Model estimates who benefits most from frequent COVID-19 boosters

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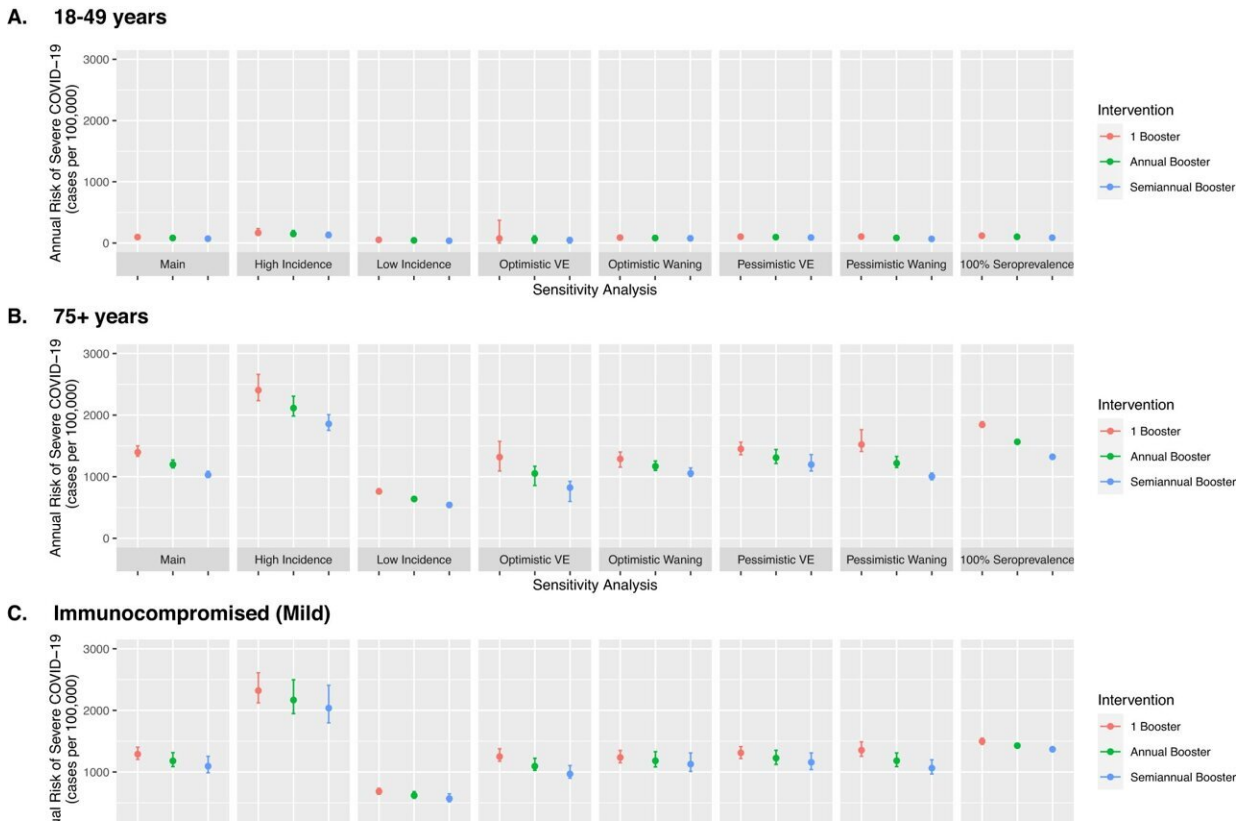

Sensitivity analysis of model parameters for COVID-19 risk and booster vaccination. We plotted results for three representative risk groups: 18–49 years (A), 75+ years (B), and the mild immunocompromised population (C). Credit: *Nature Communications* (2024). DOI: 10.1038/s41467-024-45549-9

Patients kept asking a question that Nathan Lo, MD, Ph.D., infectious

disease specialist, had a hard time answering: How often should I get my booster shot for COVID-19?

"It's a question that we have all asked. My patients have asked; friends and family members have asked," Lo said. "We point to the national vaccine recommendations, although increasingly this question has become challenging to answer. I didn't quite have the estimates on hand that I might hope to share with patients."

To build that evidence, Lo and his team at Stanford Medicine turned to their area of expertise, computational modeling. The researchers developed a simulation model using Centers for Disease Control and Prevention COVID-19 surveillance data and vaccine effectiveness estimates to predict the frequency of COVID-19 vaccination that best prevents severe disease in different U.S. populations.

