COVID-19 Pandemic: A World in Turmoil

Authors: Lauren Robertson, BA, MPT; JoAnn O'Toole, RN, BSN; Nancy Evans, BS

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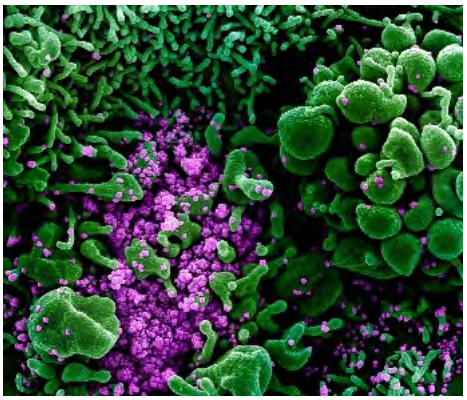

Source: National Institutes of Health

Course Summary

All of us get nearly daily updates on the coronavirus, and sometimes they contradict each other. ATrain Education has taken a long view of SARS-CoV-2 to bring you the best available comprehensive information. This includes the origin of the virus; understanding the chain of infection; an explanation of R Naught (R0, the basic reproduction number); the reason the USA can't look forward to herd immunity; the status of testing and vaccines; the reasons for public health directives; the history of coronaviruses; and the dire impacts of the virus on minority populations.

Course Objectives

When you finish this course, you will be able to:

1. Relate the 4 different types of human coronaviruses.
2. State the 6 components of the chain of infection.
3. Define R naught, the basic reproductive number.
4. Explain 3 reasons why herd immunity does not work during a pandemic.
5. Describe 3 differences between a viral test and an antibody test.
6. Differentiate between a live-attenuated vaccine and an inactivated vaccine.
7. Describe 4 of the most effective public health measures used during a pandemic.
8. Relate 5 public health measures successfully used during the SARS, MERS, and Ebola pandemics.
9. State 5 ways in which COVID-19 has adversely affected poor and minority communities.

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How COVID-19 Got Its Start

> Obviously, there is a bit of an anti-science trend in the United States, a pushing back on authority telling you what to do. Sometimes, in a good vein, that could be the independent spirit of the American people. That is part of our character. But on the other hand, it can work against you. And when you push back on someone telling you what to do, and you mix that with a trend of anti-authority, anti-science, then you get into trouble. Then you get into the situation we find ourselves now, where people are not acting in a way that is safeguarding their health.
>
> Anthony S. Fauci, MD, July 29, 2020
>
> Anthony Fauci Explains Why the U.S. Still Hasn't Beaten COVID

An outbreak of a novel, sometimes deadly, severe respiratory disease emerged in China in early 2020 and has grown rapidly in the ensuing months. The illness has spread around the world with sustained person-to-person transmission on six continents.

The virus was first seen in December of 2019 when a cluster of viral pneumonia cases was reported in Wuhan City, Hubei Province, China. Believed to have originated in a live animal market, a novel coronavirus was identified as the causative agent of the pneumonia. The virus, temporarily named 2019-nCoV (now called SARS-CoV-2), caused a widespread epidemic throughout China, with many exported cases that became the seeds for the global spread of the highly transmissible virus.

With tens of thousands of coronavirus cases reported throughout the country, Chinese health officials took the unprecedented measure of quarantining nearly 60 million people. Despite the massive quarantines, the virus spread beyond China's borders to other parts of the world.

Epidemiologists feared the outbreak had the potential to become a global health risk that might require a greater international response than Ebola, Zika, and H1N1 combined.

The United States reported its first confirmed case of person-to-person spread on January 30, 2020.

On January 31, 2020, the U.S President signed a "Proclamation on Suspension of Entry as Immigrants and Nonimmigrants of Persons who Pose a Risk of Transmitting 2019 Novel Coronavirus."

On the same day, the World Health Organization (WHO) declared a public health emergency of international concern. WHO Director-General, Tedros Adhanom Ghebreyesus, explained:

> The main reason for this declaration is not because of what is happening in China but because of what is happening in other countries. Our greatest concern is the potential for the virus to spread to countries with weaker health systems, which are ill-prepared to deal with it.

Despite these measures, by February 26, 2020 there were more confirmed COVID-19 cases outside of China than inside China. On March 11, 2020 the World Health Organization (WHO) declared a **global pandemic**.

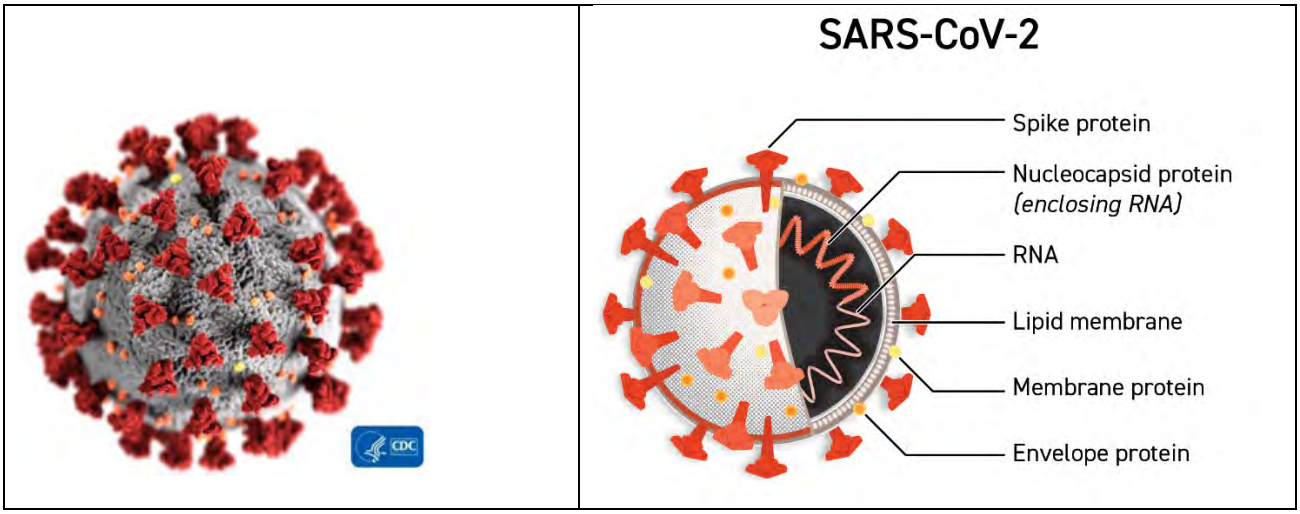
On March 13, 2020, a **national health emergency** was declared in the United States. "The goal of the measures we have taken is to slow the introduction and the impact of the disease in the United States," said Nancy Messonnier, director of the National Center for Immunization and Respiratory Diseases.

By late March 2020, the United States had surpassed China to become the country with the most confirmed cases of COVID-19. By mid-summer 2020, the United States was one of the hardest-hit countries; there were nearly 25% of global infections and 22% of global deaths from COVID-19.

What Is a Coronavirus?

There are hundreds of coronaviruses, most of which circulate among animals, including pigs, camels, bats, and cats. Sometimes these viruses jump to humans (a **spillover event**) and can cause disease, as happened with Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and now COVID-19. Coronaviruses get their name from the characteristic crown-like spikes on the surface of the virus, which resembles a corona.

CoVID-19 Virus



Left: Illustration of COVID-19 Coronavirus. Source: CDC, 2020. Right: Illustration of the SARS-CoV-2 structure. Source: Courtesy of Lisa Donohue, CoVPN, and COVID-19 Prevention Network. Used by permission.

There are four main sub-groupings of coronaviruses (alpha, beta, gamma, and delta). Only seven viruses in these sub-groups are known to cause human disease—four of which cause mild to moderate upper-respiratory illnesses such as the common cold.

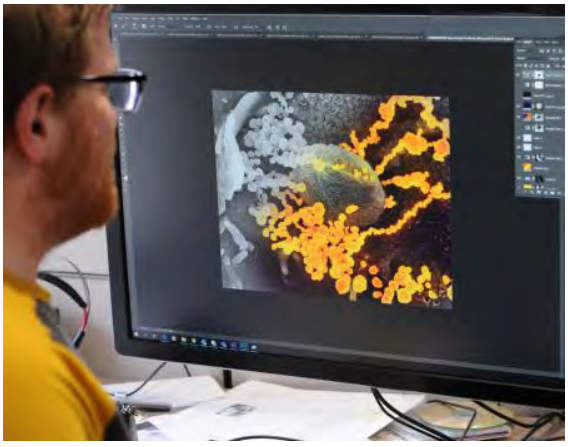
However, three times in the twenty-first century, coronavirus outbreaks have emerged from animal reservoirs to cause severe disease and global transmission concerns: SARS (SARS-CoV-1), which emerged in late 2002 and disappeared by 2004; MERS, which was first identified in 2012 and consistently jumps from dromedary camels to people; and the novel coronavirus that emerged in December 2019.

While most coronaviruses only infect animals, MERS and SARS are notable for their ability to infect a variety of species, including humans. Recent research at the National Institute of Allergy and Infectious Diseases (NIAID) shows how the MERS virus can adapt to infect cells of a new species, which suggests that other coronaviruses may be able to do the same (NIAID, 2020, April 6). It appears that COVID-19 has done just that.

How Coronaviruses Adapt to Infect Other Species

To cause infection, a virus must first attach to a receptor molecule on a cell within the host species. This interaction is highly dependent on the shape of the receptors, which are determined by the host genes.

Colorizing a Virus



Visual artist Austin Athman shown making progress colorizing a SARS-CoV-2 image at NIAID's Rocky Mountain Laboratories. Source: NIAID.

To evaluate how MERS evolved to infect host cells, scientists from NIAID tested 16 bat species and found that the virus was unable to enter cells with receptors from a common vampire bat, *Desmodus rotundus*. Scientists adapted the cells by growing virus on cells that had vampire bat receptors and observed the virus evolved to better infect the cells. After a few generations, the virus had completely adapted to the vampire bat's receptors (NIAID, 2020 April 6). By studying how the MERS virus changed over time in order to attach to the new host receptor, scientists found similarities with prior studies of the SARS virus. Thus, while these two viruses are different, they use essentially the same approach to enter the cells of new species (NIAID, 2020, April 6).

Human Coronaviruses

> The new cluster of viral pneumonia cases originating in Wuhan, China, marks the third time in 20 years that a member of the large family of coronaviruses has jumped from animals to humans and sparked an outbreak.
>
> Anthony S. Fauci, MD
>
> National Institute of Allergy and Infectious Diseases (NIAID)

There are seven coronaviruses that can infect people and cause illness. The first four are fairly common and have circulated among humans since coronaviruses were first identified in the 1960s:

1. 229E (alpha coronavirus)
2. NL63 (alpha coronavirus)
3. OC43 (beta coronavirus)
4. HKU1 (beta coronavirus) (CDC, 2020 February 15)

These viruses have been circulating among humans for many years and usually cause the mild to moderate upper–respiratory tract illnesses like the common cold. Most people become infected with these viruses at some point in their lives and their illnesses are usually of short duration. Symptoms may include:

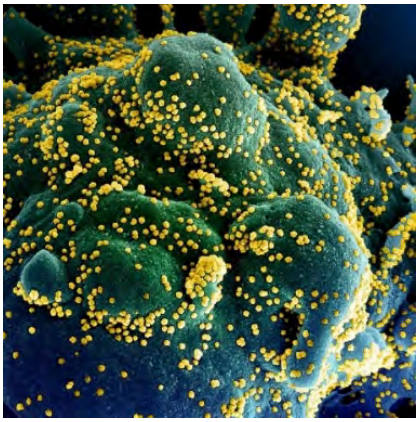
- Runny nose
- Headache
- Cough
- Sore throat
- Fever
- General feeling of being unwell (CDC, 2020 February 15)

Newer, more virulent human coronaviruses that infect animals and evolve to also infect humans are less common but more concerning:

- MERS-CoV (the beta coronavirus that causes Middle East Respiratory Syndrome)
- SARS-CoV (the beta coronavirus that causes severe acute respiratory syndrome)
- SARS-CoV-2 (the novel, beta coronavirus that causes coronavirus disease 2019, or COVID-19)

These human coronaviruses can also cause lower–respiratory tract illnesses, such as pneumonia or bronchitis; complications are more commonly seen in infants, older adults, and people with cardiopulmonary disease and/or weakened immune systems (CDC, 2020, February 15).

Scan of a Cell Infected with Coronavirus



Colorized scanning electron micrograph of an apoptotic cell (blue/green) heavily infected with SARS-COV-2 virus particles (yellow), isolated from a patient sample. Image captured at the NIAID Integrated Research Facility (IRF) in Fort Detrick, Maryland. Source: NIAID.

Coronavirus Symptoms

For confirmed COVID-19 infections, reported illnesses have ranged from people with little to no symptoms to people being severely ill and dying. Symptoms may appear 2 to 14 day after exposure. People with these symptoms or combination of symptoms may have COVID-19:

- Cough
- Shortness of breath or difficulty breathing

Or at least two of these symptoms:

- Fever
- Chills
- Repeated shaking with chills
- Muscle pain
- Headache
- Sore throat
- New loss of taste or smell

Symptoms differ with severity of disease. For example, fever, cough, and shortness of breath are more commonly reported among people who are hospitalized with COVID-19 than among those with milder disease. Atypical presentations occur often, and older adults and persons with medical comorbidities may have delayed presentation of fever and respiratory symptoms (CDC, 2020, June 30).

Although the most common symptoms reported from COVID-19 are fever, dry cough, and fatigue, additional symptoms have been widely reported. Gastrointestinal symptoms can include nausea, vomiting, and diarrhea. Painful, itchy lesions on the hands and feet have been seen in younger people with less severe infection (sometimes referred to as COVID toes). Eye problems such as sensitivity to light, swollen eyelids, and watery eyes have also been reported.

In one study of 1,099 hospitalized patients, fever was present in only 44% at hospital admission but eventually developed in 89% during hospitalization. Fatigue, headache, and muscle aches (myalgia) are among the most commonly reported symptoms in people who are not hospitalized, and sore throat and nasal congestion or runny nose also may be prominent symptoms (CDC, 2020, June 30).

Many people with COVID-19 experience gastrointestinal symptoms such as nausea, vomiting, or diarrhea, sometimes prior to developing fever and lower respiratory tract signs and symptoms. Loss of smell (**anosmia**) or taste (**ageusia**) preceding the onset of respiratory symptoms has been commonly reported in COVID-19, especially among women and young or middle-aged patients who do not require hospitalization. While many of the symptoms of COVID-19 are common to other respiratory or viral illnesses, anosmia appears to be more specific to COVID-19 (CDC, 2020, June 30).

Several studies have reported that the signs and symptoms of COVID-19 in children are similar to adults, vary by age of the child, and are usually milder compared to adults (CDC, 2020, June 30).

As we approach flu season in the Northern Hemisphere, it is helpful to understand the difference between influenza and COVID-19. Both are contagious respiratory illnesses, but they are caused by different viruses. COVID-19 is caused by infection with a coronavirus (called SARS-CoV-2) and flu is caused by infection with influenza viruses. Because some of the symptoms of flu and COVID-19 are similar, it may be hard to tell the difference between them based on symptoms alone, and testing may be needed to help confirm a diagnosis. Flu and COVID-19 share many characteristics, but there are some key differences between the two:

- Infection with COVID can cause a loss of taste or smell.
- COVID symptoms may take longer to develop than flu symptoms.
- People infected with COVID can be infectious for a longer period of time.
- COVID has produced more superspreading events than flu.
- COVID has caused blood clots in some individuals.
- Case of multi-inflammatory syndrome have occurred in children. (CDC, 2020, Jul 10)

Coronavirus Treatment and Management

There is no specific antiviral treatment recommended for COVID-19, and no vaccine is currently available. The treatment is symptomatic, and oxygen therapy represents the first step for addressing respiratory impairment. Non-invasive and invasive mechanical ventilation may be necessary in cases of respiratory failure refractory to oxygen therapy. Intensive care is needed to deal with complicated forms of the disease (Cascella et al., 2020).

The incubation period for COVID-19 is thought to extend to 14 days, with a median time of 4-5 days from exposure to symptoms onset. One study reported that 97.5% of persons with COVID-19 who develop symptoms will do so within 11.5 days of SARS-CoV-2 infection. A large cohort of >44,000 persons with COVID-19 from China showed that illness severity can range from mild to critical:

- Mild to moderate (mild symptoms up to mild pneumonia): 81%
- Severe (dyspnea, hypoxia, or >50% lung involvement on imaging): 14%
- Critical (respiratory failure, shock, or multiorgan system dysfunction): 5% (CDC, 2020 June 30)

In this study, all deaths occurred among patients with critical illness, and the overall case fatality rate was 2.3%. The case fatality rate among patients with critical disease was 49%. Among children in China, illness severity was lower with 94% having asymptomatic, mild, or moderate disease; 5% having severe disease; and <1% having critical disease. Among U.S. COVID-19 cases with known disposition, the proportion of persons who were hospitalized was 19%. The proportion of persons with COVID-19 admitted to the intensive care unit was 6% (CDC, 2020 June 30).

Mild Disease

Patients with a mild clinical presentation (absence of viral pneumonia and hypoxia) may not initially require hospitalization, and many patients will be able to manage their illness at home. The decision to monitor a patient in the inpatient or outpatient setting should be made on a case-by-case basis. This depends on the clinical presentation, requirement for supportive care, potential risk factors for severe disease, and the ability of the patient to self-isolate at home. Patients with risk factors for severe illness should be monitored closely given the possible risk of progression to severe illness, especially in the second week after symptom onset (CDC, 2020 June 30).

Severe Disease

Some patients with COVID-19 will have severe disease requiring hospitalization for management. Inpatient management revolves around the supportive management of the most common complications of severe COVID-19: pneumonia, hypoxemic respiratory failure/ARDS, sepsis and septic shock, cardiomyopathy and arrhythmia, acute kidney injury, and complications from prolonged hospitalization, including secondary bacterial infections, thromboembolism, gastrointestinal bleeding, and critical illness polyneuropathy/myopathy (CDC, 2020 June 30).

Some patients with COVID-19 may develop signs of a hypercoagulable state and be at increased risk for venous and arterial thrombosis of large and small vessels. Laboratory abnormalities commonly observed among hospitalized patients with COVID-19-associated coagulopathy include:

- Mild thrombocytopenia
- Increased D-dimer levels
- Increased fibrin degradation products
- Prolonged prothrombin time

Elevated D-dimer* levels have been strongly associated with greater risk of death (CDC, 2020 June 30).

***D-dimer**: D-dimer is a protein fragment that is made when a blood clot has formed and is in the process of breaking down. A positive test indicates that there may be significant blood clot formation and breakdown in the body.

There are several reports of hospitalized patients with thrombotic complications, most frequently deep venous thrombosis and pulmonary embolism. Other reported manifestations include:

- Microvascular thrombosis of the toes
- Clotting of catheters
- Myocardial injury with ST-segment elevation
- Large vessel strokes (CDC, 2020, June 30)

The pathogenesis for COVID-19-associated hypercoagulability remains unknown. However, hypoxia and systemic inflammation secondary to COVID-19 may lead to high levels of inflammatory cytokines and activation of the coagulation pathway. There are limited data available to inform clinical management around prophylaxis or treatment of venous thromboembolism in COVID-19 patients (CDC, 2020, June 30).

Illness among pediatric patients with COVID-19 is typically milder than among adults. Most children present with symptoms of upper respiratory infection. However, severe outcomes have been reported in children, including deaths. Data suggest that infants (<12 months of age) may be at higher risk for severe illness from COVID-19 compared with older children. CDC and partners are also investigating reports of multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 (CDC, 2020, June 30).

Guidance for Determining COVID-19 Status of Asymptomatic Persons

Person	Exposure to	Recommended precautions for the public
Individual who has had close contact (<6 feet)** for ≥15 minutes***)	Person with COVID-19 who has symptoms (in the period from 2 days before symptom onset until they meet criteria for discontinuing home isolation; can be laboratory-confirmed or a clinically compatible illness) Person who has tested positive for COVID-19 (laboratory confirmed) but has not had any symptoms (in the 2 days before the date of specimen collection until they meet criteria for discontinuing home isolation). **Note**: This is irrespective of whether the person with COVID-19 or the contact was wearing a cloth face covering or whether the contact was wearing respiratory personal protective equipment (PPE)	Stay home until 14 days after last exposure and maintain social distance (at least 6 feet) from others at all times Self-monitor for symptoms Check temperature twice a day Watch for fever*, cough, or shortness of breath, or other symptoms of COVID-19 Avoid contact with people at higher risk for severe illness from COVID-19 Follow CDC guidance if symptoms develop
All U.S. residents, other than those with a known risk exposure	Possible unrecognized COVID-19 exposures in U.S. communities	Practice social distancing and other personal prevention strategies Be alert for symptoms Watch for fever*, cough, or shortness of breath, or other symptoms of COVID-19 Check temperature if symptoms develop Follow CDC guidance if symptoms develop

*For the purpose of this guidance, fever is defined as subjective fever (feeling feverish) or a measured temperature of 100.4°F (38°C) or higher. Note that fever may be intermittent or may not be present in some people, such as those who are elderly, immunocompromised, or taking certain fever-reducing medications (e.g., nonsteroidal anti-inflammatory drugs [NSAIDS]).

** Data to inform the definition of close contact are limited. Factors to consider when defining close contact include proximity, the duration of exposure (e.g., longer exposure time likely increases exposure risk), and whether the exposure was to a person with symptoms (e.g., coughing likely increases exposure risk). While research indicates cloth face coverings may help those who are infected from spreading the infection, there is less information regarding whether cloth face coverings offer any protection for a contact exposed to a symptomatic or asymptomatic patient. Therefore, the determination of close contact should be made irrespective of whether the person with COVID-19 or the contact was wearing a cloth face covering. Because the general public has not received training on proper selection and use of respiratory PPE, it cannot be certain whether respiratory PPE worn during contact with an individual with COVID-19 infection protected them from exposure. Therefore, as a conservative approach, the determination of close contact should generally be made irrespective of whether the contact was wearing respiratory PPE, which is recommended for health care personnel and other trained users, or a cloth face covering recommended for the general public.

***Data are insufficient to precisely define the duration of time that constitutes a prolonged exposure. Recommendations vary on the length of time of exposure, but 15 minutes of close exposure can be used as an operational definition. Brief interactions are less likely to result in transmission; however, symptoms and the type of interaction (e.g., did the infected person cough directly into the face of the exposed individual) remain important.

Source: National Center for Immunization and Respiratory Diseases (NCIRD), Division of Viral Diseases, June 5, 2020.

General treatment considerations include:

- Management of comorbid conditions.
- Prevention of pulmonary coinfections and superinfections, such as hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP).
- Assessing treatable causes of shock such as bacterial sepsis, hypovolemic shock, cardiac dysfunction, or comorbid atherosclerotic disease and stress-related adrenal insufficiency.
- Management of COVID-19–induced cardiac dysfunction, including myocarditis.
- Evaluation and management of thrombotic events.
- Evaluating and managing renal and hepatic dysfunction.
- Understanding special considerations in children such as multisystem inflammatory syndrome in children.
- Evaluating drug-drug interactions.
- Monitoring risk for nosocomial infections and other complications of critical illness care, such as VAP, HAP, catheter-related bloodstream infections, and venous thromboembolism. (CDC, 2020, July 30)

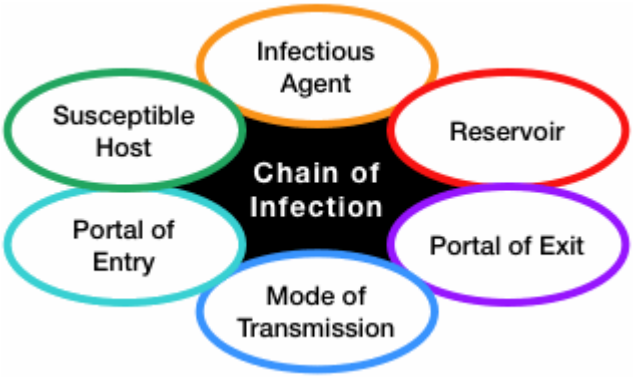
Understanding the Chain of Infection

The spread of an infection within a community is described as a “chain,” several interconnected steps that describe how a pathogen moves about. Infection control and contact tracing are meant to break the chain, preventing a pathogen from spreading.

Emerging infectious diseases are those whose incidence in humans has increased in the past two decades or are a threat to increase in the near future. These diseases, which can rapidly spread across national boundaries and communities, may challenge the ability of public health systems to prevent and control the spread of the disease, especially in resource-limited countries and regions.

The spread of infection can be described as a chain with six links:

1. Infectious agent (pathogen)
2. Reservoir (the normal location of the pathogen)
3. Portal of exit from the reservoir
4. Mode of transmission
5. Portal of entry into a host
6. Susceptible host



Infection control measures are designed to break the links and prevent a pathogen from spreading.

Infectious Agents

Infectious agents (pathogens) include not only bacteria but also viruses, fungi, and parasites. The virulence of these pathogens depends on their number, their potency, their ability to enter and survive in the body, and the susceptibility of the host. For example, the smallpox virus is particularly virulent, infecting almost all people exposed. In contrast, the tuberculosis bacillus infects only a small number of people, usually people with weakened immune function, or those who are undernourished and living in crowded conditions.

Viruses are intracellular parasites; that is, they can only reproduce inside a living cell. Some viruses, such as HIV and hepatitis B and C, have the ability to enter and survive in the body for years before symptoms of disease occur. Other viruses, such as influenza and COVID-19, quickly announce their presence through characteristic symptoms.

Reservoir

A **reservoir** is any person, animal, arthropod, plant, soil or substance (or combination of these) in which an infectious agent normally lives and multiplies. The infectious agent depends on the reservoir for survival, where it can reproduce itself in such manner that it can be transmitted to a susceptible host.

Animate reservoirs include people, insects, birds, and other animals. **Inanimate** reservoirs include soil, water, food, feces, intravenous fluid, and equipment.

Portal of Exit

Portals of exit is the means by which a pathogen exits from a reservoir. For a human reservoir, the portal of exit can include blood, respiratory secretions, and anything exiting from the gastrointestinal or urinary tracts.

Once a pathogen has exited the reservoir, it needs a mode of transmission to transfer itself into a host. This is accomplished by entering the host through a receptive portal of entry. Transmission can be by direct contact, indirect contact, or through the air.

Transmission of respiratory infections such as COVID-19 is primarily via virus-laden fluid particles (i.e., droplets and aerosols) that are formed in the respiratory tract of an infected person and expelled from the mouth and nose during breathing, talking, singing, coughing, and sneezing. The competing effects of inertia, gravity, and evaporation determine the fate of these droplets. Large droplets settle faster than they evaporate and contaminate surrounding surfaces. **Smaller droplets evaporate faster than they settle, forming droplet nuclei that can stay airborne for hours (becoming aerosolized) and may be transported over long distances** (Mittal et al., 2020, July 10).

Human-to-human transmission of COVID-19 occurs primarily via three routes: (1) large particles that are expelled with sufficient momentum so as to directly impact the recipients' mouth, nose, or conjunctiva; (2) physical contact with droplets deposited on a surface and subsequent transfer to the recipient's respiratory mucosa; and (3) inhalation of aerosolized droplet nuclei delivered by ambient air currents. The first two routes associated with large droplets are referred to as the "droplet" and "contact" routes of transmission, whereas the third is referred to as "airborne" transmission (Mittal et al., 2020, July 10).

This photograph captures a sneeze in progress, revealing the plume of salivary droplets as they are expelled in a large cone-shaped array from this man's open mouth, thereby dramatically illustrating the reason for covering your mouth when coughing or sneezing, in order to protect others from germ exposure.
Source: James Gathany, CDC PHIL, 2009.

Airborne (Aerosol) Transmission

Scant evidence describing SARS-CoV-2 transmission dynamics has led to shifting guidelines from the WHO, CDC, and other public health authorities. Evidence suggests that other emerging coronavirus diseases (e.g., SARS and MERS) have airborne transmission potential in addition to more direct contact and droplet transmission (Santarpia, et al., 2020, July 29).

