**Transcript Details**
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/medical-industry-feature/preventing-influenza-in-older-adults-a-closer-look-at-adjuvanted-vaccines/13307/

**ReachMD**
www.reachmd.com
info@reachmd.com
(866) 423-7849

Preventing Influenza in Older Adults: A Closer Look at Adjuvanted Vaccines

**Announcer:**
You're listening to ReachMD.

This medical industry feature, titled "Preventing Influenza in Older Adults: A Closer Look at Adjuvanted Vaccines" is sponsored by Seqirus. This program is intended for healthcare professionals.

Here's your host, Dr. Matt Birnholz.

**Dr. Birnholz:**
As we age, our immune system becomes weaker and therefore unable to ward off infection as easily as in our younger years.[1] And this is particularly troublesome during flu season. In fact, the CDC's Advisory Committee on Immunization Practices, or ACIP, recently looked at flu vaccine data for adults aged 65 years and older. They now recommend that this age group preferentially receive specific influenza vaccines, including higher dose and adjuvanted vaccines, over standard dose unadjuvanted flu vaccine, when available.[2]

This is ReachMD, and I'm Dr. Matt Birnholz. Joining me to discuss how we can help prevent influenza in older adults is Dr. David Canaday, professor in the Division of Infectious Diseases & HIV Medicine at Case Western Reserve University in Cleveland and attending physician of infectious disease at the Cleveland VA Medical Center.

Dr. Canaday, welcome to the program.

**Dr. Canaday:**
Thank you so much for having me talk today.

**Dr. Birnholz:**
So to start us off, Dr. Canaday, what is the burden of influenza disease in adults 65 and older?

**Dr. Canaday:**
The older we get, the more susceptible we are to influenza infection, and infection severity increases with age as well.[1]

In fact, death due to influenza is observed most frequently in adults 65 and older,with more than 31,000 estimated deaths reported per year between 2012 and 2020 in the United States.[3]

An aging immune system also increases the risk of hospitalization[3] and severe complications[4] as a result of influenza. Within those same eight years, we saw more than 302,000 hospitalizations per year in the U.S. due to influenza disease.[3]

**Dr. Birnholz:**
Wow. Well, what factors would you say influence disease burden in this age group?

**Dr. Canaday:**
So, in addition to this aging population experiencing reduced immune responses to influenza vaccines,[5] we also experience influenza strain mismatch in some flu seasons, leading to reduced vaccine efficacy.[6]

Also, some conventional vaccines may offer less protection against influenza infection—anywhere between 16 and 64 percent.[7]

These factors together reveal an unmet need: to reduce disease burden, we must have vaccines capable of broader immune system

responses to help protect our older adults against influenza.[8]

**Dr. Birnholz:**
So, with that being said, Dr. Canaday, do we have tools to help enhance the immune system response in older adults?

**Dr. Canaday:**
Yes, we do. So, we currently have two ways to create enhanced influenza vaccines for this patient population. One way is to increase the antigen in the vaccine, resulting in a higher dose.[9] The other, we'll focus on today, contains an adjuvant.

And this enhanced adjuvanted influenza vaccine is called FLUAD® QUADRIVALENT and is designed to increase the magnitude and breadth of the immune response in adults aged 65 and older.[10]

Using an oil-in-water adjuvant called MF59, FLUAD® promotes T-cell activation and B-cell expansion for influenza antibody release into the system.[11-14]

**Dr. Birnholz:**
For those just joining us, this is ReachMD, and I'm Dr. Matt Birnholz. I'm joined by Dr. David Canaday from the Case Western Reserve University in Cleveland to talk about how we can help prevent influenza in older adults.

So continuing on that track, Dr. Canaday, I'd like to review the clinical trial for FLUAD® QUADRIVALENT. What can you tell us about that?

**Dr. Canaday:**
So Seqirus conducted a pivotal phase 3 trial to evaluate the immunogenicity, efficacy, and safety of FLUAD® QUADRIVALANT. Because it was an absolute efficacy study, FLUAD® was compared with a non-influenza vaccine called Boostrix®.[15]

The study, which was conducted in 12 countries, spanned the 2016/2017 season in the northern hemisphere and the 2017 season in the southern hemisphere.[15]

We'll get to this in a bit, but it's important to note that the predominantly circulating A/H3N2 influenza strains were antigenically mismatched to the virus strains during these seasons,[15] so much so that it triggered a vaccine strain selection change in the following flu season.

