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FLUCELVAX QUADRIVALENT® (INFLUENZA VACCINE) - *CCIIV4*

Advisory Committee on Immunization Practices
Atlanta, GA – 22 June, 2016

FLUCELVAX QUADRIVALENT® (Influenza Vaccine) US Licensure - Approved 23 May, 2016

- Inactivated vaccine indicated for active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B contained in the vaccine

- Approved for use in persons 4 years of age and older

- Suspension for injection supplied in 0.5-mL single-dose pre-filled syringes

- A subunit influenza vaccine prepared from virus propagated in Madin Darby Canine Kidney (MDCK) cells, a continuous cell line.
  - These cells were adapted to grow freely in suspension in culture medium.
  - The virus is inactivated with ß-propiolactone
  - Each of the 4 virus strains is produced and purified separately then pooled to formulate the quadrivalent vaccine.

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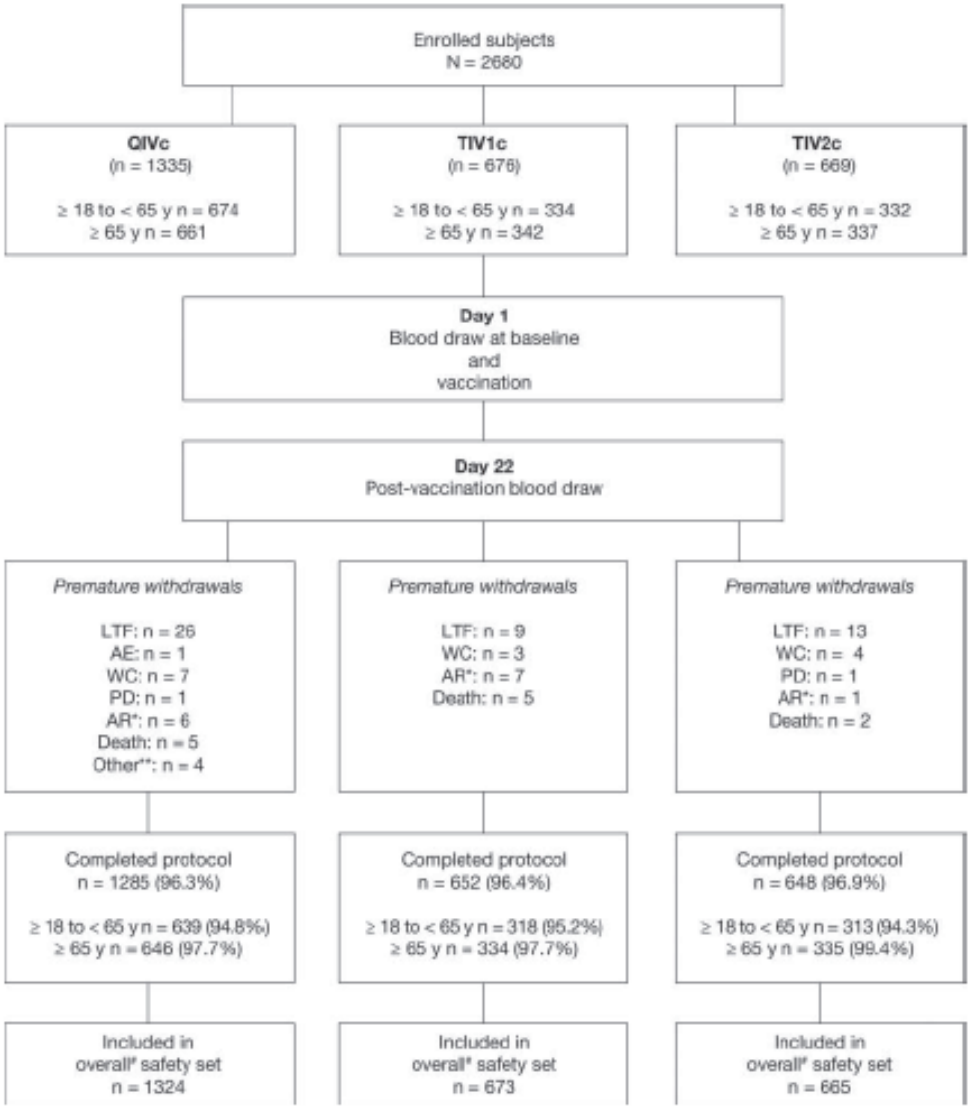
Data supporting the Licensure of FLUCELVAX QUADRIVALENT® (Influenza Vaccine)

