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Adjuvanted vs High-Dose Influenza Vaccines: A Real-World Evidence Study

**Announcer:**
Welcome to ReachMD. This medical industry feature, titled "Adjuvanted vs High-Dose Influenza Vaccines: A Real-World Evidence Study," is sponsored by CSL Seqirus. Here's your host, Dr. Jennifer Caudle.

**Dr. Caudle:**
This is ReachMD, and I'm Dr. Jennifer Caudle. And joining me today to discuss recent comparing adjuvanted and high-dose influenza vaccine effectiveness is Dr. Blen Girmay. She's a Johns Hopkins fellowship-trained primary care geriatrician at Inova Health System in Fairfax, Virginia. Dr. Girmay, welcome to the program.

**Dr. Girmay:**
Thanks, I'm happy to be here.

**Dr. Caudle:**
So to start us off, can you explain how enhanced influenza vaccine formulations for older adults are different and why they're so important?

**Dr. Girmay:**
Of course.

So as you may know, people who are 65 years and older are especially vulnerable to influenza. They account for a significant number of influenza-associated hospitalizations and nearly 90 percent of influenza-related deaths.[1,2]

Because standard-dose vaccines usually produce only modest immunogenic responses in this age group, as of June 2022, the Advisory Committee on Immunization Practices, or ACIP for short, recommended adults 65 and older receive either an adjuvanted or higher dose vaccine, including high-dose or recombinant seasonal influenza vaccines.[1,3,4] These types of vaccines provide better protection by boosting the immune response, but they take different approaches. The adjuvanted vaccine adds an agent to help stimulate the immune response, while higher-dose vaccines contain more antigen.[1,5]

**Dr. Caudle:**
I see. So, what do we know about the adjuvanted influenza vaccine?

**Dr. Girmay:**
Good question.

Randomized clinical trials have shown that the adjuvanted influenza vaccine, FLUAD®, met immunogenicity non-inferiority criteria when compared to a non-adjuvanted, standard-dose influenza vaccine, and demonstrated a favorable safety profile. The most common local and systemic adverse reactions that occurred in at least 10 percent of adults 65 years of age and older were:

- injection site pain in 16.3 percent
- fatigue in 10.5 percent and
- and headache in 10.8 percent[6]

Now, real-world evidence studies use data collected outside of randomized trials, such as from electronic health records or large claims


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databases and help complement randomized clinical trial data by providing insights into how vaccines perform in a broader, more diverse populations and in clinical practice.[7,8] And – in terms of real-world evidence – systematic reviews, observational studies, and meta-analyses have suggested that adjuvanted and high-dose influenza vaccines provide comparable protection against influenza.[1,2] But strong evidence directly comparing these two vaccines is limited and of low certainty, which makes it difficult to determine if one is consistently superior—or even non-inferior—to the other.[4]

And recently, a real-world study helped fill in an important evidence gap by directly comparing the effectiveness of adjuvanted and high-dose vaccines using lab-confirmed influenza outcomes.[3]

**Dr. Caudle:**
That's interesting. So then let's zero in on this recent real-world evidence. Can you walk us through how the study was structured?

**Dr. Girmay:**
Absolutely.

So this is the first pragmatic, head-to-head randomized study to evaluate the relative vaccine effectiveness of adjuvanted and high-dose influenza vaccines in adults 65 plus, which is significant in and of itself.[3] But the way it was randomized and designed really highlights just how thorough it was.

This study took place over two influenza seasons at a large, integrated healthcare delivery system in Northern California that regularly sees a diverse patient population. Each facility was randomized to administer either the adjuvanted quadrivalent inactivated influenza vaccine, FLUAD, or a high-dose quadrivalent inactivated influenza vaccine on an alternating weekly basis to adults 65 and older.[3] Right now, we're only focusing on the data from the first season – which was the 2023 to 2024 influenza season – since the data from the second season is not available yet.

