

# IDSE

# Infectious Disease SPECIAL EDITION

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## Children, the Latest Victims of COVID-19



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# Children, the Latest Victims of COVID-19

By MARIE ROSENTHAL, MS



If there was any consolation from the COVID-19 pandemic, it was the notion that children escaped relatively unscathed. If they did become sick, they tended to have mild symptoms that did not require hospitalization.

That tiny consolation was shattered when very sick children began turning up in hospitals in Europe and the United States (*Lancet* 2020 May 6. [Epub ahead of print]). They took clinicians by surprise, admitted Michael Levin, MBE, PhD, FRCPC, FMedSci, a professor of pediatrics and international child health at the Imperial College in London, England, where some of these cases were reported.

January was the start of COVID-19 in England, but it wasn't until the end of March that "a number of pediatricians started noticing an unusual illness, and we had children who were admitted to pediatric intensive care units, critically ill with a very unusual syndrome," Dr. Levin said.

The timing of their presentation was unusual, explained Stanford T. Shulman, MD, a professor of pediatrics in infectious diseases at Northwestern University Feinberg School of Medicine, in Chicago. "These

patients are showing up in Northern Italy, London, Spain, France and now on the East Coast of the United States about a month or so after the peak of the COVID cases that are being seen in adults," he said.

Many parents reported an exposure to COVID-19 about a month before the onset of symptoms, either a positive test in the child or a relative, added Cena Tejani, MD, the associate fellowship director of Pediatric Emergency Medicine at the Children's Hospital of New Jersey at Newark Beth Israel Medical Center.

## Heterogeneous Phenotype

The first few cases were characterized as COVID-19-related Kawasaki disease (KD) because children presented with fever, sometimes a rash, conjunctivitis and cardiac signs, some of which are hallmarks of KD (*Lancet* 2020 May 13. [Epub ahead of print]).

First described in 1967, KD is a disease that tends to affect very young children—50% are younger than 24 months—and few children are older than 6 years of age. The etiology is unknown. KD

diagnostic criteria require fever for five days, and then at least four other signs, including rash, conjunctivitis, changes in the tongue, lips or oral cavity, changes in the extremities and cervical lymphadenopathy. The most concerning cardiovascular effects of KD are coronary artery abnormalities that can lead to thrombosis, stenosis, aneurysms and myocardial infarctions (*Pediatrics* 2004;114[6]:1708-1733. doi: 10.1542/peds.2004-2182).

But as more children presented with what is now called multisystem inflammatory syndrome in children (MIS-C), they came in with a more heterogeneous phenotype that was more like toxic shock and less like classic KD. "You probably have heard about these patients who have Kawasaki disease-like features temporally associated with COVID-19. We are also seeing patients with just myocarditis. We're seeing patients with toxic shock, so it's many different phenotypes. And it's really hard to know exactly what is causing this," said Lauren Henderson, MD, MMSc, an attending physician in the rheumatology program and an assistant

professor of pediatrics at Boston Children's Hospital.

"This appears to be a syndrome that is associated with COVID-19 and has a few similarities of Kawasaki disease but much more dramatic differences," Dr. Shulman explained.

Kawasaki disease tends to affect young children; MIS-C is affecting children of all ages with a median of about 11 years old, according to Dr. Levin, who spoke during a CDC webinar ([bit.ly/2Zc3bcn-IDSE](https://bit.ly/2Zc3bcn-IDSE)). "Perhaps the most striking feature is that Kawasaki disease prior to COVID-19 was a disease of young children, and the comparison we did ... is that they tend to be older," he said.

The rate of KD also is higher among Asian children, but this syndrome is not being seen in countries like China and Japan. "So, this is a very different demographic picture," Dr. Shulman said.

