

COVID-19

Weekly Science Review

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:

Assessing COVID-19 resurgence

[Read the full Insight: Assessing COVID-19 resurgence](#)

As some countries and US states roll back the public health and social measures (PHSMs, also known as physical or social distancing) enacted over the past several weeks, many are **predicting** a new wave of COVID-19 cases as a consequence. Assessing the potential impact is critical, because timely data help governments adjust their plans if there is a spike in cases. Assessment may also give other governments insights into the safest and most effective ways to reopen their economies.

Key measures to observe going forward include tracking mobility, COVID-19 or flu-like symptoms, new confirmed cases, COVID-19 hospitalizations, COVID-19 deaths, and other excess deaths. In this insight we describe each of these measures as well as their pros and cons for identifying a potential resurgence in COVID-19.

Table: Potential indicators of COVID-19 resurgence

Measure	Time lag	When is data reported/available	Data sources (sample)	Example indicators*	Relevance to LMICs
Mobility	None	1 day to 2 weeks, depending on the platform	<ul style="list-style-type: none"> Google Facebook SafeGraph University of Maryland Apple 	<ul style="list-style-type: none"> Decrease in percent staying home Increase in miles traveled Increase in number of trips per day (work or leisure) Changes in sector mobility 	Interpret with caution if smartphones not common
Symptoms	5 days	1 day to 2 weeks	<ul style="list-style-type: none"> New York City US CDC ILI Map Facebook 	<ul style="list-style-type: none"> 3 consecutive days of outbreak level influenza or respiratory symptoms 	Yes, e.g. SARI data
Cases	7 days	1 to 5 days, depending on testing turnaround	<ul style="list-style-type: none"> Covid Tracking New York Times US CDC European CDC Johns Hopkins 	<ul style="list-style-type: none"> Increase over 5 days (slope of >0.1/100,000 per day) when case load already >10/100,000 over two weeks. Increasing testing positivity rate 	Interpret with caution if testing limited

Measure	Time lag	When is data reported/ available	Data sources (sample)	Example indicators*	Relevance to LMICs
Hospitalizations	10-13 days	Within a few days	<ul style="list-style-type: none"> Covid Tracking US CDC Inpatient bed data 	<ul style="list-style-type: none"> Increase in daily hospitalizations Increase in net hospitalizations (new hospitalizations – discharges/deaths) Capacity for new patients <ul style="list-style-type: none"> 30% space in ICU 30% space in hospital Inability to admit 2x as many COVID patients as currently in hospital 	If tertiary health care system well developed
COVID deaths					
Deaths	18 days	Confirmed COVID-19 deaths often reported quickly. Excess deaths may lag as deaths take time to be reported.	<ul style="list-style-type: none"> Covid Tracking New York Times US CDC European CDC Johns Hopkins <p>Excess deaths:</p> <ul style="list-style-type: none"> US CDC 	<ul style="list-style-type: none"> Increase in daily confirmed/probable COVID-19 deaths, using 3-day moving average Number of deaths for preceding week above expected 	Yes. Excess deaths may be most useful

*For most measures of cases, hospitalizations and deaths, it is important to use 3-day moving averages to account for random variability/fluctuation from day to day.

Children and transmission risk

From the start of the pandemic, many observed that fewer children than adults seemed to be affected, at least by clinically severe COVID-19 illness. Evidence is less clear on how easily children can become infected and to what extent they contribute to transmission of SARS-CoV-2. **In contact tracing and survey studies**, children who had close contact with a confirmed case patient in China were 24-49% less likely to become infected than adult contacts. One unpublished study demonstrated that children, once infected, **can carry the same viral load** as older persons. That finding raises concern that children could transmit infection as readily as others. In contrast, **only 3 of 31 household cluster investigations across five countries identified a child** as the index case, which suggests that children are not the main drivers of transmission. This is in contrast to outbreaks of other respiratory viruses where children may be the starting point for as many as half of transmission chains. From **studies of transmission chains within households**, children living with a COVID-19 patient were four times less likely to become infected than adults in the home. Contact investigations for 18 COVID-19 index cases among students and adult staff at Australian schools found only two instances of **possible transmission at school** among a total of 863 contacts. **Swiss health authorities recently** concluded that direct evidence of transmission from children to other members of the community was scant, and that better understanding those risks would provide important information for decisions about school closures and other measures to protect children, teachers, parents, and grandparents.

