Do quadrivalent seasonal influenza vaccines provide added benefits for at risk groups in Asia?

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Outline

- What are quadrivalent influenza vaccines?
- Influenza B
  - Evolution
  - Epidemiology
- Burden of disease
- Will quadrivalent influenza vaccines provide added benefit?

Quadrivalent influenza vaccines

What is quadrivalent vaccine?

- The quadrivalent influenza vaccine is designed to protect against four different influenza viruses;
  - A(H1N1)pdm09
  - A(H3N2) and
  - two influenza B viruses.

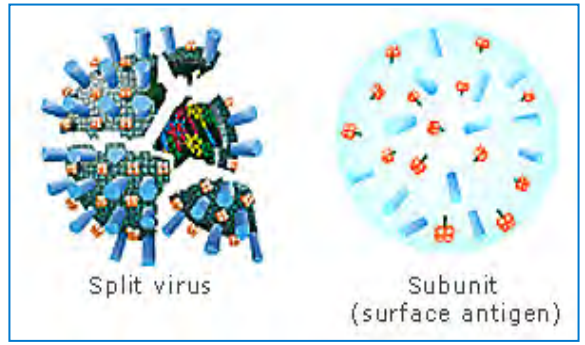
Why was the quadrivalent flu vaccine developed?

- Originally influenza vaccines were designed to protect against two different viruses (bivalent) then three viruses after the 1977 re-emergence of H1N1 (trivalent).
- Trivalent vaccines currently include
  - an A/H1N1 virus, an A/H3N2 virus and one B virus (even though 2 B lineages have been circulating since 1970's).
  - no protection against the group of B viruses not included in the vaccine.
- Adding another B virus to the vaccine aims to give broader protection against **all** circulating influenza viruses.

Quadrivalent influenza vaccines approved in the USA

Influenza vaccines – United States 2014-15 Influenza Season

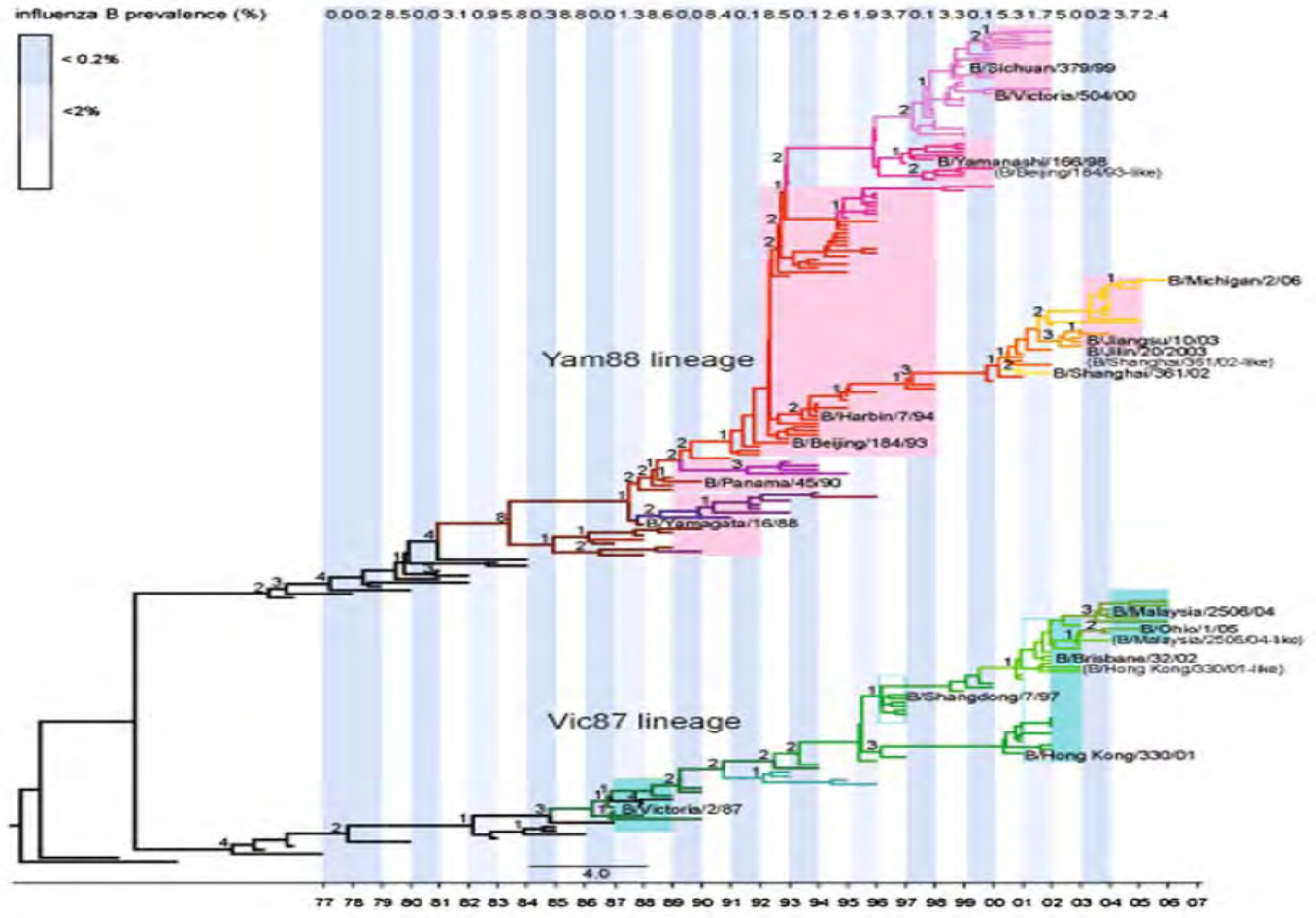
Trade name	Manufacturer	Presentation	Mercury content from thimerosal (μg Hg/0.5 mL)	Ovalbumin content (μg/0.5mL)	Age indications	Route
Inactivated influenza vaccine, quadrivalent (II4 or QIV)						
Fluarix Quadrivalent	GlaxoSmithKline	0.5 mL single-dose prefilled syringe	—	≤0.05	≥3 yrs	IM†
FluLaval Quadrivalent	ID Biomedical Corporation of Quebec (distributed by GlaxoSmithKline)	0.5 mL single-dose prefilled syringe	—	≤0.3	≥3 yrs	IM†
		5.0 mL multidose vial	<25	≤0.3	≥3 yrs	IM†
Fluzone Quadrivalent	Sanofi Pasteur	0.25 mL single-dose prefilled syringe	—	§§§	6–35 mos	IM†
		0.5 mL single-dose prefilled syringe	—	§§§	≥36 mos	IM†
		0.5 mL single-dose vial	—	§§§	≥36 mos	IM†
		5.0 mL multidose vial	25	§§§	≥6 mos	IM†
Live attenuate influenza vaccine (LAIV4)						
FluMist Quadrivalent§§	MedImmune	0.2 mL single-dose prefilled intranasal sprayer	—	<0.24 (per 0.2mL)	2–49 yrs	IN



