# Fluzone® Quadrivalent Influenza Virus Vaccine in Individuals 6 Months and Older

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# In 6 of 12 Seasons, the B-lineage in the Vaccine did not Match the Strain that Circulated

| Season | % B | % Yamagata | % Victoria | Vaccine |
|---|---|---|---|---|
| 2000–2001 | 46 | 100 | 0 | Yamagata |
| 2001–2002 | 13 | 23 | 77 | Yamagata |
| 2002–2003 | 43 | 0.4 | 99.6 | Victoria |
| 2003–2004 | 1 | 93 | 7 | Victoria |
| 2004–2005 | 25 | 74 | 26 | Yamagata |
| 2005–2006 | 19 | 22 | 78 | Yamagata |
| 2006–2007 | 21 | 24 | 77 | Victoria |
| 2007–2008 | 29 | 98 | 2 | Victoria |
| 2008–2009 | 33 | 17 | 83 | Yamagata |
| 2009–2010 | 0.2 | 12 | 88 | Victoria |
| 2010–2011 | 30 | 6 | 94 | Victoria |
| 2011–2012 | 14 | 51 | 49 | Victoria |

**Red indicates B-lineage mismatch between vaccine strain and predominant circulating strain**

**References: 1.** C. Reed et al. Vaccine 30 (2012): 1993–1998. **2.** http://www.cdc.gov/flu/weekly/fluactivitysurv.htm. Accessed 22 July 2012.

# Lineage Mismatch and Vaccine Effectiveness

- **Responses against the heterologous B virus are significantly reduced in all age groups and do not reach seroprotective levels in human volunteers[1,2]**
- **Limited protection would be expected with TIV or LAIV when the vaccine and circulating strains are from different influenza B lineages[3,4]**
  - **For example, in 2006-2007 when the vaccine strain was mismatched, VE against Type B was 19% (95% CI; -112% to 69%)[5]**

**References: 1.** Rota PA, et al. *Virology* 1990; 175:59–68. **2.** Camilloni, B, et al. *Vaccine* 27:31(2009):4099-103. **3.** Belshe RB et al. *Vaccine* 2009;28:2149-56. **4.** Belshe, R. *Vaccine* 28S (2010) D45-D53. **5.** Skowronski. *JID* 2009: Jan 15, 199(2):168-79.

# Influenza B Virus: Disease Burden[1-3]

- Represents ~20-25% of circulating strains
- Dominant circulating B lineage may vary between regions in the same year
- Causes influenza epidemics every 2 to 4 years
- Influenza B-associated hospitalization and mortality rates are lower than A/H3N2, but higher than A/H1N1
- Overall, influenza B is a significant cause of absenteeism, clinic visits, hospitalizations and deaths across all ages

