

PCV7 Reduced Penicillin-Nonsusceptible IPD

VITALS

Major Finding: Between the 2000 introduction of PCV7 and 2008, children younger than age 5 years experienced a 78% decline in penicillin-nonsusceptible IPD under the old, pre-2008 break points, and a 64% decline under the new break points.

Data Source: Analysis of 7,272 cases of serious pneumococcal infections in U.S. children younger than age 5 years in 10 ABC areas in 1998-2008.

Disclosures: Dr. Hampton reported that he had no conflicts of interest.

BY ROXANNA GUILFORD-BLAKE

FROM THE INTERNATIONAL CONFERENCE ON EMERGING INFECTIOUS DISEASES

ATLANTA — Introduction of the 7-valent pneumococcal conjugate vaccine led to a major decline in penicillin-nonsusceptible invasive pneumococcal disease among children younger than age 5 years, according to research from the Centers for Disease Control and Prevention and other public health groups. These findings were consistent regardless of which

definition of susceptibility was used, which illustrates how changing case definitions can affect measured vaccine effects, reported Dr. Lee Hampton of the CDC's Epidemic Intelligence Service.

Using the ABC (Active Bacterial Core) surveillance system, Dr. Hampton and his colleagues analyzed 7,272 cases of serious pneumococcal infections in children younger than age 5 years in 10 ABC areas throughout the United States in 1998-2008. Isolates were classified as susceptible or nonsusceptible; "nonsusceptibles" were further classified as intermediate or resistant based on both the old and new CLSI (Clinical and Laboratory Standards Institute) standards. CLSI issued new intravenous penicillin resistance break point standards in 2008.

Among cases of all types of IPD in children younger than age 5 years, 10% had intermediate susceptibility and 4% were fully resistant under the new break points. Under the old break points, 14% had intermediate susceptibility and 20% had full resistance, the researchers noted.

Between the 2000 introduction of the 7-valent pneumococcal conjugate vaccine (PCV7) and 2008, children younger than age 5 years experienced a 78% decline in penicillin-nonsusceptible IPD under the old, pre-2008 break points, and a 64% decline under the new break points.

Rates of penicillin-nonsusceptible IPD in 2008 were higher under the old break points (7.4 cases per 100,000 children) than under the new break points (4.4 cases per 100,000).

"The introduction of PCV7 was associated with dramatic reductions in penicillin-nonsusceptible invasive pneumococcal disease incidents," regardless of which break point was used, Dr. Hampton said. Abruptly switching from the old to the new penicillin break points can create the appearance of a sudden drop in penicillin nonsusceptibility, he added.

Six additional serotypes found in PCV13, but not PCV7, now account for 97% of all penicillin-nonsusceptible IPD under the new break points and 83% of penicillin-nonsusceptible IPD under the old break points, he said. If PCV13 is effective against these additional serotypes, rates of penicillin-nonsusceptible IPD should decrease.

The findings may not be generalizable outside the ABC system, Dr. Hampton said.

He emphasized the results are preliminary, but that they have significant implications for clinicians. "PCV7 has done a terrific job of reducing penicillin-resistant pneumococcal disease, no matter how you look at it. But doctors still need to avoid prescribing antibiotics when they're not needed," he said in an interview. "Clinicians should understand that more of their patients who need intravenous therapy for nonmeningitis pneumococcal disease can now be treated with penicillin. This is great, because penicillin works very well against susceptible pneumococci and promotes less antibiotic resistance than many alternatives."

Fluzone® High-Dose Influenza Virus Vaccine 2010-2011 Formula

Rx only

BRIEF SUMMARY: Please consult package insert for full prescribing information.

INDICATIONS AND USAGE

Fluzone High-Dose is an inactivated influenza virus vaccine indicated for active immunization of persons 65 years of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. This indication is based on the immune response elicited by Fluzone High-Dose; there have been no controlled clinical studies demonstrating a decrease in influenza disease after vaccination with Fluzone High-Dose.

DOSE AND ADMINISTRATION

Dosage and Schedule

Basic dosing information for Fluzone High-Dose, and its respective age indication, is presented in Table 1.

Table 1: Fluzone High-Dose

Any vaccination status	Dose/Route	Schedule
65 years and older	0.5 mL/ Intramuscular	1 dose

Administration

Inspect Fluzone High-Dose syringes visually for particulate matter and/or discoloration prior to administration. If either of these conditions exist, the vaccine should not be administered. Shake the syringe before administering the vaccine. The vaccine should not be injected into the gluteal region or into areas where there may be a major nerve trunk. For needle length, refer to the Advisory Committee on Immunization Practices (ACIP) recommendations. If Fluzone High-Dose is to be given at the same time as another injectable vaccine(s), the vaccine(s) should always be administered at separate injection sites.

Adults 65 years of age and older

Fluzone High-Dose should be administered as a single intramuscular dose preferably in the deltoid muscle.

DOSE FORMS AND STRENGTHS

Fluzone High-Dose

Sterile suspension for intramuscular injection supplied in prefilled syringes, 0.5 mL, for adults 65 years of age and older, distinguished by a gray syringe plunger rod. Each 0.5 mL dose of Fluzone High-Dose contains influenza split virus antigens that are formulated to contain a total of 180 mcg of influenza virus hemagglutinin, 60 mcg each from the 3 influenza virus strains in the vaccine.