http://www.cdc.gov/flu/pdf/protect/vaccine/influenza-vaccines-table-2014-15.pdf

Influenza B virus evolution

- Influenza B viruses have diverged into two lineages
  - B/Victoria-like
  - B/Yamagata-like
- Divergence occurred mid-1970's
- Mid-1980's- B/Victoria-like lineage predominates
- Early 1990's both lineages circulate worldwide
  - Different lineages may predominate in different countries within same region & same season

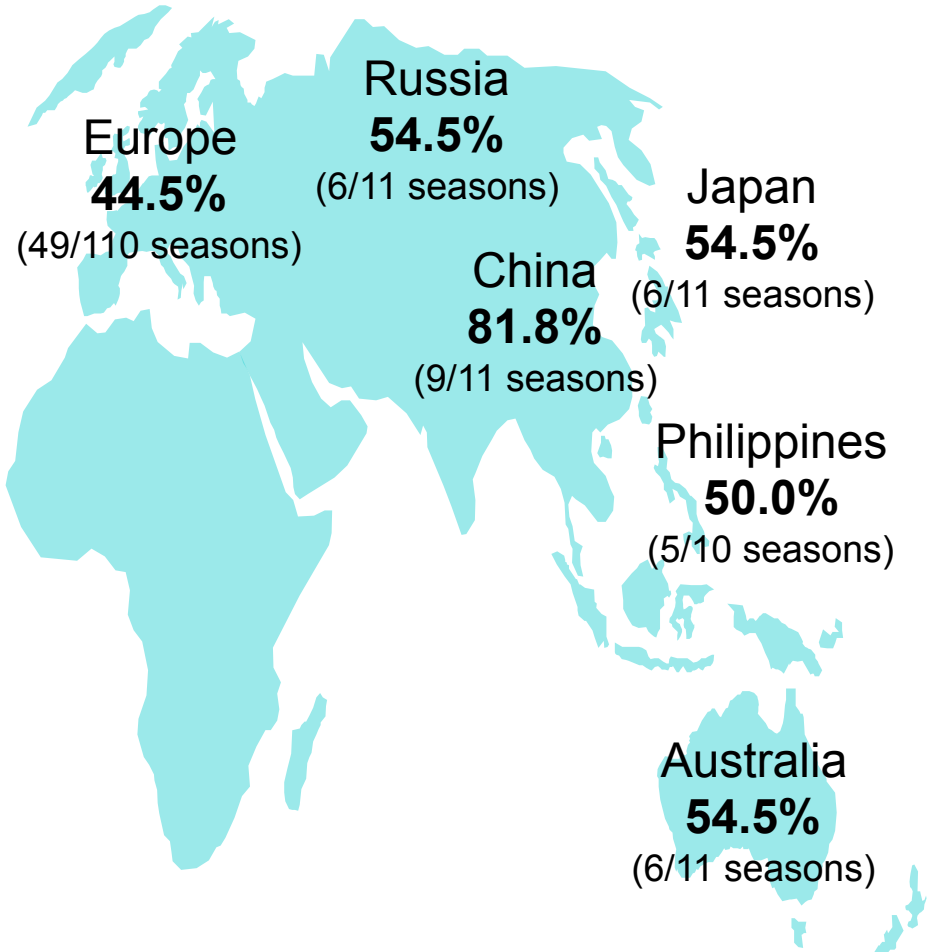


Influenza B: MAP tree of HA1 domain

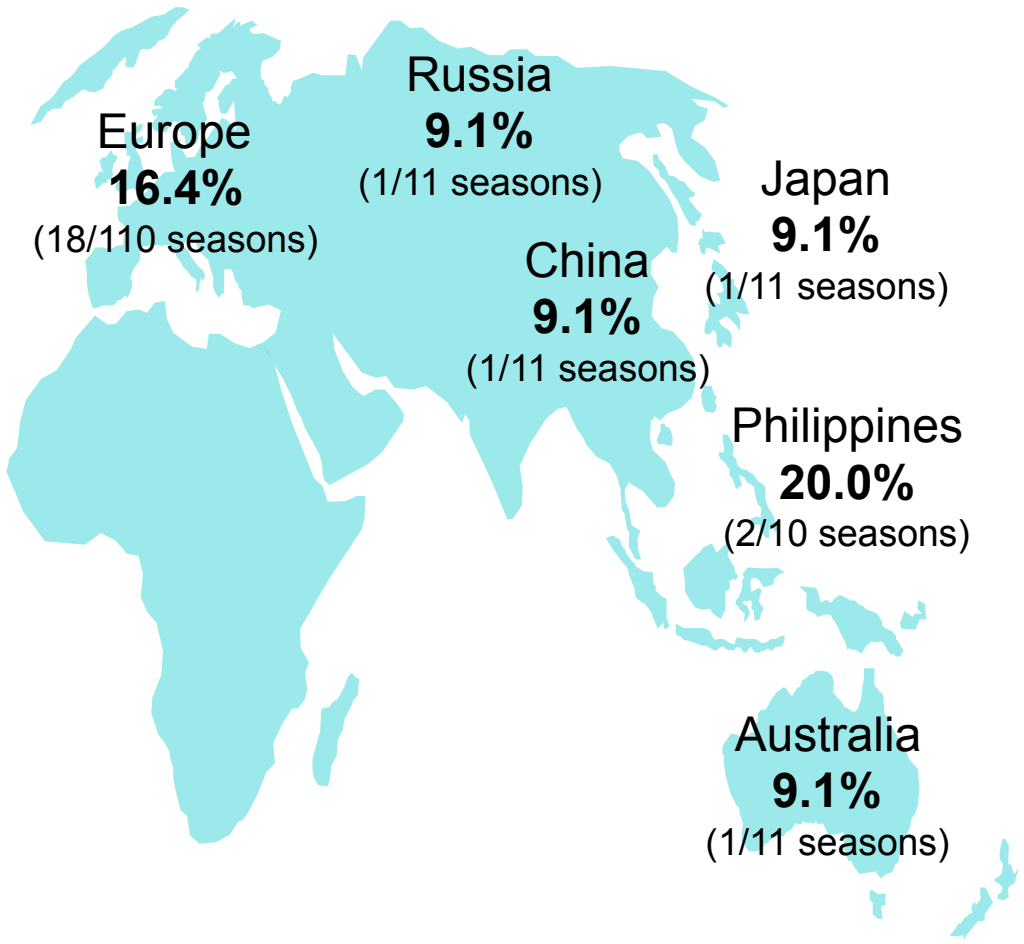
Chen & Holmes. J Mol Evol 2008;66:655-663

Epidemiology of Influenza B viruses: prevalence (2000-2011)