A large prospective study is underway to determine the incidence and potential risk factors for COVID-19-related infection and illness in children. When they are infected, a high proportion of children may be asymptomatic or only mildly ill. Large studies of children who became ill with COVID-19 have already been reported from **China** and the **United States**. Children with COVID-19 are less likely than adults to have typical symptoms such as cough, fever, and shortness of breath. Overall, children are also less likely to require hospitalization, but infants are more likely to be hospitalized than older children. Regardless of how much children contribute to transmission of SARS-CoV-2, it is important to note that a small number do experience severe illness—including some manifestations that may be unique to pediatric patients (see below)—which can be fatal. Given these potential

consequences, it is prudent to take steps to prevent children getting infected in the first place.

Hyperinflammatory shock and Kawasaki Disease with a link to COVID-19 in children

As early as April 7, a [case report](#) published in the journal *Hospital Pediatrics* described a six-month old with classic Kawasaki Disease who tested positive for COVID-19. [Kawasaki Disease](#) (KD) is a rare inflammatory disorder occurring most commonly in children under five years of age which causes swelling in the arteries throughout the body, including the arteries that supply blood to the heart. With prompt identification and treatment in classic KD, heart complications can be avoided. Although the exact cause of KD is not fully understood, it is thought to be related to infectious etiologies or an abnormally robust immune response to infection. KD has a [known association](#) with viral infections including common human coronaviruses that typically cause common-cold like symptoms. A background incidence of KD is expected, with fewer than 6,000 cases typically reported in the US each year.

More recently, a series of cases of hyperinflammatory shock affecting children and resembling classic KD, incomplete KD or [toxic shock syndrome](#) has been reported in the US, Italy, Spain and the UK and is thought to be related to COVID-19. The number of cases being reported in relation to COVID-19 is higher than the expected background incidence of KD. The clinical presentation in these recent cases is described as [“a new phenomenon affecting previously asymptomatic children with SARS-CoV-2 infection manifesting as a hyperinflammatory syndrome with multiorgan involvement similar to Kawasaki Disease shock syndrome.”](#)

New York City [alerted](#) health care personnel on May 4 about 15 cases among children between two and 15 years of age hospitalized between April 17–May 1. As of May 10, New York City [reported](#) three deaths from the syndrome and at least 73 cases have been reported to health officials. Those with severe illness have been admitted to pediatric ICUs and required cardiac, respiratory, and blood pressure support. Abdominal symptoms and diarrhea have been common at presentation. PCR testing for SARS-CoV-2 was positive in four of 15 patients, negative in 10, and indeterminate followed by negative in one. Six of the 10 patients who had negative tests on PCR had tested positive for antibodies on serologic testing. PCR tests

detect whether virus is currently present; serology tests detect infections that have either been present for a few days or have already resolved.

Among the eight patients from the UK described in a *Lancet* [article](#), all initially tested negative for SARS-CoV-2 by PCR testing and two later tested positive. One child tested positive for other viruses. Five of eight required mechanical ventilation and all required medications to support their heart and/or blood pressure. All were treated with intravenous immunoglobulin (IVIG), a standard treatment for KD, and some were treated with aspirin, another treatment for KD. One of the two patients who tested positive for SARS-CoV-2 by PCR died. On PCR testing, no infectious pathogen was identified in five patients. For all of these patients, antibody tests were positive, although specific information about the timing of those tests and the antibodies detected is not available.

This is a newly described syndrome among children that appears to be linked to infection with SARS-CoV-2 and may cause classic KD, elements of it, or shock. It is possible that currently only the most severe cases are being detected, as is common during the initial phase of a new disease or syndrome. The clinical and research community is learning more about this condition as more reports and scientific information become available.

ACE inhibitors or angiotensin receptor blockers (ARBs) and risk for severe COVID-19 disease

Angiotensin Converting Enzyme inhibitors (ACE inhibitors) and Angiotensin II Receptor Blockers (ARBs) are among the standard preferred antihypertensive agents and are also recommended standard treatments for patients with chronic kidney disease, coronary heart disease, or heart failure with reduced ejection fraction. ACE inhibitors and ARBs are life-saving treatments and are generally safe, as demonstrated by randomized clinical trials.

The angiotensin-converting enzyme 2 (ACE2) in the lung and elsewhere is believed to be a binding site for SARS-CoV-2. Early evidence from animal studies suggested that ACE inhibitors and ARBs may upregulate ACE2. Early in March 2020, several [researchers hypothesized](#) that patients taking ACE inhibitors or ARBs may be at risk for more severe COVID-19 illness because of ACE2 upregulation. At the same time, [other researchers](#) suggested the opposite: that these medications may protect against COVID-19 and hold potential as treatments of the infection.

