

## 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

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 Influvac (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 Influvac among children aged  $< 3$  years, and 10 times greater for Fluvax versus Influvac 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

\* Additional information on Afluria is available at <http://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm220730.pdf>; additional information on influenza vaccines also is available from CDC at [http://www.cdc.gov/flu/protect/vaccine/qa\\_cslfluvac.htm](http://www.cdc.gov/flu/protect/vaccine/qa_cslfluvac.htm) and from FDA at <http://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/post-marketactivities/lotreleases/ucm220649.htm>.

<sup>†</sup> Additional information is available at <http://www.cdc.gov/vaccinesafety/activities/vaers.html> and <http://vaers.hhs.gov/index>.

<sup>§</sup> Additional information is available at <http://www.cdc.gov/vaccinesafety/activities/vsd.html>.

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

\* Trivalent inactivated vaccine.

<sup>†</sup> Children aged 6 months–8 years who did not receive at least 1 dose of an influenza A (H1N1) 2009 monovalent vaccine, who have never received a seasonal influenza vaccine before, or who were vaccinated for the first time with the seasonal 2009–10 seasonal vaccine but who received only 1 dose should receive 2 doses of the 2010–11 influenza vaccine formula, spaced ≥4 weeks apart.

<sup>§</sup> For adults and older children, the recommended site of vaccination is the deltoid muscle. The preferred site for infants and young children is the anterolateral aspect of the thigh.

<sup>¶</sup> Afluria (CSL Biotherapies) is approved in the United States by the Food and Drug Administration for use in persons aged ≥6 months. However, the Advisory Committee on Immunization Practices recommends that the 2010–11 formulation of Afluria not be administered to children aged 6 months–8 years because of an increased frequency of fever or febrile seizures reported among young children (mostly children aged <5 years) who received a similar vaccine in Australia in 2010. Therefore, another age-appropriate, licensed seasonal influenza vaccine formulation should be used for prevention of influenza in children aged 6 months–8 years. If no other age-appropriate, licensed 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, 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. See second footnote above for dose information when administering Afluria to children aged 5–8 years.

\*\* Trivalent inactivated vaccine high dose. A 0.5-mL dose contains 60 mcg each of A/California/7/2009 (H1N1)-like, A/Perth/16/2009 (H3N2)-like, and B/Brisbane/60/2008-like antigens.

<sup>††</sup> Live attenuated influenza vaccine.

<sup>§§</sup> FluMist is shipped refrigerated and stored in the refrigerator at 36°F–46°F (2°C–8°C) after arrival in the vaccination clinic. The dose is 0.2 mL divided equally between each nostril. Health-care providers should consult the medical record, when available, to identify children aged 2–4 years with asthma or recurrent wheezing that might indicate asthma. In addition, to identify children who might be at greater risk for asthma and possibly at increased risk for wheezing after receiving LAIV, parents or caregivers of children aged 2–4 years should be asked: "In the past 12 months, has a health-care provider ever told you that your child had wheezing or asthma?" Children whose parents or caregivers answer "yes" to this question and children who have asthma or who had a wheezing episode noted in the medical record within the past 12 months should not receive FluMist.

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.*

### References

1. Therapeutic Goods Administration. Investigation into febrile reactions in young children following 2010 seasonal trivalent influenza vaccination. Woden, Australia: Therapeutic Goods Administration, Department of Health and Ageing; 2010. Available at <http://www.tga.gov.au/alerts/medicines/flu vaccine-report100702.htm>. Accessed August 11, 2010.