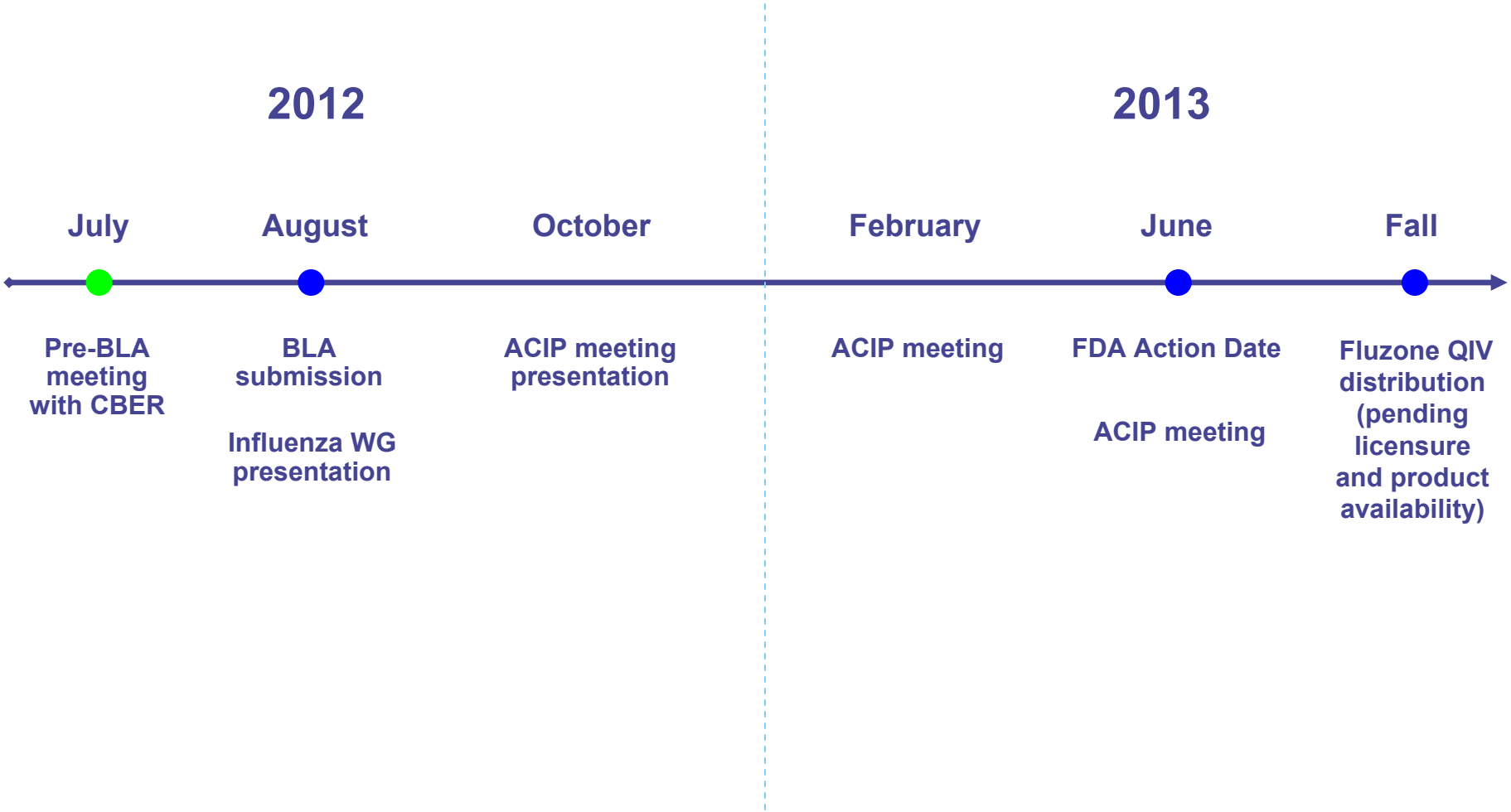
**References: 1**. http://gamapserver.who.int/GlobalAtlas/home.asp **2**. Couch R, VRBPAC Presentation, February 2007. http://www.fda.gov/ohrms/dockets/ac/07/slides/2007-4282S2_11_files/frame.htm **3**. Simonsen, et al., *JID* 2000;181:831

# Impact of Influenza B on Pediatric Patients

- **Substantial burden of influenza B in children and young adults[1-3]**
  - **Myositis, myalgia, and leukopenia appear to be more common in children infected with influenza type B than in children with type A strains[4-6]**
  - **Additional type B-associated illnesses and complications include encephalitis, encephalopathy, myelitis, pneumonia, bronchitis, bronchiolitis, croup, pharyngitis, otitis media, and sinusitis[7]**
  - **Hospitalization may be more common in children with influenza type B than in children with type A strains[4]**

**References**: **1**. Belshe RB. *Vaccine.* 2010;28(suppl 4):D45-D53. **2**. Olson DR. *PLoS Med.* 2007;4(8):1349-1361. **3**. Glezen WP. *Am J Epidemiol.* 1980;111(1):13-22. **4**. Hite LK. *Int J Infect Dis.* 2007;11(1):40-47. **5**. Hu J-J. *J Microbiol Immunol Infect.* 2004;37(2):95-98. **6**. Peltola V. *Clin Infect Dis.* 2003;36(3):299-305. **7**. Couch R, VRBPAC Presentation, February 2007. http://www.fda.gov/ohrms/dockets/ac/07/slides/2007-4282S2_11_files/frame.htm

# Fluzone Quadrivalent Vaccine: Timeline of Key Milestones



# Fluzone Quadrivalent Vaccine: Overview[1,2]

| Characteristic | Description |
|---|---|
| Form | Liquid (no diluent required) |
| Composition | Hemagglutinin from A/H1N1 & A/H3N2 and B/Victoria & B/Yamagata |
| Preservative | None |
| Route of administration | Intramuscular |
| Proposed age indication | ≥ 6 months of age |
| Presentations | 0.5 mL pre-filled syringes<br>0.25 mL pre-filled syringes (pediatric)<br>0.5 mL unit-dose vials<br>Multi-dose vials available in 2014 |

**References**: **1**. Sanofi Pasteur Inc. Data on file, February 2011. MKT22284. **2**. Sanofi Pasteur Inc. Data on file July 2011. MKT23902.