The differences might be due to virus and host factors, according to Ashraf Harahsheh, MD, FACC, FAAP, an associate professor of pediatrics at the George Washington University School of Medicine and Health Sciences, in Washington, D.C. "Some believe that the virus underwent spontaneous mutation in Italy before coming to the East Coast and spreading through Europe. Maybe the mutation made the COVID-19 act like an epitope that triggers KD-like illness in the genetically susceptible child. This might explain why we have not seen it in China, Japan, etc.," he said.

The clinical picture is also different. "With this new disease, patients may have one or two Kawasaki-type features like rash or some red eyes, but the dominant clinical features in the new syndrome are that patients have a lot of abdominal pain, diarrhea and some vomiting," Dr. Shulman said.

Although MIS-C also affects the heart, it is not limited to the arterial

signs seen in KD; children with MIS-C are developing a mild to severe myocarditis with shock and hypotension.

The laboratory features are also different, according to Dr. Shulman, an attending at the Ann & Robert H. Lurie Children's Hospital of Chicago. The inflammatory marker C-reactive protein (CRP) is "a lot higher" in patients with MIS-C, he said. B-type natriuretic peptide (BNP), a marker of heart function, typically is normal or near normal in patients with KD, but is "extremely elevated in the new syndrome in children." In addition, "white blood cell counts are substantially higher in the new syndrome and the lymphocyte counts are substantially lower," Dr. Shulman said. Most patients have evidence of COVID, either by polymerase chain reaction or antibody test, he added.

"We shouldn't be overly focused on whether or not COVID-19 triggers KD," said Michael Bell, MD, the division chief of critical care medicine at Children's National Hospital, in Washington, D.C. "It is clear that COVID-19 is triggering inflammation—the cytokine storm—in adults as well as children, on a scale that has not been seen with other respiratory viruses," he said.

On May 14, the CDC issued an emergency health alert warning about MIS-C and its apparent relationship

## Case Definition for MIS-C

- An individual younger than 21 years of age presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (>2 organ systems) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurologic); and
- No alternative plausible diagnoses; and
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology or antigen test; or COVID-19 exposure within the four weeks prior to the onset of symptoms

- Fever of at least >38.0° C for at least 24 hours, or report of subjective fever lasting at least 24 hours
- Tests should include, but not be limited to, one or more of the following: an elevated CRP, ESR, fibrinogen, PCT, D-dimer, ferritin, LDH or IL-6; elevated neutrophils; reduced lymphocytes; and low albumin
- Some individuals may fulfill the full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C
- Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection



CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL-6, interleukin 6; LDH, lactic acid dehydrogenase; MIS-C, multisystem inflammatory syndrome in children; PCT, procalcitonin; RT-PCR, reverse transcription-polymerase chain reaction  
Source: CDC

to COVID-19 and listing the diagnostic criteria for the syndrome (bit.ly/3bMfBw7-IDSE). The CDC alert describes pediatric patients with a persistent fever and a variety of signs and symptoms, including multiorgan involvement and elevated inflammatory markers.

Although the overall number of children presenting with MIS-C is still low, most of these kids are very sick; many require hospitalization; and although they are not experiencing the respiratory failure seen in adults, the children do require oxygenation. Some of these children also require ventilation or extracorporeal membrane oxygenation due to heart failure, and there have been deaths.

Dr. Tejani said children with the syndrome are coming through her ER, and she is seeing similar patients to those described by Dr. Shulman

and others. “Kawasaki disease is something that we’ve all seen for a very long time, and it involves five days of fever and has to meet certain criteria. And the patients we’re seeing with this post-COVID infection are not really fitting these criteria firmly,” she said.

“All of these kids are presenting with fevers and tachycardia. Some of them have low blood pressure, and most of them seem very irritable. They are crying a lot,” Dr. Tejani said. Because her patients have been younger, it can be difficult to pinpoint the source of the pain, but she added that in some patients it appears to be abdominal pain.

“Most of them are febrile,” Dr. Henderson said. “A lot of them may have a rash. A lot of them seem to have GI symptoms, so a lot of abdominal pain, vomiting, diarrhea, and they come in

very inflamed,” she said. “Often, they are having some type of end-organ damage.” Clinicians have seen heart involvement, GI involvement and cardiac shock. “These are the broad common brush strokes that we are seeing in these patients. But respiratory disease is not as prominent,” Dr. Henderson said.

