 4% during September 17-23. Approximately 60% of the cases reported in Latin America during September 17-23 were reported in Brazil and Argentina.

In the U.S. on September 22, the 5 most affected states were: Texas (> 4,200 cases; > 100 deaths), California (> 2,900 cases; > 120 deaths), Florida (> 2,400 cases; > 90 deaths), Missouri (> 2,100 cases; > 40 deaths), and Wisconsin (> 1,600 cases; 7 deaths). Cumulatively, since January 21, more than 7.11 million cases and more than 205,900 deaths have been reported in all

50 states and Washington, D.C., mainly in California (> 793,600 cases; > 15,200 deaths), Texas (> 751,500 cases; > 15,300 deaths), Florida (> 690,400 cases; > 13,600 deaths), New York (> 485,800 cases; > 33,100 deaths), and Georgia (> 308,200 cases; > 6,600 deaths). More than 162,300 cases and 710 deaths have been reported among health care personnel in the U.S., although these numbers reflect significant nonreporting of health care personnel status in surveillance data. As of September 22, the average daily test positivity rate over the past 7 days improved to 5%, meeting the WHO-recommended benchmark for the rate of test positivity for acute infection of ≤ 5% nationally. Currently, 30 states are above 5%, indicating that those states are, to some extent, mostly testing very ill patients who seek medical attention. Current national COVID-19 hospitalizations in the U.S. initially peaked on April 15 at more than 59,500 and, after several weeks of a consistent decrease to a nadir of approximately 27,700 on June 15, increased exponentially to a new peak of more than 59,800 on July 23 and have steadily decreased to approximately 28,900 over the past 3 days. The following states are reporting constrained or severely constrained ICU bed occupancy: Alabama, Kentucky, Rhode Island, Texas. Cumulative U.S. DoD cases, as of September 23, were 63,568.

Overall Risk Assessment

The pandemic (declared by WHO on March 11) began in China in 2019 and was last reaffirmed by WHO as a Public Health Emergency of International Concern on July 31. Weekly case numbers are currently highest in Asia and Latin America, representing approximately 35% and 23% of the total cases reported globally over the past 7 days, respectively. On September 22, more than 276,500 daily cases were reported from 161 countries, with more than 60% from Argentina, Brazil, India, Spain, and the U.S. As of September 23, approximately 978,000 deaths have been reported worldwide. In Europe, the current 365,000 weekly COVID-19 cases exceed those reported during the initial peak in March. Over half of European countries (including France, Germany, Italy, Spain, and the U.K.) have reported more than a 10% increase in the past 2 weeks. Persons aged 25-49 years account for most cases. In the U.S., daily new cases have increased slightly to approximately 41,100 per day over the past 7 days, after an exponential increase over 6 weeks to a peak of more than 78,400 on July 24. The initial peak of more than 36,000 occurred on April 24, followed by a plateau of approximately 20,000 per day (with minor fluctuations) for many weeks. Daily death numbers have plateaued at approximately 800 per day since September 1. A peak of approximately 2,800 occurred on April 22 , followed by a decrease to a nadir of approximately 280 on June 28. U.S. fatalities are projected to be between 207,000 to 218,000 by October 10, and the latest IHME projections are for 378,300 deaths by January 1, 2021, with current containment measures. In the U.S., factors affecting potential new case numbers and deaths over the next months include local containment measures, the effect of return to school and university, and the impact of any early influenza activity. A vaccine, even if introduced late in 2020, will not have an immediate population effect.

General population seroprevalence rates of less than 6% in almost all affected countries speak against widespread induction of herd immunity and support slow, staged release of mitigation measures to ensure a capable health care system response; thus far, staged openings have not been achieved in most countries. In large robust national samples, Spain and the U.K. have seroprevalence rates of 6%, and the U.S. has rates that vary from 6.9% in NYC to 1% in the San Francisco Bay Area. Overall, in the U.S., 6 to 24 times more infections were estimated per study city with seroprevalence than with COVID-19 case report data. A few highly affected urban areas globally (5%–12%), and risk groups such as HCWs, first responders, and persons experiencing homelessness (10%–30%), have reported higher rates. Among U.S. frontline health care workers, 6% had antibody evidence of previous infection; 29% of personnel with SARS-CoV-2 antibodies were asymptomatic in the preceding months, and 69% had not previously received a diagnosis of SARS-CoV-2 infection. Seroprevalence by hospital ranged from 0.8% to 31.2%. The high proportion of undetected cases may reflect limited testing of persons with obvious exposures early in the pandemic. Nursing home residents may have rates approaching more than 80% in the most affected locations. In nursing homes in England, more than 80% of the residents mounted an antibody response, including 82% of those aged > 80 years.

The feasibility, and ultimately the effectiveness, of the WHO-recommended strategy of hospitalizing and isolating all cases and quarantining all contacts remains in question; the U.S. has yet to be able to implement this strategy, which is already in use by several Asian countries (with testing upon development of symptoms). In the U.S., implementation of active contact tracing remains sporadic. Other suggested strategies to selectively isolate 93 million vulnerable (older age and underlying medical conditions) people may not be feasible.

Testing delays for those with symptoms remain problematic. Modeling indicates that the proportion of onward transmissions per index case that can be prevented ranges from up to 79.9% with a 0-day testing delay to 41.8% with a 3-day testing delay to 4.9% with a 7-day testing delay. Once the testing delay becomes 3 days or longer, even perfect contact tracing (i.e., 100% testing and tracing coverage with no tracing delay) cannot bring reproductive values below 1.

Publicly reported case numbers and deaths should be regarded as rough estimates because reporting criteria vary widely by country and often do not include cases that were never tested. Increasingly, overall national vital statistics systems are showing excess mortality during the past 5 months to be higher than the number of officially reported COVID-19 deaths. As of September

9, U.S. CDC reports that predicted number of excess deaths since February 1 from all causes is between 208,390 and 274,055, whereas excess deaths from all causes excluding COVID-19 is between 30,052 and 89,699. In the past 4 months, approximately 510,500 excess deaths have occurred in 18 countries, with the highest in the U.S. (> 149,200), the U.K. (> 65,700), Brazil (54,700), Italy (> 48,600), and Spain (> 48,500) when compared to the 290,500 deaths reported as COVID-19 related. Whether differences between excess deaths and the official counts of COVID-19 deaths reflect an undercounting of COVID-19 deaths or a surge in deaths from bystander causes is unclear and may be a mix of both.

Patients with typical mild-to-moderate disease (who represent more than 90% of cases) have infectious virus that cannot be isolated after more than 8 days of symptoms. The preponderance of studies has shown similar viral loads in asymptomatic and symptomatic individuals at the time of diagnosis; some evidence shows less likelihood of transmission to contacts of asymptomatic individuals. Patients with severe or critical COVID-19 have a duration of infectious virus shedding ranging from 0 to 20 days (median 8 days) after symptom onset. The probability of detecting infectious virus drops below 5% after 15 days. Implications from these latter data are for hospital inpatient infection control. Severe or critical patients typically require 30 or more days of hospitalization and prolonged home convalescence; these shedding intervals have no implications for return to work or the community for typical patients. For mildly ill patients, shedding of viral RNA from saliva and nasopharyngeal secretions is at peak value on the day of symptom onset, remains high for approximately 6 days, declines significantly in the second week of illness, and usually ceases by day 14. The maximum duration of positive nasopharyngeal PCR testing in several large series is 43 days from symptom onset and 28 days from symptom resolution; 19% of patients are PCR positive 2 weeks after symptom resolution. One outlier case of viral RNA shedding for 95 days following symptom onset has been reported in a patient with prolonged illness. Shedding of viral RNA from sputum (lower respiratory tract) typically persists for 21 days from symptom onset (longer for severely ill patients). Shedding of nasopharyngeal RNA fluctuates from positive to negative in many persons and may be negative for 2 or more days before being detectable again; such fluctuations should not be automatically interpreted as either reinfection or recrudescence of infectious viral replication. Asymptomatic persons may transmit to others as soon as 2 days after infection acquisition.

Seroconversion rates, including those with mild or asymptomatic disease, range from 75% to 99% depending on test platform (e.g., research laboratory, large commercial analyzer platforms, or rapid tests), antibody target investigated, and patient population. Results from large throughput platform assays from major diagnostics companies provide the most context and comparability. In a very comprehensive serosurvey involving approximately 15% of the population of Iceland and using 6 different antibody assays, total SARS-CoV-2 immunoglobulin was present in 92% of 1,797 persons with PCR-proven infection. Nearly one-third of the infections were detected in persons with asymptomatic infection. Antibody levels did not decline over a period of 4 months in this cohort. Some smaller scope studies have found seroconversion in as few as 70% to 80% of infected persons using a variety of different antibody assays, and other studies have found antibody levels that wane after 3 months. This unbiased population-level sampling confirmed elevated antibody levels in older adults and in persons who were hospitalized. Conversely, antibody levels were lower in smokers and in women who had less severe disease. In general, IgG antibodies develop over 7 to 50 days from symptom onset, with peak titers at approximately 24 days from symptom onset; the optimal timeframe for antibody testing is at least 3 to 4 weeks after symptom onset and at least 2 weeks after symptom resolution. Some studies have shown waning but still detectable antibodies at 3 months, whereas others have shown consistent antibody levels for at least 4 months. Correlation with protection to reinfection of these levels of antibodies is not yet known. Simple presence of serum antibody as detected by commercial serologic testing is not uniformly effective against reinfection, but most persons with COVID-19 will develop neutralizing antibodies (nAb) to the SARS-CoV-2 spike protein. Duration is not yet clear; nAb levels can only be studied in research laboratories at present. A small study has shown that known preexisting nAb were protective in 3 persons in a contained intense exposure setting, whereas 3 others in the same setting with detectable COVID-19 antibodies that were not nAb were not protected. Studies to date do not account for possible B- and T-cell memory, with rapid redevelopment of nAb titers on reexposure to SARS-CoV-2.

Based on available global data, the U.S. CDC best estimates (many uncertainties remain) for several parameter values are:

- R_0 (initial transmissibility in naive populations): 2.5
- IFR (considers asymptomatic and symptomatic infection together): 0.65%
- Asymptomatic infections: 40% (high compared to all other authorities and studies)
- Infectiousness of asymptomatic individuals relative to symptomatic: 75%
- Percentage of transmission occurring prior to symptom onset: 50%
- Percent that die among those hospitalized: 18-49 years: 2.0%; 50-64 years: 9.8%; ≥ 65 years: 28.1%.

The true spectrum of clinical disease—which involves ascertaining the proportions of infected persons who are asymptomatic; who are symptomatic but apparently (to others) asymptomatic; who have influenza-like illness, focal pneumonia, or severe respiratory compromise; and fatalities—is consistent across countries. Severity proportions have been roughly 80% mild to

moderate, 15% severe, and 5% critical (needing ICU admission). Approximately 5% of all infected individuals require hospitalization. In almost all studies to date, males are much more likely to be infected and much more likely (up to 2-fold) to have poor outcomes when compared to females.

Considerable numbers of heterogenous observational studies with different estimates continue to confound determination of the extent of onward transmission by "asymptomatic" carriers in the community. The difference between a true asymptomatic person (never gets sick) and a presymptomatic person (was not yet sick at the time of initial testing) is important to understand. The literature, experts, and the media often state that asymptomatic transmission has occurred when referring to a combination of "true asymptomatic" and "presymptomatic" persons. Although both may have replicating virus detectable in their respiratory system, the latter cannot be distinguished from the former until some days after transmission has occurred.

Most studies on proportions of asymptomatic cases do not provide information about onward transmission from presymptomatic or asymptomatic individuals. The proportion of these asymptomatic or presymptomatic persons present in the population who are infectious to others at any time is very difficult to ascertain without complex contact tracing and testing of large numbers of people with direct contact around a large number of confirmed COVID-19 cases. Large-scale antibody testing, as reported above, is indicating how many previously infected asymptomatic persons were in the population but will not indicate how important those persons were in community transmission. Another important factor is that many minimally symptomatic people may not appear symptomatic to others and often are in situations (e.g., nursing homes or military) where minor symptoms will not be acknowledged. The most definitive data available indicate a clear role for presymptomatic individuals in actual transmission and a less definite role for the "true asymptomatic" persons. These latter persons are, by definition, having a different clinical (especially lower viral loads) and immunologic response to their infections. In 79 studies in a range of different settings, 20% of people with SARS-CoV-2 infection remained asymptomatic during follow-up (true asymptomatic persons), but biases in study designs limit the certainty of this estimate. In contact studies, asymptomatic and presymptomatic transmission among household contacts (estimated range 17%–62% of household transmissions) is important, and quarantine of all household contacts is an important mitigation strategy. Of note, in a study of the entire population of Denmark with a very rigid definition of transmission (testing of all household contacts), the SAR was 17%, with a linear relation between acquisition risk and age. An increasing transmission risk with age of primary cases occurred for adults, whereas the risk seemed to decrease with age for children. Overall, asymptomatic and presymptomatic spread has been estimated by modeling (data from actual contact studies is insufficient) to be from 20% to 50% of all transmission.

Airborne transmission has not been proven to occur in the community; the possible role of indoor ventilation systems in viral spread remains unquantified but is likely relatively minor on its own. Aerosolized transmission occurs during medical procedures and, also, more broadly in hospital settings. Although no simple dichotomy exists between droplet and aerosol transmission of SARS-CoV-2, a continuum appears likely, with aerosol transmission beyond 2 m (6 ft) being an outlier event even in hospital settings. Epidemiologic data from several robust studies do not suggest a problem, even in health care settings that require a change to using N95 respirators instead of surgical masks (as at present). Observations by droplet scientists have yet to be correlated to the real epidemiology of the pandemic. Fecal transmission does not appear to occur despite the shedding of SARS-CoV-2 RNA in stool specimens for prolonged periods after illness resolution. Significant super-spreading events, including from business and religious gatherings from asymptomatic or minimally symptomatic persons, have already occurred in many countries but have not been proven to be important pandemic drivers.

Although age is not the only determinant and circumstances vary by country, overall, new calculations from several different countries reinforce that age is by far the strongest predictor of IFR of SARS-CoV-2 infection, which is the proportion of people infected with the virus (including those who did not show symptoms or get tested) who will die as a result. Overall, IFR for SARS-CoV-2 has been estimated as 0.65%. For those younger than age 50 years, IFR is negligible; between ages 50-64 years, IFR varies from 0.05% to 0.5%; for age > 65 years, IFR is 5% to 10%; and for age > 75 years, IFR is consistently greater than 10%. Men are consistently more likely to die by a factor of almost 2 in many countries. Overall CFRs by country/region: Italy (11.9%), Canada (6.3%), Europe (4.8%), Australia (3.2%), Brazil (3%), the U.S. (2.9%), Portugal (2.8%), and South Africa (2.4%). The U.S. CFRs have been lower in the past 2 months because treatment has improved, and hospitals have been better prepared. In the U.S., approximately 80% of deaths in diagnosed cases are in persons aged > 65 years. U.S. deaths by age cohort (%) are as follows: ≤ 17 years (less than 0.1%); 18-39 years (1.8%), 40-49 years (3.2%); 50-64 years (15.7%); 65-74 years (21.2%), 75-84 years (26.4%); ≥ 85 years (31.7%).

Predictive Modeling

Models are useful tools but are only as good as each of their many (up to dozens) assumptions; 1 or more weak assumptions based on the lack of significant knowledge of a parameter at the time the model is run can dramatically change the findings. Many of the models assume very high asymptomatic transmission rates in the community. Models can be regarded as bases for

worst-case scenarios for planning, given knowledge of current situations and current understanding of proposed or ongoing interventions; models need to be frequently rerun as knowledge evolves. Variables and intangibles (for which no current data exist) are only possible to include in future runs of the particular model. Other nonpharmaceutical and pharmaceutical preventions and treatments may come into play at uncertain times in the future, testing capacity will become more robust, and the rate of rise of immune individuals within a community is impossible to predict with a new organism. All models are wrong; some, however, are useful at the time they are run.

Models that are regularly updated include at least 37 widely used U.S. models for state-by-state predictions, such as the CU, LANL, and MOBS forecasts. Ensemble models from MIT (https://reichlab.io/covid19-forecast-hub/) and U.S. CDC (https://www.cdc.gov/coronavirus/2019-ncov/covid-data/forecasting-us.html), which superimpose all other prediction model lines and derive a consensus model, are predicting between 207,000 and 218,000 U.S. deaths by October 10. Most of these models converge in their predictions as the antecedent data has become better; consensus or ensemble predictions are now highly credible because each model uses different methods but are now coming to similar conclusions. The IHME model now predicts 378,300 deaths by January 1, 2021; daily deaths are predicted to slowly increase from approximately 650 currently modeled daily deaths at present to approximately 3,200 by January 1. If social distancing mandates continue easing, daily deaths are predicted to increase to approximately 8,500 by January 1, 2021; however, if public nonmedical mask usage is 95% nationwide, daily deaths are predicted to increase to approximately 1,300 by January 1, 2021. Changing variables, such as levels of social distancing in each state, are inconsistently considered by different models and will affect future iterations of each model. A lookback study matching previously predicted deaths in models to actual deaths indicates that accuracy of the prediction models is only high out to about 4 weeks.

Epidemic doubling time in the U.S. was 2.68 days prior to widespread mitigation efforts, increasing by 82% to 15 days during the mitigation phase. Among states without stay-at-home orders, the median increase in doubling time was 34%, whereas for states with stay-at-home orders, the median increase was 72.9%. Between March 10 and March 25, 2020, all 50 states and Washington, D.C. enacted at least 1 statewide physical distancing measure to help stop the spread of COVID-19. The average daily COVID-19–case growth rate began declining approximately 1 incubation period (i.e., 4 days) after implementation. Because the different types of physical distancing measures were generally implemented in temporal proximity to each other, the specific types of physical distancing measures that were most effective cannot be ascertained. An estimated reduction of more than 600,000 cases within 3 weeks of implementation occurred. In European countries that implemented various mitigation measures, the average time from implementation of the mitigation effort to the daily case-number peak was approximately 3 weeks. For those countries that implemented an enforced stay-at-home policy, the average time was 2 weeks. A separate analysis (using data from serological studies) modeled nonpharmaceutical interventions (including social distancing and national lockdowns) in Europe through May 4, 2020, when some countries began to relax national social distancing measures. This study found that interventions may have averted approximately 3.1 million COVID-19 deaths across 11 European countries.

R_0 is a useful tool based on sophisticated models, but it is not a constant number or intrinsic property of the virus and changes with the circumstances and evolution of an outbreak. Unfortunately, R_0 is only as good as the available data. Lack of accurate information at the time the model is run for a defined location can dramatically impact the findings. Many or most public health entities do not run R_0 models for national or small discrete subnational areas. No central repository of regularly updated R_0 values is available to help drive return-toward-normalcy initiatives. The rough surrogate of decreasing case numbers for 14 consecutive days, together with a maximum tolerable threshold of number of new cases per day per 100,000 population in as small a geographic area as current data are available, is a practical benchmark. Numerical thresholds are user- and situation-dependent. Due to significant variability within a country, widely proposed data on overall health system parameters (including testing capacity) are only going to be reliably available in a small number of sophisticated countries and need to be available down to the state or local level to be useful for return to work.

Current Disease Situation

A global overview of cumulative and daily case numbers is available. See Cases by Country.

The U.S. DoD stop movement order (internationally and domestically) for all DoD service members, all DoD civilian personnel, and DoD service member dependents on government-funded travel has been modified to allow for a conditions-based phased approach to personnel movement and travel; restrictions have been lifted at 51% of DoD installations globally. Conditions to resume unrestricted travel ("green locations") to states, territories, and other countries rest upon U.S. state and/or regional criteria based on the White House's Opening Up America Again guidance and installation-level criteria based on conditions in and surrounding DoD installations, facilities, and locations (including in host nations). This order, which remains in effect until further notice, applies to all official travel, including initiation of TDY or PCS travel as well as personal leave and nonofficial travel outside the local area; exemptions include travel related to recruiting and accessions activities, medical treatment, deployments

and redeployments, and separation or retirement. Program details can be found at https://media.defense.gov/2020/May/26/2002305766/-1/-1/1/TRANSITION-TO-CONDITIONS-BASED-PHASED-APPROACH-TO-%20COVID-19-PERSONNEL-MOVEMENT-AND-TRAVEL-RESTRICTIONS.PDF. The most recent update to "green locations" can be found at . For DoD personnel that are allowed to travel, pre- and posttravel guidance for the force health protection of service members and their dependents, DoD civilian personnel, and DoD contractors can be found at https://media.defense.gov/2020/Aug/06/2002472408/-1/-1/1/FHP-GUIDANCE-SUPPLEMENT-12.PDF.

Cases on an International Conveyance (Ships)

The current U.S. CDC No Sail Order for all cruise ships under U.S. jurisdiction extends to September 30, 2020. In a 40-page report, the U.S. CDC details the extensive resources (38,000 person hours) diverted to tracing contacts of approximately 3,000 passengers infected on board U.S.-based cruise ships prior to the shutdown. The U.S. CDC states that the onus is on cruise lines to present cruise safety plans to avoid a recurrence of such a situation and that this may not be possible prior to September 30. The U.S. CDC has reported that 80% of cruise ships (> 100) under U.S. jurisdiction were affected by COVID-19 from March 1 through July 10, 2020. Many countries continue to restrict cruise ship access to ports. See Travax Destinations.