So, during the first influenza season, almost 430 thousand adults aged 65 and older were vaccinated at their routine healthcare facilities. About 213 thousand received FLUAD and around 217 thousand received a high-dose influenza vaccine.[3] So, right off the bat, this was a very large and diverse study population. And because of the pragmatic randomized design, this population included patients who are often underrepresented in trials, such as people who are frail, high-risk, and have comorbidities.[3]

The primary outcome was PCR-confirmed influenza in any setting, while secondary outcomes were the prevention of hospitalization or emergency visits for PCR-confirmed influenza and hospitalization for all-cause community acquired pneumonia.[3]

This trial set out to determine whether FLUAD is as effective as the high-dose influenza vaccine recommended for adults 65 and over by using a non-inferiority margin of negative 20 percent. Relative vaccine effectiveness, or rVE, was calculated using hazard ratios estimated through Cox regression models.[3]

**Dr. Caudle:**
And what were the results of the first influenza season, Dr. Girmay?

**Dr. Girmay:**
The results for the first season showed that the adjuvanted vaccine, FLUAD was non-inferior to the high-dose vaccine across all outcomes.[3]

If we look at the data, the primary outcome of PCR-confirmed influenza had a lower confidence interval of negative 8.4, which is well within the non-inferiority margin set at negative 20.[3]

For secondary outcomes, the results were similar. The lower end of the confidence range was negative 3.9 for PCR-confirmed influenza cases requiring hospitalization or an emergency department visit, and negative 11.4 for hospitalizations due to all-cause community acquired pneumonia. These also stayed within the non-inferiority margin set by the study.[3]

And while the differences weren't statistically significant, patients who received FLUAD had 1.5 percent fewer PCR-confirmed flu cases, 9.1 percent fewer flu hospitalizations or emergency visits, and one percent fewer pneumonia hospitalizations compared to those who received the high-dose vaccine.[3]

So overall, there was no difference in the effectiveness of these vaccines during the first season.[3] This study demonstrates that these vaccines are just as effective as the other in protecting against multiple influenza-related outcomes.[3]

**Dr. Caudle:**


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For those of you who are just tuning in, you're listening to ReachMD.

I'm Dr. Jennifer Caudle, and today I'm speaking with Dr. Blen Girmay about adjuvanted and high-dose influenza vaccines in adults 65 and over.

So, Dr. Girmay, if we continue to look at the design of this pragmatic head-to-head, randomized study, what components make it more rigorous than previous trials and, on the flip side, what are the limitations?

**Dr. Girmay:**
Right, this is such an important point because this trial met several key criteria.

First, PCR-confirmed influenza is considered the "gold standard" for evaluating influenza vaccine protection because it's specific and provides clear-cut confirmation for influenza infection, unlike other types of study readouts.[5]

Second, the real-world setting strengthens the reliability of these findings. The only variable that changed was the vaccine each facility administered that week; otherwise, these were just people who came in for routine vaccinations.[3]

And lastly, this was a large and diverse study that evaluated over 400 thousand people in a single influenza season.[3] Despite the scale, vaccination timing remained consistent, baseline characteristics varied by less than 1.5 percent, and there was no difference in average or median age.[3] This highlights a well-balanced comparison and the efficiency of the randomization process.

It's also important to mention that the first season used quadrivalent formulations while the second season used trivalent formulations, which correspond to the vaccines licensed in the U.S. during those respective seasons.[4,9] But data from the quadrivalent formulation is still relevant to the trivalent formulation because both vaccines are manufactured using the same process and they have overlapping compositions.[6]

Now, regarding limitations, the primary outcome did *not* include individuals who didn't undergo PCR testing, which limits generalizability.[3] So there could be patients who became infected with influenza but didn't get tested and were unaccounted for during the analyses.[10]

This study was also limited to two influenza seasons, and relative vaccine effectiveness may vary across seasons depending on the match between the vaccine and the circulating strains.[10]