“Features that seem more unique to MIS-C include the propensity for direct myocardial injury manifesting as higher troponin and BNP compared with the typical KD patient,” Dr. Harahsheh said, adding that some cases have significant anemia.

Some patients also manifest the more typical inflammation of coronary arteries seen in KD, he said.

The American Heart Association recommends a series of testing for these children, which includes sequential inflammatory markers,

## Even Early On, Some Kids Did Not Fare Well

The idea that children were spared at all might be false, according to a recent study. Children, teens and young adults saw severe complications from COVID-19 all along, and those with underlying health conditions are at even greater risk (*JAMA Pediatrics* 2020 May 11. [Epub ahead of print]. doi: 10.1001/jamapediatrics.2020.1948).

“The idea that COVID-19 is sparing of young people is just false,” said study co-author Lawrence C. Kleinman, MD, MPH, a professor, the vice chair of academic development, and the chief of the Department of Pediatrics, Division of Population Health, Quality and Implementation Science, at Rutgers Robert Wood Johnson Medical School in New Brunswick, N.J. “While children are more likely to get very sick if they have other chronic conditions, including obesity, it is important to note that children without chronic illness are also at risk.”

The study followed 48 children and young adults—from newborns to 21 years of age—who were admitted to pediatric ICUs (PICUs) in the United States and Canada for COVID-19 in March and April. More than 80% had chronic underlying conditions, such as immunosuppression, obesity, diabetes, seizures or chronic lung disease.

Of those, 40% depended on technological support due to developmental delays or genetic anomalies.

More than 20% experienced failure of two or more organ systems due to COVID-19, and nearly 40% required a breathing tube and ventilator. At the end of the follow-up period, nearly 33% of the children were still hospitalized due to COVID-19, with three still requiring ventilator support and one on life support. Two of the children admitted during the three-week study period died.

“This study provides a baseline understanding of the early disease burden of COVID-19 in pediatric patients,” said Hariprem Rajasekhar, MD, a pediatric intensivist involved in conducting the study at Robert Wood Johnson Medical School’s Department of Pediatrics. “The findings confirm that this emerging disease was already widespread in March and that it is not universally benign among children.”

The researchers said they were “cautiously encouraged” by hospital outcomes for the children studied, citing the 4.2% mortality rate for PICU patients compared with published mortality rates of up to 62% among adults admitted to ICUs, as well as lower incidences of respiratory failure.



such as complete blood counts as well as differentials; CRP and erythrocyte sedimentation rate; coagulation studies such as D-dimer and ferritin; liver function tests; and a cytokine panel, according to Dr. Harahsheh. (The Royal College of Paediatrics and Child Health offers diagnostic and monitoring information: bit.ly/2X77yWp-IDSE.)

“It’s a lot of tests that we’re sending, and I think part of the problem is that we’re not exactly sure what the syndrome is. In some cases, we’ve seen elevations in all of those,” Dr. Tejani said.

“We have recently developed a stepwise protocol that helps us decide which labs to send and which patients need to be admitted to the hospital. There is still ambiguity here, but we are beginning to collect data that we need to make decisions and clarify this post-inflammatory syndrome,” she added.

### Treatment

Perhaps because the initial presentation appeared to be KD, the treatments used in KD were the first ones tried in these patients. This includes aspirin, steroids and IV immune globulin (IVIG). Although it is becoming clearer that MIS-C is probably not KD, the fact that children are responding to KD medications makes intuitive sense on the basis

of their anti-inflammatory properties, according to Jerry Siegel, PharmD, an expert in immune globulins. “IVIG has been recognized as an effective treatment to prevent coronary artery aneurysms in KD for many years,” Dr. Siegel said.

