At a February 26 press conference, President Donald J. Trump said of the novel coronavirus, “This is like a flu,” and expressed surprise that as many as 69,000 people in the US die of influenza every year.

However, the ensuing 5½ months have shown that coronavirus disease 2019 (COVID-19) is far deadlier and less predictable than seasonal influenza. Unlike influenza, COVID-19 does not appear to be seasonal, given the ever-increasing numbers of US cases this summer.

So beginning this fall, the US for the first time will have to deal with a flu season wrapped in a global pandemic. Or, as the headline on a recent editorial by Edward Belongia, MD, and Michael Osterholm, PhD, MPH, described it, “a perfect storm.”

Many questions remain about how flu season might affect the pandemic, and vice versa. For example, would coinfection with influenza worsen the course of COVID-19? Experts also aren’t certain whether influenza vaccination could help protect against COVID-19 or whether steps taken to mitigate COVID-19 will reduce the burden of the coming flu season.

Some hints have come from preliminary research conducted in China, where influenza was still widely circulating when the first novel coronavirus infections emerged, and in the southern hemisphere, which is currently in the midst of its flu season.

At least 2 things are clear: Quicker and more widely available testing is needed to distinguish between COVID-19 and influenza, which have similar symptoms, at least at first, but require different treatments. On top of that, a severe influenza season—the result of more virulent strains, inadequate vaccination rates, or a combination of both—coupled with a COVID-19 pandemic that shows no signs of abating, could overwhelm already taxed emergency departments and intensive care units.

As pulmonary and critical care specialist Benjamin Singer, MD, wrote in a recent editorial, influenza and other causes of pneumonia represent the eighth leading cause of US deaths in nonpandemic years.

“We can expect that the new reality of COVID-19 will only complicate the next influenza season,” Singer, of the Northwestern University Feinberg School of Medicine, concluded in his editorial.

Flu-Like but Not Alike

Distinguishing between influenza and COVID-19 “has important prognostic implications,” Singer said in an interview. “In many ways it matters that you find out quickly.”

While the course of influenza is rapid, COVID-19 “kind of limps along a little bit,” he said. Knowing the reason for a patient’s respiratory symptoms “helps inform what you can expect.”

Identifying the cause, of course, helps determine how best to treat respiratory symptoms, Singer noted. Although supportive care for influenza and COVID-19 is similar, drug treatments don’t overlap, he said.

“We have things that we can do for COVID if we know someone’s infected,” he said. “If they have influenza, we can give antivirals targeted against influenza.”

But mistakenly treating patients with influenza as though they have COVID-19 is wasteful and potentially harmful, Singer said.

For example, he noted, randomized controlled trials have found that intravenous remdesivir, a broad-spectrum antiviral that is not approved anywhere in the world for any use, was more effective than a placebo in treating severe and moderate COVID-19. Remdesivir has received Emergency Use Authorization to treat COVID-19 from the US Food and Drug Administration and regulatory agencies in a few other countries, but, as an unapproved drug, it has been in short supply. Meanwhile, although earlier studies found that remdesivir had antiviral activity against influenza A, the drug has not been tested in patients with the flu, so there’s no evidence it’s effective in treating that disease.

Another drug, the corticosteroid dexamethasone, appears to be effective in some patients hospitalized with COVID-19, but it could harm those who instead have influenza. A recent preliminary report found that dexamethasone resulted in a lower 28-day mortality rate among patients hospitalized with COVID-19 who were receiving respiratory support. However, in 2019 clinical practice guidelines, the Infectious Diseases
Society of America (IDSA) specifically advised against using corticosteroids to treat seasonal influenza unless clinically indicated for other reasons, such as asthma. Data from randomized controlled trials of corticosteroid treatment of influenza aren’t available, but 2 meta-analyses of observational studies suggested that corticosteroid treatment of patients hospitalized with influenza was associated with increased mortality, according to IDSA.