- Licensure of ccIIV4 is based on results from two Phase III immunogenicity and safety studies:
  - Study 1: evaluated ccIIV4 in subjects 18 years of age and above
  - Study 2: evaluated ccIIV4 in children 4 through 17 years of age

- The data from the two Phase III studies establish that ccIIV4 met the primary objectives in both studies:
  - Demonstrating non-inferiority of ccIIV4 vis-a-vis ccIIV3 and another ccIIV3 containing an alternate influenza B strain
  - The safety profile was similar between ccIIV3 and ccIIV4 and the vaccines were well tolerated in all age groups evaluated
  - Immunogenic, eliciting antibody responses against all four influenza strains

- These studies demonstrated a benefit/risk ratio supportive of product approval

ccIIV4 Adult Comparative Immunogenicity & Safety Study design



Data on file; CSR V130_01

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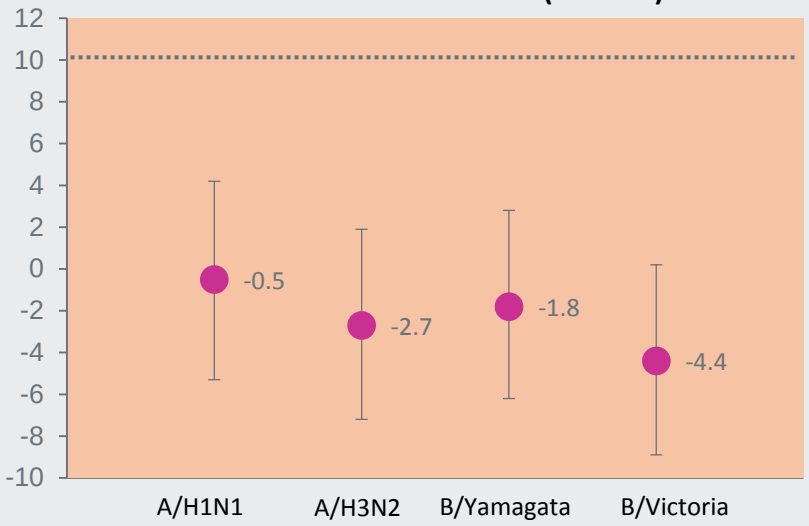
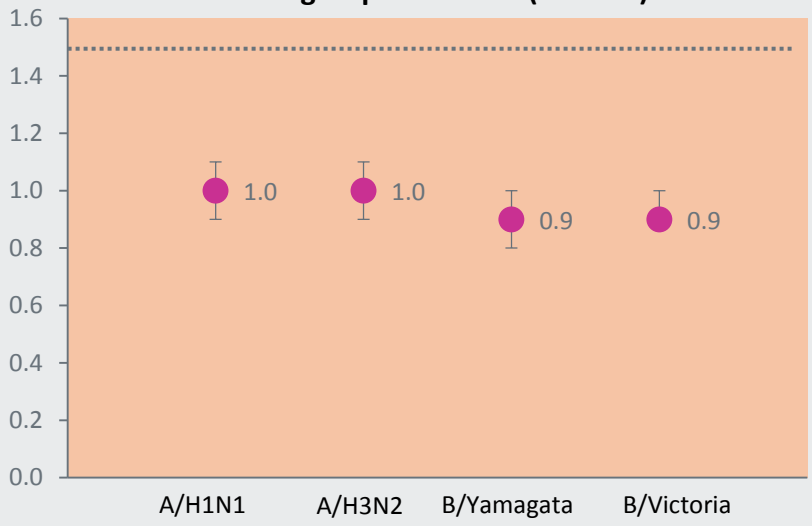
ccIIV4 non-inferior to ccIIV3 in Adults

Post-vaccination Day 22
QIVc (n=1250); TIVc (n=635)

Seroconversion rate difference (95% CIs)



Vaccine group GMT ratio (95% CIs)



- The horizontal dashed line indicates non-inferiority threshold. According to the CBER guidance criterion for noninferiority, for each of the 4 strains 1) the upper limit of the 2-sided 95% CI on the difference between the seroconversion rates (TIV1c/TIV2c−QIV) must be <10%; 2) the upper limit of the 2-sided 95% CI for the ratio of GMTs (GMT TIVc/GMTQIVc) for HI antibody should be <1.5.

