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Reevaluating Seasonal Influenza in Children and Adults: The Role of Cell-Based Vaccines

Announcer:
You're listening to ReachMD. This medical industry feature, titled "Reevaluating Seasonal Influenza in Children and Adults: The Role of Cell-Based Vaccines" is sponsored by Seqirus. This program is intended for healthcare professionals.

Your host is Dr. Charles Turck.

Dr. Turck:
The emerging cell-based technology may prove to be a valuable alternative to the traditional egg-based process to use in manufacturing.

The emerging cell-based technology may prove to be a valuable alternative to the traditional egg-based process used in manufacturing influenza vaccines. What are the challenges associated with the well-established egg-based process? How does cell-based technology offer solutions to these challenges? These are some of the questions that'll be addressed on today's program.

This is ReachMD, and I'm Dr. Charles Turck. Joining me to talk about influenza prevention and the latest evidence supporting a cell-based vaccine option is Dr. Mark Blatter. Dr. Blatter, welcome to the program.

Dr. Blatter:
Thanks so much for the invitation.

Dr. Turck:
Before we dive into the vaccine data, can you just level set for us the burden of influenza? What's currently known about that?

Dr. Blatter:
Influenza is a highly contagious infectious disease with substantial global burden and can lead to severe complications of comorbid diseases, pneumonia, and death in high-risk individuals. The symptoms of this disease include the sudden onset of high fever, sore throat, myalgia, arthralgia, headache, severe malaise, cough, and rhinitis. Globally, around 5 to 10% of adults become infected with influenza. According to the World Health Organization, globally, there are an estimated 3 to 5 million cases of severe illness reported on a yearly basis, and up to 650,000 flu-related respiratory deaths.

In the U.S. alone since 2010, the influenza virus has resulted in somewhere between 9 and 45 million illnesses each year, according to the Centers for Disease Control and Prevention. Throughout the country, the virus has led to somewhere between 140,000 to 810,000 hospitalizations, and 12,000 to 61,000 deaths each year.

Dr. Turck:
That's some great information about the impact of the disease. What can you tell us about the burden of influenza in children specifically?

Dr. Blatter:
Great question. So this viral infection can be highly contagious for the pediatric population. An estimated 90 million children under the age of 5 are infected each season, and community attack rates for children less than 6 years of age range from 2 to 21%. Globally, in children younger than 5, an estimated 1 million cases of severe pediatric influenza are reported each year, and up to 112,000 deaths occur annually. When it comes to assessing disease burden for children with influenza, there are several considerations we need to keep in mind, one of them being hospitalization rates, which are statistically higher in our younger patients.

In recent seasons in the U.S., the hospitalizations have increased in the younger age groups with the highest number of hospitalizations in the 0 to 4 age group. Additionally, more influenza-associated deaths have been reported in children under the age of 11, than older children.

We also need to take a look at prolonged viral shedding, which can increase the likelihood of transmission. Children with influenza may remain infectious for a longer period of time, which can lead to an increase in influenza-like infectious diseases in their household.

Now, moving to economic factors, the indirect cost of pediatric influenza can be quite high. And in younger patients, frequent absences from school, and loss of productivity for the child's caregiver may be higher.

The last factor I want to highlight is the immune system. For children in particular, the immune system responds poorly to many standard vaccines. Younger children have immature immune systems and aren't as exposed to influenza viruses as older children, adolescents, or adults.

Dr. Turck:
So with that background in mind, Dr. Blatter, could we touch a little bit on the factors influencing influenza effectiveness. So, what do we need to know those?

Dr. Blatter:
Vaccine effectiveness may be influenced by the following factors: immune system, the viral strain, and manufacturing.

Starting with the immune system, one of the key drivers influencing vaccine effectiveness is age-related immune vulnerability. In our older patients, the immune system becomes slower to respond, and age-related changes can lead to a decline in antibody responses to the influenza vaccine, increasing their risk of contracting the influenza virus. On the other hand, the immune systems of young children are immature and have been less exposed to the influenza viruses.

Viral strain is another critical component. Oftentimes, the circulating strain may be different from the vaccine strain, and the failure to match the circulating strain can lead to reduce cross-reactive antibodies.

