COVID-19

Weekly Science Review

May 23–29 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**.

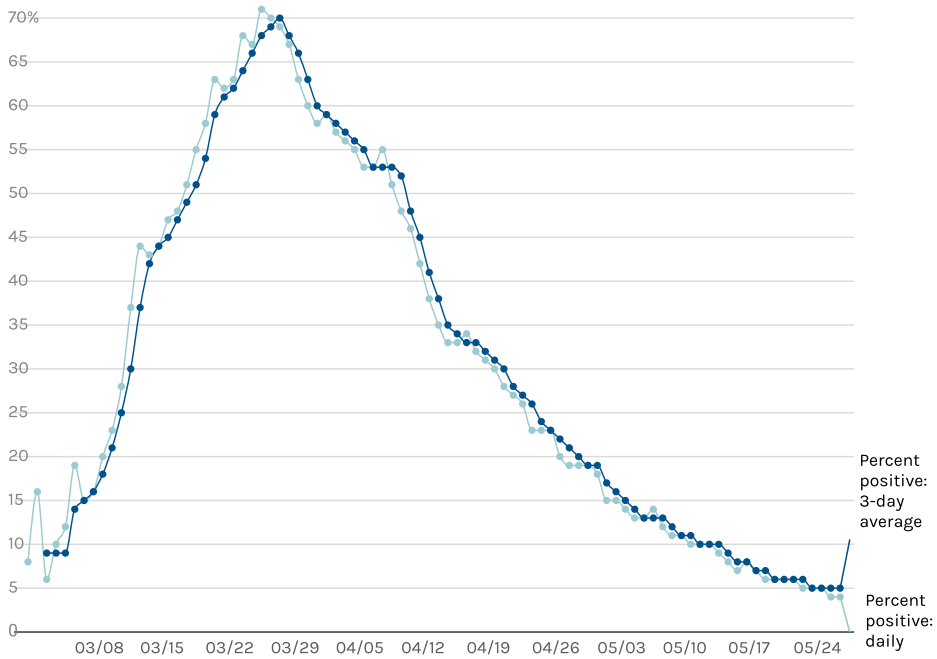
DATA INSIGHT

Testing and test data, what it can and cannot tell us

Testing is an essential component of a comprehensive response to the COVID-19 pandemic. There are several factors that should be considered when implementing and monitoring a successful testing strategy. These include the types of tests available, when they should be used, metrics that can be useful to monitor testing, and additional contextual considerations related to testing and test results. In this insight, we review some of these key questions around testing for COVID-19.

Read the full Insight ‘Testing and test data, what it can and cannot tell us’

Figure: Percent of people with positive results by date, New York City



Source: NYC

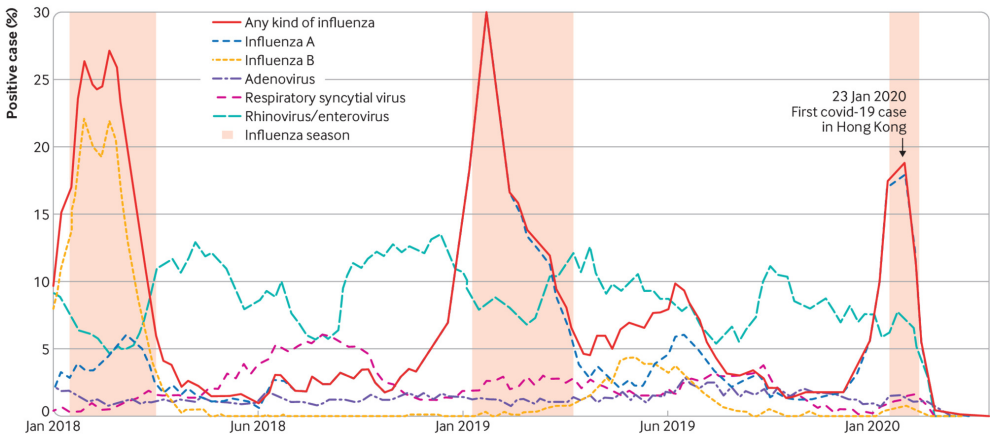
IN-DEPTH TOPICS

The influence of physical distancing on diseases other than COVID-19

Main message: Physical distancing (and related public health and social measures such as mask-wearing and handwashing) is a powerful tool to decrease the transmission of SARS-CoV-2 by reducing the chance that a person will come into contact with the virus. Physical distancing may influence the transmission of other infectious diseases as well. The effects of physical distancing on other infectious diseases is highly dependent on the transmission mechanisms of each disease. Determining the change in incidence of other infectious diseases during a pandemic can be challenging due to the changes in disease monitoring and healthcare seeking behaviors that can also occur during a pandemic.