One of the first cruise ships to resume sailing in July 2020, the MS Roald Amundsen, docked in Tromso, Norway on July 31, 2020, with 41 crew members and 21 passengers who had tested positive for COVID-19. A further 382 passengers, who were on board from July 17-31, disembarked during this period at up to 69 other ports between Bergen and Svalbard. The crew had not been tested or quarantined prior to resumption of operations.

In addition to the more than 3,200 COVID-19 cases reported on over 100 civilian cruise ships, more than 2,500 cases have been reported on over 20 naval vessels from Belgium, Chile, France, the Netherlands, Taiwan, and the U.S.; several of the outbreaks began while the affected ship was at sea.

Genetic analysis of 148 SARS-CoV-2 samples, from 148 of the 697 confirmed cases of COVID-19 in the large outbreak aboard the Diamond Princess cruise ship, strongly suggest that SARS-CoV-2 dissemination on board originated from a single passenger/crew introduction event before the quarantine in Yokohama, Japan started. All tested isolates exhibited the identical single nucleotide polymorphism at position 11083 of the genome that was different than the usual Wuhan strain. Epidemiologic evidence indicates that some case clusters on board could be linked to transmission through mass-gathering events in the recreational areas.

Currently, large cruise lines have already partially reopened or are scheduled to do so as follows (dates are 2020 unless otherwise stated): AmaWaterways (November 5), Avalon Waterways (October 4), Azamara (November 10), Bahamas Paradise (November 4), Carnival Cruise Line (November 2), Celebrity Cruises (November 2), Celestyal Cruises (March 6, 2021), Costa Cruises (September 6), Crystal Cruises (January 5, 2021), Cunard (April 26, 2021), Disney Cruise Line (December 12), Dream Cruises (August 2), Emerald Waterways (November 1), Fred Olson Cruise Lines (December 17), Holland America Line (December 19), Hurtigruten Cruises (June 16), Jalesh Cruises (November 9), Marella Cruises (November 16), MSC Cruises (September 16), Norwegian Cruise Line (November 2), Oceania Cruises (November 4), Paul Gauguin Cruises (July 29), Ponant (July 25), P&O Cruises (February 13, 2021), Princess Cruises (December 20), Regent Seven Seas Cruises (November 2), Ritz-Carlton Yacht Collection (April 22, 2021), Royal Caribbean (November 2), SAGA (November 5), Seabourn (December 5), Scenic Luxury Cruises (January 2021), Silversea Cruises (October 31), Uniworld River Cruises (November 1), Viking Ocean (January 3, 2021), Virgin Voyages (November 4), and Windstar Cruises (January 6, 2021).

Entry/Exit Procedures

Screening

Entry screening using questionnaires, fever screening, thermal scanning, or visual inspection at international ports of entry has been implemented in almost all countries. In most cases, anyone with fever and respiratory symptoms and a history of any international travel within 14 days prior to arrival may be detained and isolated or placed in self-isolation; persons without symptoms but with a similar travel history may be placed in quarantine or self-quarantine, depending on where the exposures may have taken place.

Asymptomatic Arrivals

All countries have implemented management procedures for asymptomatic travelers (including citizens and legal residents) who have been in a COVID-19–affected country within 14 days prior to arrival. These management procedures include self-observation (remaining alert for symptoms), self-monitoring (taking a temperature reading 2 times per day), social distancing, and quarantine (mandatory or self-separation from others not exposed) for 14 days. More than 90 countries now require arrivals to be

in possession of a negative COVID-19 PCR result from a test taken within a prescribed number of days prior to arriving in the respective country, and more than 30 additional countries require a negative COVID-19 PCR test result to be exempt from quarantine or other restrictions. Although antigen testing may be more readily available, only PCR test results are accepted by these countries. The current list of countries accepting foreign tourists from all countries without restrictions (any of predeparture testing, arrival testing, or arrival quarantine) is limited to Albania, Brazil, Mexico, North Macedonia, Serbia, Tanzania, and Turkey. In the U.S., international flights are allowed to arrive at any international airport. Systematic questioning or health screening for symptoms or potential exposures to SARS-CoV-2 will no longer take place for arrivals from any country. More than 60 countries require COVID-19 testing upon arrival in the respective country, some regardless of whether the traveler already had a negative COVID-19 test prior to arrival. Increasing numbers of countries (including Cayman Islands, Hong Kong, Singapore, South Korea) are using wearable tracking and biosensor (fever, respiratory rate) devices for 14 days for some or all arrivals, regardless of any personal privacy concerns. Arrivals who develop fever or respiratory symptoms within 14 days of travel to a COVID-19–affected country should self-isolate; observe respiratory hygiene hand hygiene, and social distancing; wear a nonmedical mask (e.g., cloth face covering); and contact public health authorities (or telephone ahead before presenting to a hospital). Arrival procedures for individual countries are found on the respective Destinations page.

COVID-19 viral testing (PCR) is strained in many parts of the U.S., with long waits to get testing appointments and long waits to get results. For travelers needing evidence of a negative PCR test within 72 hours prior to travel to enter a destination country, at-home sample collection kits can be shipped overnight for PCR testing, and digital results are returned to the traveler's device, usually within the required 72 hours. Travelers should verify turnaround with the vendor prior to sample submission; see Table 2: Vendors Offering At-Home Sample Collection Kits. Antigen testing is often more accessible at walk-in clinics but is not acceptable to meet entry requirements for destination countries.

Travel Recommendations

Specific Shoreland travel recommendations are available for individual countries on their respective Destinations page and in Report Builder. Each recommendation is based on aggregate national data (daily cases per 100,000), available medical care, testing positivity rates (when available), and access to testing.

The Shoreland recommendation levels are:

- All persons should avoid nonessential travel to this country.
- Healthy younger persons should avoid nonessential travel to this country if consistent masking and careful physical distancing are not possible. Vulnerable persons should avoid all nonessential travel to this country.
- Healthy younger persons should consider avoiding nonessential travel to this country if consistent masking and careful physical distancing are not possible. Vulnerable persons should consider avoiding all nonessential travel to this country.
- No recommendation against travel to this country is in place.

Because some cities or regions may have higher or lower risk within an individual country, cities/regions with risk higher than the national average will be specified on each Destination page. The Shoreland travel recommendations are updated every Tuesday evening.

The U.S. CDC has published a scheme of travel recommendations for individual destination countries. The U.S. CDC recommendation groupings correspond to risk levels of very low, low, moderate, high, and no data exist. The recommendations reflect a very cautious, numerical approach, so it is unlikely any major country will move from the high-risk category in the near future. For example, Canada, France, or Italy would need to go below an average of 18 cases per day nationwide over a 28-day period to move from the high-risk category. The country-level recommendations do not account for state-, province-, or county-level differences within a country. An explanation of the scheme is at https://www.cdc.gov/coronavirus/2019-ncov/travelers/how-level-is-determined.html (updates occur intermittently).

Shoreland and U.S. CDC travel recommendations for individual countries can be found in the COVID-19 section of Destinations and Report Builder pages.

The most recently reported backlog for U.S. passport applications is 931,000. Twenty-six passport processing centers have reopened for limited service as of September 8. Pending applications will be addressed on a first in, first out basis.

The following countries and/or organizations, among others, have also published travel recommendations for outbound travel:

Table 1: Other National Travel Advisories

Country Issuing	Avoid Travel	Avoid Nonessential Travel

Country Issuing	Avoid Travel	Avoid Nonessential Travel
Australia	**X** (all countries, including on cruise ships)	
Canada	**X** (cruise ships)	**X** (all countries)
France	**X** (all countries, except E.U. member states and Andorra, Iceland, Liechtenstein, Monaco, Norway, San Marino, Switzerland, U.K., Vatican City)	
Germany		**X** (all countries, except Turkey [Antalya, Aydin, Izmir, and Mugla provinces] and E.U. member states). Exceptions to E.U. member states/areas of E.U. member states (avoid nonessential travel applies): • Austria (Vienna) • Luxembourg • Belgium (Brussels) • Spain (except Canary Islands) • Croatia (Brod-Posavina, Dubrovnik-Neretva, Pozega-Slavonia, Sibenik-Knin, Split-Dalmatia, Virovitica-Podravina, and Zadar counties) • Czech Repubic (Prague and Central Bohemia Region) • Hungary (Budapest) • France (Île-de-France, Provence-Alpes-Côte d'Azur, Auvergne-Rhône-Alpes, Occitanie, Nouvelle-Aquitaine, Hauts-de-France, and Corsica regions) • Bulgaria (Blagoevgrad Province) • Netherlands (North and South Holland provinces) • Romania (Bucharest; Bacau, Bihor, Braila, Braşov, Caraş-Severin, Iaşi, Ilfov, Neamt, Prahova, Valcea and Vaslui counties) • Switzerland (Fribourg, Geneva, and Vaud cantons)
Japan	**X** (Afghanistan, Albania, Andorra, Algeria, Antigua and Barbuda, Argentina, Armenia, Australia, Austria, Azerbaijan, Bahamas, Bahrain, Bangladesh, Barbados, Belarus, Belgium, Belize, Bhutan, Bolivia, Bosnia and Herzegovina, Botswana, Brazil, Brunei, Bulgaria, Cabo Verde, Cameroon, Canada, Chile, China, Colombia, Comoros, Congo, Costa Rica, Côte d'Ivoire, Cuba, Cyprus, Czech Republic, Democratic Republic of Congo, Denmark, Djibouti, Dominica, Dominican Republic, Ecuador, Egypt, El Salvador, Equatorial Guinea, Estonia, Eswatini, Ethiopia, Finland, France, Gabon, Gambia, Georgia, Germany, Ghana, Greece, Grenada, Guatemala, Guinea, Guinea-Bissau, Guyana, Haiti, Honduras, Hungary, Iceland, India, Indonesia, Iran, Iraq, Ireland, Israel, Italy, Jamaica, Kazakhstan, Kenya, Kosovo, Kuwait, Kyrgyzstan, Latvia, Lebanon, Lesotho, Liberia, Libya, Liechtenstein, Lithuania, Luxembourg, Madagascar, Malawi, Malaysia, Maldives, Malta, Mauritania, Mauritius, Mexico, Moldova, Monaco, Montenegro, Morocco, Namibia, Nepal, Netherlands, New Zealand, Nicaragua, Nigeria, Northern Macedonia, Norway, Oman, Pakistan, Palestinian Territories, Panama, Paraguay, Peru, Philippines, Poland, Portugal, Qatar, Romania, Russia, Rwanda, Saint Vincent and the Grenadines, San Marino, São Tomé and Príncipe, Saudi Arabia, Senegal, Serbia, Sierra Leone, Singapore, Slovakia, Slovenia, Somalia, South Africa, South Korea, South Sudan, Spain, St. Kitts and Nevis, Sudan, Suriname, Sweden, Switzerland, Taiwan, Tajikistan, Thailand, Trinidad and Tobago, Tunisia, Turkey, U.A.E., Ukraine, U.K., U.S., Uruguay, Uzbekistan, Vatican City, Vietnam, Venezuela, Zambia, Zimbabwe)	**X** (all countries, except those listed to the left) (cruise ships)
New Zealand	**X** (all countries, including on cruise ships)	

1. Older adults and people of any age with serious, chronic medical conditions are at increased risk for severe disease and should consider postponing nonessential travel.

Country Issuing	Avoid Travel	Avoid Nonessential Travel
Singapore	**X** (all countries [except essential or official travel permitted under Green/Fast Lane arrangements])	
United Kingdom	**X** (cruise ships)	**X** (all countries, except Antigua and Barbuda, Australia, Azores, Barbados, Bermuda, British Antarctic Territory, Brunei, Cambodia, Canada, Cayman Islands, Cook Islands, Cyprus, Cuba, Curaçao, Denmark, Dominica, Estonia, Falkland Islands, Fiji, Finland, Germany, Gibraltar, Greece (except Lesbos, Tinos, Serifos, Mykonos, Crete, Santorini, and Zakynthos islands), Grenada, Hong Kong, Iceland, Ireland, Italy, Japan, Laos, Latvia, Liechtenstein, Lithuania, Macau, Madeira, Malaysia, Martinique, New Caledonia, New Zealand, Norway, Poland, Saint Barthelemy, Saint Helena, Saint Kitts and Nevis, Saint Lucia, Saint Martin, Saint Pierre and Miquelon, Saint Vincent and the Grenadines, Samoa, San Marino, Singapore, Sint Maarten, Slovakia, South Georgia and the Sandwich Islands, South Korea, Sri Lanka, Sweden, Taiwan, Thailand, Turkey, Vietnam, Wallis and Futuna)
U.S. CDC		**X** (all countries, except American Samoa, Anguilla, Bonaire, Brunei, Cayman Islands, Dominica, Falkland Islands, Guernsey, Greenland, Grenada, Isle of Man, Laos, Macau, Marshall Islands, Mauritius, Micronesia, Montserrat, New Caledonia, Palau, Saba, Saint Kitts and Nevis, Saint Lucia, Saint Pierre and Miquelon, Sint Eustatius, Taiwan, Timor-Leste) (All cruise ships. Vulnerable populations[1] consider avoiding Cambodia, Fiji, New Zealand, Saint Barthelemy, Thailand)

1. Older adults and people of any age with serious, chronic medical conditions are at increased risk for severe disease and should consider postponing nonessential travel.

Exit Restrictions, Travel Restrictions, and Internal Disruptions

Exit Restrictions

Many countries have closed their borders and restricted all scheduled, commercial air travel in and out of the country [land and sea borders may or may not be closed], making it difficult for citizens of other nations to repatriate. Please check individual countries on the respective Destinations page.

Travel Restrictions

Travel restrictions and arrival procedures (including quarantine and/or a medical certificate) for more than 230 countries are found on the respective Destinations page.

Countries open to persons who have spent the last 14 days in Canada or the U.S.:

- Afghanistan, Albania, Antigua and Barbuda, Armenia, Aruba, Azores, Bahamas, Bahrain, Bangladesh, Barbados, Belarus, Bermuda, Bolivia, Brazil, Burkina Faso, Cambodia, Chad, Channel Islands, Costa Rica, Côte d'Ivoire, Croatia, Cuba (Cuban Keys only), Democratic Republic of the Congo, Dominica, Dominican Republic, Ecuador, Egypt, Ethiopia, French Polynesia, Gabon, Ghana, Gibraltar, Grenada, Guam, Guatemala, Haiti, Honduras, Iran, Ireland, Jamaica, Jordan, Kenya, Kosovo, Kuwait, Lebanon, Liberia, Madeira, Maldives, Mali, Mexico, Montenegro, Niger, Nigeria, North Macedonia, Northern Mariana Islands, Pakistan, Puerto Rico, Rwanda, Saint Barthelemy, Saint Helena, Saint Lucia, Saint Pierre, Saint Vincent and the Grenadines, Serbia, Sint Maarten, South Sudan, Sudan, Tanzania, Turkey, Turks and Caicos, U.A.E., U.K., Zambia

Additional countries open to persons who have spent the last 14 days in Canada:

- Andorra, Bulgaria, Canary Islands, Cyprus, Czech Republic, Denmark, Estonia, Faroe Islands, France, Germany, Greece, Greenland, Iceland, Italy, Jordan, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Moldova, Monaco, Netherlands, Poland, Portugal, Romania, Seychelles, Spain, Sweden, Switzerland, Tunisia, U.S. (arrival by air only), Vatican City

See the respective Destinations page for additional entry requirements for some countries above, including medical certificates or quarantine-on-arrival rules.

The U.S. TSA screened almost 1 million air travelers on Friday, September 4, to begin the Labor Day weekend, representing the highest number of travelers since March 17 and an increase over the nadir of 87,534 in April. On the same day in 2019, nearly 2.2 million passengers were screened. Increasing numbers of airlines are flying long-haul routes with a wide variety of restrictions in place, often in excess of arrival and departure countries. Travelers should check the circumstances with individual airlines both at the time of booking and several days prior to travel.

Groups of neighboring countries have trialed "travel bubbles" or "air corridors," a mutual agreement to allow for unrestricted movement between countries limited to nationals and residents of the participating countries. All persons with a history of travel outside the perimeter of the bubble would still need to undergo a 14-day quarantine upon penetrating the bubble. Trials of this concept have mostly failed (e.g., E.U. for summer vacation travel) because 1 or more countries in the bubble eventually experienced a COVID-19 resurgence.

Entry into Saudi Arabia is suspended for the purpose of Umra and/or visiting the Prophet's Mosque in Medina and for travelers with a tourist visa from countries with a COVID-19 outbreak. However, as of October 4, 2020, pilgrims residing in Saudi Arabia may undertake Umra.

Internal Disruptions

Africa: Nigeria remains under a nationwide curfew from 12 a.m. to 4 a.m., with masks required in public spaces, and no gatherings of more than 50 people are allowed outside of workplaces. Interstate travel is allowed only outside of curfew hours. South Africa remains under lockdown, with a curfew in place from 12 a.m. to 4 a.m.; people are allowed to leave their residences for leisure activities and interprovincial travel is allowed. Health care systems across Africa have limited resources, including fewer than 5,000 available ICU beds and fewer than 2,000 ventilators.

Asia: In China, officials in Urumqi, Xinjiang Uygur Autonomous Region placed approximately 3.5 million people under lockdown and are advising people not to leave their homes. Shopping malls and hotels are closed, public gatherings are banned, and public transportation is suspended. More than 90% of flights into Urumqi have been canceled, and people leaving the city must first test negative for SARS-CoV-2. Jakarta, Indonesia has reimposed lockdown measures for an indefinite period; essential services with minimal staffing are exempt. Distance learning and work-from-home are mandated. Take-away food is allowed, and places of worship may hold small services.

Europe: In Wales, approximately one-quarter of the population is under a lockdown, restricting people from entering or leaving areas of high transmission in the southern part of the country except for school or work. In Spain, 6 districts within Madrid have gone into lockdown, affecting 850,000 residents. Movement between the districts is restricted, access to public areas may be limited, and shops are required to close by 10:00 p.m.

Latin America: In Peru, persons in select areas in 18 of 25 regions are under quarantine, with a curfew from 8 p.m. to 4 a.m. as well as an all-day Sunday curfew. The rest of the country remains under curfew from 11 p.m. to 4 a.m. In Panama, Bocas del Toro, Chiriquí, and Colón provinces are under total quarantine from Friday at 7 p.m. through Monday at 5 a.m. and are under curfew from 7 p.m. to 5 a.m. Monday through Thursday. The rest of the country remains under a nationwide curfew from 11 p.m. to 5 a.m. Monday through Friday, with total quarantine from Saturday at 11 p.m. through Monday at 5 a.m. Chile remains under a nationwide curfew from 11 p.m. to 5 a.m., and multiple cities throughout the country are under strict quarantine, only allowing residents with permits to leave their homes for essential activities (such as buying food or medicine).

Middle East: In Israel, a nationwide lockdown is in place through October 11. A 1,000 m (3,280 ft) limit on excursions from places of residence (essential activities exempted) is in effect, and indoor and outdoor gatherings are limited to 10 and 20 people, respectively. Schools and nonessential businesses are closed, and restaurants are limited to take-away.

U.S.: At least 25 states (including Texas, Florida, and California) reversed or paused reopening measures in recent months after experiencing increases in case numbers. All 50 states and Washington D.C. have reopened nonessential businesses to some extent (including salons, barber shops, retail shops, and gyms). Most states are requiring the use of masks in at least some public locations and situations, and many are requiring travelers from high-transmission states to quarantine for 14 days upon arrival. Some states may accept a negative COVID-19 PCR test in place of quarantine. See U.S. COVID-19 Map, which reflects 4 levels of risk and recommendation for travelers, based on a 7-day average of daily cases per 100,000 population. Some states

accept a negative COVID-19 PCR test within 72 hours of arrival to waive the quarantine requirement. People with underlying medical conditions and older persons should avoid large gatherings, air travel, and cruise travel.

The U.S.-Canada and U.S.-Mexico borders are closed to nonessential traffic until October 21. Trade and commuters will continue to cross the border, but travel for recreation and tourism is banned. Canada has banned large ships (> 100 total passengers and crew) in Canadian waters until October 31. Ships with more than 12 passengers are banned from the Arctic until October 31.

Australia: In Victoria State, residents of metropolitan Melbourne are under a curfew from 9 p.m. to 5 a.m. and are only allowed to leave their homes for work, essential health care, or safety reasons. From 5 a.m. to 9 p.m., residents may leave their homes for essential activities, but restrictions on movement exist (including limiting travel to within 5 km [3 mi] from residents' homes). Victoria's borders between New South Wales and South Australia remain closed.

Transmission

The detailed epidemiology of possible causative animal exposures and zoonotic transmission at the outset of the outbreak remains unclear. Many of the first cases in December 2019 were directly linked to a market in Wuhan, China that sold seafood and other wildlife (including birds). However, the symptom-onset date of the first case identified in the outbreak was December 1, 2019; the case reported no exposure to the market. No epidemiological link has been detected between this case and later cases. An initial single jump of SARS-CoV-2 directly from bat to human, or from an intermediate animal host to a human, with subsequent initial human-to-human propagation is likely, and current genetic analysis convincingly demonstrates that a host intermediate (with adaptation in that species) between bats and humans is not necessary to explain the emergence of SARS-CoV-2 in humans. A role for the market, if any, remains dubious. Existing incomplete data indicate that pangolins may carry very closely related but entirely bat-derived viruses. Analyses of both the RBD and the novel polybasic cleavage site also provide evidence that SARS-CoV-2 is neither a laboratory construct nor a purposefully manipulated virus because the precursors exist in bats. SARS-CoV-2 is not derived from any previously used or known virus backbone.

