

COVID-19

Weekly Science Review

June 6-12 2020

This weekly science review is a snapshot of the new and emerging scientific evidence related to COVID-19 during the period specified. It is a review of important topics and articles, not a guide for policy or program implementation. The findings captured are subject to change as new information is made available. We welcome comments and feedback at covid19-eiu@vitalstrategies.org.

IN-DEPTH TOPICS

MMR vaccine and COVID-19

Main message: COVID-19 afflicts and kills older adults much more frequently than younger adults and children. Some observers have suggested that childhood vaccines could play a part. Severe and fatal COVID-19 may be less prevalent than expected in places where recent measles-mumps-rubella vaccine (MMR) campaigns have occurred. Although there is a plausible biological basis for vaccines like MMR conferring some protection against COVID-19, there is no evidence to date

that would support the use of MMR as a pharmaceutical intervention to prevent or treat COVID-19.

The risk for COVID-19 illness increases with age. In studies from multiple countries, there is a pivot point around 50 years old, after which the risk of severe and fatal illness increases steadily and rapidly with each additional year of age. Older people may be more likely to die of COVID-19 for a variety of reasons, including the presence of other chronic conditions and age-related changes in the immune system. In addition, each new generation of children is exposed to different childhood vaccines as immunization programs adopt new antigens over decades. These advances have saved millions of lives, in some cases more than would be expected based only on the diseases that the vaccines targeted. In particular, live attenuated vaccines for smallpox, tuberculosis, polio and measles appear in observational and experimental studies to have **beneficial nonspecific effects** (that is, health benefits including decreased mortality beyond that expected from control of the target disease). Some **observers have suggested that exposure to specific live vaccines** might affect susceptibility to multiple infections, including COVID-19, in childhood and even years later, and that booster doses of these vaccines might protect adults from acquiring COVID-19 or from developing a grave illness if they do.

The live, attenuated MMR vaccine was introduced in 1971. Most people who are younger than 50 today have received one dose, and those under 40 at least two doses. In addition to potential nonspecific effects, some viruses may share common structures that could be targets for an immune response. In unpublished laboratory studies, researchers described **similar amino acid sequences from the viruses that cause measles, mumps, rubella, and COVID-19**. In particular, they found a key sequence in SARS-CoV-2, the coronavirus that causes COVID-19, that was a 29% match with rubella virus and that was also present in the attenuated rubella virus component of MMR. Whether these similarities create a vaccine response, and if that response could protect against COVID-19 as well as rubella, are both unknown.

[In a non-peer-reviewed preprint](#), researchers compared COVID-19 mortality rates and historical levels of MMR vaccine coverage in five countries (Italy, U.K., France, U.S., Germany), noting higher mortality in countries with lower coverage. The investigators also noted that several countries with recent supplemental MMR vaccination campaigns had recorded few COVID-19 cases and few deaths. Although these findings suggest a possible connection, the associations could be coincidental or related to another factor that wasn't measured. Observations about MMR and COVID-19 have yet to be confirmed or subjected to peer review. We reported previously on [a similar association observed between COVID-19 mortality and BCG](#), a tuberculosis vaccine, and concluded that such observational studies don't provide the robust evidence of impact that can be gleaned from experimental trials. [Animal model studies](#) and at least [one clinical trial](#) are underway to evaluate whether MMR could protect against COVID-19 infection or against the disease's most severe effects. For now, there is no evidence to support giving additional doses of MMR vaccine as a COVID-19 prevention or treatment measure, but every reason to ensure continued improvements in MMR vaccination globally. Despite the existence of a highly effective vaccine, measles still kills 100,000 children a year whose communities haven't been reached by vaccination programs.

ABO blood type and COVID-19

Main message: Scientists have been able to demonstrate a relationship between blood type and risk for infection and severity of disease from COVID-19. People with O blood types appear to be less likely to have infection and severe disease, and people with A blood types may experience more severe disease. Currently, there is no well-understood underlying mechanism for these differences. The findings may be related to other previously demonstrated relationships between varying blood types and blood clotting factors or inflammatory cascade components. The relationships that have been elicited so far will need to be studied further. People of all blood types

should continue to take recommended measures to reduce their risk for COVID-19.

