FluLaval Quadrivalent:
GSK's Inactivated Quadrivalent Influenza Vaccine Manufactured in Quebec

Varsha K. Jain, MD, MPH
Director, Vaccine Discovery & Development
Seasonal Influenza Vaccines

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Development Plan for FluLaval® (Q-TIV, Q-QIV)

- FluLaval (Q-TIV) is licensed in US for adults
- In 2012, two supplemental BLAs were filed:
  - Q-TIV : to expand age indication to 3 -17 years of age
  - Q-QIV: initial indication for 3 years of age and older
- Target Indication for FluLaval Quadrivalent (Q-QIV):
  - *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*

***Note on Nomenclature**. GSK will use QIV and TIV in most of this presentation, although ACIP & CDC have introduced new nomenclature using IIV: IIV4 being formerly known as QIV and IIV3 formerly known as TIV.*

Q-QIV & Q-TIV Pivotal Studies (for sBLAs)

Study	Key results	Groups	N
Q-TIV-008	**Demonstration of Immunogenic NI to US licensed comparator (3-17 yrs)**	- **Q-TIV** - Fluzone (TIV)	**1055** 1062
Q-QIV-003	**Demonstration of Immunogenic NI & superiority of added B strain vs US licensed comparator (3-17 yrs)**	- **Q-QIV** - Fluarix-VB - Fluarix-YB	**932** 929 932
Q-QIV-007	**Demonstration of lot consistency, immunogenic NI & superiority of added B strain vs. US licensed comparator (18+ yrs)**	- **Q-QIV TF (lot 1)** - **Q-QIV TF (lot 2)** - **Q-QIV-TF (lot 3)** - FluLaval-VB - FluLaval-YB	**423** **424** **425** 213 218
Q-QIV-006	**Demonstration of Efficacy vs US licensed non-influenza vaccine (3-8 yrs)**	- **Q-QIV** - Havrix	**2584** 2584
Safety was assessed in all subjects		**Total QIV exposed** **Children** **Adults**	**4788** **3516** **1272**

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Study Results:
Q-QIV-003 Pediatric Immunogenicity
Q-QIV-007 Adult Immunogenicity