Aerosols are small particles (≤5 μm) that can rapidly evaporate in the air, leaving behind **droplet nuclei** that are small enough and light enough to remain suspended in the air for hours (Klompas et al., 2020). Airborne transmission can occur when the residue of evaporated droplets from an infected person remain in the air long enough to be transmitted to the respiratory tract of a susceptible host.

There is increasing evidence that the COVID-19 coronavirus can move from person-to-person through the air, particularly in poorly ventilated, enclosed spaces. This means an infectious agent may remain infectious when suspended in air over long distances and time (WHO, 2020, Jun 9).

Airborne transmission of SARS-CoV-2 is known to occur during aerosol-generating medical procedures. The scientific community has been actively discussing and evaluating whether SARS-CoV-2 may also spread through aerosols in the absence of aerosol-generating procedures, particularly in indoor settings with poor ventilation (WHO, 2020, Jun 9).

Comparing airborne (aerosol) transmission to droplet transmission is an important issue because, if COVID-19 is easily transmitted via airborne particles, then distancing, facemasks, and shields may not be enough to protect someone from exposure to the virus.

Investigators have demonstrated that speaking and coughing produce a mixture of both droplets and aerosols in a range of sizes, that **these secretions can travel together for up to 27 feet**, that it is feasible for SARS-CoV-2 to remain suspended in the air and viable for hours, that SARS-CoV-2 RNA can be recovered from air samples in hospitals, and that poor ventilation prolongs the amount of time that aerosols remain airborne (Klompas et al., 2020).

During the initial isolation, of thirteen individuals from the Diamond Princess cruise ship who had COVID-19, at the University of Nebraska Medical Center, researchers collected air and surface samples to examine viral shedding from isolated individuals. They detected viral contamination among all samples, supporting the use of airborne isolation precautions when caring for COVID-19 patients (Santarpia, et al., 2020, July 29).

The presence of contamination on personal items was expected, particularly those items that are routinely handled by individuals in isolation, such as cell phones and remote controls, as well as medical equipment that is in near-constant contact with the patient. The observation of viral replication in cell culture for some of the samples confirms the potentially infectious nature of the recovered virus (Santarpia, et al., 2020, July 29).

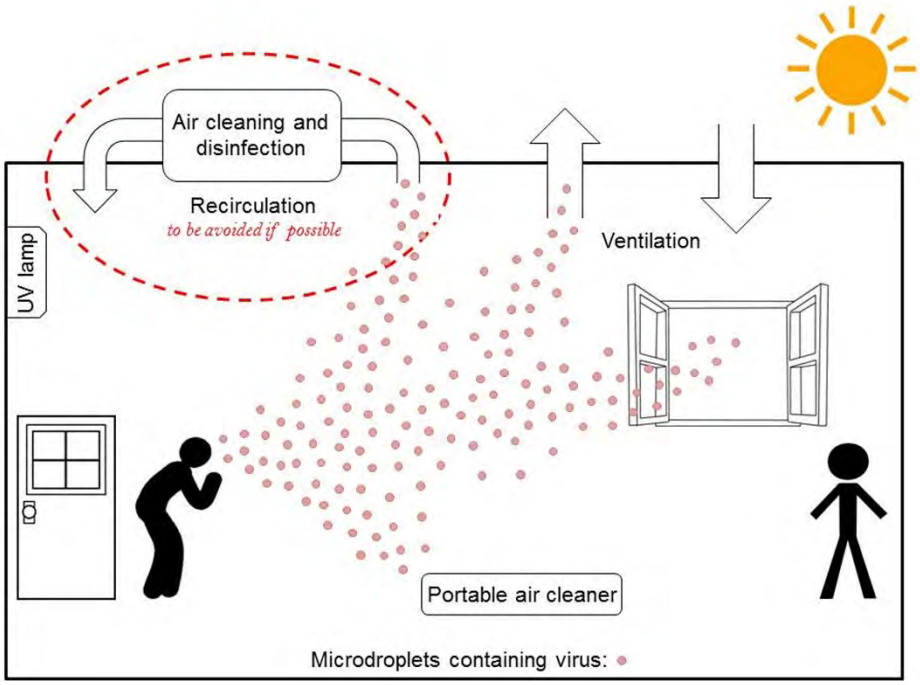
Researchers noted variability in the degree of environmental contamination from room to room and day to day. Patients with higher acuity of illness or levels of care may be associated with increased levels of environmental contamination. However, there was a lack of a strong relationship between environmental contamination and body temperature, reaffirming the fact that shedding of viral RNA is not necessarily linked to clinical signs of illness (Santarpia, et al., 2020, July 29).

The more acute patients were generally less mobile, and distribution of positive samples suggested a strong influence of airflow. Personal and high-touch items were not universally positive, yet viral RNA was detected in 100% of samples from the floor under the bed and all but one window ledge (which were not used by the patient) (Santarpia, et al., 2020, July 29).

Data from the UNMC study indicated significant environmental contamination in rooms where patients infected with SARS-CoV-2 were housed and cared for, regardless of the degree of symptoms or acuity of illness. Contamination existed in all types of samples: high- and low-volume air samples, as well as surface samples including personal items, room surfaces, and toilets. Samples of patient toilets that tested positive for viral RNA are consistent with other reports of viral shedding in stool (Santarpia, et al., 2020, July 29).

The transport of droplet nuclei over larger distances is primarily driven by ambient air flows, and indoor environments such as homes, offices, malls, aircraft, and public transport vehicles pose a particular challenge for disease transmission. The importance of ventilation in controlling airborne transmission of infections is well known. Indoor spaces can have extremely complex flows, due to ventilation systems and other factors that influence them (Mittal et al., 2020, July 10).

Diagram Showing Airborne Transmission



Engineering level controls to reduce the environmental risks for airborne transmission.
Source: Environmental International Volume 142. CC BY-NC-ND 4.0.

Indirect Contact

Indirect contact includes both vehicle-borne and vector borne contact. A **vehicle** is an inanimate go-between, an intermediary between the portal of exit from the reservoir and the portal of entry to the host. Inanimate objects such as cooking or eating utensils, handkerchiefs and tissues, soiled laundry, doorknobs and handles, and surgical instruments and dressings are common vehicles that can transmit infection. Blood, serum, plasma, water, food, and milk also serve as vehicles. For example, food can be contaminated by *E.coli* if food handlers do not practice appropriate handwashing techniques after using the bathroom. If the food is eaten by a susceptible host, such as a young child or a person with HIV/AIDS, the resulting infection can be life-threatening.

Vector-borne contact is transmission by an animate intermediary, an animal, insect, or parasite that transports the pathogen from reservoir to host. Transmission takes place when the vector injects salivary fluid by biting the host, or deposits feces or eggs in a break in the skin. Mosquitoes are vectors for malaria and West Nile virus. Rodents can be vectors for hantavirus.

Portal of Entry

Infectious agents get into the body through various **portals of entry**, including the mucous membranes, non-intact skin, and the respiratory, gastrointestinal, and genitourinary tracts. Pathogens often enter the body of the host through the same route they exited the reservoir, e.g., airborne pathogens from one person's sneeze can enter through the nose of another person.

Susceptible Host

The final link in the chain of infection is a **susceptible host**, someone at risk of infection. Infection does not occur automatically when the pathogen enters the body of a person whose immune system is functioning normally. When a virulent pathogen enters an immune-compromised person, however, infection generally follows.

Whether exposure to a pathogen results in infection depends on several factors related to the person exposed (the host), the pathogen (the agent), and the environment. Host factors that influence the outcome of an exposure include the presence or absence of natural barriers, the functional state of the immune system, and the presence or absence of an invasive device.

How COVID-19 Spreads

From the start of the COVID-19 epidemic, it was known that the virus spreads via respiratory droplets (infectious agent). In a CDC telebriefing on February 14, CDC's Messonnier said, "Based on what is now known about COVID-19, we believe this virus spreads mainly from person (reservoir) to person among close contacts (defined as about six feet) through respiratory droplets produced when an infected person coughs or sneezes." This is similar to the way influenza and other respiratory pathogens spread. These droplets can land in the mouths or noses of people (susceptible host) who are nearby or possibly be inhaled into the lungs (portal of entry).

What was not initially known was that asymptomatic people can act as a reservoir for the virus, thus infecting others. Those who do develop symptoms appear to be "shedding significant virus in their oropharyngeal compartment" up to 48 hours before developing symptoms. "This helps explain how rapidly this virus continues to spread across the country, because we have asymptomatic transmitters and we have individuals who are transmitting 48 hours before they become symptomatic," said CDC Director Robert Redfield.

We are now learning that the virus may also spread through the air via microscopic aerosol particles, which can remain suspended in the air of enclosed rooms for more than an hour. A July 9, 2020 scientific brief from the World Health Organization titled *Transmission of SARS-CoV-2: Implications for Infection Prevention Precautions*, indicates that infectious particles much smaller than droplets can become airborne and remain suspended in the air for long periods of time. These so-called aerosol particles appear to be capable of infecting people who inhale them. WHO reports that outbreaks related to activities in crowded, enclosed spaces "suggest the possibility of aerosol transmission combined with droplet transmission" during activities such as choir practice, eating in restaurants, and exercising in gyms.

Viability on Surfaces

Contamination of dry surfaces can serve as transmission route of coronaviruses. Some studies have reported that coronaviruses can survive on metals, glass, plastic, and fibers for as long as 9 days. COVID-19 can live in the air and on surfaces between several hours and several days. 2019-nCoV is viable for up to 72 hours on plastics, 48 hours on stainless steel, and 24 hours on cardboard. Copper surfaces tend to kill the virus in about 4 hours (van Doremalen et al., 2020).

Research further revealed that the virus could survive in droplets for up to 3 hours after being coughed out into the air. Furthermore, governments worldwide are quarantining bank notes, as the coronavirus pandemic puts the spotlight on the germ-spreading properties of "real" money. The United States, South Korea, and China are taking action amid concerns that the disease could be spread by paper money and coins (van Doremalen et al., 2020).

The Basic Reproduction Number: R Naught

The epidemiologic concept of R naught (R_0) is much in the news of late. This number, the basic reproduction number, is being used to calculate COVID-19 transmissibility and is a key part of the discussion on when to begin allowing cities and states to reopen.

What R Naught (R_0) Means

R naught (R_0), the *basic reproduction number*, is one of the most fundamental and often-used metrics for the study of the way a disease spreads. The symbol *R* represents the actual transmission rate of a disease and stands for reproduction. Naught, or zero, stands for the zeroth generation (**patient zero**). It refers to the first documented patient infected by a disease in an epidemic.

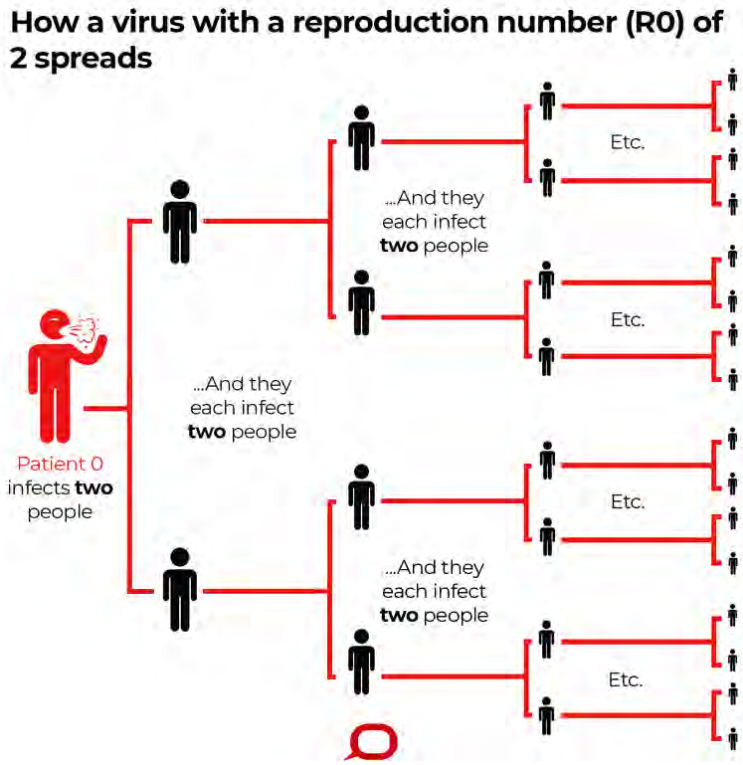
R_0 is an indicator of the contagiousness or transmissibility of infectious and parasitic agents and represent the number of new infections estimated to stem from a single case in a population that has never seen the disease before. If the R_0 is 2, then one person is expected to infect, on average, two new people (Anastassopoulou et al., 2020).

To provide some perspective, seasonal strains of flu have R_0s between 0.9 and 2.1. The R_0 value of the 1918 flu pandemic was estimated to be between 1.4 and 2.8, and for an extremely contagious disease such as the measles, R_0 is thought to lie between 12 and 18 (Healthline, 2020).

R_0 is one of the key values that can predict whether an infectious disease will spread into a population or die out. It is used to assess the severity of the outbreak, as well as the strength of the medical and/or behavioral interventions necessary for control (Breban et al., 2007).

Covid-19 R Naught

The R_0 originally estimated for COVID-19 was between 2.2 and 2.7, but data collected from case reports across China reported a much higher R_0. Results showed that the doubling time early in the epidemic in Wuhan was 2.3 to 3.3 days. From this data, researchers calculated a median R_0 value of 5.7. This means that each person infected with the virus can transmit it to 5 to 6 people rather than only 2 to 3 as previously thought (Sanche et al, 2020).



R_0 describes how many cases of a disease an infected person will go on to cause—in this imagined scenario $R_0=2$.
Source: *The Conversation*, CC BY-ND.

History of R_0

Mathematical demographer Alfred Lotka developed the **Stable Population Theory** during the early twentieth century to study the change and growth rate of certain populations. He proposed the reproduction number in the 1920s as a measure of the rate of reproduction in a given group of people and used it to count offspring.

In the 1950s, epidemiologist George MacDonald suggested using R_0 to describe the transmission potential of malaria. He proposed that if R_0 is less than 1, the disease will die out in a population, because on average an infectious person will transmit to fewer than 1 other susceptible person. On the other hand, if R_0 is greater than 1, the disease will spread (Eisenberg, 2020). Since then the reproduction number has become widely used in the field of epidemiology.

How R_0 is Used

R_0 values indicate if a disease will spread or decline within a community and how far and how rapidly transmission will occur. It can also inform public health policy decisions used to mitigate spread.

The higher the R_0, the more likely the disease will become an epidemic. There are three different possibilities that can be conveyed by R_0 (Healthline, 2020):

1. If R_0 is less than 1, the disease will not spread and will eventually die out.
2. If R_0 is 1, the disease will remain stable in the community but will not cause an epidemic.
3. If R_0 is greater than 1, the disease will spread and may cause an epidemic.

How R_0 is Calculated

R_0 is determined using complex mathematical equations that look at data from the disease's characteristics and transmissibility, human behavior, how often sick and susceptible people are expected to come into contact with each other, and where the affected community is located. Scientists may also add educated guesses.

One of the ways epidemiologists calculate R_0 is by using contact tracing data obtained at the onset of the epidemic. Once an individual is diagnosed, that person's contacts are traced and tested. R_0 is then computed by averaging the number of secondary cases caused by diagnosed individuals (Breban et al, 2007).

However, counting the number of cases of infection during an epidemic can be extremely difficult, even when public health officials use active surveillance and contact tracing to attempt to locate all infected persons. Although measuring the true R_0 value is possible during an outbreak of a newly emerging disease, there are rarely sufficient data collection systems in place to capture the early stages of an outbreak when R_0 might be measured most accurately (EID, 2019).

As a result, R_0 is nearly always estimated retrospectively from sero-epidemiologic data (which looks for the presence of antibodies in the blood) or by using theoretical mathematical models. The estimated values of R_0 generated by mathematical models are dependent on numerous decisions made by the modeler (EID, 2019).

When mathematical models are used, R_0 values are often estimated by using ordinary differential equations, but high-quality data are rarely available for all components of the model. The population structure of the model includes people who are exposed but not yet infectious, as well as assumptions about demographics such as births, deaths, and migration over time (EID, 2019).

The Effect of Vaccination

When examining the effect of vaccination, the more appropriate term to use is the **effective reproduction number (R),** which is similar to R_0 but does not assume complete susceptibility of the population and therefore can be estimated with populations having immune members (EID, 2019).

Efforts aimed at reducing the number of susceptible persons within a population through vaccination would result in a reduction of the R value, rather than R_0 value. In this scenario, vaccination could potentially end an epidemic if R can be reduced to a value <1. The effective reproduction number can also be specified at a particular time *t*, presented as R(t) or R_t, which can be used to trace changes in R as the number of susceptible members in a population is reduced. When the goal is to measure the effectiveness of vaccination campaigns or other public health interventions, R_0 is not necessarily the best metric (EID, 2019).

The potential size of an outbreak or epidemic is often based on the magnitude of its R_0 value, and R_0 can be used to estimate the proportion of the population that must be vaccinated to eliminate an infection from that population—the higher the R_0, the more people must be vaccinated (EID, 2019).

Vaccination campaigns reduce the proportion of a population at risk for infection and are highly effective in mitigating future outbreaks. This conclusion is sometimes used to suggest that an aim of vaccination campaigns is to remove *susceptible* members of the population in order to reduce the R_0 for the event to less than 1. Although the removal of susceptible members from the population will affect infection transmission by reducing the number of contacts between infectious and susceptible persons, it will technically not reduce the R_0 value because **the definition of R_0 assumes a completely susceptible population** (EID, 2019).

Cumulative Incidence Models

Another more commonly used approach is to obtain R_0 from *cumulative incidence data* which is "the probability of developing disease over a stated period of time." Theorists construct models based on Ordinary Differential Equations (ODEs) which describe the dynamics of the expected population size in different disease stages without tracking individuals. These types of modeling assumptions are hypothetical and cannot be verified using population-level data (Breban et al., 2007).

ODE models are formulated in terms of disease transmissibility and progression rates in the population, which yield a threshold parameter for an epidemic. The **epidemic threshold is a boundary where disease equilibrium becomes unstable (R_0 is greater than 1**) and an epidemic may begin (Breban et al., 2007).

Calculations of R_0 that use cumulative incidence data often use three primary parameters:

1. The duration of contagiousness after a person becomes infected (how long the virus can be transmitted by an infected person). The longer someone is contagious, the higher the R_0 is.
2. The likelihood of infection per contact between a susceptible person and an infectious person or vector.
3. The contact rate (the rate at which an infected person meets susceptible people).

Sometimes other parameters are added, such as the availability of public health resources, the policy environment, various aspects of the built environment, and other factors that might influence transmission.

R_0 can also depend on viral characteristics, how it spreads and how long it can survive in the air and on objects. It also depends on where the virus is found in the world. According to Paul Delamater, from the University of North Carolina at Chapel Hill, "There's a host of social, cultural, and demographic characteristics of places that would make the R naught value differ from place to place." For any given infectious agent, the scientific literature might present numerous R_0 values (EID, 2019).

Video: Epidemics and Infectious Diseases —1.5 Reproductive Number (4:49)

https://www.youtube.com/watch?v=8KSQRdROrwc

Difficulties Calculating R_0

Despite its place at the forefront of mathematical epidemiology, the concept of R_0 has many flaws and defining it can be difficult. Few epidemics are ever observed at the precise moment an infected individual enters a susceptible population, so calculating the value of R_0 for a specific disease relies on secondary methods (Li et al., 2016).

In the hands of experts, R_0 can be a valuable concept. However, the process of defining, calculating, interpreting, and applying R_0 is far from straightforward. The simplicity of an R_0 value masks the complicated nature of this metric. Although R_0 is a biologic reality, the interpretation of R_0 estimates derived from different models requires an understanding of the models' structures, inputs, and interactions. "Because many researchers using R_0 have not been trained in sophisticated mathematical techniques, R_0 is easily subject to misrepresentation, misinterpretation, and misapplication" (EID, 2019).

Even if the infectiousness of a pathogen and the duration of contagiousness are constant, R_0 will fluctuate if the rate of human-to-human or human-to-vector interaction varies. Any factor that can influence the contact rate—including population density, social organization, and seasonality—will ultimately affect R_0 (EID, 2019). Since a pandemic occurs across many different populations, geographies, and climates, the R_0 may vary considerably from country to country or even within a country.

Because R_0 is a function of the contact rate, the value of R_0 is a function of human social behavior and organization, as well as the innate biologic characteristics of a pathogen. More than 20 different R_0 values were reported for measles in a variety of study areas and periods, and a review in 2017 identified feasible measles R_0 values of 3.7 to 203.3. This wide range highlights the potential variability in the value of R_0 for an infectious disease dependent on local societal behavior and environmental circumstances (EID, 2019).

There are many diseases that can persist with $R_0<1$, while diseases with $R_0>1$ can die out, reducing the usefulness of the concept as a threshold for an epidemic. For example, it is possible that a disease can persist in a population when already present but would not be strong enough to invade. Also, the threshold value that is usually calculated is rarely the average number of secondary infections, diluting the usefulness of this concept even further (Li et al., 2011).

Many of the parameters included in the models used to estimate R_0 are merely educated guesses; the true values are often unknown or difficult to impossible to measure directly. This limitation is compounded as models become more complex. So, although only one true R_0 value exists for an infectious disease event occurring in a particular place at a particular time, models that have minor differences in structure and assumptions might produce different estimates of that value, even when using the same epidemiologic data (EID, 2019).

Public Health Measures That Decrease R_0

When the R_0 of a newly emerged disease indicates that an epidemic may occur, it is important to understand the processes that can limit transmission (R) of a disease in totally susceptible people in order to prevent epidemics from starting (or to limit their size). Once a country realizes that a new virus exists, measures must be taken to interrupt the chain of infection until treatments and vaccines can be developed.

Measures used successfully in previous epidemics, which have been shown to reduce the R_0 of a disease are:

- Screening
- Social distancing
- Tracking and tracing of exposed people and their contacts
- Handwashing
- Masking
- Quarantining
- Providing healthcare workers with proper protective equipment
- Vaccination

Superspreading Events

SARS-CoV-2 continues to spread. Although we still have limited information on the epidemiology of coronavirus disease, there have been multiple reports of superspreading events. During recent severe outbreaks of SARS, Middle East respiratory syndrome (MERS), and Ebola virus disease, superspreading events were associated with explosive growth early in an outbreak and sustained transmission in later stages (Frieden & Lee, 2020, June).

Superspreading events highlight a major limitation of the concept of R_0. The basic reproductive number R_0, when presented as a mean or median value, does not capture the heterogeneity of transmission among infected persons; two pathogens with identical R_0 estimates may have markedly different patterns of transmission. The goal of a public health response is to drive the reproductive number to a value <1, something that might not be possible in some situations without better prevention, recognition, and response to superspreading events. A meta-analysis estimated that the initial median R_0 for COVID-19 is 2.79 (meaning that 1 infected person will on average infect 2.79 others), although current estimates may differ because of insufficient data (Frieden & Lee, 2020, June).

Countermeasures can substantially reduce the reproductive number; on the Diamond Princess cruise ship, an initial estimated R_0 of 14.8 (~4 times higher than the R_0 in the epicenter of the outbreak in Wuhan, China) was reduced to an estimated effective reproductive number of 1.78 after on-board isolation and quarantine measures were implemented (Frieden & Lee, 2020, June).

In Wuhan, aggressive implementation of nonpharmaceutical interventions in the community, including a *cordon sanitaire** of the city; suspension of public transport, school, and most work; and cancellation of all public events reduced the reproductive number from 3.86 to 0.32 over a 5-week period. However, these interventions might not be sustainable (Frieden & Lee, 2020, June).

***Cordon sanitaire**: a quarantined geographic area, guarded to prevent the movement of people in or out of the area.

Although superspreading events appear to be difficult to predict and therefore difficult to prevent, understanding the pathogen, host, environmental, and behavioral drivers of superspreading events can inform strategies for prevention and control. This includes:

- Pathogen-specific factors
  - Binding sites
  - Environmental persistence
  - Virulence
  - Infectious dose
- Host factors
  - Duration of infection (prolonged carriage)
  - Location and burden of infection (e.g., laryngeal or cavitary tuberculosis)
  - Symptomatology
- Environmental factors
  - Population density
  - Availability and use of infection prevention and control measures in healthcare facilities
- Behavioral factors
  - Cough hygiene
  - Social customs
  - Health-seeking behavior
  - Adherence to public health guidance
- Response factors
  - Timely and effective implementation of prevention and control measures within the community and in healthcare settings
  - Rapid identification and isolation of cases
  - Effective case isolation and contact tracing (Frieden & Lee, 2020, June)

Herd Immunity

> Nationwide, the researchers estimate that about 9 percent of the U.S. population has been infected and therefore might have protective antibodies.
>
> "There's just way too little seroprevalence in all of these states to come anywhere close to achieving herd immunity," said Marcus Russi, a Yale epidemiologist.
>
> To get to herd immunity, Americans would probably have to endure a scale of death and loss many times greater than they have already suffered.
>
> Nearly 3 million people would die on a path to "natural" herd immunity, and many thousands of additional infections and deaths would be expected even after herd immunity is reached.
>
> Avi Selk, August 7, 2020
>
> Coronavirus Updates, *The Washington Post*

Epidemiologists define the herd immunity threshold for a given virus as the percentage of the population that must be immune to ensure that its introduction will not cause an outbreak. If enough people are immune, an infected person will likely come into contact only with people who are already immune rather than spreading the virus to someone who is susceptible.

Herd immunity is usually discussed in the context of vaccination. For example, if 90% of the population (the herd) has received a chickenpox vaccine, the remaining 10% (often including people who cannot become vaccinated, like babies and the immunocompromised) will be protected from the introduction of a single person with chickenpox.

Herd immunity, also called *community immunity*, occurs when enough people in a population are vaccinated against a disease, or have antibodies from surviving the disease, to interrupt the chain of infection. This means the virus cannot travel as easily from person to person and the entire community is less likely to become infected.

The term *herd immunity* comes from the observation of how a herd of buffalo forms a circle, with the strong on the outside protecting the weaker and more vulnerable on the inside. This is similar to how herd immunity works in preventing the spread of infectious diseases. Those who are strong enough to get vaccinated directly protect themselves from infection. They also indirectly shield vulnerable people who cannot be vaccinated, for example, people undergoing cancer treatment, and those whose immune systems are compromised. Often, people who cannot be vaccinated are susceptible to the most serious consequences from being infected (Vally H., 2019).

Herd immunity is a powerful public health tool. By ensuring those who can be vaccinated do get vaccinated we can achieve herd immunity and prevent the illness and suffering that comes from the spread of infectious diseases (Vally H., 2019).

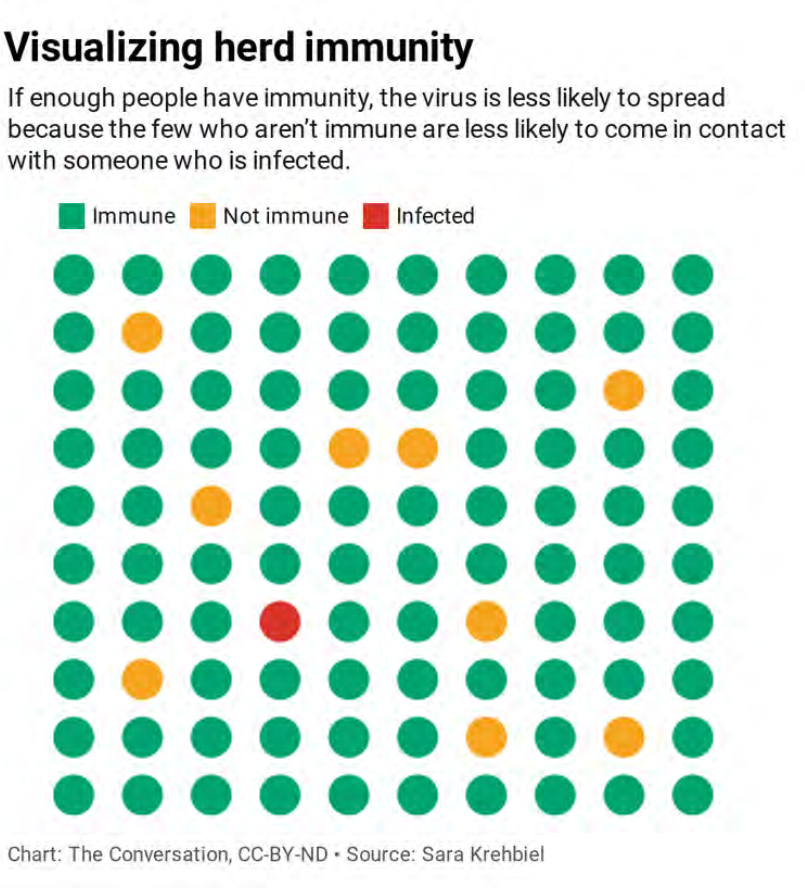
Herd Immunity Won't Solve Our COVID-19 Problem

[The following section on herd immunity is from *The Conversation* (https://theconversation.com/herd-immunity-wont-solve-our-covid-19-problem-139724). It was written by Joanna Wares, Associate Professor of Mathematics, University of Richmond, and Sara Krehbiel, Assistant Professor of Mathematics and Computer Science, Santa Clara University. CC BY-ND. Used with permission.]