A person's ABO blood type is inherited from both parents. Persons of all blood types, A, B, AB, and O, have been infected by the SARS-CoV-2 virus and developed COVID-19. Recent reports, however, indicate that having one blood type or another may affect both the chances of being infected at all (susceptibility), as well as how serious the infection may be (severity of illness). There is no evidence that a person's Rh. factor—that is, whether their blood type is positive or negative—has any effect on their susceptibility. Near the start of the pandemic, evidence began to emerge about **individual risk factors for severe disease**, such as age and coexisting serious health conditions including diabetes and cardiovascular conditions. Now, more than six months into the pandemic, scientists continue to investigate why some patients become hospitalized and need a breathing machine while others infected with the same virus have a self-limited sore throat or mild cough, and others do not become sick at all. As virologists study the virus and its mutations to look for clues as to why different people get varying levels of illness; other scientists are looking at the patients themselves for host factors that may help explain the same conundrum.

In March 2020, **reports** and **retrospective analyses** began to appear in pre-print literature from China, the first epicenter of the pandemic, about a possible association between ABO blood type and COVID-19. Specifically, researchers noticed that there was a disproportionately lower number of patients with O blood types hospitalized with the infection compared to the expected proportion based on the general population, and a disproportionately higher number of patients with A blood types. While these initial studies and reports were based on smaller series of patients, they prompted further investigation into host biological factors as a potential determinant of disease and disease severity, and also prompted researchers to pay closer attention to blood type. By April, additional studies from **China**, as well as the **U.K.** and **U.S.**, were emerging, all supporting a similar relationship with regard to susceptibility, severity of illness or both, despite differences in blood type proportions across the world.

Larger studies and reviews support the early findings with some nuances. [One preprint study](#) from Spain and Italy seeking to address whether host genetic factors could explain variation in disease severity revealed that a gene coding for a person's blood type was closely associated with severity of disease, again showing higher risk of severe illness for those with A blood types and lower risks for O blood types.

There have also been contradictory studies. Although most studies have shown some relationship between either a lower susceptibility or lower severity of illness with O blood types, others have not replicated the higher susceptibility or severity of illness of A blood types, finding instead that the O blood type conferred lower risk overall than the non-O blood types grouped together. One such study was a [report from 23andMe](#), the DNA testing company, which looked at self-reported COVID-19 infection with and without hospitalization and its relationship with blood types. From data on 750,000 people, the study concluded that people with O blood types were both less susceptible to acquiring COVID-19 as well as less likely to be hospitalized with it. In the same study, no relationship was seen for any other blood type, specifically no higher risk was seen for A blood types. The same group is currently recruiting 10,000 subjects for a more complete genetic analysis to link COVID-19 with host genetic factors.

The question of whether there is truly a relationship with susceptibility, severity, or both may be difficult to answer with the data that are currently available. Studies looking at hospitalized cohorts will have a bias toward already detecting a higher level of severity for all blood types. It may be unclear if people with blood type O are less likely to be on ventilators, for example, because their disease severity is lower, or if they are generally less susceptible to infection therefore not hospitalized in the first place. As additional larger studies are done, including population-based and community-based studies, clearer associations will likely become evident.

That [blood types can play a role in host susceptibility to infection](#) is not a novel concept. Relationships between blood type and a host of viruses, bacteria and parasites have

previously been demonstrated. **Similar reports** had been published as part of the SARS epidemic of 2002-2003 showing lower susceptibility for O blood types. Nor is the notion that one's blood type can play a role in severity of disease a novel one. ABO blood type A has **previously been associated** with higher risk of acute respiratory distress syndrome (ARDS), as well as **worse respiratory outcomes in patients with sepsis or trauma**. ABO blood type O, on the other hand, has previously been associated with **lower risk of clotting events**, a major component that may be a driving force **in COVID-19**.

Additional epidemiologic studies will shed more light on the nature of the relationship between blood type and COVID-19, while research by geneticists and molecular scientists may provide insight into the underlying mechanisms of variations in susceptibility to and severity of COVID-19 by ABO blood type. However, the practical implications of these findings for patients and doctors are limited; people of all blood types are at risk of becoming infected with, and can be killed by the virus that causes COVID-19.

Where did SARS-CoV-2 come from?

Main message: Understanding where a virus came from and how it spread into the human population may help isolate the source of the virus and prevent further human infections, support the development of therapeutics and vaccines, and inform the public health response so that future pandemics may be prevented.

Why does the origin of SARS-CoV-2 matter?