And finally, we need to consider egg-based manufacturing. Currently, the influenza vaccine is primarily produced from viruses propagated in eggs; however, mutations in hemagglutinin, or HA, can lead to a change in the antigenicity of the vaccine virus relative to circulating strains. This change can lead to an antigenic mismatch and may reduce the overall effectiveness of the vaccine.

Dr. Turck:
Now, staying with the egg-based manufacturing process for a moment, what can you tell us about some of the associated challenges?

Dr. Blatter:
To give you some background, egg-based influenza vaccine production has been a long-standing process for the development of the influenza vaccine. But this technology has presented quite a few challenges to us. One of them is the acquisition of eggs, which often requires significant lead time. And this delay can potentially limit either the response to unexpected strain changes, or the ability to increase vaccine production during a pandemic.

Another aspect that can be challenging is maintaining the reliability and quality of the embryonated egg supply, which can easily be compromised by avian influenza outbreaks.

And even when there is sufficient supply, not all virus strains can grow well in eggs, resulting in vaccine production challenges. Finally, these virus strains can introduce changes to the embryonated eggs, called egg adaptations, which may lead to vaccine and virus mismatch, resulting in reduced vaccine effectiveness.

Dr. Turck:
That was a really helpful summary of some of the challenges around egg based manufacturing. Taking those challenges into account, how does the process for using egg-based vaccines differ from the manufacturing process of cell-based vaccines?

Dr. Blatter:
Sure, while egg-based manufacturing requires growing the influenza virus in fertilized hen’s eggs, a cell-based manufacturing process uses animal cells as a host for growing the virus. After a clinical sample is isolated, both egg and cell-derived seeds can be used for influenza vaccine manufacturing.

Let's consider both egg-based and cell-based processes. As we mentioned earlier, both begin by isolating the circulating strain, which is followed by the different methods of seed strain creation. The propagation of vaccine strains differs in these two processes. With the egg-based process, embryonated chicken eggs are inoculated with the live virus, and for the cell-based process, live virus is inoculated

in a closed system. Once the live virus is harvested, the final steps in both processes come together when virus is inactivated and purified, and the strains are mixed and finally packaged under sterile conditions to create multivalent vaccines.

The key difference to know here is that using cell-derived seeds avoids egg adaptation, which can sometimes lead to antigenic mismatch.

Madin-Darby canine kidney cells, or MDCK cells, can provide an alternative platform for influenza vaccine growth and HA production. The influenza virus is propagated in these mammalian cells. And it's important to note that while the MDCK cells are highly suitable for the growth of the influenza virus, they're not suitable for the growth of other human viruses. Some additional features of the MDCK suspension cell line also include the ability to grow a wide variety of influenza strains. This production process also serves as an effective filter against most contaminant avian and human viruses. We should also note that the MDCK suspension cell line is a continuous cell line which grows the strains in a suspension. Also, this development process is free of animal-derived culture components, supports high viral yields, and is well suited to a rapid scale-up.

Dr. Turck:
For those just tuning in, you're listening to ReachMD. I'm Dr. Charles Turck. And today I'm speaking with Dr. Mark Blatter about influenza prevention and the role of cell-based vaccines.

So Dr. Blatter, taking these factors on cell-based technologies into account, let's turn our attention to the vaccine option of Flucelvax quadrivalent. But before we dive in, let's review some important safety information.

Announcer:
Indication and Usage
FLUCELVAX QUADRIVALENT is an inactivated vaccine indicated for active immunization for the prevention of influenza disease caused by influenza virus subtypes A and types B contained in the vaccine. FLUCELVAX QUADRIVALENT is approved for use in persons 6 months of age and older.

CONTRAINDICATIONS
Do not administer FLUCELVAX QUADRIVALENT to anyone with a history of severe allergic reactions (e.g. anaphylaxis) to any component of the vaccine.

WARNINGS AND PRECAUTIONS
If Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give FLUCELVAX 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.

Syncope (fainting) can occur in association with administration of injectable vaccines, including FLUCELVAX QUADRIVALENT. Syncope can be accompanied by transient neurological signs such as visual disturbance, paresthesia, and tonic-clonic limb movements. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope by maintaining a supine or Trendelenburg position.

