Supplemental Information

STUDY INCLUSION AND EXCLUSION CRITERIA

Subject Inclusion Criteria (Visit 1)

Subjects who meet all of the following criteria will be eligible to participate in this interventional study:

1. 12 to 16 months of age (ie, from the 1-year birthday until the day before 17 months of age) at the time of vaccination;
2. stable health, as determined by the investigator's clinical examination and assessment of the child's medical history;
3. has received all immunizations recommended by the ACIP during the first year of life, with the exception of rotavirus and influenza vaccines[1]*;
4. the parent(s) or legally authorized representative(s) (LAR[s]) intends for the child to receive DTaP vaccine and PCV13 in addition to this season's IIV;
5. the parent(s) or LAR(s) is willing and capable of providing permission for their child to participate through the written informed consent process;
6. the parent(s) or LAR(s) is able to comply with the requirements of the protocol (eg, completion of the memory aid [either electronic or paper diary], return for follow-up visits, respects intervals between the visits, and has telephone access);
7. the parent(s) or LAR(s) is English speaking; and
8. the parent(s) or LAR(s) agrees to sign a medical release for the child so that study personnel may obtain medical information about the child's health (if needed).

Subject Exclusion Criteria (Visit 1)

Subjects who meet any of the following criteria will not be eligible to participate in this study:

1. history of any seizure (including FS) in the child or a FS in a first-degree relative (first-degree relatives include biological parents or siblings);
2. has already completed influenza vaccination during the current season per ACIP recommendations[2†];
3. receipt of >3 previous doses of DTaP vaccine;
4. received the third dose of DTaP vaccine within 6 months of visit 1;
5. receipt of >3 previous doses of PCV13;
6. received the third dose of PCV13 within 8 weeks of visit 1;
7. history of a severe allergic reaction (eg, anaphylaxis) to a previous dose of any influenza vaccine; diphtheria toxoid–containing, tetanus toxoid–containing, or pertussis-containing vaccine; or pneumococcal vaccine;
8. history of a severe allergic reaction (eg, anaphylaxis) to any component (including egg protein) of any of the 3 vaccines used in this study or history of a latex allergy;
9. history of Guillain-Barré syndrome within 6 weeks after a previous dose of influenza, DTaP, or tetanus toxoid–containing vaccine;
10. history of a progressive neurologic disorder;
11. history of encephalopathy within 7 days of a previous dose of pertussis-containing vaccine;
12. history of collapse within 3 days after a previous dose of DTaP vaccine;
13. received any other licensed vaccines within 14 days (for inactivated vaccines) or 28 days (for live vaccines) before visit 1[3‡];14. received an experimental or investigational agent (vaccine, drug, biologic, device, blood product, or medication) within 28 days before visit 1 or expects to receive an experimental or investigational agent during the study period (up to 8 days after visit 2);
14. a moderate to severe acute illness within 72 hours of visit 1 (all vaccines can be administered to persons with a minor illness such as diarrhea or mild upper respiratory infection without fever);
15. a reported temperature ≥100.4°F (38.0°C) within 72 hours before enrollment or a temperature (measured by temporal artery thermometer) ≥100.4°F (38.0°C) at the time of enrollment (this

may result in a temporary delay of vaccination);

16. receipt of an antipyretic medication (acetaminophen or ibuprofen) within 24 hours before enrollment (this may result in a temporary delay of vaccination);
17. parent or /LAR is planning to administer a prophylactic antipyretic or medication on the day of and/or within 7 days after visit 1 or visit 2 (this exclusion does not apply if the caretaker indicates that he or she might administer antipyretics or analgesics after vaccination to reduce fever or pain);
18. long-term (at least 14 consecutive days) oral corticosteroids (prednisone 2 mg/kg per day or equivalent other glucocorticoid), any parenteral steroids, high-dose inhaled steroids (>800 μg/day of beclomethasone dipropionate or equivalent), or other immune-modifying drugs or immunosuppressants within the preceding 6 months before visit 1 (topical and nasal steroids are allowed);
19. any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and/or their provider's routine physical examination (no laboratory testing required);
20. has an active neoplastic disease, has a history of any hematologic malignancy or current bleeding disorder, or is taking anticoagulants;
21. unable to receive an intramuscular injection in the thigh (eg, a broken bone or cast for treatment of a broken bone in a lower extremity, a congenital anomaly in a lower extremity precluding administration in the affected extremity, or if deemed inappropriate by the study investigator);
22. any condition deemed by the investigator to place the child at increased risk as a result of their participation in the study; and
23. any child or grandchild of a study investigator or study team member.

