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Egg-Adaptation in Influenza Vaccine Production: A Closer Look

Announcer:
You're listening to ReachMD. This medical industry feature, titled "Egg Adaptation in Influenza Vaccine Production: A Closer Look," is sponsored by Seqirus.

This program is intended for healthcare professionals.

Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:
Influenza is responsible for a high burden of illness, hospitalizations, and deaths every year. And the best way to help reduce this burden is through annual vaccination. Most influenza vaccines available in the United States are produced in eggs. But this has some inherent challenges which can lead to reduced vaccine effectiveness.

That's why on today's program, we'll discuss the burden of influenza, explain what egg adaptations are, and how they might impact vaccine effectiveness from one season to another. And we'll end with an overview of alternative manufacturing processes.

Welcome to ReachMD. I'm your host Dr. Jennifer Caudle, and joining me today is Dr. Wendy Wright and Dr. Gary Marshall. Dr. Wright is a family nurse practitioner and founder of Wright and Associates Family Health Care in Bedford, New Hampshire. Dr. Wright, thanks so much for being here.

Dr. Wright:
Thank you so much, Dr. Caudle. It's my pleasure.

Dr. Caudle:
Well, we're happy that you're here.

And Dr. Marshall is Chief of Pediatric Infectious Diseases at Norton Children's and the University of Louisville School of Medicine in Kentucky. Dr. Marshall, it's great to have you with us.

Dr. Marshall:
Thanks for having me.

Dr. Caudle:
Well, we're all so excited that you're here. So let's first lay the groundwork by discussing the burden that influenza poses every year in the United States and globally.

So Dr. Wright, let's start with you. What can you tell us about the impact that influenza has around the world?

Dr. Wright:
Yes, I think that's a great place to start. So let's start with the United States. So here in the United States, the Centers for Disease Control and Prevention report as many as 45 million annual cases of influenza with up to 810,000 hospitalizations. And while deaths from influenza can be variable year to year, it can range from anywhere from 12,000 up to a high of 61,000.

Now globally, according to estimates from the World Health Organization, 5 to 10% of adults are infected with influenza each year, along with 20 to 30% of all children. This includes 3 to 5 million cases of severe illness. But unfortunately, this also means that we see a global toll of up to 650,000 deaths each year.

Now, some good news here is that the CDC estimates that annual influenza vaccination has prevented between 39,000 and 105,000 hospitalizations and between 3,700 and 9,800 deaths each year over the last 10 years in the United States.

But it's still important to note that although the COVID-19 pandemic mitigation measures employed in 2020 and 2021 season led to almost no circulating influenza, the three seasons before were of moderate to high severity, with the 2017 through 2018 flu season being the most severe in recent years.

Dr. Caudle:
Thanks so much for reviewing all that data with us, Dr. Wright. And now if we focus on the structure and the function of the influenza virus itself, Dr. Marshall, turning to you, can you tell us what we need to know in order to talk about the available vaccines?

Dr. Marshall:
Well, as Dr. Wright was going through all of that morbidity and mortality, I was thinking it's a good thing we understand this virus and it's a good thing we know how to make vaccines.

So the virus consists of a protein shell that encases an RNA genome, and that is surrounded by a lipid envelope, and in that envelope are embedded glycoproteins that enable the virus to attach to host cells and to egress after replication is complete.

So the key to understanding how vaccines work, is to understand that infection is initiated by the binding of one of those surface glycoproteins called the hemagglutinin to cellular receptors. Once the receptor is bound, the virus injects its RNA into the cell and essentially hijacks the cell's machinery in order to replicate.

Antibodies against the hemagglutinin molecule can block infection, which is why this molecule is the most important antigen contained in vaccines. And as we'll discuss in a minute, how you make the hemagglutinin is an important thing.

But for now, another thing to note is that the antigenic presentation of the hemagglutinin molecule changes from year to year, and even from early in the season to late in the season, because the virus evolves under the immunologic pressure in the community. So this underscores the importance of vaccines generating high-quality, high-affinity antibodies that recognize the hemagglutinin of the circulating flu strains.

Dr. Caudle:
Now clearly, preventing influenza infection is a top priority, but challenges do remain. So turning back to you, Dr. Wright, what are some of the difficulties we face with vaccine prevention of influenza?

Dr. Wright:
So it really comes down to vaccine effectiveness, and we have several factors that influence effectiveness year to year.

So along with our immune systems becoming more vulnerable to influenza as we age, a big issue that we see is influenza's high antigenic variability. This is often called antigenic drifting, that Dr. Marshall just mentioned. This constant evolution is one source of a mismatch that occurs between the vaccine and the circulating virus strain.