# Sanofi Pasteur Fluzone QIV Clinical Development Program

| Study | Purpose | Age | N[a] | Number of QIV Recipients |
|---|---|---|---|---|
| Adult (Phase II) | Safety and immunogenicity | ≥ 18 years | 570 | 190 |
| Elderly (Phase III) | Safety and immunogenicity | ≥ 65 years | 675 | 225 |
| Pediatric (Phase III) | Safety and immunogenicity | 6 months to < 9 years | 4347 | 2892 |
| Total number of QIV recipients: | | | | 3307 |

[a]Numbers of subjects in the safety analysis set

# Study Designs

- Adults (18 yr & older): randomized, open-label, multi-center
- Elderly (65 yr & older): randomized, blinded, multi-center
- Pediatric (6 mo to < 9 yr): randomized, blinded, multi-center
- All studies conducted in the United States
- Subjects randomized to one of three groups with an allocation ratio of 1:1:1 (adult, elderly) or ~4:1:1 (pediatric)
- Study groups (combined):
  - QIV (both B lineages; N=3307 subjects[a])
  - Licensed TIV (Victoria lineage; N=1149 subjects[a])
  - Alternate B TIV (Yamagata lineage; N=1136 subjects[a])

[a]Numbers represent total subjects in the safety analysis set for the 3 studies combined