After vaccination with FLUCELVAX QUADRIVALENT, immunocompromised individuals, including those receiving immunosuppressive therapy, may have a reduced immune response.

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

ADVERSE REACTIONS
In children 6 months through 3 years of age who received FLUCELVAX QUADRIVALENT, the most commonly reported injection-site adverse reactions were tenderness (27.9%), erythema (25.8%), induration (17.3%) and ecchymosis (10.7%). The most common systemic adverse reactions were irritability (27.9%), sleepiness (26.9%), diarrhea (17.9%) and change of eating habits (17.4%).

In children 2 through 8 years of age who received FLUCELVAX QUADRIVALENT, the most commonly reported injection-site adverse reactions were tenderness (28.7%), pain (27.9%) and erythema (21.3%), induration (14.9%) and ecchymosis (10.0%). The most common systemic adverse reactions were sleepiness (14.9%), headache (13.8%), fatigue (13.8%), irritability (13.8%) and loss of appetite (10.6%).

In children and adolescents 9 through 17 years of age who received FLUCELVAX QUADRIVALENT, the most commonly reported injection-site adverse reactions were injection site pain (21.7%), erythema (17.2%) and induration (10.5%). The most common systemic adverse events were headache (18.1%) and fatigue (17.0%).

In adults 18 through 64 years of age who received FLUCELVAX QUADRIVALENT, the most commonly reported injection-site adverse reactions were pain (45.4%), erythema (13.4%) and induration (11.6%). The most common systemic adverse reactions were headache (18.7%), fatigue (17.8%) and myalgia (15.4%).

In adults ≥65 years of age who received FLUCELVAX QUADRIVALENT, the most commonly reported injection-site adverse reactions were pain (21.6%) and erythema (11.9%).

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

Before administration, please see the full US Prescribing Information for FLUCELVAX QUADRIVALENT.

FLUCELVAX ® QUADRIVALENT is a registered trademark of Seqirus UK Limited or its affiliates.

Dr. Turck:
Coming back to the vaccine details, Dr. Blatter, what are some highlights we should keep in mind?

Dr. Blatter:
So Flucelvax quadrivalent is an inactivated vaccine indicated for active immunization for the prevention of influenza disease caused by influenza virus subtypes A and B contained in the vaccine for persons aged 6 months and older.

Flucelvax quadrivalent is a suspension for injection supplied in either a 0.5-ml single-dose prefilled Luer Lock syringe, or a 5-ml multidose vial containing 10 doses, where each dose is 0.5 ml. This vaccine is prescribed for intramuscular, or I.M., injection only. Flucelvax quadrivalent must be administered as a single 0.5-ml I.M. injection, preferably in the region of the deltoid muscle of the upper arm.

In younger children with insufficient deltoid mass, this vaccination should be administered in the anterolateral aspect of the thigh. Do not inject in gluteal region or areas where there may be a major nerve trunk.

Dr. Turck:
Now I was wondering if we could get a better sense of the data gathered on this vaccine option that led to its U.S. regulatory approval from the FDA? What clinical studies have been undertaken for Flucelvax quadrivalent?

Dr. Blatter:
There have been several clinical studies evaluating cell-based vaccine QIVc, Flucelvax quadrivalent. To start, there were two studies, both phase 3, randomized, double-blind, and multicenter. The first study evaluated adults, and second evaluated healthy children between the ages of 4 through 17 for non-inferiority of QIVc with a cell-based trivalent comparator, or TIVc.

There was also a clinical trial, where adults between the ages of 18 and 49 were compared for efficacy to placebo, for both TIVc and standard trivalent vaccine against strains included in the vaccine. This was a phase 3 randomized, double-blind, placebo controlled, and multicenter trial.

And finally, a phase 3/4 randomized observer blind, multicenter study evaluated healthy children between the ages of 2 through 17. They received either the Flucelvax QIV, or a non-influenza meningococcal groups A, C, Y, and W-135 oligosaccharide diphtheria CRM197 conjugate comparator vaccine to demonstrate the efficacy of QIVc against any and vaccine match strains, and safety and tolerability.