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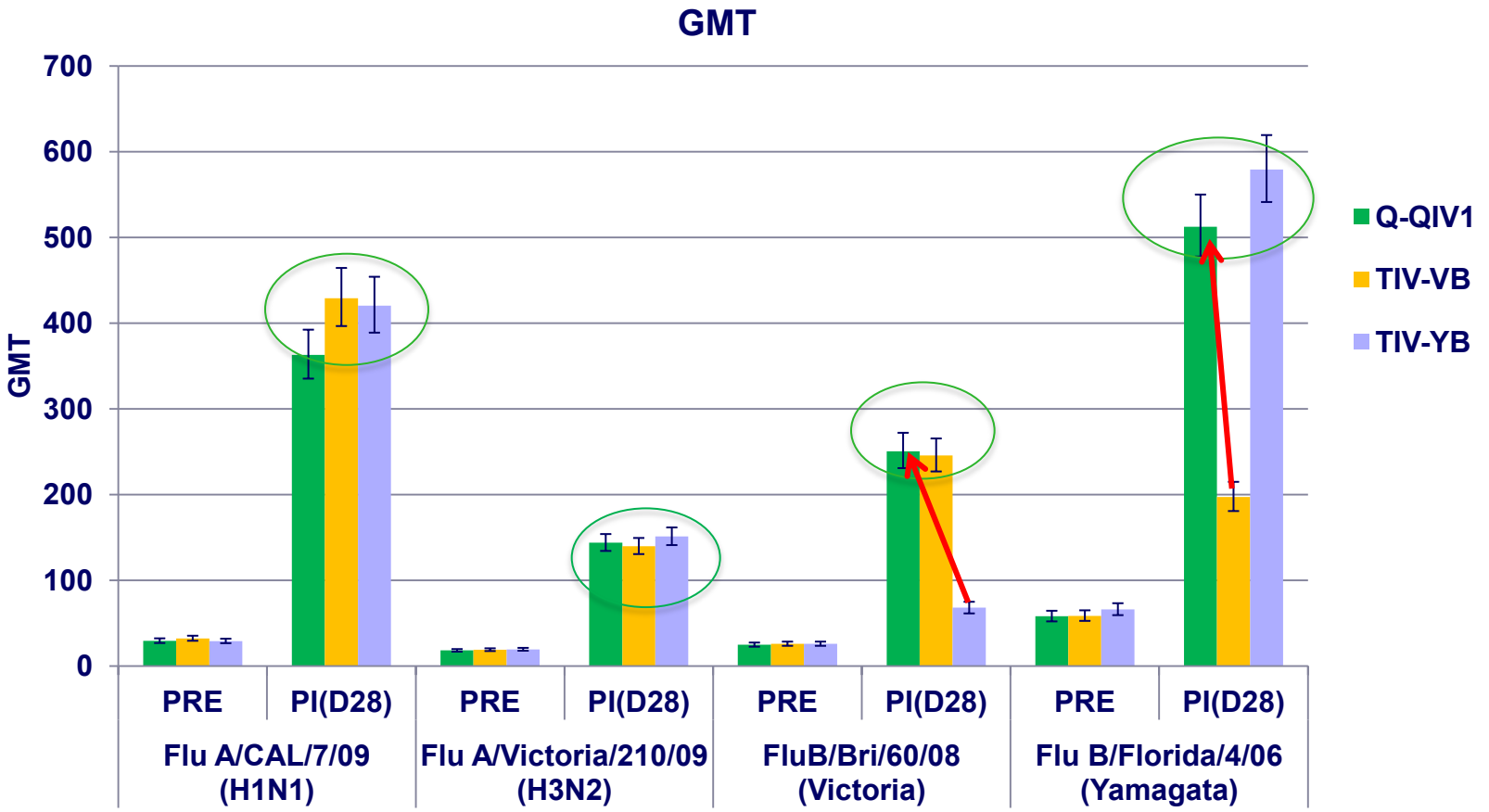