Prevalence ≥20%



Prevalence ≥ 50%



Data extracted from the WHO FluNet surveillance system. http://www.who.int/influenza/gisrs_laboratory/flunet/en

Geographic and seasonal heterogeneity of influenza B virus circulation

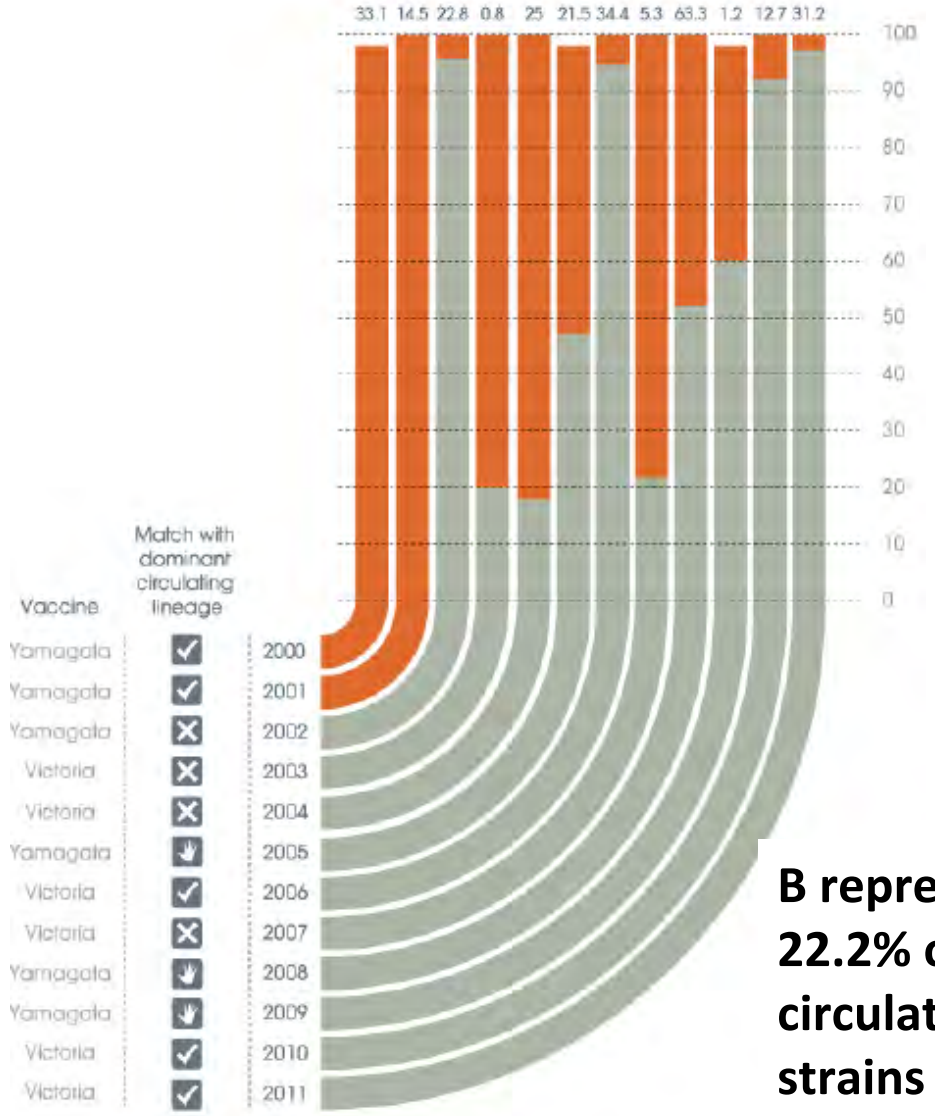
Prevalence of Influenza B / all circulating influenza strains : < 10 % | 10-25% | 25-50% | > 50%

Season	Europe	North America	Southern Hemisphere	Asia
2000-2001				
2001-2002				
2002-2003				
2003-2004				
2004-2005				
2005-2006				
2006-2007	Western Europe Romania & Russia			
2007-2008				
2008-2009				
2009-2010				
2010-2011				

