

# Update: Recommendations of the Advisory Committee on Immunization Practices (ACIP) Regarding Use of CSL Seasonal Influenza Vaccine (Afluria) in the United States During 2010--11

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## Weekly

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During the 2010 influenza season in Australia, administration of a 2010 Southern Hemisphere seasonal influenza trivalent inactivated vaccine (TIV) (Fluvax Junior and Fluvax) manufactured by CSL Biotherapies was associated with increased frequency of fever and febrile seizures in children aged 6 months through 4 years (1). Postmarketing surveillance indicated increased reports of fever in children aged 5--8 years after vaccination with Fluvax compared to previous seasons. An antigenically equivalent 2010--11 Northern Hemisphere seasonal influenza TIV (Afluria) manufactured by CSL Biotherapies is approved by the Food and Drug Administration (FDA) for persons aged  $\geq 6$  months in the United States. Prescribing information for the 2010--11 Afluria formulation includes a warning that "Administration of CSL's Southern Hemisphere influenza vaccine has been associated with increased postmarketing reports of fever and febrile seizures in children predominantly below the age of 5 years as compared to previous years" (2). In the United States, annual influenza vaccination is recommended for all persons aged  $\geq 6$  months. On August 5, 2010, the Advisory Committee on Immunization Practices (ACIP) recommended that the 2010--11 Afluria vaccine not be administered to children aged 6 months through 8 years. Other age-appropriate, licensed seasonal influenza vaccine formulations should be used for prevention of influenza in these children. If no other age-appropriate, licensed inactivated seasonal influenza vaccine is available for a child aged 5--8 years who has a medical condition that increases their risk for influenza complications (3), Afluria can be used; however, providers should discuss with the parents or caregivers the benefits and risks of Afluria use before administering this vaccine to children aged 5--8 years.

## Background

In Australia and New Zealand, use of 2010 Fluvax Junior (0.25 mL preparation) and Fluvax (0.5 mL preparation) was suspended in children aged  $< 5$  years because of reports of fever and febrile seizures occurring after receipt of these vaccines in children aged 6 months through 4 years (1,4--7). Australia and New Zealand are the only Southern Hemisphere countries in which Fluvax Junior and Fluvax have been used during 2010. Investigations in Australia indicated that administration of 2010 Fluvax or Fluvax Junior was associated with higher rates of fever in young children 4--24 hours after vaccination when compared with rates observed with TIV during previous years (1). A retrospective cohort study among children aged  $< 5$  years who received TIV in 2010 reported that the risk for fever following receipt of Fluvax was 6.5 times greater than for Influxac (Solvay/Abbott), a different TIV (1). Other data indicated that the rate of fever in 2010 was eight times greater after receipt of Fluvax Junior versus Influxac among children aged  $< 3$  years, and 10 times greater for Fluvax versus Influxac among children aged 3--4 years (1). A follow-up New Zealand study among more than 300 children aged  $< 5$  years found substantially increased febrile reactions in the 24 hours after receipt of Fluvax, but not with Vaxigrip (sanofi pasteur), another TIV (6). Postmarketing surveillance found increased reports of fever in children aged 5--8 years after receipt of 2010 Fluvax compared with reports for the same product in three previous seasons (unpublished data, CSL; 2010). An increased frequency of fever after receipt of 2009 CSL seasonal TIV compared with TIV from another manufacturer among children aged 6 months through 8 years age also was reported in a U.S. clinical trial (2).

Additional investigations determined that the higher frequencies of fever with Fluvax and Fluvax Junior in

Australia during 2010 were associated with substantially higher rates of febrile seizures in children aged 6 months through 4 years; febrile seizures occurred a mean of 7.2 hours (range: 5.9--8.4 hours) after vaccination (1). Overall, the rate of febrile seizures following Fluvax and Fluvax Junior was estimated at  $\leq 9$  per 1,000 doses administered, and approximately nine times more than expected (1). Among children aged 6 months through 2 years, the rate of febrile seizures after vaccination with Fluvax Junior was approximately 10 per 1,000 doses administered, and 1.5 (Fluvax) to 14 (Fluvax Junior) per 1,000 doses administered among children aged 3--4 years versus zero for Influvac in both age groups (1). Before Fluvax use in New Zealand was suspended in young children on April 26, 2010, nine cases of febrile seizures were reported in children aged  $< 5$  years after receiving Fluvax, and one case was reported after vaccination with an unknown influenza vaccine that was strongly suspected to be Fluvax (6). No febrile seizures were reported in an estimated 5,000 to 7,000 children aged  $< 5$  years who received approximately 10,000 to 12,000 doses of Vaxigrip, and no febrile seizures were reported after Influvac in New Zealand (6). To date, despite extensive investigations, no biological cause (e.g., contamination, incomplete virus inactivation or disruption, etc.) has been identified to explain the increase in febrile reactions and febrile seizures associated with Fluvax Junior and Fluvax among children in 2010.

In the United States, annual influenza vaccination is recommended for all persons aged  $\geq 6$  months (3). Alternative, age-appropriate, approved TIV formulations are available for children aged  $\geq 6$  months, and live attenuated influenza virus vaccine (LAIV) is approved for healthy children aged  $\geq 2$  years (Table). Studies that assessed adverse events after receipt of TIV or LAIV in the United States during past influenza seasons (8--10) and unpublished surveillance data have not demonstrated an association between TIV administration and febrile seizures.