CBER, Center for Biologics Evaluation and Research; QIVc, cell culture−derived quadrivalent influenza vaccine; TIVc, cell culture-derived trivalent influenza vaccine; CI, confidence intervals
Data on file; ISE 2015

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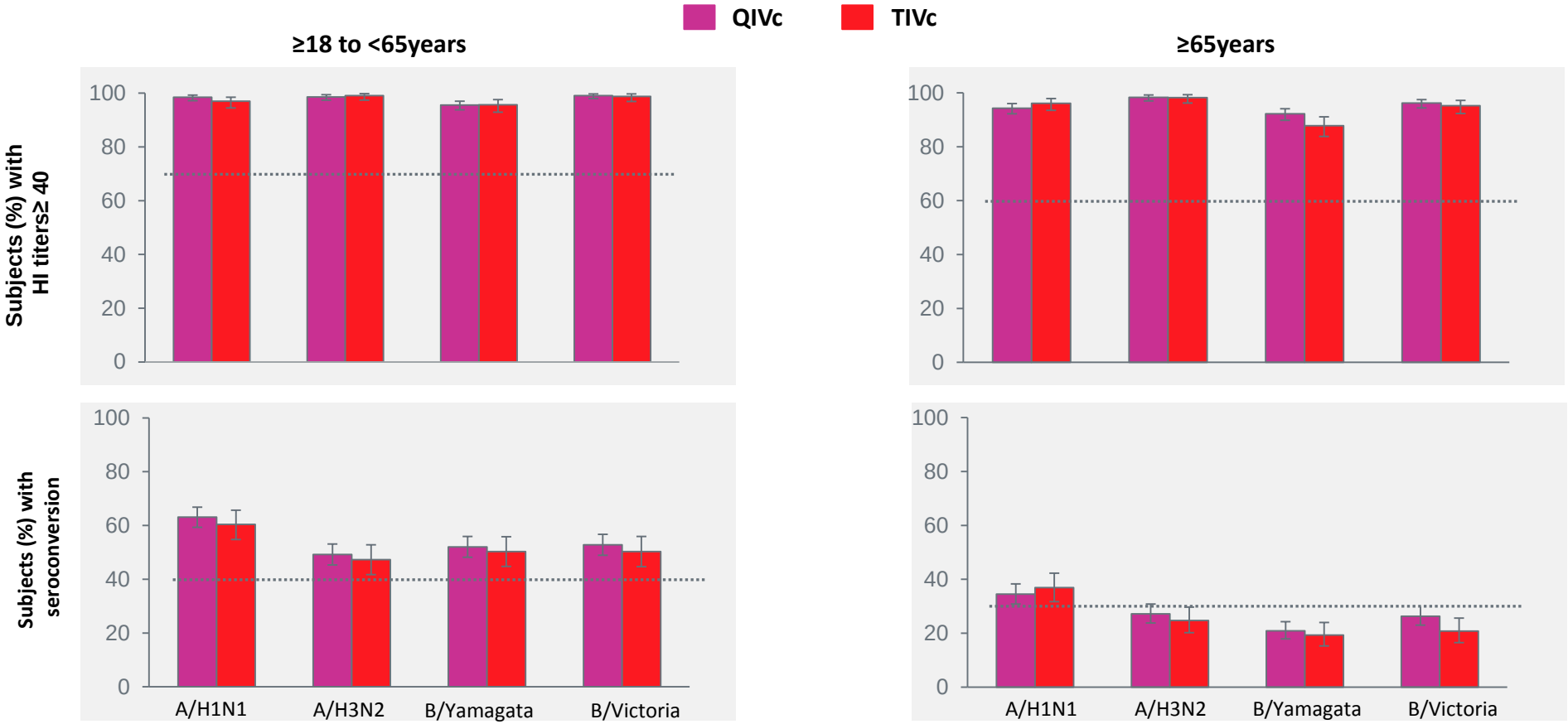
ccIIV4 induced an immune response comparable to TIVc in adults



* For ≥18 to <65 Years; The lower bound of the 2-sided 95% CI for the percentage of subjects achieving an HI antibody titer ≥1:40 should be ≥70% and the lower bound of the 2-sided 95% CI for the percentage of subjects achieving seroconversion for HI antibody should be ≥40%.