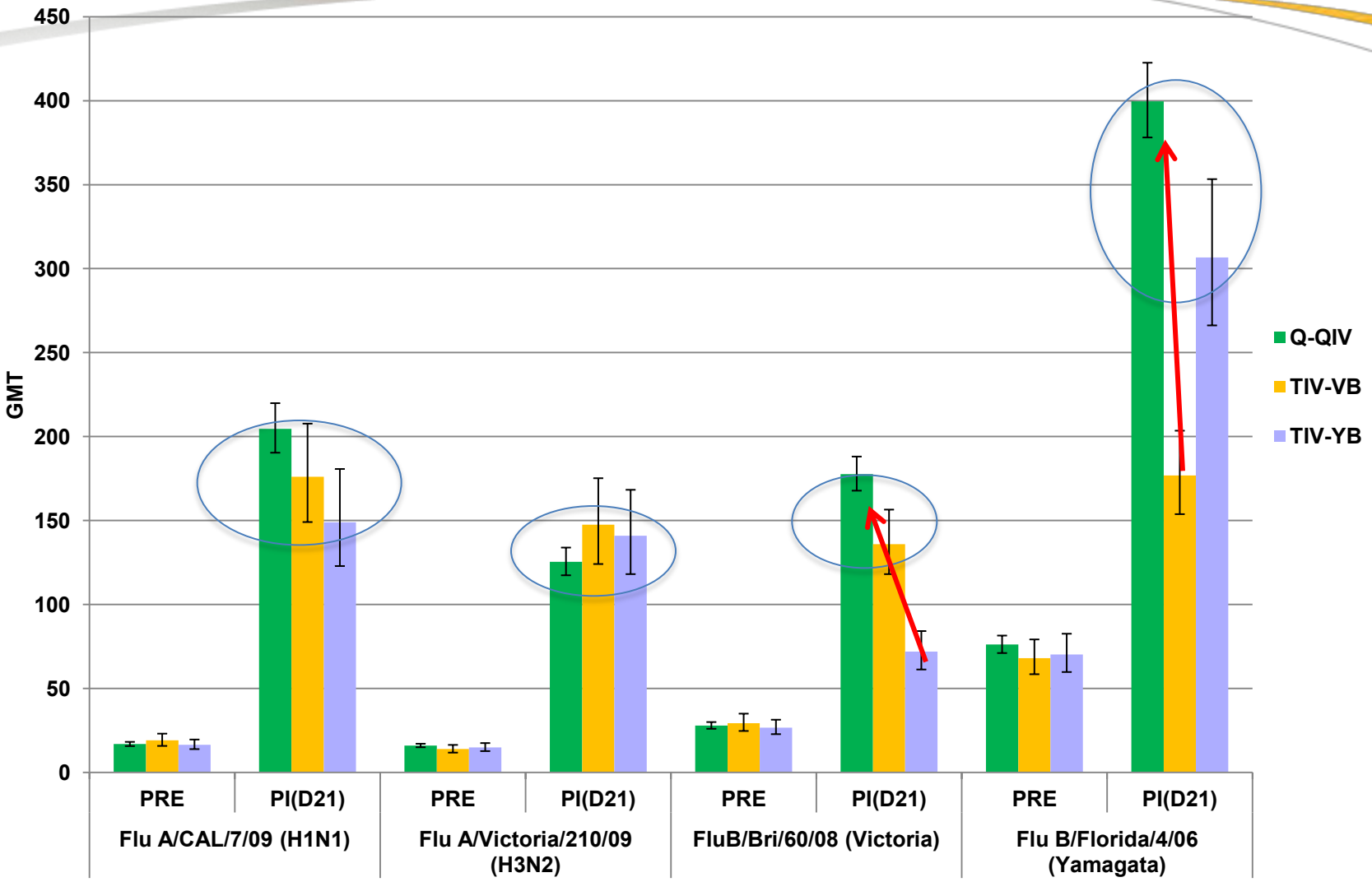
Q-QIV-003 Pediatric: HI Antibody Response (GMT)

