Clinical Development of GSK's Fluarix Quadrivalent Influenza Vaccine

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Prepared for ACIP Meeting October 24-25, 2012

Influenza B disease can be serious and is only partially addressed by TIV

- Up to 46% of influenza isolates in past decade were influenza B (range <1-46%, avg. approx 23%)[1]
- Influenza B mortality:
  - 2nd to A/H3N2, predominantly in those ≥65 years of age[2]
  - In 2010-11, 38% (44/115) of all influenza associated pediatric deaths were due to influenza B[3]
- In 6 out of the past 11 seasons, vaccine B strain was not the predominant circulating strain[1]

QIV is the logical next step to improve seasonal influenza vaccines

1. Data derived from surveillance reports in the MMWR, 2000-01 to 2010-11 (http://www.cdc.gov/flu/weekly/pastreports.htm)
2. Thompson WW et al JAMA 2003; 289(2): 179-186
3. MMWR 2011; 60(36)

GSK developed two QIV candidates

- GSK has two licensed TIV's: Fluarix and FluLaval
- GSK has submitted license applications for quadrivalent formulations:
  - **D**-QIV (Fluarix- Quadrivalent) manufactured in **D**resden, Germany and
  - **Q**-QIV (FluLaval- Quadrivalent) manufactured in **Q**uebec, Canada

- Target Indication
  - *Active immunization for the prevention of disease caused by the 2 influenza A virus subtypes and the 2 influenza B virus types contained in the vaccine in adults and children from 3 years of age*

D-QIV Pivotal Phase III Studies: Key Objectives

Pediatric 3-17y: D-QIV-003	Adult ≥ 18y: D-QIV-008
• Confirm immunogenic superiority of QIV for the added B strain vs. two TIV formulations in 3-17y	• Confirm immunogenic superiority of QIV for the added B strain vs. two TIV formulations in ≥ 18y
• Confirm immunogenic non-inferiority of QIV for the 3 common strains shared with each of the two TIVs	• Confirm immunogenic non-inferiority of QIV for the 3 common strains shared with each of the two TIVs
• Describe reactogenicity and safety	• Describe reactogenicity and safety
• Descriptive immunogenicity parameters	• Descriptive immunogenicity parameters • Demonstrate consistency of production of QIV lots

D-QIV Pivotal Phase III Study Designs:

Pediatric: D-QIV-003

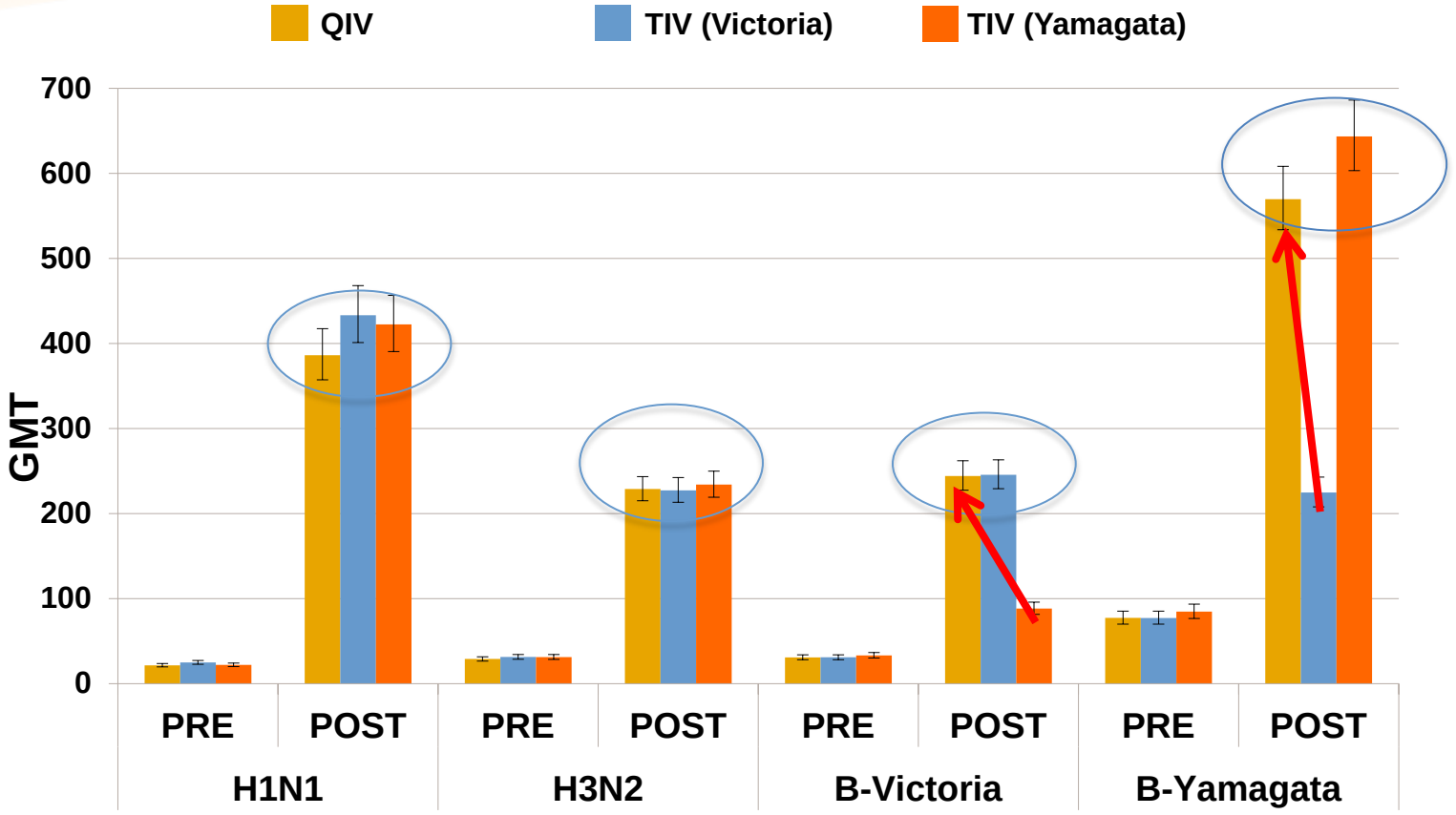
- RCT in 3-17y, age stratified 3-8, 9-17y
- N= **3,015**
- **3 groups: QIV, TIV-Vic and TIV-Yam**
- Conducted in 5 countries in 2010-11
- Primed subjects received one dose and unprimed subjects 2 doses
- Blood samples were collected pre post vaccination
- Reactogenicity and safety (D7 and 28 and at 6 months)