Shoreland review continues to assert that—in concurrence with a July 7 analysis by WHO as well as with U.S. CDC and ECDC experts—evidence to date suggests that the predominant route of transmission is via large respiratory droplets or close contact with an infected person. In summary, although no simple dichotomy exists between droplet and aerosol transmission of SARS-CoV-2, a continuum appears likely, with aerosol transmission beyond 2 m (6 ft) being an outlier event even in hospital settings. Observations by droplet scientists have yet to be correlated to the real epidemiology of the pandemic.

Airborne transmission has not been proven to occur in the community; the possible role of indoor ventilation systems in viral spread remains unquantified but is likely relatively minor on its own. Aerosolized transmission occurs during medical procedures and, also, more broadly in hospital settings. Although no simple dichotomy exists between droplet and aerosol transmission of SARS-CoV-2, a continuum appears likely, with aerosol transmission beyond 2 m (6 ft) being an outlier event, even in hospital settings. Epidemiologic data from several robust studies do not suggest a problem, even in health care settings that require a change to using N95 respirators instead of surgical masks (as at present). Airborne transmission is defined as the spread of an infectious agent caused by the dissemination of droplet nuclei (aerosols) that remain infectious when suspended in air over long distances and time. The physics of exhaled air and air flow have generated hypotheses, mostly among engineers and physicists, about possible mechanisms of SARS-CoV-2 transmission through aerosols. These theories suggest that 1) a number of respiratory droplets generate microscopic aerosols (≤ 5 μm) by evaporating, and 2) normal breathing and talking results in exhaled aerosols. Thus, a susceptible person could inhale aerosols and could become infected if the aerosols contain the virus in sufficient quantity to cause infection in the recipient. However, the proportion of exhaled droplet nuclei or of respiratory droplets that evaporate to generate aerosols and the infectious dose of viable SARS-CoV-2 required to cause infection in another person is not known (even if it has been studied for other respiratory viruses).

Experimental studies have generated aerosols of infectious samples using high-powered jet nebulizers under controlled laboratory conditions. These studies found SARS-CoV-2 RNA within aerosols in air samples for up to 3 hours in one study and 16 hours in another, which also found viable replication-competent virus. These findings were from experimentally induced aerosols that do not reflect normal human cough conditions. Some studies conducted in health care settings where symptomatic COVID-19 patients were cared for—but where aerosol-generating procedures were not performed—reported the presence of SARS-CoV-2 RNA in air samples, whereas other similar investigations in both health care and nonhealthcare settings found no presence of SARS-CoV-2 RNA. One well-done study has found viable virus in air samples up to 5 m (16 ft) from a very ill hospitalized patient in a room with hospital-grade ventilation not mimicking usual building settings.

Recent clinical reports of health workers exposed to COVID-19 index cases, not in the presence of aerosol-generating procedures, found no nosocomial transmission when contact and droplet precautions were appropriately used, including the wearing of medical/surgical masks (not N95 respirators) as a component of the PPE. These observations suggest that aerosol transmission did not occur in this context. A small study (4 COVID-19 patients in 2 double rooms) from a hospital in Rome, Italy

supports the continuation of face-mask use after COVID-19 lockdowns to contain SARS-CoV-2 droplet spread; environmental samples (headboard and sides of beds) were PCR-positive for SARS-CoV-2 in the room where patients did not wear surgical masks. In a hospital in Gainesville, Florida (U.S.), air samples collected in the room from 2 to 4.8 m (6-16 ft) away from a COVID-19 patient with acute symptoms yielded viable SARS-CoV-2, whereas air samples from the room of another COVID-19-infected PCR-negative patient tested negative. This suggests that in the absence of aerosol-generating procedures, patients with acute respiratory symptoms of COVID-19 can produce infectious aerosols.

Outside of medical facilities, some outbreak reports related to indoor crowded spaces have suggested the possibility of aerosol transmission, combined with droplet transmission (e.g., during choir practice, in restaurants, or in fitness classes). In these events, short-range aerosol transmission, particularly in specific indoor locations such as crowded and inadequately ventilated spaces, over a prolonged period with infected persons, cannot be ruled out. However, the detailed investigations of these clusters suggest that droplet and fomite transmission could also explain human-to-human transmission within these clusters.

Effective public interventions should not incur resources solely useful for the prevention of airborne transmission. When droplet/contact precautions and PPE are available and used appropriately, very few infections occur. COVID-19 has been controlled in many countries without having to purchase, fit test, and train entire populations with N95 masks.

Fomite transmission is considered a likely mode of transmission for SARS-CoV-2, given consistent findings about environmental contamination in the vicinity of infected cases and the fact that other coronaviruses and respiratory viruses can transmit this way.

The U.S. CDC estimates R_0 as 2.5 based on global data. A reproductive number, R_0, was estimated at 2–3 both by authorities in China and by multiple other international estimates for the initial outbreak. R_0 greater than 1 indicates that each case leads to more than 1 subsequent case, making control much more difficult. R_0 is not a constant number and changes with the ongoing circumstances and evolution of an outbreak.

For mildly ill patients, shedding of viral RNA from saliva and nasopharyngeal secretions is at peak value on the day of symptom onset, remains high for approximately 6 days, declines significantly in the second week of illness, and usually ceases by day 14, but may continue for 21 days and has been occasionally reported for up to 6 weeks. The preponderance of studies has shown similar viral loads in asymptomatic and symptomatic individuals at time of diagnosis; some evidence shows less likelihood of transmission to contacts of asymptomatic individuals. Asymptomatic persons may transmit to others as soon as 2 days after infection acquisition. Shedding of viral RNA from sputum (lower respiratory tract) typically persists for 21 days from symptom onset (longer for severely ill patients), outlasts the end of symptoms, and may occur for up to 6 weeks. One outlier case of viral RNA shedding for 95 days following symptom onset has been reported in a patient with prolonged illness. No culturable virus has been detected for longer than 8 days after symptom onset. Additionally, the initial viral load in asymptomatic persons is similar to that in the symptomatic persons. Patients with severe or critical COVID-19 have a duration of infectious virus shedding ranging from 0 to 20 days (median 8 days) after symptom onset. The probability of detecting infectious virus drops below 5% after 15 days. Implications from these latter data are for hospital inpatient infection control. Severe or critical patients typically require 30 or more days of hospitalization and prolonged home convalescence; these data have no implications for return to work or the community for typical patients.

During the first several months of the COVID-19 pandemic, persons in older age groups had the highest incidence. In the U.S. during June-August 2020, persons aged 20-29 years had the highest COVID-19 incidence (> 20% of all confirmed cases). The percentage of positive SARS-CoV-2 tests in adults aged 20-39 years preceded increases in adults aged ≥ 60 years by 4 to 15 days and likely contributed to transmission.

Data on the role of children in transmission continue to be published and the answer is increasingly clear. In the U.S., only 3.75% of confirmed cases are in children but few young children develop symptoms. Population-based SARS-CoV-2 serosurveys in the Netherlands and Switzerland, together with a modeling study, indicate that antibodies indicative of previous infection are present in children at approximately half the frequency of that in adults. Robust data from Germany, in 3,712 COVID-19 patients analyzed by 10-year age strata, found no significant difference in viral load between any pair of age categories, including young children. Children may be as infectious as adults in some circumstances. In the U.S., transmission of SARS-CoV-2 was documented from 12 infants and children younger than 10 years (including 2 of 3 asymptomatic children), with acquisition in day care centers and day camps attributed to at least 12 (26%) of 46 nonfacility contacts, including 1 parent who was hospitalized.

An outbreak at a summer camp in the U.S. involved both staff (who wore masks) and campers (who did not wear masks); other than masks for all, most (but not all) governmental guidelines were followed. Timing indicates that some infections were acquired prior to arrival at the camp. The overall attack rate was 44% (260 of 597 persons) and 76% (260 of 344 persons) of those tested by PCR. By age, attack rates were 51% among those aged 6-10 years, 44% among those aged 11-17 years, and 33% among those aged 18-21 years.

In an example of an effective prevention/mitigation program for children, 4 overnight camps in Maine, U.S. successfully used prearrival quarantine, pre- and postarrival testing and symptom screening, cohorting, face coverings, physical distancing, enhanced hygiene measures, cleaning and disinfecting, and maximal outdoor programming for robust transmission control. Among the attendees (staff members over 17 years of age and campers from 7-17 years) from 41 states and 6 international locations, 1,010 quarantined at home for 14 days and were tested before arrival. Four COVID-19–positive asymptomatic attendees delayed their arrival, isolated for a further 10 days, and did not receive any further testing before arrival. All campers quarantined in groups for 2 weeks on arrival. Approximately 1 week after camp arrival, all attendees were tested, and 3 asymptomatic cases were identified. Following isolation of these persons and quarantine of their contacts, no secondary transmission of SARS-CoV-2 occurred for the remaining 6 weeks of the camp season.

The high attack rates in all age groups in an area with high community transmission speak to risks inherent in school settings as reopening occurs. Although children rarely have severe COVID-19 illness, they can transmit infection. According to the U.S. 2018 National Health Interview Survey, about 40 million U.S. adults who are teachers or who live with school-aged children have definite (30 million) or possible (10 million) risk factors for severe COVID-19 illness. Day-care workers were excluded from the study. Data from a large number of countries clearly indicates that SARS-CoV spreads easily in school settings when given the opportunity and that super-spreading events will periodically occur. Different school reopening strategies in different locales are likely to have different success rates, but diligence in mitigation is clearly required.

Since late July, more than 81,000 cases of COVID-19 have occurred among students and faculty at numerous colleges and universities in all 50 U.S. states and in Puerto Rico, the U.S. Virgin Islands, and Washington, D.C. Increasing numbers of U.S. universities have moved from in-person to remote instruction as designated quarantine accommodation becomes overwhelmed. Some campuses have reported more than 1,000 cases. A fundamental problem is that most schools do not have the ability to enforce school policies off campus; military academies have resumed classes and the results of the discipline present in that setting will be important to monitor.

A survey of 500 U.S. universities in August indicated inconsistent and highly variable COVID-19 testing strategies, from available and regular (widely varying periodicity) testing for students, staff, and faculty, to no testing at all. Overall, 54% of universities are testing, with only 27% performing initial reentry testing (at least for undergraduates), and only 20% plan to test regularly to some extent. More private than public universities plan on testing (37% vs. 16%), and more universities ranked in the top 50 by *U.S. News World Report* plan on testing (96% vs. 49%). Both cost of testing (> USD20 million for weekly testing at large schools) and actual availability of testing appear to be main drivers.

In a U.S. CDC case-control investigation, symptomatic outpatients with positive SARS-CoV-2 test results were approximately twice as likely to have reported dining at a restaurant than were matched controls with negative SARS-CoV-2 test results. Attendance at bars or coffee shops showed a trend to an association with test positivity, but enrollment numbers were not adequate to attain statistical significance. When limiting the analysis to those with no known contact with COVID-19 cases, cases were 2.8 times more likely to have dined at a restaurant and 3.9 times more likely to have visited a bar or coffee shop. The case-control design is very powerful, but overall numbers were small given the variety of circumstances offered in restaurants.

Hong Kong presents a localized and well-monitored environment for contact tracing. Contact-tracing data from 1,038 SARS-CoV-2 cases in Hong Kong between January 23 and April 28, 2020, identified 4 to 7 superspreading events across 51 clusters (n = 309 cases) and estimated that 19% of cases seeded 80% of all local transmission. Transmission in social settings was eventually associated with more secondary cases than in households (when controlling for age).

Cats are susceptible to infection with SARS-CoV-2 from close contact with an infected human, and transmission between cats and other felines (including other cats) has occurred. Conclusive evidence of significant levels of human-to-dog transmission of SARS-CoV-2 exists. As with felines, whether infected dogs can transmit the virus to other animals or back to humans remains unclear. Mink-to-mink and mink-to-human (2 cases) transmission has been established. Out of an abundance of caution, persons with suspected or confirmed COVID-19 should limit contact with pets and other animals. Additionally, ferrets, hamsters, rabbits, and common marmosets are also susceptible to SARS-CoV-2 infection.

In an observational cohort study of 116 mothers with SARS-CoV-2 in NYC, none of their neonates were positive for SARS-CoV-2 at 24 hours of life, and none of 82 who were retested at 5 to 7 days were positive. The mothers were allowed to breastfeed and to give skin-to-skin care. All observed masking and hand hygiene before handling the neonate; 83% of neonates roomed in with the mother. Perinatal transmission of SARS-CoV-2 is unlikely to occur if correct hygiene precautions are taken. Rare cases of suspected perinatal SARS-CoV-2 infection have been reported in immunocompromised mothers and 1 in a mother with unusually high viremia. The American Academy of Pediatrics now recommends that newborns "room in" with infected mothers if proper hygiene precautions are observed. Limited data are available for vertical transmission for other coronaviruses (MERS-CoV and SARS-CoV). The virus was not detected in breast milk, but SARS-CoV antibodies were detected in at least 1 sample.

Fecal transmission does not appear to occur, despite the finding of intact virus particles in rectal mucosa and shedding of SARS-CoV-2 RNA in stool specimens for prolonged periods after illness resolution. Based on the limited data to date, live SARS-CoV-2 has not been detected in the breast milk of infected women, and breastfeeding has not been a source of transmission to infants. Viral RNA can be detected in semen, but no culturable virus or sexual transmission has been reported. Transmission via blood transfusion has not been reported; risk appears to be negligible for this respiratory virus, but blood safety measures should still be followed. In a small study, the SARS-CoV-2 genome was not detected in the blood of asymptomatic or mildly ill persons and was only found in the blood of a seriously ill case (a group unlikely to donate blood).

Three studies (preprints) estimate the household secondary attack rate (SAR) in non-Asian countries. In a study of the entire population of Denmark with a very rigid definition of transmission (testing of all household contacts), the SAR was 17%, with a linear relation between acquisition risk and age. An increasing transmission risk with age of primary cases occurred for adults, whereas the risk seemed to decrease with age for children. In the crowded space-constrained conditions of Lima, Peru (average 4.5 inhabitants per house), an overall SAR of 53% was found in a sample of households with at least 1 transmission in 76% of the households with an index case. In the U.K., the SAR was 37% in a sample of households with a lower SAR in larger households, increasing acquisition risk with age and suggesting that children had increased incidence of transmission. Making comparisons across studies is challenging due to differences in follow-up, symptom ascertainment or testing of all contacts, and isolation or infection-control measures in force at the time of study.

U.S. CDC epidemiologists monitored a comprehensive set of open-source public and private websites, social media, and proprietary information sources from December 31, 2019, through March 10, 2020 (i.e., the prepandemic period). Among the first cases reported from each of 99 affected countries outside of mainland China, 76% had recent travel to affected countries, and 61% had traveled to China, Italy, or Iran. Of 101 clusters identified in the prepandemic period, the most commonly identified transmission setting was households (75%), followed by nonhealthcare occupational settings (14%), and community gatherings (11%). Community gatherings resulted in 14.2 cases per cluster versus households' 2.6 cases per cluster. Only 3 clusters were attributed to air flights; no references or information were provided as to the level of evidence or the extent of transmission.

A study from U.S. NIH showed that inocula of SARS-CoV-2 at 21-23°C (69.8-73.4°F) and 40% RH remained culturable for up to 72 hours on plastic and stainless steel, for 24 hours on cardboard (simulates packaged products), and for 4 hours on copper. SARS-CoV-1 remained culturable for up to 72 hours on plastic, for 48 hours on stainless steel, and for 8 hours on either cardboard or copper. Survival appears longer on plastic compared to glass and aluminum. The surroundings of patients with mild or no symptoms have been found to have viral contamination, consistent with the increased risk of transmission to close contacts. Artificially generated aerosols (nebulizer; 21-23°C [69.8-73.4°F] and 65% RH) were collected at intervals over a 3-hour period, and both viruses remained viable and detectable throughout the 3-hour duration of the experiment. Variations of heat and humidity and viability in different matrices (such as nasal secretions, sputum, and fecal matter) were not examined. A study from Hong Kong using virus suspended in growth media indicated viability on the outside of surgical masks for 7 days versus less than 1 day on tissue paper or cloth.

Virology and Immunology

SARS-CoV-2 was initially isolated and the genome was published internationally by scientists in China on January 10. Electron microscopy demonstrates classic coronavirus particles. SARS-CoV-2 is the seventh member of the family of coronaviruses that infect humans. Novel coronaviruses from Wuhan, together with a number of bat-derived SARS-like strains, form a distinct clade in lineage B of the subgenus sarbecovirus. SARS-CoV-2 is a group 2b coronavirus (as are MERS-CoV and SARS-CoV), with a whole genome similarity of up to 80% to SARS-CoV but with a similarity between different gene segments ranging from 60% to 90%. SARS-CoV-2 exhibits a 96.5% similarity to the known bat coronavirus precursors in the same viral clade. Transgenic human ACE2 mice and Rhesus monkeys intranasally challenged by this virus isolate induced multifocal pneumonia with interstitial hyperplasia; SARS-CoV-2 was detected and isolated in the lung and intestinal tissues of the challenged animals.

Two notable features of the SARS-CoV-2 genome have been identified: 1) the presence of a uniquely configured receptor binding domain (RBD) on the virus, which appears to be optimized for binding to the human ACE2 receptor and 2) a polybasic (furin) cleavage site on the protein spike extending from the virus surface. An analysis in *Nature* indicates that SARS-CoV-2 itself is not a recombinant of any coronaviruses detected to date, and its receptor-binding motif—important for specificity to human ACE2 receptors—appears to be an ancestral trait shared with bat viruses and not one acquired recently via natural or artificial laboratory recombination. Phylogenetic dating methods with 3 independent methods were shown to be consistent for 2 different prior specifications of evolutionary rates based on HCoV-OC43 and MERS-CoV. Divergence dates between SARS-CoV-2 and the bat coronavirus reservoir were estimated as 1948, 1969, and 1982, indicating that the lineage (containing the key ACE2-binding residues) giving rise to SARS-CoV-2 has been circulating unnoticed in bats for decades. The new analysis is consistent with the virus having evolved in bats and resulting in bat coronaviruses that can replicate in the upper respiratory tract of both

humans and pangolins. The shared ACE2-specific residues appear to have been present in the common ancestors of both SARS-CoV-2 and Pangolin Guangdong 2019. A host intermediate (with adaptation in that species) between bats and humans is not necessary to explain the emergence of SARS-CoV-2 in humans.

The analyses above of both the RBD and the novel polybasic cleavage site also provides evidence that SARS-CoV-2 is neither a laboratory construct nor a purposefully manipulated virus as the precursors exist in bats. SARS-CoV-2 is not derived from any previously used or known virus backbone. Although SARS-CoV-2 is well suited to human infection, the unique RBD is not structured in such a way that someone with intent to manipulate would have predicted using current computational models and previously known coronavirus constructs. Convincing evidence also exists that the polybasic cleavage site insertion was acquired by the lineage leading to SARS-CoV-2 when it was still in bats. Thus, all unique features of SARS-CoV-2 are features shown to have come together in a bat virus, helping it infect and spread in the bats.

Sequencing of over 90,000 viral isolates sequentially over time indicates limited diversity across SARS-CoV-2 genomes; in a subset of 18,514 sequences, only 11 sites show polymorphisms in more than 5% of sequences. Because SARS-CoV-2 is being transmitted more rapidly than it evolves, the viral population is becoming more homogeneous, with a median of 7 nucleotide substitutions between genomes. Little evidence of diversifying selection exists, with substitution rates comparable across structural versus nonstructural genes. The Wuhan-Hu-1 reference sequence for the spike protein matches all the different optimized vaccine candidate inserts and is identical to an ancestral sequence and 1 mutation away from the current consensus sequence. Each single vaccine candidate should be efficacious against currently circulating lineages.

The virus can now be divided into multiple clades. Clades S, L, and V initially predominated in Asia and in the initial waves of pandemic spread. Currently, Clade GH predominates in North America, GR in Europe and most of the rest of the world, and G is spread globally. In Asia, a more diverse group of other clades predominate. Clades are useful for tracing the timing and routes of spread of SARS-CoV-2. A SARS-CoV-2 variant carrying the spike protein amino acid change G614 (from D614) has become the predominant form globally in the last few months. In models, the change is predictive of better binding to a viral receptor. G614 may thus have a fitness advantage; in infected individuals, G614 is associated with lower PCR cycle thresholds (suggestive of higher upper respiratory tract viral loads) and grows more easily in culture. G614 does not appear to cause more severe disease or increased transmissibility.

Emerging sophisticated studies of cell-line and animal models of SARS-CoV-2 infection, in addition to transcriptional and serum profiling of COVID-19 patients, consistently reveal a unique and inappropriate inflammatory response. SARS-CoV-2 infection drives low interferon levels (normally protective in viral infections) and elevated chemokine expression (including IL-6 and IL1RA) as the defining and driving features of the proinflammatory disease state associated with COVID-19. This response in the aging population prevents successful inhibition of viral spread at early stages of infection, further exacerbating the morbidity and mortality observed for this age group, likely due to inflammatory damage to type II pneumocytes.