Per Protocol Immunogenicity Cohort: Q-QIV=878, TIV-VB=871, TIV-YB=878



Q-QIV-007 Adult: HI Antibody Response (GMT)

Per Protocol Immunogenicity Cohort: Q-QIV=1246, TIV-VB=204, TIV-YB=211



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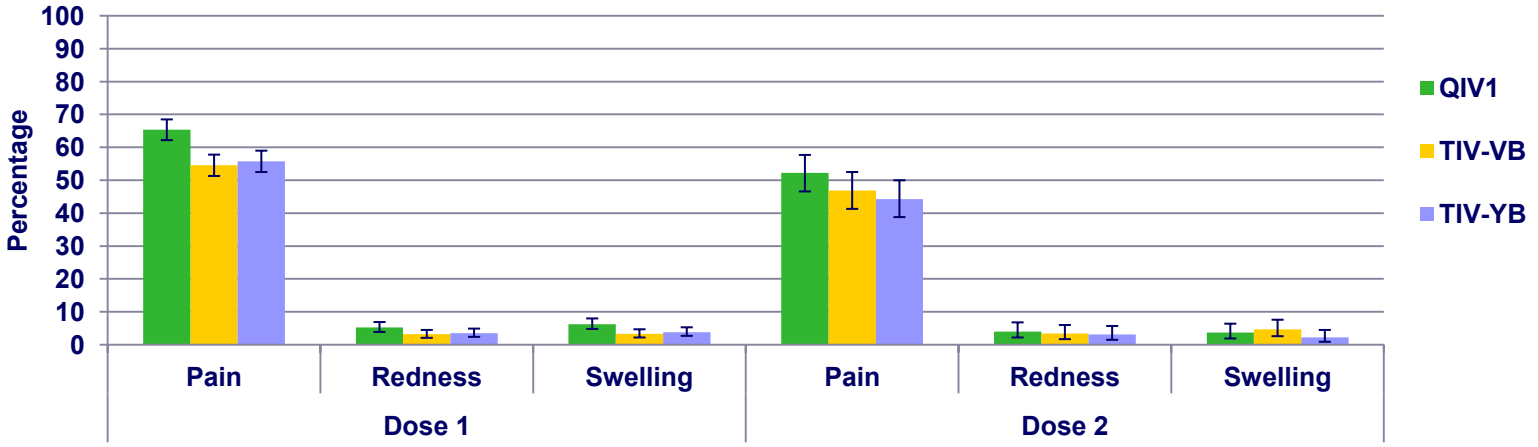
Increased Immune Response of Q-QIV over TIV for the Added B Strain

		Pediatric	Adult
GMT Ratio (95% CI)	Q-QIV / TIV-Vic (increase for B-Yamagata)	2.6	2.4
	Q-QIV / TIV-Yam (increase for B-Victoria)	3.8	2.2
SCR* Difference (95% CI)	Q-QIV minus TIV-Vic (increase for B-Yamagata)	33.9%	21.5%**
	Q-QIV minus TIV-Yam (increase for B-Victoria)	44.6%	25.7%**

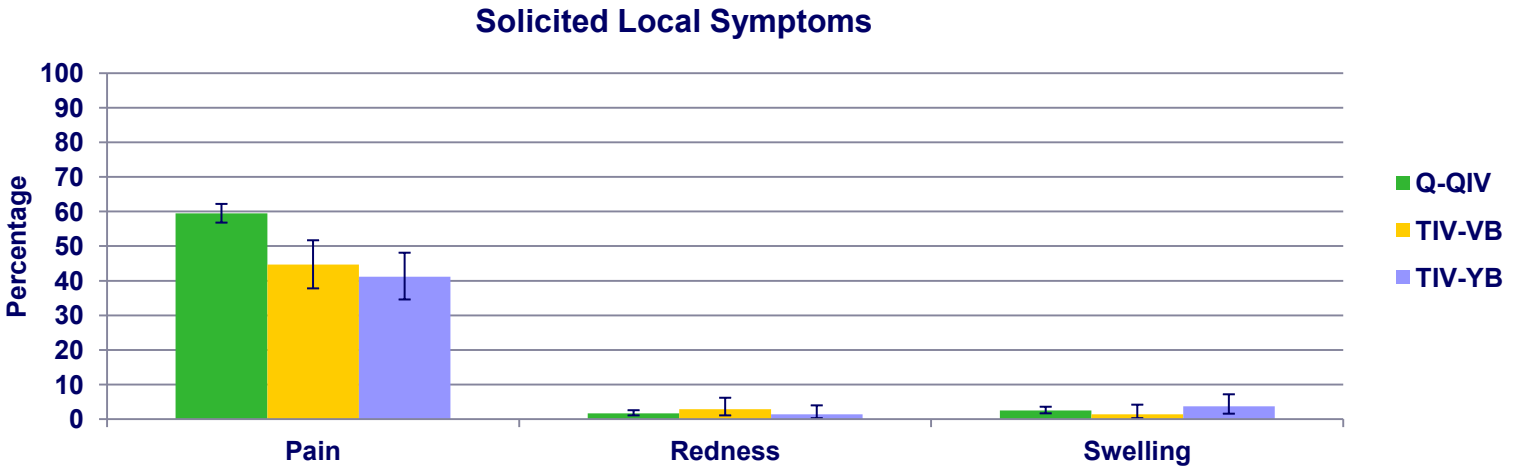
- *SCR is defined as the percentage with either a pre-vaccination titer <1:10 and a post-vaccination titer ≥1:40 or a pre-vaccination titer ≥1:10 and at least a four-fold increase in post-vaccination titer
- **.Post hoc analyses