Physical distancing is a set of non-pharmaceutical interventions designed to prevent the spread of infectious diseases by reducing the number and extent of interactions people have with one another. The basic goal of physical distancing is to reduce the effective reproduction number (Rt) of a disease, meaning the average number of new infections caused by a single infected individual. When the Rt stays below one, the disease will eventually stop spreading. **Public health guidelines define physical distancing as a set of community-based measures** that include staying at least six feet away from others and avoiding group and mass gatherings. Although the terminology may have been different, concepts in physical distancing are not new to infectious disease control efforts; **versions of physical distancing were practiced during the Spanish Flu epidemic** in the early 20th century. SARS-CoV-2 and influenza have common transmission routes (direct contact with infected individuals, contact with contaminated objects, and inhalation of virus) and it is not surprising that physical distancing may have helped control the Spanish Flu epidemic in some cities. More recently, during the 2003 Hong Kong SARS epidemic, **reductions in the incidence of other respiratory viruses** were attributed to SARS control efforts. This leads to the question of whether physical distancing to reduce transmission of SARS-CoV-2 has had or will have an impact on the transmission of other infectious diseases.

Globally, hundreds of thousands of people die each year from seasonal influenza. Typically, seasonal flu cases in the northern hemisphere peak in February and tail off in May. This year, **based on reports from national influenza laboratories in 71 countries**, the number of lab-confirmed cases of influenza dropped precipitously in early April, a few weeks after the COVID-19 pandemic was declared on March 11. **A study from Hong Kong** showed that compared with winter influenza seasons from 2015-16 through 2018-19, the 2019-20 winter influenza season was 63% shorter and the number of deaths from laboratory confirmed influenza in adults was 62% lower. These reductions coincided with the implementation of COVID-19 epidemic mitigation strategies. This figure shows percentages of different pathogens in all respiratory specimens analyzed during 2018-20 in Hong Kong. The width of each pink bar represents the duration of each influenza season, colored lines represent the individual pathogens isolated from patients presenting with influenza-like illness, and the date of isolation of the first COVID-19 case in Hong Kong is marked.



Source: **https://www.bmj.com/content/369/bmj.m1628**

Another study from Hong Kong estimated a 44% (95% CI 34–53%) reduction in the transmissibility of influenza A H1N1 in the community due to COVID-19-related measures: the Rt for influenza fell from 1.28 (95% CI 1.26–1.30) before the start of the school closures to 0.72 (95% CI 0.70–0.74) during the closure weeks. **In Singapore,** influenza data from several weeks of 2020 during which COVID-19 containment measures were in place, compared with the same time period in 2019, showed that the estimated daily number of influenza cases was 76% lower and

the influenza positivity rate of clinical specimens was 64% lower in 2020. In Taiwan, there were fewer per capita outpatient diagnoses of influenza-like illness and a lower influenza positivity rate of clinical specimens during the first 12 weeks of 2020, compared with the same time period in 2019. Interestingly, the same study also noted that the number of varicella (chickenpox) diagnoses per 1,000 outpatient visits remained similar in 2020 and 2019. This may suggest that the number of people seeking healthcare was not significantly affected in Taiwan and that the observed decrease in influenza cases was not significantly affected by changes in healthcare seeking behavior. Indeed, reported decreases in influenza cases may reflect the effects of hygiene and physical distancing measures, but they may also reflect how the COVID-19 pandemic is affecting healthcare seeking behavior, staffing in influenza sentinel sites, as well as testing capacities in some settings. Of note, the chickenpox data from Taiwan may also illustrate the importance of considering transmission routes and at-risk populations when exploring what effects an infectious disease

Similar to respiratory viruses, other infectious diseases can be categorized by type of pathogen (i.e. virus or bacteria) and by transmission route. In some environments, physical distancing may decrease the incidence of some enteric (gastrointestinal) diseases that are transmitted via ingestion of contaminated food or water, direct contact with infected individuals, or contact with contaminated surfaces. CDC data on norovirus outbreaks in the United States show that there were 21 outbreaks in March 2020 compared with 104 outbreaks in March 2019. Further analyses of these data are not available, but it is conceivable that reduced utilization of the environments that are high risk for norovirus outbreaks (healthcare facilities, restaurants and catered events, school and child care centers, and cruise ships) has had an impact on the incidence of norovirus outbreaks. For sexually transmitted infections (STIs) it is unclear whether current decreases in case counts are reflective of decreased transmission due to physical distancing. Many STI programs have reduced or suspended diagnostic and treatment programs; there is concern that transmission has not truly fallen and that restructuring of