CONTRAINDICATIONS

Do not administer Fluzone High-Dose to anyone with a known hypersensitivity to egg proteins or any component of the vaccine, or life-threatening reactions after previous administration of any influenza vaccine.

WARNINGS AND PRECAUTIONS

Guillain-Barré Syndrome

If Guillain-Barré syndrome (GBS) has occurred within 6 weeks of previous influenza vaccination, the decision to give Fluzone High-Dose should be based on careful consideration of the potential benefits and risks.

Altered Immunocompetence

If Fluzone High-Dose is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the immune response may be diminished.

Preventing and Managing Allergic Reactions

Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine. The tip caps of the Fluzone High-Dose prefilled syringes may contain natural rubber latex which may cause allergic reactions in latex sensitive individuals.

Limitations of Vaccine Effectiveness

Vaccination with Fluzone High-Dose may not protect all recipients.

ADVERSE REACTIONS

Clinical Trial Experience

Fluzone High-Dose

A total of 3,876 individuals 65 years of age and older were randomized to receive either Fluzone High-Dose or Fluzone in a phase 3, multi-center, active-controlled, double-blind trial conducted in the US. The safety analysis set included 2,573 Fluzone High-Dose recipients and 1,260 Fluzone recipients.

Table 2 summarizes solicited injection site and systemic adverse events collected within 7 days post vaccination via diary cards. Onset was usually within the first 3 days after vaccination and majority of the reactions resolved within 3 days.

Table 2: Frequency of Solicited Injection Site and Systemic Adverse Events within 7 Days Post-Vaccination

	Fluzone High-Dose (N=2573) Percent	Fluzone (N=1260) Percent
Injection site reactions		
Pain	35.6	24.3
Erythema	14.9	10.8
Swelling	8.9	5.8
Systemic adverse events		
Myalgia	21.4	18.3
Malaise	18.0	14.0
Headache	16.8	14.4
Fever	3.6	2.3

*N is the number of subjects in the Safety Analysis Set.

Solicited injection site reactions and systemic adverse events were more frequent after vaccination with Fluzone High-Dose compared to standard Fluzone in adults 65 years of age and older.

Table 3 summarizes the severity of solicited adverse events that occurred during the first week after vaccination.*

Table 3: Frequency and Severity of Solicited Injection Site and Systemic Adverse Events within 7 Days Post-Vaccination

	Fluzone High-Dose (N=2573) Percent	Fluzone (N=1260) Percent
Injection Site Pain		
Mild	31.5	22.5
Moderate	3.7	1.7
Severe	0.3	0.2
Injection Site Erythema		
Mild	11.3	9.4
Moderate	1.9	0.8
Severe	1.8	0.6
Injection Site Swelling		
Mild	5.8	3.9
Moderate	1.6	1.3
Severe	1.5	0.6
Myalgia		
Mild	15.6	14.8
Moderate	4.2	3.2
Severe	1.6	0.2
Malaise		
Mild	11.7	9.8
Moderate	4.7	3.7
Severe	1.6	0.6
Headache		
Mild	12.6	11.7
Moderate	3.1	2.5
Severe	1.1	0.3

Table 3 (continued): Frequency and Severity of Solicited Injection Site and Systemic Adverse Events within 7 Days Post-Vaccination

	Fluzone High-Dose (N=2573) Percent	Fluzone (N=1260) Percent
Fever		
Mild	2.5	2.0
Moderate	1.1	0.2
Severe	0.0	0.1

*N is the number of subjects in the Safety Analysis Set.

The rates of Serious Adverse Events (SAEs) were comparable between the two groups: 156/2573 (6.1%) of Fluzone High-Dose recipients and 93/1260 (7.4%) of Fluzone recipients experienced SAEs. No deaths were reported within 28 days post-vaccination. A total of 23 deaths were reported during the follow-up period of the study: 16/2573 (0.6%) among Fluzone High-Dose recipients and 7/1260 (0.6%) among Fluzone recipients. The majority of these participants had a medical history of cardiac, hepatic, neoplastic, renal, and/or respiratory diseases.

Post-Marketing Experience

The following events have been reported during the post-approval use of Fluzone. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

- **Blood and Lymphatic System Disorders:** Thrombocytopenia, lymphadenopathy
- **Immune System Disorders:** Anaphylaxis, other allergic/hypersensitivity reactions (including urticaria, angioedema)
- **Nervous System Disorders:** Guillain-Barré syndrome (GBS), convulsions, myelitis (including encephalomyelitis and transverse myelitis), facial palsy (Bell's palsy), optic neuritis/neuropathy, brachial neuritis, syncope (shortly after vaccination), dizziness, paresthesia
- **Vascular Disorders:** Vasculitis, vasodilatation/flushing
- **Respiratory, Thoracic and Mediastinal Disorders:** Dyspnea, pharyngitis, rhinitis
- **Skin and Subcutaneous Tissue Disorders:** Stevens-Johnson syndrome
- **General Disorders and Administration Site Conditions:** Pruritus, asthenia/fatigue, pain in extremities, chest pain

Other Adverse Events Associated with Influenza Vaccines

Anaphylaxis has been reported after administration of Fluzone and other influenza vaccines. Although Fluzone and Fluzone High-Dose contain only a limited quantity of egg protein, this protein can induce immediate hypersensitivity reactions among persons who have egg allergy. Allergic reactions include anaphylaxis, angioedema, hives, and asthma.