Data from WHO, FluNet surveillance system

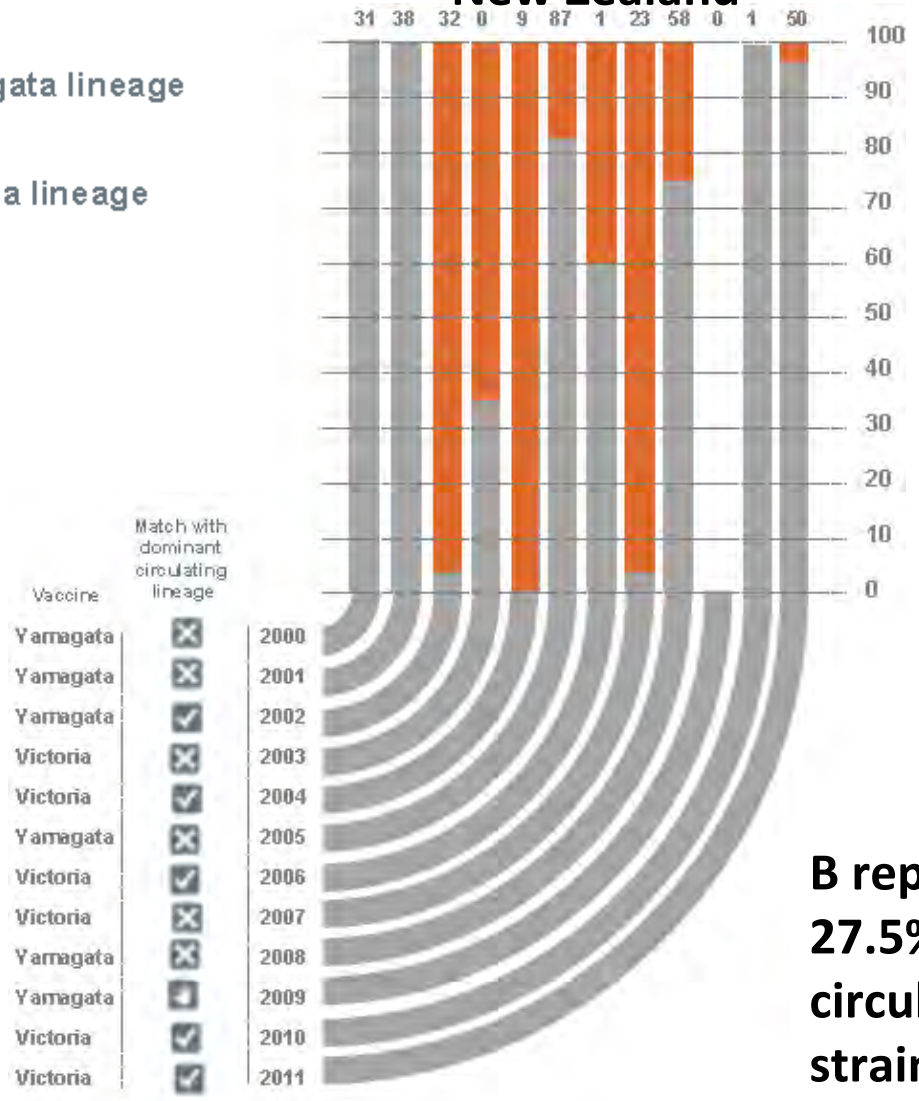
Heterogeneous and unpredictable influenza B virus circulation in Southern Hemisphere

Australia



B represents 22.2% of circulating strains

New Zealand

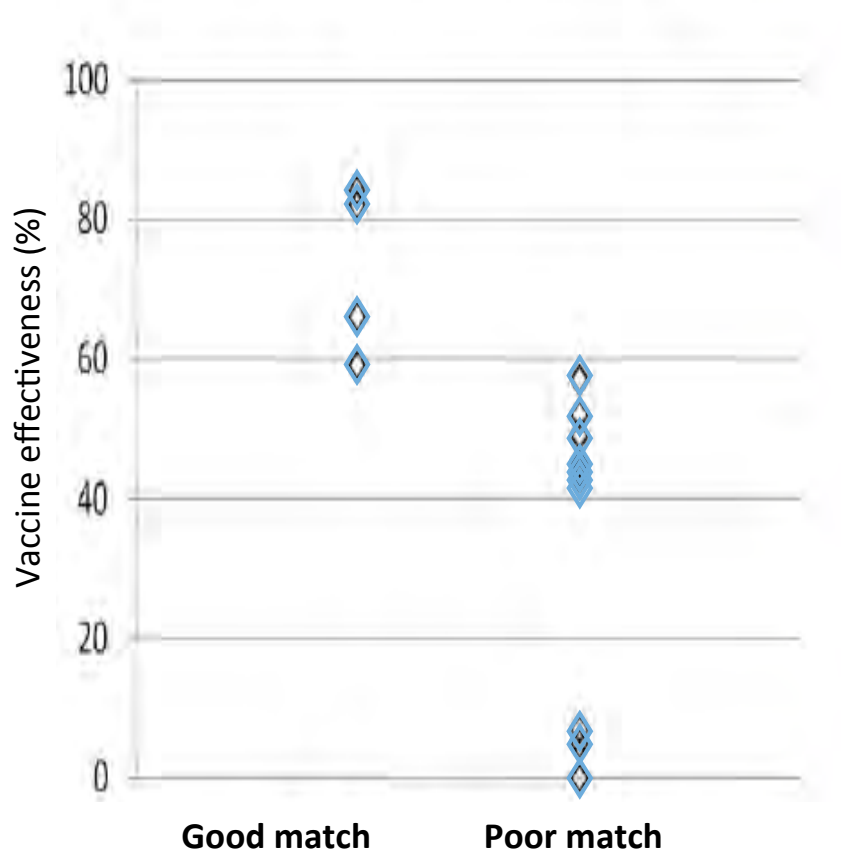


B represents 27.5% of circulating strains

Source: A Forde, SanofiPasteur 2015

Correlation between vaccine match and vaccine effectiveness: children in Europe

Point estimates of TIV effectiveness according to vaccine match during seasons with normal influenza activity **in children < 5 years old**