Several studies recently **published** in the *New England Journal of Medicine* assessed potential harms of ACE inhibitors or ARBs in the context of COVID-19. Across different patient populations and using different observational study designs, there was no evidence of increased risk of COVID-19 infection or more severe COVID-19 in patients taking ACE inhibitors or ARBs. Observational studies of medication risks are prone to *confounding by indication*: ACE inhibitors and ARBs are prescribed for patients with hypertension, diabetes, coronary heart disease, heart failure, or chronic kidney disease. These same conditions are also risk factors for more severe COVID-19. All of the observational studies employed matching or statistical adjustment methods to minimize confounding by indication. The results of two studies, one from **China** and one **global study**, suggested a possible *benefit* of ACE inhibitors or ARBs in reducing risk for more severe COVID-19 outcomes. But this result was not consistent across all of the studies, and given the observational design, there is currently no direct evidence of benefit. Based on available observational evidence as of April 24, the WHO also indicated that there was **“low certainty evidence” that patients on ACE inhibitors or ARBs are not at higher risk from COVID-19.**

Randomized controlled trials will provide more information about the impact of ACE inhibitors and ARBs on COVID-19. Even before the results of these recent studies were published, **professional societies recommended against discontinuing these medications** except in the case of a medical indication for discontinuation (low blood pressure or side effects). The latest evidence reinforces this recommendation.

In summary, based on recent observational studies there is no evidence to support claims that ACE inhibitors or ARBs raise the risk for more severe COVID-19 illness.

FAQS

What are COVID toes?

Although the most characteristic symptoms of COVID-19 remain cough, shortness of breath, and fever, followed by sore throat, headache, fatigue, general weakness, muscle aches, and loss of smell or taste, the list of possible symptoms continues to grow. Recently, dermatologists have begun to report on skin manifestations including “COVID toes,” a condition resembling chilblains, marked by red or purple flat patches on the toes which can be painful and associated with blistering or minor swelling. Some patients get these manifestations while exhibiting other symptoms of COVID-19, whereas others get them two or three weeks after recovering from other symptoms. Still others manifest COVID toes as the only sign they were ever infected with the SARS-CoV-2 virus. The finding is benign and self-limited. It does not require specific treatment, and the discoloration goes away on its own over time. Exactly what causes COVID toes is still unknown; theories include tiny clots in small blood vessels or inflammation of these blood vessels due to the immune system’s reaction to the infection. Based on preliminary evidence, COVID toes may be more common in younger patients but can affect persons at any age. Researchers are continuing to learn more about COVID toes and other skin manifestations of COVID-19.



Epidemiology

Public Health Response to COVID-19 Cases in Correctional and Detention Facilities — Louisiana, March–April 2020

(MMWR, 8 May 2020)

Main message: Active surveillance for COVID-19 in correctional and detention facilities, together with information on the policies and procedures implemented to stop epidemic spread in those facilities, highlights the unique challenges of interrupting SARS-CoV-2 transmission in congregate settings. Despite awareness among facility leadership of CDC guidance on reducing the spread of SARS-CoV-2 in such environments, physical and logistical constraints make implementation of public health measures difficult.

- In March 2020, the Louisiana Department of Health began surveillance for COVID-19 in correctional and detention facilities and, in partnership with the CDC, developed the COVID-19 Management Assessment and Response (CMAR) tool, a telephone-based instrument to facilitate provision of technical assistance to facilities across Louisiana.
- During March 25–April 22, 489 laboratory-confirmed COVID-19 cases among inmates and detainees and 253 cases among staff members were reported across 46 (32%) of 144 facilities in Louisiana. Two facilities conducted testing among asymptomatic close contacts of confirmed COVID-19 cases; the majority of contacts tested PCR-positive for SARS-CoV-2 at the end of their 14-day quarantine period.
- 24 facilities participated in CMAR; all reported implementing CDC recommendations for suspending visitation, providing hand hygiene supplies, and symptom screening of new intakes. Barriers to implementing CDC guidelines included lack of space to isolate COVID-19 patients and quarantine close contacts, and the inability of inmates to socially distance due to crowding. Leadership reported disincentives to report symptoms, including the prospect of medical isolation and monetary costs for medical visits.
- Case counts may have been underestimated: case counts among staff were not available for all facilities and case finding was dependent on each facility's

surveillance and testing practices. CMAR participation was voluntary and results may not be representative of all facilities in Louisiana.

- Further guidelines for correctional and detention facilities are available from the CDC [here](#).

Clinical Characteristics and Results of Semen Tests Among Men with Coronavirus Disease 2019.