“While this new syndrome may be different from Kawasaki disease, there has been favorable response to high-dose (2-g/kg) IVIG, 30 to 50 mg/kg aspirin and steroids. The use of IVIG in these cases would be as an anti-inflammatory agent,” he said.

Some physicians are also giving interleukin inhibitors, and some institutions have had success with anakinra, an interleukin-1 receptor antagonist protein indicated for rheumatoid arthritis.

### Referral?

Most children testing positive for SARS-CoV-2 still have no or mild symptoms of disease, and do not have MIS-C, so some pediatricians and parents might be unsure when to refer because children with MIS-C should receive a multidisciplinary work-up.

“The public message in the UK was that patients should try and stay at home and not attend hospital because hospitals were under pressure,” Dr. Levin said. “And so children were remaining home with fevers for longer than they might have normally and arriving in a very seriously ill state.

Now that we’ve become more familiar with this problem, there’s been a very clear public health message—if children have persistent fever, they do need to be evaluated,” he said.

### Don’t Forget KD

Dr. Harahsheh said some of the children might actually have KD, which could be missed, so don’t totally discount it in your differential (*J Pediatr* 2020 May 6. [Epub ahead of print]). “Early in the COVID-19 pandemic, we KD experts were worried that more attention would be given to COVID-19 and cases of Kawasaki disease would be missed,” Dr. Harahsheh told *Infectious Disease Special Edition*. “We saw three cases, one at Children’s National, one at Boston and one in San Diego that presented late into their illness—more than 10 days from onset of fever. Our worry when we wrote this letter was missing KD in children,” he said.

### A Final Consideration

Just about as quickly as the cases were reported, people started asking experts whether they finally discovered the etiology of KD. Both Drs. Shulman and Harahsheh, who have been researching KD for a long time, said that was unlikely.

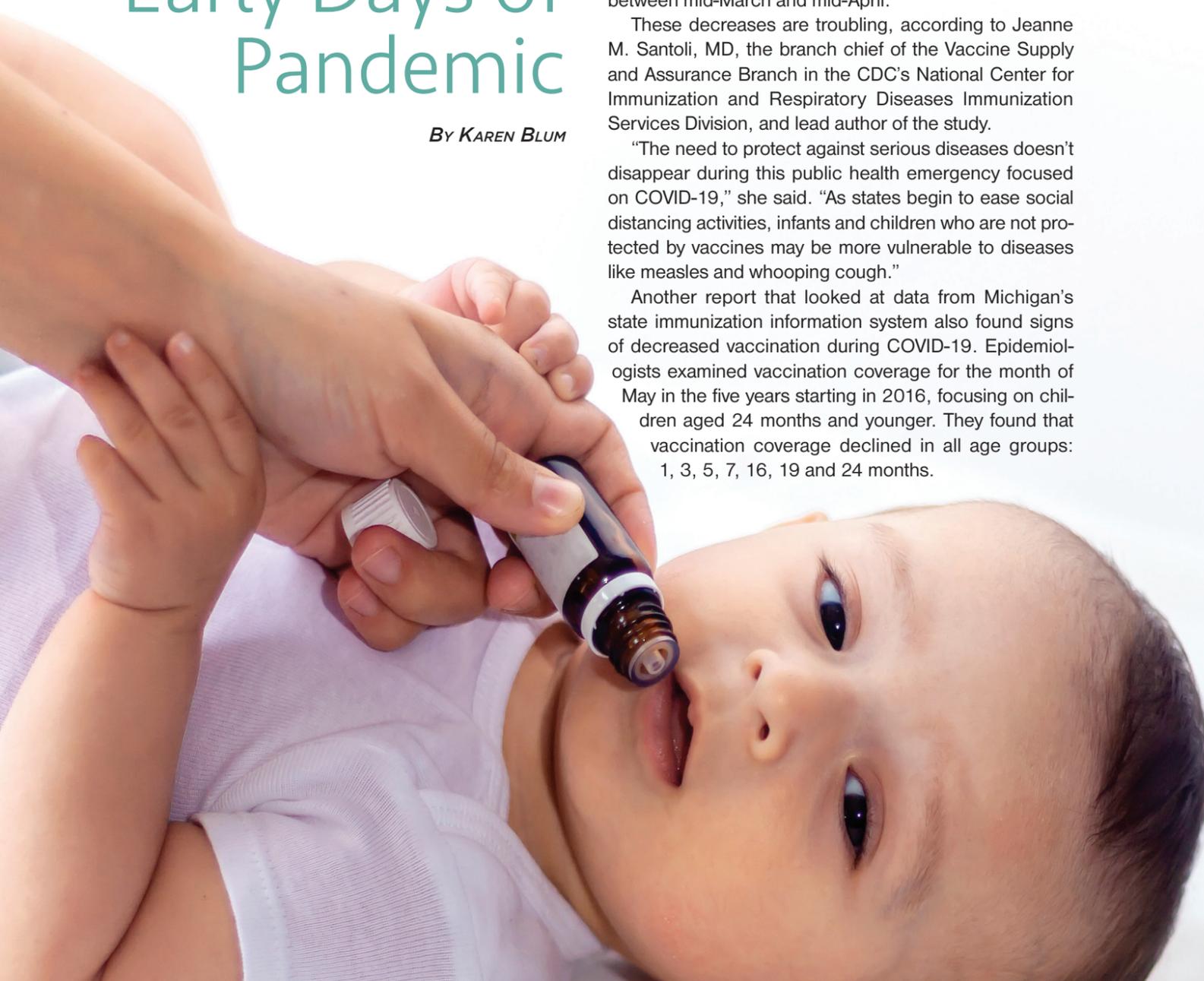
“Kawasaki disease has been around at least for 60 years,” Dr. Shulman said. “This new virus has been around for a couple of months. Clearly, the new virus is not the cause of Kawasaki.”