For ≥65 years; the percentage of subjects achieving an HI titer ≥1:40 should be ≥ 60% and the lower bound of the 2-sided 95% CI for the percentage of subjects achieving seroconversion for HI antibody ≥30%. seroconversion is defined as in subjects seronegative at baseline (ie, HI titer <1:10 at day 1) a postvaccination HI titer ≥1:40, and in subjects seropositive at baseline (ie, HI titer ≥1:10 at day 1) as a minimum of a 4-fold increase in postvaccination HI titer.

[1] Data on file; ISE 2015

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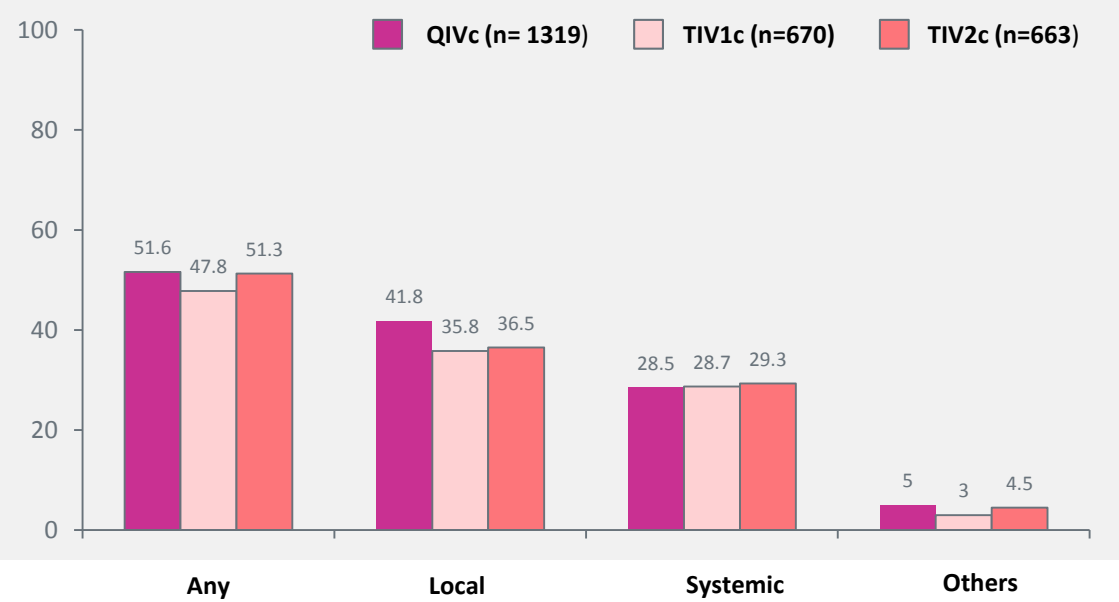
The tolerability profiles of ccIIV4 and ccIIV3 were similar in adults



- Solicited AEs were more frequently reported in ≥18 to <65 years age cohort (57–62%) across all vaccine groups than in the ≥65years age cohort (39–43%)
- Most commonly reported solicited local and systemic AEs were injection-site pain [QIVc (34%) and TIV1c/TIV2c (27–29%)] and fatigue [QIVc (13.5%) and TIV1c/TIV2c (12–16%)]
- Fever (≥38°C) rates were low (0.5–0.7%) across vaccine groups; no reports of fever ≥40°C