Since the start of the coronavirus pandemic, use of the term *herd immunity* has spread almost as fast as the virus. But its use is fraught with misconceptions.

In the United Kingdom, officials briefly considered a herd immunity strategy to protect the most vulnerable members of its population by encouraging others to become exposed and develop immunity to the virus. Others re-ignited the discussion by focusing on how far we are from herd immunity. But trying to reach herd immunity without a vaccine would be a disastrous pandemic response strategy.

As mathematics and computer science professors, we think it is important to understand what herd immunity actually is, when it's a viable strategy, and why, without a vaccine, it cannot reduce deaths and illnesses from the current pandemic.



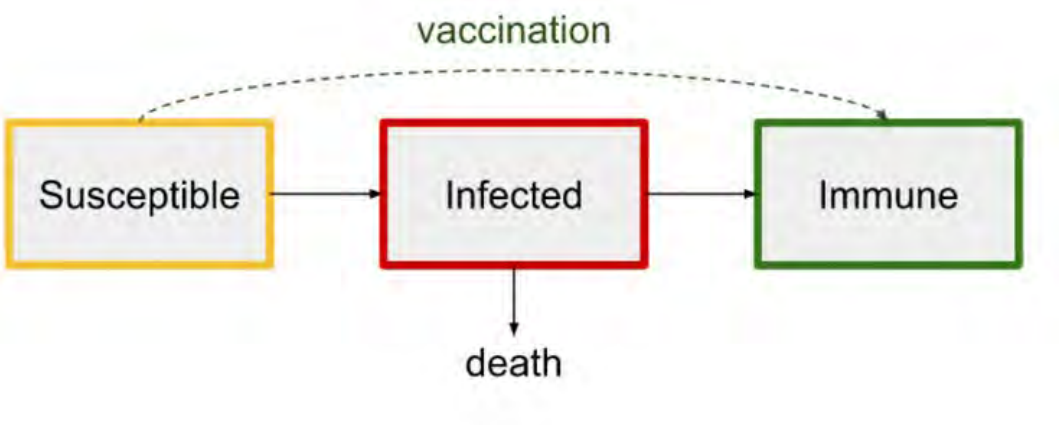
But herd immunity from SARS-CoV-2 is different in several ways:

- **We do not have a vaccine**. As biologist Carl Bergstrom and biostatistician Natalie Dean pointed out in a *New York Times* op-ed in May, without a widely available vaccine, most of the population—60% to 85% by some estimates—must become infected to reach herd immunity, and the virus's high mortality rate means millions would die.
- **The virus is not currently contained**. If herd immunity is reached during an ongoing pandemic, the high number of infected people will continue to spread the virus and ultimately many more people than the herd immunity threshold will become infected—likely over 90% of the population.
- **The people most vulnerable are not evenly spread across the population**. Groups that have not been mixing with the "herd" will remain vulnerable even after the herd immunity threshold is reached.

Reaching Herd Immunity Without a Vaccine Is Costly

For a given virus, any person is either susceptible to being infected, currently infected, or immune from being infected. If a vaccine is available, a susceptible person can become immune without ever becoming infected.

Without a vaccine, the only route to immunity is through infection. And unlike the case of chickenpox, many people infected with SARS-CoV-2 die from it.



Source: Sara Krehbiel, CC BY-ND.

By the end of July 2020, more than 150,000 people in the United States had died from COVID-19, and the disease can have lingering health consequences for those who survive. Moreover, scientists don't yet know the extent to which people who recover are immune from future infections.

A vaccine is the only way to move directly from susceptibility to immunity, bypassing the pain from becoming infected and possibly dying.

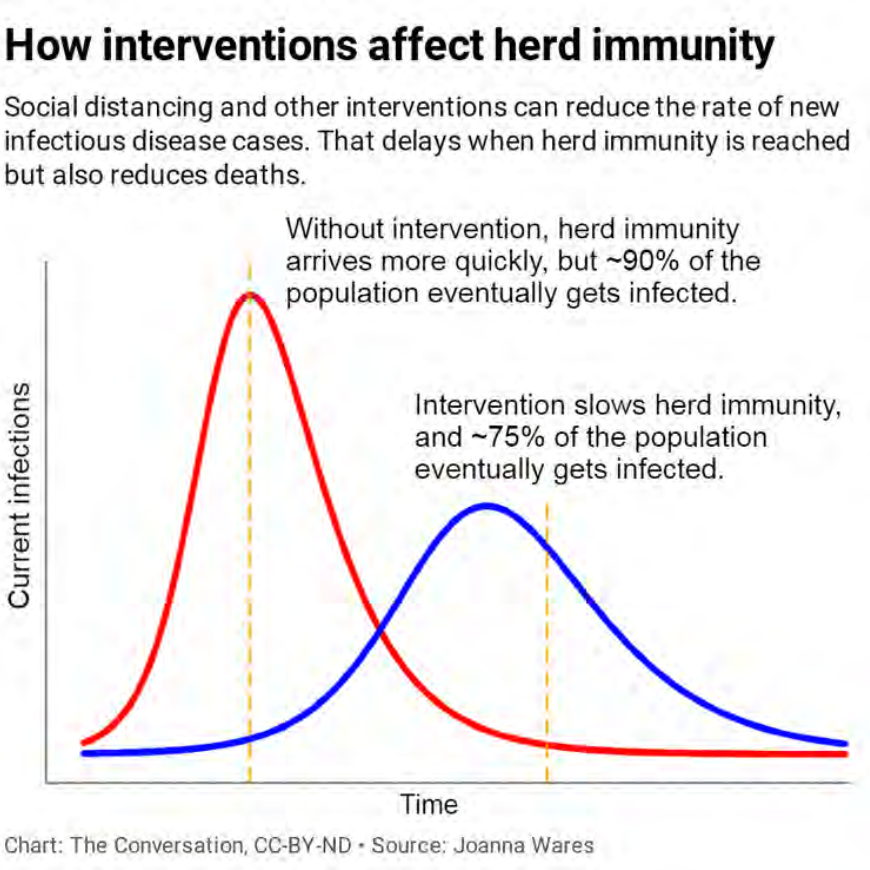
Herd Immunity Reached During a Pandemic Does Not Stop the Spread

An ongoing pandemic doesn't stop as soon as the herd immunity threshold is reached. In contrast to the scenario of a single person with chickenpox entering a largely immune population, many people are infected at any given time during an ongoing pandemic.

When the herd immunity threshold is reached during a pandemic, the number of new infections per day will decline, but the substantial infectious population at that point will continue to spread the virus. As Bergstrom and Dean (2020, May 1) noted, "A runaway train doesn't stop the instant the track begins to slope uphill, and a rapidly spreading virus doesn't stop right when herd immunity is attained."

If the virus is unchecked, the final percentage of people infected will far overshoot the herd immunity threshold, affecting as many as 90% of the population in the case of SARS-CoV-2.

Proactive mitigation strategies like social distancing and wearing masks flatten the curve by reducing the rate that active infections generate new cases. This delays the point at which herd immunity is reached and also reduces casualties, which should be the goal of any response strategy.



Herd Immunity Does Not Protect the Vulnerable

People who are particularly vulnerable to COVID-19, such as people over 65, have been urged to stay inside to avoid exposure. However, many of these people live and socialize in communities of people in the same cohort.

Even if the herd immunity threshold is reached by the population at large, a single infected person coming in contact with a vulnerable community can cause an outbreak. The coronavirus has devastated nursing homes, which will remain vulnerable until vaccines are available.

How to Respond to a Pandemic Without a Vaccine

Without a vaccine, we should not think of herd immunity as a light at the end of the tunnel. Getting there would result in millions of deaths in the United States and would not protect the most vulnerable.

For now, washing hands, wearing masks, and social distancing remain the best ways to lessen the destruction of COVID-19 by flattening the curve to buy time to develop treatments and vaccines.

Herd Immunity Threshold

The more contagious a disease, the higher the herd immunity threshold (Vally H., 2019). If the threshold is *reached*, then each case will lead to one more case. If the threshold for herd immunity is *surpassed*, new cases will decline.

COVID-19's revised R_0 means its threshold for herd immunity is greater than previously thought. If the new R_0 value is 5.7, then it is estimated that at least 82 percent of the population must become immune to the virus, either by vaccination or by acquiring antibodies after surviving infection, in order to confer herd immunity from COVID-19 on a population. Unfortunately, it is still not known if surviving the disease provides immunity (Sanche et al., 2020).

What is herd immunity and how many people need to be vaccinated to protect a community?

Herd Immunity Threshold

Disease	Reproduction number (R_0)	Vaccine coverage needed
Diphtheria	6-7	85%
Measles	12-18	92-94%
Mumps	4-7	75-86%
Pertussis (whooping cough)	12-17	92-94%
Polio	2-15	50-93
Rubella	6-7	83-85%
Smallpox	5-7	80-85%
Influenza	1.4-4	30-75%
Ebola	1.5-2.5	No vaccine
COVID-19	5.7	83%

Estimates of reproduction number and vaccine coverage needed vary and depend on mathematical models.
Source: Vally H., *Am J Epidemio*.

COVID-19 Testing

Months into the pandemic, states are still wrestling with how to expand testing. The federal government has offered little guidance on how to test more people, leaving state officials with difficult questions about how to measure the spread and make decisions about reopening their economies.

Angela Fritz and Avi Selk

The Washington Post, June 10, 2020

Tests are used in community, outpatient, and hospital-based surveillance systems to identify cases of SARS-CoV-2 infection. Data from tests can identify areas of ongoing circulation, determine trends, provide insight into the impact of the disease over time and inform disease forecasts. Clinical criteria for considering testing have been developed based on what is known about COVID-19 and are subject to change as additional information becomes available (CDC, 2020, July 2).

As noted earlier, two kinds of tests are available for COVID-19:

1. **Diagnostic viral test** tells you if you have a current infection and need to take steps to quarantine or isolate yourself. There are two main viral tests:
    - Molecular (RT-PCR)
    - Antigen tests
2. **Antibody test** tells you if you had a previous infection. It looks for antibodies made by the immune system in response to the viral threat.

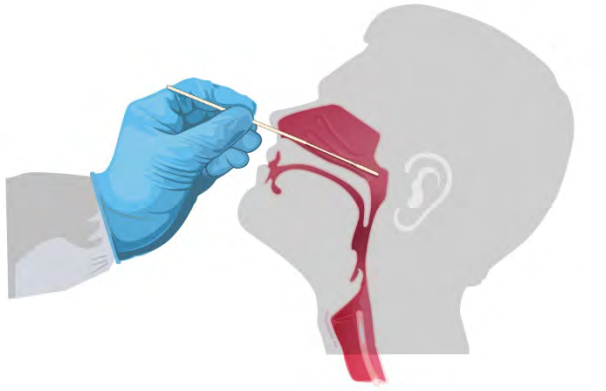
Viral Diagnostic Tests

Viral tests check samples (such as a nasal swab) from the respiratory system to determine whether an infection with SARS-CoV-2 is present. Viral tests are used to **diagnose** acute infection (CDC, 2020 July 2). Ideally, diagnostic testing would be conducted for all patients with a syndrome consistent with COVID-19, people with known high-risk exposures, and people likely to be at repeated risk of exposure, such as healthcare workers and first responders (NAIAD-RML, 2020, July 30).

Viral tests can be point-of-care tests, meaning results may be available at the testing site in less than an hour. Other viral tests must be sent to a lab for analysis, a process that takes 1 to 2 days (or longer) once received by the lab.

CDC recommends that nasopharynx samples be used to detect SARS-CoV-2. Nasal swabs or oropharyngeal swabs may be acceptable alternatives. Lower–respiratory tract samples have a higher yield than upper-tract samples, but often they are not obtained because of concerns about aerosolization of virus during sample collection procedures (NAIAD-RML, 2020, July 30).

Gathering a Respiratory Specimen



Nasopharyngeal swab. Source: CDC.

While initial diagnostic tests for SARS-CoV-2 infection have relied on reverse transcriptase polymerase chain reaction platforms, more recent tests have included a variety of additional platforms. More than twenty diagnostic tests for SARS-CoV-2 infection have received Emergency Use Authorization by the Food and Drug Administration. Formal comparisons of these tests are in progress (NAIAD-RML, 2020, July 30).

Molecular diagnostic and antigen tests can yield false-negative results. In people with a high likelihood of infection based on exposure history and/or clinical presentation, a single negative test result does not completely exclude SARS-CoV-2 infection and repeat testing should be considered. When a person who is strongly suspected to have SARS-CoV-2 infection has a negative result on an initial antigen test, repeat testing using a molecular diagnostic test may be warranted (NIH, 2020, Jun 11).

Video: COVID-19 Diagnostics: Performing a Nasopharyngeal and Oropharyngeal Swab (3:54)

https://www.youtube.com/watch?v=syXd7kgLSN8&feature=emb_rel_end

Molecular Diagnostic Tests

Molecular diagnostic testing combines laboratory testing with the precision of molecular biology to investigate the human, viral, and microbial genomes, their genes, and the products they encode. Molecular diagnostic tests are increasingly being used, and have supplanted numerous conventional tests, in many areas of laboratory medicine including oncology, infectious diseases, clinical chemistry, and clinical genetics (CDC, 2019, Nov 5).

Molecular tests detect a virus's genetic material. They are used to diagnose COVID-19 (or active coronavirus infection) using a sample from the patient's nose or throat. The CDC 2019 Novel Coronavirus Real-Time Reverse Transcriptase (RT)–PCR Diagnostic Panel detects the SARS-CoV-2 virus in upper -and lower-respiratory specimens. It is designed to be used with an existing RT-PCR testing instrument commonly used to test for seasonal influenza virus (CDC, 2020, July 15.)

SARS Test Kit

CDC's laboratory test kit for the SARS-CoV-2 virus. Source: CDC, 2020, July 15.

A **positive** test result for COVID-19 indicates that RNA from SARS-CoV-2 was detected, and the patient is presumptively infected with the virus and presumed to be contagious. Laboratory test results should always be considered in the context of clinical observations and epidemiologic data in making final diagnosis and patient management decisions. Patient management decisions should be made with a healthcare provider and follow current CDC guidelines (CDC, 2020, June 12).

A **negative** test result for this test means that SARS-CoV-2 RNA was not present in the specimen above the limit of detection. However, a negative result does not rule out COVID-19 and should not be used as the sole basis for treatment or patient management decisions. A negative result does not exclude the possibility of COVID-19 (CDC, 2020, June 12).

When diagnostic testing is negative, the possibility of a false negative result should be considered in the context of a patient's recent exposures and the presence of clinical signs and symptoms consistent with COVID-19. The possibility of a false negative result should especially be considered if the patient's recent exposures or clinical presentation indicate that COVID19 is likely, and diagnostic tests for other causes of illness (e.g., other respiratory illness) are negative. If COVID-19 is still suspected based on exposure history together with other clinical findings, re-testing should be considered by healthcare providers in consultation with public health authorities (CDC, 2020, June 12).

Molecular tests are not 100 percent accurate due to these factors:

- The swab might not collect the virus from a person's nose or throat.
- The swab or mucus sample may be accidentally contaminated by the virus during collection or analysis.
- The nasal or throat swab may not be kept at the correct temperature before it can be analyzed.
- The chemicals used to extract the virus genetic material and make copies of the virus DNA may not work correctly. (FDA, 2020, July 16)

Antigen Tests

Antigens are molecules on the surface of viruses that trigger an immune response. Antigens have specific surface features that are recognized by the immune system. The SARS-CoV-2 virus has several surface antigens, one of which is the "spike protein" visible on the surface of the virus. When a person is infected with COVID-19, the immune system begins to produce antibodies, which attack the surface antigens.

Antigen tests usually provide results faster than molecular tests, but antigen tests have a higher chance of missing an active infection. If an antigen test shows a negative result, indicating that you do not have an active coronavirus infection, your healthcare provider may order a molecular test to confirm the result (FDA, 2020, July 16).

Priorities for Diagnostic Testing

CDC has established a priority system for diagnostic testing for SARS-CoV-2 infection based on the availability of tests; the CDC testing guidance is updated periodically.

High priority

- Hospitalized patients with symptoms
- Healthcare facility workers, workers in congregate living settings, and first responders with symptoms
- Residents in long-term care facilities or other congregate living settings, including prisons and shelters, with symptoms

Priority

- Persons with symptoms of potential COVID-19 infection, including fever, cough, shortness of breath, chills, muscle pain, new loss of taste or smell, vomiting or diarrhea, and/or sore throat
- Persons without symptoms who are prioritized by health departments or clinicians, for any reason, including but not limited to public health monitoring, sentinel surveillance, or screening of other asymptomatic individuals according to state and local plans (NIH, 2020, Jun 11)

Antibody Tests

Antibody tests, a type of serologic test, detect antibodies present in the blood when the body is responding to or has responded to a specific infection. **Antibody tests detect the body's immune response to the infection** caused by the virus rather than detecting the virus itself. Antibody tests should not be used to diagnose current SARS-CoV-2 infection (FDA, 2020, May 4).

Antibody tests can be used to determine if individual patients may have been exposed to and infected with a virus, and also can be used to understand how many people in a population have antibodies (then they are known as *surveillance tests*, or *sero-surveys*) (FDA, 2020, May 4). Antibodies can take several days or weeks to develop after an infection and may stay in the blood for several weeks or more after recovery.

People who have developed antibodies against SARS-CoV-2 may qualify to donate blood that can be used to manufacture **convalescent plasma**, an investigational product for use with those who are seriously ill from COVID-19 (FDA, 2020, May 4). In general, a positive antibody test is presumed to mean a person has been infected with SARS-CoV-2 at some point in the past. It does not mean they are currently infected. Antibodies start developing within 1 to 3 weeks after infection. It is not known whether someone will be immune and protected from reinfection if they have antibodies to the virus (CDC, 2020, May 28).

Antibody Test

An image showing two antibodies (red/gold) with a white COVID-19 test cartridge in the middle. Source: NIH Director's Blog. Public domain.

Here is a summary of CDC advice for healthcare providers, laboratory professionals, and public health professionals using antibody tests for SARS-CoV-2, the virus that causes COVID-19.

- Choose antibody tests that have Emergency Use Authorization (EUA) from the U.S. Food and Drug Administration.
- Do not use antibody tests to determine a person's immune status until evidence confirms that antibodies provide protection, how much antibody is protective, and how long protection lasts.
- Antibody test results should not be used to diagnose someone with an active infection.
  - Antibody tests can support the clinical assessment of COVID-19 illness for people who are being tested 9 to 14 days after illness onset, in addition to recommended virus detection methods such as PCR. This will maximize sensitivity because the sensitivity of nucleic acid detection is *decreasing* and serologic testing is *increasing* during this time period.
  - Antibody testing can help establish a clinical picture when patients have late complications of COVID-19 illness, such as multisystem inflammatory syndrome in children. (CDC, 2020, May 28)

Caveat

Antibody test results should not be used to determine if someone can return to work. Antibody test results should not be used to group people together in settings such as schools, dormitories, and correctional facilities.

Source: CDC, 2020, May 28.

Antibody tests are not authorized by FDA for such diagnostic purposes. In certain situations, serologic assays may be used to support clinical assessment of persons who present late in their illnesses when used in conjunction with viral detection tests. In addition, if a person is suspected to have post-infectious syndrome caused by SARS-CoV-2, serologic assays may be used (CDC, 2020, July 2)

Serologic assays for SARS-CoV-2 can play an important role in understanding the transmission dynamic of the virus in the general population and identifying groups at higher risk for infection. Unlike viral direct detection methods, such as nucleic acid amplification or antigen detection tests that can detect acutely infected persons, antibody tests help determine whether the individual being tested was previously infected—even if that person never showed symptoms (CDC, 2020, July 2).

Video: An Introduction to COVID-19 Tests (2:47)

https://www.hhs.gov/coronavirus/testing/index.html

Different Types of Coronavirus Tests

	Molecular test	Antigen test	Antibody test
Also known as…	Diagnostic test, viral test, molecular test, nucleic acid amplification tests (NAAT), RT-PCR tests, LAMP test	Rapid diagnostic test (Some molecular tests are also rapid tests.)	Serological test, serology, blood test, serology test
How sample taken…	Nasal or throat swab (most tests) Saliva (a few tests)	Nasal or throat swab	Finger stick or blood draw
How long for results…	Same day (some locations) or up to a week	One hour or less	Same day (many locations) or 1-3 days
Is another test needed…	This test is typically highly accurate and usually does not need to be repeated.	Positive results are usually highly accurate but negative results may need to be confirmed with a molecular test	Sometimes a second antibody test is needed for accurate results.
What it shows…	Diagnoses active coronavirus infection	Diagnoses active coronavirus infection	Shows if you've been infected by coronavirus in the past
What it can't do…	Show if you ever had COVID-19 or were infected with the coronavirus in the past	Definitively rule out active coronavirus infection. Antigen tests are more likely to miss an active coronavirus infection compared to molecular tests. Your health care provider may order a molecular test if your antigen test shows a negative result, but you have symptoms of COVID-19.	Diagnose active coronavirus infection at the time of the test or show that you do not have COVID-19

Source: Coronavirus Testing Basics, U.S. Food and Drug Administration, 2020, July 16.

When to Test

[Material in this section is from the CDC: Evaluating and Testing Persons for Coronavirus Disease 2019 unless otherwise noted.]

Clinicians should use their judgment to determine if a patient has signs and symptoms compatible with COVID-19 and whether the patient should be tested. Asymptomatic infection with SARS-CoV-2 has been reported. Most patients with confirmed COVID-19 have developed fever and/or symptoms of acute respiratory illness but some people may present with other symptoms as well.

Other considerations that may guide testing are epidemiologic factors such as known exposure to an individual who has tested positive for SARS-CoV-2, and the occurrence of local community transmission or transmission within a specific setting or facility. Clinicians are strongly encouraged to test for other causes of respiratory illness, such as influenza, in addition to testing for SARS-CoV-2. Another population in which to prioritize testing of minimally symptomatic and even asymptomatic persons are long-term care facility residents, especially in facilities where one or more other residents have been diagnosed with symptomatic or asymptomatic COVID-19.

SARS-CoV-2 can cause asymptomatic, pre-symptomatic, and minimally symptomatic infections, leading to viral shedding that may result in transmission to others who are particularly vulnerable to severe disease and death. Even mild signs and symptoms should be evaluated among potentially exposed healthcare personnel, due to their extensive and close contact with vulnerable patients in healthcare settings.

New Testing Technologies

The National Institutes of Health is investing $248.7 million in new technologies to address challenges associated with COVID-19 testing. NIH's Rapid Acceleration of Diagnostics (RADx) initiative has awarded contracts to seven biomedical diagnostic companies to support a range of new lab-based and point-of-care tests that could significantly increase the number, type, and availability of tests by millions per week as early as September 2020. With national demand estimated to be millions more tests per day above current levels, these technologies are expected to make a significant contribution to expanding the nation's testing capacity (NIH, 2020, July 31).

Here are some new diagnostic tests available:

- **Rapid, point-of-care diagnostic tests** use a mucus sample from the nose or throat but can be analyzed at the doctor's office or clinic where the sample is collected, and results may be available in minutes. These may be molecular or antigen tests.
- **At-home collection tests**, available only by prescription from a doctor, allow the patient to collect the sample at home and send it directly to the lab for analysis.
- **Saliva tests** allow a patient to spit into a tube rather than get their nose or throat swabbed. Saliva tests may be more comfortable for some people and may be safer for healthcare workers who can be farther away during the sample collection. (FDA, 2020, July 16)

Left: Point-of-care testing. Quidel's Sofia 2 point-of-care instrument delivers test results for COVID-19 in 15 min. Source: NIH.
Right: Visual read test to detect virus. Mesa Biotech's Accula System is a visually read test using RT-PCR technology to detect SARS-CoV-2 at the point of care and provides lab-quality results in ~30 min. Source: NIH.

Vaccines and Therapeutics

Immunity is the ability of the human body to tolerate substances indigenous to the body and to eliminate foreign substances. Immunity is generally specific to a single organism or group of closely related organisms. The ability to eliminate foreign substances lies in the immune system. Since most organisms are identified as foreign, the ability to identify and eliminate these substances provides protection from infectious disease (Pink Book, 2020, June 29).

The immune system develops a defense against foreign substances. This defense is known as the **immune response** and usually involves the production of protein molecules (immunoglobulins or antibodies) by B-lymphocytes (B-cells) and specific cells, including T-lymphocytes (Pink Book, 2020, June 29).

The most effective immune responses are generally produced in response to antigens present in a live organism; however, an antigen does not necessarily have to be present in a live organism to produce an immune response. Some antigens, such as hepatitis B surface antigen, are easily recognized by the immune system and produce adequate protection. In some cases, the immune response may not provide good protection.

Vaccines stimulate the immune system to produce immune responses that protect against infection. Vaccines provide a safe, cost-effective, and efficient means of preventing illness, disability, and death from infectious diseases.

Did You Know. . .

> In late July 2020, NIAID reported that two doses of an experimental vaccine to prevent COVID-19 induced robust immune responses and rapidly controlled the coronavirus in the upper and lower airways of rhesus macaques exposed to SARS-CoV-2. The candidate vaccine, mRNA-1273, was co-developed by scientists at the NIAID Vaccine Research Center and at Moderna, Inc., Cambridge, Massachusetts (NIAID, 2020, July 28).

Vaccines

There is more than one type of vaccine, although each is designed to teach the immune system how to fight off certain kinds of pathogens—and the serious diseases they cause. Types of vaccines include:

- Live-attenuated vaccines
- Inactivated vaccines
- Subunit, recombinant, polysaccharide, and conjugate vaccines
- Nucleic acid vaccines

Live-attenuated and Inactivated Vaccines

[Unless otherwise noted, the information in the following sections is taken from NIAID, Vaccine Types, July 1, 2019]

Traditional vaccines consist of entire pathogens that have been killed or weakened so that they cannot cause disease. Such whole-pathogen vaccines can elicit strong protective immune responses. Many of the vaccines in clinical use today fall into this category. However, not every disease-causing microbe can be effectively targeted with a whole-pathogen vaccine.

Did You Know

> The more similar a vaccine is to the disease-causing form of the organism, the better the immune response to the vaccine.

Advances in tissue culture techniques have enabled development of **live-attenuated vaccines**, which contain a version of the living microbe that has been weakened in the laboratory. These vaccines elicit strong immune responses and can confer life-long immunity after only one or two doses. Live-attenuated vaccines are relatively easy to create for certain viruses, but difficult to produce for more complex pathogens like bacteria and parasites. Live vaccines are used to protect against:

- Measles, mumps, rubella (MMR combined vaccine)
- Rotavirus
- Smallpox
- Chickenpox
- Yellow fever

In 1954 Thomas Peebles and John Enders collected blood from students with measles at a private school near Boston. The measles virus was isolated and used to create a series of vaccines. The picture shows a thin-section transmission electron microscopic image of a single measles virus particle, with the viral nucleocapsid situated underneath the viral envelope, surrounded by surface projections. Source: Courtesy of CDC/Cynthia S. Goldsmith; and William Bellini, Ph.D. Used by permission.