(JAMA, 7 May 2020)

Main message: Few studies have examined the possibility of sexual transmission of COVID-19. In this study, SARS-CoV-2 was detected in a minority of men at various states of COVID-19 infection. This is in contrast to a **prior pre-print study** by different authors which found no evidence of SARS-CoV-2 in semen. More studies are needed to understand factors important for sexual transmission, including virus shedding, survival time and concentration in semen.

- This study enrolled 38 men for semen testing in Shangqiu, China from late January to early February.
- Six (16%) of the men had SARS-CoV-2 in their semen, including 27% of men who were acutely infected and 9% of men who were recovering. There was no difference in test results by age, days since symptom onset, days since hospitalization or days since clinical recovery.
- This was a small study with a short follow-up period which limits our understanding of virus survival time.

Features of 16,749 hospitalised UK patients with COVID-19 using the ISARIC WHO Clinical Characterisation

(MedRxiv pre-print 28 April 2020)

Main message: Investigators were able to rapidly conduct a large prospective observational cohort study of patients hospitalized with COVID-19 in the United Kingdom (UK) using a pre-approved protocol designed by the International Severe Acute Respiratory and emerging Infections Consortium (ISARIC) and endorsed by the World Health Organization (WHO) to facilitate immediate gathering and analysis of clinical data in the event of a pandemic. Results confirm the findings of a number of smaller studies from various settings, including associations between survival and age, sex and underlying comorbidities, as well as high mortality rates especially among the critically ill.

- Clinical information from the health records of patients with COVID-19 admitted to hospitals across England, Scotland and Wales was extracted and analyzed. The analysis was limited to those admitted more than 14 days prior to data extraction to reduce the proportion with yet-to-be determined outcomes.
- Between February 6 and April 18, investigators recruited 16,749 patients admitted with COVID-19 (14.7% of all confirmed cases in the UK) to 166 hospitals. The median age was 72 years and 60% were male. The most common symptoms on presentation were respiratory although nearly 30% of patients had gastrointestinal symptoms. Current COVID-19 testing criteria in the UK would have missed 7% of participants.
- Among those admitted to non-critical and critical wards, 33% and 45% died, respectively. Increased age was a strong predictor of mortality after adjusting for comorbidities. Other independent predictors of mortality included male sex, malignancy, obesity, dementia and chronic cardiac, pulmonary or kidney disease. Among female participants of childbearing age, only 6% were pregnant, and pregnancy was not associated with mortality.
- Treatment-limiting care decisions were not captured. Many participants were co-enrolled in other studies, and those analyses as well as further analyses of these data are forthcoming.

Humoral immune response and prolonged PCR positivity in a cohort of 1343 SARS-CoV-2 patients in the New York City region

(MedRxiv pre-print 5 May 2020)

Main message: More than 99%, of PCR-positive COVID-19 cases from a New York City area study seroconverted and showed evidence of IgG antibodies to SARS-CoV-2 on serologic testing. In patients with suspected COVID-19 without laboratory confirmation of viral infection by PCR, 35% tested positive for antibodies, further supporting expanded access to PCR testing. Some patients required repeat testing to have strongly positive antibody titers, and the authors suggest that the optimal timing for serological testing is likely at least three to four weeks after symptom onset and at least two weeks after symptom resolution.

- The researchers recruited 1,343 persons with suspected or lab-confirmed COVID-19 in the New York City area through an online survey. Participants were tested for SARS-CoV-2 antibodies using an ELISA serologic test and also tested for persistent PCR-positivity.
- Among 624 patients reporting lab-confirmed COVID-19 with a PCR test positive for SARS-CoV-2, 89% had a positive antibody titer on their first test (82% strongly positive and 7% weakly positive). When the 11% who initially tested negative underwent repeat serologic testing more than one week later, all but three patients had a positive antibody titer (>99% overall seroconversion). Patients with suspected COVID-19 were less likely to have a positive antibody titer. Some patients had persistently positive PCR tests for SARS-CoV-2 up to 43 days after symptom onset. The implications of persistent PCR positivity for disease transmission after recovery are not understood.
- Some of the information in this study, including positive PCR test date and symptom onset date, was self-reported and may limit the accuracy of the time estimates from this study. The patients in this study will be followed for six more months to get a more long-term perspective on antibody activity in recovered COVID-19 patients.