Dr. Turck:
Well, thank you for walking us through some of the details of those clinical trials. Let's focus for a moment on that last study extending to children ages 2 through 17. What more could you tell us about that?

Dr. Blatter:
Sure. So this study was designed to demonstrate the clinical benefit of Flucelvax quadrivalent in children as young as 2 years of age to anyone under the age of 18. The primary objective was to demonstrate the efficacy to prevent laboratory-confirmed influenza due to any strain of either A or B type in children ages 2 through 17 years of age by comparing with a non-influenza vaccine. In this instance, the comparator in the trial was Menveo, a conjugated meningococcal ACYW vaccine, because it's licensed and marketed for use in children 2 years of age and older, has a dosing regimen that is comparable to QIVc, and would not interfere with national immunization programs in the countries that participated in this study.

This study was conducted over three influenza seasons from 2017 through 2019 at 39 centers across 8 different countries. And over the course of the three seasons, a total of 4,514 subjects were enrolled. During the first season back in 2017, the patients were enrolled

from three southern hemisphere countries, while in the second and third seasons in 2018 and 2019, patients were enrolled from five participating northern hemisphere countries.

Dr. Turck:
And what were the findings from this study, Dr. Blatter?

Dr. Blatter:
The primary efficacy objective in this study was demonstrated in the overall study population of children ages 2 through 17. There were 175 cases, or about 8%, of RT-PCR, or culture-confirmed influenza in the QIVc group, compared with 364 cases, or about 16%, in the control group, resulting in absolute vaccine efficacy of 54.6%, which exceeded the predefined success threshold of 20% for the lower limit of the 95% confidence interval.

Dr. Turck:
And can you give us some insight into the side effect profiles observed?

Dr. Blatter:
The most reported solicited local adverse events in both the QIVc and comparator vaccine groups were tenderness in 29 and 25% of the subjects, respectively, pain in 24 and 19% of the subjects, respectively, and erythema in 19 and 21% of the subjects, respectively. And, except for a slightly higher rate of pain and tenderness in the QIVc group, there were no noticeable differences in rates of solicited local adverse events observed between the QIVc and comparator groups.

Severe solicited local adverse events were uncommon and found in less than 2% of subjects in both vaccine groups. And the majority of solicited local adverse events resolved spontaneously within the first few days after vaccination.

The most frequently reported solicited systemic adverse events reported in both QIVc and the comparator groups were headache in about 17% and 16% of subjects, fatigue and/or tiredness in about 16% and 16% of subbjects, and sleepiness in about 15% and 18% of subjects. There were no notable differences in rates of solicited systemic adverse events observed between QIVc and comparator groups.

Severe systemic solicited adverse events were uncommon, and generally less than 1%, except for sleepiness. Close to 2% of subjects in the comparator group reported sleepiness. A fever of greater than or equal to 38 degrees Celsius was reported by about 5% of subjects in the QIVc and comparator groups, but severe fever, or a fever of greater than or equal to 40 degrees Celsius, was much less common, and reported in less than 1% of the QIVc group and comparator groups.

Dr. Turck:
Well, Dr. Blatter, we've covered a lot of ground on cell-based vaccines today. But before we close, are there any additional thoughts that you want our audience to come away with today?

Dr. Blatter:
Absolutely. Influenza vaccine production using cell-based technology is a modern, efficient, and well-defined technique. And cell-based vaccines could potentially be a valuable alternative to overcome some of the manufacturing vulnerabilities associated with egg-based production. I think the best way to decrease the influenza burden is to encourage our qualified patients to get vaccinated yearly. As their healthcare providers, we are a trusted voice that can speak to the impact that vaccines have on decreasing illnesses, hospitalizations, and overall burden of diseases due to influenza.

Dr. Turck:
That’s a great comment for us to think about as we come to the end of today's program. I want to thank my guest, Dr. Mark Blatter, for helping us better understand the emerging role of cell-based vaccines for influenza prevention. Dr. Blatter, it was great speaking with you today.

Dr. Blatter:
It's been a pleasure.

Announcer:
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