SARS-recovered patients have been shown to still possess long-lasting memory T cells reactive to SARS-CoV (which displayed robust cross-reactivity to SARS-CoV-2) 17 years after the 2003 outbreak. Surprisingly, SARS-CoV-2–specific T cells in individuals with no history of SARS, COVID-19, or contact with SARS/COVID-19 patients (n = 37) were also found. These very preliminary T-cell analyses speak positively to the possibility of long-term immunity to SARS-CoV-2 (natural or vaccine-induced), even in the absence of prolonged detectable antibodies in those exposed to either SARS-CoV-2 or more benign coronaviruses.

Seroconversion rates, including those with mild or asymptomatic disease, range from 75% to 99% depending on test platform (e.g., research laboratory, large high throughput commercial analyzer platforms, or rapid tests), antibody target investigated, and patient population. Results from large platform assays from major diagnostics companies provide the most context and comparability. In a very comprehensive serosurvey involving approximately 15% of the population of Iceland and using 6 different antibody assays, total SARS-CoV-2 immunoglobulin was present in 92% of 1,797 persons with PCR-proven infection. Nearly one-third of the infections were detected in persons with asymptomatic infection. Antibody levels did not decline over a period of 4 months in this cohort. Some smaller scope studies have found seroconversion in as few as 70% to 80% of infected persons using a variety of different antibody assays, and other studies have shown antibody levels that wane after 3 months. This unbiased population-level sampling confirmed elevated antibody levels in older adults and in persons who were hospitalized. Conversely, antibody levels were lower in smokers and in women who had less severe disease. Nursing home residents may have antibody rates approaching more than 80% in the most affected locations. In nursing homes in England, more than 80% of the residents mounted an antibody response, including 82% of those aged > 80 years. IgG antibodies develop over 7 to 50 days from symptom onset, with peak titers at approximately 24 days from symptom onset; the optimal timeframe for antibody testing is at least 3 to 4 weeks after symptom onset and at least 2 weeks after symptom resolution.

Correlation with protection to reinfection of these levels of antibodies is not yet known. Simple presence of serum antibody as detected by commercial serologic testing is not uniformly effective against reinfection, but most persons with COVID-19 will develop neutralizing antibodies (nAb) to the SARS-CoV-2 spike protein. Duration is not yet clear; nAb levels can only be studied

in research laboratories at present. A small study has shown that known preexisting nAb were protective in 3 persons in a contained intense exposure setting, whereas 3 others in the same setting with detectable COVID-19 antibodies that were not nAb were not protected. Studies to date do not account for possible B- and T-cell memory, with rapid redevelopment of nAb titers on reexposure to SARS-CoV-2.

U.S. CDC Case Definition Criteria

The following surveillance case definitions (based on clinical and laboratory criteria and epidemiologic linkage) enable PHA to classify and count cases consistently across report jurisdictions and are not intended to be used for making a clinical diagnosis.

Case Definitions

Confirmed:

- Meets confirmatory laboratory evidence

Probable:

- Meets clinical criteria *and* epidemiologic evidence with no confirmatory COVID-19 laboratory testing performed
- Meets presumptive laboratory evidence *and* either clinical criteria or epidemiologic evidence
- Meets vital records criteria (death certificate lists COVID-19/SARS-CoV-2 as cause of or significant condition contributing to death) with *no* confirmatory COVID-19 laboratory testing performed

Laboratory Criteria

Confirmatory laboratory evidence (test meets U.S. FDA standards):

- Detection of SARS-CoV-2 RNA in a clinical specimen using a molecular amplification test

Presumptive laboratory evidence (test meets U.S. FDA standards):

- Detection of specific antigen in a clinical specimen
- Detection of a specific antibody in serum, plasma, or whole blood indicative of a new or recent infection

Clinical Criteria

Any of the following criteria are acceptable when no alternative more likely diagnosis exists.

- At least 2 of the following symptoms: fever (subjective or measured as ≥ 38°C [100.4°F] for the general population or ≥ 37.8°C [100°F] for HCWs), chills, rigors, myalgia, headache, sore throat, new smell and taste disorder(s) *or*
- At least 1 of the following symptoms: cough, shortness of breath, or difficulty breathing *or*
- Severe respiratory illness with at least 1 of the following: clinical or radiographic evidence of pneumonia or ARDS

Older adults often have a normal (baseline) temperature that is lower than in younger adults; therefore, a single reading higher than ≥ 37.8°C (100°F), multiple readings above ≥ 37.2°C (99°F), or a single reading increase of more than 1.1°C (or 2°F) above baseline temperature may be a sign of infection.

Epidemiologic Linkage

One or more of the following exposures in the 14 days before symptom onset:

- Close contact (≤ 2 m [6 ft]) for a prolonged period of time (> 15 min; any duration for HCWs during an aerosol-generating procedure) with a symptomatic COVID-19 case (laboratory-confirmed or probable), a person with clinically compatible illness and linkage to a confirmed COVID-19 case, or an asymptomatic COVID-19 case (laboratory confirmed) during a period from 48 hours before symptom onset (or specimen collection in the instance of an asymptomatic case) to meeting criteria for discontinuation from home isolation in an area with widespread community transmission, irrespective of whether the COVID-19 case or the contact was wearing a mask.
- Travel to or residence in an area with sustained, ongoing SARS-CoV-2 transmission
- Member of a risk cohort as defined by PHA during an outbreak

Clinical Manifestations

An incubation period of 2 to 7 days appears most common (5 days is typical across many studies), with an upper range of 14 days. As with any infection, very small numbers of outliers with longer incubation periods have been reported. In contrast to SARS-CoV infection, the serial interval is 4 days, which is less than the incubation period, supporting presymptomatic transmission. Most cases exhibit symptoms of fever, dry cough, progressing to breathlessness in the second week, and

pneumonia in those who progress further; sputum production has been reported in one-third of cases; 25% to 43% of patients are afebrile at the time of presentation. Loss of the senses of smell and taste as a symptom of infection was found in up to 80% of patients in a multicenter European study, with higher frequency in women. In 12% of cases, anosmia/ageusia was the initial symptom. In one large series, after a mean follow-up of 47 days, 37% of patients still reported subjective loss of smell, 14% reported partial recovery, and 49% reported complete recovery. A biopsy study of 23 non-COVID-19 patients showed ACE2 receptor (cellular binding site for SARS-CoV-2) expression was 200- to 700-fold greater in the apical layer of nasal and olfactory mucosa relative to other areas of the nose and trachea; ACE2 was not detected on olfactory neurons. An earlier biopsy study from COVID-19 patients had revealed the presence of infiltrative macrophages harboring SARS-CoV-2 antigen in the nasal and olfactory mucosal stroma. Other symptoms may include chills, myalgia, headache, sore throat, congestion, runny nose, nausea, vomiting and diarrhea. Mild illness may occur for up to 14 days, with late and often very acute onset of severe respiratory compromise; influenza has a much more sudden onset. White blood cell counts are typically normal, and a lymphocyte count of less than 1.5×10^9/L is frequently seen in patients. Abnormal liver function tests, especially LDH, appear to be common and may be a poor prognostic sign. Diarrhea may occur, but incidence has been highly variable in several cohorts. Elevated red blood cell distribution width (RDW) and increasing RDW during the hospital course may be associated with increased mortality.

Asymptomatic patients with CT scan abnormalities occur with some frequency. Symptomatic patients with CT scan abnormalities but negative viral (PCR) tests on upper respiratory samples appear to occur with some frequency. A study in the *American Journal of Roentgenology* compared CT scans in 52 patients with PCR-proven COVID-19 to 45 patients with proven influenza. No significant differences were found between the 2 viral pneumonias in terms of the properties of the largest lesion, presence of ground glass opacities, presence of consolidation, presence of mosaic attenuation, bronchial wall thickening, centrilobular nodules, interlobular septal thickening, crazy paving pattern, air bronchogram, unilateral or bilateral distribution, or longitudinal distribution of lesions. During the upcoming influenza season, where delays in PCR test results may occur, CT imaging should not be used to differentiate between COVID-19 and influenza.

Based on the global experience to date, approximately 5% of infected individuals require hospitalization; of the hospitalized cases, more than 80% have mild to moderate presentations, 14% are severe, and 5% are critical. In almost all studies to date, males are much more likely to be infected and much more likely to have poor outcomes when compared to females; a potentiating effect of androgens has been implicated. Analysis of pediatric COVID-19 hospitalization data from 14 U.S. states found that although the cumulative rate of COVID-19–associated hospitalization among children (8.0 per 100,000 population) is low compared with that in adults (164.5), 1 in 3 hospitalized children was admitted to an ICU.

Risk of severe COVID-19 increases independently and steadily as a person gets older and is higher in persons (regardless of age) with underlying medical conditions (the more conditions, the higher the risk of severe illness). The U.S. CDC has stratified the risk of more severe disease associated with co-morbidities by level of evidence:

- Strong evidence: serious heart conditions (heart failure, coronary artery disease, cardiomyopathies, or pulmonary hypertension), cancer, chronic kidney disease, COPD, obesity (BMI > 30), sickle cell disease, solid organ transplantation, and type 2 diabetes
- Mixed evidence: asthma (moderate to severe), cerebrovascular disease, hypertension, pregnancy, smoking (a history of or currently), and use of corticosteroids or other immunosuppressive medications
- Limited evidence: bone marrow transplantation, HIV (persons with low CD4 count or not on effective HIV treatment), other immunodeficiencies, inherited metabolic disorders, liver disease (especially cirrhosis), neurological conditions, other chronic lung diseases (including idiopathic pulmonary fibrosis and cystic fibrosis), pediatrics (those with serious genetic, neurologic, or metabolic disorders or genital heart disease), type 1 or gestational diabetes, and thalassemia

No data are available on whether the risk factors of diabetes and hypertension are related to a history/diagnosis of currently controlled or uncontrolled disease.

Up to 5% of patients with COVID-19 have developed acute respiratory distress syndrome. Clinical management includes supportive care, including hemodynamic support, supplemental oxygen, and mechanical ventilatory support when indicated. Whether prone positioning can prevent intubation in patients with severe COVID-19 is unclear but should be avoided in patients whose condition is rapidly deteriorating to avoid indicated intubation and mechanical ventilation. For patients with persistent hypoxemia despite increasing supplemental oxygen requirements and in whom endotracheal intubation is not otherwise indicated, a trial of awake prone positioning may be considered to improve oxygenation. CT scans may not offer information beyond what is in the chest x-ray of a patient in the ICU. Hypercoagulability, including pulmonary emboli and cerebral stroke (up to 1% of hospitalized cases; including in young persons), and highly elevated levels of D-dimer have been clearly demonstrated. The U.S. NIH guidelines state that for nonhospitalized patients with COVID-19, anticoagulants and antiplatelet therapy should not be initiated for prevention of venous thromboembolism (VTE) or arterial thrombosis unless other indications exist. Hospitalized adults with COVID-19 should receive VTE prophylaxis per the standard of care for other hospitalized adults, but full

anticoagulation therapy should only initiated for suspected or proven thrombotic events. The proportion of COVID-19 patients with bacterial infection is 7.1% overall and 8.1% in critically ill patients. Nevertheless, most hospitalized patients with COVID-19 receive antibiotics (71.3%), raising concerns about long-term increases in antibiotic resistance in many countries.

COVID-19 manifests uniquely in children and is usually mild. Of 121 SARS-CoV-2 deaths among persons in the U.S. younger than 21 years, 10% were infants and 70% were aged 10-20 years. Non-Caucasian persons accounted for 78% of these deaths; 33% of deaths occurred outside of a hospital. A peer-reviewed database study examined outcomes in 3,222 young adults (age 18-34 years) who required hospitalization for COVID-19 in 1,030 U.S. hospitals and health care systems: 21% required ICU admission, 10% required mechanical ventilation, and 2.7% died. Young adults with more than 1 comorbidity (morbid obesity, hypertension, and diabetes) faced risks comparable with middle-aged adults without them. More than half of those requiring hospitalization were Black or Hispanic. In South Korea, where children with COVID-19 were uniquely observed and followed while in the hospital from the time of a positive PCR test, 22% of 91 children who were studied remained asymptomatic. Only 8.5% of symptomatic cases were recognized as possible cases and tested at the time of symptom onset, whereas 66.2% had unrecognized and nonspecific symptoms before diagnosis, and 25.4% developed symptoms after diagnosis (many were contacts or returned travelers). Disease was mild or moderate and lasted a mean of 11 days. Similar to adults, SARS-CoV-2 RNA was detected for a mean of 17.6 days overall and 14.1 days in asymptomatic cases.

The case definition of an uncommon Kawasaki-disease-like, multisystem inflammatory syndrome in children (MIS-C) includes hospitalization, age younger than 21 years, fever for ≥ 24 hours, laboratory evidence of inflammation (most with 4 or more elevated biomarkers), multisystem involvement, and evidence of SARS-CoV-2 based on PCR, serology, or exposure to a COVID-19 case within 1 month. Studies to date indicate that the gastrointestinal system is the most frequently involved (92%), followed by the cardiovascular (including coronary aneurysms; 80%), hematologic (76%), mucocutaneous (74%), and respiratory (70%) systems. CFR was 2%. Approximately 55% of cases are male, 70% are Hispanic/Latino or non-Hispanic Black, and more than 80% are aged 1-14 years. In the U.K., of 651 children younger than 19 years admitted to 138 hospitals, 42% had at least 1 comorbidity and 1% died, all of whom had severe multiple comorbidities. Of the 18% of all children who were admitted to the ICU, major risk factors were age younger than 1 month, age 10-14 years, and black ethnicity. Although 11% of admitted children met WHO MIS-C criteria and had high risk of ICU admission, none died.

Sequelae from severe illness include lung fibrosis, myocardial injury, arrhythmias, cardiomyopathy, heart failure, and prolonged neuropsychiatric deficits. The frequency and degree of direct cardiac damage by SARS-CoV-2 itself remain unclear. Two new studies examine viral effect on cultured cardiomyocytes. In one study (preprint), robust transcriptomic and morphological signatures of damage included a distinct pattern of sarcomere fragmentation, with specific cleavage of thick filaments, and cardiomyocytes that lacked nuclear DNA. Autopsy specimens from COVID-19 patients also displayed these changes. In the other study, microscopy and RNA sequencing demonstrated that SARS-CoV-2 can enter cardiac cells via the ACE2 receptor (receptor density on cardiomyocytes increases with age), replicate, and induce cellular apoptosis and cessation of beating after 72 hours of infection. In a study of 100 German patients 2 to 3 months after recovery from COVID-19 (one-third mild cases), magnetic resonance imaging revealed cardiac involvement in 78% and ongoing myocardial inflammation in 60%, independently of preexisting conditions, the severity and overall course of the acute illness, and the time from the original diagnosis. Changes in serum troponin and left-ventricular ejection fraction (60 in controls vs. 56 in COVID-19 patients) were relatively minor, and no further follow-up has been reported at this time. These findings indicate the need for ongoing investigation of the long-term cardiovascular sequelae of COVID-19.

A "long COVID-19 syndrome," manifested by prolonged fatigue, altered mental status, neurocognitive defects, memory loss, anosmia, and affective disorders is well reported but needs systematic studies to differentiate a direct viral effect or thrombotic events from the effects of a critical illness with a cytokine storm syndrome. The neurologic effects are reported in mild cases as well as in severe cases. Of symptomatic adults in the U.S. who had a positive outpatient test result for COVID-19, thirty-five percent had not returned to their usual state of health when interviewed 2 to 3 weeks after testing. Broken down by age, 26% of those aged 18-34 years, 32% of those aged 35-49 years, and 47% of those aged ≥ 50 years had not returned to their usual state of health. Among persons aged 18-34 years with no chronic medical condition, 19% reported not having returned to their usual state of health. A recovery time of at least 6 weeks for persons with severe or critical disease is common. Prolonged fatigue and markedly diminished exercise tolerance for 3 or more months occurs is not uncommon.

Scattered reports of cases of COVID-19 reinfection have been anecdotal or without definitive laboratory proof. The University of Hong Kong has now published data (peer-reviewed) on a 33-year-old immunocompetent patient, first infected in March in Hong Kong and again in August while traveling in Spain. The sequence of the virus from the patient’s 2 infections were from separate SARS-CoV-2 clades and differed by 24 nucleotides/71 amino acids, indicating separate infection events. The second infection was asymptomatic and detected on airport screening on arrival in Hong Kong. SARS-CoV-2 IgG (neutralization testing not done) was detectable for the first time 5 days into the second infection. Three similar reinfections with different virus strains spaced by 2 months or more have been reported in the media from academic institutions in the Netherlands (immunocompromised patient),

U.S., and Belgium. Two of the 3 were mildly symptomatic and 1 had severe disease; other than negative HIV testing, a complete immune screen was not done on the latter patient. These events provide a signal to pursue further studies, but single, scattered events may be outliers and should not affect approaches or policy without further evidence. One explanation for the first 3 cases is that the first infection in these cases may still have induced immunity to significant disease but not to reinfection.

Pregnant women are generally more susceptible to viral respiratory infections, including COVID-19. Pregnant women are less likely to present with fever (odds ratio [OR] = 0.43) when compared to matched nonpregnant women. Pregnant women are more likely to need ICU admission (OR = 1.62) and invasive ventilation (OR = 1.88) but do not have increased mortality. Obesity, hypertension, diabetes, and increased age are associated with severe COVID-19 in pregnancy, and preexisting maternal co-morbidity increases risk of ICU admission. Additionally, pregnant women are more likely to experience preterm birth and their neonates are more likely to be admitted to a neonatal ICU; other adverse pregnancy outcomes (e.g., pregnancy loss or low birth weight) have not been found to be more common. No information is available on long-term health effects of SARS-CoV-2 infection in utero.

Diagnosis

Two types of COVID-19 tests are available, a viral (PCR or antigen) test for current acute infection using respiratory samples (e.g., nasal, nasopharyngeal, or oropharyngeal swabs) and an antibody (serology) test for a previous infection using blood samples (e.g., finger stick or venous blood sample). Viral tests may have false negatives dependent on test type, specimen type, sampling problems, and storage time. With a combination of these factors, worse case scenarios of 30% false negatives have been reported. In general, antibody tests are less accurate than viral tests with more false positives, especially with rapid point-of-care tests compared to tests run in a laboratory. The detection of antibodies does not necessarily indicate protective immunity or even past infection and should not be used to detect acute infection when viral tests were negative or were not performed early after symptom onset.

In the U.S., most large academic medical centers mandate that patients needing elective surgery or other procedures have a negative COVID-19 PCR test within 72 hours of surgery/procedure. A simple rule is the 3-midnight rule: a negative test result is valid as long as no more than 3 midnights have passed since the sample was obtained. A similar policy may be suitable for settings where potentially infected persons need to be excluded.

Acute Disease: Nucleic Acid and Antigen Testing

Nucleic Acid Testing

PCR diagnostic kits to detect active infection with replicating virus are available globally, but adequate testing capacity is still lacking in many countries (including the U.S.) and undertesting of minimally symptomatic persons is still occurring. PCR testing capacity across the U.S. is approximately 860,000 patients per day (7-day rolling average) but may be adversely affected by supply shortages. Nearly half of U.S. commercial, hospital, and public health laboratories continue to experience diagnostic testing supply shortages (e.g., test kits, reagents, and swabs); 25% of laboratories are unable to process all requested tests within a week and, test results are currently delayed for a week or longer in hot-spot communities. A pooled testing strategy, whereby RNA from multiple patient swabs are run in the same test reaction and only positive pools are retested as single specimens, may be considered to conserve testing supplies. The implementation of this strategy and pool size depend on the community prevalence of SARS-CoV-2 but will not provide increased efficiency in very high incidence communities. The Quest SARS-CoV-2 rRT-PCR (Quest Diagnostics), LabCorp COVID-19 RT-PCR Test (LabCorp), USCD RC SARS-CoV-2 Assay (University of California San Diego Health), Poplar SARS-CoV-2 TMA Polling Assay (Poplar Healthcare), Verily COVID-19 RT-PCR Test (Verily Life Sciences), and BayCare SARS-CoV-2 RT PCR Assay (BayCare Laboratories, LLC) are the only tests to be granted a U.S. FDA EUA for pooled testing. Dilution of specimens in such a strategy may dilute the RNA and result in an increased number of false negatives. See Criteria for Testing of Possible Cases.

In the U.S., an FDA EUA has been granted for the SalivaDirect diagnostic test (Yale School of Public Health, Department of Epidemiology of Microbial Diseases). The saliva sample can be collected in any sterile container, is validated for use with a variety of commonly used reagents and instruments, and does not require a separate nucleic acid extraction step (thus reducing the need for scarce testing resources). Data so far indicate performance similar to more complex saliva-based options. This test is currently run only at Yale, but the protocol is open-source.

In the U.S., an FDA EUA has been granted for more than 195 available RT-PCR tests and 4 antigen tests; see https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#2019-ncov. An EUA is not equivalent to full FDA scrutiny and authorization, and many EUAs have been granted

within a short period during the pandemic. Additionally, all states can authorize tests developed and used by laboratories in their states without federal oversight, but U.S. CDC testing guidelines must still be met; these tests will not be discussed here.