There has been much discussion of the origin of SARS-CoV-2, the virus that causes COVID-19. There is **scientific consensus** that SARS-CoV-2 is a zoonosis, or a pathogen that can be

transmitted between humans and nonhuman animals. The majority of human pathogens can infect, or originally came from, nonhuman animals. Humans frequently interact with nonhuman animals, including their pets, their livestock, and wild animals. In addition, animals can appear healthy even when carrying pathogens that can make people sick. Some zoonoses are transmitted to humans via direct animal contact (anthrax, influenza, leptospirosis), but zoonoses may also be transmitted by vectors such as fleas, mosquitoes and ticks (Rocky Mountain spotted fever, Lyme disease, typhus, yellow fever), through consumption of contaminated food or water (salmonellosis, shigellosis, trichinosis), or through multiple routes. **The three most devastating pandemics in human history, the Black Death, Spanish influenza of 1918, and HIV/AIDS, were caused by zoonoses.** Zoonoses that newly emerge in human populations can pose great threats to global health and the global economy, in part because many people may die and many societies may be disrupted as a new disease is being identified and response measures are put in place. In addition, all or most people may be susceptible because they have never been exposed to the new pathogen. In the midst of a global pandemic, one may wonder why the origins of the causative virus matter. Understanding where a virus came from and how it spread into the human population may help isolate the source of the virus and prevent further human infections, support the development of therapeutics and vaccines, and inform the public health response so that future pandemics may be prevented.

How do researchers investigate the origins of SARS-CoV-2 and what have they discovered?

There are several research strategies that may be used to identify the source of a zoonosis such as SARS-CoV-2, the virus that causes COVID-19. One method is epidemiologic analysis of early human cases to establish possible infectious contacts (whether human or not) and to narrow the geographic area and time frame of any spillover events. **Many of the early reported COVID-19 cases had a direct link to a seafood market in**

Wuhan, China—a “wet market,” where both farm-raised and wild animals were sold. **Environmental samples taken from the market in December 2019 tested positive for SARS-CoV-2.** Although this may suggest that the market was the source of the outbreak, some of the earliest COVID-19 patients could not be epidemiologically linked to the market. Alternatively, the market environment may have played a role in early amplification of the outbreak, even if the spillover event happened somewhere else.

A second approach to identifying the source of a zoonosis is to conduct genetic analysis. Viruses that are genetically similar may come from a similar source. In early January 2020, scientists first sequenced the genome of SARS-CoV-2 and **published it online.** We now know that SARS-CoV-2 is a betacoronavirus, or a member of a subgroup of coronaviruses that also includes SARS-CoV, the virus that caused severe acute respiratory syndrome (SARS), and MERS-CoV, the virus that causes Middle East respiratory syndrome (MERS). Bats serve as a host species for many betacoronaviruses, and the genome of SARS-CoV-2 is **96% identical to the genome of a bat betacoronavirus** isolated in China. Although bats likely serve as reservoir hosts of the betacoronavirus from which SARS-CoV-2 originated, a 4% genetic difference is significant. The SARS-CoV-2 genes that shape the part of the virus that binds to human cells are **similar to genes of coronaviruses that infect pangolins**, a mammal covered in protective scales that is hunted for its meat and scales. It has been shown that SARS-CoV-2 can effectively bind not just to human cells but also to cells from ferrets, cats and various other animal species. Thus, the viral progenitor of SARS-CoV-2 may have been transmitted from bats to another animal species in which viral evolution occurred before transmission to humans. There are other examples of this: the SARS virus likely originated in bats and was transmitted to civets, a relative of the mongoose with a catlike appearance, before being transmitted to humans. The virus that causes MERS likely originated in bats and was transmitted to camels before spilling over to humans.

Why haven't we definitively established the source of SARS-CoV-2?

It is not unusual to lack definitive proof of the reservoir species (in which the pathogen normally lives) or the method of spillover transmission (from nonhuman animal to human). For example, it took years of epidemiologic research to demonstrate that Nipah virus, a zoonosis that can cause fatal encephalitis in humans, may **infect humans when they consume date palm sap from collection pots into which infected bats have urinated**, and there have been decades of study and debate on the **origins of HIV. For spillover transmission to occur, a number of dynamic processes must align**. The pathogen must be present at a given point in time and space, a human must come into contact with that pathogen, and the human must be susceptible to the pathogen. For pathogens that may be transmitted readily among humans (Ebola virus, HIV, influenza H1N1), factors contributing to spillover may be difficult to disentangle, as new human cases may be far removed from spillover events. When there is zero or limited human-to-human transmission (rabies, West Nile virus), spillover events may be easier to identify. The human-to-human transmissibility of SARS-CoV-2 has resulted in global spread in just a few months, but genetic analysis of SARS-CoV-2 virus from different patients suggests that the outbreak began with one or just a few introductions into the human population. This is in contrast with the MERS virus, which cannot be transmitted easily between people; there have been **multiple spillover events from camels to humans**. Although no animal coronavirus has been identified as the direct progenitor of SARS-CoV-2, the diversity of coronaviruses in nonhuman animal species has not been fully described. There is **evidence of low-level human population exposure in some parts of China to coronaviruses related to the virus that causes SARS**, suggesting previous undetected spillovers of bat coronaviruses. It took years of searching and sampling for researchers to find **potential viral progenitors of the SARS virus among horseshoe bats in one area of China**.

