

## Medical News &amp; Perspectives

# Influenza's Unprecedented Low Profile During COVID-19 Pandemic Leaves Experts Wondering What This Flu Season Has in Store

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A feared “twindemic”—an influenza epidemic wrapped in a COVID-19 pandemic—never materialized, much to the relief of critical care specialists and their hospitals’ administrators.

Instead, flu cases and deaths in the US and worldwide dropped to unprecedented lows, and influenza remained scarce this summer for the second consecutive flu season in the Southern Hemisphere.

Between October 3, 2020, and July 24, 2021, of the 1.3 million specimens tested by clinical laboratories and reported to the US Centers for Disease Control and Prevention (CDC), 2136 were positive for influenza virus, and 748 deaths were coded as influenza, according to CDC data provided to *JAMA*.

In a typical season, 75 to 150 children die of influenza in the US, pediatric infectious disease specialist Paul Offit, MD, director of the Vaccine Education Center at the Children’s Hospital of Philadelphia, noted in an interview. Last flu season, he said, 1 child died.

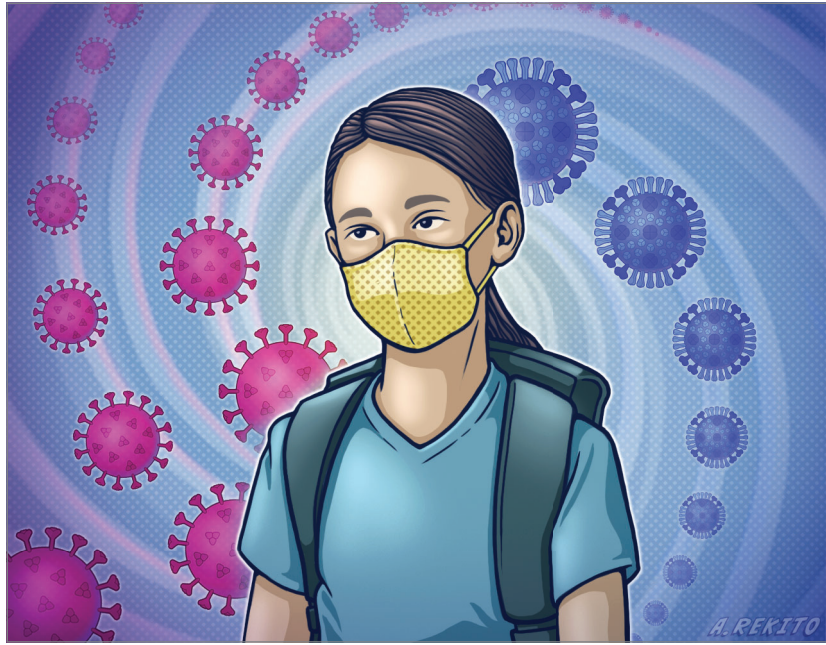
As in previous years, “it is likely that there were many more” flu deaths in the US, a CDC spokesman noted in an email. Not all flu deaths are reported to the CDC, and not all deaths due to flu-related complications are listed as such on death certificates.

However, that doesn’t explain the eye-popping differences between the 2020-2021 flu season and its predecessor. In the 2019-2020 season, more than 38 million people in the US became sick with influenza and nearly 22 000 of them died, the CDC [estimates](#).

Except for a few places, such as western Africa, “the flu was essentially nowhere” this past fall and winter, virologist Richard Webby, PhD, of St Jude Children’s Research Hospital, 1 of 6 World Health Organization (WHO) Collaborating Centers for influenza, told *JAMA* in an interview.

How more than a year with virtually no influenza bodes for the coming flu season is unknown, and potential scenarios range from a repeat of last season’s numbers to an explosion in cases.

Several what ifs will determine the upcoming season’s magnitude: the COVID-19



pandemic’s severity this fall and winter, the extent to which SARS-CoV-2 mitigation measures continue to be used, and how well vaccines are matched to circulating influenza viruses.

## Unmasking Flu Season?

The unexpected but welcome plummeting of influenza cases during the COVID-19 pandemic “certainly showed that many of the social-distancing things we were doing were very effective,” Vanderbilt University School of Medicine infectious disease and health policy professor William Schaffner, MD, said in an interview.

On top of mask wearing, social distancing, and handwashing, Schaffner noted, most international travel was halted and many countries closed schools, keeping children—“the great engine of the distribution of influenza virus”—at home and away from each other.

“It’s impossible to tease out which of those had the biggest effect,” epidemiologist Alicia Budd, MPH, of the CDC’s Influenza Division, said in an interview.

Despite these mitigation measures, COVID-19 continued to spread, demonstrating that SARS-CoV-2 is much more

contagious than the influenza virus, Schaffner added.

“Obviously, since we’re now all opening up and going back to school, we anticipate that these old methods of spreading the flu virus will come into play this fall,” he said.

The CDC recently [recommended](#) face masks for all students, faculty, and staff in K-12 schools this fall, but [Texas](#), [Arkansas](#), and [Arizona](#) have banned mask mandates and Florida Governor Ron DeSantis [has pledged](#) to do the same. In a recent [statement](#), Nebraska Governor Pete Ricketts said, “Schools should convene in person without mask or vaccine requirements.”

In Japan, as well as in some other parts of Asia, it has long been customary for people to wear masks when sick, but “I don’t think there is any evidence that flu seasons have been milder in Japan,” epidemiologist Benjamin Cowling, PhD, of The University of Hong Kong School of Public Health, told *JAMA* in an email.