Inactivated, or killed, microbes have the ability to induce immunity. These **inactivated vaccines** are produced by killing the pathogen with chemicals, heat, or radiation. Inactivated vaccines usually do not provide immunity that is as strong as live vaccines. Several doses over time (booster shots) may be needed to get ongoing immunity against diseases. Inactivated vaccines are used to protect against:

- Hepatitis A
- Flu (shot only)
- Polio (shot only)
- Rabies

A child receiving a flu shot. Source: Shutterstock.

Modern genetic engineering techniques have enabled creation of *chimeric viruses*, which contain genetic information from, and display biologic properties of, different parent viruses. A NIAID-developed live-attenuated chimeric vaccine consisting of a dengue virus backbone with Zika virus surface proteins is undergoing early-stage testing in humans.

Subunit Recombinant, Polysaccharide, and Conjugate Vaccines

In a difference from the entire pathogen, subunit vaccines include only the components, or **antigens**, that best stimulate the immune system. Although this design can make vaccines safer and easier to produce, it often requires the incorporation of adjuvants* to elicit a strong protective immune response because the antigens alone are not sufficient to induce adequate long-term immunity.

***Adjuvants**: substances formulated as part of a vaccine to boost immune responses and enhance the vaccine's effectiveness.

Including only the essential antigens in a vaccine can minimize side effects, as illustrated by the development of a new generation of pertussis vaccines. The first pertussis vaccines, introduced in the 1940s, contained inactivated *Bordetella pertussis* bacteria. Although effective, whole-cell pertussis vaccines frequently caused minor adverse reactions such as fever and swelling at the injection site. This caused many people to avoid the vaccine, and by the 1970s decreasing vaccination rates had brought about an increase in new infections. Research led to the development of acellular pertussis vaccines that are based on individual, purified *B. pertussis* components. These vaccines are similarly effective to whole-cell vaccines but much less likely to cause adverse reactions.

Some vaccines to prevent bacterial infections are based on the polysaccharides, or sugars, that form the outer coating of many bacteria. The first licensed vaccine against *Haemophilus influenzae* type B (Hib) was a polysaccharide vaccine. However, its usefulness was limited because it did not elicit strong immune responses in infants—the age group with the highest incidence of Hib disease. Researchers then developed a so-called conjugate vaccine in which the Hib polysaccharide is attached, or **conjugated**, to a protein antigen to offer improved protection. This formulation greatly increased the ability of the immune systems of young children to recognize the polysaccharide and develop immunity.

Other vaccines against bacterial illnesses, such as diphtheria and tetanus vaccines, aim to elicit immune responses against toxins (disease-causing proteins) secreted by the bacteria. The antigens in these so-called toxoid vaccines are chemically inactivated toxins, known as toxoids.

In the 1970s, advances in laboratory techniques ushered in the era of genetic engineering. A decade later, recombinant DNA technology—which enables DNA from two or more sources to be combined—was harnessed to develop the first recombinant protein vaccine, the hepatitis B vaccine. The vaccine antigen is a hepatitis B virus protein produced by yeast cells into which the genetic code for the viral protein has been inserted.

Vaccines to prevent human papillomavirus (HPV) infection also are based on recombinant protein antigens. In the early 1990s, scientists discovered that proteins from the outer shell of HPV can form particles that closely resemble the virus. These virus-like particles prompt an immune response similar to that elicited by the natural virus, but the virus-like particles are non-infectious because they do not contain the genetic material the virus needs to replicate inside cells.

Scientists are also developing new strategies to present protein subunit antigens to the immune system. As part of efforts to develop a universal flu vaccine, NIAID scientists designed an experimental vaccine featuring the protein *ferritin*, which can self-assemble into microscopic pieces called **nanoparticles** that display a protein antigen. An experimental nanoparticle-based influenza vaccine is being evaluated in an early-stage trial in humans.

Other relatively recent advances in laboratory techniques, such as the ability to solve atomic structures of proteins, have contributed to advances in subunit vaccine development. For example, by solving the three-dimensional structure of a protein on the RSV surface bound to an antibody, NIAID scientists identified a key area of the protein that is highly sensitive to neutralizing antibodies. They were then able to modify the RSV protein to stabilize the structural form it displays in the neutralization-sensitive site.

Antibody Binding to Virus

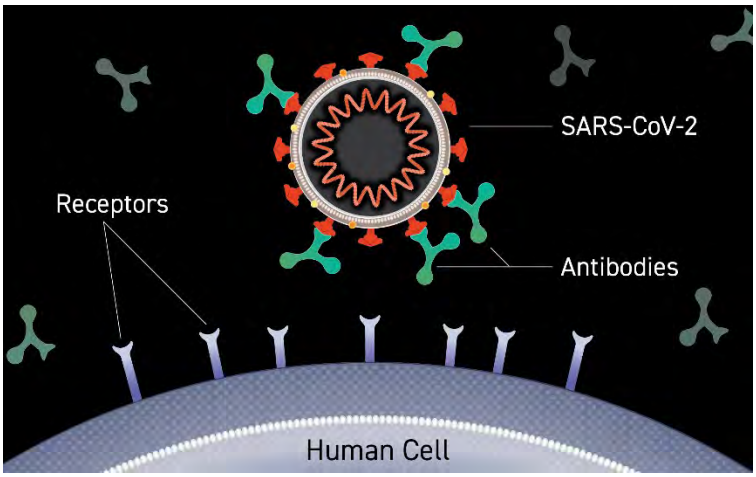


Illustration of an antibody binding to the surface of a virus, blocking entry into a person's cells.
Credit: Courtesy of Lisa Donohue, CoVPN, and COVID-19 Prevention Network. Used by permission.

While most subunit vaccines focus on a particular pathogen, scientists also are developing vaccines that could offer broad protection against various diseases. In 2017 scientists launched an early-phase clinical trial of a vaccine to prevent mosquito-borne diseases such as malaria, Zika, chikungunya, and dengue fever. The experimental vaccine, designed to trigger an immune response to mosquito saliva rather than a specific virus or parasite, contains four recombinant proteins from mosquito salivary glands.

Subunit, recombinant, polysaccharide, and conjugate vaccines are used to protect against:

- Hib (*Haemophilus influenzae* type b) disease
- Hepatitis B
- HPV (Human papillomavirus)
- Whooping cough (part of the DTaP combined vaccine)
- Pneumococcal disease
- Meningococcal disease
- Shingles

Nucleic Acid Vaccines

Another investigational approach to vaccination involves introducing genetic material encoding the antigen or antigens against which an immune response is sought. The body's own cells then use this genetic material to produce the antigens. Potential advantages of this approach include the stimulation of broad long-term immune responses, excellent vaccine stability, and relative ease of large-scale vaccine manufacture. Many such vaccines are in the research pipeline, although none are currently licensed for human use.

DNA plasmid vaccines comprise a small circular piece of DNA called a *plasmid* that carries genes encoding proteins from the pathogen of interest. The manufacturing process for DNA plasmid vaccines is well-established, allowing experimental vaccines to be quickly developed to address emerging or re-emerging infectious diseases. NIAID's Vaccine Research Center has developed candidate DNA vaccines to address several viral disease threats during outbreaks, including SARS-CoV-1 in 2003, H5N1 avian influenza in 2005, H1N1 pandemic influenza in 2009, and Zika virus in 2016. The time from selection of the viral genes to be included in the vaccine to initiation of clinical studies in humans was shortened from 20 months with SARS-CoV-1 to slightly longer than 3 months with Zika virus.

Vaccines based on messenger RNA (mRNA), an intermediary between DNA and protein, are also being developed. Recent technologic advances have largely overcome issues with the instability of mRNA and the difficulty of delivering it into cells, and some **mRNA vaccines** have demonstrated encouraging early results. For example, NIAID-supported researchers developed an experimental mRNA vaccine that protected mice and monkeys against Zika virus infection after a single dose.

RNA scientists believe mRNA vaccine can be a suitable solution in a time-pressed pandemic because the mRNAs can serve as instruction molecules to direct a person's immune system to make their own protein reserve to combat a viral invasion. In this sense, recipients use the immune cells within their own bodies as a manufacturing hub for antibodies, rather than relying on external manufacturing capabilities, which is expected to save time when compared to traditional ways of manufacturing vaccines (Chin, 2020, July 20).

mRNA vaccines have other key advantages over traditional vaccines or DNA-based vaccine. The first and foremost is safety. mRNA is noninfectious, so it will not be integrated into the recipient's genome and it can be digested by normal cellular processes. Through various chemical modifications, the longevity of these mRNAs in the body can be controlled (Chin, 2020, July 20).

In addition, the efficiency of mRNA delivery can be increased through designing and packaging the mRNA into protective carrier molecules, which would enhance stability and encourage rapid uptake by the cells. Furthermore, mRNA vaccine can not only be a rapid alternative but it is also scalable, as it relies on *in vitro* transcriptions (chemical reactions that are commonly practiced in laboratories) rather than on external factors such as the availability of hen's eggs and the need for laboratory manipulation (Chin, 2020, July 20).

Rather than delivering DNA or mRNA directly to cells, some vaccines use a harmless virus or bacterium as a vector, or carrier, to introduce genetic material into cells. Several such **recombinant vector vaccines** are approved to protect animals from infectious diseases, including rabies and distemper. Many of these veterinary vaccines are based on a technology that uses weakened versions of a poxvirus to deliver the pathogen's genetic material. Today, NIAID-supported scientists are developing and evaluating recombinant vectored vaccines to protect humans from viruses such as HIV, Zika virus, and Ebola virus.

Vaccine Adjuvants

[Unless otherwise noted, the following information is from NIAID, Vaccine Adjuvants, July 2, 2019.]

Efforts to develop safe and effective vaccines increasingly involve the use of **adjuvants**—substances formulated as part of a vaccine to boost immune responses and enhance the vaccine's effectiveness. Adjuvants help the body to produce an immune response strong enough to protect people from the disease they are being vaccinated against. Adjuvanted vaccines can cause more local reactions (such as redness, swelling, and pain at the injection site) and more systemic reactions (such as fever, chills and body aches) than non-adjuvanted vaccines.

Vaccine adjuvants accelerate, enhance, and prolong the immune responses triggered by antigens—the vaccine components that elicit pathogen-specific immune responses. Certain populations, such as people with compromised immune systems, elders, and the very young particularly benefit from vaccines with adjuvants because their immune systems may require an extra boost to provide protection. Adjuvants can also allow vaccine developers to use less antigen, which in some cases may be in short supply, or costly. Moreover, adjuvanted vaccines can elicit more durable immune responses, reducing or eliminating the need for booster vaccinations.

Aluminum-containing adjuvants, collectively termed *alum*, have been safely used in vaccines since the 1930s and are still widely used today. Aluminum is among the most common metals found in nature and is present in food and water. Scientific research has shown that the trace amounts of aluminum in vaccines are safe and not readily absorbed by the body.

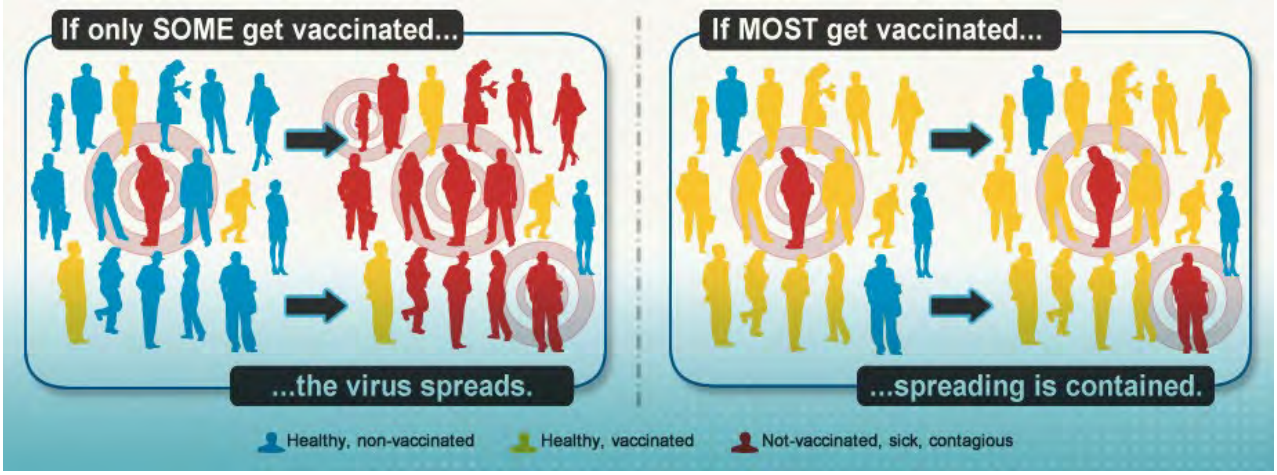
For many years, alum was the only adjuvant added to vaccines in the United States. In recent decades, however, scientific advances have increased our understanding of human immunity, and these insights have led to the identification of new adjuvants and promising adjuvant candidates. In 2009 FDA-approved Cervarix, a human papillomavirus vaccine containing a novel adjuvant called AS04. Since then, several additional vaccines containing novel adjuvants have been approved for use in the United States.

Learning more about how adjuvants work to stimulate specific immune responses is critical to the development of new and improved vaccines. Adjuvant research lays a foundation for vaccine developers to improve the protection that current vaccines offer, design vaccines for emerging infectious diseases, expedite efforts to develop vaccines to protect against diseases without preventive inoculations (e.g., HIV, tuberculosis), and develop vaccines to treat allergies, autoimmune diseases, and cancer.

What Happens If We Stop Vaccinating?

Before the middle of the last century, diseases like whooping cough, polio, measles, flu, and rubella struck hundreds of thousands of infants, children, and adults in the United States. Thousands died every year from them. As vaccines were developed and became widely used, rates of these diseases declined, until today most of them are nearly gone from our country (CDC, 2018, June 29).

- Before there was a vaccine, nearly everyone in the United States got measles, and hundreds died from it each year. Today, most doctors have never seen a case of measles.
- More than 15,000 Americans died from diphtheria in 1921, before there was a vaccine. Only 2 cases of diphtheria have been reported to CDC between 2004 and 2014.
- An epidemic of rubella (German measles) in 1964–1965 infected 12½ million Americans, killed 2,000 babies, and caused 11,000 miscarriages. Since 2012, 15 cases of rubella were reported to CDC. (CDC, 2018, June 29)



If one or two cases of disease are introduced into a community where most people are not vaccinated, outbreaks will occur. In 2013, for example, several measles outbreaks occurred around the country, including large outbreaks in New York City and Texas—mainly among groups with low vaccination rates. If vaccination rates dropped to low levels nationally, diseases could become as common as they were before vaccines. Source: CDC, 2018.

Anti-Viral, Immune-based, and Adjunctive Therapies

The COVID-19 pandemic has led to a global struggle to cope with the sheer numbers of infected people, many of whom require intensive care. The outbreak has been managed by a combination of public health measures and supportive care for those who are affected. To date, there is no specific anti–COVID-19 treatment. However, the urgency to identify supportive treatments has led to the emergence of several investigational drugs as potential candidates to improve outcomes, especially in the severe to critically ill. While many of these adjunctive drugs are being investigated in clinical trials, professional groups have attempted to clarify situations where the use of these drugs may be considered as *off-label* or *compassionate* (Xu et al., 2020).

Antiviral Drugs

Antiviral therapies inhibit viral entry, viral membrane fusion, and endocytosis.* Because viral replication may be particularly active early in the course of COVID-19, antiviral therapy may have the greatest impact before the illness progresses into the hyperinflammatory state seen in later stages of the disease. For this reason, understanding the role of antivirals in treating mild, moderate, severe, and critical illness is necessary to optimize treatment for people with COVID-19 (NIAID-RML, 2020, July 30).

*__Endocytosis__: a cellular process by which substances are brought into the cell. It is a type of active transport that moves particles, such as large molecules, parts of cells, and even whole cells, into a cell.

Remdesivir is an IV investigational treatment. It inhibits viral replication through premature termination of RNA transcription. It has demonstrated *in vitro* activity against SARS-CoV-2 (NIAID-RML, 2020, July 30).

Because remdesivir supplies are limited, the *COVID-19 Treatment Guidelines* panel recommends that remdesivir be prioritized for use in hospitalized patients with COVID-19 who require supplemental oxygen but who are not on ventilation (noninvasive or mechanical), extracorporeal membrane oxygenation (ECMO), or high-flow oxygen (NIAID-RML, 2020, July 30).

The panel recommends using remdesivir for 5 days or until hospital discharge, whichever comes first.

- If a patient who is on supplemental oxygen while receiving remdesivir progresses to requiring high-flow oxygen, noninvasive or invasive mechanical ventilation, or ECMO, the course of remdesivir should be completed.
- Because there is uncertainty regarding whether starting remdesivir confers clinical benefit in these groups of patients, the panel cannot make a recommendation either for or against starting remdesivir. (NIAID-RML, 2020, July 30)

Immune-based Therapies

Given the hyperactive inflammatory effects of SARS-CoV-2, agents that modulate the immune response are being explored as adjunctive treatments for the management of moderate to critical COVID-19. These agents include human blood–derived products and immunomodulatory therapies (NIAID-RML, 2020, July 30).

Some human blood–derived products are obtained from individuals who have recovered from SARS-CoV-2 infection (e.g., convalescent plasma, immunoglobulin products). These products are thought to have either direct antiviral properties, such as in convalescent plasma, and/or immunomodulatory effects. Additionally, neutralizing monoclonal antibodies directed against SARS-CoV-2 have been developed and are under investigation in clinical trials (NIAID-RML, 2020, July 30).

Other agents in this group include therapeutics currently approved for the treatment of other immune and/or inflammatory syndromes. These agents include corticosteroids (e.g., *gluco*corticoids), which as a class possess a broad array of mechanisms to treat systemic inflammation, and more targeted anti-inflammatory treatments such as interleukin inhibitors, interferons, kinase inhibitors, and others (NIAID-RML, 2020, July 30).

Adjunctive Therapies

Antithrombotic Therapy. Infection with SARS-CoV-2 has been associated with inflammation and a prothrombotic state, with increases in fibrin, fibrin degradation products, fibrinogen, and D-dimers. In fact, these markers have been associated with worsened clinical outcomes. Although the true incidence of these complications among those with differing severities of disease is not completely defined, there have been reports of increased incidence of thromboembolic disease associated with COVID-19 in patients in the intensive care unit.

For a summary of the use of antithrombotic therapy in patients with COVID-19, please go here.

Vitamin C. Vitamin C (ascorbic acid) is a water-soluble vitamin that is thought to have beneficial effects in patients with severe and critical illnesses. It is an antioxidant and free radical scavenger that has anti-inflammatory properties, influences cellular immunity and vascular integrity, and serves as a cofactor in the generation of endogenous catecholamines (NIAID-RML, 2020, July 30).

Because humans may require more vitamin C in states of oxidative stress, vitamin C supplementation has been evaluated in numerous disease states, including serious infections and sepsis. Because serious COVID-19 may cause sepsis and acute respiratory distress syndrome (ARDS), researchers are studying the potential role of high doses of vitamin C in ameliorating inflammation and vascular injury in patients with COVID-19. Nevertheless, insufficient data are available for the *COVID-19 Treatment Guidelines* panel to recommend either for or against the use of vitamin C for treatment of COVID-19 in noncritically ill patients (NIAID-RML, 2020, July 30).

Vitamin D. Vitamin D is critical for bone and mineral metabolism. Because the vitamin D receptor is expressed on immune cells such as B cells, T cells, and antigen-presenting cells, and because these cells can synthesize the active vitamin D metabolite, vitamin D also has the potential to modulate innate and adaptive immune responses (NIAID-RML, 2020, July 30).

Vitamin D deficiency is common in the United States, particularly among Black persons or those of Hispanic ethnicity. Vitamin D deficiency is also more common in older patients and patients with obesity and hypertension; these factors have been associated with worsened outcomes in patients with COVID-19. In observational studies, low vitamin D levels have been associated with an increased risk of community-acquired pneumonia in older adults and children. Vitamin D supplements may increase the levels of T regulatory cells in healthy individuals and patients with autoimmune diseases; vitamin D supplements may also increase T regulatory cell activity (NIAID-RML, 2020, July 30).

In a meta-analysis of randomized clinical trials, vitamin D supplementation was shown to protect against acute respiratory tract infection. However, in two randomized, double-blind, placebo-controlled clinical trials, administering high doses of vitamin D to critically ill patients with vitamin D deficiency (but not COVID-19) did not reduce the length of the hospital stay or the mortality rate when compared to placebo. High levels of vitamin D may cause hypercalcemia and nephrocalcinosis. Overall, insufficient data exist to recommend either for or against the use of vitamin D for the prevention or treatment of COVID-19 (NIAID-RML, 2020, July 30).

Zinc Supplementation. The *COVID-19 Treatment Guidelines* panel recommends against using zinc supplementation above the recommended dietary allowance for the prevention of COVID-19, except in a clinical trial.

Increased intracellular zinc concentrations impairs replication in a number of RNA viruses. Zinc has been shown to enhance cytotoxicity and induce apoptosis* when used *in vitro* with a zinc ionophore such as chloroquine. Chloroquine has also been shown to enhance intracellular zinc uptake *in vitro*. The relationship between zinc and COVID-19, including how zinc deficiency affects the severity of COVID-19 and whether zinc supplements can improve clinical outcomes, is currently under investigation (NIAID-RML, 202, July 30).

*__Apoptosis__: Apoptosis is the process of programmed cell death. It is a process that rids the body of cells that have been damaged beyond repair. Apoptosis also plays a role in preventing cancer.

Corticosteroids

Dexamethasone is recommended in patients who are mechanically ventilated and in patients who require supplemental oxygen but who are not mechanically ventilated. The new *COVID-19 Treatment Guidelines* discusses the clinical data on the use of other corticosteroids in patients with COVID-19, the potential adverse effects of corticosteroids, other considerations in use of corticosteroids, as well as providing recommendations for the use of dexamethasone in pregnant patients (NIAID-RML, 2020, July 30).

On July 30, 2020 the recommendations were updated to allow the use of alternative corticosteroids (i.e., hydrocortisone, methylprednisolone, prednisone) in situations where dexamethasone may not be available (NIAID-RML, 2020, July 30).

Chloroquine or Hydroxychloroquine

Chloroquine is an antimalarial drug that was developed in 1934. Hydroxychloroquine, an analogue of chloroquine, was developed in 1946 and is used to treat autoimmune diseases [e.g., systemic lupus erythematosus (SLE), rheumatoid arthritis]. In general, hydroxychloroquine has fewer and less severe toxicities and fewer drug–drug interactions than chloroquine (NIAID-RML, 2020 July 30).

High-dose chloroquine has been associated with more severe toxicities than lower-dose chloroquine. A comparative trial compared high-dose chloroquine and low-dose chloroquine in patients with COVID-19; in addition, all participants received azithromycin, and 89% of the participants received oseltamivir. **The study was discontinued early** when preliminary results showed higher rates of mortality and QTc prolongation in the high-dose chloroquine group (NIAID-RML, 2020 July 30).

The *COVID-19 Treatment Guidelines* recommend against the use of chloroquine or hydroxychloroquine for the treatment of COVID-19, except in a clinical trial. The panel recommends **against the use of high-dose chloroquine** for the treatment of COVID-19 (NIAID-RML, 2020, July 30).

Additional Public Health Measures

> We in the public health sector must be crystal clear in articulating exactly what we know and what we still need to know about the threat, and in helping people understand how this new risk compares to risks they willingly assume every day. With that perspective, people will be better able to understand what rational steps they can take to protect themselves.
>
> Anthony Fauci, MD
>
> Communicating About COVID-19

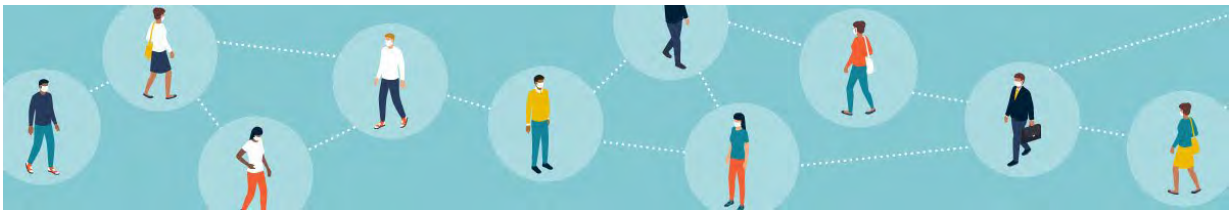
There is currently no vaccine to prevent a COVID-19 infection. The best way to prevent infection is to avoid being exposed to the virus. Everyday actions to help prevent the spread of respiratory viruses include contact tracing, testing, social distancing, facemasks, handwashing, and isolation.

Case Investigation and Contact Tracing

> In order to save lives, reduce COVID-19's burden on our healthcare system, ease strict social distancing measures, and confidently make progress toward returning to work and school, the United States must implement a robust and comprehensive system to identify all COVID-19 cases and trace all close contacts of each identified case. It is estimated that each infected person can, on average, infect 2 to 3 others. This means that if 1 person spreads the virus to 3 others, that first positive case can turn into more than 59,000 cases in 10 rounds of infections.*
>
> Johns Hopkins, 2020
>
> Bloomberg School of Public Health

*A National Plan to Enable Comprehensive COVID-19 Case Finding and Contact Tracing in the United States. Johns Hopkins Bloomberg School of Public Health.

Contact Tracing



Source: CDC.

Case investigation and contact tracing involve working with a person who has been diagnosed with an infectious disease to identify and provide support to people who may have been infected through exposure to that person. This process prevents transmission of disease by separating people who have (or may have) an infectious disease from people who do not. It is a core disease control measure that has been employed by public health agency personnel for decades (CDC, 2020, May 26). Contact tracing ensures the best possible chance of control and the longest possible time to local take-off (Kwok et al., 2019).

Contact tracing and followup control measures such as quarantine and isolation were crucially important during the SARS outbreak in 2003 and the Ebola outbreak in West Africa in 2014, as well as to the eradication of smallpox. With current advances in vaccine development technologies, the role of contact tracing and followup control measures in the initial stage of an epidemic is especially important (Kwok et al., 2019).

Contact Tracing

Contact tracing is known to be highly effective for diseases that spread slowly by close contact, and hence is used for many sexually transmitted infections.

Source: Keeling et al., 2020.

These traditional public health measures are essential safety measures to allow gradually reopening parts of our country that have been shuttered to prevent the spread of the novel coronavirus. All infected people must be identified and isolated, and the contacts of each patient must be alerted and traced and then quarantined for 14 days after their last exposure—either at home or, if necessary, on a voluntary basis in healthcare facilities or dedicated isolation facilities.

Did You Know?

Contact tracing is a core disease control activity. It has been used for decades by state and local health departments to slow or stop the spread of infectious disease.

Contact Identification, Listing, and Followup

Contact tracing consists of three basic steps: identification, listing, and followup.

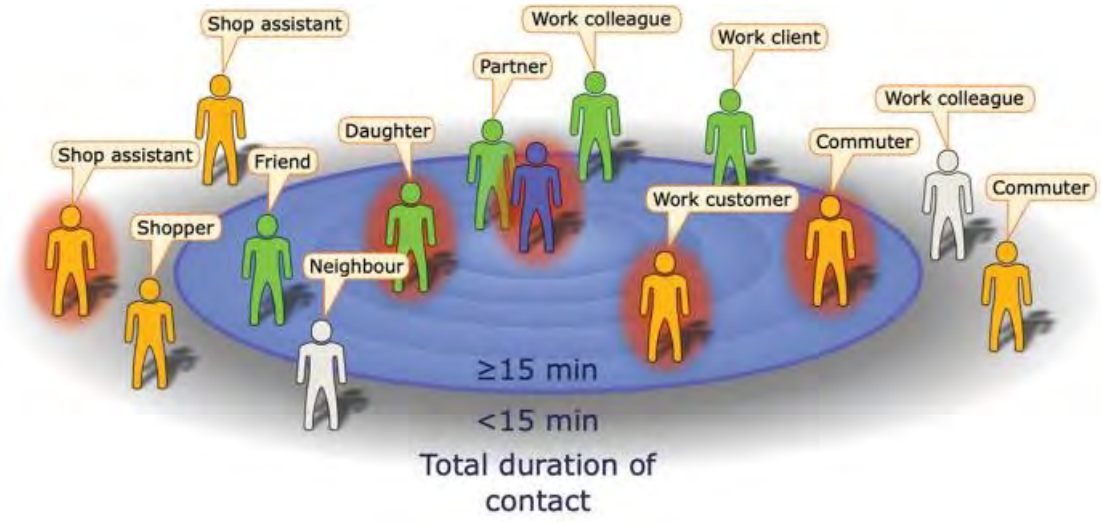
All infected people must be **identified** and isolated. A public health official then calls a confirmed or "clinically compatible case in regions of widespread ongoing transmission" and **compiles a list** of the patient's recent contacts, including family members, co-workers, healthcare providers, and friends (WHO, 2017).