public health department efforts away from STI services may actually result in increased transmission. For vector-borne diseases such as malaria, which is carried by mosquitoes, physical distancing is less likely to significantly decrease transmission. In fact, the COVID-19 pandemic is anticipated to increase morbidity and mortality related to malaria; many aspects of the COVID-19 pandemic, including physical distancing, are expected to have a harmful impact on bed net distribution, mosquito control programs and on malaria diagnosis and treatment capabilities. For vector-borne diseases that are endemic to the United States, such as Lyme Disease which is carried by ticks, physical distancing may have an impact on transmission if those measures influence human outdoor behaviors that bring people into contact with ticks.

If physical distancing interventions continue into the Fall, it is possible that not only COVID-19, but also influenza and other infectious diseases, may occur at lower than usual levels.

Indoor versus outdoor transmission of COVID-19

Main message: Transmission of COVID-19 in closed environments indoors is significantly more likely than in open-air environments outdoors. Appropriate infection prevention measures should be taken in both environments when interacting with others, including protective face coverings, hand-washing, physical distancing, and avoiding large, crowded gatherings.

After weeks of sheltering in place, and with the unofficial start of summer underway, many in the US are eager to resume some of their activities both indoors and outdoors. All 50 states are now allowing for increased movement and activity of their residents, however the risk of contracting COVID-19 is not zero.

There are data to guide what activities and settings carry lower risk than others. A recent **preprint study** from Japan examined the secondary cases generated by 110 index cases and identified that the odds of transmitting disease in a closed environment was 19 times higher than in an open-air environment. Another preprint **study from China** looked more closely at instances where there was transmission from one infected person to multiple other people, and again, the most likely venues that led to this type of transmission were indoor. Specifically, homes were the most common venues resulting in transmission to multiple persons, followed by transportation and indoor retail/restaurant/recreation settings. Among 318 outbreaks with three or more cases identified, only one occurred in an open-air environment outdoors where one person transmitted disease to two other people.

It is intuitive that for a virus that predominantly spreads by droplet transmission, improved ventilation and absence of recirculated air, as in the outdoor open-air environment, likely decreases the risk of transmission. Even indoors, there is **data to support** that there is less detectible virus in well ventilated areas than poorly ventilated ones. There are also data to support that **exposure to sunlight**, both UV as well as visible light, results in rapid inactivation of the virus, especially on surfaces, leading to an additionally lower risk environment outdoors.

Experts recommend continuing measures to reduce risk of transmission even outdoors, such as wearing face coverings when interacting within six feet of people other than household members, avoiding sharing food and drinks, and maintaining excellent hand hygiene. People should continue to avoid large gatherings.

Weekly Article Highlights

Period of infectivity to inform strategies for de-isolation for COVID-19 patients

(Academy of Medicine, Singapore, 23 May 2020)

Main Message: The National Centre for Infectious Diseases and the Chapter of Infectious Disease Physicians in Singapore reviewed accumulated epidemiological, clinical, and laboratory evidence on how long patients with COVID-19 can effectively transmit the infection. They conclude: "the infectious period of SARS-CoV-2 in symptomatic individuals may begin around 2 days before the onset of symptoms, and persists for about 7—10 days after the onset of symptoms." They suggest revised criteria for discharge from hospital and release from isolation could be based on symptom timing rather than repeated testing for viral RNA.

- Epidemiological studies of well-characterized transmission pairs estimate the **serial interval** (time between symptom onset for a primary case and a secondary case) for symptomatic COVID-19 illness is 5.8 days and most symptomatic **secondary cases become ill** within 5 days of infection.
- Laboratory data consistently indicate that infectiousness begins just prior to and with the onset of symptoms and then rapidly declines within the first week. Even if viral RNA can still be detected up to a month longer, it does not necessarily represent transmissible infection. Viral cultures from throat and lung samples are consistently negative beyond the first eight days of symptoms and subgenomic messenger RNAs—present only in actively infected cells—**are undetectable by day 10 or 11**.
- The timing of symptom onset and period of infectivity are predictable in the vast majority of symptomatic cases. Rather than repeat viral testing, a more practical basis for recommendations about discharge and terminating isolation could be based on the number of days following symptom onset. For example, **CDC recommends that patients can be released from isolation 10 days after illness onset** and at least 3 days (72 hours) after recovery (where recovery specifically refers to resolution of fever

without the use of fever-reducing medications and progressive improvement or resolution of other symptoms).