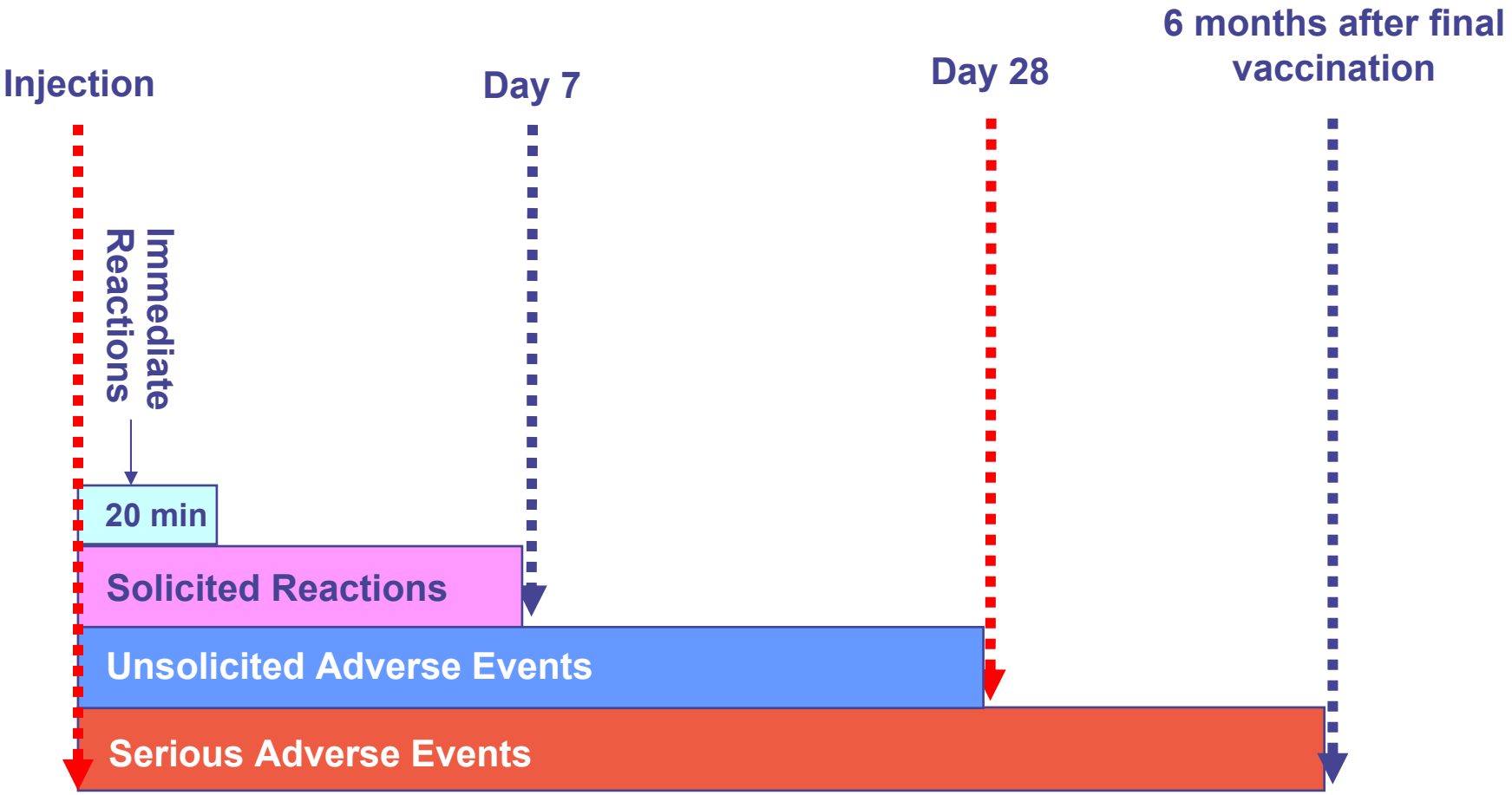
# Study Designs *(cont'd)*

- In each study, all vaccines contained the same A/H1N1 and A/H3N2 strains,[a] but differed with respect to their B strains
- Each study vaccine contained 15 mcg hemagglutinin (HA) per strain per 0.5 mL dose (7.5 mcg HA per strain per 0.25 mL dose for children age 6 mo to < 36 mo)
- Adults and elderly: 1 dose administered on Day 0
- Pediatric:
  - 1 dose or 2 doses administered 4 weeks apart as per ACIP[b] recommendations for the 2010-2011 influenza season
  - 0.25 mL dose for children age 6 mo to < 36 mo and 0.5 mL dose for children age 3 yr to < 9 yr

[a]Adult study: A/Brisbane/59/2007(H1N1) and A/Uruguay/716/2007(H3N2); Elderly and pediatric studies: A/California/07/2009 (H1N1) and A/Victoria/210/2009 (H3N2)

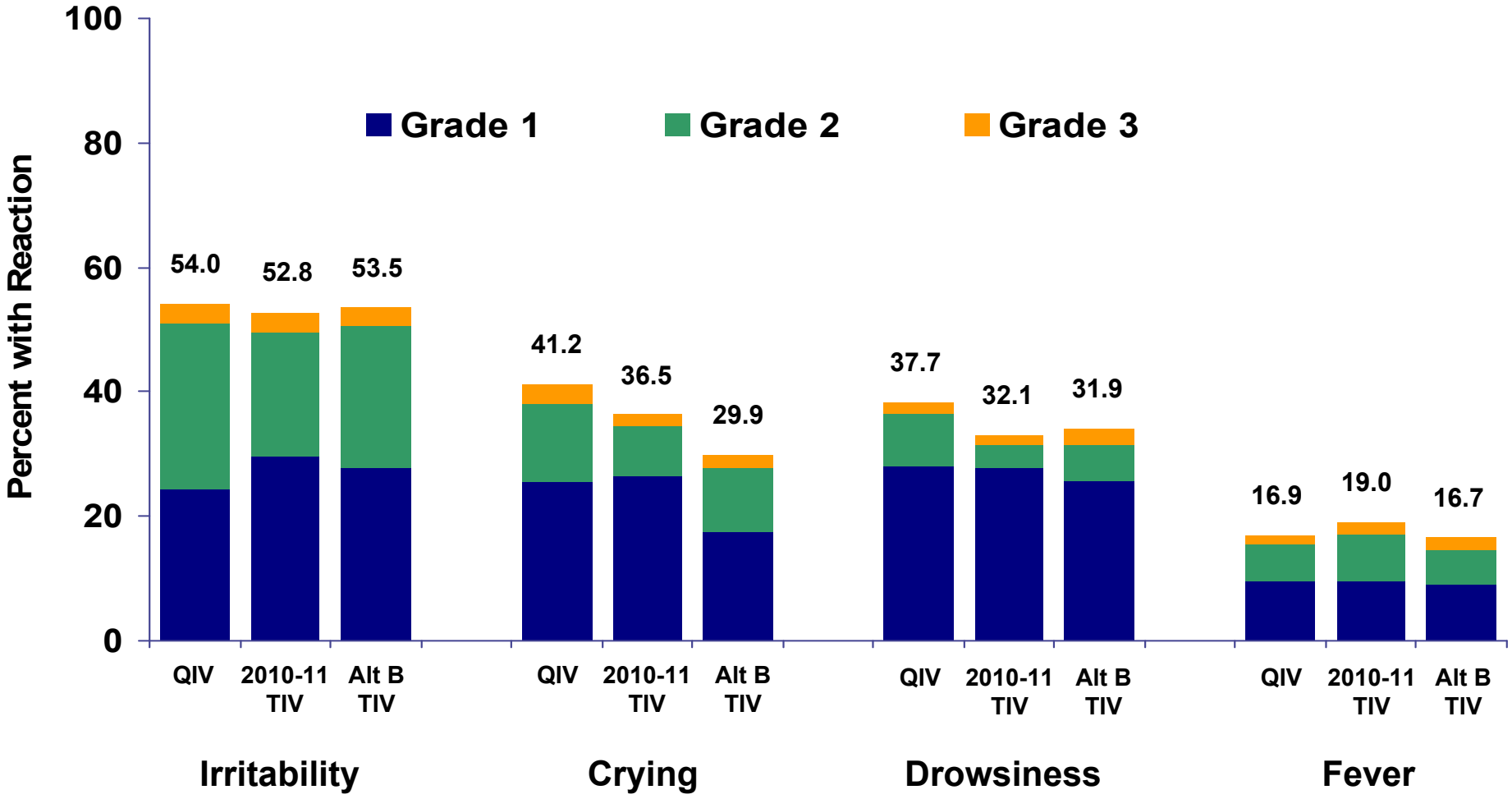
[b]Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention

# Safety Data Collection for Pediatric Study




Adult and elderly studies: Solicited reactions monitored for 3 or 7 days, respectively; unsolicited and serious adverse events monitored for 21 days (both studies).