And despite the fact that the large integrated healthcare system serves a diverse population of patients, it may not be representative of other populations in the United States.[10]

**Dr. Caudle:**
So when it comes to analyzing the second part of this trial, what key factors should we watch out for?

**Dr. Girmay:**
Well, we certainly hope to see consistent results, but one of the most significant variables that could influence outcomes is the match between the vaccine and circulating influenza strains. The influenza virus is constantly evolving, and the effectiveness of any given vaccine can vary depending on how well it aligns with the predominant strain in a particular season.[3,10] So this is one of the reasons why it's important to perform season-specific *and* multiple-season analyses to evaluate vaccine effectiveness.

**Dr. Caudle:**
And before we wrap up today's discussion, Dr. Girmay, what key takeaways would you like to leave with our audience?

**Dr. Girmay:**
Data from the first season of this pragmatic study reinforces that the adjuvanted vaccine, FLUAD, was associated with a level of protection against influenza in adults 65 and older that was similar to that observed with a high-dose vaccine.[3] These findings are consistent with the ACIP's preferential recommendation of enhanced influenza vaccines, including FLUAD, for adults 65 plus.[3]

But importantly, this data builds on the existing body of evidence, providing strong clinical support for both vaccines – thanks to the randomization, real-world setting, and large population size.[3] But this is just half of the story, so be on the lookout for data from the 2024 to 2025 influenza season.[3]

**Dr. Caudle:**
Well, as those final comments bring us to the end of today's program, I'd like to thank my guest, Dr. Blen Girmay, for discussing the new


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data comparing adjuvanted and high-dose influenza vaccines for adults 65 and over.

Dr. Girmay, it was great speaking with you today.

**Dr. Girmay:**
Thanks for having me.

**Dr. Caudle:**
For ReachMD, I'm your host Dr. Jennifer Caudle.

Please stay tuned to hear some Important Safety Information.

**Announcer:**
**FLUAD® (Influenza Vaccine, Adjuvanted)**

**INDICATION AND IMPORTANT SAFETY INFORMATION**

**INDICATION AND USAGE**
FLUAD is a vaccine indicated for active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. FLUAD is approved for use in adults 65 years of age and older.

This indication is approved under accelerated approval based on the immune response elicited by FLUAD. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

**IMPORTANT SAFETY INFORMATION**

**CONTRAINDICATIONS**
Do not administer FLUAD to anyone with a history of a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine, including egg protein, or to a previous influenza vaccine.

**WARNINGS AND PRECAUTIONS**
If Guillain-Barré Syndrome (GBS) has occurred within six weeks of previous influenza vaccination, the decision to give FLUAD should be based on careful consideration of the potential benefits and risks.

Appropriate medical treatment must be immediately available to manage potential anaphylactic reactions following administration of FLUAD.

Syncope (fainting) may occur in association with administration of injectable vaccines including FLUAD. Procedures should be in place to avoid injury from fainting.

The immune response to FLUAD in immunocompromised persons, including individuals receiving immunosuppressive therapy, may be lower than in immunocompetent individuals.

Vaccination with FLUAD may not protect all vaccine recipients against influenza disease.

**ADVERSE REACTIONS**
The most common (≥10%) local and systemic adverse reactions in adults 65 years of age and older who received FLUAD were injection site pain (25%), injection site tenderness (21%), myalgia (15%), fatigue (13%) and headache (13%).

Other adverse events may occur.

**To report SUSPECTED ADVERSE REACTIONS, contact CSL Seqirus at 1-855-358-8966 or VAERS at 1-800-822-7967 and www.vaers.hhs.gov.**

**Before administration, please see the full US Prescribing Information for FLUAD.**

This medical industry feature was sponsored by CSL Seqirus. If you missed any part of this discussion, visit Industry Features on ReachMD.com, where you can Be Part of the Knowledge.

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