- It is less clear what portion of SARS-CoV-2 transmission originates from completely asymptomatic persons and pre-symptomatic cases, but their viral clearance dynamics may be similar to those of symptomatic patients. Transmission risk from patients with **immunocompromised conditions** may be less reliably predictable and a test based strategy may be more appropriate for this group in settings where resources allow.

Remdesivir for 5 or 10 Days in Patients with Severe Covid-19

(NEJM, 27 May 2020)

Main message: In this industry-sponsored trial, patients with severe COVID-19 were randomly assigned to receive five or ten days of treatment with remdesivir. There was not a significant difference in efficacy between the two treatment groups. There were significantly more serious adverse events among those treated for ten days. This trial did not assess the efficacy of remdesivir versus placebo. Results suggest that if remdesivir is an effective treatment for COVID-19, shorter durations of therapy may be equally clinically efficacious and safer.

- Investigators at 55 hospitals in 8 countries enrolled patients of at least 12 years of age with COVID-19 and either radiographic evidence of pneumonia or low oxygen saturation. Patients were excluded if there was evidence of organ failure, including a need for mechanical ventilation, or if other treatments with potential activity against SARS-CoV-2 were given. Patients were randomly assigned to receive intravenous treatment with remdesivir for five days or ten days. Endpoints included clinical status after 14 days (on a scale ranging from discharge to death) and adverse events for up to 30 days after the last dose of remdesivir.

- Results:
    - Patients: 397 patients began treatment under study protocols and were included in the analysis. In the 5-day group, 200 started treatment and 86% completed the course (8% stopped due to hospital discharge and 4% had adverse events). In the 10-day group, 197 started treatment and 44% completed the course (35% stopped due to hospital discharge, 11% had adverse events, and 6% died). At baseline, the clinical status of patients in the ten-day group was significantly worse than those in the five-day group.
    - Efficacy: 65% of patients in the 5-day group showed clinical improvement by day 14, compared with 54% of patients in the 10-day group. After adjusting for baseline clinical status, patients in the two groups had a similar distribution in clinical status at Day 14.
    - Safety: The proportion of patients experiencing adverse events was similar in the two groups: 70% in the 5-day group and 74% in the 10-day group. After adjusting for baseline clinical status, serious adverse events were significantly more common among those in the ten-day group. The most common severe adverse event was acute respiratory failure.
- Limitations include the absence of a placebo-controlled arm, so the efficacy of remdesivir could not be determined. This was an open-label trial, in part to allow patients to be discharged as soon as possible, which reduced the proportion of patients in the ten-day group who completed treatment. Further evaluation of longer treatment durations in high-risk subgroups of patients is warranted.

Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial

(Lancet, 22 May)

Main message: In this Phase 1 trial of a new vaccine for preventing COVID-19, the researchers studied administering different doses of a vaccine directed at one of the key targets on the SARS-CoV-2 virus and measured the recipient's immune system response as well any adverse events. The vaccine was able to produce a robust immune system response with measurable antibodies after two weeks and a peak response after four weeks. The vaccine, which uses a weakened common cold virus incapable of causing disease to deliver parts of the SARS-CoV-2 virus and stimulate immune response, was well tolerated with no serious adverse events in the first 28 days after vaccination. Many recipients did report pain at the injection site, as well as other adverse effects such as fever, headache, muscle pain, and fatigue. These results are encouraging for further study of this vaccine.

- The researchers recruited 108 healthy participants in China and administered a single dose of vaccine to each at a low, medium, or high dose. They then tested several components of the body's immune response including antibodies and T cells at two time points. They also monitored for safety and adverse events.
- Evidence of both cellular and humoral immune response was apparent on testing of vaccine recipients. Immunoglobulin antibodies and neutralizing antibodies were present on day 14, and peaked on day 28, while T-cell levels peaked on day 14. Mild and moderate adverse events were common in the first seven days after vaccination, with 81% of vaccine recipients overall reporting at least one. The most common local adverse event was pain at the injection site. The most common systemic adverse events were fever and headache. No serious adverse events were reported during the 28 day follow up.
- The study confirms that the vaccine is well tolerated by recipients and that it is immunogenic. The low and medium dose vaccine will be recommended for a Phase 2 clinical trial as a next step.

Suggested citation: Cash-Goldwasser S, Kardooni S, Kachur SP, Cobb L, Bradford E and Shahpar C. Weekly COVID-19 Science Review May 23–29 2020. Resolve to Save Lives. 2020 June 2. Available from https://preventepidemics.org/coronavirus/weekly-science-review/