Based on our current knowledge of the origin of SARS-CoV-2, what actions have been taken?

It is important to recognize the critical ecological niches filled by many different animal species. For example, bats eat pests, pollinate plants and disperse seeds. **Human economies and food security would be heavily affected if bats went extinct.** Research shows that **human activities** such as increasing encroachment on wildlife habitats and the use of certain food production practices create conditions that facilitate zoonotic disease spillover. If human activities increase spillover risk, we have the capacity to address this risk. There are many **public health approaches** to reduce the burden of emerging zoonoses. Decreasing human contact with potential pathogens can reduce the risk that zoonotic spillover occurs at all. Given current evidence on the origin of SARS-CoV-2, **efforts to reduce wildlife consumption and trade** have been made. The effects these measures will have on human behavior and zoonotic disease risk remain to be seen.

FAQS

What do we know about smoking, vaping and COVID-19?

COVID-19 can cause severe respiratory illness and breathing problems, and these can be more severe in people with underlying chronic lung issues. Smoking is a leading cause of chronic lung problems, and can affect the ability of the lungs' immune apparatus to respond to infection. It may take months before there is enough data to clearly define the relationship between smoking and COVID-19. In this time, it could be detrimental to take a lenient stance on tobacco use, a deadly habit that is responsible for millions of deaths each year, with or without an infectious disease pandemic. Smoking itself is associated with other risk factors for severe illness from COVID-

19 such as heart disease, diabetes and high blood pressure, making it difficult to parse out the presence or magnitude of the relationship between smoking and COVID-19 alone. Despite some studies questioning the association between smoking and COVID-19, and some even claiming that fewer smokers than expected are being hospitalized with the disease, the message from experts and public health entities is clear and concise: smoking increases risk for respiratory infections and is strongly associated with factors that increase the severity of illness in COVID-19. The WHO states, “Available research suggests that smokers are at higher risk of developing severe COVID-19 outcomes and death.” Because of the hand-to-mouth action required for smoking cigarettes and vaping or e-cigarette use, there may be a higher chance of getting COVID-19 in the first place. Vaping or using e-cigarettes can also cause severe lung disease. Tobacco is harmful to health, and use is likely increase the potential for worse outcomes from COVID-19. The results of any single study showing otherwise should be strictly scrutinized in the face of decades of sound science and knowledge about the risks of tobacco use and a similarly long history of interference with science by the tobacco industry.

What is a preprint article?

A **preprint article** is an author’s own original or draft version of their paper before any peer review has taken place and before it is published—sometimes in a peer-reviewed journal. In the COVID-19 pandemic, there has been a substantial increase in the amount of scientific research being conducted and published, much of it on preprint servers such as **medRxiv** (pronounced “med-archive”), which is focused on the health sciences. According to **one preprint article**, the scientific community released more than 16,000 COVID-related scientific articles within four months of the first confirmed case, of which at least 6,000 were hosted by preprint servers.

Why would someone put their research on a preprint server? It allows for research to be shared as quickly as possible, and for feedback to be collected prior to publication. Upon creating a

preprint, an article is assigned a digital object identifier (DOI) that can be linked to a final version of the publication, making it easy to cite the work. Preprints have commonly been used in other academic fields such as economics as a means of sharing preliminary analyses and obtaining critical feedback from colleagues before final publication. Until the COVID-19 pandemic, preprints were not extensively used or cited in most health fields. It is important to remember, however, that a preprint article has not been vetted by independent subject matter experts. Assessing the technical merits of a preprint article requires additional expertise in research methodology and relevant subject matter. For these reasons, medRxiv and others provide an important disclaimer about the articles on their server: “Caution: Preprints are preliminary reports of work that have not been certified by peer review. They should not be relied on to guide clinical practice or health-related behavior and should not be reported in news media as established information.” This disclaimer is important to remember when reading news articles that cover findings based on preprint research alone. It is also important for anyone disseminating information to clearly communicate the source of scientific information or results and where they originated.