Adult: D-QIV-008

- RCT in 18 y, age stratified 18-64, ≥64
- N= **4,656**
- **3 groups: QIV, TIV-Vic and TIV-Yam**
- Conducted in 6 countries in 2010-11
- Each subject received one dose
- Blood samples pre and post vaccination
- Reactogenicity and safety (D7 and 21 and at 6 months)

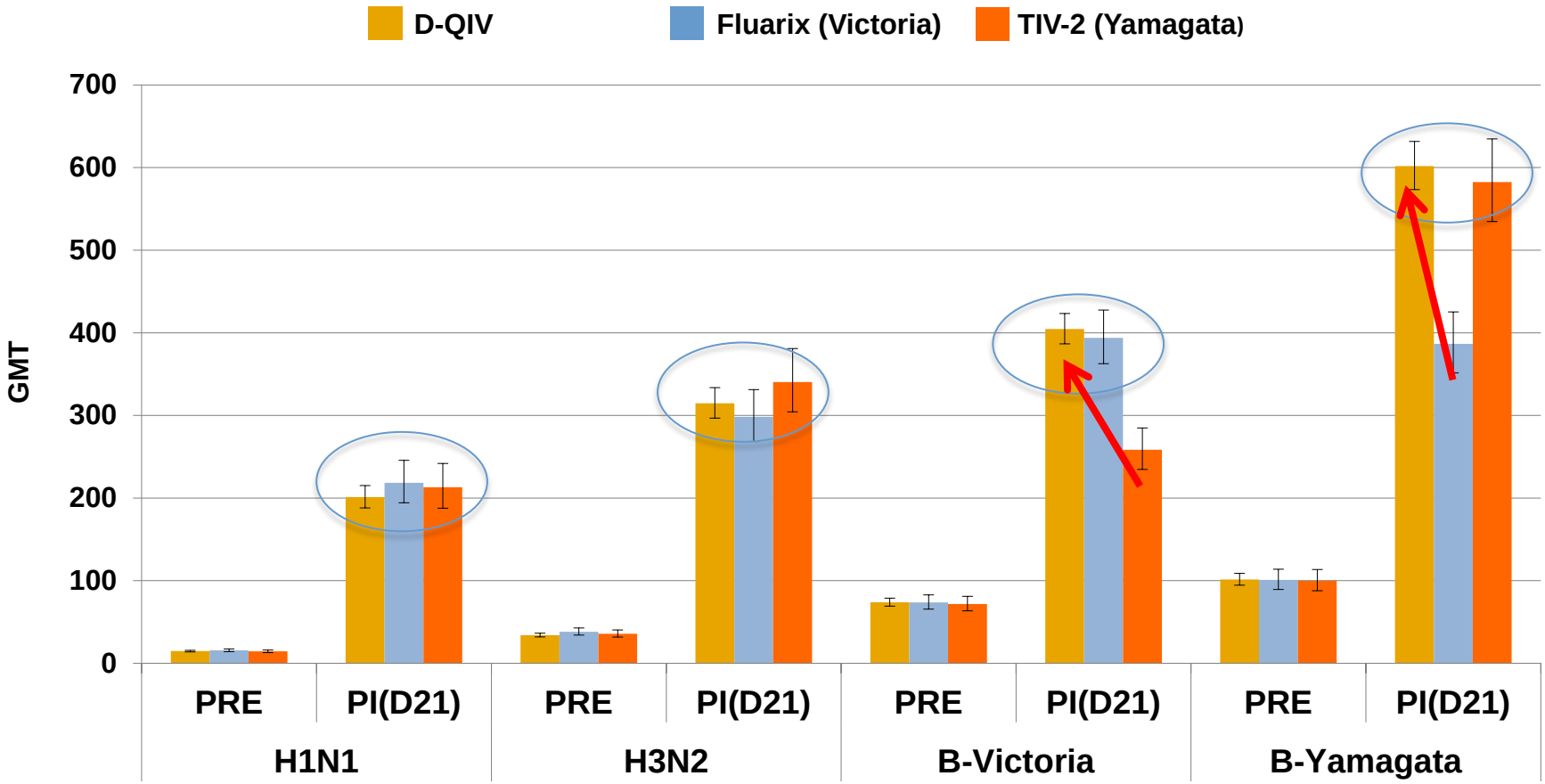
Pediatric: HI antibody response (GMT)