Dr. Harahsheh agreed. “With more than 50 years since it was first described by Dr. [Tomisaku] Kawasaki, and more than 20 years of focused research, no single pathogen that triggers KD has been identified,” he said. ■

*The sources reported no relevant financial relationships.*

# Routine Childhood Vaccinations Decline in Early Days of Pandemic

By KAREN BLUM



The U.S. vaccination program appears to be another victim of the COVID-19 pandemic: Routine childhood vaccinations are declining, and public health experts fear outbreaks of vaccine-preventable diseases down the road.

A report that evaluated vaccines ordered through the federal Vaccines for Children Program, which immunizes 50% of children in the country, and vaccine administration data from the CDC's Vaccine Safety Datalink found 2.5 million fewer vaccines were ordered from mid-March to mid-April 2020 compared with previous years (*MMWR Morb Mortal Wkly Rep* 2020;69[19]:591-593). The report also found that the weekly number of doses of measles-containing vaccines administered fell from an average of nearly 5,000 doses per week from January to mid-March 2020, to approximately 1,300 doses per week between mid-March and mid-April.

These decreases are troubling, according to Jeanne M. Santoli, MD, the branch chief of the Vaccine Supply and Assurance Branch in the CDC's National Center for Immunization and Respiratory Diseases Immunization Services Division, and lead author of the study.

"The need to protect against serious diseases doesn't disappear during this public health emergency focused on COVID-19," she said. "As states begin to ease social distancing activities, infants and children who are not protected by vaccines may be more vulnerable to diseases like measles and whooping cough."

Another report that looked at data from Michigan's state immunization information system also found signs of decreased vaccination during COVID-19. Epidemiologists examined vaccination coverage for the month of May in the five years starting in 2016, focusing on children aged 24 months and younger. They found that vaccination coverage declined in all age groups: 1, 3, 5, 7, 16, 19 and 24 months.

At age 5 months, for example, up-to-date status for all recommended vaccines declined from approximately two-thirds of children (66%-68%) during May of the years 2016-2019 to just less than half (49.7%) in May 2020 (*MMWR Morb Mortal Wkly Rep* 2020;69[20]:630-631).