Heikkinen & Heinonen Vaccine 2011;29:7529-7534

- Match between vaccine and circulating strains of influenza viruses is one of the key drivers of vaccine effectiveness
- In seasons with good antigenic match, inactivated influenza vaccines are clearly effective in children <5 (& <2) years of age

Correlation between vaccine match and vaccine effectiveness: meta-analysis

Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis

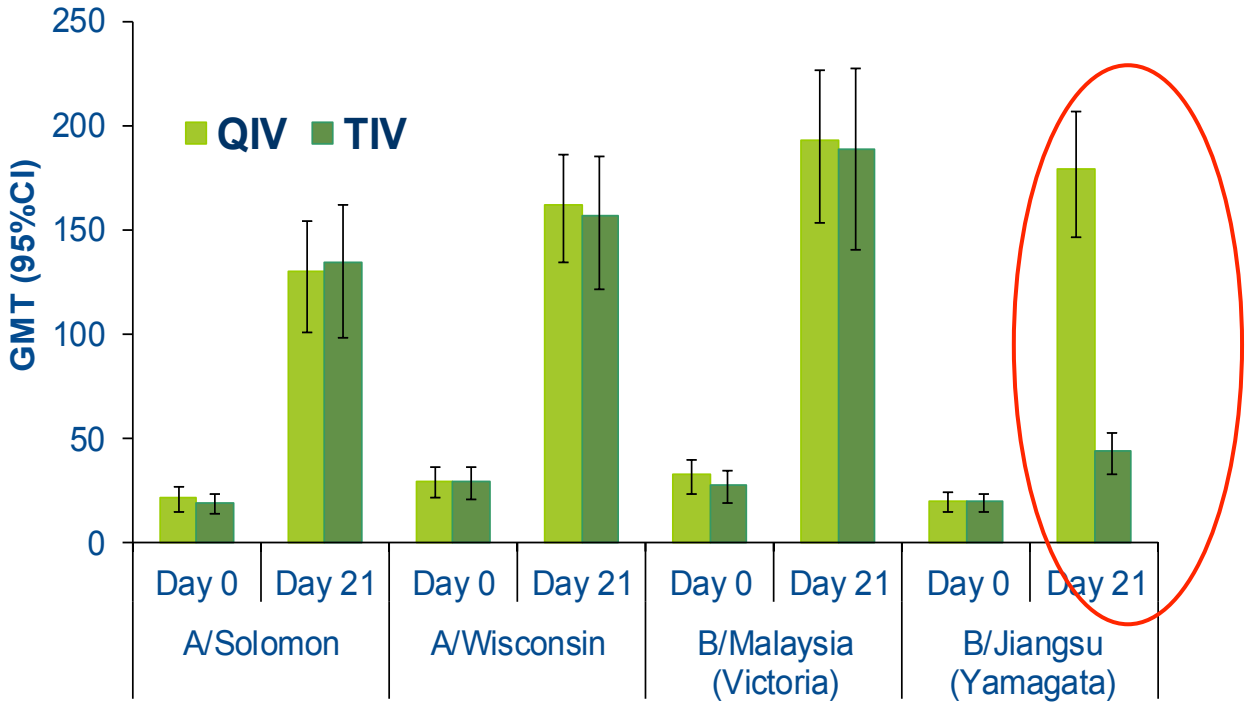
Michael T Osterholm, Nicholas S Kelley, Alfred Sommer, Edward A Belongia

Effect of B mismatches and B circulation on vaccine efficacy

Study	Season and Country	# subjects Overall /TIV arm	Attack rate (%)	TIV Vaccine Efficacy % (95%CI)	# (%) of B strains isolates	B mismatch (%)
Beran, 2009	2005-2006 Czech Republic	6,203 / 4,137	TIV arm: 28/4,137 (0,7) Overall: 46/6,203(0,7)	22 (-49;59)	Overall: 36 (78)	97
Beran, 2009A	2006-2007 Czech Republic Finland	7,652 / 5,103	TIV arm: 63/5,103 (1,2) Overall: 145/7652 (1,9)	61,6 (46,0;72,8)	TIV arm: 3 (5) Overall: 6 (4,1)	100
Frey, 2010	2007-2008 USA Finaland, Poland	11,404 /3,638	TIV arm: 49/3638 (1,35) Overall: 231/11,257 (2,05)	Overall: 63,0 (46,7)* A/H1N1: 81,5 (60,9)* A/H3N2: 49,3 (-9,0)* B: 53,2 (22,2)*	TIV arm: 27 (55) Overall: 118 (51)	100
Jackson, 2010	2005-2006 2006-2007 USA	3514/1,706 4144/2,011	05-06: 19/1,706 (1,1) 06-07: 11/2,011 (0,5) Overall: 30/3714 (0,8)	50 (4;71) 50 (-3;75)	No data provided	100 in 2005-2006
Ohmit, 2006	2004-2005 USA	1,247/522	TIV arm: 7/522 (1,3) Overall: 32/1247 (2,5)	75 (42;90)	Overall: 18 (56)	61
Ohmit, 2008	2005-2006 USA	1,205/867	13/867 (1,5)	16 (-171;70)	1 (8)	100
Monto, 2009	2007-2008 USA	1,952/813	TIV arm: 28/813 (3,4) Overall: 119/1952 (6,1)	Overall: 68 (46-81) A: 72 (49;74) B: 40 (-189;86)	TIV arm: 6 (21,4) Overall: 11 (9,2)	100

Osterholm M *et al*. The Lancet Infectious Diseases, 2012;12, Issue 1:36 - 44

Quadrivalent influenza vaccines (QIV *vs* TIV)