Modified Exclusion Criteria (Visit 2)

Subjects who meet any of the following exclusion criteria will not be eligible to continue participation in this study:

1. has already completed influenza vaccination during the current season per ACIP recommendations;
2. has a history of a severe allergic reaction (eg, anaphylaxis) to a previous dose of any influenza vaccine;
3. history of a severe allergic reaction (eg, anaphylaxis) to any component (including egg protein) of the influenza vaccine used in this study;
4. history of Guillain-Barré syndrome within 6 weeks after a previous dose of any influenza vaccine;
5. received an experimental or investigational agent (vaccine, drug, biologic, device, blood product, or medication) after random assignment or expects to receive an experimental or investigational agent during the remaining study period (up to 8 days after visit 2);
6. a moderate to severe acute illness within 24 hours of visit 2, which may result in a temporary delay of visit 2 and/or vaccination (all vaccines can be administered to persons with a minor illness such as diarrhea or mild upper respiratory infection without fever);
7. a reported temperature ≥100.4° F (38.0°C) within 24 hours before visit 2 or a temperature (measured by a temporal artery thermometer) ≥100.4°F (38.0°C) at the time of visit 2 (this may result in a temporary delay of visit 2 and/or vaccination);
8. receipt of an antipyretic medication (acetaminophen or ibuprofen) within 24 hours before visit 2 (this may result in a temporary delay of visit 2 and/or vaccination);
9. parent(s) or LAR is planning to administer a prophylactic antipyretic or medication on the day of and/or within 7 days after visit 2 (this exclusion does not apply if the caretaker indicates that he or she might administer antipyretics or analgesics after visit 2 to reduce fever or pain);
10. unable to receive an intramuscular injection in the thigh (eg, a broken bone or cast for treatment of a broken bone in a lower extremity, a congenital anomaly in a lower extremity precluding administration in the affected extremity, or if deemed inappropriate by the study investigator); and
11. any condition deemed by the investigator to place the child at increased risk as a result of their participation in the study.

SUPPLEMENTAL TABLE 5 Grading of Solicited Systemic Adverse Events

	Fever Assessment and Solicited Systemic Adverse Events			
	None	Grade 1	Grade 2	Grade 3
Temperature[a]	≤37.9°C (≤100.3°F)	≥38.0°C to ≤38.5°C (≥100.4°F to ≤101.3°F)	≥38.6°C to ≤39.5°C (≥101.4°F to ≤103.1°F)	≥39.6°C (≥103.2°F)
Fussiness or irritability	None	Less playful than usual but not requiring more attention and able to console	Requiring increased attention but able to console	Unable to console
Change in eating habits	None	Eating less than normal for 1–2 feeds or meals	Missed 1 or 2 feeds or meals completely	Refuses ≥3 feeds or meals or refuses most feeds or meal
Drowsiness or sleepiness	None	Drowsy but still interested in surroundings and did not miss a feed or meal	Not interested in surroundings or did not wake up for a feed or meal	Sleeps most of the time or is difficult to wake up

[a] Cutoff values for fever are referenced from the Fluzone Quadrivalent package insert.[11]

SUPPLEMENTAL TABLE 6 Medical Care Use and Antipyretic Use From Memory Aid

Question	Yes	No
Did you give your child fever or pain medicine?	Yes	No
If yes, was it for fever?	Yes	No
If yes, was it for pain?	Yes	No
If yes, check the type or types of medicine given		
Acetaminophen (eg, Tylenol)		
Ibuprofen (eg, Motrin, Advil)		
Other		
Did your child receive medical attention?	Yes	No
If yes, was it related to fever?	Yes	No
If yes, check the type or types of attention received		
Telephone call for medical advice		
Medical office visit, including urgent care visit		
Emergency department visit		
Hospital admission		
If yes, provide the reason for medical attention		
Did your child have a seizure?	Yes	No
If yes, was it related to fever?	Yes	No

SUPPLEMENTAL TABLE 7 Occurrence of Any Fever (Temperature ≥ 38.0°C) and Grade 2 or 3 Fever (Temperature ≥ 38.6°C) by Follow-up Time Period (Days 1–2 and Days 3–8) after Visit 1 and Visit 2 Combined and Visit 1 and Visit 2 Separately, ITT Population

