BA.4/BA.5 Omicron subvariants over 4 times more resistant to mRNA vaccines

Written by Annie Lennon on July 13, 2022 — Fact checked by Jennifer Chesak

John Smith/VIEWpress/Getty Images

- **Omicron subvariants BA.4 and BA.5 are currently the dominant strains of new COVID-19 cases in the United States.**
- **Researchers have found the two subvariants are over 4 times more resistant to mRNA vaccines than earlier strains of Omicron.**

treatments and plan for public health initiatives.

As of July 13, the Centers for Disease Control and Prevention (CDC) reported that Omicron subvariants BA.5 and BA.4 are the dominant strains of SARS-CoV-2 in the United States, accounting for over 80% of

It's unclear whether the BA.4 and BA.5 subvariants evolved from the original Omicron variant, as 専門家は信じている they likely evolved from the previously dominant BA.2 Omicron variant.

The two new subvariants were initially spotted in South Africa in April and quickly spread around the globe and have a high transmission rate. They carry mutations on their spike protein — the part of the virus that attaches to ACE2 receptors on human cells so they can enter them.

Understanding how current vaccines and treatment options perform against new Omnicron subvariants could inform the development of new therapeutics and help plan public health initiatives.

In a new study recently published in the journal 自然, researchers conducted lab experiments to see how well antibodies from vaccinated individuals can neutralize the new subvariants. The findings show that, when compared to BA.2, BA.4 and BA.5 are at least 4 times more resistant to antibodies in individuals who received mRNA vaccines.

> Although the new research shows that immunity against the dominant Omicron subvariants appears to be waning, it's important to note that mRNA vaccines continue to provide very durable B and T cell-based protection against severe outcomes from COVID-19, including hospitalization and death. In addition, preliminary data shows that natural infection — occurring up to 14 months ago — remains 97% protective against the current Omicron subvariants. In general, T cell immunity from mRNA vaccines remains protective across all COVID-19 variants.

COVID-19 antibodies

For the study, the researchers collected blood samples from people who received three doses of an mRNA COVID-19 vaccine. They also collected samples from individuals who received two mRNA COVID-19 vaccines and had previously contracted a non-Omicron SARS-CoV-2 variant.

The researchers then tested antibodies from these individuals against various "pseudoviruses" of the Omicron subvariants. (Pseudoviruses are safe for studying and cannot replicate.)

They found that Omicron BA.2.12.1 — the dominant SARS-CoV-2 variant in the U.S. between May and June — was 1.8 fold more resistant to antibodies from vaccinated and boosted individuals than the BA.2 subvariant.

However, BA.4 and BA.5 were 4.2 times more resistant to antibodies from vaccinated and boosted individuals.

The researchers also tested the pseudoviruses against 21 monoclonal antibody treatments, which are made in a lab and are usually given via infusion to help the immune system against infection. Of the 21 monoclonal antibody treatments, only one remained highly effective against BA.2.12.1, BA.4, and BA.5.

Subvariants and mutations

According to the study authors, as the Omicron lineage of SARS-CoV-2 continues to evolve, it is both more transmissible and more evasive to antibodies.

They noted that it is important to remain vigilant when monitoring dominant variants of SARS-CoV-2 but to remain mindful that they emerged randomly and unexpectedly.

When asked about why current dominant Omicron subvariants are better at evading vaccines, Dr. Clarence Buddy Creech II, MPH, director of the Vanderbilt Vaccine Research Program at Vanderbilt University, told

“As we see subvariants emerge, it is not surprising that they are capable of evading immunity; variants that are easily neutralized by our immune system will have a difficult time becoming the dominant strain now that the vast majority of individuals have been vaccinated or infected with COVID-19.”

Dr. Creech added that future subvariants “may do the same, recognizing that the virus can only change so much before those mutations begin to severely weaken the virus.”

Amira Roess, PhD, MPH, professor of Global Health and Epidemiology at George Mason University, added that we should expect to see more subvariants.

> “As microbes evolve they are more likely to mutate in ways that allow them to escape immunity that we have either from vaccines or natural infection.”
>
> – Amira Roess, PhD, MPH

Possible limitations

When asked about the limitations of the study, Dr. Creech noted that the findings may be limited as they only address the role of antibodies produced by individuals and monoclonal antibodies and not the cellular immune system in neutralizing the virus.