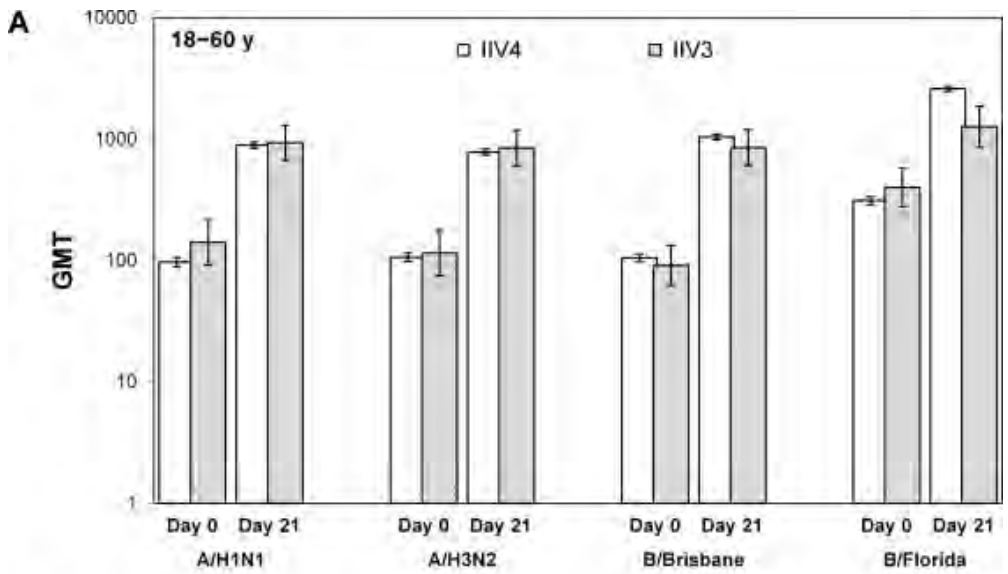
QIV Phase II Study, GSK, 2011

- HI antibody GMTs greater with QIV for B/Jiangsu (Yamagata lineage) at Day 21

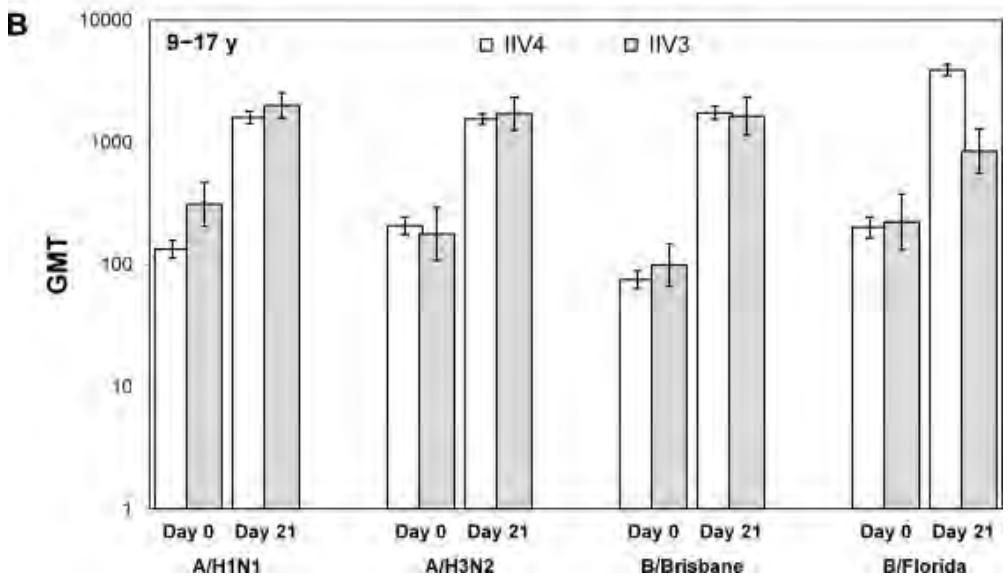
QIV in children, adolescents, and adults: A randomized, controlled, phase III trial

- GMT for IIV4 and IIV3. HAI titers were measured on day 0 (pre-vaccination) and 21 days post-vaccination.
- Meets EMA immunogenicity criteria for adults