Data on file; ISS 2015

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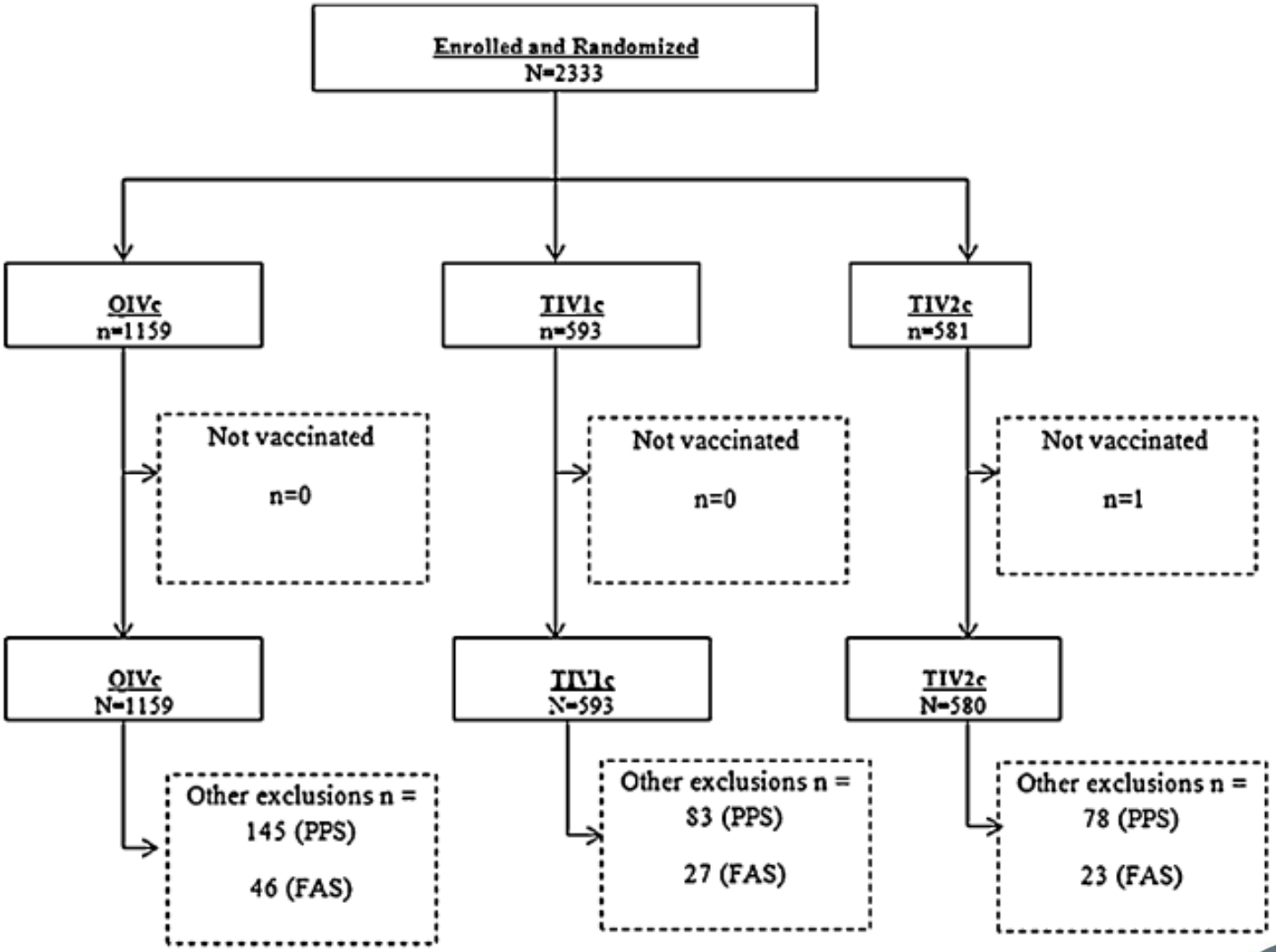
ccIIV4 Pediatric Comparative Immunogenicity & Safety Study design



Hartvickson R., et.al., Int. Jr. of Inf. Diseases. 41 (2015) 65-72.

