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Bloomberg News

It was meant to be a summer vacation to celebrate. Thousands of revelers flocked to Provincetown, Massachusetts, for the July Fourth holiday, fully immunized against COVID-19 and ready to enjoy new freedoms, including socializing without face masks.

Instead, the weather turned cool and rainy, and the festivities shifted indoors to pubs, clubs and private homes, creating a crucible for the effectiveness of vaccines used to contain the uber-transmissible delta variant. More than 1,000 COVID-19 cases ensued over the following two weeks, rocking confidence in the inoculations and prompting the U.S. Centers for Disease Control and Prevention to reinstate an indoor masking mandate.

Four months later, researchers studying those who contracted the virus are gaining important insights into the immunity-bolstering effects of natural infection after vaccination. Importantly, their findings offer clues about the immune protection needed for the coronavirus to cease being a public health menace and, ultimately, to end the pandemic.

“Our data really puts a different perspective on the Provincetown cohort,” said Dan Barouch, a Harvard Medical School professor and head of Boston’s Beth Israel Deaconess’ Center for Virology and Vaccine Research. “Initially, it was viewed as evidence of vaccine failures. I would actually argue it’s evidence of vaccine success. These vaccines are doing what they are intended to do.”

The outbreak in Provincetown, the small resort town located at the tip of Cape Cod that’s known colloquially as “P-town,” was the first well-described, large cluster of infections with the delta variant in a highly vaccinated population. Some three-quarters of the Covid cases occurred in people who had two doses of either the Pfizer Inc. or Moderna Inc. vaccines, or the single Johnson & Johnson shot, at least 14 days earlier.

Almost 80% of these so-called breakthrough infections were symptomatic. Although the majority led to only mild-to-moderate illness, the COVID-19

surge in the face of high vaccination rates prompted an intense investigation by state and local health officials.

They found the amount of viral material on nasal swabs was similar in vaccinated and unvaccinated people. That surprising finding undercut overly optimistic expectations that the inoculations could eliminate SARS-CoV-2 transmission, particularly given the twice-as-infectious delta strain.

Disease detectives at Boston's Broad Institute used genomic sequence data to trace the outbreak to just a handful of infected people, including one who was the likely source of more than 80% of cases. Their work proved Covid could spread between fully vaccinated people. Intriguingly, the disease sleuths also found those infected in Provincetown — who came from 21 states — contributed only modestly to the delta-fueled U.S. epidemic after they returned home.

The outcome was comforting because it backed what's already known about immunization, said Helen Petousis-Harris, a vaccinologist at the University of Auckland.

"Vaccination against COVID-19 is the best way to prevent getting severely ill and dying from COVID, but it doesn't completely stop everyone who gets it from being infected with the SARS-CoV-2 virus or from transmitting it," she said. "However, if you are vaccinated and you get infected, you're less likely to spread the virus than if you're unvaccinated."

Detailed analysis performed in Barouch's Harvard lab helps explain why. He and colleagues studied the immune responses of 35 vaccinated people tested for COVID-19 in the Provincetown outbreak. Those who got a breakthrough infection had a dramatic increase in levels of virus-blocking antibodies and virus-killing T cells, including 34-fold higher neutralizing antibody levels against the delta variant, compared with those who weren't infected.

An infection five to six months after vaccination jolted the body's immune memory into gear to generate potent, delta-specific antibodies and T cells that helped clear the virus before it caused severe illness or had the chance to spread.

“We think that this is likely the reason why vaccinated people who get breakthrough infections generally have a mild course of disease in the vast majority of cases, because they have a rapid onset of very potent antibody and T cell responses that likely control the virus,” Barouch said over Zoom. “It is likely that those individuals will have high levels of immunity for a prolonged period of time.”

He’s planning to follow the people who had a breakthrough infection to understand the duration of their immunity.

“Do those responses maintain themselves at that high level, or do they then go down over time?” Barouch asked. “That’s a very important question to address.”

Scientists call it an “anamnestic response,” where waning immunity is boosted by subsequent exposure to the virus. The pattern is likely to play out on a larger scale as the coronavirus continues to circulate worldwide, including among people with varying levels of immunity.

More than 7.52 billion doses of COVID-19 vaccine have been given worldwide, though administration has been uneven. Less than 10% of people in much of sub-Sahan Africa have been immunized, data from the Bloomberg COVID-19 Vaccine Tracker show.

It’s expected that the severity of disease and the propensity for onward transmission will decline as each exposure trains the immune system to recognize and respond to the coronavirus faster, including current and future variants. Over time, SARS-CoV-2 will likely cease being a public health menace and resemble something akin to the coronaviruses that cause the common cold, said University of Auckland’s Petousis-Harris.

“We would, of course, prefer that people have a bump in their immune responses from getting additional booster vaccines,” said Barouch, who helped develop the Johnson & Johnson COVID-19 shot. “But in reality, there will be cases of breakthrough infections and those are not rare and they’re not overly concerning because, in the vast majority of cases, they result in only mild disease.”

More studies on breakthrough infections are needed, including to gauge the risk of persistent symptoms often called long COVID, and the levels of immunity that protect against it, he said.

“An expectation for many diseases is that periodic low-grade exposure, resulting in either no infection or asymptomatic infection, boosts immunity and memory,” said Shane Crotty, a professor in the Center for Infectious Disease and Vaccine Research at San Diego’s La Jolla Institute for Immunology. “If that’s observed for SARS-CoV-2 with asymptomatic breakthrough infections, that will be clear evidence of the same phenomenon.”