Per Protocol Immunogenicity Cohort



Per Protocol Immunogenicity Cohort N= D-QIV = 791, TIV-Vic= 819, TIV-Yam = 801

Adults: HI antibody response (GMT)
Per Protocol Immunogenicity Cohort



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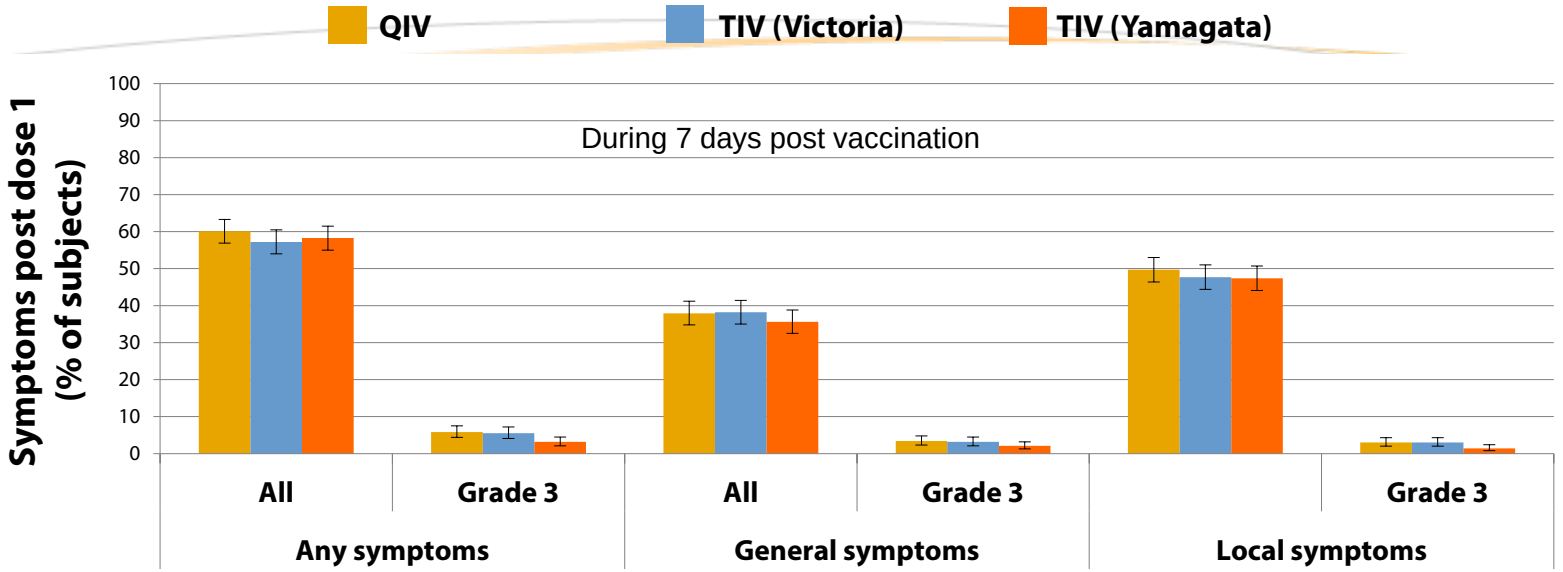
Increased immune response of QIV over TIV for the added B strain

		Pediatric	Adult
GMT Ratio (95% CI)	QIV/TIV-Vic (increase for B-Yamagata)	2.5	1.5
	QIV/TIV-Yam (increase for B-Victoria)	2.9	1.6
SCR Difference (95% CI)	QIV-TIV-Vic (increase for B-Yamagata)	30.5%	16.1%
	QIV-TIV-Yam (increase for B-Victoria)	40.4%	10.5%

Pediatric: Similar reactogenicity and safety of D-QIV vs. TIV controls (Total Vaccinated Cohort)



	Reporting period	QIV	TIV Victoria	TIV Yamagata
At least one unsolicited AE (considered related by investigator)	D0-27	31% (2.0%)	33.4% (2.1%)	33.8% (2.5%)
At least one grade 3 unsolicited AE (considered related by investigator)	D0-D27	2.2% (0.1%)	4.1% (0%)	2.9% (0.3%)
At least one MAE (considered related by investigator)	D0-D180	29.6% (0.2%)	30.5% (0.4%)	33.3 (0.4%)
At least one SAE (considered related by investigator)	D0-D180	0.9% (0%)	0.7% (0%)	0.8% (0%)

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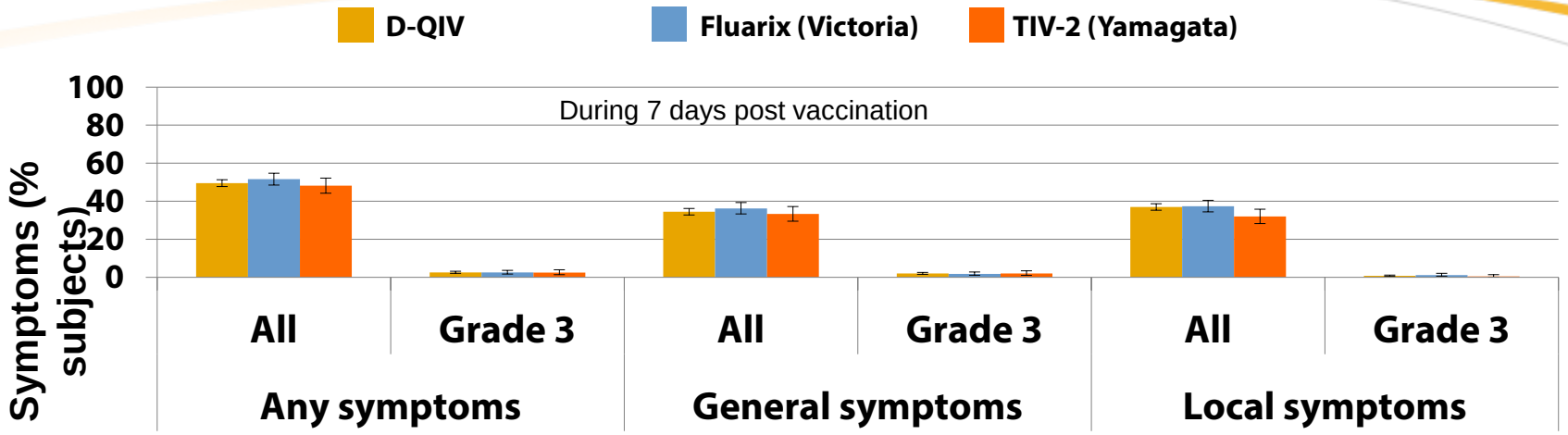
Adult: Similar reactogenicity and safety of D-QIV vs. TIV controls (Total Vaccinated Cohort)



