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Your nose is a battlefield

The FluMist influenza vaccine can activate protective immune cells hidden deep within the nasal passages

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Highlights:

- Scientists at La Jolla Institute for Immunology (LJI) have discovered that the influenza vaccine FluMist can stimulate immunity in the upper airways of adults.
- This is the first time researchers have tracked how immune cells in the upper airways respond to an intranasal vaccine (given via a spray in the nose).
- The new study gives scientists a guide for measuring the effectiveness of new intranasal vaccines against RSV, COVID-19, and other respiratory diseases.

LA JOLLA, CA—Your nose may be the gateway to a stronger immune system.

At the moment, an influenza vaccine called FluMist is the only licensed intranasal vaccine approved for use in humans. The vaccine is administered through a spray of fluid in the nose, rather than with an injection.

FluMist has proven effective in children, and is licensed for adults—but for a long time there has been no measurable “correlate of protection.” Scientists saw no sign of influenza-fighting immune cells circulating in the blood after adults received FluMist.

Now scientists at La Jolla Institute for Immunology (LJI) have discovered that FluMist can trigger an immune response directly in nasal tissue in adults. The vaccine trains immune cells in the upper nasal passages to recognize and fight influenza virus infection. This immune response stays in the upper airways and can't be detected via blood samples.

"The general thinking was that the FluMist vaccine didn't do much of anything in most adults," says LJI Professor and Chief Scientific Officer Shane Crotty, Ph.D., senior author of the new *Science Translational Medicine* study. "But we've shown that actually, surprisingly the majority of people actually are responding to the vaccine directly in their nasal tissues."

The researchers are still determining whether this immune cell response is strong enough to offer lasting protection against the flu. Meanwhile, the findings may guide the development of new intranasal vaccines—for all ages.

"Understanding how FluMist works opens the doorway to understanding other next-generation vaccine platforms," says LJI Postdoctoral Fellow Hannah Stacey, Ph.D., first author of the new study.

Protecting our airways

For the study, the LJI team tapped into a hidden immune cell population. Many immune cells live in the blood, but many immune cells patrol organs, not blood. In 2024, LJI scientists captured a first look at how these cells defend our upper airways. To do this, the scientists pioneered a new deep nasal swab technique.

[Read: LJI scientists capture immune cells hidden in nasal passages]

At last, the scientists could witness how immune cells operate on the front lines of respiratory infections. Many viruses, such as influenza, respiratory syncytial virus (RSV), and SARS-CoV-2 (which causes COVID-19), try to gain a foothold in the upper airways on their way to infect the lungs.

The researchers used deep nasal swabbing to reveal that immune cells in the upper airways can respond quickly to viral infections. Immune cells such as tissue-resident memory B cells could even remember past infections and remain on guard. This immune cell activity was only detectable in the upper airways, not the blood.

Could an intranasal vaccine boost that immune protection? It was time to study FluMist in an entirely new way.

FluMist vs. flu shot

For the study, Stacey worked closely with experts in LJI's John and Susan Major Center for Clinical Investigation. "This study was only possible because we work at LJI, and we have the support of core facilities staff and scientists," says Stacey.

Together, researchers collected and analyzed nasal swab samples from 25 adult study volunteers before and after they received FluMist.

Although the body has many types of immune cells, Stacey and her colleagues focused on tissue-resident B cells, which are important because they produce antibodies to fight viruses.

The team found that the study participants had dramatically increased influenza-fighting B cells in their upper airways following FluMist vaccination. Even better, this immune response was durable, and Stacey could still detect the immune cells six months after vaccination.

These protective B cells stayed in the upper airways and didn't circulate in the bloodstream. "This really speaks to the point that if you only look in the blood following an intranasal or a mucosal vaccination, you probably are missing some really interesting immunology," says Stacey.

The team also collected nasal swabs from 25 volunteers before and after they received a traditional intramuscular vaccine (flu shot). Things looked completely different in this group.

The volunteers who received an intramuscular injection didn't develop a protective B cell response in their upper airways. Instead, these volunteers showed a "systemic" response—an increase in influenza-fighting antibodies in the bloodstream.

Each vaccine approach stimulated a unique immune cell response. The ability to compare these vaccine approaches is a huge leap forward.

As Crotty explains, researchers can now use deep nasal swabs to measure the effectiveness of new kinds of intranasal vaccines, including proposed vaccines against RSV and COVID-19.

And vaccine innovation doesn't need to stop there.

"Let's say you have a new intranasal vaccine, and you want to test the effectiveness of four different doses," says Crotty. "You can use the deep nasal swabbing technique to compare vaccine responses in small groups of people. Then you could make a science-based decision for which vaccine should move forward. This could really speed up future vaccine development for needle-free vaccines"

Authors of the study, "Local B cell immunity and durable memory following live-attenuated influenza intranasal vaccination of humans," included Lucas Garin-Ortega, Paul G. Lopez, Parham Ramezani-Rad, Sydney I. Ramirez, Farhoud Faraji, Disha Bhavsar, Gina Levi, and Florian Krammer.

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