Q-QIV-003 Pediatric: Reactogenicity and Safety (Total vaccinated cohort)



Safety endpoint	Q-QIV N = 932	TIV-VB N = 929	TIV-YB N = 932
Any AE(s) throughout study period, n (%)	430 (46.1)	432 (46.5)	441 (47.3)
Medically attended AE(s) throughout study period, n (%)	346 (37.1)	335 (36.1)	350 (37.6)
Any SAE(s), n (%) [n SAEs related to the vaccine]	3 (0.3) [0]	6 (0.6) [0]	5 (0.5) [1]

Q-QIV-007 Adult: Reactogenicity and Safety
(Total vaccinated cohort)



Safety endpoint	Q-QIV N = 1272	TIV-VB N = 213	TIV-YB N = 218
Any AE(s) throughout study period, n (%)	457 (35.9)	80 (37.6)	89 (40.8)
Medically attended AE(s) throughout study period, n (%)	330 (25.9)	51 (23.9)	64 (29.4)
Any SAE(s), n (%) [n SAEs related to the vaccine]	35 (2.8) [0]	3 (1.4) [0]	7 (3.2) [0]

Q-QIV-006: Vaccine Efficacy Study in Children

Study Design (NCT01218308)

Randomization 1:1

Age stratified 3–4 and 5–8 years

Q-QIV (n = 2,600)

HAV (n = 2,600)

N = 5,168

Surveillance for ~180 days during the 2010-11 influenza season

Day 0	Day 28	Day 56	Day 180	Visit
Vaccination Blood sample	Vaccination$^{\$}$ Blood sample*	Blood sample$^{\$}$	Blood sample	↑

*Only for primed subjects

$^{\$}$Only for unprimed

HAV= GSK's Hep A vaccine, Havrix

HAV dose 2* or 3$^{\$}$ for control group

Key Confirmatory Objectives

- Evaluate QIV efficacy for the prevention of:
  - Any RT-PCR confirmed influenza A/B
    (success criterion: LL 95% CI >30%)
  - Moderate to severe RT-PCR confirmed influenza A/B
    (success criterion: LL 97.5% CI >0%)

Case Definitions for Influenza
Confirmed by RT-PCR in a nasal/throat swab

➢ Any influenza is:

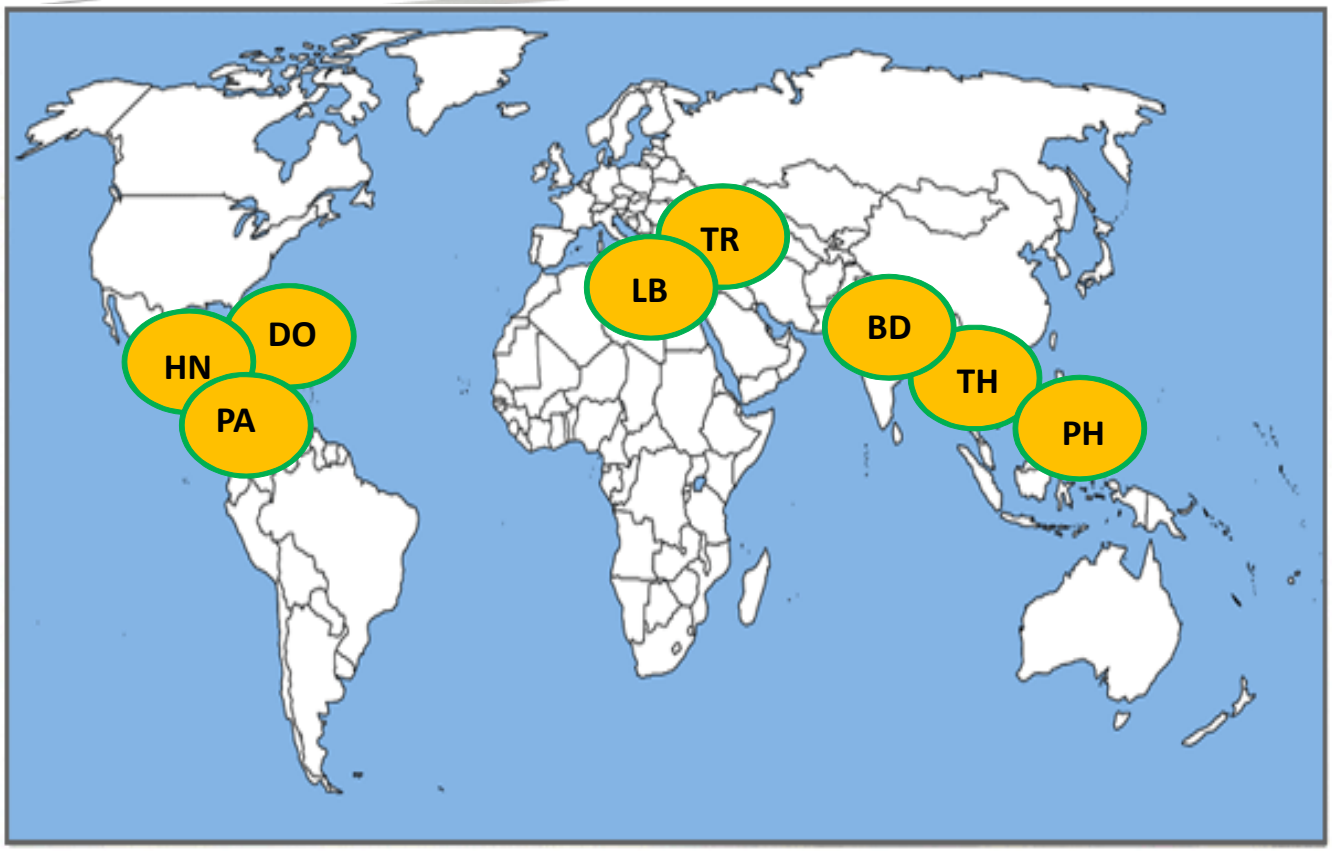
- Temperature ≥37.8°C, and
- One or more symptoms on the same day
  (cough, sore throat, runny nose or nasal congestion)