Going back to the study, immunogenicity was evaluated by Center for Biologics Evaluation and Research criteria—also known as CBER for short—assessed with a hemagglutinin inhibition assay performed on serum samples collected on days 1 and 22.[15] It measured the proportion of subjects with a seroconversion rate and a hemagglutinin inhibition titer of greater than or equal to 1:40 at day 22.[15]

And as it turns out,FLUAD® QUADRIVALENT elicited good immune responses against all influenza virus strains. In fact, between 60 and 85 percent of subjects achieved at least a fourfold rise in titers, and 80 percent of those subjects' demonstrated titers of greater or equal to 1:40—which is considered as protective—by the hemagglutinin inhibition assay. And this satisfied the CBER criteria for immunogenicity for all four strains.[15]

**Dr. Birnholz:**
Now, I understand that the trial ran into some challenges. So, what can you tell us about that?

**Dr. Canaday:**
Well, patients were monitored for influenza-like illness, or ILI for short, over the course of 181 days,[15] but there are several different criteria that can be used for ILI. And this study used two different ILI criteria for the primary and secondary endpoints and did a post hoc analysis using criteria put forth by the CDC and the WHO.[15]

Now, the protocol definition of ILI for the primary endpoint was broad, and patients only needed to show at least one respiratory and one systemic symptom to be tested for influenza.[15]

But in the post-hoc analysis, again, the CDC and the WHO ILI criteria were used, and they're much more specific, requiring a fever greater than or equal to 37.8 degrees Celsius—or 100 degrees Fahrenheit—plus cough or sore throat, and a fever greater than 38 degrees—or 100.5 degrees Fahrenheit—plus cough, respectively.[15]

**Dr. Birnholz:**
And how did this affect study outcomes, Dr. Canaday?

**Dr. Canaday:**
So, the pre-specified success criteria were defined as a lower-level 95 percent confidence interval for vaccine efficacy of greater than 40 percent.[15]

Absolute vaccine efficacy for the primary endpoint—which again, was the ILI criteria of one respiratory and one systemic symptom confirmed by PCR test—was only 19.8 percent, and it was not statistically significant.[15] I should point out though that this 19.8 percent is in line with the global vaccine effectiveness estimates of 20 percent in that season for older adults.[15]

So, while the study didn't meet its primary efficacy endpoint, we wouldn't expect the vaccine to protect against all infection with a mismatched flu A/H3N2 strain as I mentioned earlier, and that's consistent with what we saw globally.[15]

**Dr. Birnholz:**
So then Dr. Canaday, although this study did not meet its primary endpoint, is there other information we can gather here?

**Dr. Canaday:**
Yes, we should note that a post-hoc analysis looking at more stringent definitions of ILI that include fever, absolute efficacy is higher and becomes statistically significant; in fact, it's as high as 51.1 percent according to the WHO-defined criteria for influenza-like illness.[15]

Going back to study design, randomized clinical trials, or RCTs for short, have their benefits, including internal validity and reduction of confounding factors, but RCTs in general also present limitations, such as limited sample sizes, selected study populations, and limited duration of treatment effect.[16]

So, while RCTs are a well-established requirement for determining vaccine safety and efficacy,[17] influenza seasons and vaccines change year to year,[16] and randomized trials can only assess these vaccines in a narrow, protocol-defined population within a narrow window of time.[16,17]

**Dr. Birnholz:**
And with that being said, where else can we look to find additional evidence of vaccine effectiveness?

**Dr. Canaday:**
Well, we can look to real-world evidence, or RWE for short.

RWE is complementary to RCTs but uses data collected outside of randomized trials to develop clinical evidence about the use or potential risk-to-benefit ratio of a drug.[18]

Data can be collected via prospective observational studies, retrospectively from electronic health records, from large claims databases, or from patient/disease registries.[17]

Now, we have peer-reviewed RWE study data on FLUAD® from Europe and the United States spanning the last 20 years. And these studies explored FLUAD®'s relative vaccine effectiveness on clinical outcomes with other influenza vaccines.