	Reporting period	QIV	TIV Victoria	TIV Yamagata
At least one unsolicited AE (considered related by investigator)	D0-D20	12.5% (2.1%)	13.7% (2.6%)	15.1% (2.3%)
At least one grade 3 unsolicited AE (considered related by investigator)	D0-D20	1.3% (0.1%)	0.7% (0%)	0.3% (0%)
At least one MAE (considered related by investigator)	D0-D180	22.7% (0.4%)	21.4% (0.4%)	NA (no D-180 follow up)
At least one SAE (considered related by investigator)	D0-D180	2.3% (0%)	2.6% (0%)	NA (no D-180 follow up)

Summary

- D-QIV: All objectives in the pediatric and adult studies were met
  - A superior immune response to the additional B lineage was demonstrated
  - No compromise in immune response to the three shared strains
  - An acceptable reactogenicity and safety profile, similar to TIV
- D-QIV expected to improve protection against influenza B relative to TIV
- D-QIV license anticipated December 2012
- Q-QIV license anticipated 2013
  - QIV supply: Capability to supply up to15MM doses for the US for 2013-14 influenza season and up to 75MM doses for the 2014-15 influenza season
  - TIV will be available for the 2013-14 influenza season

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End of Presentation

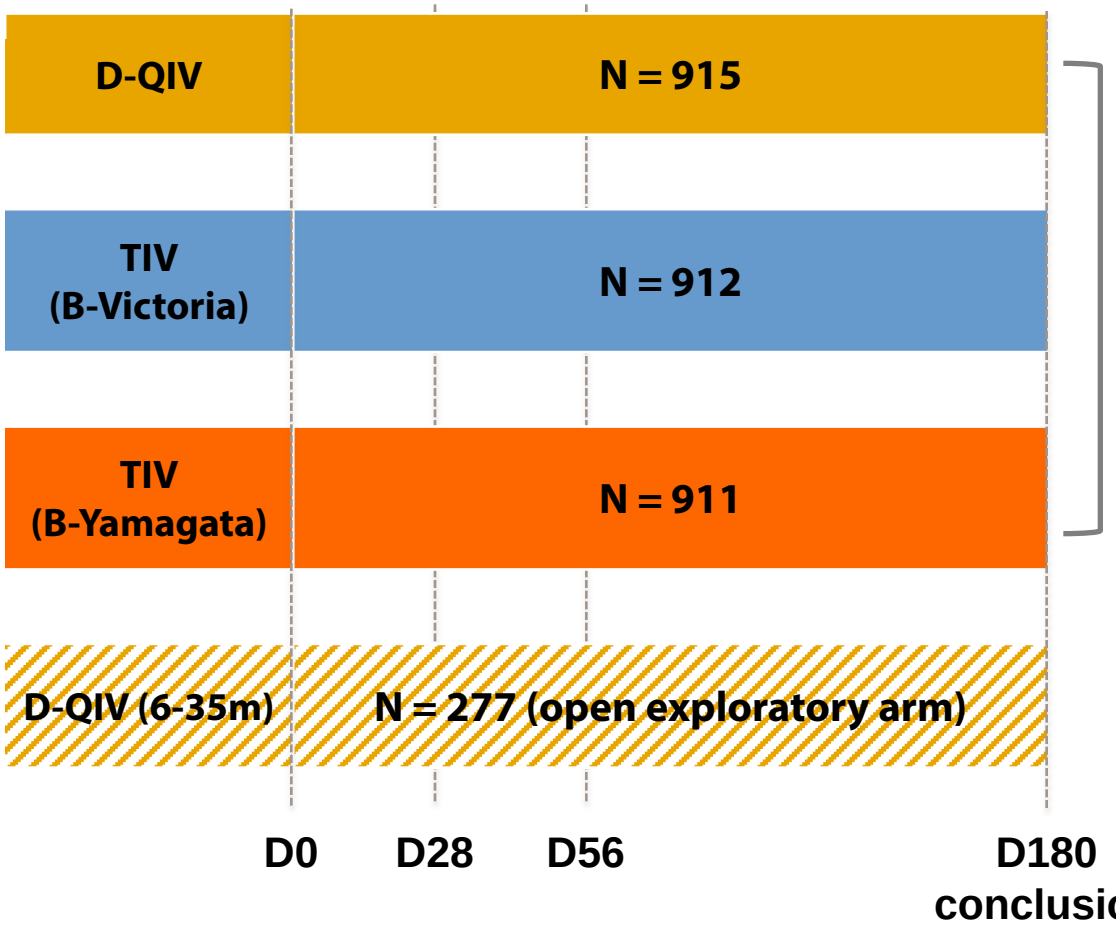
Backup

D-QIV-003: Study Design

Enrolled: US (1065); Philippines (837); Germany (707); Czech Republic (235); France(183)