- Food and Drug Administration. Afluria, influenza virus vaccine 2010 [package insert]. CSL Limited; Food and Drug Administration; 2010. Available at <http://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm220730.pdf>. Accessed August 11, 2010.
- CDC. Prevention and Control of Influenza with Vaccines. Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. Available at <http://www.cdc.gov/mmwr/pdf/rr/rr59e0729.pdf>. Accessed August 11, 2010.
- Investigation into febrile convulsions in young children after seasonal influenza vaccination. Interim findings and recommendations. Woden, Australia: Department of Health and Ageing; 2010. Available at [http://www.health.gov.au/internet/main/publishing.nsf/content/c8d6beb67768e80aca257735002424bf/\\$file/dept%20010610.pdf](http://www.health.gov.au/internet/main/publishing.nsf/content/c8d6beb67768e80aca257735002424bf/$file/dept%20010610.pdf). Accessed August 11, 2010.
- Department of Health and Ageing. Investigation into febrile convulsions in young children after seasonal influenza vaccination. Woden, Australia: Department of Health and Ageing; 2010. Available at [http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/content/431453bbf1fb2fca25776d007d9ff4/\\$file/factsheet-30jul10.pdf](http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/content/431453bbf1fb2fca25776d007d9ff4/$file/factsheet-30jul10.pdf). Accessed August 11, 2010.

6. Department of Health and Ageing. Australian Technical Advisory Group on Immunisation (ATAGI) statement: clinical advice for immunisation providers on resumption of the use of 2010 trivalent seasonal vaccines in children less than 5 years of age. Woden, Australia: Department of Health and Ageing; 2010. Available at [http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/B4A8DC125C08290ACA25776D001DA89B/\\$File/atagi-statement-tiv.pdf](http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/B4A8DC125C08290ACA25776D001DA89B/$File/atagi-statement-tiv.pdf). Accessed August 11, 2010.
7. New Zealand Ministry of Health. Fever and convulsions in children receiving flu vaccine. Wellington, New Zealand: New Zealand Ministry of Health; 2010. Available at <http://www.moh.govt.nz/moh.nsf/indexmh/fever-and-convulsions-in-children-receiving-flu-vaccine?open>. Accessed August 11, 2010.
8. Hambidge SJ, Glanz JM, France EK, et al.; Vaccine Safety Datalink Team. Safety of trivalent inactivated influenza vaccine in children 6 to 23 months old. *JAMA*. 2006 Oct 25;296(16):1990-7.
9. France EK, Glanz JM, Xu S, et al. Safety of the trivalent inactivated influenza vaccine among children: a population-based study. *Arch Pediatr Adolesc Med* 2004;158:1031-6.
10. Greene SK, Kulldorff M, Lewis EM, et al. Near real-time surveillance for influenza vaccine safety: proof-of-concept in the Vaccine Safety Datalink Project. *Am J Epidemiol* 2010;171:177-88.

## Announcement

### Interactive CDC DengueMap Available Online

CDC, in collaboration with HealthMap, has created a new online tool for displaying global dengue activity. The interactive DengueMap shows areas where CDC considers dengue to be endemic and sites of recent, location-specific reports of disease. Unlike the CDC map that is compiled every 2 years for the CDC Travelers' Health Yellow Book to characterize general dengue risk based on traditional public health data sources, HealthMap reports are updated hourly and include both professional sources, such as the World Health Organization and ProMED-mail, and informal sources such as local media reports. Combined, these data provide a more dynamic and immediate picture of where transmission of dengue viruses might occur and where disease is actually occurring. DengueMap is available at <http://healthmap.org/dengue> and <http://www.cdc.gov/dengue>. Additional information regarding HealthMap is available at <http://healthmap.org>.

## Erratum: Vol. 59, No. RR-8

In the *MMWR Recommendations and Reports* "Prevention and Control of Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010," on page 18, the first two sentences under the heading "Pregnant Women and Neonates" should read, "FDA has classified FluLaval, Fluarix (GlaxoSmithKline Biologicals), and Agriflu (Novartis Vaccines and Diagnostics Limited) influenza vaccines as "Pregnancy Category B" medications, indicating that animal reproduction studies have not demonstrated a fetal risk, but there are no controlled studies in pregnant women; all other influenza vaccines are classified as "Pregnancy Category C" medications, indicating that adequate animal reproduction studies have not been conducted. Available data do not indicate that any influenza vaccine causes fetal harm when administered to a pregnant woman, and any of the approved TIV formulations may be used for vaccinating pregnant women."

## Errata: Vol. 59, No. 30

In the report, "Launching a National Surveillance System After an Earthquake — Haiti, 2010," errors occurred in one of the charts in Figure 2 on page 937. The corrected chart is below.