The main commercial PCR platforms in use are:

- Abbott ID NOW (not true PCR): fast, point-of-care tabletop device, low-volume (1 specimen per run), insensitive; specimen must be collected within 7 days of symptom onset.
- Cepheid GeneXpert: fast, sensitive, low-volume, easy, expensive, short-supply
- Abbott, Roche (plus others) PCR kits: for high volume behemoth analyzers running hundreds of samples per hour, slower, sensitive
- Biofire, Luminex multiplex panels for 20 respiratory pathogens: expensive per sample, slower, low volume

Three multiplex PCR tests have been granted a U.S. FDA EUA for the simultaneous qualitative detection and differentiation of SARS-CoV-2, influenza A, and/or influenza B in a single nasal or nasopharyngeal sample. The U.S. CDC Influenza SARS-CoV-2 (Flu SC2) Multiplex Assay test kit will be distributed to state and local public health laboratories but is not commercially available to health care providers or hospitals directly. The sequences of the primers and probes used with this kit have been shared by the U.S. CDC so that other laboratories may manufacturer their own reagents. The cobas SARS-CoV-2 & Influenza A/B test (Roche) is run on Roche's widely available high-throughput cobas 6800/8800 systems, which can provide 384 to 1,056 results in 8 hours depending on the system used. The cobas SARS-CoV-2 & Influenza A/B Nucleic Acid Test for use on the cobas Liat System (Roche) is run on Roche's Liat System, with point-of-care results in 20 minutes. Roche will deliver as many tests as possible within the limits of supply and anticipates release to all public health laboratories prior to influenza season.

At-home sample collection kits from various manufacturers are each matched to certain PCR platforms. A physical provider visit is not necessary, but a short online questionnaire may be required.

Table 2: Vendors Offering At-Home Sample Collection Kits

Vendor/Lab	URL	Sample Type	Cost	Shipping	Results (time after receipt by lab)[1]
Everlywell	https://www.everlywell.com/products/covid-19-test/	Nasal swab	USD109	Overnight to lab	Digital (72 hrs)
Let's Get Checked	https://www.letsgetchecked.com/us/en/home-coronavirus-test/	Nasal swab	USD119	Overnight to lab	Digital (24-72 hrs)
Kroger	https://www.thelittleclinic.com/home-testing/	Nasal swab (remote supervision)		Employer or benefit provider ID code required; overnight to lab	Digital (48-72 hrs)
Phosphorus Diagnostics	https://www.phosphorus.com/covid-19-order-now	Saliva	USD140	Overnight to lab	Digital (72 hrs)
P23 Labs	https://p23labs.com/covid-19-kit	Saliva	USD142	Overnight to lab	Digital (72 hrs)
Fulgent	https://picturegenetics.com/covid19	Nasal swab	USD119	Overnight to lab	Digital (24-48 hrs)
LabCorp	https://www.pixel.labcorp.com/covid-19	Nasal swab	USD119	Overnight to lab	Digital (48-72 hrs)
QuestDiagnostics	https://questdirect.questdiagnostics.com/products/covid-19-active-infection/2713afd8-3d0c-4819-b877-6880a776cc46	Nasal swab	USD129	Overnight to lab	Digital (1 wk)
Vitagene	https://vitagene.com/products/covid-19-saliva-test-kit/	Saliva	USD129	Overnight to lab	Digital (72 hrs)

1. Time to receipt of test results may vary with demand, check immediately prior to shipping to ensure receipt of result on personal device prior to flight departure if needed.

Vendor/Lab	URL	Sample Type	Cost	Shipping	Results (time after receipt by lab)[1]
Vault	https://www.vaulthealth.com/covid	Saliva (remote supervision)	USD150	Overnight to lab	Digital (48-72 hrs)

1. Time to receipt of test results may vary with demand, check immediately prior to shipping to ensure receipt of result on personal device prior to flight departure if needed.

Any negative test results that are not consistent with a patient's clinical presentation or necessary for patient management should be confirmed with another test. HKU1, NL63, 229E, and OC43 are human coronaviruses that are detected by some routine multiplex PCR panels used in routine clinical practice and lab reports should be read carefully.

Antigen Testing

Antigen tests detect the presence of unamplified specific viral proteins, in contrast to the amplified viral RNA detected by PCR tests, and are thus inherently less sensitive than PCR tests. The main advantages of antigen tests are the potential scale and low cost of manufacture and the lack of cross-reactivity with other high-prevalence respiratory pathogens. More data are required before definitive use can be recommended in asymptomatic contacts or in screening programs in congregate settings, where testing over several consecutive days may be required to detect infected individuals with low viral loads who are early in the course of infection. Persons with very high suspicion for infection who test negative with antigen testing can be retested by PCR instead of with daily antigen tests. Persons who have been symptomatic for 5 days or more should be tested only by PCR; an antigen test will most often be negative at this point, even in true infection. The higher the prevalence of COVID-19 in the community, the higher the performance of antigen testing.

Four rapid antigen tests, 1) Sofia 2 SARS Antigen FIA (Quidel Corporation), 2) BD Veritor System for Rapid Detection of SARS-CoV-2 (Beckton, Dickinson and Company), 3) LumiraDx SARS-CoV-2 Ag Test (LumiraDx UK Ltd.), and 4) BinaxNOW COVID-19 Ag Card (Abbott) have been granted an EUA by the U.S. FDA and are approved for use in CLIA laboratories and point-of-care patient care settings (under a CLIA waiver) to detect acute infection using a nasopharyngeal or nasal swab. The first 3 tests are run on small table-top analyzers that produce results in 15 minutes and are available in tens of thousands of hospitals, clinics, practices, and retail pharmacies in all 50 U.S. states. The BinaxNOW visually read card test requires no machinery and takes only 15 minutes to get a result but is not an at-home test; a trained human reader is required and self-use in travelers is not likely to be feasible. The manufacturer’s claim of 97% sensitivity and 98.5% specificity on nasal swab specimens is based on only 102 samples in an in-house laboratory. Specificity of antigen tests using the Binax platform are generally high. The BinaxNOW card test for influenza, using identical technology, is known to be only 70% as sensitive as PCR. Tens of millions of tests (cost: USD5 each) will be shipped in September, with plans to ship 50 million tests per month beginning in October.

Evidence of Earlier Infection: Antibody Testing

Over 99.5% of symptomatic COVID-19 patients seroconvert to the SARS-CoV-2 spike protein. IgG antibodies develop over 7 to 50 days from symptom onset and 5 to 49 days from symptom resolution; the medians to higher antibody titers are 24 days from symptom onset and 15 days from symptom resolution. Conclusions are that the optimal timeframe for widespread antibody testing is at least 3 to 4 weeks after symptom onset and at least 2 weeks after symptom resolution. Such methodology is critical for an accurate estimate of population-based asymptomatic and case-fatality rates and to properly effect mitigation and suppression strategies. The use of serologic testing alone is not recommended by any governmental authority (U.S.CDC, U.S. NIH, ECDC, WHO) for any patient-centered purpose, including diagnosis of acute disease and immunity to SARS-CoV-2 for return-to-work or entry/exit requirements. Serologic testing only has a place in public health surveillance of populations. According to the Infectious Diseases Society of America, serology should be considered only in the following situations: use IgG antibody to provide evidence of SARS-CoV-2 infection in symptomatic patients with a high clinical suspicion and repeatedly negative NAAT testing; if needed, use SARS-CoV-2 IgG or total antibody 3 to 4 weeks after symptom onset to detect evidence of past SARS-CoV-2 infection.

To date, 46 antibody tests, either point-of-care rapid tests or high-throughput antibody tests that are run on large autoanalyzer platforms to detect IgM and/or IgG in persons who are more than 2 weeks beyond onset of symptoms, have been granted a U.S. FDA EUA, and their use is limited to laboratories certified to perform moderate-and high-complexity tests. In the setting of a relatively low seroprevalence, any serologic test would need to have excellent performance characteristics. According to robust

data from the U.S. FDA and several other sources, the SARS-CoV-2 IgG test (Abbott) and the Elecsys Anti-SARS-CoV-2 IgG test (Roche) both have sensitivity and specificity over 99.5%, and the VITROS Immunodiagnostic Products Anti-SARS-CoV-2 IgG Reagent Pack (Ortho-Clinical Diagnostics, Inc.) and Anti-SARS-CoV-2 ELISA IgG test (EUROIMMUN US Inc.) have positive and negative predictive values above 99.5%.

In the U.S., LabCorp and Quest Diagnostics now offer direct-to-consumer COVID-19 high-throughput antibody testing. A provider visit is not required, but a short online questionnaire must be completed before making an appointment and the request will be reviewed by a physician providing clinical oversight to the laboratory. Persons with recent known exposures or current or recent symptoms compatible with COVID-19 will not be allowed into testing centers. The LabCorp test does not require upfront payment (covered by insurance or federal reimbursement) and the Quest Diagnostics tests costs USD119. Test results are available within 48 hours after collection of a venous blood sample at a Lab Corp or Quest Diagnostics patient service center. Antibody tests for immunity to infection appear contrary to Equal Employment Opportunity Commission (EEOC) laws, and the EEOC has already ruled against them.

Point-of-Care Antibody Testing

All rapid point-of-care antibody tests formally reviewed by the U.S. FDA had less than optimal performance in comparison with high-throughput platforms. The consensus by clinical laboratory directors is also that almost all such tests are of extremely poor quality. Tests run on high-throughput analyzers (above) from large established companies are far superior to point-of-care tests from startup firms.

Criteria for Testing of Possible Cases

Clinicians should work with their local and state health departments to coordinate testing through public health laboratories or use clinical laboratory diagnostic testing (nucleic acid or antigen) authorized under an EUA; antibody testing alone is not recommended for diagnostic purposes. Nucleic acid (PCR) or antigen testing priorities are designed to ensure optimal care, decrease community spread, and ensure the health of essential workers. Testing the same person more than once in a 24-hour period is not recommended. Preadmission or preprocedure testing may be considered to inform decisions about deferring elective care or the required level of PPE for nonelective care.

Symptomatic persons

Clinicians should use their clinical judgment to determine whether a patient with COVID-19–compatible signs and symptoms (including fever, dry cough, breathlessness, new loss of the senses of smell and taste, chills, myalgia, headache, sore throat, vomiting, or diarrhea) should be tested for acute disease. Testing of HCWs and persons with extensive and close contact with vulnerable persons is a priority and should be performed even with just 1 of the aforementioned signs or symptoms (mild or severe). Local epidemiology of COVID-19 as well as the clinical course of the illness should be considered in the decision making, and appropriate testing for other causes of respiratory infections (including influenza) should be performed. Persons who test positive or do not get tested should self-isolate until ≥ 24 hours have passed since their last fever without the use of fever-reducing medications and ≥ 10 days have passed since symptom onset. If self-isolation is not possible, such persons should observe respiratory and hand hygiene, social distancing, and wear a nonmedical mask, especially if in contact with vulnerable populations. A positive test does not need to be repeated after recovery.

Asymptomatic persons *with* known or suspected exposure

Asymptomatic persons with close contact to a person with COVID-19 or attendance at a high-risk event do not necessarily need to be tested according to U.S. CDC, unless they are a vulnerable person or testing is recommended by other health authorities. WHO (reviewed August 19, 2020) and many or most national authorities outside the U.S. recommend that close contacts of a confirmed case remain quarantined for 14 days after last contact and only be tested if they become symptomatic. These persons should observe respiratory and hand hygiene, social distancing, and wear a nonmedical mask, especially if in contact with vulnerable populations. In addition, they should self-observe for symptoms and then follow guidelines for symptomatic persons if symptoms develop.

Asymptomatic persons *without* known or suspected exposure

Testing is not recommended, but asymptomatic persons without exposure who have been tested should self-quarantine at home until their test results are known; the self-quarantine recommendation does not apply to routine workplace or school screening or surveillance.

Asymptomatic persons *without* known or suspected exposure but with setting specific factors

Broad-based asymptomatic testing may be considered in certain settings: 1) places that house vulnerable populations (e.g., long-term care facilities, prisons, and shelters); 2) in critical infrastructure workplaces where workers may be disproportionately

affected (e.g., HCWs and first responders) or continuity of operations is a high priority; and 3) routine screening or surveillance in the workplace or academic institutions. Approaches include initial testing of all residents, students, and/or employees, regular (e.g., weekly) testing, and testing of new entrants (residents, students, and/or employees) or those reentering after an absence. Asymptomatic persons who were tested as part of broad-based testing do not need to self-quarantine while awaiting test results.

Case definitions now specify that a contact includes a person who was exposed during a period from 48 hours before through 10 days after the onset of symptoms of a probable or confirmed case. Contact includes any amount of direct physical contact or face-to-face contact at less than 2 m (6 ft) for more than 15 minutes, irrespective of whether the COVID-19 case or the contact was wearing a mask. Fever may be subjective or confirmed (≥ 38°C [100.4°F] for the general population or ≥ 37.8°C [100°F] for HCWs). Older adults often have a normal (baseline) temperature that is lower than in younger adults; therefore, a single reading higher than ≥ 37.8°C (100°F), multiple readings above ≥ 37.2°C (99°F), or a single reading increase of more than 1.1°C (or 2°F) above baseline temperature may be a sign of infection.

Close contact is also defined as having direct contact with infectious secretions of a COVID-19 case (e.g., being coughed on or shaking hands).

Persons with COVID-19, to determine resolution of infection

A symptom-based strategy is preferred over a test-based strategy to determine discontinuation of isolation, but a test-based strategy may be considered if a person needs to return to work earlier than the symptom-based strategy would allow. However, the test-based strategy often results in prolonged isolation or work exclusion because of continued shedding of detectable (but not infectious) SARS-CoV-2 RNA beyond the duration used for the symptom-based strategy.

Persons in the community, as part of public health surveillance

Diagnostic testing (nucleic acid or antigen) may be used in community, outpatient, and hospital-based surveillance systems to identify COVID-19 cases that may not have been identified otherwise under the aforementioned categories. These data help identify areas of ongoing transmission and geographic trends.

Therapeutic Drugs

No drugs have been fully approved for the treatment of COVID-19. Only the most promising agents or data on randomized controlled trials will appear in Travax. Controlled data on any of the proposed COVID-19 therapies (including immune plasma) currently remain insufficient, and no drug, including IV remdesivir (an antiviral drug) or dexamethasone (or other steroid), appears to be in the highly potent "game-changer" category. The U.S. NIH have published official treatment guidelines developed by a panel of federal agencies and professional societies. The guidelines are updated regularly (but not immediately) as published data and other authoritative information become available at https://covid19treatmentguidelines.nih.gov/introduction.

Antivirals

In the U.S., the FDA EUA for remdesivir has been expanded to include all (not just oxygen-dependent) hospitalized adult and pediatric COVID-19 patients based on limited new data on endpoints indicating slightly shorter hospitalization times. Considering current supply shortages, remdesivir should be prioritized for use in hospitalized patients with COVID-19 who require supplemental oxygen but who are not on high-flow oxygen, noninvasive ventilation, or mechanical ventilation. Remdesivir therapy duration for nonintubated patients on supplemental oxygen alone is 5 days or until hospital discharge, whichever comes first; for patients who progress to requiring more than supplemental oxygen, the course of remdesivir should be completed. Some experts extend therapy duration to 10 days for patients who have not shown adequate improvement after 5 days of therapy. The U.S. NIH makes no recommendation for or against the use of remdesivir for patients who require high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO), whereas IDSA recommends its use in this population. The U.S. NIH makes no recommendation for or against the use of remdesivir for patients with mild-to-moderate COVID-19, whereas IDSA recommends against its use in this population.

IV remdesivir remains the most promising antiviral drug candidate. Published data from a randomized trial (n = 1,063) showed a recovery time for COVID-19 patients that was reduced from 15 days in the placebo group to 11 days in the remdesivir group (statistically significant). Patients receiving invasive or mechanical ventilation at time of enrollment (n = 272) did not show a time-to-recovery benefit, and patients receiving more than low-flow oxygen had an even more modest benefit than the overall group. Black and Asian patients had poorer outcomes; no gender difference was found. The mortality rate at 14 days was reduced from 11.9% in the placebo group to 7.1% in the remdesivir group (not statistically significant). The results indicate a modest benefit of remdesivir monotherapy in those less ill and not requiring ICU admission but no real improvement in those where the so-called cytokine storm phase had already begun. The safety and effectiveness of remdesivir for COVID-19 treatment have not been evaluated in pregnant patients. Remdesivir should not be withheld from pregnant patients if it is otherwise indicated.

In moderately ill patients (good prognosis) with pneumonia but no hypoxia, 5 days of IV remdesivir led to a 76% rate of improvement (n = 191) by day 11 compared to 66% in those given standard of care (n = 200), which was statistically significant. Ten days of remdesivir (n = 193) was not statistically different than the standard-of-care group.

A noncontrolled trial compared 5 days (dose conserving) versus 10 days of IV remdesivir treatment in 397 patients with severe COVID-19 illness not requiring mechanical ventilation at time of enrollment. At day fourteen, 65% of patients in the 5-day group and 54% of patients in the 10-day group achieved clinical recovery, with some small benefit to treatment earlier in the illness. Mortality was approximately 10% in each group. Because this trial only evaluated a few patients who were on mechanical ventilation, the appropriate duration of remdesivir treatment for critically ill patients is still unclear.

Preliminary results from the U.S. NIH-sponsored Adaptive COVID-19 Treatment Trial (ACTT-2) have also been announced by Eli Lilly (via press release only). The trial (1,000 patients) examined the efficacy and safety of a 4 mg dose of baricitinib plus remdesivir versus remdesivir in hospitalized patients with COVID-19. A statistically significant, approximately one-day reduction in median recovery time for population treated with baricitinib was found. A combination of an antiviral drug and an anti-inflammatory drug may be the optimal approach for patients with moderate-to-severe disease where the cytokine storm phase of infection has begun. A trial of remdesivir in combination with a monoclonal antibody or monoclonal antibody cocktail or an interferon is likely to be the next trial to be undertaken by this consortium. Separately, Roche has announced a trial of remdesivir in combination with the U.S. FDA-approved anti-inflammatory tocilizumab. A Phase 1a clinical trial (safety) of nebulized, inhaled remdesivir (Gilead) to treat nonhospitalized COVID-19 patients has begun and will enroll 60 healthy participants aged 18-45 years. The U.S. NIH-sponsored ACTT-3 randomized, controlled clinical trial of remdesivir plus the immunomodulator interferon beta-1a began in early August; enrollment of more than 1,000 hospitalized adults at up to 100 sites in the U.S. is expected.

The U.S. government has designated a drug wholesaler to distribute remdesivir to state health departments that, in turn, are distributing the doses (including remaining amounts of previously donated remdesivir) to appropriate hospitals based on current community-level needs; a list of hospitals is not available. More than 150,000 treatment courses (940,000 vials) of donated remdesivir were shipped to states from May through June 2020. An additional 500,000 treatment courses secured by HHS will be distributed through September 2020 to hospitals based on COVID-19 patient load; more than 380,000 treatment courses have been allocated as of early September. Many locations experiencing a significant increase in case numbers and hospitalizations do not have an adequate supply of remdesivir due to the inequity of drug distribution. More than 2 million treatment courses are expected to be produced by the end of the year. Cost is USD3,120 per treatment course for all nonfederal entities (including state hospitals), which will generally be covered by Medicare or private insurance or by HHS for those without insurance. Remdesivir has now been granted emergency or conditional authorization in the U.S., Canada, Europe, Japan, Singapore, and Australia. In general, remdesivir (sometimes branded as Veklury) is not yet available through commercial channels and is being distributed by Gilead under governmental guidance. Labeled indications are for severe pneumonia and patients requiring supplemental oxygen; in some countries, patients on mechanical ventilation are lower priority due to supply limits. Children younger than 12 years and pregnant women are not authorized to receive the drug. In addition to the 1.5 million vials of remdesivir donated globally by Gilead, 5 generic pharmaceutical companies (in India and Pakistan) have permission to manufacture and distribute remdesivir to more than 125 mainly low- and lower-middle–income countries.

Immunomodulators

Dexamethasone (6 mg/day) is recommended only for the treatment of COVID-19 in patients who are mechanically ventilated and in patients who require supplemental oxygen but who are not mechanically ventilated for up to 10 days or until hospital discharge, whichever comes first. Whether other corticosteroids have a similar benefit as dexamethasone is not known, but these agents may be used if dexamethasone is unavailable. The total daily dosed equivalencies for dexamethasone 6 mg are prednisone 40 mg, methylprednisolone 32 mg, and hydrocortisone 160 mg. No data are available on the combination of remdesivir and dexamethasone, but some clinicians are using this approach in critically ill patients. A WHO meta-analysis of 7 existing randomized controlled trials reaffirms a highly significant reduction of 28-day mortality with dexamethasone treatment of severely ill COVID-19 patients. In the pivotal U.K. RECOVERY trial in the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%) and among the heterogenous group receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%), but not among those who were receiving no respiratory support at randomization (17.8% vs. 14.0%). Dexamethasone reduced all-cause deaths at day 28 by one-third in ventilated patients (29.3% vs. 41.4%). Overall, 22.9% in the dexamethasone group and 25.7% in the usual care group died within 28 days after randomization. Thus, the between-group differences in mortality varied considerably according to the level of respiratory support that the patients were receiving at the time of randomization. The trial compared 2,104 patients randomized to receive dexamethasone (6 mg once per day for 10 days or up to time of discharge, orally or intravenously) to 4,321 patients randomized to receive usual care alone. The median number of days of treatment was 6. Mortality reduction was restricted to those with symptoms for more than 7 days. Small but significant advantages in secondary outcomes (such as

duration of hospitalization) were found in the dexamethasone group, and the risk of progression to invasive mechanical ventilation was lower among those allocated to dexamethasone. No information was collected on physiological, laboratory, or virologic parameters. Dexamethasone is the first drug to be shown to improve survival in patients diagnosed with COVID-19; remdesivir has been shown to improve clinical scores and days of hospitalization but not mortality. Dexamethasone (licensed and inexpensive in every country) has potent immunosuppressive effects and should not be used in mild disease or during the first week of symptoms when virus levels are highest. Steroid use in persons with undiagnosed strongyloidiasis may result in disseminated *Strongyloides* (e.g., hyperinfection or dissemination syndrome), which has a high mortality rate. However, the benefit of dexamethasone for the treatment of severe COVID-19 likely outweighs the risk of disseminated *Strongyloides*; empiric treatment with ivermectin may be considered in COVID-19 patients in or from countries with moderate to high risk of *Strongyloides* infection (e.g., the Caribbean, Latin America, sub-Saharan Africa, or Southeast Asia).