Outcome	Study Group	Fever Absent, *n* (%)	Fever Present, *n* (%)	*P*	RR (95% CI)[a]
Days 1–2					
Any fever after visit 1 and visit 2 combined	Simultaneous	101 (91.8)	9 (8.2)	.845	0.92 (0.39–2.16)
	Sequential	101 (91)	10 (9)		
Grade 2 or 3[b] fever after visit 1 and visit 2 combined	Simultaneous	106 (96.4)	4 (3.6)	.539	0.68 (0.20–2.33)
	Sequential	105 (94.6)	6 (5.4)		
Any fever after visit 1	Simultaneous	101 (91.8)	9 (8.2)	.966	1.02 (0.42–2.46)
	Sequential	102 (91.9)	9 (8.1)		
Grade 2 or 3[b] fever after visit 1	Simultaneous	106 (96.4)	4 (3.6)	.756	0.82 (0.23–2.94)
	Sequential	106 (95.5)	5 (4.5)		
Any fever after visit 2	Simultaneous	105 (100)	0 (0)	.326	—
	Sequential	110 (99.1)	1 (0.9)		
Grade 2 or 3[b] fever after visit 2	Simultaneous	110 (100)	0 (0)	.326	—
	Sequential	110 (99.1)	1 (0.9)		
Days 3–8					
Any fever after visit 1 and visit 2 combined	Simultaneous	99 (90)	11 (10)	.976	1.01 (0.46–2.23)
	Sequential	100 (90.1)	11 (9.9)		
Grade 2 or 3 fever after visit 1 and visit 2 combined	Simultaneous	107 (97.3)	3 (2.7)	.314	0.50 (0.13–1.96)
	Sequential	105 (94.6)	6 (5.4)		
Any fever after visit 1	Simultaneous	104 (94.5)	6 (5.5)	.590	0.75 (0.27–2.10)
	Sequential	(92.8)	8 (7.2)		
Grade 2 or 3[c] fever after visit 1	Simultaneous	107 (97.3)	3 (2.7)	.482	0.61 (0.15–2.47)
	Sequential	106 (95.5)	5 (4.5)		
Any fever after visit 2	Simultaneous	99 (94.3)	6 (5.7)	.470	1.57 (0.46–5.36)
	Sequential	107 (96.4)	4 (3.6)		
Grade 2 or 3[d] fever after visit 2	Simultaneous	110 (100)	0 (0)	.313	—
	Sequential	110 (99.1)	1 (0.9)		

—, not applicable.

[a] The sequential group is the reference group, and adjustment was made for study sites.

[b] No grade 3 fever (temperature ≥ 39.6°C) was reported on days 1 to 2 after visit 1 or 2. Grade 2 fever was a temperature ≥38.6°C to ≤39.5°C.

[c] One child in the simultaneous group and 2 children in the sequential group had grade 3 fever during days 3 to 8 after visit 1. Of these, only 1 (sequential group) received measles, mumps, rubella, and varicella vaccines.

[d] No grade 3 fever was reported on days 3 to 8 after visit 2.

SUPPLEMENTAL TABLE 8 Antipyretic Use for Parent-Reported Fever and for Any Indication on Day 1 or 2 After Visit 1 and Visit 2 and Visit 1 and Visit 2 Combined, ITT Population

Reason for Antipyretic Use	Study Group	No Antipyretic Use, *n* (%)	Antipyretic Use, *n* (%)	*P*	RR (95% CI)[a]
Parent-reported fever after visit 1 and visit 2 combined	Simultaneous	91 (82.7)	19 (17.3)	.114	1.74 (0.87–3.51)
	Sequential	110 (90.1)	11 (9.9)		
Any indication after visit 1 and visit 2 combined	Simultaneous	63 (57.3)	47 (42.7)	.004	1.75 (1.18–2.58)
	Sequential	84 (75.7)	27 (24.3)		
Parent-reported fever after visit 1	Simultaneous	92 (83.6)	18 (16.4)	.103	1.82 (0.87–3.77)
	Sequential	101 (91)	10 (9)		
Any indication after visit 1	Simultaneous	66 (60)	44 (40)	.005	1.77 (1.17–2.66)
	Sequential	86 (77.5)	25 (22.5)		
Parent-reported fever after visit 2	Simultaneous	104 (99)	1 (1)	.969	1.06 (0.07–16.5)
	Sequential	110 (99.1)	1 (0.9)		
Any indication after visit 2	Simultaneous	100 (95.2)	5 (4.8)	.678	1.31 (0.36–4.74)
	Sequential	107 (96.4)	4 (3.6)		

[a] The sequential group is the reference group and adjustment was made for study sites.

SUPPLEMENTAL REFERENCES

18. Centers for Disease Control and Prevention. Table 1. Recommended child and adolescent immunization schedule for ages 18 years or younger, United States, 2017. Available at: https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html. AccessedMay 9, 2017