They published a study describing that model and its results in the journal *Nature Communications*, led by Lo, who is the senior author of the study and an assistant professor of medicine.

The model's results largely square with data on who is most at risk of bad outcomes from COVID-19: For those older than 65 or who are immunocompromised, more frequent boosters—at least annually—go further to protect against hospitalization or death. For younger populations, the benefit of frequent boosting against severe disease is more modest.

The researchers hope this model can help inform both individuals making decisions about when to get boosters as well as public health policy makers.

"We're in the fourth year of the pandemic now, and we're shifting toward more long-term mitigation strategies," said Stanford Medicine

research data scientist Hailey Park, who is the lead author on the study. "We know that protection from vaccination wanes, and we know that disease risk is very heterogeneous in the population. So how do we come up with a more optimal timing for boosters?"

Simulating the population

The model is what's known as a microsimulation, meaning it simulates a large population with results at the individual level, Park said. She and her colleagues built a simulation of millions of individuals with their unique traits, aiming to mimic the overall U.S. adult population—except these simulated people had received their initial COVID-19 vaccinations.

Using the CDC's weekly COVID-19 surveillance data starting in September 2022, when the bivalent booster was first available, the model predicted how many severe infections leading to hospitalization or death would result in different age or health status groups over the course of two years. The team estimated outcomes if those individuals received just one COVID booster, a booster every year or a shot every six months.

For those over 75 years, receiving a yearly booster reduced annual severe infections from around 1,400 cases per 100,000 people to about 1,200 cases. Bumping the booster up to twice a year dropped severe infections to just over 1,000 per 100,000.

The numbers are similar for those who are moderately or severely immunocompromised, and about half that reduction for those aged 65 to 74. For younger, healthy people, the drop is much smaller: Annual or twice-yearly boosters reduced severe infections in people aged 18 to 49 by only 14 to 26 cases per 100,000 people.

"These high-risk populations benefit from more frequent boosters relative to younger and healthier individuals, and I think that's intuitive," Lo said. "But it's helpful to see the numbers; what is the difference in magnitude of risk?"

These findings support current CDC recommendations and the benefit of at least annual boosters to people 65 and older and immunocompromised populations, and suggest that public health strategies to increase booster uptake could get the most bang for their buck by focusing on the high-risk populations.

A thorny question

"In this study we focused on a goal of reducing severe COVID-19 leading to hospitalization, but there are numerous other considerations that influence vaccine decisions," Lo said.

The team considered how novel variants and overall transmission play into decisions on how frequently to receive booster vaccines. They looked at the effect of new viral variants with regard to evasion of the immune system and found that the benefit of more frequent boosters for all groups was larger if new vaccine formulations were better matched to the latest variants.

In addition, the team looked at the impact of transmission: Compared with more restricted booster programs targeting only higher risk populations, more inclusive frequent booster programs (for all age and risk groups) led to lower transmission, with additional benefit for the highest risk groups.

The researchers note that frequent vaccination also helped reduce non-severe cases in all risk groups. "There are a multitude of considerations here, and the optimal vaccine recommendations will depend on what is

factored into the decision," Lo said.

The scientists also included prior COVID-19 infection in their model, finding less benefit from frequent vaccination to prevent severe disease for those who had previously had a case of COVID-19 compared with those who hadn't. Prior infection gives a short window of protection against infection, so the booster's protection on top of that is smaller.

Due to a lack of data and to simplify the model, some variables weren't accounted for in the study: The likelihood of infection for each group was assumed to be the same over time, even though infection risk differs in real life.

The model was also based on data from earlier circulating variants and vaccine formulations. Immunocompromised people were clustered into two groups in the model, although these populations are actually much more variable, and the model did not address vaccine hesitancy or the risks of long COVID.

Lo and his colleagues plan to share their findings with policymakers and will update the model with new data as it becomes available, hoping to shed even more light on the tricky question of vaccine frequency.

"In science, there are some questions that get easier over time and some that get more challenging over time," Lo said. "This is one of the latter."

Researchers from the Yale School of Public Health; the University of California, San Francisco; and the California Department of Public Health also contributed to the study.

More information: Hailey J. Park et al, Comparing frequency of booster vaccination to prevent severe COVID-19 by risk group in the United States, *Nature Communications* (2024). DOI:

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