He noted, however, that an implication of the study is that current monoclonal antibody therapies may no longer be effective for those at high risk for COVID-19.

How Omicron subvariants affect hospitalization rates

Different countries have different immune profiles against COVID-19 due

- vaccination rates
- circulating strains
- general risk profiles (i.e., age, public safety measures, etc.)

These varying factors mean that BA.4 and BA.5 may affect countries differently. Nevertheless, higher case numbers of BA.4 and BA.5 were recently linked to a small rise in hospitalizations in 南アフリカ, although a slightly lower death rate than the country's previous Omciron wave.

Countries such as Portugal are seeing a more significant effect from BA.4 and BA.5. Although it has a higher vaccination rate than South Africa, it also has an older population. There, rates of hospitalization and death are similar to those in the first Omicron wave, although still less than those caused by earlier waves.

> "It is possible that BA.4 and BA.5 may lead to increased hospitalizations, particularly among the unvaccinated, the immunosuppressed, and those of advanced age. This is why vaccination is so important; while we see cases increasing, we have seen fewer hospitalizations than at other times in the pandemic because of the impact of immunity."
> – Dr. Clarence Buddy Creech II, MPH

When asked about whether BA.4 and BA.5 will lead to more hospitalizations, Dr. Roess said: "We hope that there is enough underlying immunity that we will not see severe illness, and some studies indicate this."

"Other studies show that severe illness is mainly observed among those who have significant underlying conditions or are of advanced age," Roess concluded.

COVID-19

FEEDBACK:

New Omicron subvariants are spreading: Should we worry?

Written by Katharine Lang on May 19, 2022 — Fact checked by Alexandra Sanfins, Ph.D.

Despite what many of us might like to believe, COVID-19 has not gone away. South Africa recently identified two new subvariants of Omicron — designated BA.4 and BA.5. These subvariants have now spread to several other countries, including the United Kingdom and the United States. Should we be concerned about them? Medical News Today assessed the evidence and spoke to experts in the U.S. and the U.K. to find out.

A member of the Western Cape Metro Emergency Medical Services takes vaccines from an ambulance converted to facilitate vaccinations at a COVID-19 vaccination event in Manenberg on December 8, 2021, in Cape Town. Image credit: RODGER BOSCH/Getty Images.

Alpha, Beta, Gamma, Delta, Omicron — the list of SARS-CoV-2 variants continues to expand. And no sooner have we got used to one variant than another appears.

Latest on the list are the Omicron subvariants BA.4 and BA.5, which were identified recently in South Africa, one of the few countries that are still sequencing large numbers of COVID-19 tests.

South Africa has seen a rapid increase in positive tests for COVID-19, and authorities believe that BA.4 and BA.5 are responsible. The National Institute of Clinical Diseases in South Africa reports that BA.4 and BA.5 are "Omicron viruses with a new combination of mutations."

Scientists in this country first detected BA.4 on January 10, 2022, and it has since spread throughout South Africa, now making up 35% of positive tests. BA.5 was identified on February 25, and now accounts for 20% of cases in several South African regions.

Both subvariants are similar to Omicron BA.2, which is currently dominant in the U.K., continental Europe, and the U.S.

BA.4 and BA.5 have identical mutations on their spike protein — the part of the virus that attaches to receptors on human cells — that differentiate them from BA.2. Each subvariant has its own different mutations in other areas of the virus.

> "We have learned that the [COVID-19-causing variants] are more mutable than we initially thought. Periodically we get major new variants — that's a big shift. But we also get little, what we call 'drift variants.' You can think of them as members of the same family [...] they're like cousins."
>
> – Prof. William Schaffner, professor of infectious diseases at the Vanderbilt University School of Medicine in Nashville, TN

Where are the variants?

So far, BA.4 and BA.5 have been identified in several countries in addition to South Africa. According to a report from the U.K. Health Security Agency (UKHSA), with data up to April 22, BA.4 was present in Austria, the U.K., the U.S., Denmark, Belgium, Israel, Germany, Italy, Canada, France, the Netherlands, Australia, Switzerland, and Botswana.