Additionally, the number of non-influenza vaccine doses administered to children aged 24 months and younger decreased 15.5% during January to April 2020 compared with the same time period the previous two years.

This means there is a population of disease-susceptible children, and as the country reopens they will need to make up those appointments in an already-stressed health care system, said senior author of the Michigan report, Angela Shen, ScD, MPH, a visiting scientist at Children's Hospital of Philadelphia (CHOP) and retired captain with the U.S. Public Health Service. She and her colleagues are continuing to track numbers as states begin to reopen businesses and services.

It's difficult to predict what will happen, she said, although she anticipates the numbers going back up.

Both sources show steep declines beginning the week after the president declared a national emergency on March 13.

In communities where schools are planning to open in the fall, Dr. Santoli said, providers may experience a high demand for vaccination appointments, and if children are not up-to-date, schools may have to provide more vaccination waivers than usual, which could increase the risk for school-associated outbreaks.

There's some wiggle room in the timing for booster shots for 4- to 6-year-olds and vaccines for 11- to 13-year-olds, but you don't want to get behind on the primary immunization series, said Paul Offit, MD, the director of the Vaccine Education Center and a professor of pediatrics at CHOP.

"You really do need to get it in two months, four months, six months and 12 to 15 months," he said, noting that once children fall off, it's hard to catch up. "It's fair to say as we move into the next year or two, we're going to have a larger number of children who are either unvaccinated or undervaccinated. It's another piece of collateral damage of this virus."

While social distancing may help avert outbreaks of vaccine-preventable diseases, the data raise worries about the accumulation of susceptible children who could fuel future outbreaks, said Walter Orenstein, MD, the associate

director of the Emory Vaccine Center and a professor of medicine, epidemiology, global health and pediatrics at Emory University, in Atlanta. There already were enough cases of measles reported last year (1,282 in 31 states, according to the CDC) that the country almost lost its elimination status, he said: "This puts us at risk for a return or resurgence of [vaccine-preventable] diseases."

To encourage vaccinations now, Dr. Shen said, pediatric offices can employ strategies such as dedicating separate clinic rooms or appointment times for sick visits and well visits; reducing the number of patients on-site at any given time; or having patients check in by phone and receive vaccinations in the parking lot.

CHOP had recommended its practices bring in all children under 24 months of age for quick measurements and immunizations to avoid getting behind on the primary series, Dr. Offit said. While doctors were willing to follow that, many parents were scared to come in and risk exposure for themselves and their children.

One action that will become imperative this fall is getting influenza vaccines, Dr. Offit said, as it's likely that both SARS-CoV-2 and influenza will circulate simultaneously.

"The whole goal with COVID was to not overwhelm the health care system," he said. The 2019-2020 flu season resulted in 700,000 hospitalizations and 62,000 deaths, he noted, but it was mostly ramping down by the time SARS-CoV-2 hit. "If they both occur at the same time, you can see how easily that could overwhelm the health care system, and the odds are that we're not going to have a vaccine [for SARS-CoV-2] by the end of the year."

The influenza vaccine will be important in several ways, Dr. Orenstein added. It will reduce the number of respiratory illnesses, and therefore the number of people getting tested for COVID-19. It also will reduce the likelihood that someone will need to go to a doctor's office to be evaluated for flu, and potentially catch the coronavirus from someone else in the waiting room.

"Almost all of our vaccine-preventable diseases are transmitted person-to-person," he said. "If we fail to get our children vaccinated at the recommended times, we run the risk of returns of these diseases because they are prevalent in many parts of the world, and we've seen with COVID how worldwide problems can invade the U.S. It's very important that parents try to make the effort to get their kids vaccinated." ■

The sources reported no relevant financial relationships.

**2.5 million fewer vaccines were ordered from mid-March to mid-April 2020 compared with previous years**

Source: *MMWR Morb Mortal Wkly Rep* 2020;69[19]:591-593.