# Solicited Systemic Reactions After Any Dose, Days 0-7 Post-vaccination (Ages 6 Mos to < 24 Mos)

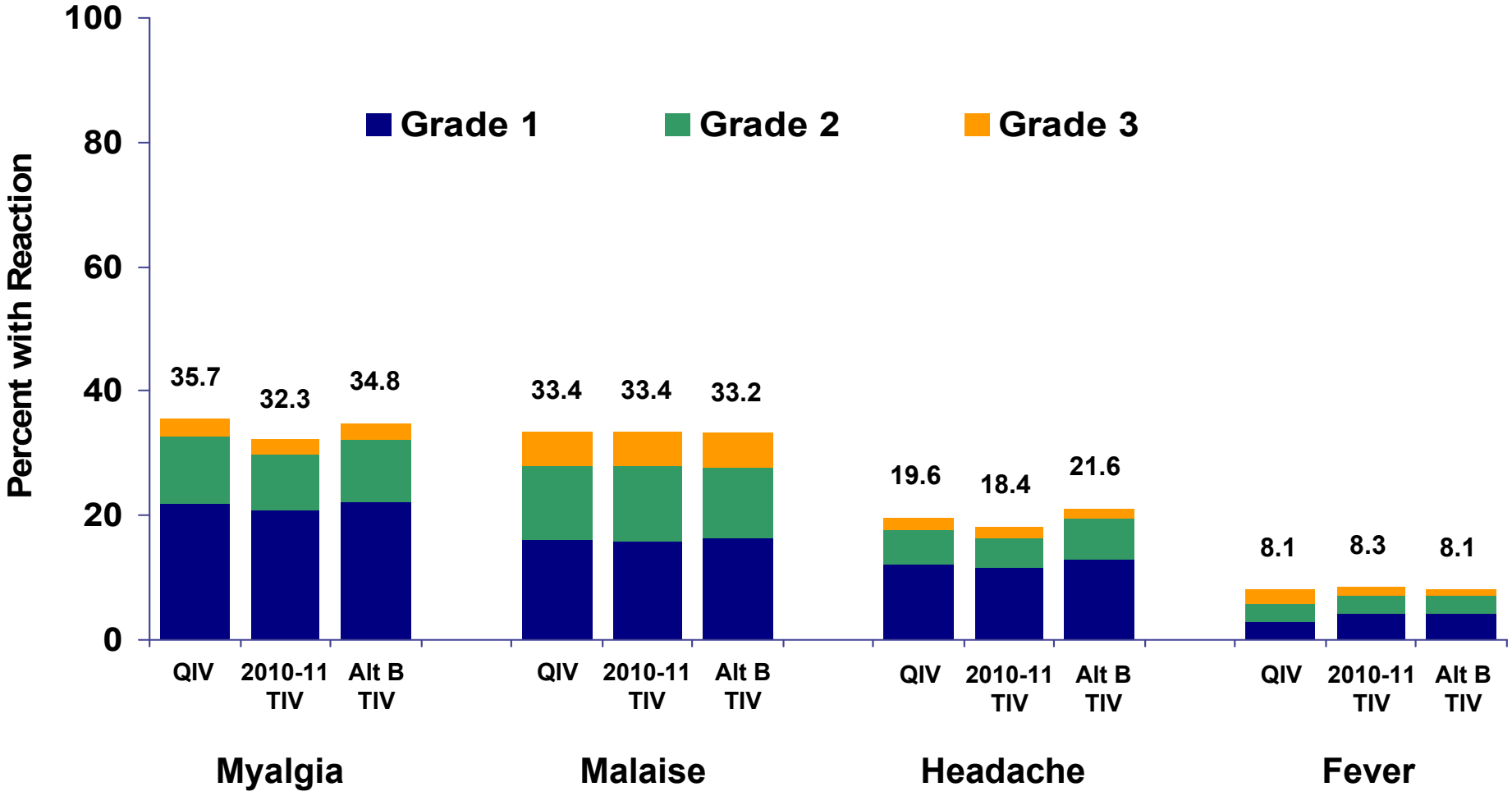



2010-2011 TIV contained B/Brisbane; Alt B TIV contained B/Florida

Fever: Grade 1: ≥ 100.4ºF to ≤ 101.3ºF; Grade 2: > 101.3ºF to ≤ 103.1ºF; Grade 3: > 103.1ºF