Encouraging preliminary results in the BLAZE-1 clinical trial have been announced by Eli Lilly (via press release only) on a randomized, double-blind, placebo-controlled Phase 2 study of LY-CoV555, a SARS-CoV-2 neutralizing monoclonal antibody. In mild-to-moderate recently diagnosed COVID-19 outpatients, a 2,800 mg dose met the prespecified primary endpoint of a change from baseline in viral load at day 11; other doses, 1 higher and 1 lower were ineffective. Subsequent hospitalizations or emergency department visits occurred in 1.7% (5/302) of LY-CoV555 patients pooled across dose groups, compared to 6% (9/150) of placebo patients, which corresponds to a 72% risk reduction in this limited population. Three U.S. NIH-sponsored trials of LY-CoV555 (Eli Lilly; created from blood samples of COVID-19 survivors) have started in: 1) 2,400 nursing home residents and staff; 2) 220 symptomatic COVID-19–positive volunteers who are not hospitalized; and 3) 300 volunteers hospitalized with mild-to-moderate COVID-19 with fewer than 13 days of symptoms. Phase 3 U.S. NIH-sponsored trials of the REGN-COV2 (Regeneron) double monoclonal antibody cocktail have started: 1) a prevention trial (n = 2,000) that will assess SARS-CoV-2 infection status at approximately 100 U.S. sites; and 2) treatment trials in hospitalized (n = 1,850) and nonhospitalized (n = 1,050) patients conducted at approximately 150 sites in the U.S., Brazil, Mexico, and Chile.

According to Roche, in a global, randomized, double-blind, placebo-controlled Phase 3 trial of tociluzimab monotherapy, the primary endpoint of improved clinical status in patients with COVID-19–associated pneumonia was not met. The key secondary endpoint of reduced patient mortality was also not met. Roche will continue trials combining tociluzimab with an antiviral. Tociluzimab had been the most promising of the anti-inflammatory agents to date, considering a number of uncontrolled and retrospective trials, and these results represent another setback in drug discovery.

Antithrombotic Therapy

Anticoagulants and antiplatelet therapy should not be initiated in nonhospitalized COVID-19 patients for prevention of venous thromboembolism (VTE) or arterial thrombosis unless other indications exist. Hospitalized adults with COVID-19 should receive VTE prophylaxis per the standard of care for other hospitalized adults, but full anticoagulation therapy should only be initiated for suspected or proven thrombotic events. Data remain insufficient to recommend either the use of interleukin-6 (IL-6) inhibitors or IL-1 inhibitors.

Blood-Derived Products

In the U.S., an FDA EUA mechanism for the use of convalescent plasma has replaced an FDA Expanded Access program. No changes in patient access or level of availability of plasma are expected. The widespread availability of convalescent plasma in major treatment centers without having to risk randomization to placebo in a trial has hampered enrollment in formal prospective controlled trials; despite more than 100,000 patients being treated to date, no new data are available and are insufficient to recommend for or against the use of convalescent plasma outside of a clinical trial. A preprint of an unblinded study (without a randomized control group) published in early August 2020 describes 35,322 severe COVID-19 patients in 2,807 U.S. hospitals with heterogeneous demographic and clinical characteristics who received convalescent plasma. The analysis was derived from web-based self-enrollment by clinicians treating patients under an FDA Expanded Access program, using plasma from local sources. Of enrollees, 52.3% were in the ICU and 27.5% were receiving mechanical ventilation at the time of transfusion. Thirty-day crude mortality for patients who received high-IgG, medium-IgG, and low-IgG plasma was 22.3%, 27.4%, and 29.6% respectively. In the high-IgG group 30-day mortality was reduced to 16.7% from 25.4% (approximately 35% relative reduction) if plasma was given 3 or fewer days after diagnosis. These dose-response and early treatment data provide an encouraging signal in a very sick population, but randomized controlled studies are still necessary. The study did not control for concomitant drug or other therapeutic interventions that were almost certainly used in this very ill population.

Hydroxychloroquine

HCQ is not recommended for treatment or prophylaxis of COVID-19 by any authoritative body. In a publication in *Nature*, HCQ showed antiviral activity in VeroE6 cells but not in a model of reconstituted human airway epithelium. Earlier cell-based studies

that had shown some HCQ activity were all done using Vero cells which lack appropriate receptors for SARS-CoV-2. Testing in macaques (in comparison to placebo) before and after peak viral load, alone or in combination with azithromycin (AZTH), showed that neither HCQ nor HCQ+AZTH showed a significant effect on the viral load levels in any of the tested compartments. Preexposure prophylaxis with HCQ did not confer protection against acquisition of infection in macaques.

In COVID-19 patients ill enough for hospitalization, the U.K. NHS RECOVERY trial showed 26.8% of COVID-19 patients given HCQ (n = 1,561) had died after 28 days compared with 25.0% who were given standard hospital treatment (n = 3,155). Those who received HCQ who were not on mechanical ventilation at baseline were more likely to reach the composite endpoint of invasive mechanical ventilation or death (29.8% vs. 26.5%). The WHO Solidarity Trial discontinued the trial's HCQ arms based on the results to termination date for either HCQ versus standard-of-care in prospective randomized trials carried out by Solidarity. A randomized placebo-controlled trial conducted in 40 states and 3 Canadian provinces published in Annals of Internal Medicine showed that HCQ monotherapy did not significantly reduce symptom severity in outpatients with early, mild COVID-19, most of whom started the drug within 1 day of symptom onset. At 14 days, 24% (49 of 201) of participants receiving HCQ had ongoing symptoms compared with 30% (59 of 194) of those receiving placebo. A randomized controlled trial in the *New England Journal of Medicine* comparing HCQ to a placebo for COVID-19 prophylaxis after high-risk exposure (household or health care worker) showed that the incidence of a new illness compatible with COVID-19 did not differ significantly between participants receiving HCQ (49 of 414 [11.8%]) and those receiving a placebo (58 of 407 [14.3%]).

A propensity score-adjusted analysis was conducted on all veterans with rheumatological conditions in the U.S. Veterans Health Administration clinical administrative database, and no association was found with a preventive effect against SARS-CoV-2 infection. Each patient on chronic treatment with HCQ (n = 10,703) was matched to 2 patients who were not receiving HCQ (control, n = 21,406). No significant difference in the incidence of active SARS-CoV-2 infections (0.3% vs. 0.4%) exists between the 2 groups. Among patients who developed active SARS-CoV-2 infection, no difference in hospital admission, intensive care requirement, or mortality associated with SARS-CoV-2 was identified. The overall mortality was lower in the HCQ group (odds ratio = 0.70).

One more clinical trial (n = 1,483) on HCQ (once weekly or twice weekly as preexposure prophylaxis for COVID-19) has preliminarily announced that no significant reduction exists in COVID-19 incidence compared to a placebo.

Concomitant Medications

According to the American Heart Association, the American College of Cardiology, and the Heart Failure Society of America, and consistent with data from several robust peer-reviewed studies, COVID-19 patients who have underlying hypertension, heart failure, or ischemic heart disease should not stop taking their ACEIs or ARBs. The use of ACEIs and ARBs for the treatment of COVID-19 is not recommended except in a clinical trial. WHO, U.S. FDA, and the EMA state that no scientific evidence exists to establish a link between ibuprofen and worsening of COVID-19. Drug compatibility issues may occur with concomitant use of any of the candidate COVID-19 therapies and other medications. Quick reference and detailed interaction guidance can be found at https://www.covid19-druginteractions.org/.

Adjunctive Therapy

In the U.S., FDA EUAs have been granted for a number of blood filtration or purification systems to treat confirmed COVID-19 cases aged ≥ 18 years admitted to the ICU with confirmed or imminent respiratory failure. These devices work by filtering inflammatory mediators (e.g., cytokines) from the blood during the cytokine storm that occurs in some COVID-19 cases. No controlled data on these systems are available.

Insufficient data exist to recommend for or against the use of vitamin C for the treatment of COVID-19.

Insufficient data exist to recommend for or against the use of vitamin D for the prevention or treatment of COVID-19.

Insufficient data exist to recommend for or against the use of zinc for the treatment of COVID-19. Zinc supplementation above the recommended daily allowance is not recommended for the prevention of COVID-19.

Prevention

The U.S. government has published 3-phased Guidelines for Opening Up America Again, with a focus on mitigating risk of resurgence, protecting the most vulnerable persons, and implementing the guidelines on a statewide or county-by-county basis at each governor's discretion. Certain criteria must be met before beginning the phased approach, including downward trajectory of influenza-like illnesses, COVID-19–like syndromic cases, documented or positive cases within a 14-day period, and the ability of hospitals to treat all patients without crisis care and test at-risk HCWs. Details can be found at https://www.whitehouse.gov/openingamerica.

As communities reopen, daily activities are being resumed and events and gatherings are being held. The risk of spread is increased with interactions that are closer, longer, or with multiple people and is further increased by interaction with new people or with those not wearing masks. Risk stratification is as follows:

- **Highest risk**: Large in-person gatherings (e.g., weddings, funerals, parties, concerts, sporting events, parades) where social distancing is not maintained and attendees travel from outside the local area
- **High risk**: Medium in-person gatherings where social distancing is maintained and attendees travel from outside the local area
- **Moderate risk**: Small outdoor and in-person gatherings of persons from different households (but from the same local community) where social distancing is maintained, nonmedical masks are worn, and objects are not shared
- **Lowest risk**: Virtual-only activities, events, and gatherings

In European countries that implemented various mitigation measures (cancellation of mass gatherings; closure of public spaces, schools, and childcare centers; or a recommended stay-at-home policy), the average time from implementation of the mitigation effort to the daily case-number peak was approximately 3 weeks. For those countries that implemented an enforced stay-at-home policy, the average time was 2 weeks.

If a household includes a person at higher risk of a poor outcome (e.g., older adults or those with underlying medical conditions), then all persons in the household should take preventive measures as if they themselves are at higher risk and maintain as much physical distance as possible with the vulnerable household member.

Nonpharmaceutical Interventions

Three comprehensive review papers by a highly established group in Hong Kong did not find evidence to support a protective effect of nonpharmaceutical interventions in preventing or substantially reducing influenza transmission during a pandemic. This conclusion reflects the poverty of the database, gaps in the understanding of the biology of influenza virus transmission, low adherence to preventive measures, and the inherent speed of pandemic transmission and spread of influenza. Evidence indicates that SARS-CoV-2 may transmit more like influenza than other zoonotic coronaviruses affecting humans; lessons here may be applicable to the current COVID-19 outbreak. See *Literature Watch Review:* Delaying the Spread of Influenza—A 3-Armed Policy Review of Nonpharmaceutical Measures for Pandemic Influenza in Nonhealthcare Settings.

Social distancing (remaining out of congregate settings such as shopping centers, movie theaters, and stadiums, avoiding mass gatherings and public transportation, and maintaining a distance of 2 m [6 ft] from others), respiratory hygiene (cough and sneeze etiquette), and hand hygiene (frequent, thorough handwashing with soap and water for 20 seconds [or using a hand sanitizer containing 60% alcohol]) are a key strategies for controlling COVID-19. Masks are recommended when distancing is not possible; persons aged ≥ 60 years and persons with underlying conditions should wear a medical mask, especially during travel and on public conveyances. Other persons may wear nonmedical masks during travel.

Correctly worn masks (covering the nose, mouth, and underneath the chin) can prevent the spread of SARS-CoV-2 by preventing a healthy person from acquiring the virus and by preventing an infected person (symptomatic or asymptomatic) from spreading the virus (i.e., source control). Studies show that mask wear significantly reduces the spread of SARS-CoV-2 both in and outside health care settings and data suggest that persons in the community who wear a nonmedical mask but do become infected may be less likely to develop severe disease. No evidence exists to suggest that mask-wearing increases the spread of SARS-CoV-2 by reducing adherence to other preventive measures (e.g., hand hygiene and social distancing). Not all masks perform equally and those made from high-thread count cotton and tightly woven hybrid materials (e.g., cotton combined with a synthetic) as well as those with multiple layers (ideally 3 layers of different material: inner layer of absorbent material [e.g., cotton]; middle layer of nonwoven material [e.g., polypropylene]; and an outer layer of nonabsorbent material [e.g., polyester]) perform best; the latter construction is beyond the capabilities of most individual households. Effectiveness is reduced if the fit is poor or the mask is not worn correctly; bandanas and neck gaiters should always be avoided. Masks should fit snuggly so that unfiltered air does not pass around the edges of the mask and should be changed or washed (if washable) regularly, ideally daily. In contrast to most national guidelines, WHO recommends that N95 respirators are to be worn only for aerosol-generating procedures; masks should be changed after removal (for any reason) or if the mask becomes soiled.

All health authorities recommend that masks be worn by symptomatic persons to prevent onward transmission (source control). To prevent onward transmission from asymptomatic cases, many health authorities recommend that nonmedical masks be worn consistently and correctly by all persons in areas of widespread transmission where physical distancing is difficult, such as on public transport, in shops, or in other confined or crowded environments, especially if ventilation is poor or close-contact conversations occur. Face masks or respirators with an exhalation valve are not recommended because they release unfiltered air and do not prevent virus spread; they have been banned in some locations. Face shields are not recommended as a substitute for masks in the community. However, if used without a mask, the face shield should wrap around the sides of the

wearer's face and extend below the chin. In practice, very few persons are able to use medical masks appropriately for significant periods of time when out in the community, but increased compliance will result in effective mitigation. The threshold level of implementation in asymptomatic persons that would have a given effect on transmission is not clear. N95 respirators are perhaps less effective among the public than in health care settings. In Singapore, where the population is highly cooperative, only 13% of participants who were given an illustrated instruction sheet for putting on an N95 respirator were able to pass a visual mask-fit test. Consideration must also be given to the likelihood that almost all symptomatic persons are already at home or in the hospital. No population-based controlled trial of masks versus no-masks during a pandemic has ever demonstrated efficacy of masks. See *Literature Watch Reviews:* Effect/Efficacy of Face Masks on Respiratory Virus Shedding and Physical Distancing, Medical-Grade Face Masks, and Eye Protection for Prevention of COVID-19.

Notably, the U.S. CDC has reported on the absence of transmission of SARS-CoV-2 at a hair salon with a well-enforced universal face covering policy for stylists and clients. One stylist initially infected another while unmasked but, subsequently, both were masked for 8 days, each serving 139 clients without any secondary transmission occurring. *JAMA* reports on a dramatic decrease in HCW infections in a 75,000-employee hospital system after the implementation of universal masking for all employees and all patients giving or receiving any kind of care anywhere in the system. Anecdotally, this same result has been seen in every health care environment in the U.S. since universal masking was adopted in March and April. In all these scenarios, most individuals (except for HCWs on dedicated COVID-19 units) would have been utilizing cloth or nonmedical masks. Cloth masks have been shown in laboratory settings to be effective source control but have not yet been validated in community-based studies.

Insufficient evidence exists to recommend the regular use of gloves as a preventive measure for the general public and persons in most nonhealthcare-related occupations. Use of gloves in the community may lead to the misconception that hand hygiene (an important preventive measure) is unnecessary, thus increasing the risk of transmission by inadvertent touching of the face with contaminated gloves. Hand hygiene consists of frequent, thorough handwashing with soap and water for 20 seconds (or using a hand sanitizer containing 60% alcohol). Hand-sanitizer products from Mexico may contain methanol (often used to create fuel and antifreeze) that can cause blindness and death when absorbed through the skin and are life-threatening when ingested. A list of affected products that are undergoing recall by the U.S. FDA can be found at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-hand-sanitizers-methanol.

HCWs entering the room with a PUI should use standard precautions, contact precautions, airborne precautions, and eye protection (e.g., goggles or a face shield). Eyewear (e.g., safety or trauma glasses) with gaps between the glasses and the face likely do not adequately protect eyes from all splashes and sprays. PUIs for COVID-19 should be asked to wear a mask as soon as they are identified and be evaluated in a private room with the door closed, ideally in an airborne-infection isolation room if available. Increased experience in the U.S. is indicating that contact and droplet isolation in a regular room is likely to be just as effective as placement in an airborne-infection isolation room. The ideal outpatient scenario is a dedicated triage desk where any person with fever and/or upper respiratory infection symptoms would initially present (whether the patient comes as a walk-in or by ambulance). When patients come via EMS, the ambulance staff should be wearing N95 respirators. The person working the triage desk should wear an N95 respirator. Any PUI should be provided with a mask at the earliest opportunity and should wear it at all times in the clinical spaces and upon leaving the clinic. PUIs should be escorted from the triage desk to a negative pressure examination and treatment area by personnel who are wearing N95 respirators.

Selected clinic staff wearing N95 respirators should provide services to PUIs. Staff that are not involved in this care do not need to take N95 respirator precautions.

Although SARS-CoV-2 has not been detected in the breast milk of infected women, symptomatic mothers well enough to breastfeed should do so and wear a nonmedical mask and observe hand hygiene. Symptomatic mothers not well enough to breastfeed should wear a nonmedical mask and observe hand hygiene while expressing milk for bottle feeding. Infants being breastfed by a mother confirmed to have COVID-19 should be considered to have suspected COVID-19 for the purpose of infection control for the duration of the mother's isolation and 14 days thereafter.

Disinfection of Surfaces

Historically, studies have demonstrated survivability of zoonotic coronaviruses on different surfaces ranging from a few hours up to 9 days (longest on plastic), depending on ambient conditions, including temperature, humidity, and the specific infected bodily fluid contaminating the surface. The risk of spread is very low from items shipped at ambient temperatures over several days. No evidence exists of SARS-CoV-2 transmission associated with imported goods; no associated cases have been reported to date.

See Survival on Surfaces.

Disinfection processes that are effective for other zoonotic coronaviruses should be followed. Clean daily all "high-touch" surfaces, such as counters, tabletops, hard-backed chairs, doorknobs, light switches, handles, desks, bathroom fixtures, toilets,

phones, remote controls, keyboards, and bedside tables. Also, clean any surfaces that may have blood, bodily fluids, and/or secretions or excretions on them. After cleaning solid materials using a detergent, use a diluted bleach solution or an EPA-approved household disinfectant. All products listed on the following website are within traditional classes of disinfectant (alcohol, quaternary ammonium, thymol, bleach [hypochlorite derivatives], peroxide, and lactic/citric acid) and meet EPA's criteria for use against SARS-CoV-2: https://www.epa.gov/pesticide-registration/list-n-disinfectants-use-against-sars-cov-2-covid-19. Many new products are being marketed, but other than vendor claims, no confirmatory science or regulatory endorsements have been published.

To make a bleach solution, add 20 mL (4 teaspoons) of bleach to 1 L (1 quart) of water; for a larger supply, add 75 mL (5 tablespoons) of bleach to 4 L (1 gallon) of water. For surfaces sensitive to bleach, at least 70% ethanol should be used. Alcohol-based hand disinfectants and common hospital personal disinfectants are all effective against SARS-CoV-2 but provide no ongoing protection between uses.

Ultraviolet nonionizing radiation (UVC) with an unobstructed path to SARS-CoV-2 will destroy/inactivate the virus. UVC and UV as used in the scientific, medical and technical literature for disinfection, refers to UVC light energy (200-280 nm light; most often 254 nm) in the germicidal range, which is not the same as the UVA and UVB used in tanning beds or sunlight exposure. UVC with sufficient energy to inactivate the virus will also be harmful to human skin and organs. As per long-standing cleaning protocols in many hospital settings, UVC (mobile robots or fixed machines) should be used in collaboration with established standard cleaning and disinfection practices because where UVC light cannot reach a particular pathogen, that pathogen will not be disinfected. Far UVC light (usually 222 nm) kills human coronavirus and is likely safe for human skin but further study is needed. Some airlines have begun UVC disinfection of either flight decks or passenger areas.

WHO has definitively stated that large-scale spraying or fumigation in outdoor spaces (such as streets or open market places) is not recommended. Streets and sidewalks are not considered routes of infection for SARS-CoV-2. Spraying disinfectants (even outdoors) can be noxious, with adverse health effects. Separately, spraying of persons with disinfectants (such as in a tunnel, cabinet, or chamber as is being trialed for businesses and airports) is not recommended under any circumstance. Such practices could be physically and psychologically harmful and would not reduce the spread of the virus through droplets or contact immediately thereafter.