Since COVID-19 can be spread before symptoms occur or when no symptoms are present, case investigation and contact tracing activities must be swift and thorough. Remote communications for the purposes of case investigation and contact tracing should be prioritized; in-person communication may be considered only after remote options have been exhausted (CDC, 2020, May 26).

Prompt identification, voluntary quarantine, and monitoring of COVID-19 contacts can effectively break the chain of disease transmission and prevent further spread of the virus in a community. While case investigation and contact tracing for COVID-19 may be new, health departments and frontline public health professionals who perform these activities have experience conducting them for tuberculosis, sexually transmitted infections, HIV, and other infectious diseases (CDC, 2020, May 26).

All contacts of the infected person are placed on a list and notified by a public health worker of their exposure to the infectious disease, what it means, and the actions that will follow. Depending on the type of contact that occurred between the infected and the exposed person, he or she may be asked to self-quarantine for 14 days and notify the health department and their doctor if any symptoms develop (WHO, 2017).

All contacts must be **followed up** to monitor their symptoms until diagnostic results show that a person is either not infected or beyond the incubation period of the virus (WHO, 2017).



Example of the encounters made during a day by an infectious index case (central figure) with contacts positioned by their total contact duration. Here, the definition of a contact is someone with whom the index case encountered for 15 min or longer (United Kingdom) or 30 min (United States). Some contacts will be identifiable (green), while others will be unidentifiale (orange). Source: Keeling, et al., 2020. Re-use permitted under CC BY.

Public Health Challenges Associated with Contact Tracing

> One of the biggest challenges is misinformation being disseminated on social media. BuzzFeed News reports that “Facebook posts and YouTube videos spreading hoaxes and lies about contact tracers have received hundreds of thousands of views.”
>
> Some of these posts compare tracers to Nazi secret police and falsely say they take people to internment camps. Others suggest they should be greeted with guns. Contact tracers report they have faced death threats.
>
> *Scientific American*, July 21, 2020

The current pandemic presents many new challenges to public health departments. Public health agencies are being asked to trace and isolate huge numbers of people in the United States during an epidemic with widespread community transmission. And they are being asked to do this without adequate funding and in the absence of a national strategic plan.

Contact tracing is a specialized skill. To be done effectively, it requires people with the training, supervision, and access to social and medical support for patients and contacts. Requisite knowledge and skills for contact tracers include:

- The ability to conduct interviews without violating confidentiality.
- Understanding of the principles of exposure, infection, infectious period, potentially infectious interactions, symptoms of disease, pre-symptomatic and asymptomatic infection.
- Excellent and sensitive interpersonal, cultural sensitivity, and interviewing skills.
- Basic skills of crisis counseling, and the ability to refer patients and contacts for further care if needed.
- Resourcefulness in locating patients and contacts who may be difficult to reach or reluctant to engage in conversation.
- Cultural competency appropriate to the local community. (CDC, 2020, April 29)

Left Source: CDC. Right Source: CDC.

It is estimated that at least 100,000 people will have to be hired to carry out contact tracing in the United States, at a cost of billions of dollars. The new contact tracers will have to be trained and supervised to ensure the quality of their work. Because of the huge number of people needed to carry out contact tracing, it is important to use technology as a “force multiplier” to enable each tracer to be more efficient, connect with a greater number of contacts, and conduct tracing without being exposed to infection (Watson et al., 2020).

Time is of the essence. Identifying contacts and ensuring they do not interact with others is critical to protect communities from further spread. If communities are unable to isolate patients effectively and ensure contacts can separate themselves from others, rapid community spread of COVID-19 is likely to increase to the point that strict mitigation strategies will again be needed to contain the virus (CDC, 2020, April 29).

Contact investigation of patients with COVID-19 potentially exposed at work and patients in healthcare facilities, congregate living settings, or housing with many people is complex. Healthcare professionals recommend appropriate engagement with infection control and occupational health programs. Priority settings include:

- Healthcare facilities, including long-term care facilities
- Group homes/boarding
- Homeless shelters
- Federal, state and local correctional facilities
- Crowded, multigenerational housing

In addition to healthcare workers, it is important to assess interactions between residents and all staff, including but not limited to activity coordinators, food service staff, and sanitation management. Transitional case management plans should be put in place for patients in isolation, and contacts who are separated for monitoring. Management plans should also be created for transitioning from one setting to another—such as transitions from hospitals to acute or long-term care facilities or home isolation, or from prison and jail to parole and probation (CDC, 2020, April 29).

Social Distancing

[Material from this section is taken from Matrajt & Leung, 2020.]

Social distancing is one of the most important tools used to reduce the R_0 of a disease. The term **flatten the curve**, which originated from CDC, has been used widely to describe the effects of social distancing interventions.

Research shows that the timing of social distancing interventions can affect the epidemic curve. Interventions put in place and lifted early only delay the epidemic and do not flatten the epidemic curve. Where an intervention was put in place later, we noted a flattening of the epidemic curve.

Left: Social distancing. Source: CDC. Right: *Distanciamiento social*. Source: CDC.

The effectiveness of the intervention depends on the ratio of susceptible, infected, and recovered people in the population at the beginning of the intervention. An accurate estimate of the number of current and recovered cases is crucial for evaluating possible interventions. Expanding testing capabilities in all affected countries is critical to slowing and controlling the pandemic.

Even in the more optimistic scenario in which all age groups reduce their contact rates by >85%, the epidemic will rebound once the social distancing interventions are lifted. Social distancing interventions can give communities vital time to strengthen healthcare systems and restock medical supplies, but these interventions, if lifted too quickly, will fail to mitigate the current pandemic.

Did You Know. . .

> Even in the more optimistic scenario in which all age groups reduce their contact rates by >85%, the epidemic will rebound once the social distancing interventions are lifted.

Numerous studies have suggested that extended periods of social distancing will be needed to control transmission. However, sustaining social distancing interventions over several months might not be feasible economically and socially. Therefore, a combination of social distancing interventions, testing, isolation, and contact tracing of new cases is needed to suppress transmission of SARS-CoV-2. In addition, these interventions must happen in synchrony around the world because a new imported case could spark a new outbreak in any given region (Matrajt & Leung, 2020).

N-95 Respirator Masks, Surgical Masks, and Facemasks

Source: CDC.

Wearing a mask will help protect people around you, including those at higher risk of severe illness from COVID-19 and workers who frequently come into close contact with other people. Masks are most likely to reduce the spread of COVID-19 when they are widely used by people in public settings.

Early Twentieth Century

During the early twentieth century, various types of cloth masks (made of cotton, gauze, and other fabrics) were used in U.S. hospitals. Healthcare workers who used masks made of 2 to 3 layers of gauze experienced low rates of respiratory infections. Cloth masks were also used to protect healthcare workers from diphtheria and scarlet fever (Chughtai et al., 2020).

Nursing in the 1918 Flu Pandemic

A nurse wears a cloth mask while treating a patient at Walter Reed Hospital in Washington, DC during the 1918-1919 flu pandemic. Source: Harris & Ewing Photographers / Library of Congress / Public Domain.

During the 1918 Spanish influenza pandemic, masks made of various layers of cotton were widely used by healthcare workers and the public. Gauze masks were used during the second Manchurian plague epidemic in 1920–1921 and a plague epidemic in Los Angeles in 1924; infection rates among healthcare workers who wore masks were low. During the 1930s and 1940s, gauze and cloth masks were also used by healthcare workers to protect themselves from tuberculosis (Chughtai et al., 2020).

Red Cross Volunteers Making Masks (1918)

Red Cross volunteers making cloth masks during the 1918 flu pandemic. Source: CDC Public Health Matters Blog / Public Domain.

Mid Twentieth Century

In the middle of the twentieth century, after disposable medical masks had been developed, use of cloth masks decreased; however, cloth mask use is still widespread in many countries. During the outbreak of SARS in China, cotton masks were widely used by healthcare workers and the public, and observational studies found them to be effective (Chughtai et al., 2020).

2020

The primary transmission routes for COVID-19 are thought to be inhalation of respiratory droplets and close contact. Recommendations to wear masks to protect the wearer from droplet infections assumed that droplets travel short distances only, generally 1–2 m. However, of 10 studies of horizontal droplet distance, 8 showed that droplets travel >2 m, and in some instances, ~8 m. A recent study also showed that SARS-CoV-2 may be transmitted up to 4 m. Therefore, ideally all frontline healthcare workers should use a respirator; however, demand for personal protective equipment has increased during the COVID-19 pandemic, and respirator shortages in previous pandemics were also reported (Chughtai et al., 2020).

An N-95 Respirator Mask

An N-95 respirator mask, if properly fitted, has a tight-fitting face seal, which reduces wearer's exposure to particles including small particle aerosols and large droplets.

Source: FDA.

If respirator masks are unavailable, healthcare workers could use a surgical mask but may be at increased risk if they do so. CDC and the European Centre for Disease Prevention and Control initially recommended that all healthcare workers use respirators; however, because of shortages, they later recommended respirator use for high-risk situations only. Some countries also recommend sterilizing and decontaminating respirators for reuse; however, limited evidence supports these practices, and they may not be feasible in low- and middle-income countries (Chughtai et al., 2020).

Surgical Mask

A surgical mask is a loose-fitting, fluid-resistant, disposable device that creates a physical barrier between the mouth and nose of the wearer and others as well as potential contaminants in the immediate environment. They do not provide full protection from inhalation of airborne pathogens, such as viruses. These are often referred to as *face masks*, although not all face masks are regulated as surgical masks.

Source: FDA.

Do's and Don'ts of mask wearing. Source: CDC.

The filtration, effectiveness, fit, and performance of cloth masks are inferior to those of surgical masks and respirators. Cloth mask use should not be mandated for healthcare workers, who should be provided proper respiratory protection. Cloth masks are a more suitable option for community use when surgical masks are unavailable. Protection provided by cloth masks may be improved by selecting appropriate material, increasing the number of mask layers, and using those with a design that provides filtration and fit. Cloth masks should be washed daily and after high-exposure use by using soap and water or other appropriate methods (Chughtai et al., 2020).

Because COVID-19 likely spreads via aerosol mists in addition to respiratory droplets, proper ventilation needs to be added to our armamentarium of distancing, masks, and hand hygiene.

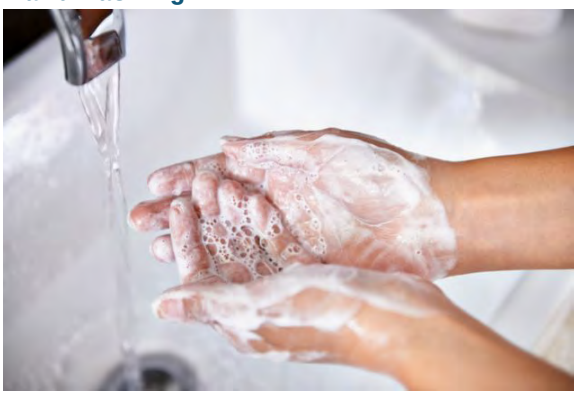
The Importance of Hand Hygiene

Historical Perspective

[Unless otherwise noted, the material in the following section is taken from CDC *Guideline for Hand Hygiene in Health-Care Settings* (2002).]

For generations, handwashing with soap and water has been considered a measure of personal hygiene. The concept of cleansing hands with an antiseptic agent probably emerged in the early nineteenth century. As early as 1822, a French pharmacist demonstrated that solutions containing chlorides of lime or soda could eradicate the foul odors associated with human corpses and that such solutions could be used as disinfectants and antiseptics. In a paper published in 1825, this pharmacist stated that physicians and other persons attending patients with contagious diseases would benefit from moistening their hands with a liquid chloride solution.

Handwashing



Source: CDC.

In 1846 Ignaz Semmelweis observed that women whose babies were delivered by students and physicians in the First Clinic at the General Hospital of Vienna consistently had a higher mortality rate than those whose babies were delivered by midwives in the Second Clinic. He noted that physicians who went directly from the autopsy suite to the obstetrics ward had a disagreeable odor on their hands despite washing them with soap and water upon entering the obstetrics clinic. He postulated that the puerperal fever (“childbed fever”) that affected so many parturient women was caused by "cadaverous particles" transmitted from the autopsy suite to the obstetrics ward via the hands of students and physicians.

Perhaps because of the known deodorizing effect of chlorine compounds, starting in May 1847 Semmelweis insisted that students and physicians clean their hands with a chlorine solution between each patient in the clinic. The maternal mortality rate in the First Clinic subsequently dropped dramatically and remained low for years. This intervention by Semmelweis represents the first evidence indicating that cleansing heavily contaminated hands with an antiseptic agent between patient contacts may reduce healthcare-associated transmission of contagious diseases more effectively than handwashing with plain soap and water.

A few years before (1843), Oliver Wendell Holmes had concluded that puerperal fever was spread by the hands of health personnel. Although he described measures that could be taken to limit its spread, his recommendations had little impact on obstetric practices at the time. However, as a result of the seminal studies by Semmelweis and Holmes, handwashing gradually became accepted as one of the most important measures for preventing transmission of pathogens in healthcare facilities.

During the Crimean War (1853–1856), Florence Nightingale initiated handwashing in army hospitals and other facilities behind the lines, and she later published her findings in a book that established nursing as a profession (Nightingale, 1860).

In 1975 and 1985, formal written guidelines on handwashing practices in hospitals were published by CDC. These guidelines recommended handwashing with non-antimicrobial soap between the majority of patient contacts and washing with antimicrobial soap before and after performing invasive procedures or caring for patients at high risk. Use of waterless antiseptic agents (e.g., alcohol-based solutions) was recommended only in situations where sinks were not available.

In 1988 and 1995, guidelines for handwashing and hand antisepsis were published by the Association for Professionals in Infection Control (APIC). Recommended indications for handwashing were similar to those listed in the CDC guidelines. The 1995 APIC guideline included more detailed discussion of alcohol-based hand rubs and supported their use in more clinical settings than had been recommended in earlier guidelines.

In 1995 and 1996, the Healthcare Infection Control Practices Advisory Committee (HICPAC) recommended that either antimicrobial soap or a waterless antiseptic agent be used for cleansing hands upon leaving the rooms of patients with multidrug-resistant pathogens (e.g., vancomycin-resistant enterococci [VRE] and methicillin-resistant Staphylococcus aureus [MRSA]). These guidelines also provided recommendations for handwashing and hand antisepsis in other clinical settings, including routine patient care. Although the APIC and HICPAC guidelines have been adopted by the majority of hospitals, adherence of healthcare workers to recommended handwashing practices had remained problematic until the onset of COVID-19.

Normal Bacterial Skin Flora

To understand the objectives of different approaches to hand cleansing, a knowledge of normal bacterial skin flora is essential. Normal human skin is colonized with bacteria; different areas of the body have varied total aerobic bacterial counts. Total bacterial counts on the hands of medical personnel have ranged from 3.9 x 104 to 4.6 x 106 colony-forming units.

Traditionally, bacteria recovered from the hands are divided into two categories: transient and resident. *Transient flora*, which colonize the superficial layers of the skin, are more amenable to removal by routine handwashing. Transient flora are the organisms most frequently associated with healthcare-associated infections. *Resident flora*, which are attached to deeper layers of the skin, are more resistant to removal. In addition, resident flora are less likely to be associated with such infections.

The hands of healthcare workers may become *persistently* colonized with pathogenic flora (e.g., S. aureus), gram-negative bacilli, or yeast. Investigators have documented that, although the number of transient and resident flora varies considerably from person to person, it is often relatively constant for any specific person.

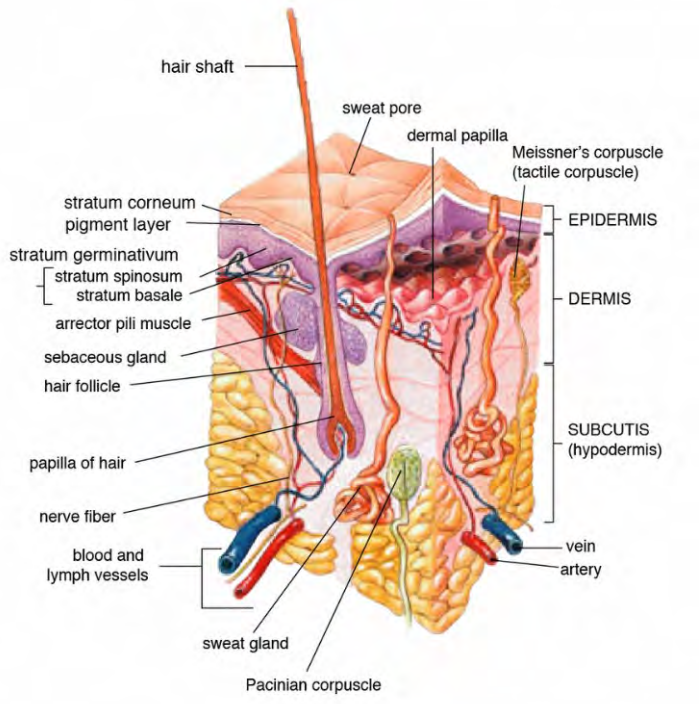
Skin Function

The primary function of the skin is to reduce water loss, provide protection against abrasive action and microorganisms, and act as a permeability barrier. The basic structure of skin includes, from outer- to inner-most layers,

- Stratum corneum
- Viable epidermis
- Dermis
- Hypodermis

The *stratum corneum* or horny layer is the most superficial layer of the skin and is 10- to 20-µm thick. The *viable epidermis* is 50- to 100-µm thick. The *dermis* is 1- to 2-mm thick, and the innermost layer, the *hypodermis* is 1- to 2-mm thick. The barrier to percutaneous absorption lies within the stratum corneum, which is the thinnest and smallest compartment of the skin.

Directly under the stratum corneum is a stratified epidermis, which is composed primarily of 10 to 20 layers of keratinizing epithelial cells that are responsible for the synthesis of the stratum corneum. This layer also contains melanocytes involved in skin pigmentation; Langerhans cells, which are important for antigen presentation and immune responses; and Merkel cells, whose precise role in sensory reception has yet to be fully understood. The viable epidermis does not contain a vascular network, and the keratinocytes obtain their nutrients from below by passive diffusion through the interstitial fluid.



Anatomy of the Human Skin

Source: US-gov/Public domain.

The skin is a dynamic structure. The current understanding of the formation of the stratum corneum has come from studies of the epidermal responses to disruption of the skin barrier. Skin irritation caused by chemicals, removal of tape, and other physical disruptions lead to a decrease in skin–barrier function. Detergents and acetones remove glycerol-lipids and sterols from the skin, which are necessary for barrier function. It takes time for normal barrier function to return: 50% to 60% of barrier recovery typically occurs within 6 hours, but complete normalization of barrier function requires 5 to 6 days.

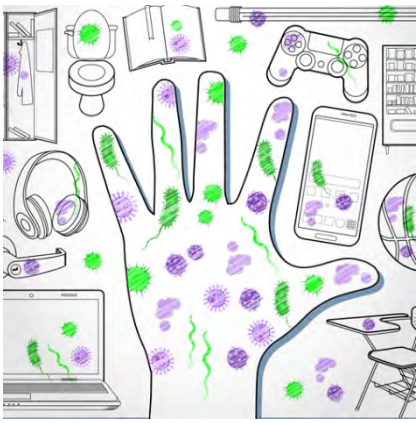
Transmission of Pathogens on Hands

Transmission of healthcare-associated pathogens from one patient to another via the hands of healthcare workers requires the following sequence of events:

1. Organisms present on the patient's skin, or that have been shed onto inanimate objects in close proximity to the patient, must be transferred to the hands of healthcare workers. The organisms must be capable of surviving for at least several minutes on the hands of personnel.
2. Handwashing or hand antisepsis by the worker must be inadequate or omitted entirely, or the agent used for hand hygiene must be inappropriate.
3. The contaminated hands of the caregiver must come in direct contact with another patient, or with an inanimate object that will come into direct contact with the patient.

Healthcare-associated pathogens can be recovered not only from infected or draining wounds but also from frequently colonized areas of normal, intact patient skin. The perineal or inguinal areas are usually most heavily colonized, but the axillae, trunk, and upper extremities (including the hands) are frequently colonized.

Colonization from the Hand



Germs are all around you. Source: CDC.

The number of organisms present on intact areas of the skin of certain patients can vary. Persons with diabetes, patients undergoing dialysis for chronic renal failure, and those with chronic dermatitis are likely to have areas of intact skin that are colonized with *S. aureus*. Patient gowns, bed linen, bedside furniture, and other objects in the patient's immediate environment can easily become contaminated with patient flora. Such contamination is particularly likely to be caused by staphylococci or enterococci, which are resistant to desiccation (drying).

Data are limited regarding the types of patient-care activities that result in transmission of patient flora to the hands of personnel. Nurses can contaminate their hands during "clean" activities (e.g., lifting a patient; taking a patient's pulse, blood pressure, or oral temperature; or touching a patient's hand, shoulder, or groin). In one study, the hands of nurses who touched the groins of patients heavily colonized with *P. mirabilis* were cultured and the organism was recovered from the nurses' hands.

Other researchers studied the contamination of healthcare workers' hands during activities that involved wound care, IV catheter care, respiratory-tract care, and the handling of patient secretions. Data from this study indicated that direct patient contact and respiratory-tract care were most likely to contaminate the fingers of caregivers. Gram-negative bacilli accounted for 15% of isolates and *S. aureus* for 11%. Duration of patient-care activity was strongly associated with the intensity of bacterial contamination.

Healthcare workers can contaminate their hands with gram-negative bacilli, *S. aureus*, enterococci, or *C. difficile* by performing "clean procedures" or touching intact areas of the skin of hospitalized patients. Personnel caring for infants with respiratory syncytial virus (RSV) infections have acquired RSV by performing certain activities (e.g., feeding infants, changing diapers, and playing with infants). Personnel who had contact only with surfaces contaminated with the infants' secretions also acquired RSV by contaminating their hands with RSV and inoculating their oral or conjunctival mucosa. Other studies have documented that healthcare workers can contaminate their hands (or gloves) merely by touching inanimate objects in patient rooms.

Preparations Used for Hand Hygiene

Plain (Non-antimicrobial) Soap

Soaps are detergent-based products that possess a cleansing action. They are available in various forms including bar, tissue, leaflet, and liquid preparations. Their cleansing activity is due to their detergent properties, which removes of dirt, soil, and various organic substances from the hands. Plain soap refers to detergents that do not contain antimicrobial agents or contain low concentrations of antimicrobial agents that are effective solely as preservatives.

Plain soaps have minimal, if any, **antimicrobial activity** (destroys or inhibits the growth of microorganisms) however, handwashing with plain soap can remove loose transient flora. In several studies, handwashing with plain soap failed to remove pathogens from the hands of hospital personnel. Handwashing with plain soap can result in paradoxical increases in bacterial counts on the skin.

Non-antimicrobial soaps may be associated with considerable skin irritation and dryness, although adding emollients to soap preparations may reduce their propensity to cause irritation. Plain soaps can become contaminated, which may lead to colonization of hands with gram-negative bacilli.

Alcohols

The majority of alcohol-based hand antiseptics contain either isopropanol, ethanol,* n-propanol, or a combination of two of these products. The majority of studies of alcohols have evaluated individual alcohols in varying concentrations. Other studies have focused on combinations of two alcohols or alcohol solutions containing limited amounts of hexachlorophene, quaternary ammonium compounds, povidone-iodine, triclosan, or chlorhexidine gluconate.

*But, on July 5, 2020 the CDC issued a warning against any and all hand sanitizers that include *methanol*, which it stated could even cause blindness or death (CDC, 2020, July5).

The antimicrobial activity of alcohols can be attributed to their ability to denature proteins. Alcohol solutions containing 60% to 95% alcohol are most effective, and higher concentrations are less potent because proteins are not denatured easily in the absence of water.

Alcohol-based Sanitizer

Use an alcohol-based hand sanitizer that contains at least 60% alcohol if soap and water are not available. Source: CDC.

Alcohols have excellent *in vitro* (i.e., laboratory) germicidal activity against gram-positive and gram-negative vegetative bacteria, including multidrug-resistant pathogens (e.g., MRSA, VRE), *Mycobacterium tuberculosis*, and various fungi. Certain viruses—such as herpes simplex virus, HIV, influenza virus, respiratory syncytial virus, and vaccinia virus—are susceptible to alcohols when tested *in vitro*. Hepatitis B virus is somewhat less susceptible but is killed by 60% to 70% alcohol; hepatitis C virus also is likely killed by this percentage of alcohol. Despite their effectiveness against these organisms, alcohols have very poor activity against bacterial spores, protozoan oocysts, and certain nonenveloped (nonlipophilic) viruses.

Numerous studies have documented the *in vivo* antimicrobial activity of alcohols. Alcohols effectively reduce bacterial counts on the hands. Alcohols are rapidly germicidal when applied to the skin, but they have no appreciable **persistent activity** (prolonged or extended antimicrobial activity that prevents or inhibits the proliferation or survival of microorganisms after application of the product). However, regrowth of bacteria on the skin occurs slowly after use of alcohol-based hand antiseptics, presumably because of the sub-lethal effect alcohols have on some of the skin bacteria. Addition of chlorhexidine, quaternary ammonium compounds, octenidine, or triclosan to alcohol-based solutions can result in persistent activity.

Alcohols, when used in concentrations present in alcohol-based hand rubs, also have *in vivo* activity against several non-enveloped viruses (e.g., rotavirus, adenovirus, and rhinovirus, hepatitis A, poliovirius).

Enveloped Virus

COVID-19 is an *enveloped* virus, meaning it is easier to kill than small or large non-enveloped viruses. Similar to other coronaviruses, it is sensitive to ultraviolet rays and heat.

Source: Cascella et al., 2020.

The inactivation of non-enveloped viruses is influenced by temperature, disinfectant-virus volume ratio, and protein load. Ethanol has greater activity against viruses than isopropanol. Further *in vitro* and *in vivo* studies of both alcohol-based formulations and antimicrobial soaps are warranted to establish the minimal level of viricidal activity that is required to interrupt direct contact transmission of viruses in healthcare settings.

Alcohols are not appropriate for use when hands are visibly dirty or contaminated with proteinaceous materials. However, when relatively small amounts of proteinaceous material (e.g., blood) are present, ethanol and isopropanol may reduce viable bacterial counts on hands more than plain soap or antimicrobial soap.

Alcohol can prevent the transfer of healthcare-associated pathogens. In one study, gram-negative bacilli were transferred from a colonized patient's skin to a piece of catheter material via the hands of nurses in only 17% of experiments after antiseptic hand rub with an alcohol-based hand rinse. In contrast, transfer of the organisms occurred in 92% of experiments after handwashing with plain soap and water. This experimental model indicates that when the hands of healthcare workers are heavily contaminated, an antiseptic hand rub using an alcohol-based rinse can prevent pathogen transmission more effectively than can handwashing with plain soap and water.

Alcohol-based products are more effective for standard handwashing or hand antisepsis than soap or antimicrobial soaps. In all but two of the trials that compared alcohol-based solutions with antimicrobial soaps or detergents, alcohol reduced bacterial counts on hands more than washing hands with soaps or detergents containing hexachlorophene, povidone-iodine, 4% chlorhexidine, or triclosan. In studies examining antimicrobial-resistant organisms, alcohol-based products reduced the number of multidrug-resistant pathogens recovered from the hands of healthcare workers more effectively than did handwashing with soap and water.

Alcohols are effective for preoperative cleaning of the hands of surgical personnel. In multiple studies, bacterial counts on the hands were determined immediately after using the product and again 1 to 3 hours later; the delayed testing was performed to determine if regrowth of bacteria on the hands is inhibited during operative procedures. Alcohol-based solutions were more effective than washing hands with plain soap in all studies, and they reduced bacterial counts on the hands more than antimicrobial soaps or detergents in the majority of experiments. In addition, the majority of alcohol-based preparations were more effective than povidone-iodine or chlorhexidine.