Adults



Children



Cadorna-Carlos et al. Vaccine 2015;33:2485-92

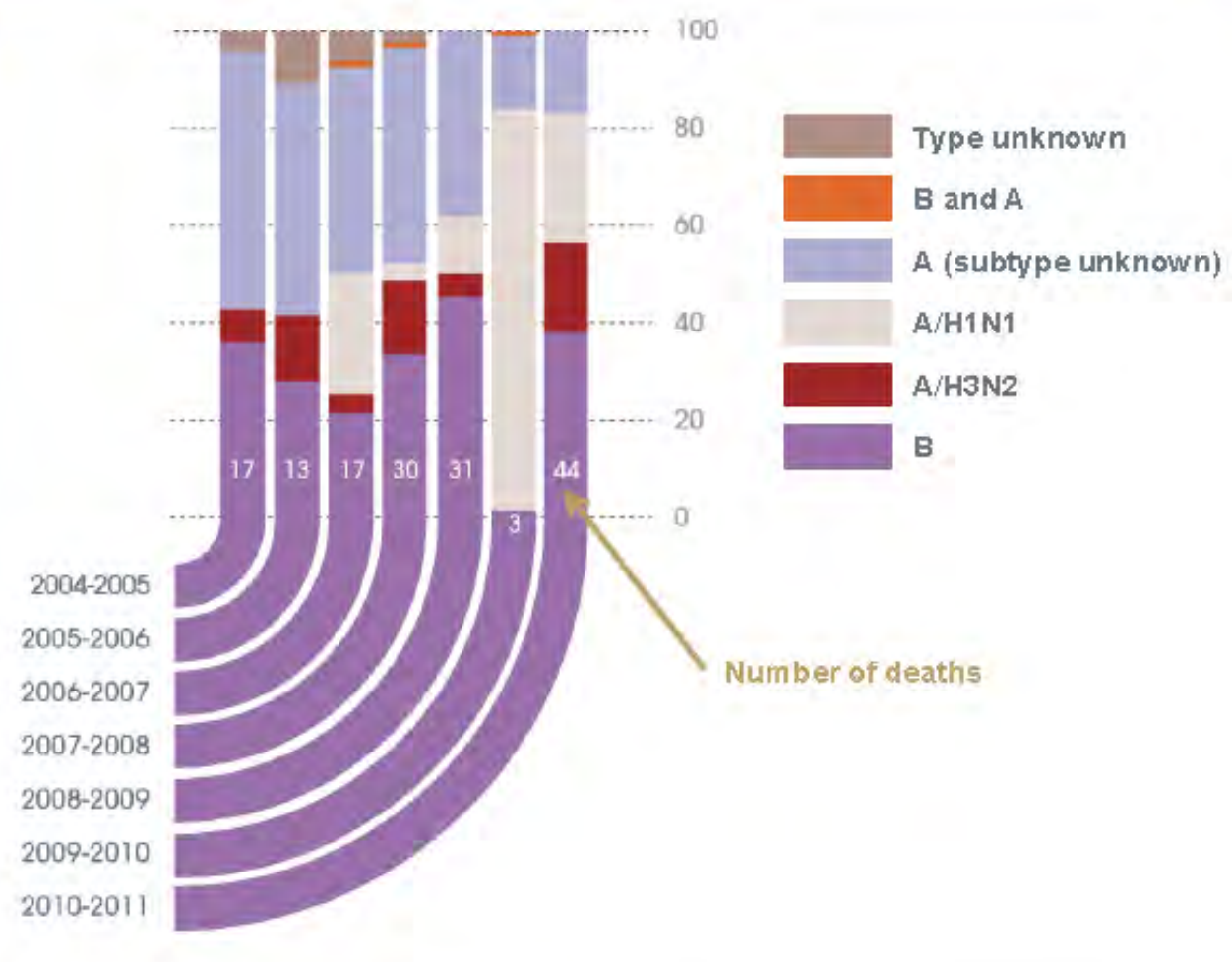
Burden of influenza B disease

- Influenza B represents ~25% of circulating strains
- Circulating B lineages may vary between countries in the same years & the same region (heterogeneity)
- Influenza B causes epidemics every 2-4 years
- What about hospitalisation & mortality?

Influenza B as a cause of US pediatric deaths – 2004-2011

Disproportionate mortality

- With the exception of the 2009–2010 pandemic, influenza B was responsible for **22–44%** of reported influenza deaths in children 0–18 y of age each season.
- Overall, during this period, influenza B was responsible for **34%** of reported pediatric influenza deaths.
- Influenza B hospitalisation and mortality lower than A/H3N2 but higher than A/H1N1 **(McCullers *et al.* 2012 JID)**



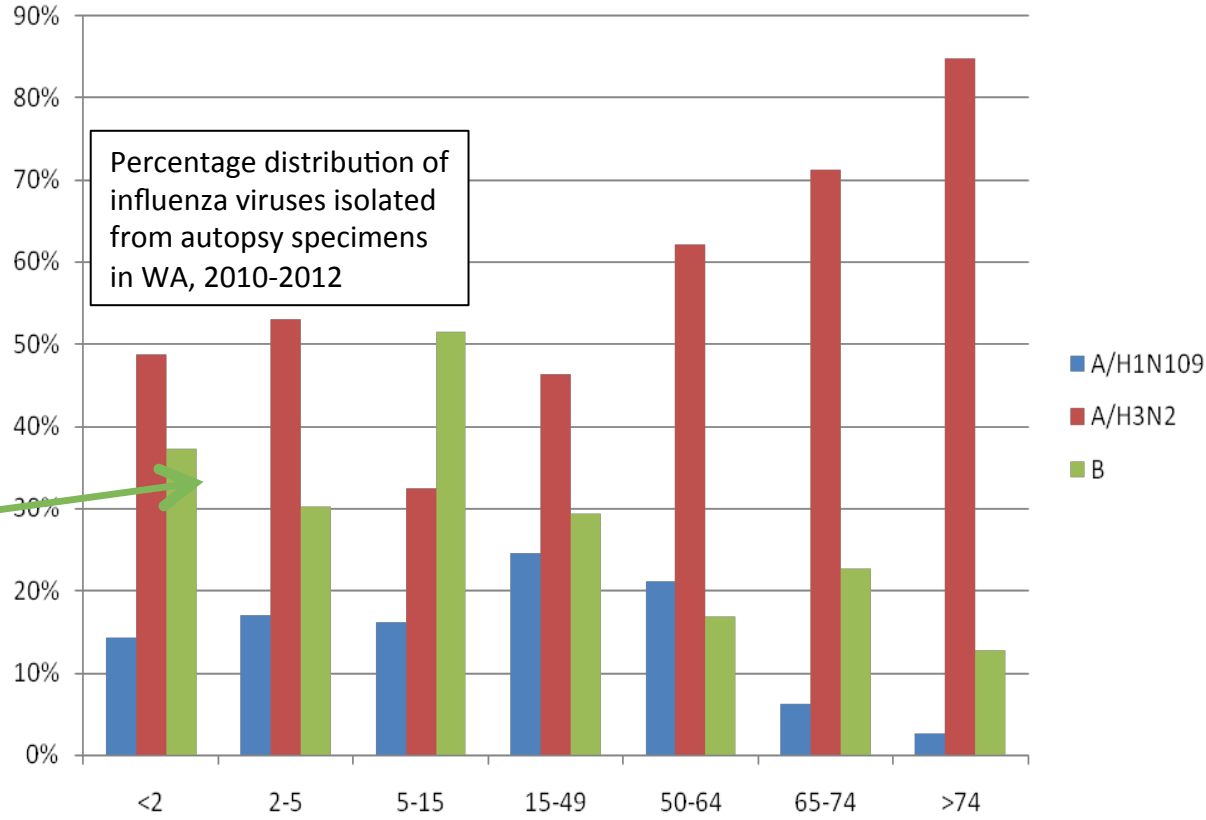
Ambrose CS, Levin MJ. Human Vaccines & Immunotherapeutics. 2012;8: 1-8. www.cdc.gov/flu/weekly/pastreports.htm