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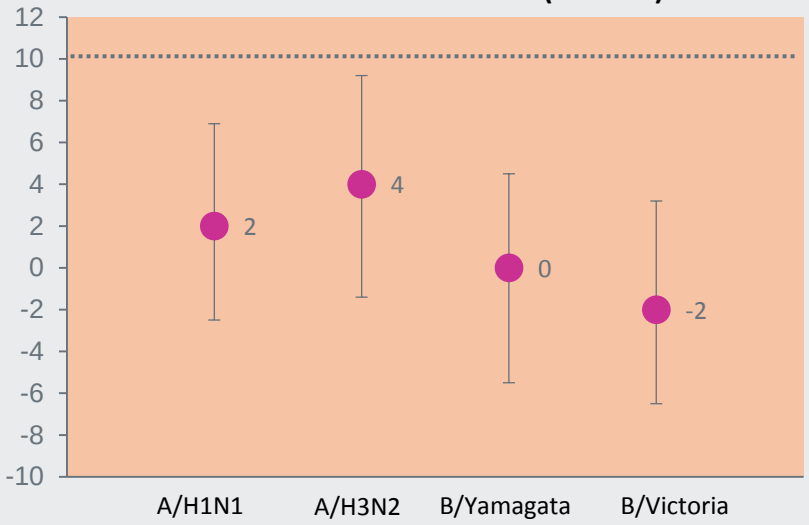
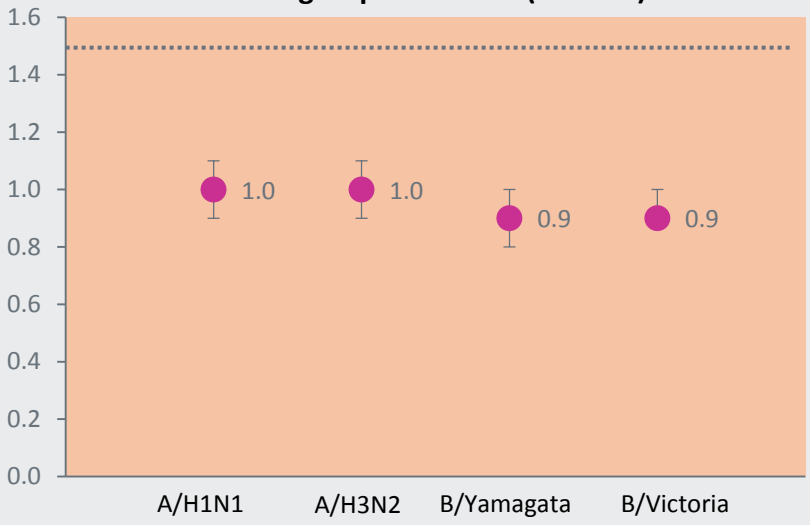
ccIIV4 non-inferior to ccIIV3 in pediatric population

Post-vaccination Day 22/50[a]
QIVc (n=1014); TIVc (n=510)

Seroconversion rate difference (95% CIs)



Vaccine group GMT ratio (95% CIs)



- The horizontal dashed line indicates non-inferiority threshold. According to the CBER guidance criterion for noninferiority, for each of the 4 strains 1) the upper limit of the 2-sided 95% CI on the difference between the seroconversion rates (TIV1c/TIV2c−QIV) must be <10%; 2) the upper limit of the 2-sided 95% CI for the ratio of GMTs (GMT TIVc/GMTQIVc) for HI antibody should be <1.5.

CBER, Center for Biologics Evaluation and Research; QIVc, cell culture−derived quadrivalent influenza vaccine; TIVc, cell culture-derived trivalent influenza vaccine; CI, confidence intervals

[a]Analysis was performed on Day 22 for previously vaccinated subjects and Day 50 for not previously vaccinated subjects

[b]The H1N1, H3N2 and B1 influenza strain ratio of GMTs was calculated as TIV1c/QIVc, whereas the B2 influenza strain ratio of GMTs was calculated as TIV2c/QIVc

Hartvickson R., et.al., Int. Jr. of Inf. Diseases. 41 (2015) 65-72.

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ccIIV4 induced an immune response comparable to ccIIV3 in a pediatric population

Both CBER and all three CHMP immunogenicity criteria were met by the QIVc and the TIV1c/TIV2c vaccines for all 4 influenza strains at 3 weeks after the last vaccination[a] [FAS]

Endpoint	Criteria	Values across all vaccine groups[b]				Criteria met?
		H1N1	H3N2	B1	B2	
CBER	LL of the 95% CI on the SCR is ≥40%	≥70%	≥44%	≥61%	≥68%	✓
	LL of the 95% CI on the % achieving ≥1:40 is ≥70%	≥98%	≥98%	≥90%	≥88%	✓
CHMP	SCR is >40%	>72%	>46%	>65%	>71%	✓
	% achieving (≥1:40) is >70%	>98%	>98%	>91%	>90%	✓
	GMR is >2.5	>10	>3.6	>6.1	>8.1	✓

CBER, Center for Biologics Evaluation, Research and Review; CHMP, Committee for Medicinal Products for Human Use; CI, confidence interval; FAS, full analysis set; GMR, geometric mean ratios (Day22 or day 50/day1); LL, lower limit; SCR, seroconversion rate

[a]Analysis was performed on Day 22 for previously vaccinated subjects and Day 50 for not previously vaccinated subjects

[b]For H1N1, H3N2 and B1 influenza strains TIV1c data is presented, whereas for B2 influenza strain TIV2c data is presented

Hartvickson R., et.al., Int. Jr. of Inf. Diseases. 41 (2015) 65-72.