The efficacy of alcohol-based hand-hygiene products is affected by several factors, including the type of alcohol used, concentration of alcohol, contact time, volume of alcohol used, and whether the hands are wet when the alcohol is applied. Applying small volumes (i.e., 0.2–0.5 mL) of alcohol to the hands is not more effective than washing hands with plain soap and water. One study documented that 1 mL of alcohol was substantially less effective than 3 mL. The ideal volume of product to apply to the hands is not known and may vary for different formulations. However, if hands feel dry after rubbing hands together for 10to 15 seconds, an insufficient volume of product likely was applied. Because alcohol-impregnated towelettes contain a limited amount of alcohol, their effectiveness is comparable to that of soap and water.

Alcohol-based hand rubs intended for use in hospitals are available as low-viscosity rinses, gels, and foams. Limited data are available regarding the relative efficacy of various formulations. One field trial demonstrated that an ethanol gel was slightly more effective than a comparable ethanol solution at reducing bacterial counts on the hands of healthcare workers. However, a more recent study indicated that rinses reduced bacterial counts on the hands more than the gels tested. Further studies are warranted to determine the relative efficacy of alcohol-based rinses and gels in reducing transmission of healthcare-associated pathogens.

Frequent use of alcohol-based formulations for hand antisepsis can cause drying of the skin unless emollients, humectants, or other skin-conditioning agents are added to the formulations. The drying effect of alcohol can be reduced or eliminated by adding 1% to 3% glycerol or other skin-conditioning agents. Moreover, in several recent prospective trials, alcohol-based rinses or gels containing emollients caused substantially less skin irritation and dryness than the soaps or antimicrobial detergents tested. These clinical studies used both subjective and objective methods for assessing skin irritation and dryness. Further studies are warranted to establish whether products with different formulations yield similar results.

Even well-tolerated alcohol hand rubs containing emollients may cause a transient stinging sensation at the site of any broken skin. Alcohol-based hand-rub preparations with strong fragrances may be poorly tolerated by healthcare workers with respiratory allergies. Allergic contact dermatitis or contact urticaria syndrome caused by hypersensitivity to alcohol or to additives present in alcohol hand rubs occurs only rarely.

Alcohols are flammable. The flash point of alcohol-based hand rubs ranges from 21ºC to 24ºC, depending on the type and concentration of alcohol present. As a result, alcohol-based hand rubs should be stored away from high temperatures or flames in accordance with National Fire Protection Agency recommendations. In Europe, where alcohol-based hand rubs have been used extensively for years, the incidence of fires associated with such products has been low.

One recent U.S. report described a flash fire that occurred as a result of an unusual series of events, which included an healthcare worker applying an alcohol gel to her hands, immediately removing a polyester isolation gown, and then touching a metal door before the alcohol had evaporated. Removing the polyester gown created a substantial amount of static electricity that generated an audible static spark when the healthcare worker touched the metal door, igniting the unevaporated alcohol on her hands. This incident emphasizes the necessity to rub hands together after application of alcohol-based products until all the alcohol has evaporated.

Because alcohols are volatile, containers should be designed to minimize evaporation. Contamination of alcohol-based solutions has seldom been reported. One report documented a cluster of pseudo-infections caused by contamination of ethyl alcohol by *Bacillus cereus* spores.

Chlorhexidine

Chlorhexidine gluconate was developed in England in the early 1950s and was introduced into the United States in the 1970s. Chlorhexidine base is only minimally soluble in water, but the digluconate form is water-soluble. The antimicrobial activity of chlorhexidine is likely attributable to attachment to, and subsequent disruption of, cytoplasmic membranes, resulting in precipitation of cellular contents. Chlorhexidine's immediate antimicrobial activity occurs more slowly than that of alcohols.

Chlorhexidine has good activity against gram-positive bacteria, somewhat less activity against gram-negative bacteria and fungi, and only minimal activity against tubercle bacilli. Chlorhexidine is not sporicidal. It has *in vitro* activity against enveloped viruses (e.g., herpes simplex virus, HIV, cytomegalovirus, influenza, RSV) but substantially less activity against nonenveloped viruses (e.g., rotavirus, adenovirus, enteroviruses [polio]).

The antimicrobial activity of chlorhexidine is only minimally affected by the presence of organic material, including blood. Chlorhexidine gluconate has been incorporated into a number of hand-hygiene preparations. Aqueous or detergent formulations containing 0.5% or 0.75% chlorhexidine are more effective than plain soap, but they are less effective than antiseptic detergent preparations containing 4% or even 2% chlorhexidine gluconate.

Chlorhexidine has substantial residual activity. Addition of low concentrations of chlorhexidine to alcohol-based preparations results in greater residual activity than alcohol alone. When used as recommended, chlorhexidine has a good safety record. Minimal, if any, absorption of the compound occurs through the skin. Care must be taken to avoid contact with the eyes when using preparations with >1% chlorhexidine, because the agent can cause conjunctivitis and severe corneal damage. Ototoxicity precludes its use in surgery involving the inner or middle ear. **Direct contact with brain tissue and the meninges should be avoided.**

The frequency of skin irritation is concentration-dependent, with products containing 4% most likely to cause dermatitis when used frequently for antiseptic handwashing; allergic reactions to chlorhexidine gluconate are uncommon. Occasional outbreaks of nosocomial infections have been traced to contaminated solutions of chlorhexidine.

The U.S. Food and Drug Administration (FDA) is warning that rare but serious allergic reactions have been reported with the widely used skin antiseptic products containing chlorhexidine gluconate. Although rare, the number of reports of serious allergic reactions to these products has increased over the last several years. As a result, the FDA is requesting the manufacturers of over-the-counter antiseptic products containing chlorhexidine gluconate to add a warning about this risk to the Drug Facts labels. Prescription chlorhexidine gluconate mouthwashes and oral chips used for gum disease already contain a warning about the possibility of serious allergic reactions in their labels (FDA, 2017).

Chloroxylenol

Chloroxylenol, also known as parachlorometaxylenol (PCMX), is a compound that has been used as a preservative in cosmetics and other products and as an active agent in antimicrobial soaps. It was developed in Europe in the late 1920s and has been used in the United States since the 1950s.

The antimicrobial activity of PCMX likely is attributable to inactivation of bacterial enzymes and alteration of bacterial cell walls. It has good *in vitro* activity against gram-positive organisms and fair activity against gram-negative bacteria, mycobacteria (leprosy, TB), and certain viruses. PCMX is less active against *P. aeruginosa*, but addition of ethylene-diaminetetraacetic acid (EDTA) increases its activity against *Pseudomonas spp*. and other pathogens.

A limited number of articles focusing on the efficacy of PCMX-containing preparations intended for use by healthcare workers have been published in the last 25 years, and the results of studies have sometimes been contradictory. The disparities among published studies may be associated with the various concentrations of PCMX included in the preparations evaluated and with other aspects of the formulations tested, including the presence or absence of EDTA.

PCMX is not as rapidly active as chlorhexidine gluconate or iodophors, and its residual activity is less pronounced than that observed with chlorhexidine gluconate. In 1994 FDA TFM tentatively classified PCMX as a Category IIISE active agent (i.e., insufficient data are available to classify this agent as safe and effective).

The antimicrobial activity of PCMX is minimally affected by the presence of organic matter, but it is neutralized by nonionic surfactants. PCMX, which is absorbed through the skin, is usually well-tolerated, and allergic reactions associated with its use are uncommon. PCMX is available in concentrations of 0.3% to 3.75%. In-use contamination of a PCMX-containing preparation has been reported.

Iodine and Iodophors

Iodine has been recognized as an effective antiseptic since the 1800s. However, because iodine discolors skin and often causes irritation, iodophors have largely replaced iodine as the active ingredient in antiseptics.

Iodine molecules rapidly penetrate the cell wall of microorganisms and inactivate cells by forming complexes with amino acids and unsaturated fatty acids, resulting in impaired protein synthesis and alteration of cell membranes. Iodophors are composed of elemental iodine, iodide or triiodide, and a polymer carrier (the complexing agent) of high molecular weight. The amount of molecular iodine present (so-called free iodine) determines the level of antimicrobial activity of iodophors. "Available" iodine refers to the total amount of iodine that can be titrated with sodium thiosulfate. Typical 10% povidone-iodine formulations contain 1% available iodine and yield free iodine concentrations of 1 ppm.

Combining iodine with various polymers increases the solubility of iodine, promotes its sustained release, and reduces skin irritation. The most common polymers incorporated into iodophors are polyvinyl pyrrolidone (i.e., povidone) and ethoxylated nonionic detergents (i.e., poloxamers). The antimicrobial activity of iodophors also can be affected by pH, temperature, exposure time, concentration of total available iodine, and the amount and type of organic and inorganic compounds present (e.g., alcohols, detergents).

Iodine and iodophors have bactericidal activity against gram-positive, gram-negative, and certain spore-forming bacteria (e.g., clostridia and *Bacillus spp.*) and are active against mycobacteria, viruses, and fungi. However, in concentrations used in antiseptics, iodophors are not usually sporicidal. *In vivo* studies have demonstrated that iodophors reduce the number of viable organisms that are recovered from the hands of personnel. Povidone-iodine 5%-10% has been tentatively classified by FDA TFM as a Category I agent (i.e., a safe and effective agent for use as an antiseptic handwash and a healthcare worker handwash).

The extent to which iodophors exhibit persistent antimicrobial activity after they have been washed off the skin is unclear. In one study, persistent activity was noted for 6 hours; however, several other studies demonstrated persistent activity for only 30-60 minutes after washing hands with an iodophor. In studies in which bacterial counts were obtained after gloves were worn for 1-4 hours after washing, iodophors have demonstrated poor persistent activity. The *in vivo* antimicrobial activity of iodophors is substantially reduced in the presence of organic substances (e.g., blood or sputum).

The majority of iodophor preparations used for hand hygiene contain 7.5% to 10% povidone-iodine. Formulations with lower concentrations also have good antimicrobial activity because dilution can increase free iodine concentrations. However, as the amount of free iodine increases, the degree of skin irritation also may increase. Iodophors cause less skin irritation and fewer allergic reactions than iodine, but more irritant contact dermatitis than other antiseptics commonly used for hand hygiene. Occasionally, iodophor antiseptics have become contaminated with gram-negative bacilli as a result of poor manufacturing processes and have caused outbreaks or pseudo-outbreaks of infection.

Quaternary Ammonium Compounds

Of this large group of compounds, alkyl benzalkonium chlorides are the most widely used as antiseptics. Other compounds that have been used as antiseptics include benzethonium chloride, cetrimide, and cetylpyridium chloride. The antimicrobial activity of these compounds was first studied in the early 1900s, and a quaternary ammonium compound for preoperative cleaning of surgeons' hands was used as early as 1935. The antimicrobial activity of this group of compounds likely is attributable to adsorption to the cytoplasmic membrane, with subsequent leakage of low molecular weight cytoplasmic constituents.

Quaternary ammonium compounds are primarily bacteriostatic and fungistatic, although they are microbicidal against certain organisms at high concentrations; they are more active against gram-positive than gram-negative bacteria. Quaternary ammonium compounds have relatively weak activity against mycobacteria and fungi and have greater activity against lipophilic viruses. Their antimicrobial activity is adversely affected by the presence of organic material, and they are not compatible with anionic detergents.

Quaternary ammonium compounds are usually well tolerated. However, because of weak activity against gram-negative bacteria, benzalkonium chloride is prone to contamination by these organisms. Several outbreaks of infection or pseudo-infection have been traced to quaternary ammonium compounds contaminated with gram-negative bacilli. For this reason, in the United States, these compounds have been seldom used for hand antisepsis during the last 15 to 20 years. However, newer handwashing products containing benzalkonium chloride or benzethonium chloride have recently been introduced for use by healthcare workers.

A study of surgical ICU personnel found that cleaning hands with antimicrobial wipes containing a quaternary ammonium compound was about as effective as using plain soap and water for handwashing; both were less effective than decontaminating hands with an alcohol-based hand rub. One laboratory-based study reported that an alcohol-free hand-rub product containing a quaternary ammonium compound was efficacious in reducing microbial counts on the hands of volunteers. Further studies of such products are needed to determine if newer formulations are effective in healthcare settings.

Triclosan

Triclosan is a nonionic, colorless substance that was developed in the 1960s. It has been incorporated into soaps for use by healthcare workers and the public and into other consumer products. Concentrations of 0.2% to 2% have antimicrobial activity. Triclosan enters bacterial cells and affects the cytoplasmic membrane and synthesis of RNA, fatty acids, and proteins.

Triclosan has a broad range of antimicrobial activity, but it is often bacteriostatic. Triclosan's activity against gram-positive organisms (including MRSA) is greater than against gram-negative bacilli, particularly *P. aeruginosa*. The agent possesses reasonable activity against mycobacteria and *Candida spp.,* but it has limited activity against filamentous fungi.

Like chlorhexidine, triclosan has persistent activity on the skin. Its activity in hand-care products is affected by pH, the presence of surfactants, emollients, or humectants and by the ionic nature of the particular formulation. Triclosan's activity is not substantially affected by organic matter.

The majority of formulations containing <2% triclosan are well-tolerated and seldom cause allergic reactions. Certain reports indicate that providing hospital personnel with a triclosan-containing preparation for hand antisepsis has led to decreased MRSA infections. Triclosan's lack of potent activity against gram-negative bacilli has resulted in occasional reports of contamination.

Triclosan can be found in many places today. It has been added to many consumer products—including clothing, kitchenware, furniture, and toys—to prevent bacterial contamination. Because of that, people's long-term exposure to triclosan is higher than previously thought, raising concerns about the potential risks associated with the use of this ingredient over a lifetime (FDA, 2019).

In addition, laboratory studies have raised the possibility that triclosan contributes to making bacteria resistant to antibiotics. Some data shows this resistance may have a significant impact on the effectiveness of medical treatments, such as antibiotics (FDA, 2019).

Other Agents

Approximately 150 years after Semmelweis demonstrated puerperal fever–related maternal mortality rates to be reduced by use of a hypochlorite hand rinse, the efficacy of rubbing hands for 30 seconds with an aqueous hypochlorite solution was studied once again. The solution was demonstrated to be no more effective than distilled water. The regimen used by Semmelweis, which called for rubbing hands with a 4% [w/w] hypochlorite solution until the hands were slippery (approximately 5 minutes), has been revisited by other researchers. This more current study indicated that the regimen was 30 times more effective than a 1-minute rub using 60% isopropanol. However, because hypochlorite solutions are often irritating to the skin when used repeatedly and have a strong odor, they are seldom used for hand hygiene.

Certain other agents are being evaluated by FDA for use in healthcare–related antiseptics. However, the efficacy of these agents has not been evaluated adequately for use in handwashing preparations intended for use by healthcare workers. Further evaluation of these agents is warranted. Products that use different concentrations of traditional antiseptics (e.g., low concentrations of iodophor) or contain novel compounds with antiseptic properties are likely to be introduced for use by healthcare workers. For example, preliminary studies have demonstrated that adding silver-containing polymers to an ethanol carrier (i.e., Surfacine) results in a preparation that has persistent antimicrobial activity on animal and human skin. New compounds with good *in vitro* activity must be tested *in vivo* to determine their abilities to reduce transient and resident skin flora on the hands of healthcare workers.

Historical Context: SARS, MERS, and Ebola

Three historically important epidemics have occurred since 2000: severe acute respiratory syndrome (SARS-CoV-1) in 2003, Middle East respiratory syndrome (MERS) in 2013, and Ebola virus disease in 2014. The first two were caused by coronaviruses and the third by ebolavirus. All three were eventually contained using now-familiar public health measures.

Why Learn About SARS, MERS, and Ebola?

In the West, we often shrug off what we consider to be exotic epidemics in regions of the world little-known to most of us. But in 2014, a great deal of uproar ensued when two Ebola-infected aid workers from a clinic in Liberia came down with Ebola and were transferred to Emory University Hospital in Atlanta for treatment. Many people raised fears of the virus spreading throughout this country. Both aid workers recovered.

Shortly thereafter, a man returned home to Texas from Sierra Leone by commercial airline. He became sick with Ebola about 5 days after he arrived home. Epidemiologists immediately began *contact tracing,* introduced earlier as a surveillance technique in which health officials find everyone who has been in direct contact with the Ebola patient. Contacts are watched for 21 days from the last day they were in touch with the Ebola patient. If a contact develops symptoms of Ebola, the new patient is isolated, tested, and provided with supportive care while all of his or her contacts are found and watched for 21 days.

It is striking to note that no matter where (or when) an outbreak occurs, we in the United States face many of the same difficulties other countries have faced. Distrust of science, lack of political leadership, limited resources, environmental destruction, and refusal to follow public health guidelines have greatly contributed to the spread of pandemic viruses.

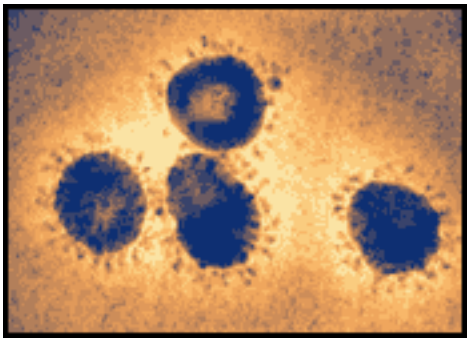
SARS-CoV-1 (2003–2004)

Severe acute respiratory syndrome (SARS) is a viral respiratory illness caused by a highly pathogenic beta coronavirus, called SARS-associated coronavirus (SARS-CoV). Now referred to as **SARS-CoV-1**, it was an atypical pneumonia first detected in eastern China during the winter of 2002–2003. Symptoms included fever, chills, and body aches that usually progressed to pneumonia. Classic public health measures of isolation and containment brought the outbreak to an end. No human cases of SARS-CoV-1 have been reported anywhere in the world since 2004.

The SARS-CoV-1 outbreak brought back memories of the influenza pandemic of 1918–1919 in which as many as 50 million people died worldwide. The World Health Organization (WHO) called for immediate action against SARS and directed its Global Outbreak and Response Network in Geneva, Switzerland to coordinate efforts to monitor the spread of SARS throughout the world.

The illness spread to more than two dozen countries in North America, South America, Europe, and Asia before the SARS global outbreak of 2003 was contained. There were more than 8,000 recorded cases, including 774 deaths, and the pandemic cost the global economy billions of dollars.

Bronchitis Viral Particles



Infectious bronchitis virus particles, a coronavirus in the same family as SARS-CoV, as seen in a colorized electron microscopic image. Virions contain characteristic club-like projections emanating from the viral membrane.
Source: F.A. Murphy and S. Whitfield, CDC.

The 2003 SARS outbreak provided a modern example of how to contain a global epidemic using traditional or nonmedical public health measures. Interventions included finding and isolating case-patients; quarantining contacts; measures to "increase social distance," such as canceling mass gatherings and closing schools; recommending that the public augment personal hygiene and wear masks; and limiting the spread of infection by domestic and international travelers by issuing travel advisories and screening travelers at borders (Bell, 2004).

Some measures were implemented pursuant to recommendations of the World Health Organization; others were implemented by governments on their own initiative. A novel technology, **infrared scanning**, was used extensively in some countries to try to identify persons with fever at international borders and in public places. After the outbreaks, WHO sought information to help assess the effectiveness of interventions in preventing the transmission of SARS both in the community and internationally (Bell, 2004).

Public campaigns to accelerate reporting and evaluating symptomatic patients appeared to decrease the interval between onset of symptoms and isolation of ill patients in several areas. Novel interventions included:

- Urging the entire population of affected areas to measure their temperature at least once daily
- Fever telephone hotlines
- Fever evaluation clinics with appropriate infection control measures

Thermal scanning in public places was implemented in several areas where community transmission was suspected. Data on the effectiveness of this practice are not available, but in Beijing thermal screening did not prove to be an efficient way to detect cases among intercity travelers (Bell, 2004).

Measures to increase social distance, such as canceling mass gatherings; closing schools, theaters, and public facilities; and requiring masks for all persons using public transport, working in restaurants, or entering hospitals, were implemented in areas where extensive unlinked community transmission of SARS coronavirus was suspected. Many persons in these areas also chose to wear masks outside their homes (Bell, 2004).

These measures were often applied simultaneously with other measures, including enhanced contact tracing, which makes their independent effectiveness difficult to assess. However, the simultaneous introduction of a variety of measures was temporally associated with dramatic declines in new SARS cases (Bell, 2004).

A case-control study in Beijing found that wearing a mask more frequently in public places may have been associated with increasing protection. Another case-control study in China–Hong Kong found that using a mask "frequently" in public places, washing hands >10 times per day, and "disinfecting living quarters thoroughly" appeared to be protective. The types of masks used were not specified (Bell, 2004).

In some areas, disinfectants were applied inside the homes and vehicles of persons with SARS, on ambulance tires, and over pedestrian walking zones. Little information exists on the effectiveness of disinfectant use in reducing community or hospital transmission. In Hong Kong, disinfecting living quarters thoroughly (not otherwise defined and reported retrospectively by telephone) appeared to be protective (Bell, 2004).

Travel advisories, along with advice to postpone nonessential travel, were issued by WHO and various governments. Air travel to areas affected by the advisories decreased dramatically during the epidemic, although the impact of advisories compared with other sources of information to travelers, such as news media reports of SARS cases, is difficult to assess (Bell, 2004).

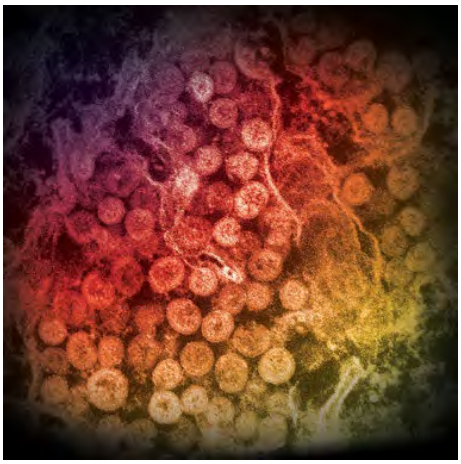
SARS-CoV-1 was contained in human populations in 2003 largely by aggressive use of traditional public health interventions: case finding and isolation, quarantine of close contacts, and enhanced infection control measures in settings where care was provided to persons with SARS, especially in healthcare facilities and homes. These measures also contained a smaller SARS outbreak in 2004 that originated from a laboratory-acquired infection. Measures to decrease the interval between onset of symptoms and isolation were effective in containing community transmission. It should be noted that presymptomatic transmission was not observed and infectivity was low at the onset of illness (Bell, 2004).

MERS-CoV (2012)

Middle East Respiratory Syndrome (MERS) is a beta coronavirus believed to have jumped from animals to humans in 2012. The first case was believed to occur in Jordan in April 2012. A second, larger outbreak occurred in the Republic of Korea in 2015 (associated with a traveler from the Arabian Peninsula). So far, all cases of MERS have been linked through travel to, or residence in, countries in and near the Arabian Peninsula (CDC, 2019).

MERS caused severe respiratory illness with symptoms of fever, cough, and shortness of breath. The virus spread from ill people to others through close contact, such as caring for or living with an infected person. Patients ranged in age from younger than 1 to 99 years old.

MERS-CoV



An electron micrograph of a thin section of MERS-CoV, showing the spherical particles within the cytoplasm of an infected cell. Source: Cynthia Goldsmith/Azaibi Tamin, CDC.

About 3 or 4 out of every 10 people reported with MERS died. Most of the people who died had a pre-existing medical condition that weakened their immune system or an underlying medical condition that had not yet been diagnosed (CDC, 2019).

A wide clinical spectrum of MERS-CoV infection has been reported, ranging from asymptomatic infection to acute upper respiratory illness, and rapidly progressive pneumonitis, respiratory failure, septic shock, and multi-organ failure resulting in death. Most MERS-CoV cases have been reported in adults (median age approximately 50 years, male predominance), although children and adults of all ages have been infected. Most hospitalized MERS-CoV patients have had chronic co-morbidities. Among confirmed MERS-CoV cases reported to date, the case fatality proportion is approximately 35% (CDC, 2019).

Laboratory findings at admission may include leukopenia, lymphopenia, thrombocytopenia, and elevated lactate dehydrogenase levels. Co-infection with other respiratory viruses and a few cases of co-infection with community-acquired bacteria at admission have been reported; nosocomial bacterial and fungal infections have been reported in mechanically ventilated patients. MERS-CoV virus can be detected with higher viral load and longer duration in the lower, compared to the upper, respiratory tract and has been detected in feces, serum, and urine (CDC, 2019).

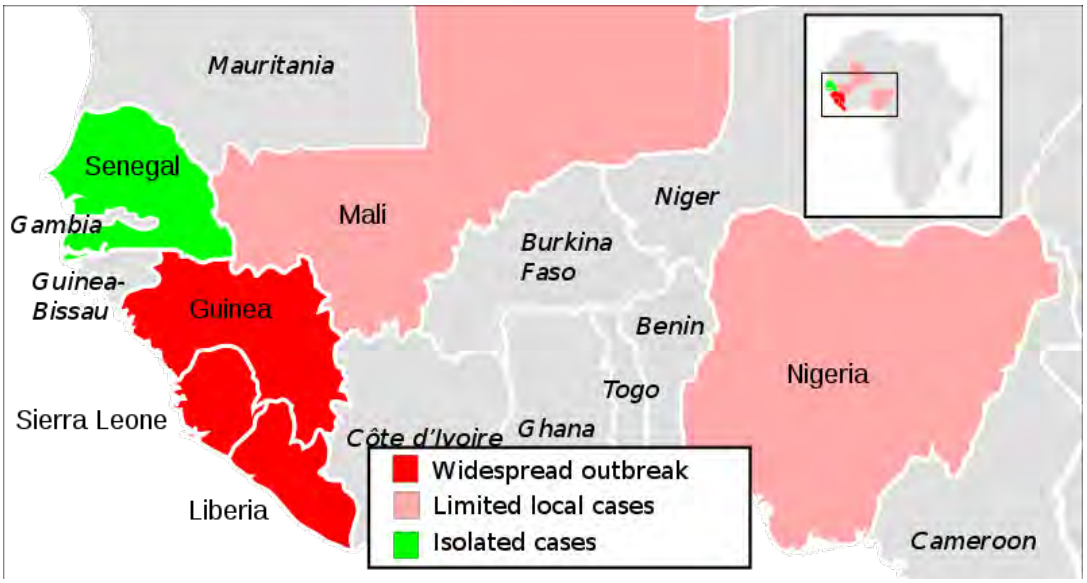
Duration of MERS-CoV shedding in the respiratory tract is typically longer in more severely ill patients than mildly ill patients, and evidence of virus has been detected in survivors for a month or more after onset. Limited data are available on the duration of extrapulmonary MERS-CoV shedding (CDC, 2019).

Unlike SARS, which was eliminated within several months of the initial outbreak, MERS continues to smolder due to sporadic transmission from camels—the virus's intermediate host—to people, and limited chains of person-to-person transmission.

Ebola Virus Disease (2014)

In 2014 **Ebola virus disease**, also called *Ebola hemorrhagic fever,* emerged in West Africa, causing the largest outbreak of Ebola ever recorded. What began as a single case in the West African nation of Guinea quickly spread to neighboring Sierra Leone, Liberia, Senegal, and Nigeria with devastating impact. A lack of healthcare services, governments weakened by decades of civil war, and grossly inadequate infection prevention procedures and equipment hampered efforts to contain its spread. Distrust of the government, misconceptions about how Ebola spreads, and in some cases disbelief that Ebola even exists prevented public health efforts to contain the disease. The inability to isolate and trace those who had come in contact with the virus were chief concerns.

2014 Ebola Outbreak in West Africa—Distribution



A map showing the extent of the Ebola virus epidemic in West Africa. Source: ZeLonewolf / CCO / Public domain.

Although undeniably deadly, previous outbreaks of Ebola were effectively contained using strict infection control, surveillance, and isolation procedures. There is evidence that sporadic, unrecognized or misdiagnosed, outbreaks with low levels of secondary transmission may occur relatively frequently (Kinsman, 2012).