Weekly Research Highlights

(Preprint articles noted, if any)

SARS-CoV-2 Infections and Serologic Responses from a Sample of Navy Service Members – USS Theodore Roosevelt, April 2020

(MMWR, Early Release, June 9)

Main message: Based on experience from a U.S. Navy aircraft carrier, symptom-based surveillance may not be as effective in detecting COVID-19 infections in young healthy adults, who may

have only mild or no symptoms. Use of face coverings and observing physical distancing were associated with lower odds of infection during an outbreak of COVID-19 among aircraft carrier personnel, and sharing living quarters or reporting contact with someone known to have COVID-19 increased the odds of infection. Most (90%) of the study participants who were already known to have a positive test by RT-PCR prior to the investigation, which detects presence of the virus itself, showed evidence of seroconversion, that is, they had antibodies in their blood detected by serologic testing known as ELISA. Overall, 59.7% of the participants had a positive ELISA test for antibodies, of which 59.2% also had a positive test for neutralizing antibodies.

- Among 1,417 servicemembers previously on board the USS Theodore Roosevelt or on a base in Guam where the ship docked, 382 participated in a survey questionnaire and provided blood samples for ELISA antibody testing, with 267 of these also providing samples for RT-PCR antigen testing.
- Overall, 238 of the participants tested positive by RT-PCR, ELISA, or both. Of these, 81.5% reported at least one symptom, with the most common symptom being loss of smell and/or taste (61.3%). Nearly one-fifth (18.5%) of the participants with past or current infection reported no symptoms, and only two (0.8%) were hospitalized. Evidence of antibodies with positive ELISA was evident in 90.2% of study participants with a known prior positive PCR test. Many also tested positive for neutralizing antibodies.
- This study is limited in that it reports findings from a convenience sample that is not representative of the general population in demographics of living/working arrangements. In addition, data was collected at a single time point, leading to bias from recall and selection, as well as lack of follow up.

The Role of Children in the Dynamics of Intra Family Coronavirus 2019 Spread in Densely Populated Area

(Pediatric Infectious Disease Journal, June 1)

Main message: We previously reviewed evidence that **children were less likely than adults to acquire COVID-19 infection**, even when their exposure is similar. In this study, investigators calculated the attack rate by age from family clusters of COVID-19 investigated in Bnei Brak, Israel, an area densely populated with young families. Children 0-4 years old were 47% less likely to become infected compared to adults, and those between 5 and 17 years old were 61% less likely to become infected. These findings add to the accumulating evidence of infection risk by age, which will be valuable for informing decisions about how to slow the pandemic.

- 13 family clusters of COVID-19 illness were investigated. In 12 families the index case was an adult; in one family the first case occurred in an adolescent infected at school. No additional information was given on transmission from this 14.5-year-old adolescent, and whether he was the source of spread to others who became ill in the household later is not known.
- SARS-CoV-2 PCR testing was completed on 94 additional people in the 13 families. Viral RNA was detected in:
 - 2 of 18 children under 5 (attack rate 11.8%)
 - 13 of 40 children 5-17 years old (attack rate 32.5%)
 - 21 of 36 adults 18 to 48 years old (attack rate 58.3%)
- Even in this community, where 42% of the population is under 15 years of age and crowded conditions supported high attack rates within affected families, adults appear to be the main drivers of transmission.
- This study site may be unusual in the low numbers of older adults included in the family clusters and is not necessarily representative of the level of risk for people living outside an affected household. Differences in attack rates could be due

to biological or behavioral factors among children and adults, or a combination of the two.

Occurrence and Timing of Subsequent SARS-CoV-2 RT-PCR Positivity Among Initially Negative Patients

(Clinical Infectious Diseases, June 7)

Main message: Researchers at two academic medical centers studied the short-term occurrence of newly positive SARS-CoV-2 RT-PCR results among 20,912 patients who had initially tested negative. Results from both institutions suggest that false negative RT-PCR results occur at a lower rate than suggested in other studies.

