How Immune-Evasive Omicron Offspring and a Lack of Mitigation Measures Could Shape a COVID-19 Winter Wave

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Wintertime and the living may not be easy—thanks to an ever-mutating SARS-CoV-2 and an ever-growing number of people who think that the pandemic is behind them.

While US COVID-19 cases, hospitalizations, and deaths neared pandemic lows this fall, the numbers were climbing in some European countries. When it comes to COVID-19, what happens in Europe doesn’t usually stay in Europe, and many prognosticators have expressed concern that numbers will soon begin rising in the US as well, as more immune-evasive Omicron subvariants continue to chip away at BA.5’s dominance. In the week ending October 29, BA.5’s estimated proportion of circulating SARS-CoV-2 variants in the US slipped just below 50% for the first time in months, according to the US Centers for Disease Control and Prevention (CDC). Two weeks later, BA.5 represented only 29.7% of circulating variants, with newer Omicron variants BQ.1 and BQ.1.1 accounting for a total of 44.2%, the CDC estimated.

Experts point to a combination of factors, some modifiable, some not, that could produce a third consecutive COVID-19–riddled winter in the US. “While there are many different scenarios, what I think is clear is that a substantial wave in the winter is a serious possibility,” epidemiologist Marc Lipsitch, DPhil, director of science at the Center for Forecasting and Outbreak Analytics at the CDC, said in an interview.

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“One possibility is that we will do a little better than in some parts of the world, including Europe,” because the US has had a higher infection rate, providing at least some temporary immunity, Lipsitch added. He cautioned that “[t]he scale on which immunity from prior infection wanes is actually pretty hard to measure.”

Michael Osterholm, PhD, MPH, divides the pandemic into 4 phases, with the US a phase behind Europe. In phase 1, variants were just a gleam in the eye of what the World Health Organization (WHO) calls the SARS-CoV-2 “index virus,” sequenced from the first cases. “People were vaccinated and thought they were done,” Osterholm, founder and director of the Center for Infectious Disease Research and Policy at the University of Minnesota, explained in an interview.

But then the world began learning the Greek alphabet, variant by variant. Phase 2 of the pandemic, according to Osterholm, began with the Alpha variant in December 2020 and continued with Delta in the summer of 2021 and Omicron a few days after that Thanksgiving. This phase was a period of peaks and valleys in case numbers and deaths, he noted.

Since this past spring, though, the US has stalled on the plateau of phase 3, Osterholm said. No new variants have been identified, only highly contagious Omicron subvariants that are increasingly immune-evasive, rendering monoclonal antibody treatments ineffective against them.

Europe has moved on to phase 4 of the pandemic, Osterholm noted. Immune-evasive subvariants, waning immunity against the virus, and the inadequate uptake of COVID-19 boosters combined to drive up cases and deaths there, he said. (The pooled COVID-19 case rate in Europe finally began falling in the last 2 weeks of October, and the overall mortality began to fall in the final week of October, although it increased in a handful of countries, according to the European Union’s European Centre for Disease Prevention and Control.)

The US is likely not far behind Europe’s fall increase in COVID-19 numbers, Osterholm predicted. After all, he said, “the world has given up on COVID.”

Boosters Need a Boost

It’s now clear that messenger RNA (mRNA) COVID-19 vaccines don’t provide lifelong, or even yearlong, protection.

But in the US fewer than half the 227 million people who’d completed their
primary COVID-19 vaccine series, or about 112 million, had received even 1 booster by November 1, according to the CDC.

Updated booster shots, which combine the prototype COVID-19 vaccines with components of the Omicron BA.5 subvariant, have been available since early September of this year. Experts interviewed for this story talked about the critical role these bivalent boosters will play in preventing severe illness and death this winter.

“I have some confidence that the booster, at least for a short period, is going to give people some immunity against infection if they would just get the thing,” Marcus Plescia, MD, MPH, chief medical officer of the Association of State and Territorial Health Officials, said in an interview.

So far, though, the new boosters have had relatively few takers, and a Kaiser Family Foundation poll conducted soon after the shots became available found that only a third of adults said they’d already gotten one or intended to do so “as soon as possible.” About 10% of adults said they would get one of the new boosters “only if required,” while 12% said they would “definitely not get” the updated booster.

As of November 9, about 31.4 million people in the US had received a bivalent booster, according to the CDC. That represented only 10.1% of those who were eligible for an updated booster, which, as of October 12, included individuals aged 5 years or older who completed their primary vaccination. Only 23% of adults aged 65 years or older, who are at increased risk of hospitalization and death from COVID-19, had received the bivalent shot.

