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COVID-19

Are covid-19 tests still working?

Nearly five years after the pandemic started, Marianne Guenot investigates whether current antigenic tests still work against the mutated virus

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The summer of 2024 has seen a wave of covid-19 infections spreading across the globe, causing a noticeable increase in reported covid-19 cases and, in some places, hospital admissions.[1] Wastewater surveillance indicates that the true level of exposure is much higher.[2]

But social media sites are full of people describing covid-19-like symptoms but getting negative results on their rapid at-home tests. This has prompted many to ask if the tests we have are still fit for purpose.

Why covid tests still work against new variants

"Most existing tests used to detect covid-19 [virus] appear to be effective with currently circulating variants," the US Food and Drug Administration (FDA) told *The BMJ* in a statement.

Maria Sundaram, an associate research scientist at the Marshfield Clinic Research Institute and editor of the Infectious Disease Society of America's Real Time Covid-19 Learning Network website, says that there is currently very little available data that proves that antigenic tests, also known as rapid diagnostic or laminar flow tests, detect currently circulating variants of SARS-CoV-2, the virus behind covid-19.

But that might be moot. "The vast majority of currently circulating variants (including the so called FLiRT variants fuelling the current wave) are descendants of the omicron variant—and existing evidence suggests that rapid antigen tests still perform well at identifying omicron (versus non-omicron) variants," Sundaram says, citing work done by the FDA on omicron variants as late as 2022.[3]

Sundaram and others tell *The BMJ* that many of the mutations that define variants aren't expected to change the sensitivity of the tests. That's partly because these mutations often affect the spike protein of the virus, whereas the tests, for the most part, target proteins that are much more preserved over time.

"Popular at-home antigenic tests, including BinaxNow, Flowflex, Clinitest, are based on antibodies that target the nucleocapsid of the virus, rather than the changeable spike protein," Sundaram says. "The fact that we are able to detect this 'summer wave' using our existing test capacity is, I hope, a good endorsement for the general test performance for these emerging variants."

Guarding against complacency

Still, scientists are aware of complacency. "Nothing is perfect, and nature always surprises us," says Wilbur Lam, a professor of biomedical engineering at Emory and the Georgia Institute of Technology. A mutation could unexpectedly shake up the complex 3D structure of the protein these at-home tests rely on for detection, for example.

Lam is a principal investigator for the Atlanta Center for Microsystems Engineered Point of Care Technologies (https://www.acmepoct.org/), which acts as the national test verification centre for the US Rapid Acceleration of Diagnostics programme for covid-19. They work with the US National Institutes of Health and the FDA to evaluate whether variations of covid-19 could influence the sensitivity of antigenic tests. When a variant of concern emerges, "we get samples of those variants from around the world," says Lam. These are grown in their category 3 laboratory and tested on the kits. The scientists can also generate mutated proteins in the laboratory and test the antibodies used in the tests in a high throughput, cell based assay. "We've been doing this work repeatedly, every time there's a variant of concern," he adds.

Andrew Pekosz, a professor of microbiology and immunology and virologist at the Johns Hopkins Bloomberg School of Public Health, says that companies that produce antigenic tests can usually tell from virus sequences alone whether they will affect test performance. But they can also challenge their tests with variants collected from recent infections in the laboratory—although these can take a few months to isolate and propagate in vitro. "You can couple that with viral sequencing, so you know exactly what the virus is in those samples," he tells *The BMJ*.

Lam said that, since his team started evaluating these tests (which was before the products were even rolled out to the market), no variant has substantially affected the detection of the rapid at-home kits. Early unpublished data from their research indicate that, if anything, manufacturers have improved the sensitivity of the antibodies in their newer generation of tests. This includes the over-the-counter multiplex assays that screen for covid-19 and flu simultaneously.

I have symptoms. Why am I testing negative for covid?

There are several reasons why a test might come back negative for someone with covid-19 symptoms. Sundaram notes that a few studies indicate that the performance of the test depends on the viral load in the upper respiratory tract, which varies throughout the infection.[4] A large systematic review of 155 studies led by the Cochrane Library in 2022 found that tests are most sensitive for samples taken in the first week after developing symptoms.[5]

"Particularly for individuals who are asymptomatic and testing negative (but have a known or suspected exposure), a negative test result could be a result of testing 'too early' or 'too late' during the infection," she says.

These tests are also known to have a fairly high rate of false negatives—a trade-off for their rapidity and ease of use. The same 2022 Cochrane review found that tests accurately detected an average 73% of cases in people with symptoms and only 55% of cases before symptoms developed.[5] Lam recommends always doing a second test, at least 24 hours after a negative test, before ruling out an infection completely, adding that by doing that, the level of sensitivity of these at-home tests is comparable to that of a laboratory run PCR test.[4]

Another reason a test might not work is that it was poorly stored, is out of date, or that the person using it isn't following the instructions, which can vary between manufacturers. "Read the instructions because if you don't do it right, that makes the test less effective and decreases the sensitivity," says Lam.

The FDA also notes that there were "significant issues with counterfeit covid-19 tests during the pandemic" in the US, although it is not clear if this is still happening. The agency has a landing page containing information on how to spot counterfeit tests that encourages people experiencing issues with covid-19 testing to report them through the MedWatch voluntary reporting form.[6]

Lastly, experts say that there's a good chance that a completely different disease is causing the covid-19-like symptoms that prompted the testing in the first place. Says Lam, "[Covid-19] has really become a much less dangerous disease, not only because a good proportion of the world's population now has been vaccinated or has gotten the disease—so there's herd immunity now—but because the disease is attenuated in terms of severity."

"It's become very flu-like, so the likelihood that the two can get confused is pretty high," he says. That's why multiplex assays are so important, he adds. Flu and covid-19 require very different medical interventions. "That's important, especially for people who are immune compromised or elderly."

Lam and others emphasise the importance of continuing to test, even though the tests might seem like they're not working or people might not want to know (and thus have to isolate and change their plans). It might seem like the current circulating strains are no worse than a bad case of flu, but infection still carries a risk of developing long covid, which is lowered but not eradicated by vaccination.[7]

Moreover, without the baseline data to know how much of the population is carrying SARS-CoV-2, it is very difficult to assess whether a strain is getting more dangerous. "These tests are so important for public health," says Lam, "If enough people use them, we can get a really nice sense of viral dynamics and how these viruses are spreading throughout the community."

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