Afluria\* was approved by FDA in 2007 for persons aged  $\geq 18$  years. Since November 2009, Afluria has been approved by FDA for persons aged  $\geq 6$  months. The manufacturing process for 2010 Fluvax and Fluvax Junior is the same as for 2010--11 Afluria, and the vaccines strains are antigenically equivalent, although the influenza A (H3N2) virus strains are different. For the 2010--11 influenza season, the warning and precautions section of the Afluria package insert was revised to include the increased incidence of fever and febrile seizures in young children, predominantly among those aged  $< 5$  years, based on postmarketing reports from Australia and New Zealand (2). Limited information is available about seasonal influenza vaccine coverage or the risk of febrile seizures or fever in children aged  $\geq 5$  years from Australia and New Zealand. However, available data to date suggest that children aged 5--8 years might experience higher incidence of fever after vaccination with Fluvax. No information is available on the risk of febrile seizures in children aged 5--8 years, although febrile seizures from any cause are uncommon in this age group.

## Recommendations

Based on the available information, ACIP recommendations for the 2010--11 influenza season in the United States include the following:

- Afluria should not be used in children aged 6 months through 8 years.
- Other age-appropriate, licensed seasonal influenza vaccine formulations, including other TIVs and LAIV, have not been associated with an increased risk of fever or febrile seizures, are safe, and should be used for prevention of influenza in children aged 6 months through 8 years.
- If no other age-appropriate, licensed inactivated seasonal influenza vaccine is available for a child aged 5--8 years who has a medical condition that increases the child's risk for influenza complications (3), Afluria can be used; however, providers should discuss with the parents or caregivers the benefits and risks of influenza vaccination with Afluria before administering this vaccine.
- Afluria may be used in persons aged  $\geq 9$  years.

## Safety Monitoring









Although CSL Southern Hemisphere 2010 seasonal influenza vaccine is the only influenza vaccine to be associated with increased reports of fever and febrile seizures in young children, as in previous seasons, CDC,

FDA, and other federal agencies will closely monitor the safety of seasonal influenza vaccines during 2010--11. CDC will rely primarily on the Vaccine Adverse Event Reporting System (VAERS)<sup>†</sup> and the Vaccine Safety Datalink (VSD)<sup>§</sup> to conduct safety monitoring. VAERS is a passive reporting system, co-managed by CDC and FDA, which identifies potential vaccine safety problems in the United States. VAERS reports following 2010--11 influenza vaccinations will be reviewed regularly with special attention to reports of febrile seizures in children aged <9 years. VSD is a collaboration of eight managed-care organizations with more than 9 million members that links computerized vaccination and health-care encounter data. VSD will be used for rapid, ongoing analyses to monitor for serious adverse events associated with vaccination against seasonal influenza, including seizures in young children. VSD also is available to evaluate possible associations detected by VAERS or other sources, as needed.

## Reported by

*Advisory Committee on Immunization Practices (ACIP); ACIP Influenza Work Group; Immunization Safety Office, National Center for Emerging and Zoonotic Infectious Diseases; Influenza Div, Immunization Services Div, National Center for Immunization and Respiratory Diseases; CDC.*

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**TABLE. Influenza vaccines recommended by the Advisory Committee on Immunization Practices (ACIP) for different age groups --- United States, 2010--11 season**

| Vaccine         | Trade name        | Manufacturer     | Presentation                 | Mercury content      | Age group | No. of doses | Route          |
|-----------------|-------------------|------------------|------------------------------|----------------------|-----------|--------------|----------------|
|                 |                   |                  |                              | (mcg Hg/0.5 mL dose) |           |              |                |
| TIV*            | Fluzone           | sanofi pasteur   | 0.25mL prefilled syringe     | 0                    | 6--35 mos | 1 or 2†      | Intramuscular§ |
|                 |                   |                  | 0.5 mL prefilled syringe     | 0                    | ≥36 mos   | 1 or 2†      | Intramuscular§ |
|                 |                   |                  | 0.5 mL vial                  | 0                    | ≥36 mos   | 1 or 2†      | Intramuscular§ |
|                 |                   |                  | 5.0 mL multidose vial        | 25.0                 | ≥6 mos    | 1 or 2†      | Intramuscular§ |
| TIV             | Fluvirin          | Novartis Vaccine | 5.0 mL multidose vial        | 25.0                 | ≥4 yrs    | 1 or 2†      | Intramuscular§ |
|                 |                   |                  | 0.5 mL prefilled syringe     | <1.0                 |           |              |                |
| TIV             | Agriflu           | Novartis Vaccine | 0.5 mL prefilled syringe     | 0                    | ≥18 yrs   | 1            | Intramuscular§ |
| TIV             | Fluarix           | GlaxoSmithKline  | 0.5 mL prefilled syringe     | 0                    | ≥3 yrs    | 1 or 2†      | Intramuscular§ |
| TIV             | FluLaval          | GlaxoSmithKline  | 5.0 mL multidose vial        | 25.0                 | ≥18 yrs   | 1            | Intramuscular§ |
| TIV             | Afluria¶          | CSL Biotherapies | 0.5 mL prefilled syringe     | 0                    | ≥9 yrs    | 1            | Intramuscular§ |
| TIV High-Dose** | Fluzone High-Dose | sanofi pasteur   | 0.5 mL prefilled syringe     | 0                    | ≥65 yrs   | 1            | Intramuscular§ |
| LAIV††          | FluMist§§         | MedImmune        | 0.2 mL sprayer, divided dose | 0                    | 2--49 yrs | 1 or 2†      | Intranasal     |

Use of trade names and commercial sources is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services.

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