N = 3,015
Randomization
1:1:1

Age stratification
2:1
3-8y and 9-17y



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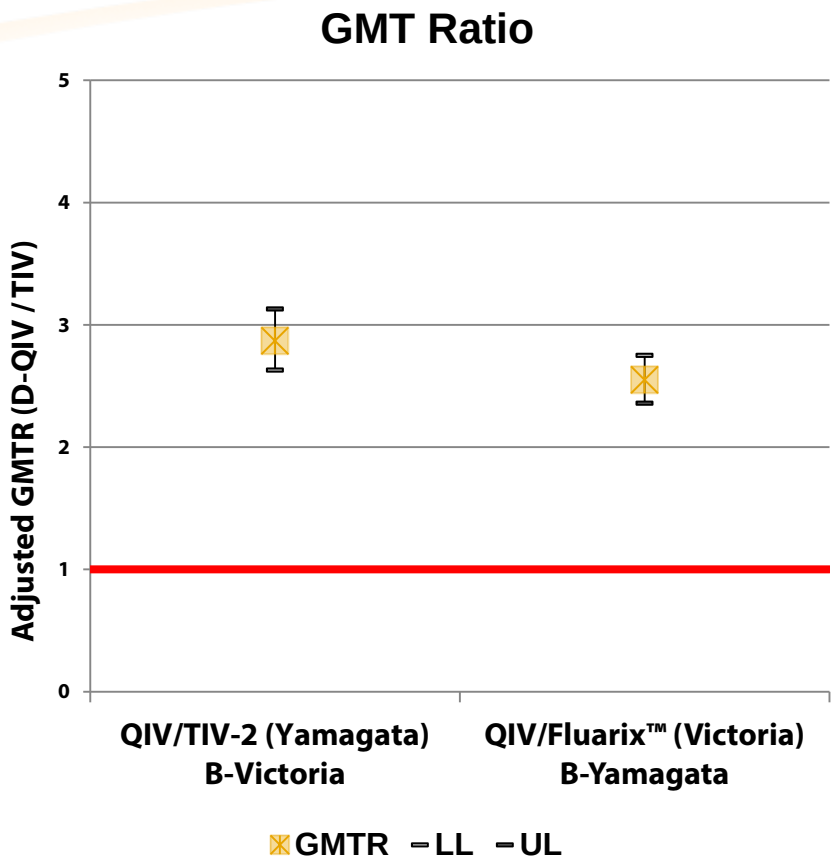
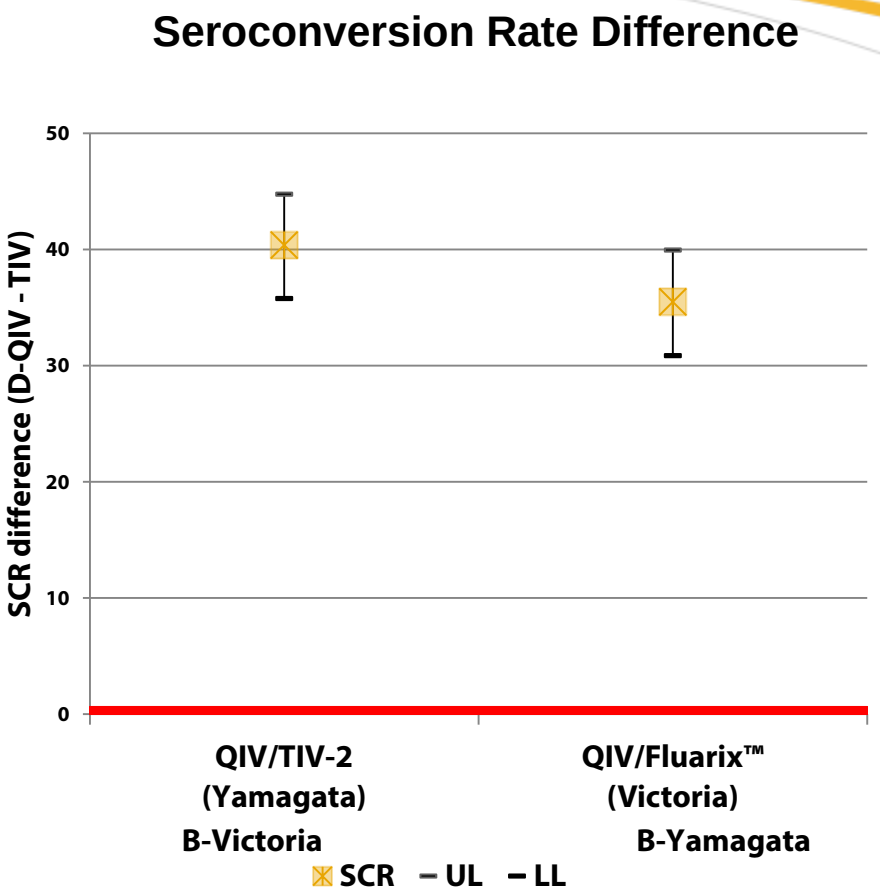
D QIV-003: Superiority Analysis, D-QIV vs. TIV, GMT Ratio & Seroconversion Rate Difference, Day 28