Avoidance of Health Care Settings

Exposed HCWs may be sent back to work and be required to wear a medical mask (vs. a nonmedical mask) and report their temperature and absence of symptoms for 14 days. Such persons will only be tested and sent home if symptoms develop.

Persons in the U.S. should avoid presenting to hospitals with other than serious or immediately life-threatening illness; elective procedures should be rescheduled. Telemedicine visits should be used for all but essential care or to screen for the necessity of an in-person visit. Routine vaccination services are essential during the COVID-19 pandemic to protect individuals and communities from vaccine-preventable diseases and outbreaks; vaccination of infants and young children aged ≤ 24 months is a top priority in the context of well-child care and should be prioritized when possible. Consider scheduling well-child visits in the morning and sick visits in the afternoon to reduce the risk of contagious-disease exposure. Additional vaccination considerations include:

- Emphasize influenza vaccination in 2020-21 to reduce influenza incidence and conserve medical resources for COVID-19 patients; influenza and SARS-CoV-2 coinfection may increase risk of death. Vaccination should be prioritized for adults at higher risk of a poor outcome from COVID-19, including staff and residents at long-term care facilities, persons with underlying illnesses, the black or African American communities, and persons in the critical infrastructure sector. Most influenza vaccines will begin shipping in August/September 2020.
- Assess vaccinations that are due and/or overdue at each patient visit and administer during that visit as appropriate.
- Proactively contact patients to ensure administration of scheduled vaccinations.
- Apply COVID-19–based infection prevention practices to all patient vaccination encounters.
- Wear gloves (in addition to standard infection control) when administering intranasal or oral vaccines; administration of these vaccines is not considered an aerosol-generating procedure.
- Use alternate approaches to vaccination, such as fixed site drive-through vaccination services, curbside clinics, mobile outreach units, or home visits.

Health care facilities in the U.S. have been directed to implement universal source-control measures for everyone (HCWs, patients, and visitors) entering a facility, regardless of symptoms. These measures include limiting entry points, wearing a mask (including in pharmacies), actively screening for fever and symptoms of COVID-19, and isolating symptomatic persons as soon as possible. Patients and visitors should wear their own nonmedical mask upon arrival; if they do not, a mask may be provided by the facility if supplies are available. Nonmedical masks are designed to prevent the wearer from spreading respiratory secretions

but are not considered PPE (as are medical masks and N95 respirators), and their capability to protect the wearer is unknown. HCWs should only wear medical masks if their duties require PPE. Universal use of PPE (including eye protection) is recommended in areas with moderate-to-substantial community transmission; eye protection and respirator use is optional in areas with minimal-to-no community transmission. Other HCWs (e.g., those with clerical duties or nondirect patient care duties) may wear a nonmedical mask. Most medical facilities perform a viral test for COVID-19 from 24 to 48 hours before any type of medical procedure and for all patients presenting to the emergency department or admitted to hospital.

Travel and Transportation

IATA, the airline trade association, is projecting that revenue passenger miles worldwide will not return to 2019 levels until at least 2024, and longer if the virus is not contained by a vaccine or nonpharmaceutical intervention. Short-haul flying may allow absolute passenger numbers to return to 2019 levels by 2023. IATA is strongly advocating for COVID-19 testing (administered by others prior to flight) to play a role in facilitating travel.

Travelers (especially those at higher risk of poor outcome, such as older adults and persons with underlying medical conditions) going to countries with community transmission should observe hand hygiene and social distancing and avoid contact with ill-appearing persons and animals (alive or dead), animal markets, and products that come from animals (such as uncooked meat). Those at higher risk of poor outcome should consider postponing travel, especially if by airplane or cruise ship. Current influenza vaccination is recommended to decrease the risk of simple influenza being mistaken for COVID-19 upon return.

Travelers or business travelers should only use prearranged, solo (e.g., alone or only with existing traveling companions) transportation and consider arranging for a larger vehicle to facilitate social distancing from the driver; use touchless payment when available, and handle luggage personally. Nonmedical mask use is indicated in high-transmission destinations. In lodging establishments, avoid contact with any valets at the entrance, book rooms on low floors and use the stairs, clean all high-touch surfaces in the room, minimize housekeeping visits during the stay (leave room before arrival of housekeeping personnel), and avoid the gym. For food service, travelers should preferentially use contactless room service if available and completely avoid self-service buffets. Ensure lodging establishments comply with distancing for guests and staff (especially at check-in) and other guidance issued by public health authorities, such as U.S. CDC or ECDC.

The ECDC has provided guidance on operating procedures related to restarting travel, expatriation, or operations at foreign locations. Limitations on the true availability of decision-quality data were synthesized. Reported levels of transmission depend on local, regional, or national testing policy and capacity, contact-tracing capacity, and surveillance-system characteristics, and therefore may reflect the real circulation of the virus to a greater or lesser extent. Even if no community transmission is reported in a specific area, this can only be confirmed if extensive, population-based testing of all individuals with COVID-19–compatible symptoms is undertaken. In the absence of a universal approach to testing and case reporting, the underlying epidemiological situation in each country or subregion is difficult to verify at this point, and the validity of comparisons based on routine monitoring data may be limited. Hospital capacity fluctuates when a flare up in one area of a country causes spillover to a destination area of interest, which creates a regional bed requirement that may not reflect local conditions.

IATA (the airline trade group) guidelines are available. The section below does not cover flight crew medical issues. Stated policies are general in nature without specific detail on manner of implementation, and airlines normally must comply with regulatory prohibitions in operating countries. Several studies have reported a limited number of clusters of in-flight transmission that have occurred despite the large number of flights that are known to have had many persons on board. Contact tracing was conducted on international passengers arriving to or departing from Greece from February 26 through March 9, 2020. This included persons sitting less than 2 m (6 ft) apart for more than 15 minutes, including passengers seated 2 seats around the index case, all crew members, and persons who had close contact with the index case. Among 18 international flights with 2,224 passengers and 110 crew members investigated, identified cases included 21 index cases and 891 contact-traced cases, including 6 index cases who were symptomatic during the flight. Two COVID-19 index cases were associated with 4 passengers and 1 crew member that developed laboratory-confirmed infection (3 symptomatic and 2 asymptomatic). Nevertheless, follow-up and testing of all passengers on flights with 1 or 2 COVID-19 cases is not routinely done. On June 20, twenty-six passengers distributed throughout the Boeing 777 (mostly Pakistani nationals on an Emirates flight from Dubai to Hong Kong) tested positive for COVID-19 on the mandatory arrival PCR; all remaining passengers were asymptomatic, tested negative on arrival, and were followed in quarantine for 12 days per Hong Kong procedures. Two passengers subsequently tested positive and may have been infected en route but may also have been infected prior to departure; one of these was seated in the same row with 5 passengers who tested positive on arrival. Almost all passengers originated in Pakistan, passed symptom and temperature screening in Dubai, and were certainly infected prior to departure given the short duration of travel. In 1 known event of suspected onboard transmission to a large number of people, 1 symptomatic passenger flying from London, U.K. to Hanoi, Vietnam on March 1 appears to have infected up to 14 other passengers (12 of whom were seated in neighboring rows in

business class) and a cabin crew member; attack rate was 62% and proximity of seating was associated with increased infection risk (risk ratio = 7.3).

Key points from IATA include:

- Any preflight temperature screening should take place prior to arrival at the boarding area. Temperature screening is insensitive for detection of infected individuals but may act as a deterrent to travel for those that feel feverish or unwell.
- Symptom screening at the airport or during online check-in is a useful adjunct to other measures but depends on the honesty of the traveler. Nevertheless, screening may be a useful deterrent to travel for those who feel unwell.
- Preflight testing for active viral infection by PCR is a viable additional layer of protection. IATA suggests that specific PCR tests be validated by reputable national authorities in countries issuing certificates to achieve less than 1% false negatives and the lowest possible false positive rate and for airports to preferably use saliva, which does not require PPE by administering staff.
- Antibody testing and so-called immunity passports do not have sufficient evidence to be acceptable for any use by airlines.
- Governments should implement mandatory online preflight registration databases for the purpose of later contact tracing rather than rely on airlines to perform this function.
- Nonmedical masks should be required for all passengers and crew throughout boarding, the flight, and disembarkation. Airlines could supply masks or have a bring-your-own policy. Novel social distancing strategies during boarding and disembarkation will be airline specific but will need to integrate with individual airport policies.
- Middle seat occupancy, seat spacing, barriers between seats, or distancing between passengers are at airline discretion but declared to be economically unviable by IATA members.
- Lavatory access should be controlled by flight attendants on a person-by-person basis.
- In-flight meals may involve a bagged food placed on seats prior to boarding with a sealable bio-safety bag for final disposal.
- Individual drink cups should not be refilled by crew.
- Passengers may demask to eat.
- Sanitizer wipes may be placed on seats for individual passengers to wipe down their area upon boarding.
- Strict carry-on limitations should be implemented to avoid crowding during boarding and frequent opening of overhead bins.
- Cleaning frequency is airline specific; ethanol sprays remain the mainstay, with some airlines now using electrostatic misting with bleach derivatives. Proposed novel methods currently do not have regulatory approval or sufficient science.
- More frequent cleaning of lavatories in-flight by crew is necessary.

The U.S. government has officially published guidance for airports and airlines for COVID-19 mitigation, which provides general recommendations (without specific detail in most cases) but no mandates or enforceable regulations. Some highlights of the 40-page document:

- Airlines should provide flexible re-accommodation policies, so passengers do not feel pressure to fly if sick or uncomfortable.
- Airports and airlines may have innovative, creative, and practical solutions for mitigation, and dialogue on those is welcome. Methods to achieve social distancing in airports, during embarkation/disembarkation (including ground transport vehicles), and on airplanes are at the discretion of the airport or airline.
    - Airlines should consider the feasibility of limiting seat availability to enable passengers to maintain social distance from each other during the flight.
- Everyone should correctly wear a mask or cloth face covering at all times in the passenger air transportation system; airports and airlines should have masks or cloth face coverings available if needed.
- Airlines should implement health attestations to reinforce that passengers will not travel when ill or having been exposed to a COVID-19–infected person. Airlines should promulgate this policy to passengers in advance of check-in, and travelers should present the attestation document at the earliest feasible opportunity at check-in, preferably online. At time of completion, the passenger should affirm awareness and willingness to follow required measures while on the aircraft.
- Some individual airports or airlines may decide to use temperature screening; use at first point of contact with the airport is recommended.
- The check-in process should be contactless.
- On-board service should be limited to minimize contact between crew and passengers.
- Passenger lavatory use should be based on seat assignment, and disinfectant wipes should be placed in lavatories for passengers to use on entry and exit.
- Insufficient data currently supports the use of COVID-19 testing at any stage of the journey.
- Port of entry health screening, if used, only represents 1 point in time and must be part of a broad set of measures, applied across the passenger journey.

The U.S. TSA now allows 1 liquid hand sanitizer container up to 0.35 L (12 oz) per passenger in carry-on bags; these larger containers need to be screened by hand, which may result in slight delays for the passenger.

In the Workplace, Critical Infrastructure Sectors, and Communities

To help prevent workplace exposure to acute respiratory illnesses, including COVID-19, U.S. CDC recommends that employers actively encourage (through generous leave policies) employees with fever (≥ 38°C [100.4°F] for the general population or ≥ 37.8°C [100°F] for HCWs) using an oral thermometer), signs of fever, or symptoms of respiratory illness to remain at home, to observe hand hygiene (frequent, thorough handwashing with soap and water for 20 seconds [or using a hand sanitizer containing 60% alcohol]), to observe respiratory hygiene (cough and sneeze etiquette) and social distancing if possible, to avoid sharing of household items, and to avoid contact with pets or other animals. Employees who become ill at work should be immediately isolated from other employees and sent home. Areas used by these ill employees, as well as areas used less than 7 days prior by ill employees later diagnosed with COVID-19, should be closed off for 24 hours and then cleaned and disinfected; areas used ≥ 7 days prior by ill employees do not need additional cleaning and disinfection. Generous leave policies should also be applied to employees that must stay home to care for an ill household member. Contingency planning guidance is provided by U.S. CDC at https://www.cdc.gov/coronavirus/2019-ncov/guidance-business-response.html.

As businesses reopen, strict social distancing, worksite hygiene measures and disinfection, and employee and customer protection must be ensured throughout the process. Some employees (e.g., older adults or those with underlying medical conditions) are at higher risk of poor outcome from COVID-19 and should be encouraged to self-identify so that steps can be taken to reduce their risk of exposure; options include telework or performing duties that minimize contact with others. Additional workplace preventive measures for all employees may be necessary, such as: 1) performing routine, daily health checks of all employees; 2) ensuring that ventilation systems are working properly and opening windows and doors (only if it does not pose a safety risk) to increase circulation of outdoor air; 3) closing off communal spaces (such as break rooms) or staggering their use and cleaning and disinfecting between uses; 4) using larger meeting rooms with more personal space per participant; 5) limiting nonessential visitors or external groups or organizations; 6) canceling all nonessential travel and only resuming in accordance with state and local guidance; 7) staggering shifts to limit the number of employees in the workplace at the same time; and 8) encouraging telework for as many employees as possible, especially for those who use public transportation.

Contacts (in the workplace, community, or school) of a confirmed COVID-19 case should follow the guidance in Table 4: U.S. Guidance for the Management of Asymptomatic Persons with Potential SARS-CoV-2 Exposure. Contact tracing apps in the workplace are too new, without applicable laws, and will likely need to be tested in the courts.

Return to Work for Health Care Workers

Symptomatic HCWs (confirmed or suspected COVID-19) may return to work based on a symptom-based strategy once they are free of fever for ≥ 24 hours without the use of fever-reducing medications and other symptoms have improved and ≥ 10 days have passed since symptom onset (up to 20 days for HCWs with severe to critical illness or severe immunocompromise [defined case by case] in consultation with an infectious disease expert).

A test-based strategy may be used in rare situations where an HCW (immunocompetent or immunocompromised) may need to return to work earlier than would be allowed based on the symptom-based strategy. The HCW must test negative for SARS-CoV-2 (at least 2 negative consecutive respiratory specimens collected ≥ 24 hours apart) and be free of fever without the use of fever-reducing medications and have improvement in other symptoms. HCWs returning to work early should wear a medical mask (vs. a nonmedical mask) until all symptoms are completely resolved and then revert to their facility policy regarding universal source control; contact with severely immunocompromised patients should be avoided until 14 days have passed since symptom onset.

Asymptomatic HCWs (who never showed symptoms but had laboratory-confirmed COVID-19) may return to work based on either a time-based or test-based strategy once 1) ≥ 10 days have passed from the date of their first positive test (up to 20 days for severely immunocompromised [defined case by case] HCWs) and they have remained asymptomatic, or 2) they test negative for SARS-CoV-2 (at least 2 negative consecutive respiratory specimens collected ≥ 24 hours apart).

HCWs who have COVID-19 ruled out and have an alternate diagnosis (e.g., influenza) may return to work based on the criteria for that illness.

Return to Work for Other Employees

Symptomatic employees (with confirmed or suspected COVID-19) may return to work based on a symptom-based strategy once they are free of fever for ≥ 24 hours without the use of fever-reducing medications and other symptoms have improved and ≥ 10 days have passed since symptom onset (up to 20 days for persons with severe to critical illness or severe immunocompromise in consultation with an infectious disease expert).

A test-based strategy may be used in consultation with infectious disease experts for symptomatic immunocompromised persons. The person must test negative for SARS-CoV-2 (at least 2 negative consecutive respiratory specimens collected ≥ 24 hours apart) and be free of fever without the use of fever-reducing medications and have improvement in other symptoms.

Asymptomatic employees (who never had symptoms but had laboratory-confirmed COVID-19) may return to work once ≥ 10 days have passed from the date of their first positive test and they have remained asymptomatic.

Persons previously diagnosed with symptomatic COVID-19 who remain asymptomatic after recovery should not be retested within 3 months after the date of symptom onset for the initial infection, not because they are immune to reinfection with SARS-CoV-2 during this period of time, but rather because they may continue to test positive for up to 3 months yet not be infectious to others. Additionally, quarantine is not recommended for these persons during this time in the event of close contact with a SARS-CoV-2 infected person. If new symptoms do develop within the 3 months and an alternative etiology cannot be identified, retesting may be warranted following consultation with an infectious disease expert. Quarantine may be considered during the evaluation period, especially if symptoms developed within 14 days after close contact with an infected person.

Critical Infrastructure Sectors

To ensure continuity of operations of essential functions, persons in critical infrastructure sectors may continue to work (at the discretion of state and local health authorities) following potential exposure to SARS-CoV-2 as long as they remain asymptomatic and additional precautions are implemented. These persons should self-observe (remaining alert for symptoms), self-monitor (taking a temperature reading 2 times per day) under the supervision of their employer's occupational health program, wear a mask (medical or nonmedical depending on their job) at all times in the workplace for 14 days after last exposure, observe social distancing, and regularly clean and disinfect all shared areas and equipment. Symptom assessment and a temperature reading should be taken prior to starting work, ideally before they enter the facility. Critical infrastructure sectors include commercial and government facilities, communications, critical manufacturing, defense, emergency services, energy, financial, food and agriculture, hazardous materials, health care and public health, information technology, public works (services to maintain safety, sanitation, and essential operation of infrastructures), and water and wastewater systems. Exposure is defined as a household member or a close contact (less than 2 m [6 ft]) for a prolonged period (> 15 min) of a suspected or confirmed COVID-19 case during a period from 48 hours before symptom onset, irrespective of whether the COVID-19 case or the contact was wearing a mask. Employees who become ill at work should be immediately isolated from other employees and sent home. Surfaces in their workspace should be cleaned and disinfected. Persons who had direct or close contact with the ill employee (while symptomatic and during a period from 48 hours before symptom onset) are considered exposed and should follow the aforementioned guidance. This guidance means that infected and potentially infectious asymptomatic and presymptomatic persons will be present in these workplaces for the foreseeable future. Shoreland recommends that consideration be given to continuing to exclude vulnerable workers from these workplaces, especially when the above distancing procedures cannot be fully adhered to.

Vaccine Development

Preliminary data from primate experiments indicate acquired immunity to reinfection in animals recovered from a primary infection and development of protective antibodies in 10 to 14 days. The Wuhan-Hu-1 reference sequence for the spike protein matches all the different optimized vaccine candidate inserts and is identical to an ancestral sequence and 1 mutation away from the current consensus sequence. Each single vaccine candidate should be efficacious against currently circulating lineages. The negligible-to-slow mutation rate also provides hope that a potent single vaccine construct may be protective for subsequent years. The approaches being applied for COVID-19 vaccine development—which involve a new virus target and mostly novel vaccine technology platforms (DNA, RNA, viral vectors) as well as novel development paradigms—are likely to increase the risks and costs associated with delivering a licensed vaccine and will require careful evaluation of effectiveness and safety at each step. One hundred sixty-five COVID-19 vaccines are in development; many come from companies that are small and/or inexperienced in large-scale vaccine manufacture.

Most of the active projects are in exploratory or preclinical stages. Due to the large number of vaccine candidates, Shoreland will not be reporting results of preclinical testing in animals or cell culture until clinical trials begin. Ten COVID-19 vaccine candidates (of more than 30 in clinical trials) are in (or nearing entry into) Phase 3 trials; vaccine platforms include inactivated virus, nonreplicating viral vector, recombinant protein, and RNA. Possible end points for consideration in vaccine trials include varying severity of clinical disease and/or asymptomatic infection. What constitutes protective immunity remains unclear, but emerging data indicate that potential vaccines should induce both nAb and cell-mediated immune responses.

Table 3: Candidate Vaccines with Phase 3 Trials Announced

Vaccine	Developer	Platform	Doses	Phase 3 Start Date
CoronaVac	SinoVac Biotech Co.	Inactivated	2 doses 14 days apart	July 2020 8,870 target enrollment Approved for limited use in China
Pathogen-specific aAPC	Sinopharm/Beijing Institute of Biological Products	Inactivated	2 doses 14 or 21 days apart	July 2020 5,000 target enrollment Approved for limited use in China and in HCWs in U.A.E.
Pathogen-specific aAPC	Sinopharm/Wuhan Institute of Biological Products	Inactivated	2 doses 14 or 21 days apart	July 2020 5,000 target enrollment Approved for limited use in China and in HCWs in U.A.E.
AZD1222	AstraZeneca/University of Oxford	Nonreplicating viral vector	1 dose	May 2020 30,000 target enrollment
Gam-COVID-Vac	Gamaleya Research Institute	Nonreplicating viral vector	1 dose	Not yet announced; vaccine approved for use in Russia under a "conditional registration certificate" 40,000 target enrollment
Ad26.COV2.S	Johnson & Johnson (Janssen)	Nonreplicating viral vector	2 doses 56 days apart	September 2020 60,000 target enrollment
Ad5-nCoV	CanSino Biologics/Beijing Institute of Biotechnology	Nonreplicating viral vector	1 dose	September 2020 8,000 target enrollment Approved for limited use in Chinese military
NVX-CoV2373	Novavax	Protein subunit	2 doses 21 days apart	October 2020
S-protein +_ AS03 adjuvant	Sanofi Pasteur/GSK	Protein subunit	2 doses 21 days apart	December 2020
mRNA-1273	Moderna	RNA	2 doses 28 days apart	July 2020 26,000 enrolled of 30,000 target enrollment
BNT162	BioNTech/Pfizer	RNA	2 doses 28 days apart	July 2020 29,000 enrolled of 30,000 target enrollment

In the U.S., the order of population prioritization for vaccine administration remains under discussion. More than 200 million U.S. residents are included in the categories of healthcare workers (including those working in nursing homes), essential workers, those having underlying medical conditions, and those aged > 65 years. Persons not in these groups should anticipate vaccination at least several months after a vaccine first becomes available. A COVID-19 vaccine that requires distribution and storage at ultra-low frozen temperatures will require diligent vaccine management to minimize waste and will make it very difficult for community clinics and local pharmacies to administer and will necessitate that most vaccine be administered at centralized sites. Vaccinating health care personnel at centralized sites with high throughput is anticipated to be the best allocation of initial supply. The mRNA vaccines are unstable and some (e.g., BNT162b2 [Pfizer/BioNTech]) must be kept at -70°C (-94°F), requiring expensive medical-grade freezers; whereas standard inactivated vaccines need to be kept at 2-8°C (36-46°F), which can be accomplished using a standard refrigerator. The overall COVID-19 vaccine development effort could potentially experience delays due to an insufficient number of minority volunteers (10% of 350,000 volunteers to date) expressing interest in large-scale clinical trials in the context of 50% of U.S. cases occurring in minorities.