➢ Moderate to severe influenza is any influenza plus:

- Fever >39°C, or
- Physician-verified acute otitis media, or
- Physician-verified lower respiratory tract manifestations
  (shortness of breath, croup, wheezing, pulmonary congestion, bronchiolitis, bronchitis, pneumonia), or
- Physician-diagnosed serious extra-pulmonary complication of influenza
  (including myositis, myocarditis, seizure or encephalitis)

(detects the more clinically consequential outcomes of influenza)

Countries and Enrollment

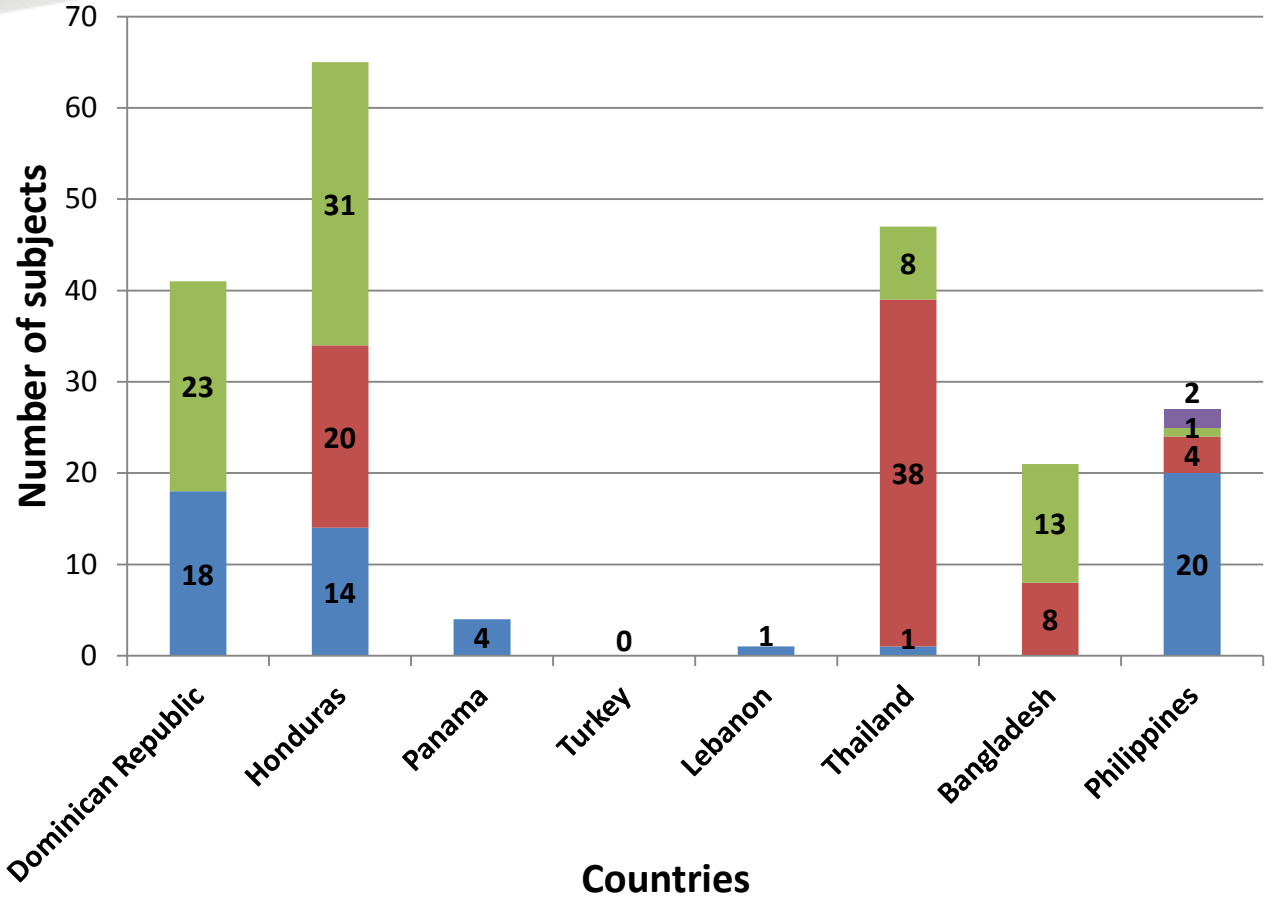


Country	N
Dom Rep	1200
Philippines	1100
Thailand	1008
Bangladesh	1000
Honduras	400
Panama	204
Lebanon	150
Turkey	106

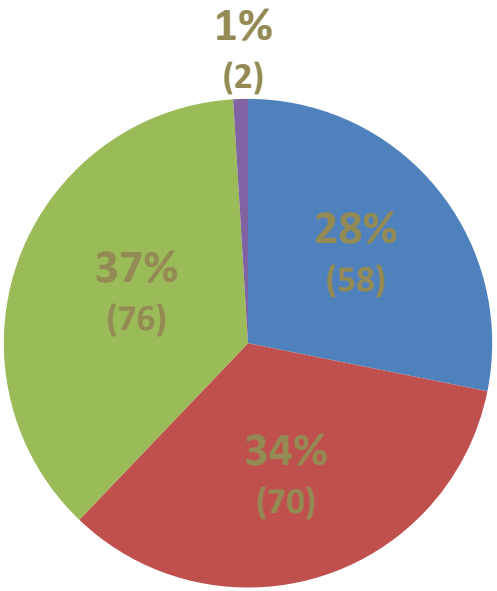
- Demography similar between groups: mean age 5.4 ± 1.7 years; ~48% female
- Majority of children were vaccine unprimed → received 2 doses

Subtype/Lineage Distribution by Country

(Total vaccinated cohort - from 14 days after vaccination)



Overall distribution:



(All RT-PCR positive cases: 206)

H1N1 H3N2 B-Victoria B-Yamagata

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Vaccine Efficacy - Cases Confirmed by RT-PCR

(Per-protocol cohort for efficacy - from 14 days after vaccination)

				Attack rate (95% CI)				Vaccine efficacy (95% CI)		
Endpoint	**Group**	**N**	**n**	**%**	**LL**	**UL**	**T/N**	**%**	**LL**	**UL**
Any influenza	Q-QIV	2,379	58	2.44	1.86	3.14	5.1	**55.38**	39.15	67.29
	HAV	2,398	128	5.34	4.47	6.31	5.0	–	–	–
				Attack rate (97.5% CI)				Vaccine efficacy (97.5% CI)		
Endpoint	**Group**	**N**	**n**	**%**	**LL**	**UL**	**T/N**	**%**	**LL**	**UL**
Moderate to severe influenza	Q-QIV	2,379	14	0.59	0.29	1.05	5.2	**73.08**	47.11	86.30
	HAV	2,398	52	2.17	1.56	2.93	5.1	–	–	–

N = number of subjects included in each group

n = number of subjects reporting at least 1 event in each group

T = sum of follow-up periods (months) in each group

T/N = mean follow-up period (months) in each group

Vaccine efficacy assessed using Cox Regression model adjusted for age category, region and priming status

Moderate to Severe Influenza

(Total vaccinated cohort – from 14 days after vaccination)