“It’s just not top of mind,” epidemiologist Caitlin Rivers, PhD, MPH, a senior scholar at the Johns Hopkins Center for Health Security, said of the need to get the updated booster.

The CDC recommends getting a bivalent booster if it’s been 2 months or more since the last monovalent booster dose or 3 months or more since a COVID-19 infection. But some people may be delaying their bivalent booster in the hope that they’ll “have more robust immunity around the holidays,” Plescia speculated. Or perhaps “most people are just waiting until there’s a new threat,” infectious disease specialist David Freedman, MD, a professor emeritus at the University of Alabama at Birmingham (UAB), suggested in an interview.

But Plescia thinks the main problem might be that pandemic-weary people are simply tuning out the CDC and other federal agencies that are urging them to get the bivalent booster. “I don’t know how effective government messaging is anymore,” Plescia said.

The Kaiser Family Foundation poll found that awareness of the updated boosters was “relatively modest,” with 17% of adults saying they’d heard “a lot” and 33% saying they’d heard “some” about the new shots.

To increase uptake of the boosters, states are trying to encourage more health care professionals to provide COVID-19 vaccination. In their office, Plescia noted. “People do listen to their health care providers,” he said. “Maybe we need to change the messenger.”

One barrier to increasing the number of clinicians offering COVID-19 boosters is how the vaccine is packaged, Plescia said. The bivalent boosters come fewer doses per vial than the prototype vaccines and boosters, but they’re still not the ideal single-serve vials, he explained. Some clinicians have worried about having to discard leftover doses in an open vial at the end of the day.

“We more or less told them [to] just waste it,” Plescia noted, because it’s worth opening a vial even if only 1 patient wants a booster shot that day. Fact sheets for updated boosters from both Pfizer-BioNTech and Moderna say leftover vaccine must be discarded 12 hours after opening a vial.

The importance of COVID-19 vaccines and treatments “will be greatest if there’s a large winter surge, but they will bear fruit regardless under any possible scenario,” Lipsitch, who is also director of the Center for Communicable Disease Dynamics at the Harvard T.H. Chan School of Public Health, pointed out.

More Omicron Offspring

Omicron has been the most prolific SARS-CoV-2 variant so far. By November 12 of this year, 14 different Omicron subvariants had been detected in the US, although not all of them were still circulating, according to the CDC.

Omicron appeared on the scene almost exactly 1 year ago, on November 24, 2021, when the new variant was first reported to the WHO by South Africa. A week later, the first Omicron case in the US was reported. By then, the WHO had already declared Omicron a variant of concern.

While the WHO also considers all Omicron subvariants to be variants of concern that should be monitored as distinct lineages by public health authorities, none has warranted a different Greek letter, even though their spike proteins, the target of vaccines, bear little resemblance to each other.

“There is, indeed, no clear boundary between the 2 terms,” immunologist Yunglong Richard Cao, PhD, said when asked about the difference between a variant and a subvariant. “Subvariant is used when you want to emphasize that the involved variant is a derivative related to a known variant.”

The Omicron subvariant BA.5 now has its own subvariants, BF.7 (also known as BA.5.2.1.7), BQ.1, and BQ.11. Grandchildren of the original Omicron variant, Cao, an assistant professor at Peking University in Beijing, said in an email. “Although some of these Omicron subvariants seem to be vastly different from the original Omicron variant, clearly they still are subvariants of Omicron and evolutionarily related to Omicron.”

Anthony Fauci, MD, who will retire this December from his position as director of the National Institute of Allergy and Infectious Diseases, made headlines in early October when he suggested that a new variant could emerge “that would elude the immune response that we’ve gotten from infection and/or from vaccination.”

Cao coauthored a recent study, which had not yet been peer reviewed, that suggested such variants have already arrived in the form of Omicron offspring.

He and his coauthors assessed neutralizing antibodies in plasma from people who received 2 primary doses and 1 booster dose of the CoronaVac vaccine, an inactivated whole virus vaccine developed by the Chinese company SinoVac that is not available in the US. Some of the individuals had also had breakthrough infections from the original Omicron variant, BA.1, or the BA.2 or BA.5 subvariants. (“Results from mRNA vaccines should have overall higher neutralizing titers. But the immunity waning trend and immune evasion pattern should be highly similar,” Cao tweeted on October 23.)