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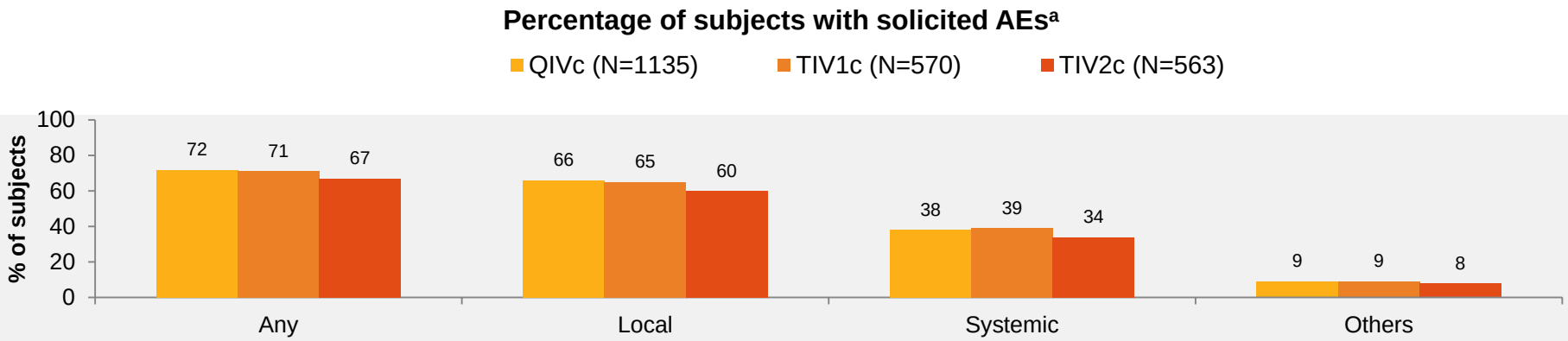
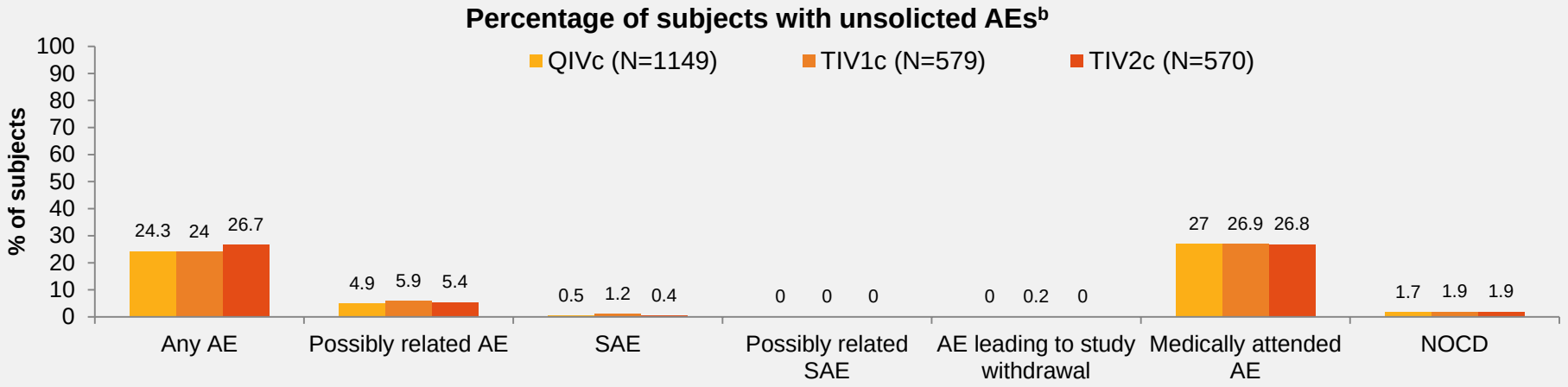
The tolerability profiles of ccIIV4 and ccIIV3 were similar in a pediatric population