Whether outbreaks are small or large, they have a profound psychological impact on the people living and working in the affected areas. “Alarm and near panic” were reported among health workers at Maridi Hospital in Sudan in 1976—an understandable reaction given that 61 of the hospital’s 154 nursing staff had fallen ill, of whom 33 then died (Kinsman, 2012).

During a 1995 epidemic in Kikwit, Zaire, health workers constituted 25% of the 315 Ebola cases, and fear of infection led many to quit their posts. Those who stayed at work subsequently reported feeling stigmatized because many people feared that they might act as carriers of the virus into the wider community. In some cases, neighbors threw stones, while others were chased from their houses (Kinsman, 2012).

The 2014 Ebola epidemic had a similar effect. When compared to previous Ebola outbreaks, however, the epidemic did not quickly abate. On September 30, 2014 the first laboratory-confirmed, travel-associated case of Ebola was reported in the United States. The traveler did not have symptoms on the flight back from West Africa and, fortunately, Ebola is contagious only if the person has active symptoms.

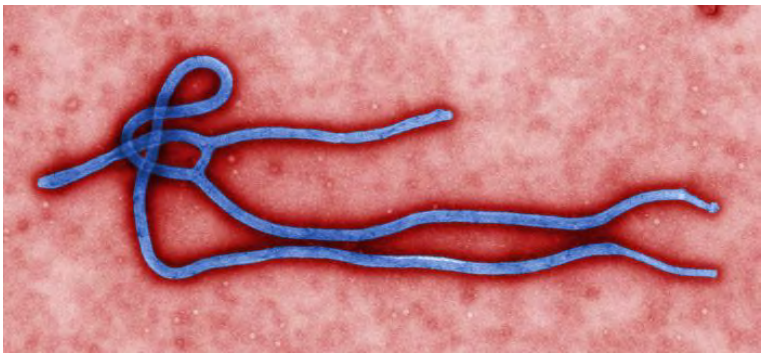
During the spring and summer of 2014, the World Health Organization, which one would expect to be at the center of efforts to control the spread of Ebola, was harshly criticized for its lack of response. In a September 4, 2014 *New York Times* article, reporter Sheri Fink noted the Ebola epidemic “has exposed gaping holes in the [Word Health Organization’s] ability to tackle outbreaks in an increasingly interconnected world, where diseases can quickly spread from remote villages to cities housing millions of people” (Fink, 2014).

With a lack of response by the World Health Organization, local hospitals and clinics struggled to contain new infections. The lack of a coordinated effort, the failure of WHO to quickly provide much-needed supplies and support, meant that healthcare workers were unable to protect themselves against infection. Many healthcare workers died as a result (Nossiter & Solomon, 2014).

One deputy nurse matron in Sierra Leone, Josephine Finda Sellu, who continued to work despite the dangers, lost 15 of her nurses to Ebola in rapid succession during June and July of 2014. Although the hospital has extensive experience dealing with Lassa fever, another type of hemorrhagic fever, and has modern infection prevention procedures in place, it was simply overwhelmed by as many as 80 new Ebola patients each day.

The most comprehensive early efforts to address the Ebola epidemic were undertaken by Doctors Without Borders. Joanne Liu, the organization’s director at the time, criticized WHO’s efforts and called on the United Nations to encourage countries with experience in biologic threats to set up mobile laboratories and field hospitals to treat Ebola patients. “It is your historic responsibility to act,” Dr. Liu said. “We cannot cut off the affected countries and hope this epidemic will simply burn out. To put out this fire, we must run into the burning building” (Sengupta, 2014).

Ebola Virus Particle



Digitally colorized, transmission electron microscopic image which demonstrates the filamentous, branching structure of an Ebola virus particle.
Source: CDC / Cynthia Goldsmith.

Although significantly less contagious than many viral diseases (particularly airborne disease such as measles, diphtheria, pertussis, and COVID-19), Ebola virus is nevertheless highly contagious. Once a person is exposed, symptoms may appear anywhere from 2 to 21 days after exposure—although 8 to 10 days is most common. Some who become sick with Ebola recover, while others do not. The reasons for this are not yet fully understood. However, it is known that patients who die usually have not developed a significant immune response to the virus at the time of death.

The clinical presentation of viral hemorrhagic fever is often nonspecific, with frank bleeding seen in a minority of cases—so cases may be mistaken for other more common diseases or, in the case of Guinea, Lassa fever, which is endemic in the area of the outbreak. Nor are laboratory diagnostics routinely available in West Africa for most viral hemorrhagic fevers. Ebola virus testing of human serum samples collected as far back as 1996 as part of surveillance for Lassa fever in the same region as the current outbreak could help reveal whether humans had exposure to Ebola virus prior to this outbreak (Bausch & Schwarz, 2014).

Fever, coughing, severe headache, muscle and joint pain, vomiting, diarrhea, loss of appetite, abdominal pain, shortness of breath, chest pain, and a maculopapular rash (a skin rash consisting of discoloration and raised spots) are common early symptoms of Ebola infection. These clinical features are strikingly similar to many other diseases endemic to Africa making early identification difficult. Nevertheless, early recognition is crucial for infection control and treatment.

Learning about Ebola is important on two counts: (1) it allows us to identify an infectious disease that is unfamiliar, which means treatment can begin early in the course of the disease; and (2) it also helps us prevent the spread of erroneous information.

Surveillance During the Ebola Pandemic

A common characteristic of large Ebola and Marburg viral disease outbreaks is the breakdown (or absolute lack of) public health surveillance, resulting in long periods of time before public health officials can identify the outbreak. With aggressive surveillance, early chains of transmission can be identified and outbreak response efforts rapidly applied (MacNeil & Rollin, 2012). For example, during the reemergence of Ebola viral disease in Luwero district, Uganda in 2011, viral hemorrhagic fever was immediately suspected in the index (and only case) by clinicians at the hospital. Luwero is in a rural area less than 2 hours by vehicle from the capital of Uganda (Kampala).

A confirmatory laboratory diagnosis was acquired in less than a week, and outbreak response activities started within 24 hours. While contacts of this Ebola case fortunately did not develop disease, the ability to identify and followup all contacts would have resulted in prevention of further spread of the virus, should secondary cases have developed (MacNeil & Rollin, 2012).

Laboratory diagnostics are a crucial component of public health surveillance, and efforts need to be made to ensure capacity for rapid diagnostic testing across sub-Saharan Africa, as well as the ability to rule out other tropical infections. In the above noted Ebola hemorrhagic fever case in Uganda in May 2011, in-country laboratory capacity was available, and a rapid diagnosis was made on the index case, allowing for an immediate public health response (MacNeil & Rollin, 2012).

In sub-Saharan African countries, there is a high burden of infectious disease and non-specific symptoms are commonly seen in many patients, especially those presenting to health clinics and hospitals with malaria and complications of HIV. This means that during a viral hemorrhagic fever outbreak there are many people coming to healthcare facilities near to the epicenter who may have similar symptoms to those with viral hemorrhagic fevers, but who are not exposed or infected (Parkes-Ratanshi et al., 2014).

When cases of the disease do appear, healthcare workers must be able to recognize a case of Ebola virus disease and be ready to employ isolation precautions and barrier-nursing techniques. They should also have the capability to request diagnostic tests or prepare samples for shipping and testing elsewhere.

Treatments Tried in Previous Ebola Outbreaks

When an Ebola outbreak occurs, healthcare providers, family members, townspeople, government officials, and traditional healers try everything at their disposal to treat infected patients and stop the spread of the virus.

In previous filovirus (Ebola, Marburg) outbreaks, in many cases, antibiotics were used to prevent or treat secondary bacterial infections. Analgesics, antipyretics, and antiemetic drugs were typically available and administered as needed. Unfortunately, many patients did not receive any further care. Other symptomatic treatments occasionally available included antidiarrheal drugs, sedatives, and antipsychotic drugs to reduce anxiety and agitation (Clark et al., 2012).

Oral rehydration was routinely encouraged, but at times not administered partially due to the close proximity required to prop up a severely ill patient so they can drink. Oral rehydration was typically preferred to administration of IV fluids, partially due to the perceived risk of transmission associated with the use of needles as well as resource constraints. Fluid and electrolyte monitoring and supplementation were universally applied to patients in well-equipped hospitals, but these measures were not routinely available during most outbreaks (Clark et al., 2012).

Various blood products, clotting factors, inhibitors of fibrinolysis, and regulators of coagulation were administered to counteract hemorrhage. Transfusion of blood components included whole blood, packed red blood cells, fresh frozen plasma, and platelets. Clotting factors and other regulators of coagulation administered included fibrinogen, and prothrombin, proconvertin, Stuart-factor and anti-hemophilic globulin B, and vitamin K. In contrast, anticoagulants (heparin) and rheologic agents (pentoxyfylline)* were given to some patients to prevent thrombosis and disseminated intravascular coagulation (Clark et al., 2012).

***Rheologic agents**: Agents that alter blood viscosity, possibly improving blood flow.

None of the supportive care strategies used in the field during previous filovirus outbreaks have been prospectively evaluated to determine treatment efficacy. Transfusion of blood from convalescent patients* was highlighted as potentially useful in Kikwit, Zaire when only 1 of 8 patients receiving a transfusion died. However, these patients received substantially better care than those in the early stages of the epidemic. Ebola convalescent serum had been administered to three additional patients in two separate outbreaks, all of whom survived. Five patients in four separate outbreaks received IV heparin; 2 of the 5 patients survived. Dehydration was noted in several outbreaks as potentially contributing to the high mortality but, as with other therapies, the effect of IV fluid administration has not been rigorously evaluated (Clark et al., 2012).

Convalescent serum: Using blood from people who have recovered from an infection to treat patients still fight the infection.

Towards the end of the West Africa outbreak, trials for a new vaccine began, and by late 2016 had shown promising evidence that the vaccine was both safe and effective against the Zaire strain of Ebola virus. This vaccine, known as rVSV-ZEBOV, is now being used in responding to the ongoing Ebola outbreak in Democratic Republic of Congo. But for several reasons, including not having official licensure for the vaccine, it must be used under very restrictive conditions that severely limit the speed, and therefore the reach, of vaccination efforts (MSF, 2020).

How COVID-19 has Affected Minority Communities

The COVID-19 pandemic continues to devastate the United States and the world, killing more than 155,000 Americans by the first week of August 2020; however, not all communities have been affected equally. There is increasing evidence that some racial and ethnic minority groups are being affected by COVID-19 in much greater numbers than non-Hispanic white and Asian Americans.

Populations with Social Inequities

According to a CDC surveillance report from January 22, 2020 (when the first case was confirmed) through May 30, 2020, African Americans, Native Americans, and Hispanic people are dying at rates much greater than their population share. Among cases with known race and ethnicity, 33% were Hispanic, 22% were Black, and 1.3% were American Indian or Alaska Native. The report notes: "These findings suggest that persons in these groups, who account for 18%, 13%, and 0.7% of the U.S. population, respectively, are disproportionately affected by the COVID-19 pandemic (CNN, 2020)." Recent studies have shown that minority children are also being disproportionately affected.

Other vulnerable populations, particularly immigrant communities that have similar socioeconomic status and rates of comorbidities, are also being hit hard by the coronavirus. There are over 46.7 million immigrants currently living in the United States, of which 11 million are undocumented. Poverty, limited access to healthcare, and fear of legal repercussions place vulnerable immigrant communities within the United States at high risk for acquiring SARS-CoV-2 and developing severe COVID-19 illness (Clark et al., 2020).

Longstanding systemic health and social inequities have put many people from racial and ethnic minority groups at increased risk of getting sick and dying from COVID-19. The term *racial and ethnic minority groups* includes people of color with a wide variety of backgrounds and experiences. But some experiences are common to many people within these groups and social determinants of health, such as poverty and healthcare access, have historically prevented them from having fair opportunities for economic, physical, and emotional health (CDC, 2020a).

As in past pandemics, social and economic determinants strongly influence susceptibility to and health outcomes of COVID-19. Health differences between racial and ethnic groups result from inequities in living, working, health, and social conditions that have persisted across generations (CDC, 2020a).

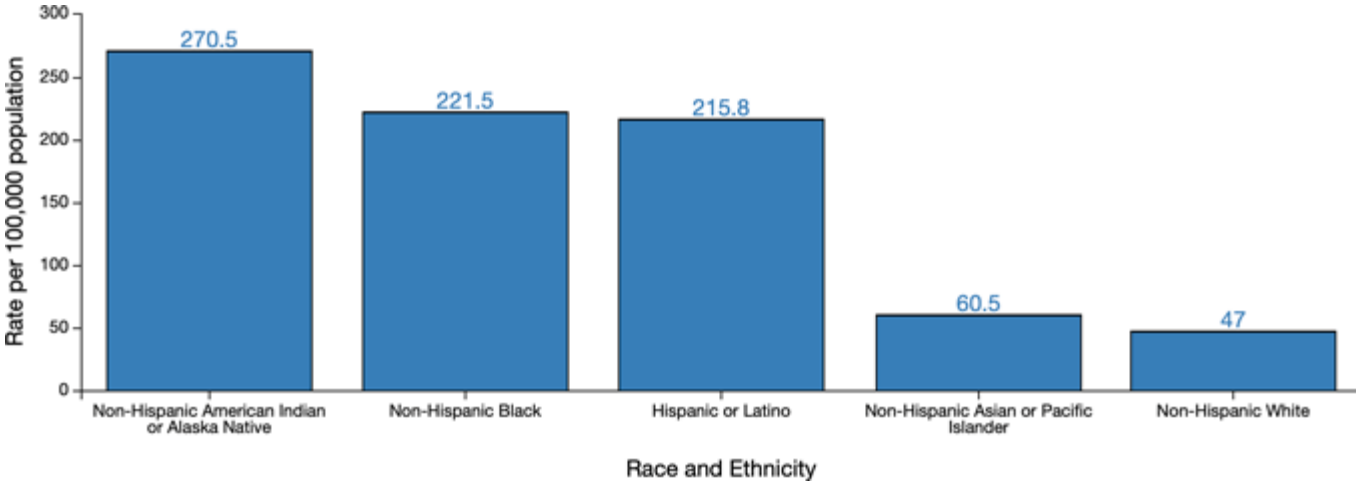
Illnesses such as heart disease, diabetes, and lung disease are more prevalent in African American, American Indian, and Hispanic communities. Unfortunately, these diseases are also leading risk factors for severe disease and death from COVID-19 (Nania, 2020).

Hospitalization Rates

Among some racial and ethnic minority groups—including African Americans, Hispanics, American Indians, and Alaska Natives—evidence points to higher rates of hospitalization from COVID-19 than among non-Hispanic white persons. As of July 4, CDC data shows (CDC, 2020b):

- American Indians or Alaska Natives have an age adjusted hospitalization rate approximately 5.7 times that of non-Hispanic white persons
- Black people have a hospitalization rate approximately 4.7 times that of non-Hispanic white persons
- Hispanic or Latino persons have a hospitalization rate approximately 4.6 times that of non-Hispanic white persons

Age-adjusted COVID-19-associated Hospitalization Rates by Race and Ethnicity, COVID-NET, March–July 4, 2020



Death Rates

According to the CDC, in 35 of the 47 states that report racial statistics of the pandemic, Black people generally had disproportionately high death rates—more than twice as high as white and Asian Americans. American Indians and Alaska Natives were highest in five states, Asian Americans in four states, white Americans in two states, and Native Hawaiian and Pacific Islanders in one state (Baranauckas et al., 2020).

As of August 4, 2020, statistics show death rates for all Americans are as follows (APM Research Lab, 2020):

- 1 in 1,250 Black Americans has died (80.4 deaths per 100,000)
- 1 in 1,500 American Indians has died (66.8 deaths per 100,000)
- 1 in 1700 Pacific Islander Americans has died (58.7 deaths per 100,000)
- 1 in 2200 Hispanic Americans has died (45.8 deaths per 100,000)
- 1 in 2800 white Americans has died (35.9 deaths per 100,000)
- 1 in 3,000 Asian Americans has died (33.1 deaths per 100,000)

Factors That Increase Risks From COVID-19

Living Conditions

For many people from racial and ethnic minority groups, living conditions can contribute to poor health conditions and make it harder to follow steps to prevent getting sick with COVID-19 or to seek care if they do get sick.

Members of racial and ethnic minorities are more likely to live in densely populated areas because of **institutional racism** in the form of residential housing segregation. In addition, overcrowding is more likely in tribal reservation homes and Alaska Native villages compared to the rest of the nation. People living in densely populated areas and homes may find it harder to practice social distancing (CDC, 2020a).

Racial housing segregation is linked to health conditions (e.g., asthma and other underlying medical conditions) that put people at increased risk of getting severely ill or dying from COVID-19. Some communities with higher numbers of racial and ethnic minorities also have higher levels of exposure to pollution and other environmental hazards (CDC, 2020a).

Homes on Native American reservations are more likely to lack full plumbing when compared to the rest of the nation, making handwashing and disinfection harder.

Many members of racial and ethnic minority groups live in neighborhoods that are far from grocery stores and medical facilities, and may lack safe and reliable transportation, making it harder to stock up on supplies that would allow them to stay home and to receive care if sick.

Members of racial and ethnic minority groups may be more likely to rely on public transportation, which makes it challenging to practice social distancing.

People living in multigenerational households and multifamily households (more common among some racial and ethnic minority groups), may find it hard to protect older family members or isolate those who are sick if space in the household is limited.

Work Circumstances

Some types of work and workplace policies can put workers at increased risk of getting COVID-19. Members of racial and ethnic minority groups are more likely to work in these conditions (CDC, 2020a).

The risk of infection is greater for workers in essential industries such as healthcare, meat packing, groceries, and factories. These workers cannot work from home and must be at the job site despite outbreaks in their communities, and some may need to continue working due to economic circumstances. Many essential workers in lower paying jobs do not get paid sick leave and thus may be more likely to keep working when they are sick (CDC, 2020a).

On average, racial and ethnic minorities earn less than non-Hispanic whites, and have less accumulated wealth, lower levels of education, and higher rates of joblessness. These factors affect the quality of the social and physical conditions in which people live, learn, work, and play, and can have an impact on health outcomes (CDC, 2020a).

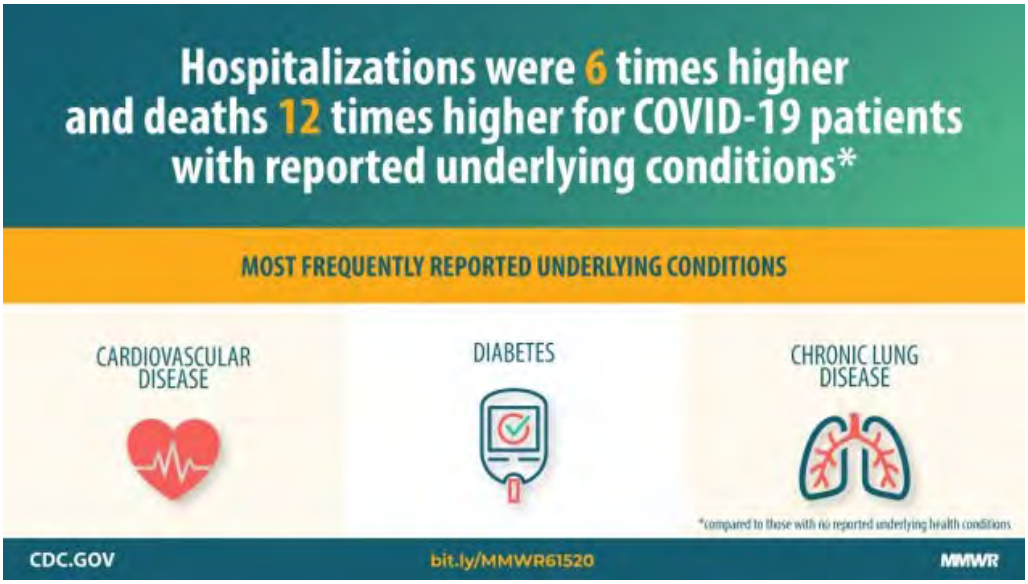
Healthcare Inequities and Underlying Conditions

Compared to non-Hispanic whites, Hispanics are almost 3 times as likely to be uninsured, while African Americans are almost twice as likely to be uninsured. In all age groups, Blacks are more likely than non-Hispanic whites to report not being able to see a doctor in the past year because of cost. In 2017 almost 3 times as many American Indians and Alaska Natives had no health insurance coverage compared to non-Hispanic whites (CDC, 2020a).

Racism and systemic inequities undermine prevention efforts, increase levels of chronic and toxic stress, and ultimately sustain health and healthcare inequities. Minorities may not receive care because of distrust of the healthcare system, language barriers, or cost of missing work (CDC, 2020a).

Underlying medical conditions put people at increased risk for severe illness from COVID-19. Compared to non-Hispanic whites, Blacks experience higher rates of chronic conditions at earlier ages as well as higher death rates. American Indian and Alaska Native adults are more likely to be obese, have high blood pressure, and smoke cigarettes than non-Hispanic white adults (CDC, 2020a).

Poor healthcare and poor nutrition contribute to conditions like high blood pressure, diabetes, heart disease, and lung disease that are the most commonly reported illnesses in people with severe outcomes from COVID-19 (CDC, 2020a).



Source: CDC.

African Americans

“We have a particularly difficult problem of an exacerbation of a health disparity,” Anthony Fauci, M.D., director of the National Institute of Allergy and Infectious Diseases, said at a recent White House coronavirus task force briefing. The things that get people into intensive care and require them to be put on a ventilator — something that often leads to death — are the very factors, Fauci said, “that are, unfortunately, disproportionately prevalent in the African American population.” (Nania, 2020).

Infection and Death Rates Among African Americans

In the United States, Black people are dying at 2.5 times the rate of white people. At least 29,380 Black lives have been lost to COVID-19 since the pandemic began. Black people account for 23% of COVID-19 deaths where race is known (*Atlantic,* 2020).

There are eight states in the United States where the African American death rate is twice the share of the population. The largest disparities are seen in the states of Kansas and Wisconsin. In these two states, Black people make up only 6% of the population, but 29% and 26% of deaths from COVID-19, respectively. Black people make up 12% of the population of Missouri, but account for 37% of coronavirus deaths (Pew Research Center, 2020).

In New York State, Black people account for 33% of COVID-19 hospitalizations but make up only 18% of the state’s population. They are dying of coronavirus twice as often as white people in New York City, according to early data (WebMD, 2020).

Health Disparities in African American Communities

Increased coronavirus cases and deaths among African Americans can be linked to the same factors that are affecting other minority communities. Discrimination exists in systems meant to protect well-being or health, including healthcare, housing, education, criminal justice, and finance. Discrimination, which includes racism, can lead to chronic and toxic stress, and shapes social and economic factors that put some people from racial and ethnic minority groups at increased risk for COVID-19 (CDC, 2020a).

African Americans are more likely than white people to live in densely populated, unsafe areas with less green space, fewer healthy food options, and less access to healthcare. Social distancing is difficult in crowded neighborhoods and unhealthy food and inadequate healthcare leads to chronic health conditions that make people in these neighborhoods more likely to have serious outcomes from the coronavirus (Brookings, 2020).

Black people are less likely to have health insurance and less likely to seek healthcare because they tend to distrust the government and the medical establishment that are responsible for inequities in their treatment. Incidents like the Tuskegee Study of Untreated Syphilis in the African American Male and sterilization without people's permission have made many Black people distrustful of the medical system (CDC, 2020a).

About a quarter of all public transit users are African Americans and they are more likely than whites to be so-called **essential workers** and unable to work from home, further heightening their exposure to other people. "Blacks represent nearly 30% of bus drivers and nearly 20% of all food service workers, janitors, cashiers, and stockers. During a highly contagious pandemic like COVID-19, Black workers, and consequently their families, are overexposed" (Brookings, 2020).

The highly contagious coronavirus spreads easily and rapidly in high-density communities that are filled with people who may have underlying health problems and cannot social distance or work from home. Chronic underlying health conditions make people more likely to have severe outcomes from this disease.

American Indians and Alaska Natives

> If Native American tribes were counted as states, the five most infected states in the country would all be native tribes, with New York dropping to No. 6, according to a compilation by the American Indian Studies Center at U.C.L.A.
>
> Kristof, 2020, May 30

Data collected as of July 7, 2020 indicate that American Indians and Alaska Natives have a death rate of 51.3 deaths per 100,000 people compared to 30.2 deaths per 100,000 in non-Hispanic white communities and 29.3 deaths per 100,000 in Asian American communities (APM Research, 2020).

> This crisis—and the underlying conditions tribal communities face—are the result of centuries of colonial violence and neglect that continue to this day.
>
> Doshi et al., 2020

Even before the pandemic, American Indians and Alaska Natives had shorter life expectancies than most other Americans. Lower life expectancy and a disproportionate disease burden exist because of inadequate education, disproportionate poverty, discrimination in the delivery of health services, and cultural differences. These are broad quality-of-life issues rooted in economic adversity and poor social conditions (IHS, 2019).

The U.S. government signed treaties with tribal nations when their lands and resources were taken from them, ensuring the "promise of all proper care and protection." This **trust responsibility** included a "legal obligation to defend tribal treaty rights, lands, assets, and resources, as well as a duty to provide health services." Unfortunately, there is a tradition of underfunding the Indian Health Service which is therefore unable to provide adequate health care for Native Americans (Warne & Frizzell, 2014). Only $3,943 is provided by the U.S. government to the Indian Health Service for Native American healthcare while the Bureau of Prisons spends $8,603 for each prisoner's healthcare (Kristof, 2020, May 30).

American Indians and Alaska Natives born today have a life expectancy that is 5.5 years less than other Americans when all races are combined (73.0 years to 78.5 years, respectively). Heart disease, cancer, unintentional injuries, and diabetes are leading causes of death in American Indians and Alaska Natives. Chronic liver disease and cirrhosis, assault/homicide, intentional self-harm/suicide, and chronic lower respiratory disease all occur at much higher rates in indigenous people than in other Americans. Because of these underlying conditions, COVID-19 is hitting Native Americans and Alaska Natives particularly hard (IHS, 2019).

The Navajo Nation

The Navajo nation is the largest reservation in area in the United States, spread out over parts of Arizona, New Mexico, and Utah. It is suspected that the virus arrived there in early March 2020 when someone infected with the virus attended a Christian revival on the reservation. The virus then spread widely through community events and as a result of crowded living conditions. Social distancing is not possible in the small and crowded Native homes and, since 40% of reservation homes lack running water, hand washing is difficult. Coronavirus testing came back 28% positive compared to 8.7% nationally during the first week of July 2020 (Kristof, 2020 May 30; CDC, 2020a).

It has been difficult to gain a true understanding of the impact of COVID-19 on American Indian/Alaska Native communities. They are often designated as "other" when racial data is collected or categorized as Hispanics due to surnames or appearance, which could cause an undercount of the pandemic's severity. A real picture of how the virus is affecting these communities would enable targeted solutions to help stop the spread, such as supplies of water, improved plumbing facilities, increased access to healthcare, and health literature translated into languages other than English (PBS Newshour, 2020).

Hispanics

Hispanics make up an increasing proportion of deaths in the United States from COVID-19. By the beginning of August 2020, more than 25,000 had lost their lives to the disease, accounting for nearly 20% of all deaths among Hispanic people (Thebault & Fowers, 2020).

Although Hispanics in the United States have a long life-expectancy (81.8 years), they endure poverty, discrimination, and lower rates of health insurance than both whites and Blacks. A study published June 18, 2020 in the *Journal of the American Medical Association* found that Hispanics are disproportionately affected by the coronavirus. Out of a total of 38,000 people tested for COVID-19 at Johns Hopkins Health System in the Washington DC area, 16% overall were positive. But, of 4,169 Hispanic people tested during the study, almost 43% were positive (US News and World Report, 2020).

Recent data made available by the CDC show that this disease disparity holds true throughout the United States and in all age groups. Data from New Jersey show that although 19% of the total population in that state is Hispanic they make up 30% of COVID-19 cases. In Utah, 14% of the total population is Hispanic but they account for 38% of COVID-19 cases. In Washington State, 13% of the total population is Hispanic, but they make up 34% of the COVID-19 cases (Calo et al., 2020). In California, Hispanic residents make up about 55% of the more than 356,000 infections while they make up just 39% of the state's population (Yoon-Hendricks, 2020, July 16).