Still, said Cowling, who studies the epidemiology of influenza, “I would encourage people to consider wearing masks to protect others if they are having flu symptoms and using public transport or visiting

crowded areas." In addition, he said, people who are worried about contracting influenza, such as those who are immunocompromised, should probably wear a mask during flu season.

"I anticipate we will see masks used more often in the post-COVID era than we used to observe in the pre-COVID era," Cowling added.

### Best Case, Worst Case

Ask anyone whose work focuses on influenza to describe the scourge in a single word, and they are likely to reply "unpredictable."

Past flu seasons have followed no pattern. A mild one is sometimes followed by a severe one, sometimes by another mild one, and vice versa.

"It's hard to say what the impact of a very, very low influenza season is," Ann Moen, MPA, chief of influenza preparedness and response at the WHO, said in an interview. "If it continues like this, it wouldn't be unreasonable to think that you're going to have a more severe season."

The reason? "I think some locations that have fully reopened will be vulnerable to large flu seasons because of the loss of population immunity in the past 18 months," Cowling said.

Worldwide, 10% to 30% of the population is exposed to the flu during a typical season, Webby noted. "Take away 2 full seasons, and that's a lot of people" without immunity, he said, adding that it's difficult to project the magnitude of the impact this could have.

"I don't think anybody is willing to put down their dollars and bet on what horse is going to win here, because flu is so darn fickle," Schaffner said.

A recent [article](#) by researchers in Spain discussed whether the COVID-19 mitigation measures could have been a double-edged sword.

The article focused on influenza and [respiratory syncytial virus](#) (RSV), which also [plummeted last winter](#). The authors noted that "the absence of circulation of certain pathogens can lead to a decrease in herd immunity against them. This can promote the rise of more serious, longer-lasting epidemics that start sooner." Indeed, Australia experienced a [delayed seasonal RSV surge](#) in late September 2020 when physical distancing restrictions were relaxed, and researchers at a New York City hospital recently [reported](#) similar findings.

Important measures to counteract a potentially serious influenza pandemic may in-

clude increased influenza vaccine production and massive influenza immunization programs along the lines of those for COVID-19, the authors in Spain concluded.

"With all the focus on COVID vaccine, we want people to keep in mind this year the importance of flu vaccine," Budd said.

Flu vaccine manufacturers project they will deliver [188 million to 200 million doses](#) in the US for the upcoming flu season, according to the CDC. GlaxoSmithKline recently [announced](#) that it expects to distribute 50 million doses of its influenza vaccine in the US, more than in any previous flu season.

And that's after this past flu season set a record for vaccine distribution, with about [194 million](#) doses distributed by the end of February. As of early February, 55% of US adults had been immunized against the flu—10 percentage points higher than the estimated coverage a year earlier.

Out of caution this past flu season, the CDC's Advisory Committee on Immunization Practices advised intervals of at least 2 weeks between receiving a COVID-19 vaccine and any other vaccine. But the CDC now [deems](#) that practice unnecessary, so people can be immunized against both COVID-19 and influenza at the same visit.

### Making a Match

Influenza viruses mutate regularly, which is why—at least for now—the vaccines are updated annually.

Every February, based on surveillance data, the WHO recommends the 4 vaccine viruses for the northern hemisphere's upcoming flu season. It can't be a last-minute decision because it takes [at least 6 months](#) for manufacturers to produce large quantities of vaccines.

The WHO conducts influenza surveillance 24/7-year-round, Moen noted. "We bend over backwards to make sure if flu is out there, we'll find it."

But what if only a tiny amount of influenza is circulating? Does that make it more difficult to predict which strains the vaccines should target? And is there a greater chance that this season's vaccines won't be a good match to circulating strains?

"That's an absolutely valid question," Webby said. "I think there was a little bit more apprehension about the selection" of influenza strains for the 2021-2022 vaccines.

In their best years, vaccines reduce immunized individuals' chances of con-

tracting the flu by about 60%, [according to the CDC](#), which began tracking effectiveness in the 2003-2004 season. But even in years in which flu vaccines aren't a great match for circulating viruses, millions of cases are prevented.

Early on, the pandemic disrupted influenza surveillance in most countries, although it recovered in many by early 2021.

"Globally, we saw as much or more testing than usual for influenza, but many countries did struggle to maintain influenza surveillance in the face of the COVID-19 pandemic," Moen said. "Some countries did not maintain influenza surveillance for a variety of reasons, such as lack of reagents, prioritization for just COVID-19 testing, and diversion of flu staff to COVID-19 work."

From September 1, 2020, to January 31, 2021, 139 countries, areas, or territories reported data to [FluNet](#), the global influenza surveillance platform, [according to the WHO](#). That's compared with 161 countries, areas, or territories a year earlier.

Overall sampling of specimens might have been up, in part because countries were testing for both SARS-CoV-2 and influenza. "We made an all-out effort to help countries see that they could do both," Moen said. But far fewer turned up influenza than in previous years. For example, Moen noted, in late June and early July of 2021, the 6 WHO Collaborating Centers, which include the CDC, tested 156 000 specimens, only 600 of which were positive for influenza.

So despite increased testing, the WHO based its recommendations for the 2021-2022 northern hemisphere flu vaccine on significantly less data about circulating influenza viruses than in typical years, which the organization said raises uncertainty about the full extent of the viruses' genetic and antigenic diversity. In other words, with relatively few viruses available for characterization, it's possible that some likely to pose a threat went undetected. Even so, the WHO noted that new groups of influenza virus subtype A(H3N2) were found, leading to an update in the recommendation for the A(H3N2) component of vaccines.

"There's never any guarantee about these things," Moen acknowledged. "Of course, you want to have as many [virus specimens] as possible to make a decision, but you can only make a decision with what you have." ■

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