Intranasal Flu Vaccine Shows Promise in Early Trial

— The vaccine appeared to prompt responses to a range of H5N1 clades

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Key Takeaways

- In a phase I trial, an intranasal adjuvanted recombinant influenza vaccine appeared to result in response to a range of H5N1 clades.
- The adjuvanted vaccine elicited seroconversion against clade 2 subclades, including the avian influenza H5N1 clade.
- Post-dose reactogenicity symptoms to the adjuvanted vaccine were common and mostly mild.

An intranasal adjuvanted recombinant influenza vaccine appeared to safely prompt a robust response to a range of H5N1 clades, according to a phase I trial.

Immune responses among the three groups that received one of three doses of the adjuvanted clade 2.1 influenza A/H5 recombinant hemagglutinin glycoprotein (rH5) vaccine were improved from baseline and they were better than those in comparator groups who received an unadjuvanted vaccine or placebo, reported Justin R. Ortiz, MD, of the Center for Vaccine Development and Global Health at the University of Maryland in Baltimore, and colleagues in *Nature Communications*.

"We can actually prime the immune system using the intranasal vaccine," co-author Franklin Toapanta, MD, PhD, also of the Center for Vaccine Development and Global Health, told *MedPage Today*. With the adjuvanted vaccine, the immune system "was able to recognize several strains of the influenza virus, which means there was a breadth of the immune response that was triggered by the vaccine."

Intramuscular flu vaccines trigger systemic immune responses that can prevent symptomatic illness, but they can be less effective at preventing transmission and infection. Mucosal vaccines stimulate an immune response at the entry points where flu viruses infect the body, which may provide better protection against transmission and viral shedding. But assessing their systemic immune impact can be challenging.

"We have overlooked mucosal vaccines for a long time," Toapanta noted. "In the event of a pandemic, the ability of these vaccines to induce a broad response would be a plus."

The investigators randomized 40 healthy volunteers ages 18-45 years (mean age 30.2, 45% women) to one of five groups with eight members each. Three groups received the shelf-stable rH5 vaccine at 25 mcg, 50 mcg, or 100 mcg, with a nanoemulsion adjuvant. One group received

an unadjuvanted rH5 vaccine at 100 mcg, and one group received placebo. All groups received two doses, at day 1 and day 29. The trial ran from July 2022 to October 2023.

For intramuscular vaccines, the standard hemagglutination inhibition (HAI) titer used to infer immune protection is at least 40. Mucosal vaccines have trouble meeting that mark, including the FDA-approved live attenuated intranasal flu vaccine.

"There is not a clear indication of correlates of protection when the vaccine is delivered intranasally," Toapanta explained. "That has hampered the development of intranasal vaccines."

The research team used a trick to reveal the intranasal vaccine's systemic immune impact, Toapanta said. The team gave study participants an intramuscular flu vaccine 6 months after the intranasal vaccine, with all groups receiving a shot of an unadjuvanted inactivated clade 1 influenza A/H5N1 vaccine (H5N1 IIV). The resulting immune response allowed researchers to measure HAI titers and assess whether the intranasal vaccine had indeed primed the immune system.

All five groups had low baseline immunity to rH5's clade 2.1 and H5N1 IIV's clade 1, with HAI geometric mean titers (GMT) no greater than 5.5. At day 57 and 197 after intranasal vaccination, GMT didn't increase significantly. Four weeks after the H5N1 IIV shot, however, the low-dose and high-dose rH5 groups had significant GMT responses relative to baseline and day 57 ($P<0.05$) for rH5's clade 2.1 (GMT 95.1 and 80.0, respectively) and H5N1 IIV's clade 1 (GMT 103.8 and 56.6, respectively).

At day 225 -- 4 weeks after the H5N1 IIV dose -- the geometric mean fold rise (GMFR) to rH5's clade 2.1 was 17.4 in the low-dose adjuvanted rH5 group (95% CI 4.6-66.0), 3.7 for the medium-dose group (95% CI 0.82-16.4), and 14.7

for the high-dose group (95% CI 10.1-21.3). In contrast, the GMFR at day 225 was 1.1 in the unadjuvanted rH5 group (95% CI 0.9-1.4) and 1.6 in the placebo group (95% CI 0.5-5.2).

Against H5N1 IIV's clade 1, the GMFR at day 225 was 20.7 in the low-dose adjuvanted rH5 group (95% CI 10.4-41.3), 3.1 in the medium-dose group (95% CI 0.9-11.0), and 10.4 in the high-dose group (95% CI 3.9-27.5). The GMFR in the unadjuvanted rH5 group was 7.2 (95% CI 1.1-48.6) and 2.2 in the placebo group (95% CI 0.8-6.5).

The researchers also analyzed serum microneutralization responses to other H5N1 clades. They found that the adjuvanted rH5 vaccine elicited seroconversion against clade 2.2 (50% to 62.5%), clade 2.2.1 (50% to 62.5%), clade 2.3.4 (75% to 87.5%), and the avian influenza H5N1 clade 2.3.4.4b (75% to 87.5%).

Post-dose reactogenicity symptoms to the adjuvanted rH5 vaccine were common and mostly mild. There were no adverse events of moderate or greater severity after the second intranasal vaccine dose.

Terrence Rudd is a staff writer at MedPage Today, covering the infectious diseases beat. He has been a medical writer and editor for more than 30 years.

Disclosures

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Ortiz reported relationships with GSK, Pfizer, Moderna, ENA Respiratory, and BlueWillow Biologics.

Toapanta had no disclosures.

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