PP Immunogenicity Cohort

Superiority criteria: LL 95%CI for GMT Ratio >1.0
LL 95%CI for SCR difference >0%

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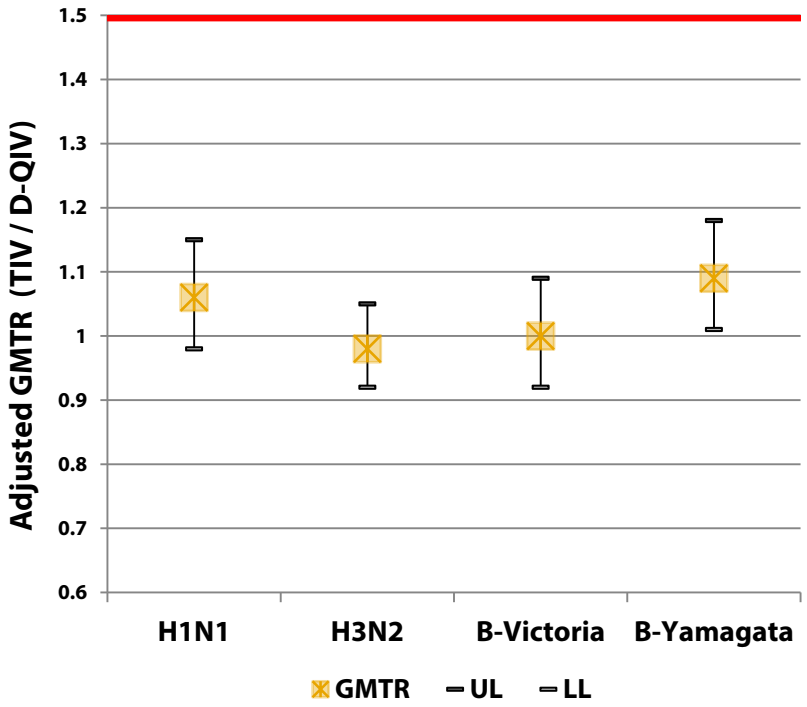
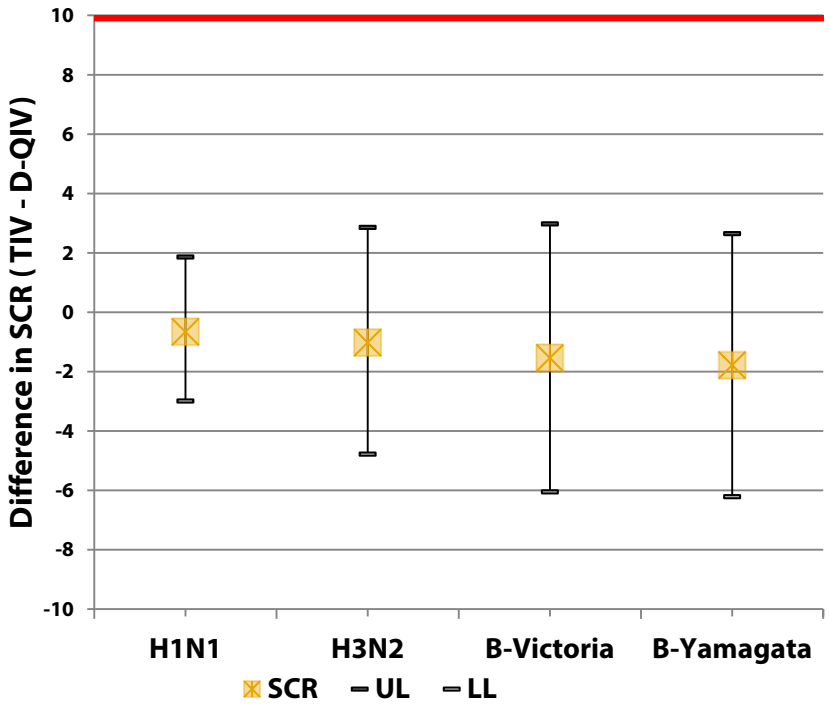
D-QIV-003: Non-Inferiority Analysis, D-QIV vs. TIV, GMT Ratio & Seroconversion Rate Difference, Day 28

GMT Ratio



Seroconversion Difference



PP Immunogenicity Cohort

Non-inferiority criteria: UL 95%CI for GMT Ratio <1.5
UL 95%CI for SCR difference <10%