The 1976 swine influenza vaccine was associated with an increased frequency of Guillain-Barré syndrome (GBS). Evidence for a causal relation of GBS with subsequent vaccines prepared from other influenza viruses is unclear. If influenza vaccine does pose a risk, it is probably slightly more than 1 additional case/1 million persons vaccinated.

USE IN SPECIFIC POPULATIONS

Fluzone High-Dose

Pediatric Use: Safety and effectiveness of Fluzone High-Dose in children have not been established.

Geriatric Use: Fluzone High-Dose is indicated for adults 65 years of age and older.

CLINICAL STUDIES

Immunogenicity of Fluzone High-Dose in Adults 65 Years of Age and Older

A total of 3,876 individuals 65 years of age and older were randomized to receive either Fluzone High-Dose or Fluzone in a phase 3, multi-center, randomized, active-controlled, double blind trial conducted in the US. Of those, 3,851 (2,576 randomized to Fluzone High-Dose and 1,275 randomized to Fluzone) were included in the immunogenicity analysis according to the vaccine they were randomized to receive.*

The primary endpoint of the study was HI titer 28 days after vaccination. Pre-specified statistical superiority criteria required that (1) the lower limit (LL) of the 2-sided 95% CI of the GMT ratio [Fluzone High-Dose/Fluzone] be greater than 1.50 for at least two of the strains, and if one strain failed, non-inferiority of that strain must be demonstrated (LL>0.67), and that (2) the lower limit of the 2-sided 95% CI of the seroconversion rate difference [Fluzone High-Dose - Fluzone] be greater than 10% for at least two of the strains, and if one strain failed, non-inferiority of that strain must be demonstrated (LL>10%). As shown in Table 4, statistically superior HI titers after vaccination with Fluzone High-Dose compared to standard dose Fluzone were demonstrated for two of the three influenza strains. There are no data demonstrating clinically relevant prevention of culture-confirmed influenza or its complications after vaccination with Fluzone High-Dose compared to standard dose Fluzone in individuals 65 years of age and older.

Table 4: GMT Ratios and Seroconversion Rates Following Vaccination with Fluzone High-Dose

	GMT		GMT Ratio	Seroconversion % ^b		Difference	Met Both Pre-defined Endpoints? ^c
Influenza Strain	Fluzone High-Dose N=2576	Fluzone N=1275	Fluzone High-Dose over Fluzone (95% CI)	Fluzone High-Dose N=2576	Fluzone N=1275	Fluzone High-Dose minus Fluzone (95% CI)	
A (H1N1)	115.8	67.3	1.7 (1.6; 1.8)	48.6	23.1	25.4 (22.4; 28.5)	Yes
A (H3N2)	608.9	332.5	1.8 (1.7; 2.0)	69.1	50.7	18.4 (15.1; 21.7)	Yes
B	69.1	52.3	1.3 (1.2; 1.4)	41.8	29.9	11.8 (8.6; 15.0)	No

Note: As defined in the study protocol:

^aSeroconversion: Paired samples with pre-vaccination HI titer <1:10 and post-vaccination (day 28) titer ≥1:10 or a 4-fold increase for those with pre-vaccination titer ≥1:10.

^bN is the number of subjects in the Immunogenicity Analysis Set.

^cPredefined superiority endpoint for seroconversion: the lower limit of the two-sided 95% CI of the difference of the seroconversion rates (Fluzone High-Dose minus Fluzone) is >10%. Predefined superiority endpoint for GMT ratio: the lower limit of the 95% CI for GMT ratio (Fluzone High-Dose divided by Fluzone) is >1.5.

REFERENCES

- Centers for Disease Control and Prevention. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2009;58(RR-9):1-52.
- NCT00391053: www.clinicaltrials.gov.

HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

The tip caps of the Fluzone High-Dose prefilled syringes may contain natural rubber latex.

Fluzone High-Dose

Prefilled syringe, without needle, 0.5 mL, package of 10 prefilled syringes per carton - NDC 49281-385-65.

Storage and Handling

Store Fluzone High-Dose refrigerated at 2° to 8°C (35° to 46°F). DO NOT FREEZE. Discard if vaccine has been frozen. Do not use after the expiration date shown on the label.

PATIENT COUNSELING INFORMATION

Inform the patient or guardian that Fluzone High-Dose contains killed viruses and cannot cause influenza. Fluzone High-Dose does not prevent other respiratory infections.

- Vaccine recipients and guardians should be instructed to report any severe or unusual adverse reactions to their health care provider and/or to VAERS.

Fluzone is a registered trademark of Sanofi Pasteur Inc.

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