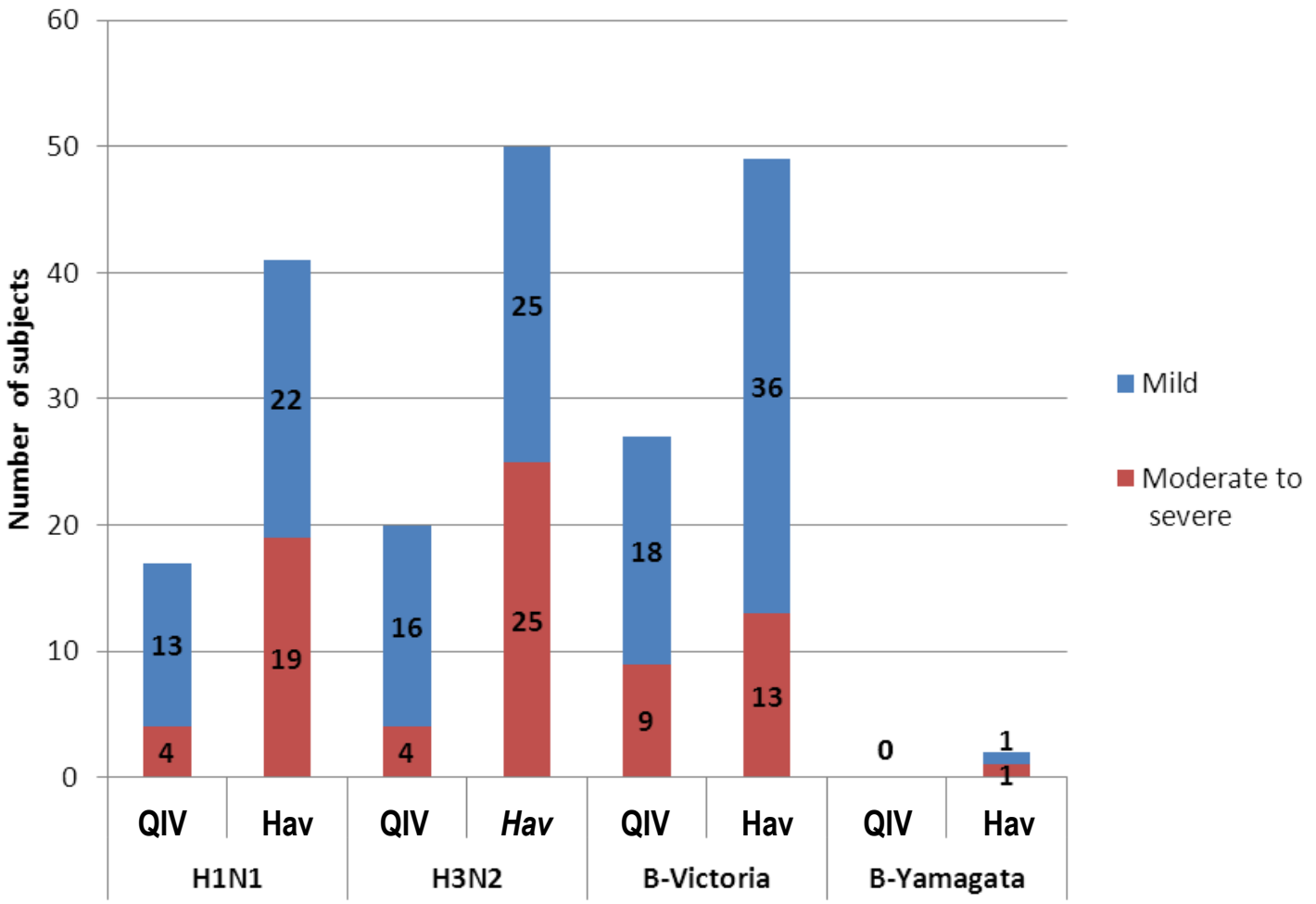
Manifestation justifying classification as moderate to severe disease	Q-QIV N=2584 n	*HAV* N=2584 n	RR	95% CI
All moderate to severe cases	16	57		
Only fever >39ºC	14	46	0.29	0.16 – 0.56
Only acute otitis media	0	1		
Lower respiratory infection	2	10	0.20	0.04 – 0.92
Wheezing (and fever >39ºC)	1	1		
Bronchitis	1	0		
Bronchitis (and fever >39ºC)	0	1		
Shortness of breath	0	3		
Shortness of breath (and fever >39ºC)	0	2		
Pneumonia	0	2		
Pneumonia with congestion	0	1		
Extra-pulmonary complication	0	0		

n = number of subjects as unique cases

RR = Relative risk

Influenza Severity by Subtype/Lineage

(Total vaccinated cohort – from 14 days after vaccination)