A retrospective study from Wuhan, China, suggested that lopinavir-ritonavir combination therapy led to faster resolution of pneumonia than standard care alone among patients with both COVID-19 and influenza. However, the World Health Organization (WHO) on July 4 discontinued the lopinavir-ritonavir arm of its Solidarity trial because interim results found the treatment, which is approved for HIV, produced little or no mortality reduction in patients hospitalized with COVID-19. “Although we need more data to confirm the conclusion, we prefer to use the lopinavir-ritonavir to treat all COVID-19 patients with influenza,” coauthor Rui Zeng, MD, PhD, a kidney specialist on the faculty of Wuhan’s Tongji Medical College at Huazhong University of Science and Technology, said in an email.

Another reason it’s important to determine whether respiratory symptoms are due to influenza or to COVID-19 (or both) is that mitigation efforts for the former aren’t as strict as for the latter. “We’ve never told people with influenza to isolate themselves from everyone else,” Osterholm, founder and director of the Center for Infectious Disease Research and Policy at the University of Minnesota, said in an interview.

Without quickly learning which virus they have, some people with COVID-19 during flu season might mistakenly attribute their symptoms to influenza and not take the necessary precautions to prevent spreading severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is more easily transmitted, he said.

In addition, distinguishing between COVID-19 and influenza will be vital for disease surveillance, the authors of a recently published letter noted. Given the overlap of symptoms, systematic testing for SARS-CoV-2 and influenza will be needed during the upcoming flu season to determine the contributions of each viral illness to the burden of respiratory disease, the authors wrote.

Considering Coinfection
Physicians in several countries have reported patients who tested positive for both COVID-19 and seasonal influenza. “We have seen patients with both viruses,” Singer said. “It was early on, in March.”

But such patients have represented a small minority. “The chances are more likely that they have one or the other,” Osterholm said, noting that only 3% or 4% of the population have SARS-CoV-2 infection, while 10% to 20% might become infected with influenza virus, so the odds of being infected with both are small. Early reports from China suggested that coinfection with other respiratory diseases was extremely rare in patients with COVID-19. For example, in a study of 99 patients with COVID-19 admitted to Wuhan Jinyintan Hospital from January 1 to January 20, none tested positive for any of 9 other respiratory pathogens, including influenza A and influenza B.

However, Zeng’s study, conducted at Wuhan’s Tongji Hospital, which the government had designated for treating patients with severe COVID-19, produced a much different finding. Of 544 patients with polymerase chain reaction–confirmed COVID-19 who were admitted from January 28 to February 18, 11.8% were coinfected with influenza A or influenza B. Zeng noted that the influenza infection rate in his study was similar to that reported in the US during the 2018-2019 influenza season.

“Coinfection was a significant risk factor for prolonged hospital stay,” Zeng said. In addition, his study found that COVID-19 patients who were coinfected with influenza shed SARS-CoV-2 longer than other COVID-19 patients (17 days vs 12 days on average). “We don’t know the reason.”

Studying coinfection in the US have found rates more in line with those at Jinyintan Hospital than at Tongji Hospital. A recent study in JAMA found that out of 1996 patients hospitalized with COVID-19 in metropolitan New York City who were tested for other respiratory viruses, only 42 (2.1%) were coinfected, and only 1 was coinfected with influenza. The patients were hospitalized between March 1 and April 4.

In Northern California, laboratories that simultaneously tested for SARS-CoV-2 and other respiratory pathogens found a 10-fold higher co-infection rate (20.7%) than the New York study, but only 0.9% of specimens were coinfected with influenza. The authors, who reported their findings in a JAMA research letter, studied 1217 specimens, 116 of which had tested positive for SARS-CoV-2 and 318 for other respiratory pathogens. Of the 116 that were positive for SARS-CoV-2, 24 were positive for at least 1 other respiratory pathogen. However, only 1 of the 116 was positive for influenza.