Cao’s team found that certain newer Omicron subvariants, including BQ.1.1 and particularly XBB—which hasn’t yet cracked the list of variants tracked by the CDC—had evolved to the point where they were unrecognizable by most neutralizing
antibodies generated by previous Omicron infections or by vaccination. "Our results suggest that current herd immunity and BA.5 vaccine boosters may not provide sufficiently broad protection against infection with these new subvariants," Cao said in his email to JAMA. "It’s highly likely that new waves of infections will emerge this winter, and the next wave may not be driven by a single subvariant but a collection [or] swarm of subvariants."

However, in the first couple of weeks during which BQ.1.1 began gaining ground in the US, cases had not yet shot up, according to the CDC’s COVID-19 data tracker. The same was true in France, where BQ.1.1 was the dominant variant, Eric Topol, MD, founder and director of the Scripps Research Translational Institute, tweeted November 3.

A study that had not yet been peer-reviewed, posted November 1, found that the bivalent COVID-19 boosters elicited superior neutralizing activity against all the Omicron subvariants compared with the monovalent boosters. Even with the bivalent booster, though, antibody titers against BQ.1.1 and BA.2.75.2 were greatly reduced compared with the response against BA.5, tweeted corresponding author Mehul Suthar, PhD, an immunologist at the Emory Vaccine Center. (BA.2.75.2 represents a far smaller share of circulating variants in the US than BQ.1.1, although the 2 subvariants carry the same immune-evasive mutation on their spike proteins.)

Overall, findings in studies comparing the monovalent and bivalent boosters’ effectiveness against BA.5 have been mixed, although Topol noted that might be due to some studies’ use of live virus assays, which he said are likely more accurate than pseudovirus assays.

In a November 4 news release, Pfizer and BioNTech announced that their bivalent booster elicited 4 times higher levels of neutralizing antibodies against Omicron BA.4 and BA.5 sublineages in people older than 55 years than the original COVID-19 vaccine did. Like Suthar’s study, Pfizer’s used a live virus assay.

On the other hand, 2 studies that also had not yet been peer-reviewed, posted October 24 and October 25, did not find a bivalent booster to be superior to an original monovalent booster in eliciting neutralizing antibodies to the BA.4 and BA.5 sublineages. These studies, as did Cao’s, used pseudovirus assays.

Concerns About Counts
Getting a handle on SARS-CoV-2 infection rates this winter will be more challenging than ever, given that most people who test—if they do test—use at-home rapid antigen assays and don’t report the results to public health agencies. While a pandemic peak of 17.4 million test results were reported to the CDC in the week ending January 12 of this year, during the original Omicron surge, that number had dropped to 2.3 million in the week ending October 26.

“The quality of the data is getting worse, and that is making it harder to inform decisions,” Lipsitch said. "On the other hand, at-home testing has finally made it possible for people to make real-time good decisions.”

Like Lipsitch, Rivers believes that the benefits of rapid antigen tests, namely their relatively low cost and accessibility, outweigh the drawback of increased difficulty in tracking COVID-19 trends. “I think we’ve just had to adapt how we understand the data,” she said in an interview, noting that surveillance of many infectious diseases doesn’t involve counting every case. For example, many people sick with influenza don’t ever test to confirm that diagnosis.

“The [CDC] would say hospitalization is really what matters most. I think that’s true,” Plescia said. The problem, however, is that cases begin to rise before hospitalizations do, he said. “You’re missing this moment of opportunity because of the lag.”

And, vaccine epidemiologist Avnika Amin, PhD, said in an interview, hospitalization rates today aren’t as meaningful as they were before vaccines became available, when they “sort of reflected the tip of the case burden.” COVID-19 vaccines are so effective in preventing hospitalizations that it’s much harder to gauge whether infections overall are surging, said Amin, a postdoctoral fellow at Emory University’s Rollins School of Public Health.

Immune evasion doesn’t necessarily correlate with more severe disease. Lipsitch said, noting that the original Omicron variant was more immune evasive than previous variants but not more severe.

Still, he said, if COVID-19 cases increase, so will hospitalizations: “The vaccines are not perfectly protective.” Although vaccinated individuals have a lower risk of becoming seriously ill with COVID-19, their risk is not zero, he pointed out. “When ever hospitalizations and deaths go up, it’s something to be watched and be concerned about,” he said.

Back to Basics
One reason Plescia and other public health experts are counting so heavily on the bivalent boosters to curb serious COVID-19 illness this winter is because nonpharmaceutical interventions (NPIs) to stop the spread of SARS-CoV-2, such as social distancing and wearing face masks, have been all but abandoned in the US.

CDC Director Rochelle Walensky, MD, MPH, drew heat for not mentioning some of these NPIs in an October 21 tweet about protecting against respiratory infections. Get an updated COVID-19 booster and an annual flu shot, stay home if sick, and “practice good hand hygiene,” Walensky recommended.