Specific data on the most promising vaccines:

- mRNA-1273 vaccine (Moderna): In promising Phase 1 studies published in the *New England Journal of Medicine*, 3 different doses of mRNA-1273 induced high-titer anti–SARS-CoV-2 neutralizing antibodies (nAb) in all 45 participants after 2 doses spaced by 28 days. Antibody levels were similar to those in the upper half of the distribution of a panel of control convalescent-serum specimens. Limitations include the following: No subject over age 55 years (mean = 33 years); 40 of 45 subjects were Caucasian; subjects were not prescreened by PCR or serology; only half had antibodies after the first dose; no

safety record with any RNA vaccines in humans is available, which will be readily apparent to the public. Preliminary data from a small study of subjects aged > 55 years showed serum antibody levels similar to that of control convalescent-serum specimens. Vaccination of 8 nonhuman primates with mRNA-1273 induced significant SARS-CoV-2 neutralizing activity, CD4 T-lymphocyte responses, protection in the upper and lower airways in 7 of 8 animals, and no pathologic changes in the lungs. A large Phase 3 trial (started in late July 2020) has enrolled more than 26,000 (29% minorities) of its goal of 30,000 total subjects; the minority enrollment targets for mRNA-1273 may not be reached by the end of September 2020. The trial will determine whether nAb responses correlate with real-life efficacy and how long immunity lasts. The mRNA-1273 vaccine is shipped at -20°C (-4°F) and may be stored at this temperature (within the range of typical biologic storage freezers) for up to 6 months but may be stored at 2-8°C (36-46°F) for up to 7 days after receipt.

- AZD1222 (previously called ChAdOx1; AstraZeneca/University of Oxford): AZD1222 is a replication deficient live adenovirus vectored recombinant vaccine expressing the SARS-CoV-2 spike protein. In a Phase 1/2 clinical trial of AZD1222 published in *The Lancet*, subjects (n = 534) all had robust spike protein antibodies that peaked at 28 days after a single vaccine dose; nAb responses against SARS-CoV-2 were detected in 32 (91%–100%) of a subset of 35 participants. After a booster dose at day 28, all participants showed a boosting effect and 100% had neutralizing activity; nAb responses correlated strongly with antibody levels measured by ELISA. Spike protein specific T-cell responses peaked on day 14 (n = 43) and were induced in all participants. No relationship was found between presence of low-level antibodies to AZD1222 on the day of vaccination and the ELISA titer to SARS-CoV-2 spike protein; a concern with adenovirus vectored vaccines is the preferential induction of antiadenovirus antibodies. No serious adverse effects were reported. Subjects were aged 18-55 years only (median = 35 years) and 90% Caucasian. Local and systemic adverse events occurred commonly but were tolerable and mostly ameliorated by acetaminophen. AZD1222 protected primates against severe disease but not against infection. The large, 80-site (62 in the U.S.), 30,000 subject, Phase 3 study was put on hold on September 6, 2020, due to a single occurrence of a serious adverse event (transverse myelitis) in a study subject in the U.K. The annual incidence of transverse myelitis in the U.K. is 0.0005%, and a causal association with vaccine administration or occurrence of a simple coincidence is not yet known. Such events automatically trigger a trial pause for review by a neutral Data and Safety Monitoring Board (DSMB), which has the option to immediately resume the trial, to permanently stop the trial, or to recommend a modification to the trial. The trial has been cleared to recommence at all clinical sites across the U.K., South Africa, and Brazil; resumption of trials in the U.S. is pending further review. Human challenge trials with direct infection of volunteers with SARS-CoV-2 are planned to begin by December 2020.
- Ad5-nCoV (CanSino Biologics): A randomized, double-blind, placebo-controlled Phase 2 trial study in China of Ad5-nCoV, a recombinant adenovirus type-5 (Ad5) vectored COVID-19 vaccine expressing the spike protein involved 508 healthy human volunteers and tested 2 different dosages. Seroconversion occurred in more than 96% of participants and nAb responses were generated in about 85%. More than 90% had T-cell responses. People older than 55 years of age had somewhat lower humoral responses (although still higher than placebo), as did people with previous vector immunity, but these factors did not affect T-cell responses. Adverse effects were less than with a previous higher dose used in Phase 1 trials. Concerns about Ad5-vectored vaccines remain that the immune system will focus on the Ad5 parts of the vaccine rather than the SARS-Cov-2 part. Phase 3 studies are planned.
- CoronaVac (Sinovac): A randomized, double-blinded, placebo-controlled Phase 2 trial of CoronaVac inactivated virus vaccine showed induction of nAb responses in 97.6% of those receiving 2 vaccine doses either 2 or 3 weeks apart; nAb titers were twice as high in the latter group. No serious adverse events occurred. A Phase 3 clinical trial will take place in Brazil.
- BNT162b2 (Pfizer/BioNTech): Pfizer and BioNTech released a preprint with Phase 1 data for their BNT162b2 mRNA vaccine candidate, which, at 7 days after the second dose, elicited SARS-CoV-2-neutralizing geometric mean titers (GMTs) in younger adults (aged 18-55 years) that were 3.8 times the GMT of a panel of 38 sera of SARS-CoV2 convalescent patients. In older adults (aged 65-85 years) the vaccine candidate elicited a neutralizing GMT 1.6 times the GMT of the same panel. BNT162b2 was well tolerated, with fewer side effects (especially in persons aged ≥ 65 years) than a similar earlier candidate. A 2-dose regimen of BNT162b2, which encodes an optimized SARS-CoV-2 full-length spike glycoprotein (S), moved in early July to a pivotal Phase 2/3 global study in up to 30,000 participants; approximately 29,000 participants have enrolled to date; total enrollment is planned to expand to 44,000 subjects to allow for additional safety and efficacy data as well as to include older adolescents and persons with chronic, stable HIV, hepatitis C, or hepatitis B. In contrast to other competitors, Pfizer has long-standing vaccine development experience, increasing the chance of rapid licensure. BNT162b2 is shipped directly to the end user on dry ice at -70°C +/- 10°C (-94°F +/- 11.25°F) and may be stored at this temperature in an ultra-low temperature freezer for up to 6 months or in the specially designed shipping container (unopened) for up to 10 days. BNT162b2 may be stored at 2-8°C (36-46°F) for up to 24 hours or kept at room temperature for up to 2 hours after thawing.
- AD26.COV2.S (Johnson & Johnson/Janssen): Following positive Phase 2 trial data (yet to be published), Ad26.COV2.S has entered a Phase 3 trial with a planned enrollment of 60,000 subjects at 215 locations across the U.S., Argentina, Brazil, Chile, Colombia, Mexico, Peru, and South Africa. Ad26.COV2.S will be administered as 1 dose to subjects aged ≥ 18 years,

including a significant enrollment of subjects aged 60 years. A parallel Phase 3 trial using a 2-dose series will occur in multiple countries in collaboration with the U.K. Preliminary trial results are not expected for at least 2 months; if the vaccine is proven safe and effective, earliest availability is expected to be in early 2021. Ad26.CoV.S may be stored at -20°C (-4°F) for up to 2 years or at 2-8°C (36-46°F) for up to 3 months.

- NVX-CoV2373 (Novavax): Published Phase 1/2 results from Novavax show that their conventional recombinant protein COVID-19 vaccine, NVX-CoV2373 (with and without adjuvant), induced anti-SARS-CoV-2 nAbs in 100% of participants. A 2-dose (0, 21 days) adjuvanted regimen induced geometric mean antispike IgG and nAb responses that exceeded geometric mean responses in convalescent serum from mostly symptomatic COVID-19 patients. NVX-CoV2373 adjuvanted with Matrix-M (a novel adjuvant) induced T-lymphocyte and nAb responses approximately 4-fold higher than seen in convalescent-serum specimens. Subjects were aged 18-59 years (mean = 31 years) and 79% Caucasian. Separately, vaccination of nonhuman primates with NVX-CoV2373 induced sterile immunity that prevented viral replication in the upper and lower respiratory tracts, thus showing potential to reduce SARS-CoV-2 transmission. NVX-CoV2373 is a conventional recombinant protein vaccine, unlike the more novel constructs used for other leading candidate vaccines also under preapproval production under Operation Warp Speed.

Peer-reviewed (but sparse) Phase 2 human data (n = 40 mostly young males) have been published on a prime-boost 21-day sequential regimen of Gam-COVID-Vac (Gamaleya Research Institute, Russia), an adenovirus type 26 (rAd26) then rAd5 live nonreplicating vectored vaccine with inserted genes for the SARS-CoV-2 spike protein. The strategy includes an attempt to reduce the induction of overwhelming antivector antibodies by using different vectors for priming and boosting doses. At day 42, this vaccine elicited antispike protein IgG and very high nAb titers in 100% of participants (equivalent to convalescent plasma) as well as cell-mediated responses in all participants. The vaccine was moderately well-tolerated, but no comparator control group was included; safety is paramount with novel vaccine designs. No Phase 3 efficacy data are available on this vaccine, now approved for use in Russia under a "conditional registration certificate."

Operation Warp Speed is an accelerated development, manufacturing, and distribution public-private partnership in the U.S. designed to deliver more than 300 million doses of a safe and effective COVID-19 vaccine by early 2021. Currently funded companies include AstraZeneca/University of Oxford, BioNTech/Pfizer, GSK, Inovio, Johnson & Johnson (Janssen), Merck, Moderna, Novavax, Sanofi, and Vaxart. The funding pays for large-scale production of vaccine prior to any efficacy data being generated and large-scale manufacturing has already been initiated for some of the leading candidates to enable rapid distribution if approval is granted. Sanofi has indicated that vaccine doses produced in the U.S. may be used for U.S. patients first. The following countries have advanced-purchase agreements for some of the leading COVID-19 vaccines (adjuvanted COVID-19 vaccine [Sanofi/GSK], Ad26.COV2.S [Janssen], AZD1222 [AstraZeneca/University of Oxford], BNT162b2 [BioNTech/Pfizer], CVnCoV [CureVac], mRNA-1273 [Moderna], NVX-CoV2373 [Novavax]) for the number of doses, noted in millions (M).

- U.S. (800M): Adjuvanted COVID-19 vaccine (100M), Ad26.COV2.S (100M), AZD1222 (300M), BNT162b2 (100M), mRNA-1273 (100M), NVX-CoV2373 (100M)
- Canada (190M): Ad26.COV2.S (38M), BNT162b2 (20M), mRNA-1273 (56M), NVX-CoV2373 (76M)
- E.U. (1.5 billion): Adjuvanted COVID-19 vaccine (300M), Ad26.COV2.S (200M), AZD1222 (400M), BNT162b2 (300M), CVnCoV (225M), mRNA-1273 (80M)
- U.K. (160M): Adjuvanted COVID-19 vaccine (60M), AZD1222 (100M)
- Australia (25M): AZD1222 (25M)

An approved vaccine will likely not protect 100% of recipients; protection rates will be lower in older persons. Influenza vaccine is only 50% to 70% effective, even in seasons with good matches to circulating strains. The U.S. FDA will require vaccines to be 50% effective for licensure. Most vaccine candidates aim to induce nAb responses against the viral surface protein referred to as the "spike protein." At present, nAb responses being measured in clinical trials are thought to reflect protection but this has yet to be definitively demonstrated. All current clinical trials count both mild and severe cases when measuring vaccine efficacy; therefore, the efficacy against severe disease may not be evident in small trials given that severe disease is less common. Duration of protection for a vaccine will only be known after time on the market and is not possible to reliably predict based on short-term trials. ACIP is scheduled to meet October 28-29, 2020, just prior to the U.S. elections, and will likely consider U.S. FDA licensure versus EUA for 1 or more COVID-19 vaccines and appropriate vaccination implementation.

Management of Asymptomatic Persons with Community or Direct Exposure to COVID-19

Specific contact tracing is not part of current mitigation measures in the U.S. and most European countries but is widely implemented in many Asian countries.

Persons who develop fever or respiratory symptoms within 14 days of domestic community exposure or travel to countries with community transmission should self-isolate; observe respiratory hygiene (cough and sneeze etiquette), hand hygiene, and social distancing; wear a nonmedical mask; and contact public health authorities (or telephone ahead before presenting to a hospital).

Management strategies for asymptomatic persons are based on the person's exposure category, as shown in the following table.

Table 4: U.S. Guidance for the Management of Asymptomatic Persons with Potential SARS-CoV-2 Exposure

Exposure Category	Movement Restrictions and Public Activities	Monitoring
Any international or domestic travel Possible unrecognized community exposure[1]	Observe social distancing, respiratory hygiene, and hand hygiene; wear a nonmedical mask.	Self-observation Self-monitoring if other symptoms develop
Travel from another country, a U.S. state, or a county experiencing high levels of COVID-19; see the respective Destinations page. Travel on a cruise ship or river boat Attendance at large social or mass gatherings (e.g., weddings, funerals, parties, concerts, sporting events, parades) Being in crowds (e.g., restaurants, bars, airports, bus and train stations, movie theaters)	Remain at home or in a comparable setting as much as possible until 14 days after arrival or last exposure.[2] Observe social distancing, respiratory hygiene, and hand hygiene; wear a nonmedical mask. Avoid contact with persons at risk of poor outcome (unless they live in the same home and had the same exposure).	Self-observation Self-monitoring if other symptoms develop Consider getting tested for COVID-19
Contact exposure (irrespective of whether the COVID-19 case or the contact was wearing a mask)[3]	Remain at home or in a comparable setting as much as possible until 14 days after last exposure.[2] Observe social distancing, respiratory hygiene, and hand hygiene; wear a nonmedical mask. Avoid contact with persons at risk of poor outcome (unless they live in the same home *and* had the same exposure).	Self-observation Self-monitoring

Definitions:

Self-observation: remaining alert for symptoms (fever, cough, or difficulty breathing)

Self-monitoring: taking a temperature reading 2 times per day

Social distancing: remaining out of congregate settings (crowded places such as shopping centers, movie theaters, and stadiums), avoiding mass gatherings and public transportation, and maintaining a distance of 2 m (6 ft) from others

Discontinuation of home isolation: Confirmed or suspected COVID-19 cases may discontinue home isolation 1) ≥ 24 hours have passed since last fever without the use of fever-reducing medications *and* improvement of symptoms *and* ≥ 10 days have passed since symptom onset or 2) once they test negative for SARS-CoV-2 (at least 2 negative consecutive respiratory specimens collected ≥ 24 hours apart) *and* fever has resolved without the use of fever-reducing medications *and* symptoms have improved.

1. All other U.S. residents (other than those with a known exposure risk).
2. Exception: Persons in critical infrastructure sectors (commercial and government facilities, communications, critical manufacturing, defense, emergency services, energy, financial, food and agriculture, hazardous materials, health care and public health, information technology, public works [services to maintain safety, sanitation, and essential operation of infrastructures], and water and wastewater systems) *may continue to work* (at the discretion of state and local health authorities) as long as they remain asymptomatic and additional precautions are implemented. These persons should self-observe, self-monitor under the supervision of their employer's occupational health program, wear a nonmedical mask at all times in the workplace for 14 days after last exposure, observe social distancing, and regularly clean and disinfect all shared areas and equipment. Symptom assessment and a temperature reading should be taken prior to starting work, ideally before they enter the facility.
3. 1) Household member, intimate partner, or caregiver (in a nonhealthcare setting) who did not use recommended precautions for home care or home isolation or 2) a close personal, community, workplace, or school contact (< 2 m [6 ft]) for a prolonged period of time (> 15 min) of a symptomatic COVID-19 case (laboratory-confirmed or clinically compatible illness) or an asymptomatic COVID-19 case (laboratory confirmed) during a period from 48 hours before symptom onset (or specimen collection in the instance of asymptomatic cases) to meeting criteria for discontinuation of home isolation in an area with widespread community transmission, irrespective of whether the COVID-19 case or the contact was wearing a mask.

Some health authorities recommend that nonmedical masks be worn by all persons to prevent onward transmission (source control) in order to encompass asymptomatic transmission. The public use of nonmedical masks by all persons may prevent onward transmission from asymptomatic persons. Household members of a PUI should observe hand hygiene and social distancing if possible and should avoid sharing household items. Such persons should self-monitor, and employers should consider the various options above, including exclusion from the workplace until 14 days after the last possible day of infectiousness for a PUI.

Household members of asymptomatic individuals in self-quarantine after arrival from COVID-19–affected countries or community exposure are not generally considered case contacts and may continue their daily activities (e.g., work or school) while continually monitoring their health and seeking medical attention if symptoms develop. However, businesses may conservatively opt to implement restrictions on a case-by-case basis.

Caregivers of a confirmed case or a PUI should take additional precautions to include the use of disposable gloves, gowns, and medical masks and the proper disposal of these items.

Key Unanswered Questions

- Extent of damage to various organ systems and long-term sequelae
- Extent of asymptomatic transmission and proportion of transmission from asymptomatic persons
- Role of children as reservoirs and the necessity of school closures
- Relevance of different transmission modes (e.g., droplets, airborne, fecal, surfaces/objects)
- Dispersion by building and aircraft ventilation systems (too low vs. too high)
- Effective reproductive number (R_e): how to calculate correctly to use effectively
- Efficacy of different PPE modalities, including the use of masking strategies in the community
- Efficacy and duration of social distancing, border controls, and quarantine
- Efficacy of various proposed treatment and prophylaxis modalities at different disease stages and exposure scenarios
- Level of vaccine-induced immunity, duration of immunity, adverse effects of novel constructs, and production capacity
- Optimal strategies/timing of de-escalation of community mitigation measures
- Population-based serostatus to understand the extent of infection at the population level and assess potential preexisting immunity (including for return-to-work strategies)
- Likelihood of secondary epidemic waves and/or establishment of endemicity of SARS-CoV-2

Abbreviations/Definitions

ACEI = angiotensin-converting enzyme inhibitor
ACIP = Advisory Committee on Immunization Practices
ARB = angiotensin-receptor blocker
ARDS = acute respiratory distress syndrome
BMI = body mass index
CE Mark = Conformitè Europëenne Mark
CFR = case-fatality rate
CLI = COVID-19–like illness
CLIA = Clinical Laboratory Improvement Amendments
COPD = Chronic obstructive pulmonary disease
COVID-19 = coronavirus disease 2019
CU = Columbia University
DEA = Drug Enforcement Agency
DoD = Department of Defense
DOT = Department of Transportation
ECDC = European Centre for Disease Prevention and Control
EEA = European Economic Area
ELISA = enzyme-linked immunosorbent assay
EMA = European Medicines Agency
EPA = Environmental Protection Agency
EU = European Union
EUA = Emergency Use Authorization
FEMA = Federal Emergency Management Agency
HCQ = hydroxychloroquine
HCW = health care worker
HHS = Health and Human Services
IATA = International Airline Transport Association
ICU = intensive care unit
IDSA = Infectious Disease Society of America

IHME = Institute for Health Metrics and Evaluation
ILI = influenza-like illness
IV = intravenous
LANL = Los Alamos National Laboratory
Medical mask = FDA-regulated surgical mask (includes liquid barrier protection) or nonsurgical mask (no liquid barrier protection)
MERS-CoV = Middle East respiratory syndrome coronavirus
MIT = Massachusetts Institute of Technology
MOBS = Laboratory for the Modeling of Biological + Socio-technical Systems
NAAT = Nucleic acid amplification testing
NIAID = National Institute of Allergy and Infectious Diseases
NIH = National Institutes of Health
Nonmedical mask = various forms of home-made or non-FDA-regulated commercial cloth face coverings or masks made of other textiles or materials
NYC = New York City
NYU = New York University
PCR = polymerase chain reaction
PCS = permanent change of station
PHA = public health authorities
PPE = personal protective equipment
PUI = person under investigation
RH = relative humidity
RT-PCR = reverse transcription polymerase chain reaction
SARS-CoV = severe acute respiratory syndrome coronavirus
SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2
SNS = Strategic National Stockpile
TDY = temporary duty
TSA = Transportation Security Administration
UCSF = University of California San Francisco

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