So if we have a mismatch that occurs between the vaccine and the virus in circulation, then we have a vaccine that's less effective that year. Unfortunately, this evolution is largely out of our control. But then there's the vaccine manufacturing process, which is one thing we can actually control.

Egg-based influenza vaccines have been the standard for more than six decades and have helped us through some really tough flu seasons. But egg adaptations are another source of mismatch, and mutations in hemagglutinin can change antigenicity of the vaccine relative to the circulating strains each year.

Dr. Caudle:
Now with that being said, I'd like to stay on the subject of egg adaptation a bit longer. Dr. Marshall, what are some of the challenges of egg-based manufacturing from your vantage point?

Dr. Marshall:
Well, I'm not sure how the chickens feel about it because we do need large quantities of embryonated hen's eggs in order to make these vaccines.

Another key factor here is that the strains that are isolated from humans and chosen for the vaccine have to learn how to replicate efficiently in the eggs. So after injection into the egg, the virus needs to bind to and infect avian cells to produce enough virus to create the vaccine. Part of that learning process can involve changes in the hemagglutinin molecule that allow for adapting to avian cell surface receptors, which differ from the human receptors. So as the virus becomes more fit for growing in avian cells, it may drift a bit from the

virus that originated in humans.

Dr. Caudle:
For those of you who are just tuning in, you're listening to ReachMD, and I'm your host, Dr. Jennifer Caudle. Today I'm speaking with Dr. Wendy Wright and Dr. Gary Marshall about the challenges surrounding egg-based influenza vaccine manufacturing methods.

So let's dig into virus adaptation and the possibility of poor growth in eggs. Dr. Wright, is there a way to overcome these challenges?

Dr. Wright:
Yes, so as Dr. Marshall explained a bit earlier, egg adaptation occurs when the influenza virus hemagglutinin protein mutates to better bind to the surface receptors on the avian cell.

In the end, the strain that emerges from this process, which can be used to mass produce our vaccines, looks a little different to the human immune system than the circulating natural strain.

So after a person is vaccinated, the antibodies that they make may recognize the egg-adapted vaccine hemagglutinin well, but the circulating virus hemagglutinin less well, so vaccine effectiveness may be suboptimal.

So the bottom line here is that our vaccination remains our best defense against influenza, though a challenge such as egg adaptation during our manufacturing process could impact vaccine effectiveness.

The good news, however, is that we can avoid the antigenic changes due to egg adaptation by moving to newer vaccine technologies that don't rely on the growth of the virus in the eggs.

Dr. Caudle:
Now with that being said, let's turn back to you, Dr. Marshall. Can you fill us in on those alternatives?

Dr. Marshall:
Yes, so recently, we've seen the advent of alternative platforms that do not use eggs to create the vaccines. This includes cell-based manufacturing, as well as recombinant DNA technology. And these avoid the variability associated with egg adaptation.

So in my opinion, pediatricians and primary care physicians need to understand the science that we've been talking about behind egg adaptation and appreciate the growing availability of alternatives to eggs.

Dr. Caudle:
Thanks, Dr. Marshall. Now we're just about out of time for today, but before we close, I'd like to hear from each of you. Starting with you, Dr. Wright, what are some key takeaways you'd like our audience to remember?

Dr. Wright:
So first, I think it's important to remember that egg-based influenza vaccines have been the mainstay for more than 60 years and, in general, have done very well at keeping the flu at bay for many people.

However, as we discussed, there is a risk for strain mismatch from egg adaptation during that manufacturing process. And in fact, a strain mismatch occurred in 6 of the 10 influenza seasons between 2010 and 2011 and between 2019 and 2020 here in the United States. And half of them were caused by egg adaptation in the vaccine strains during vaccine production.

Dr. Caudle:
Thanks for that, Dr. Wright. And the same question to you, Dr. Marshall, what would you like to leave our audience with today?

Dr. Marshall:
So I think it's really important to understand that between season and within season, antigenic drift is inevitable. And it's difficult to predict which natural strains will predominate in any given season.

So one variable we may be able to address in helping to improve influenza vaccine effectiveness is reducing the drift that occurs during our manufacturing processes. The more ways that we can try to improve vaccine effectiveness, the better chance we have to control influenza outbreaks.

Dr. Caudle:
Well, given the toll that influenza takes on patients, healthcare providers, and on the overall healthcare system, those are some great comments for us to think about as we come to the end of today's program.

I'd like to thank my guests for helping us better understand egg adaptation and influenza vaccines. Dr. Wright and Dr. Marshall, it was great speaking with you today.

Dr. Wright:
Thank you so much. It's been my pleasure to be here.

Dr. Marshall:
Same here.

Dr. Caudle:
Thank you, guys. I'm Dr. Jen Caudle and thanks for tuning in.

Announcer:
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