"[H]ow can you avoid the obvious suggestions at this point??" Kimberly Prather, PhD, tweeted in response to Walensky’s advice. "How about clean indoor air and wear a good mask? Nowhere on your list.” Prather, the distinguished chair in atmospheric chemistry at the Scripps Institution of Oceanography, was elected to the National Academy of Sciences in 2020 for her contributions to aerosol chemistry, including her work on how airborne bacteria and viruses, such as SARS-CoV-2, are spread.

At least a couple of countries appear to be less reluctant than the US to resume requiring NPIs.

Germany, which is seeing rising SARS-CoV-2 infections, instituted new mask and testing mandates effective October 1, the country’s Deutsche Well News reported. Passengers aged 15 years or older must wear FFP2 masks, similar to N95 masks, on long-distance trains, and health ministers in all 16 German states are requiring passengers on local buses and trains to at least wear surgical masks. FFP2 masks must also now be worn in hospitals, nursing homes, and physicians’ offices, and people must show that they’ve tested negative for SARS-CoV-2 before visiting a nursing home or hospital. The German states also have the authority to require masking in shops and restaurants and testing at schools and daycare centers.

In Singapore, one of the world’s most vaccinated countries, mask-wearing is still required on all public transportation. The highly immune-evasive XBB Omicron subvariant made up more than half of new daily
cases in Singapore in the week ending October 9. In response to surging case numbers, the Ministry of Health tightened “visitor safe management measures” at all hospitals and residential care homes from October 14 through November 10, around the time the XBB wave was expected to peak. (Total daily cases, virtually all of which have been asymptomatic or mild illness, appear to have peaked October 18, according to the Singapore health ministry.) Visitors had to be masked and could visit only 1 at a time. The ministry also encouraged visitors to do an at-home rapid test before arriving.

It’s unlikely that NPI mandates for COVID-19 will ever be reinstated in the US, though, Plescia noted: “I think that a lot of our leadership are reluctant to push people to take precautions.” That’s because “the prepare for the worst and hope for the best adage is not really working anymore,” he said. If the worst doesn’t happen, Plescia explained, people might jump to the conclusion that public health leaders who urged precautions overreacted—not that the precautions might have worked.

“I understand some of the scaling back on wearing masks,” Plescia acknowledged. “But there could be a little more of a balance there.” For example, he said, more people could choose on their own, as he does, to wear a mask in certain situations, such as on a flight.

“I’m still wearing an N95 mask in crowded places,” said Freedman, who founded the Travelers Health Clinic at UAB. “That includes air travel.”

In the best-case scenario, 1% to 2% of passengers on any given flight are infected with SARS-CoV-2, Freedman said. The same is true for cruise lines, which, like airlines, have dropped vaccination and testing requirements for passengers before boarding.

“We know people are getting pretty tired of masking and having to get vaccinated,” Amin said. “The core tenet of public health is trying to meet people where they’re at and trying to nudge them in the right direction.”

However, she said, at this point in the pandemic, “we’re in this very odd place where we’re putting the onus of public health on the individual.”

Instead, public health leaders should be encouraging people to layer preventive measures, including getting vaccinated and wearing a mask in crowded indoor spaces, Amin said.

Meanwhile, Lipsitch said his family, like many in the US, was “planning our usual pre-pandemic multigenerational Thanksgiving” with about 20 guests, including some over 80 years of age.

“It’s certainly not a situation where we can say there is no risk,” Lipsitch said. Most likely, he and his family members will test before they get together to make sure no one is infected. “It is a way of preventing transmission. Nobody wants to be the source of infection for our relatives or anyone else.”

For many people in the US, Thanksgiving and the winter holidays this year will look a lot more like they did prepandemic. Still, experts say precautions should be taken to reduce the chance that SARS-CoV-2 will join the celebrations.

“I’m not advising people not to gather,” Rivers said. “That’s not on the table anymore.” But, she added, it wouldn’t hurt to crack open the windows a bit and run an air filter when company comes.

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Conflict of Interest Disclosures: Dr Lipsitch reports having received consulting fees from Merck and Janssen and payments or honoraria for lectures, presentations, speakers’ bureaus, manuscript writing, or educational events from Sanofi Pasteur. He also reports previously serving as an unpaid participant on a Pfizer data and safety monitoring board or advisory board. Dr Cao reports holding a patent on SA58 and SA55, monoclonal antibodies that he says are effective against the new Omicron subvariants and are licensed to Sinovac for clinical development. He also reports cofounding Singlomics Biopharmaceuticals.

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