Irritability, crying, and drowsiness: definitions available upon request

# Solicited Systemic Reactions After Any Dose, Days 0-7 Post-vaccination (Ages 2 Yrs to < 9 Yrs)




2010-2011 TIV contained B/Brisbane; Alt B TIV contained B/Florida

Fever: Grade 1: ≥ 100.4ºF to ≤ 101.1ºF; Grade 2: ≥ 101.2ºF to ≤ 102.0ºF; Grade 3: ≥ 102.1ºF

All others: Grade 1: No interference with activity; Grade 2: Some interference with activity; Grade 3: Prevents daily activity

# Serious Adverse Events (SAEs)

- **Adult (18+ yr):**
  - **2 SAEs[a]: 1 QIV recipient and 1 TIV recipient; both reported as unrelated to vaccination**
- **Elderly (65+ yr):**
  - **3 SAEs[b]: None occurred among QIV recipients and all 3 reported as unrelated to study vaccine**
- **Pediatric (6 mo to < 9 yr):**
  - **3 SAEs reported as possibly related to vaccination**
    - **13-month-old with croup 3 days after 1st dose of QIV**
    - **4-year-old with febrile seizure 1 day after 1st dose of licensed TIV**
    - **11-month-old with febrile seizure 8 hours after 2nd dose of alternate B TIV**

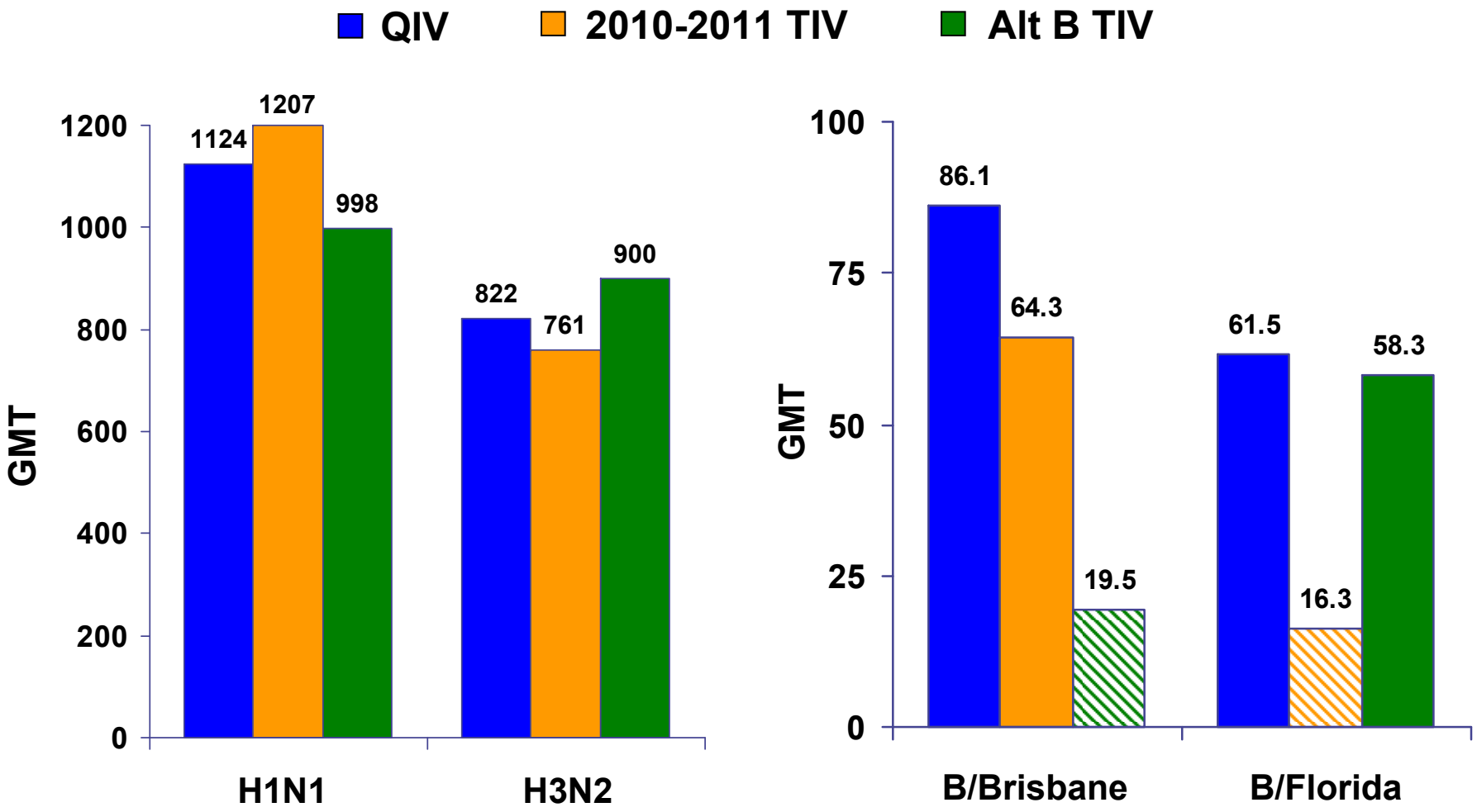
[a]QIV: benign paroxysmal positional vertigo and unspecified chest pain 12 days post-vaccination. 2008-2009 TIV: gastrointestinal bleeding 26 days post-vaccination.