On the same date, health authorities had identified BA.5 in Portugal, Germany, the U.K., the U.S., Denmark, France, Austria, Belgium, Hong Kong, Australia, Canada, Israel, Norway, Pakistan, Spain, and Switzerland.

Few countries are sequencing large numbers of positive tests, despite the Director-General of the World Health Organization (WHO) stating on May 4 that "testing and sequencing remain absolutely critical."

> — Dr. Tedros Adhanom Ghebreyesus, WHO Director-General

He is not alone in his concern about the lack of sequencing. Prof. Christina Pagel, professor of operational research at University College London (UCL) and director of the UCL Clinical Operational Research Unit, told *Medical News Today* that "[w]e are opening ourselves up to a serious new wave — particularly in winter — that we would not be able to spot in time."

Variants of concern

Although the numbers recorded for both variants are currently low, the actual case numbers are likely to be much higher. Without sequencing of positive tests, the variants that cause COVID-19 cannot be identified.

On May 12, the European Centre for Disease Prevention and Control (ECDC) reclassified BA.4 and BA.5 as variants of concern. This followed a sharp rise in cases in Portugal, where the Portuguese National Institute of Health estimated on May 8 that BA.5 was responsible for around 37% of all positive cases.

The ECDC reports that although there is no evidence yet of increased severity over previous variants, BA.4 and BA.5 do appear to be more transmissible.

> "The Omicrons are an extraordinarily contagious family. There are some data that say these subvariants are even more contagious. [...] Do they have the capacity to produce more severe disease? At the moment, if anything, Omicron seems to be on the milder side."
>
> – Prof. William Schaffner

The U.K. has not yet followed suit. However, the UKHSA published a risk assessment of the two subvariants comparing them with Omicron BA.2. This suggests that the new subvariants may be better at evading the immune system than BA.2, but that the data is insufficient to draw firm conclusions.

In South Africa, which has identified the greatest number of cases, symptoms and severity seem similar to those of disease caused by Omicron BA.2. So far, the number of hospitalizations there has increased only slightly.

Vaccines and the new subvariants

Some good news from GAVI — the vaccine alliance — is that although antibodies from previous Omicron infection do not seem to afford much protection against the new variants, antibodies from vaccination appear to be much more effective.

Prof. Schaffner agreed that vaccines should protect against severe disease from the new variants: “These are slightly different mutations of the spike protein — are they so different that they cannot be responsive to our vaccines? The answer is ‘no’.”

However, he is concerned that “vaccine fatigue” may be having an effect:

> “Of course, vaccines don’t prevent disease — vaccination

> persuade people to come forward yet again to be vaccinated? There is clearly vaccine fatigue out there."

He added that "[t]he more people we can vaccinate around the world [the more we can] reduce the chance of these rogue variants popping up."

Prof. Jonathan Stoye, FRS, principal group leader, and international affairs ambassador at the Francis Crick Institute in London, U.K., agreed: "It does not seem unreasonable to ask whether a greater emphasis should not be placed on attempting to provide and deliver a vaccine which can be administered to all the world's unprotected people, particularly those in lower and middle-income countries."

Surveillance is vital

It is likely that BA.4 and BA.5 will spread further, and that they will not be the last new variants.

Prof. Pagel expressed concern that lack of testing and sequencing may mean that variants are not detected early: "[I]n England, for instance, we are only really doing PCR tests on hospital admissions [...] [and] because admissions are skewed towards older populations, it will take longer for variants to show up if they spread first among children and young people — as has been typical so far."

These concerns were echoed by Prof. Schaffner, who said that "[w]e require a coordinated international surveillance system, and critical to that is the sequencing of viruses. Number one: To detect these minor subvariants. It's always better to know than not [to] know."

"And then, of course, the sequencing is utterly important to pick up that rare event when we would get another rogue strain that could evade the protection of our vaccines," he added.

It is likely that COVID-19, in whatever form, will be with us for some years to come — the key question is, can we keep it under control as we try to get life back to normal?

> “As we’ve moved from pandemic phase to endemic, how will we cope? Are we going to come to some sort of fraught truce with this virus? We haven’t figured out how to do that yet.”
>
> — Prof. William Schaffner

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