D-QIV-008: Study Design

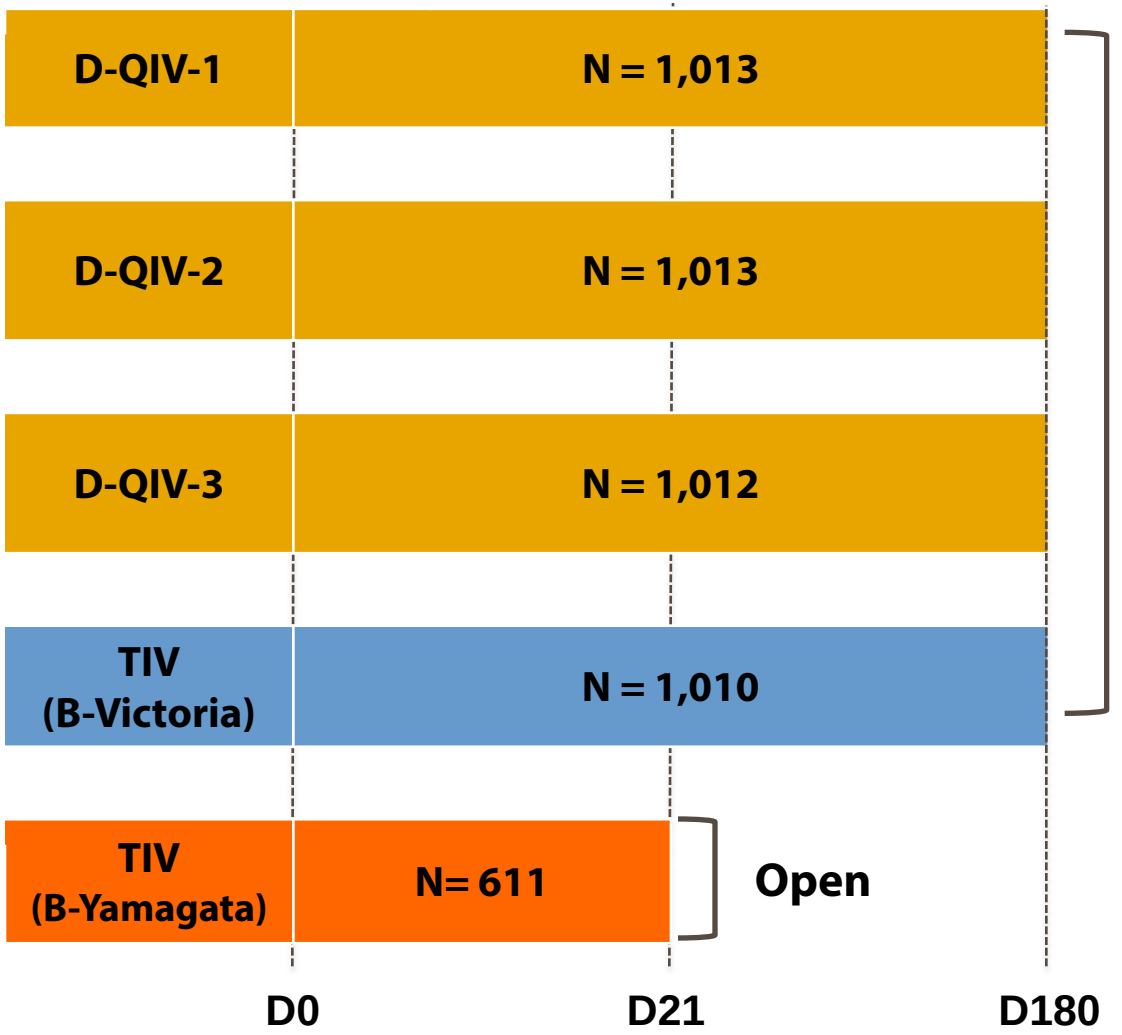
US (1,451) Germany (651); Romania (650); Spain (672); Korea (832); Taiwan (400)

N = 4,656

Age stratification: 18-64y ≥ 65y 50% each

Randomization: 5:5:5:5:3

Blood samples: ~600 subjects each group



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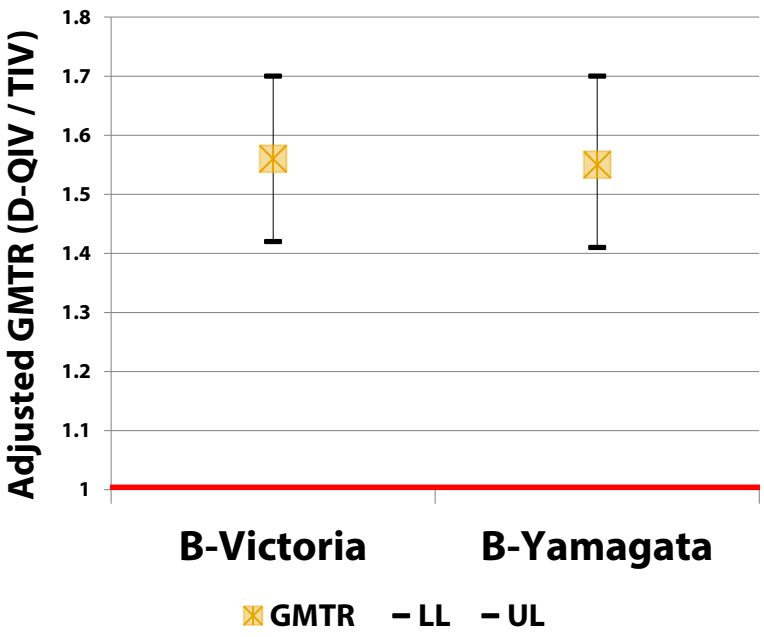
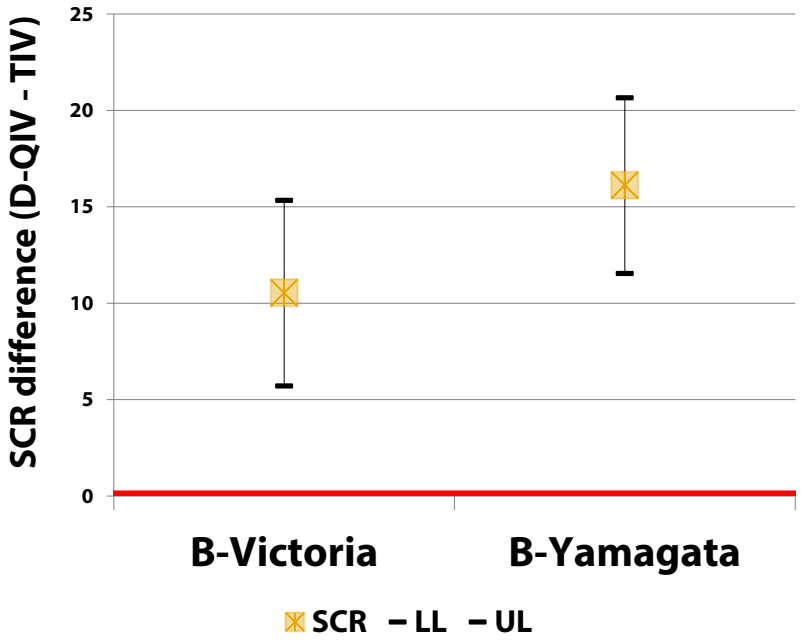
D-QIV-008: Superiority Analysis, D-QIV vs TIV, GMT Ratio & Seroconversion Rate, Day 21