COVID-19 Protection From Flu Shots? A study conducted at Ohio’s Wright-Patterson Air Force Base during the 2017-2018 flu season recently caught the attention of Luigi Marchionni, MD, PhD, an oncologist and computational biologist at Johns Hopkins University. The study compared the influenza vaccination status of approximately 6000 Department of Defense personnel with their respiratory virus status.

“The paper didn’t find vaccination was making people more likely or less likely to get another infection from another virus,” Marchionni explained. However, it did find that influenza vaccination was associated with a higher risk of non-SARS coronavirus infection, offset by a lower risk of influenza, parainfluenza, respiratory syncytial virus, and some other respiratory infections.

Marchionni wondered whether the finding of an association between flu shots and coronavirus infections might bode ill for influenza vaccination in the middle of a coronavirus pandemic. So he and his coauthors explored a possible county-level association between influenza vaccination coverage in people aged 65 years or older and the number of COVID-19 deaths.

Their findings, which have not yet been peer-reviewed, suggest that influenza vaccination in that age group is negatively associated with COVID-19 mortality. Marchionni said he and his coauthors have submitted an expanded version of their paper to a peer-reviewed journal.

“I’m quite confident in the fact that influenza vaccination in the population is associated with less [COVID-19] mortality,”
Marchionni said, “There are many plausible biological explanations.”

Another study that has not yet undergone peer review also found that patients with COVID-19 who were immunized against influenza fared better than those who had not. The authors analyzed data from 92,664 confirmed COVID-19 cases in Brazil and found that recently vaccinated patients had, on average, an 8% lower chance of needing intensive care, an 18% lower chance of requiring invasive respiratory support, and a 17% lower chance of dying.

**Can We Curb Flu Along With COVID-19?**

Intuitively, it makes sense that wearing masks, social distancing, working from home, closing schools, and other strategies to minimize the spread of COVID-19 would lessen transmission of other respiratory infectious diseases as well.

That appeared to be the case in Taiwan, researchers concluded in a recent brief report. They compared 25 weeks of case data for severe influenza, invasive Streptococcus pneumoniae disease, and pneumonia deaths from 2016 to 2020. All 3 trended downward in 2020 compared with the previous 5 seasons. They speculated that high awareness among the Japanese public of measures to reduce COVID-19 transmission early in the year might explain their finding, according to a recent research letter in *JAMA*.

And researchers in Qatar recently reported a “dramatic decrease” of laboratory-confirmed influenza A after the state closed schools on March 10, although laboratory-confirmed cases of other respiratory pathogens, including influenza B, barely budged. Seasonal variations likely do not explain the 30-fold drop in laboratory-confirmed influenza A cases between February 13 to March 14 and March 15 to April 11, because a similar decline was not seen between the same periods in 2019, the authors wrote.

The situation in the southern hemisphere might provide more clues as to what the northern hemisphere can expect in the upcoming flu season. Or, as Osterholm cautioned, it might not.

“We’re seeing an incredibly mild flu season in the southern hemisphere,” he said. “To date, we’ve seen virtually little, little activity... We don’t know what’s going on right now.” And that’s throughout the southern hemisphere, including COVID-19 hotspots such as Brazil, Osterholm noted. “We have to be careful not to assume that’s what’s going to happen in the northern hemisphere.”

The best-case explanation for the southern hemisphere’s mild flu season is that COVID-19 mitigation strategies are tamping down the spread of other respiratory viruses, said Brendan Flannery, PhD, coauthor of the letter calling for systematic testing for both influenza and COVID-19. But the worst-case scenario is that COVID-19 has overwhelmed health care systems, so people with the flu are staying home and not being counted or seeking care but getting lost in the crowd of COVID-19 patients, said Flannery, lead investigator from the US Centers for Disease Control and for the US Flu Vaccine Effectiveness Network.

“We’re all going to learn a lot,” Osterholm said of the upcoming flu season. “We can speculate until we’re blue in the face, and I don’t think we know yet what’s going to happen.”

**Note:** Source references are available through embedded hyperlinks in the article text online.