[b]2010-2011 TIV: partial detached retina 16 days post-vaccination; right hand cellulitis secondary to a cat bite wound 9 days post-vaccination. Alt B TIV: malignant melanoma 7 days post-vaccination

# Safety Summary: Adult, Elderly, and Pediatric Studies

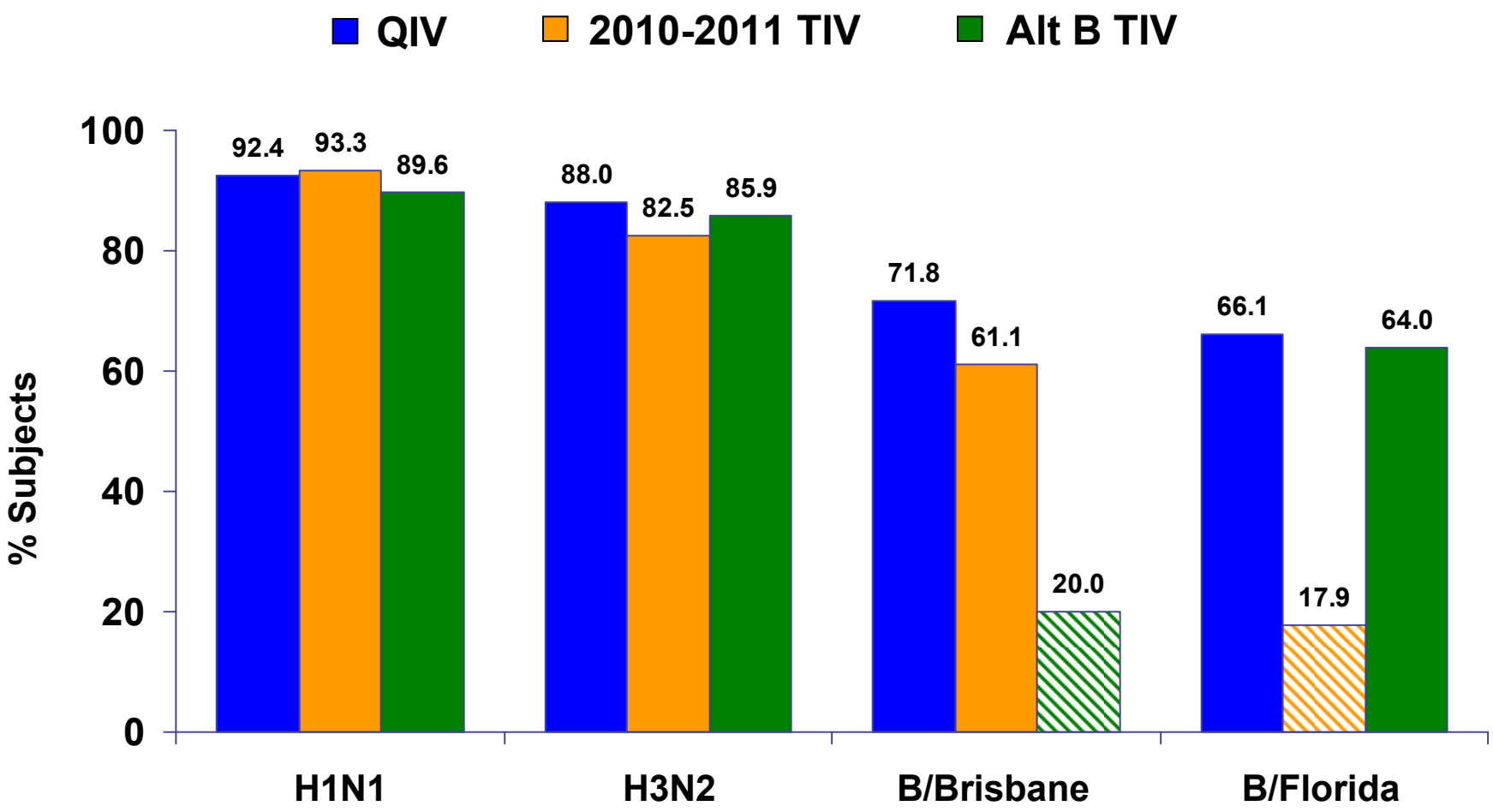
- **The safety profile of QIV was comparable to that of each control TIV, as assessed by rates of solicited injection-site and systemic reactions, unsolicited adverse events, and serious adverse events**
- **Most frequently reported:**
  - Solicited injection-site reaction: pain or tenderness
  - Solicited systemic reactions: myalgia, headache, and malaise (irritability, crying, and drowsiness in young children)
- **Most solicited reactions were grade 1 or 2 in intensity**
- **Most unsolicited adverse events were in injection-site (eg, ecchymosis), respiratory (eg, cough), and gastrointestinal (eg, diarrhea) categories**