GMT Ratio



Seroconversion Rate Difference



Superiority criteria: LL 95%CI for GMT Ratio >1.0
LL 95%CI for SCR difference >0%

PP Immunogenicity Cohort N= D-QIV = 1809, Fluarix =608, TIV-2=534

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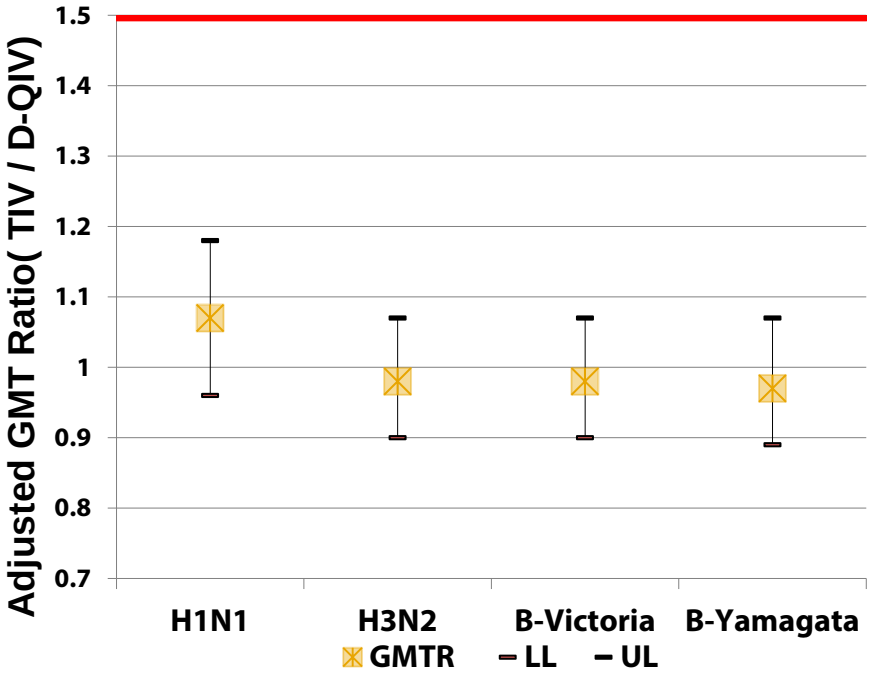
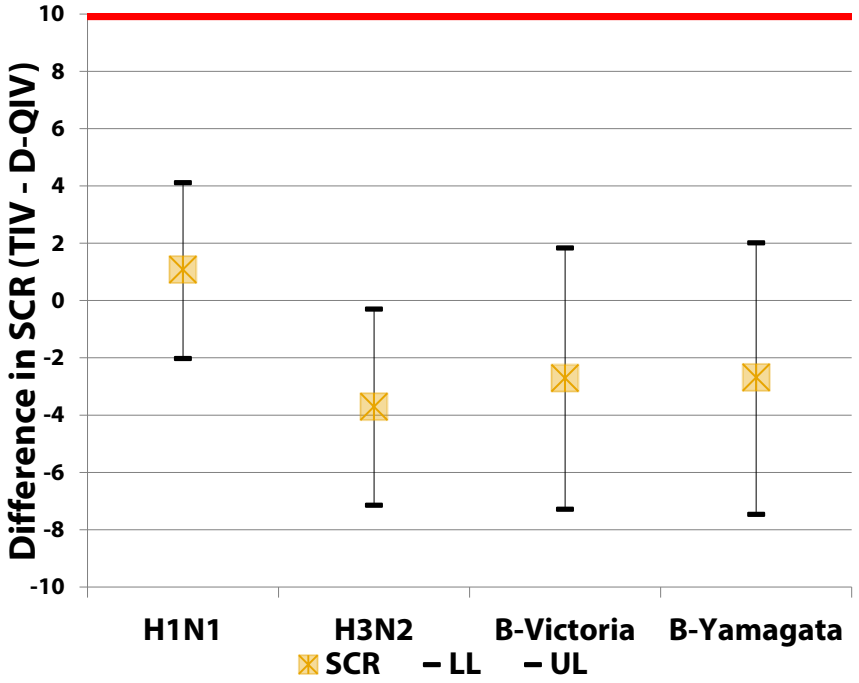
D-QIV-008: Non-inferiority Analysis, D-QIV vs TIV, GMT Ratio & Seroconversion Rate, Day 21

GMT Ratio



Seroconversion Rate Difference



Non-inferiority criteria UL 95%CI for GMT ratio <1.5
UL 95%CI for SCR difference <10%

For H1N1 and H3N2, TIV-Vic and TIV-Yam were pooled
PP Immunogenicity Cohort N= D-QIV = 1809, TIV-Vic=608, TIV-Yam=534

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