**Dr. Birnholz:**
And can you speak more to those clinical outcomes, Dr. Canaday?

**Dr Canaday:**
Clinical outcomes included influenza-related hospitalizations or ER visits, cardiorespiratory hospitalizations, and influenza-related office visits.[19-30]

Considering multiple seasons of real-world data comparing FLUAD® with a non-adjuvanted, standard influenza vaccine,[19-20,22] we've certainly seen increased benefit.

Likewise, in comparisons with a high-dose influenza vaccine,[24-30] we also have results showing parity overall.

However, key limitations in several of these RWE studies included, but are not limited to potential for residual confounding, lack of laboratory confirmation, and results not being adjusted by unmeasurable confounders.[24-30]

These results aligned with a recent systematic review of enhanced influenza vaccines for older adults by the CDC's Advisory Committee on Immunization Practices, which included FLUAD® along with high-dose and recombinant influenza vaccines. The review concluded that each of these vaccines provided benefit over standard influenza vaccines but note there was no strong evidence favoring one of the

enhanced vaccines over the other.[2]

Based on this systematic review and evidence to recommend, ACIP members voted in favor of the following:

ACIP recommends that adults aged 65 years and older preferentially receive any one of the following higher dose or adjuvanted influenza vaccines: quadrivalent high-dose inactivated influenza vaccine (HD-IIV4), quadrivalent recombinant influenza vaccine (RIV4), or quadrivalent adjuvanted inactivated influenza vaccine (aIIV4).[2]

If none of these three vaccines is available at an opportunity for vaccine administration, then any other age-appropriate influenza vaccine should be used.[2]

**Dr. Birnholz:**
Well, Dr. Canaday, we're almost out of time for today. But given these RWE data, what can we conclude about the effectiveness of FLUAD® QUADRIVALENT in older adults?

**Dr. Canaday:**
In my opinion, there are too many variables at play to only observe a vaccine's efficacy for one or two seasons.

Instead, we need to continually study vaccine effectiveness over multiple seasons with a large number of patients. RCTs inherently can only show a portion of the vaccine efficacy picture and must be complemented with RWE to provide the full picture with a robust data set.[17] Additionally, these trials for influenza need to be presented in the context of vaccine match and the circulating viral strain during the study period, or we won't see reliable results.

But when we examine the real-world evidence over multiple seasons, we see that the benefit of FLUAD® QUADRIVALENT is favorable compared to standard influenza vaccines as well as high-dose vaccines for adults 65 and older.[19-30]

**Dr. Birnholz:**
Thank you, those are great practical takeaways to consider as we end today's program. And I want to thank my guest, Dr. Canaday, for helping us better understand the importance of real-world evidence when determining vaccine effectiveness. Dr. Canaday, it was great speaking with you today.

**Dr. Canaday:**
Thanks, my pleasure also.

**Dr. Birnholz:**
I'm Dr. Matt Birnholz. Please stay tuned to hear some important safety information.

**Announcer:**
**INDICATIONS AND USAGE**
FLUAD QUADRIVALENT is an inactivated influenza vaccine indicated for active immunization against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. FLUAD QUADRIVALENT is approved for use in persons 65 years of age and older.

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

**CONTRAINDICATIONS**
Severe allergic reaction to any component of the vaccine, including egg protein, or after a previous dose of any influenza vaccine.

**WARNINGS AND PRECAUTIONS**

- If Guillain-Barré Syndrome (GBS) has occurred within six weeks of previous influenza vaccination, the decision to give FLUAD QUADRIVALENT should be based on careful consideration of the potential benefits and risks.
- Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.
- The immune response to FLUAD QUADRIVALENT in immunocompromised persons, including individuals receiving immunosuppressive therapy, may be lower than in immunocompetent individuals.
- Syncope (fainting) may occur in association with administration of injectable vaccines including FLUAD QUADRIVALENT. Ensure procedures are in place to avoid injury from falling associated with syncope.

**ADVERSE REACTIONS**
FLUAD QUADRIVALENT administered by needle and syringe:

- The most common (≥ 10%) local and systemic reactions in elderly subjects 65 years of age and older were injection site pain (16.3%), headache (10.8%) and fatigue (10.5%).

Other adverse events may occur. For a comprehensive list of local and systemic adverse reactions, please see full prescribing information.

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

**Announcer:**
This program was sponsored by Seqirus. If you missed any part of this discussion, visit reachmd.com/industryfeature. This is ReachMD. Be part of the knowledge.