- At the University of Washington in Washington state and at Stanford University in California, nasopharyngeal samples from adult and pediatric patients were tested for SARS-CoV-2 by RT-PCR. Patients had presented to a variety of clinical settings, including inpatient, outpatient and drive-through testing locations. The majority of tested patients had possible COVID-19 symptoms combined with pertinent risk factors (a small subset was asymptomatic, undergoing screening in the pre-operative setting). A subset of patients who initially tested negative were retested within seven days because of persistent or worsening symptoms.
- SARS-CoV-2 RT-PCR tests were performed on 23,126 samples from 20,912 patients (8,977 University of Washington, 11,935 Stanford). The results showed that 91% (90.7% University of Washington, 91.2% Stanford) of those patients had initially tested negative for SARS-CoV-2. A small proportion of those patients, 338 (4.1%) at University of Washington and 268 (2.6%) at Stanford, underwent repeat testing within seven days. Overall, 3.5% of patients who were retested were found to be positive on the second test: 14 (4.1%) at University of Washington and eight (2.8%) at Stanford.

- A limitation of the study is that sensitivity and specificity of the RT-PCR test could not be determined, due to study design. The cause of false negative results could not be determined, but some result discordance could have been due to newly acquired infections. In addition, it was unclear what biases may have existed in the selection of patients for retesting versus those who did not get retested.

Public Attitudes, Behaviors, and Beliefs Related to COVID-19, Stay-at-Home Orders, Nonessential Business Closures, and Public Health Guidance —United States, New York City, and Los Angeles, May 5-12, 2020

(MMWR, Early Release, June 12)

Main message: A survey conducted among adults in New York City (NYC), Los Angeles (LA), and across the U.S. in early May showed majority support for public health and social measures (PHSMs) aimed at reducing risk and transmission of COVID-19. This type of information—focusing on attitudes, behaviors and beliefs around restrictions put in place during the pandemic—can help guide the acceptability and feasibility of continued restrictions during reopening.

- From May 5 to May 12, more than 4,000 adults were invited to participate in an online survey measuring opinions about stay-at-home orders, physical distancing, nonessential business closures, face coverings, avoiding large gatherings, and whether their states were meeting the right balance of restrictions. Of these invitees, 2,221 met criteria and completed the survey, with 1,676 from the U.S. cohort, 286 from the NYC cohort, and 259 from the LA cohort.
- There was broad support across the three cohorts—U.S., NYC, and LA—for stay at home orders and business closures (79.4%, 86.7%, 81.5% respectively), and most people in each

cohort reported always or often wearing a face covering (74.1%, 89.6%, 89.8% respectively). Respondents also showed support for their jurisdiction's balance of restrictions (84.3%, 89.7%, and 79.7% respectively). Most people reported that they would not feel safe if mitigation strategies were lifted nationwide at the time of the survey (74.3%, 81.5%, 73.4% respectively).

- There are always limitations to survey data. Notably, data on adherence to behaviors are self-reported. In addition, African Americans were underrepresented among the people who responded to the survey. The respondents were also limited to people with access to a computer device and the internet and were willing to participate in an online survey.

Clusters of Coronavirus Disease in Communities, Japan, January–April 2020

(EID, Early release June 10)

Main Message: This study of COVID-19 clusters in Japan revealed that in addition to healthcare settings, many clusters occurred in venues with heavy breathing in close proximity including karaoke parties, cheering, bars and gyms. Primary case-patients were generally younger but none were under 20 years old. Over half of transmission from the primary case occurred before symptom onset.

- The analysis included 2,875 confirmed cases of local transmission in 61 clusters of 5 or more people infected at a common event or venue outside of the household. Of the 2,875 cases, 1,760 (61%) had epidemiologic links to known cases (and notably ~40% did not). Most (64%) of the clusters involved 5-10 cases.
- Clusters occurred in a variety of venues, including healthcare facilities (30%), other care facilities (16%), restaurants or bars (16%), workplaces (11%) and other

locations such as, concerts, choir rehearsals, karaoke parties, gyms and an airplane.

- In non-healthcare settings, there were 22 probable primary case-patients who were believed to have contributed to the new clusters. Of these, 11 (50%) were between the ages of 20-39 which was generally younger than other case patients, but no primary cases were less than 20 years old. Nine (41%) were presymptomatic or asymptomatic at the time of transmission. of those who were symptomatic, only 1/13 (8%) had a cough.
- Of 16 primary cases with clear dates of transmission to other case-patients, 9 (56%) had transmission occur 1-3 days before illness onset, 4 (25%) on the day of illness onset, and only 3 (19%) had transmission occur 1-3 days after illness onset.
- Study limitations included recall bias as some case-patients could not disclose contact history or epidemiologic links, and information was obtained only through interviews.

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