AE, adverse event; NOCD, new onset of chronic diseases; SAE, serious adverse event; TIVc, cell culture-derived trivalent influenza vaccines; QIVc, cell culture-derived quadrivalent influenza vaccine

[a]Solicited AEs were reported from Day 1 including 30 minutes data through Day 7

[b]Unsolicited AEs were collected 3 weeks after the last vaccination, whereas SAEs, medically attended AEs, AEs leading to withdrawal from the study and NOCDs were collected from Day 1 through study termination

Data on file; ISS 2015

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Overall summary

- **Influenza vaccine production using cell-based technology is a modern, efficient and well-defined technique**
  - *Could potentially be a valuable alternative to overcome some of the manufacturing problems and vulnerabilities associated with egg-based production, particularly in the event of a pandemic*

- **ccIIV4 elicited an immune response in children (≥ 4 years of age) and adults**
  - Immune response against all four influenza strains of ccIIV4 was non-inferior to those for TIV1c/TIV2c for the strains included in the corresponding trivalent influenza vaccine.
  - Superiority of the ccIIV4 vaccine compared with the unmatched influenza B strains of the TIV1c and TIV2c vaccines was also established.

- **ccIIV4 safety and tolerability profile similar to licensed trivalent influenza vaccines in in children (≥ 4 years of age) and adults**
  - Safety profile of MDCK cell-derived QIV was similar to that of TIVc vaccines, including a similar reactogenicity profile.
  - No unexpected safety concerns were otherwise identified.

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Indication and Usage for FLUCELVAX QUADRIVALENT® (Influenza Vaccine)

FLUCELVAX QUADRIVALENT® is an inactivated vaccine indicated for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. FLUCELVAX QUADRIVALENT is approved for use in persons 4 years of age and older.[1]

Important Safety Information

Contraindication

- Do not administer FLUCELVAX QUADRIVALENT to anyone with a history of severe allergic reaction (e.g. anaphylaxis) to any component of the vaccine.[1]

Warnings & Precautions[1]

- **Guillain-Barré Syndrome (GBS):** If GBS has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give FLUCELVAX QUADRIVALENT should be based on careful consideration of the potential benefits and risks.
- **Preventing and Managing Allergic Reactions:** Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.
- **Syncope:** Syncope (fainting) can occur in association with administration of injectable vaccines, including FLUCELVAX QUADRIVALENT. Syncope can be accompanied by transient neurological signs such as visual disturbance, paresthesia, and tonic-clonic limb movements. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope by maintaining a supine or Trendelenburg position.
- **Altered Immunocompetence:** After vaccination with FLUCELVAX QUADRIVALENT, immunocompromised individuals, including those receiving immunosuppressive therapy, may have a reduced immune response.
- **Limitations of Vaccine Effectiveness:** Vaccination with FLUCELVAX QUADRIVALENT may not protect all vaccine recipients against influenza disease.

Most Common Adverse Reactions[1]

- The most common (≥10%) local and systemic reactions in adults 18-64 years of age were injection site pain (45.4%) headache (18.7%), fatigue (17.8%) and myalgia (15.4%), injection site erythema (13.4%), and induration (11.6%).
- The most common (≥10%) local and systemic reactions in adults ≥65 years of age were injection site pain (21.6%) and injection site erythema (11.9%).
- The most common (≥10%) local and systemic reactions in children 4 to <6 years of age were tenderness at the injection site (46%), injection site erythema (18%), sleepiness (19%), irritability (16%), injection site induration (13%), and change in eating habits (10%).
- The most common (≥10%) local and systemic reactions in children 6 through 8 years of age were pain at the injection site (54%), injection site erythema (22%), injection site induration (16%), headache (14%), fatigue (13%), myalgia (12%).
- The most common (≥10%) local and systemic reactions in children and adolescents 9 through 17 years of age were pain at the injection site (58%), headache (22%), injection site erythema (19%), fatigue (18%) myalgia (16%), and injection site induration (15%).

Please see accompanying full Prescribing Information for FLUCELVAX QUADRIVALENT.

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