Public Health

Report 19: The Potential Impact of the COVID-19 Epidemic on HIV, TB and Malaria in Low- and Middle-Income Countries

(Imperial College London, 1 May 2020)

Main message: There could be a substantial number of additional deaths and life-years lost to human immunodeficiency virus (HIV), tuberculosis (TB), and malaria in high-burden low- and middle-income countries (LMIC) due to the COVID-19 epidemic. The authors of this study conceptualized the impacts of COVID-19 on these other health priorities as occurring via 1) mitigation strategies that lead to scaling back of care-seeking, and 2) reduced capabilities of the healthcare system to prevent and treat disease. Results show that maintaining capabilities to prevent and treat HIV, TB, and malaria are potentially critical ways to reduce the impact of the COVID-19 epidemic in LMIC.

- Authors modeled four possible COVID-19 response scenarios: ‘no action’ in which the epidemic progresses without intervention, ‘mitigation’ in which the effective reproduction number (R_t) is somewhat reduced for 6 months, ‘suppression-lift’ in which the R_t is dramatically reduced but for only 2 months before restrictions are lifted, and ‘suppression’ in which the R_t is dramatically reduced for 1 year; the effects of ‘suppression’ can be ‘well managed’ (25% reduction in treatment services) or ‘unmanaged’ (50% reduction in treatment services). These response scenarios were assumed to result in different levels of excess demand on the healthcare system.
 - Over 5 years, deaths related to HIV, TB, and malaria may be increased by up to 10%, 20% and 36%, respectively, compared to if there were no COVID-19 epidemic. In a setting with a high burden of HIV, TB, and malaria, the number of life-years lost due to the indirect effects of COVID-19 could be up to 60% of the life-years lost to COVID-19 directly. Regarding the nature of the impacts of different response scenarios:
 - COVID-19: mortality and the impact on health services vary significantly between response scenarios.
 - HIV: excess mortality is largely driven by interruption of treatment for those already in care; impact is greatest when there is highest demand on the healthcare system.
 - TB: excess mortality is largely driven by duration, rather than intensity, of treatment interruption.
 - Malaria: excess mortality is influenced by timing and duration of the peak malaria season relative to the COVID-19 epidemic, and interruptions in preventive efforts have a significant effect.
- Table: COVID-19 deaths per million per capita and impacts on healthcare systems, and numbers of additional deaths per million per capita due to HIV, TB, and malaria,**

during 2020. For each disease, baseline ‘high’ and ‘moderate’ prevalence settings were modeled.

COVID-19 epidemic scenario	COVID-19	HIV		TB		Malaria	
		High	Moderate	High	Moderate	High	Moderate
	5,965						
No action	*Healthcare system: 4 weeks of extremely high demand and 2 weeks of high demand	161	84	-1	0	1978	1018
	4,393						
Mitigation	*Healthcare system: Period of high demand but no extremely high demand.	21	>11	51	3	2041	1225
	5,965						
Suppression-lift	*Healthcare system: 2 months of disruption followed by ‘no action’ sequence	45	23	21	1	2009	1092
	0						
Managed suppression	*Healthcare system: 12 months of low-level disruption	11	5	56		82	93
	0						
Unmanaged suppression	*Healthcare system: 12 months of disruption but no high demand	42	21	69	3	2149	1348

- Model predictive capability may be impacted by limited data on the spread of COVID-19, the extent of healthcare service disruption, and COVID-19 mortality rates in Africa. Some types of impact on healthcare systems, such as staff shortages and supply chain issues, were not considered. Diseases were modeled separately so most interactions between diseases were not considered.

Effects of COVID-19 Pandemic on Routine Pediatric Vaccine Ordering and Administration – United States, 2020

(MMWR, 8 May 2020)

Main message: There has been a substantial decrease in the ordering and administration of childhood vaccines in the US since the March 13 declaration of a national emergency in response to the novel coronavirus pandemic. Children and communities in the US may face increased risk of vaccine preventable disease and outbreaks as restrictions to reduce transmission of COVID-19 are lifted in many parts of the country. These findings highlight the need for healthcare delivery to adapt and safely meet ongoing needs even in extenuating circumstances. Catch-up vaccination campaigns will be necessary.

- The CDC examined two data sources to track ordering and administration of non-influenza childhood vaccines to patients in eight large health care systems.
- Following the declaration of a national emergency in mid-March due to COVID-19, there was a sharp decline in the number of vaccines ordered when compared to the same time period the previous year. This decline in ordering vaccines corresponded to a decrease in administration of vaccines and was more pronounced for children over 24 months of age. There has been some rebound in administration of vaccines for the youngest children as measured by this sample of patients from eight large health care organizations.
- Both patient and provider factors may influence delays in routine childhood visits that would normally have included vaccinations. Study findings may not be representative of all communities and healthcare organizations in the US.

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<https://preventepidemics.org/coronavirus/weekly-science-review/>