# Geometric Mean Titers (GMTs), Post-vaccination (Ages 6 Mos to < 9 Yrs)




2010-2011 TIV contained B/Brisbane; Alt B TIV contained B/Florida
Striped bar represents strain not contained in the respective TIV

# Seroconversion Rates, Pre- to Post-vaccination (Ages 6 Mos to < 9 Yrs)




Seroconversion = Paired samples with pre-vaccination HAI titer < 1:10 and post-vaccination titer ≥ 1:40 or a 4-fold increase for those with pre-vaccination titer ≥ 1:10

2010-2011 TIV contained B/Brisbane; Alt B TIV contained B/Florida

Striped bar represents strain not contained in the respective TIV

# Immunogenicity Summary: Adult, Elderly, and Pediatric Studies

- **The immunogenicity profile of QIV was comparable to those of the control TIVs as evaluated by GMTs, seroconversion rates, and seroprotection rates**
- **QIV induced statistically non-inferior GMTs and seroconversion rates to each A strain (H1N1 and H3N2) and each B-lineage strain (Brisbane and Florida) compared with each control TIV containing the respective strains in 35 of 36 analyses in adults, elderly, and children**
  - **Among subjects ≥ 65 years of age, the seroconversion rate for A/H1N1 was 4% lower in the QIV group than in the control TIV group; the point estimate was OK but the CI was too wide. The GMT to A/H1N1 met non-inferiority and the seroprotection rate against this strain was 91%.**

# Immunogenicity Summary: Adult, Elderly, and Pediatric Studies *(cont'd)*

- **QIV induced statistically superior GMTs and seroconversion rates to each B-lineage strain compared with each control TIV not containing the respective strain in 15 of 16 analyses in elderly and children**
  - **Among subjects ≥ 65 years, the GMT for B/Brisbane was 74 in the QIV group and only 42 in the comparative group. Due to small sample sizes and wide CIs, statistical superiority was not demonstrated but the result was non-inferior and superiority was demonstrated for seroconversion rates**

# The Need for QIV

- Since 2001, Victoria and Yamagata B lineages have co-circulated, making it difficult to predict the next season's predominant lineage
- In 6 of the last 12 seasons, the B-lineage strain in the vaccine did not match the predominant circulating strain
  - Consequently, VRBPAC repeatedly asked that manufacturers develop vaccines containing both B lineages
- Limited protection is afforded by TIV when the vaccine and circulating strains are from different B lineages
- Influenza B is a significant cause of morbidity and mortality across all age groups, especially in children

# The Value of QIV

- The safety profile of Fluzone QIV was comparable to that of each control TIV for all safety endpoints across all studies and age groups
- Fluzone QIV induced antibody responses that were non-inferior to each TIV for all 4 strains and in all age groups
- Furthermore, Fluzone QIV demonstrated an advantage over each TIV by inducing robust antibody responses to both B-lineage strains simultaneously
- QIV may particularly benefit children because of their relative lack of exposure to influenza viruses and reduced cross-protection between the two B lineages
- QIV represents the next logical step and an improved standard of care for the prevention of influenza

# Sanofi Pasteur Plans for QIV in 2013-2014

- **Sanofi Pasteur will manufacture and distribute a limited supply of Fluzone QIV in 2013-2014 due to the timing of our anticipated license**
  - Licensure is expected mid-year 2013
  - Fluzone TIV pre-orders will be completed well before QIV is licensed
  - Our sales representatives will only be able to speak to HCPs about Fluzone QIV after it is licensed; consequently many of these discussions will take place after HCPs start receiving TIV
  - Coverage for QIV may not be in place with all private payers at the beginning of the 2013 influenza vaccination season

# Thank you