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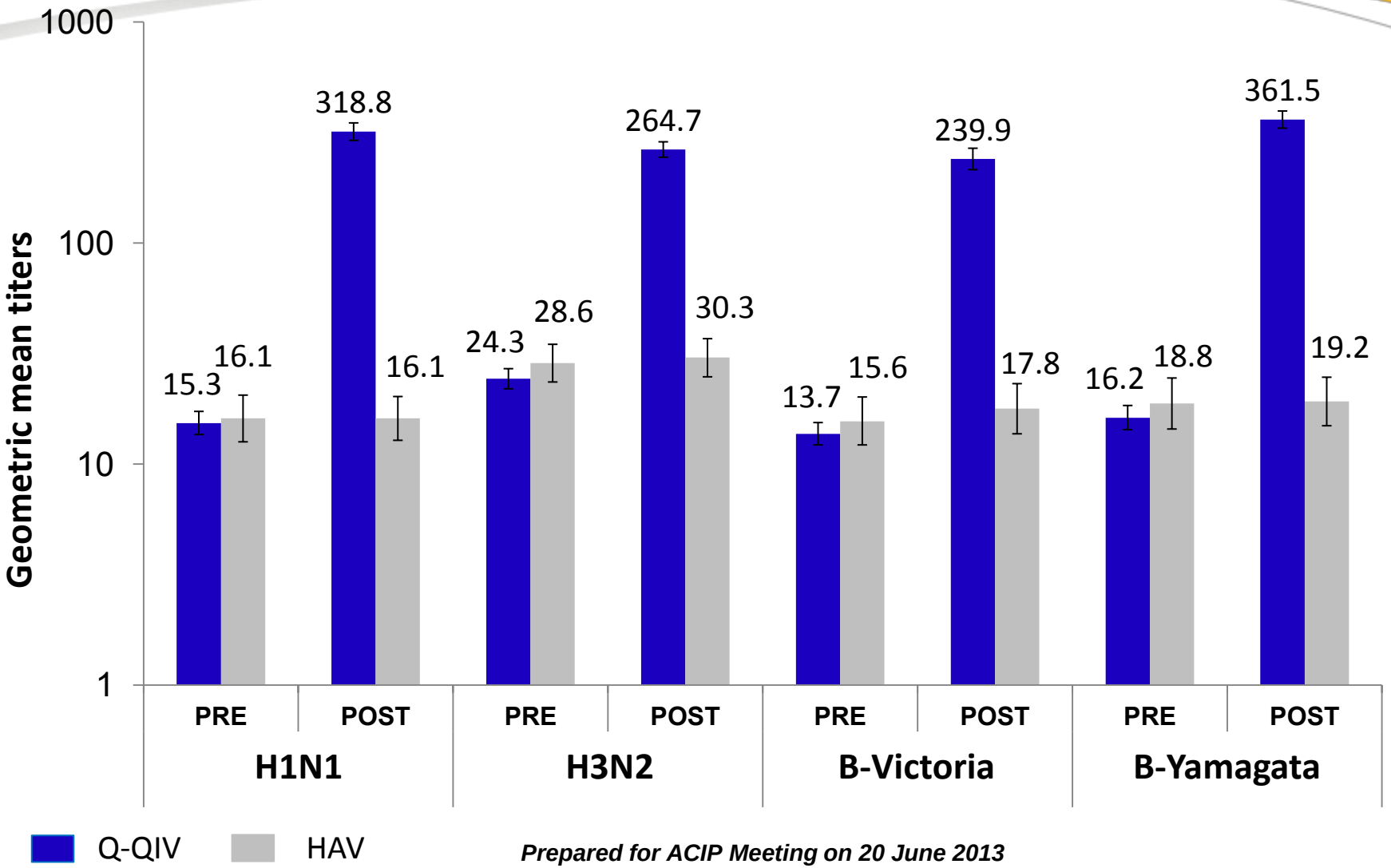
Immunogenicity - Geometric Mean Titer

28 days after vaccination (Per-protocol immunogenicity subset)



Incidence of Adverse Events

(Total vaccinated cohort)

	Q-QIV (N=2,584)				HAV (N=2,584)			
	n	%	95% CI		n	%	95% CI	
			LL	UL			LL	UL
Within 7 days of vaccination:								
Any AE (solicited and unsolicited)	1467	56.8	54.8	58.7	1253	48.5	46.5	50.4
Any general AE (solicited and unsolicited)	880	34.1	32.2	35.9	836	32.4	30.6	34.2
Any local AE (solicited and unsolicited)	1219	47.2	45.2	49.1	890	34.4	32.6	36.3
During entire study:								
Serious adverse events	36	1.4	1	1.9	24	0.9	0.6	1.4
Medically attended events	792	30.7	28.9	32.5	749	29.0	27.2	30.8
Grade 3 medically attended events	26	1.0	0.7	1.5	17	0.7	0.4	1.1
Medically attended events with causal relationship to vaccination	6	0.2	0.1	0.5	13	0.5	0.3	0.9

n/% = number/percentage of subjects reporting at least 1 event in each group

Summary

- FluLaval (Q-TIV) has non-inferior immunogenicity vs a US licensed comparator in 3-17yo (PIDJ, 2012;31:605)

- FluLaval Quadrivalent (Q-QIV) met all objectives in pediatric/adult studies:
  - Efficacy was shown for any influenza (55%) and moderate to severe influenza (73%) in children 3-8 years of age
  - A superior immune response to the additional B lineage was demonstrated
  - Additional B strain did not interfere with the response to TIV strains
  - Acceptable safety profile relative to licensed TIV/HAV from >4500 individuals receiving Q-QIV

Anticipated Availability of FluLaval (TIV and QIV)

- Q-QIV and Q-TIV license anticipated for 3 years of age and older in mid Aug 2013
- Q-QIV and Q-TIV will have same presentations:
  - Multi-dose vials (10-doses) with preservative (thimerosal)
  - Prefilled single-dose syringes, preservative free

- FluLaval TIV will be available for the 2013-14 influenza season and GSK will make limited supply of FluLaval Quadrivalent available as well, pending FDA approval

Questions