Partial COVID-19 death data show that Hispanic people are also dying at a rate above what population data would suggest. For example, CDC population data show that in Pennsylvania, where Hispanic people make up 7.6% of the total state population, 11% of COVID-19 deaths were among Hispanic people. In the United States as a whole, over 26% of COVID-19 deaths were among Hispanic people, who represent only 18% of the total U.S. population. (Calo et al., 2020).

The Vulnerability of Hispanic Communities

Vulnerability to COVID-19 can arise from many factors, including differential exposure, susceptibility, language barriers, and lack of access to health care.

Work Circumstances

Many Hispanic people work in frontline jobs in grocery stores, waste management, cleaning and sanitation services, and food delivery, putting them at constant exposure to people or materials that may be infected with COVID-19 (Calo et al., 2020).

Living Conditions

In addition to work circumstances, living conditions may also increase exposure to COVID-19 among Hispanic families. Twenty-five percent of Hispanic people live in multigenerational households (compared with only 15% of non-Hispanic white people), which makes it challenging to protect older family members or to isolate those who are sick if space in the household is limited (Calo et al., 2020).

Chronic Illness

Although having a chronic disease does not increase the risk of contracting the new coronavirus, the presence of chronic disease can worsen the outcome of COVID-19. Emerging data from the State of New York show that among those who died of COVID-19 (23,083 people as of May 20, 2020), the leading underlying illnesses were hypertension (54% of deaths) and diabetes (36% of deaths). This is alarming for Hispanic people because they have higher rates of both hypertension and diabetes as compared with non-Hispanic white people (Calo et al., 2020).

Language Barriers and Access to Healthcare

The lack of reliable information in Spanish has impeded efforts to combat the spread of the virus in Hispanic communities among those with language barriers, making them more likely to be unaware of best practices. In addition, Hispanic people are the largest population segment without healthcare insurance in the United States, leaving those with presumptive symptoms or with a positive COVID-19 test having limited access to needed healthcare (Calo et al., 2020).

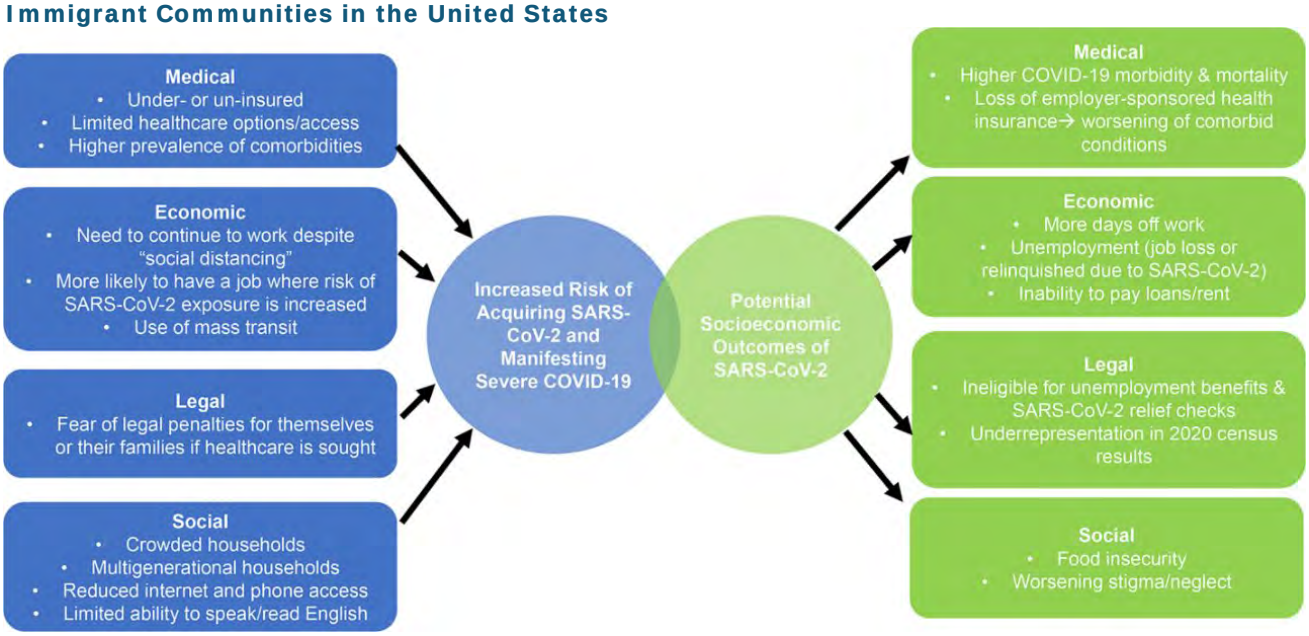
Immigrants and COVID-19

[Material in this section is from Clark et al, 2020 unless otherwise cited.]

Poverty, limited access to healthcare, and fear of legal repercussions place vulnerable immigrant communities within the United States at high risk for acquiring SARS-CoV-2 and developing severe COVID-19. There are over 46.7 million immigrants currently living in the United States, of which 11 million are undocumented.

Houston is an example of a large, prosperous U.S. city that has a significant population of immigrants (and is dependent upon them). Currently, there are an estimated 1.6 million immigrants (23.3% of the population) living in Houston; they emigrated from Mexico (40.2%), El Salvador (7.6%), Vietnam (5.9%), India (5.5%), and Honduras (3.6%). More than 500,000 of these immigrants (37.2%) are **undocumented**. In Texas as a whole, an estimated 32% of undocumented immigrants live below the poverty level and 64% are uninsured, with limited options to meet their medical needs.

Disproportionate Impact of the COVID-19 Pandemic on Immigrant Communities in the United States



From PLOS.org, https://journals.plos.org/plosntds/article/figure?id=10.1371/journal.pntd.0008484.g001.

As with other minority groups, the lack of readily accessible, affordable healthcare is particularly consequential during the COVID-19 pandemic. Early diagnosis and monitoring of persons with COVID-19 is critical both to optimize the individual patient's outcome and to prevent further community transmission. Many vulnerable immigrants are under- or un-insured and thus depend upon Federally Qualified Health Centers (FQHCs), safety-net public health systems, or free clinics. These organizations are often underfunded, limiting their ability to provide testing, management, and followup services to their patients.

Lack of access to preventive medicine leads to increased risk of underlying health conditions such as obesity, hypertension, and diabetes—comorbidities that have been linked to more severe COVID-19 manifestations. In a national evaluation of health conditions in immigrant populations, 27.7% of those from Mexico, the Caribbean, and Central America had hypertension; 71.5% had obesity; and 9.6% had diabetes; compared with the age-adjusted prevalence of 45.4%, 42.4%, and 8.2%, respectively, in the U.S. general population. Within this population, the comorbidities tend to be higher in minority groups when compared to whites; for instance, while the prevalence of diabetes in the U.S. general population was 8.2% overall, it was 12.5% for people of Hispanic origin, 11.7% for non-Hispanic Blacks, and 7.5% for non-Hispanic whites.

Depending on their mode of entry into the United States, immigrants may also be at risk for excessive stress related to poverty, trauma, and poor social support, which leads to mental health conditions such as post traumatic stress disorder (PTSD), depression, and anxiety. These psychological stressors may be worsened during a pandemic, certainly for those with limited healthcare resources, high risk of job loss, or high risk of SARS-CoV-2 exposure.

Many immigrants are at increased risk both because their economic situation requires continuation of work despite social distancing and stay-at-home recommendations and because the types of jobs most commonly worked by immigrants often require face-to-face interactions. In Texas, immigrants make up more than 20% of the work force and are employed most commonly in the construction, hospitality, food services, healthcare, and manufacturing industries; these are “essential” professions that do not lend themselves to working from home. In addition, immigrants who continue working are more likely to use mass transit to get to their jobs, which further increases their risk of SARS-CoV-2 exposure.).

In the home, immigrants are more likely to live in large, multigenerational family groups or with multiple roommates. Nearly 29% of Asian, 27% of Hispanic, and 26% of Black Americans live in multigenerational households, a practice that is particularly common in those who are foreign-born. If one person living in a crowded home is infected with SARS-CoV-2, their cohabitants, including elders and the immunosuppressed, will likely be exposed. In addition, recent immigrants and their families are less likely to have cell phones or internet access and to speak and read English. In Texas, for example, approximately 50% of undocumented immigrants lack English proficiency; consequently, they may be less likely to receive and understand public health messages, warnings, and updates.

Minority Children and COVID-19

[Material in this section is from Kim et al, 2020 unless otherwise cited.]

A recent CDC report reveals that minority children are disproportionately affected by COVID-19. Analysis of pediatric hospitalization data from 14 states from March 1 to July 25, 2020 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 intensive care unit (about the same rate as adults).

Most reported cases of COVID-19 in children under 18 years of age appear to be asymptomatic or mild. Less is known about severe COVID-19 illnesses requiring hospitalization of children. From March 21to July 25, weekly hospitalization rates steadily increased among children (from 0.1 to 0.4 per 100,000, with a weekly high of 0.7 per 100,000). Overall, Hispanic and Black children had higher cumulative rates of COVID-19–associated hospitalizations (16.4 and 10.5 per 100,000, respectively) than did non-Hispanic white children (2.1). Among 208 (36.1%) hospitalized children with complete medical chart reviews, 69 (33.2%) were admitted to an intensive care unit; 12 of 207 (5.8%) required invasive mechanical ventilation, and one patient died during hospitalization.

From March 1 to July 25, 576 children hospitalized with COVID-19 were reported to COVID-NET, a surveillance system that collects data on laboratory-confirmed COVID-19–associated hospitalizations in 14 states. Infants aged <3 months accounted for 18.8% of all children hospitalized with COVID-19. Among 526 children for whom race and ethnicity information were reported, 241 (45.8%) were Hispanic, 156 (29.7%) were Black, 74 (14.1%) were white; 24 (4.6%) were non-Hispanic Asian or Pacific Islander; and 4 (0.8%) were non-Hispanic American Indian/Alaska Native.

Overall weekly hospitalization rates among children increased steadily during the surveillance period (from 0.1 to 0.4 per 100,000, with a weekly high of 0.7 per 100,000). COVID-19–associated hospitalization rates were higher among Hispanic and Black children than among white children. The rates among Hispanic and Black children were nearly 8 times and 5 times, respectively, the rate in white children.

Although reasons for disparities in COVID-19-associated hospitalization rates by race and ethnicity are not fully understood, the highest rates of COVID-19–associated hospitalization were found among Hispanic children. Other recent studies have found a higher prevalence of COVID-19 infection in the Hispanic community as a whole, when compared to other racial and ethnic communities. It has been suggested that Hispanic adults are at increased risk for infection because they are overrepresented in essential and direct-service occupations with decreased opportunities for social distancing, which might also affect children living in those households.

Forty-two percent of children in the CDC analysis had one or more underlying medical conditions, with higher occurrences among Hispanic and Black children (45.7% and 29.8%, respectively) compared with white children (14.9%). This suggests that the greater prevalence of underlying conditions in minority children puts them at a higher risk for COVID-19-associated hospitalizations compared with white children.

This study and other studies of hospitalized children with COVID-19, found that obesity was the most prevalent underlying medical condition. Childhood obesity affects almost 1 in 5 U.S. children and is more prevalent in Black and Hispanic children. Recent studies have shown that even mild obesity is a major risk factor for hospitalization and critical illness (Gander, 2020).

Higher rates of **multisystem inflammatory syndrome (MIS-C)** are seen in children; this is a rare but serious complication of coronavirus that can lead to organ failure, shock, and death. More than 74% of the 570 of MIS-C cases reported to the CDC by July 29 were in Black and Hispanic children (Mascarenhas et al., 2020).

COVID-19 has severely impacted the American and global community, placing marginalized populations at high risk of contracting the virus and of developing severe COVID-19.

Concluding Remarks

In early 2020, COVID-19 burst upon the worldwide scene, spreading rapidly through a completely susceptible population. It is the fourth coronavirus outbreak to occur since 2000, alarming many public health experts. COVID-19 is thought to be a “spillover” event in which a pathogen present in animals finds a way to infect humans.

There are seven coronaviruses that infect humans, most causing only mild symptoms. Recent outbreaks of more virulent and deadly coronaviruses include SARS-CoV-1, MERS, and SARS-CoV-2 (COVID-19). These three pathogens cause more severe symptoms and can lead to death in compromised individuals. At this point in the pandemic, treatment is supportive with no vaccine yet available.

As we face the dire effects of this pandemic, it is important to understand how a pathogen infects a susceptible population. This is best described using the concept of a chain of infection in which a pathogen moves from one link to the next until the chain is broken. If the chain is broken—using public health measures—a pathogen is less likely to achieve its goal of infecting more individuals.

Understanding how many people in a susceptible population are infected and how easily a pathogen spreads from person to person is calculated using a mathematical concept that produces what is referred to a the basic reproduction number of a disease (called *R naught*). Although determining the R naught for an infectious disease is fraught with difficulties, it nevertheless gives public health officials and broad idea of how transmissible a disease is and, in the absence of effective public health measures, how many people may become infected.

R_0 is one of the most widely used metrics in epidemiology to determine how far and how easily a disease spreads. Called the basic reproduction number, it is an indicator of the contagiousness or transmissibility of infectious and parasitic agents and represents the number of new infections estimated to stem from a single case in a population that has never seen the disease before.

R_0 is one of the key values that can predict whether an infectious disease will spread into a population or die out. It is used to assess the severity of the outbreak, as well as the strength of the medical and/or behavioral interventions necessary for control.

If the R_0 of a disease is 2, then each infected person will spread the illness to an average of 2 people. A disease with an R_0 below 1 is expected to eventually die out while an R_0 of 1 means a disease will remain stable in a population but will not cause an epidemic. If the R_0 is greater than 1, an epidemic may occur.

In the hands of experts, R_0 can be a valuable concept. However, the process of defining, calculating, interpreting, and applying R_0 is far from straightforward. When used by those who are not trained, R_0 is easily subject to “misrepresentation, misinterpretation, and misapplication”.

Herd immunity threshold for a given virus as the percentage of the population that must be immune to ensure that its introduction will not cause an outbreak. Many people erroneously think that once a large percentage of the population is infected with a pathogen, there is no longer a threat of infection. There are a number of reasons why this is an ineffective strategy: it will lead to many more deaths than would occur if public health measures are widely adopted, it fails to protect vulnerable segments of the population, and during a pandemic, herd immunity will not stop the spread of a disease.

Testing is critical for the identification and tracking of COVID-19 infections. Diagnostic tests, such as antigen tests and molecular diagnostic tests, are used to help with the diagnosis of COVID-19. Antibody tests can be used to detect the presence of antibodies in a person who has recovered from a bout of COVID-19.

Currently, there is no vaccine for COIVD-19 although many are in various stages of testing and trials. There are a number of anti-viral, immune-based, and adjunctive therapies in development that have shown promise in treating some of the worst symptoms of the virus.

Because no vaccine is currently available, tried and true public health measures such as contact tracing, social distancing, masks, and handwashing are recommended. Many in the U.S. are ignoring these important public health measures, which have the power to greatly diminish the spread of the virus if widely followed.

For historical guidance, we can look to successful public health responses during past pandemics and epidemics. Since 2000, three major outbreaks have occurred involving coronaviruses. The first two were contained without blossoming into pandemics. We are in the third outbreak now.

There is no doubt that this pandemic has severely affected poor and minority communities. Across the globe, poverty, lack of access to healthcare, food and water insecurity, and lack of coordinated government leadership has had disastrous consequences.

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Quiz starts on next page.

Course Quiz

1. Since 2000, there have been 3 major coronavirus outbreaks. These include:

a. Ebola, monkeypox, and MERS.

b. SARS-CoV-1, MERS-CoV, and COVID-19.

c. Measles, influenza, and COVID-19

d. Polio, MERS, and SARS.

2. Some key differences between flu and COVID-19 symptoms are:

a. Infection with COVID-19 can cause a loss of smell.

b. People infected with COVID can stay infectious for a longer period of time than with flu.

c. COVID has caused blood clots in some individuals.

d. All of the above.

3. The most common symptoms reported from COVID-19 are fever, dry cough, and fatigue. Additional symptoms can include:

a. Nausea, vomiting, and diarrhea.

b. A drop in temperature, hallucinations, and migraine headaches.

c. Left-sided weakness, constipation, vaginal bleeding.

d. Dilated pupils, diarrhea, resting tremor.

4. Inpatient management of severe COVID-19 revolves around the supportive management of the most common complications, which can include:

a. Constipation, blood clots, and liver failure.

b. Decreased D-dimer levels, mild thrombocytopenia, and excessive hunger pains.

c. Fatigue, diarrhea, and decreased D-dimer levels.

d. Pneumonia, respiratory failure, sepsis, arrhythmia, and acute kidney injury.

5. The chain of infection includes which of the following components?

a. Pathogen, host, an epidemic, and close contact with the infected person.

b. A virus, bacterium, pathogen, and a reservoir.

c. Pathogen, reservoir, portal of exit from the reservoir, method of transmission, portal of entry, and a susceptible host.

d. A reservoir, mode of transmission, poor infection control practices, and a compromised immune system.

6. The virulence of a pathogen depends on which of the following factors?

a. Its potency, ability to enter and survive in the body, and the susceptibility of the host.

b. Its ability to enter the body only and the lack of a vaccine.

c. Its potency only.

d. The number of people infected with the pathogen (the herd).

7. A pathogen can be transmitted from one person to another through which of the following modes?

a. Person-to-person transmission of pathogens through touching, biting, sneezing, kissing, and singing.

b. Cooking or eating utensils, handkerchiefs and tissues, soiled laundry, doorknobs, surgical instruments, and dressings.

c. Blood, serum, plasma, water, food, and milk.

d. All of the above.

8. Infectious agents get into the body through various portals of entry, including the mucous membranes, non-intact skin, and the respiratory, gastrointestinal, and genitourinary tracts.

a. True

b. False

9. Which of the following biological and environmental factors increase the risk of infection?

a. A compromised immune system, invasive diagnostic or therapeutic procedures, and contaminated water supply.

b. A healthy immune system, exposure to a pathogen, and contaminated equipment.

c. A compromised immune system, good air circulation, and invasive procedures.

d. Aging, lack of exercise, and excessive body fat.

10. According to the CDC, the single most important measure to reduce the risks of transmitting organisms from one person to another or from site to another on the same patient is:

a. Prompt and thorough reporting

b. Handwashing

c. Isolation of infected patients

d. Use of gloves

11. The "R" in R naught (R_0) stands for:

a. The reliability of epidemiological data.

b. The basic reproduction number.

c. The actual transmission rate of a disease.

d. Relative transmissibility.

12. R_0 refers to:

a. The actual transmission rate of a disease.

b. The basic reproduction number—the number of new infections estimated to stem from a single case in a population that has never seen the disease before.

c. How much immunity to a specific disease there is in a community.

d. How many people are expected to die from a specific virus.

13. The R_0 of COVID-19 has been estimated to be:

a. <1

b. 8.2

c. 5.7

d. 10.2

14. If the R_0 of a disease is less than 1:

a. The disease will not spread and will eventually die out.

b. The disease will likely become an epidemic.

c. Each infected person can spread the disease to an average of 10 people.

d. The disease will remain stable in the community until it causes a pandemic.

15. Vaccines can affect R_0 by:

a. Lowering the R_0 value of a disease.

b. Affecting infection transmission by reducing the number of contacts between infectious and susceptible people.

c. Causing an increase in the number of susceptible people and should not be used.

d. Increasing the number of infected people.

16. The concept of R_0:

a. Is rarely used in epidemiology.

b. Is simple to calculate.

c. Can be determined by many methods that always yield the same number.

d. Can be a valuable concept when calculated and interpreted by experts.

17. Herd immunity is:

a. The number of new infections estimated to stem from a single case in a population that has never seen the disease before.

b. A valuable metric for bacterial infections but not for viral infections.

c. The percentage of the population that must be immune to ensure the introduction of a pathogen will not cause an outbreak.

d. Extremely useful during a pandemic.

18. Herd immunity will not stop the spread of COVID-19 because:

a. We do not have a vaccine.

b. The virus is not currently contained.

c. The people most vulnerable are not evenly spread across the population.

d. All of the above.

19. The herd immunity threshold for a disease:

a. Is reached when 50% of the population has recovered from a disease.

b. Is the minimum percentage of people in the population that must be vaccinated to ensure a disease does not persist in the population.

c. Is a valid and successful strategy for addressing a pandemic in the absence of a vaccine.

d. Proved to be a successful strategy during the 2013 Ebola epidemic in West Africa.

20. An antigen is:

a. A substance produced by the immune system that attacks red blood cells.

b. A substance that detects antibodies present in the blood when the body is responding to or has responded to a specific infection.

c. Molecular structures on the surface of viruses that trigger an immune response.

d. A substance formulated as part of a vaccine to boost immune responses and enhance vaccine effectiveness.

21. Viral tests:

a. Check for antibodies in the blood when a person is responding to a specific infection.

b. Check samples from your respiratory system to tell you if you currently are infected with SARS-CoV-2.

c. Are used to test for the presences of bacterial infections but are not used for viral infections.

d. Have yet to be developed for SARS-CoV-2.

22. Antibody tests:

a. Check samples from your respiratory system to tell you if you currently have an infection.

b. Detect antibodies present in the blood when the body is responding to or has responded to an infection.

c. Diagnoses active coronavirus infection at the time of the test.

d. Detects the virus itself.

23. People at high priority for COVID-19 testing include:

a. Hospitalized patients with symptoms.

b. Healthcare workers, workers in congregate living settings, and first responders with symptoms.

c. Residents in long-term care facilities or other congregate living settings, including prisons and shelters, with symptoms.

d. All of the above.

24. A vaccine is:

a. Ineffective against viruses.

b. A substance designed to teach the immune system how to fight off certain kinds of pathogens.

c. Only used for bacterial infections.

d. A substance that attacks a person's immune system.

25. If most people get vaccinated against a disease, spreading stops.

a. True

b. False

26. Vaccine adjuvants are:

a. Human blood-derived products are obtained from individuals who have recovered from SARS-CoV-2 infection.

b. Substances that contain a version of the living microbe that has been weakened in the laboratory.

c. Substances added to a vaccine to boost immune responses and enhance the vaccine's effectiveness.

d. Fibrin and fibrin degradation products.

27. The COVID-19 Treatment Guidelines Panel recommends against the use of chloroquine or hydroxychloroquine for the treatment of COVID-19, except in a clinical trial.

a. True

b. False

28. Contact tracing and case investigation is:

a. Using Facebook to track a person's activities during a pandemic.

b. Setting up a tracking device in front of a person's residence to track their comings and goings.

c. Working with a person who has been diagnosed with an infectious disease to identify contacts who may have been infected through exposure to the person.

d. Tracking down potentially infected people and forcing them to wear a mask.

29. In the absence of a vaccine, the optimistic scenario in which all age groups reduce their contact rates by >85%:

a. The pandemic will subside even if social distancing is stopped.

b. The virus will spread easily by other means.

c. The epidemic will rebound once the social distancing interventions are lifted.

d. Other mitigation efforts can be stopped.

30. The hands of healthcare workers can become persistently colonized with pathogenic flora, gram-negative bacilli, or yeast.

a. True

b. False

31. Transmission of pathogens via the hands of healthcare workers requires the following sequence of events:

a. Organisms must be capable of surviving for at least several minutes on the hands of healthcare workers.

b. Handwashing or hand antisepsis by the worker must be inadequate or omitted entirely.

c. The contaminated hands must come in direct contact with a patient, or with an inanimate object that will come into direct contact with the patient.

d. All of the above.

32. During the 2003 SARS pandemic, public health measures that appeared to dramatically decrease the spread of infections included:

a. "SARS" parties designed to reach herd immunity as quickly as possible.

b. Social distancing, masks, closing schools, and enhanced contact tracing.

c. Thermal screening, testing of pre-symptomatic individuals, and encouraging international travel.

d. Closing down nursing homes and quarantining anyone over the age of 80.

33. In 2014, which of the following factors contributed to the rapid spread of Ebola virus disease?

a. A lack of healthcare services, governments weakened by decades of civil war, and grossly inadequate infection prevention procedures and equipment.

b. Distrust of the government, misconceptions about how Ebola spreads.

c. Disbelief that Ebola even existed.

d. All of the above.

34. What ethnic and/or racial groups in the United States have been hardest hit by COVID-19?

a. Russian and Chinese immigrants

b. African American, American Indian/Alaska Natives and Hispanics

c. Japanese and Korean Americans

d. Non-Hispanic whites

35. How many deaths per 100,000 people have occurred in American Indians as of August 4, 2020?

a. 33.1 deaths

b. 80.4 deaths

c. 66.8 deaths

d. 35.9 deaths

36. What conditions are believed to make members of minority communities more likely to become infected with COVID-19?

a. Living in multi-family homes and underlying health conditions

b. Living in single family homes in the suburbs

c. Being exposed to the virus at live animal markets

d. Refusing to wear masks or social distance

37. What 3 underlying conditions are most frequently reported that result in death for COVID-19 patients?

a. HIV, hepatitis, and lupus

b. Influenza, herpes, and heart disease

c. Diabetes, heart disease, and arthritis

d. Cardiovascular disease, diabetes, and chronic lung disease

38. Hispanics make up an increasing proportion of deaths in the U.S. from COVID-19. By the beginning of August 2020, COVID-19 accounted for what percentage of all deaths among Hispanic people?

a. 80%

b. 20%

c. 30%

c. 10%

39. What possible causes are there for the disproportionate numbers of COVID-19 cases in minority children?

a. There are higher numbers of minority children with lupus.

b. Minority children are more likely to have AIDS.

c. They are more likely to live in multi-family households with parents who are working essential jobs and are more likely to be obese than non-Hispanic white children.

d. They are more likely to be isolated from the outside community than non-Hispanic white children.

Answer Sheet

Name (Please print your name)_____

Date_____

Passing score is 80%

1. _____	20. _____
2. _____	21. _____
3. _____	22. _____
4. _____	23. _____
5. _____	24. _____
6. _____	25. _____
7. _____	26. _____
8. _____	27. _____
9. _____	28. _____
10. _____	29. _____
11. _____	30. _____
12. _____	31. _____
13. _____	32. _____
14. _____	33. _____
15. _____	34. _____
16. _____	35. _____
17. _____	36. _____
18. _____	37. _____
19. _____	38. _____
	39. _____

Course Evaluation

Please use this scale for your course evaluation. Items with asterisks * are required.

5 = Strongly agree 4 = Agree 3 = Neutral 2 = Disagree 1 = Strongly disagree

*Upon completion of the course, I was able to:

1. Relate the 4 different types of human coronaviruses.	5 4 3 2 1
2. State the 6 components of the chain of infection.	5 4 3 2 1
3. Define R naught, the basic reproductive number.	5 4 3 2 1
4. Explain 3 reasons why herd immunity does not work during a pandemic.	5 4 3 2 1
5. Describe 3 differences between a viral test and an antibody test.	5 4 3 2 1
6. Differentiate between a live-attenuated vaccine and an inactivated vaccine.	5 4 3 2 1
7. Describe 4 of the most effective public health measures used during a pandemic.	5 4 3 2 1
8. Relate 5 public health measures successfully used during the SARS, MERS, and Ebola pandemics.	5 4 3 2 1
9. State 5 ways in which COVID-19 has adversely affected poor and minority communities.	5 4 3 2 1
*The author(s) are knowledgeable about the subject matter.	5 4 3 2 1
*The author(s) cited evidence that supported the material presented.	5 4 3 2 1
*Did this course contain discriminatory or prejudicial language?	Yes No
*Was this course free of commercial bias and product promotion?	Yes No
*As a result of what you have learned, will make any changes in your practice?	Yes No

If you answered Yes above, what changes do you intend to make? If you answered No, please explain why.

*Do you intend to return to ATrain for your ongoing CE needs?

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_____Yes, definitely. _____Possibly. _____No, not at this time.

*What is your overall satisfaction with this learning activity? 5 4 3 2 1

*Navigating the ATrain Education website was:

_____Easy. _____Somewhat easy. _____Not at all easy.

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_____60 minutes (or more) per contact hour _____59 minutes per contact hour

_____40-49 minutes per contact hour _____30-39 minutes per contact hour

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_____A library computer. _____A tablet.

_____A cellphone. _____A paper copy of the course.

Please enter your comments or suggestions here:

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