Burden of Influenza B disease

Western Australia

- 7/17 (41%) laboratory confirmed influenza-associated mortuary cases in 2012 involved influenza B
- 4/7 were children
- All had secondary bacterial infection

B deaths disproportionately high in children, esp <5 year olds

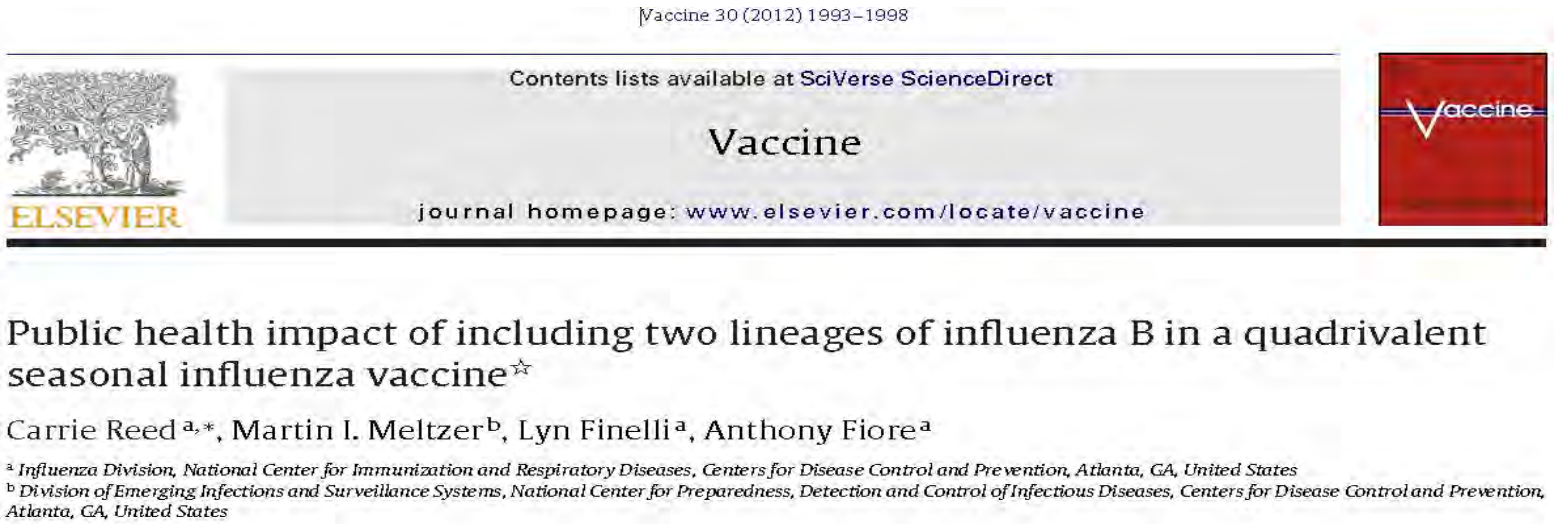


Source D Smith, A Levy, PathWest 2014

Public health considerations

- Will QIV reduce the number of influenza cases, hospitalisations deaths?

QIV public health benefits: US CDC model



Vaccine 30 (2012) 1993–1998

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Public health impact of including two lineages of influenza B in a quadrivalent seasonal influenza vaccine☆

Carrie Reed [a,*], Martin I. Meltzer [b], Lyn Finelli [a], Anthony Fiore [a]

[a] Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA, United States
[b] Division of Emerging Infections and Surveillance Systems, National Center for Preparedness, Detection and Control of Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA, United States

- A static model to estimate the public health impact that QIV would have had on influenza related health outcomes over 10 influenza seasons, if QIV had been used instead of TIV

Reed et al. Vaccine 2012;30:1993-98

QIV public health benefits: US CDC model

- Difference in influenza-related outcomes between the expected incidence with a QIV and the observed incidence with a TIV (excluding the impact of vaccine capacity reduction)

Season	% of B			Lineage included in TIV	Net outcomes averted QIV vs. TIV		
	Among all flu viruses	From Yam. lineage	From Vic. lineage		Cases	Hosp.	Deaths
2001-2002	13%	23%	77%	Yamagata	273,056	1412	137
2002-2003	43%	0.4%	99.6%	Victoria	**2242**	**14**	**1**
2003-2004	1%	93%	7%	Victoria	20,332	166	10
2004-2005	25%	74%	26%	Yamagata	327,902	2070	164
2005-2006	19%	22%	78%	Yamagata	348,894	2034	174
2006-2007	21%	24%	77%	Victoria	57,989	487	29
2007-2008	29%	98%	2%	Victoria	**1,325,828**	**12,472**	**663**
2008-2009	33%	17%	83%	Yamagata	385,332	2786	193

In bold: the min and max / In orange: seasons with a high percent circulation of B strains plus a high mismatch

QIV could have reduced the annual:

- cases (range: 2,242-1,325,828),
- hospitalisations (range: 14-12,472)
- deaths (range: 1-663) more than the current TIVs

Reed et al. Vaccine 2012;30:1993-98

Conclusions from CDC model

When TIV supply exceeds demand:

- The use of QIV is expected to result in an annual reduction in influenza-associated health outcomes when compared to TIV
- The potential net impact of QIV on influenza-associated outcomes is expected to vary between seasons, depending on annual variability in the incidence of influenza caused by the two influenza B lineages, vaccine coverage & effectiveness.
- The impact is expected to be greatest in years when influenza B strains are dominant & the B lineage is mismatched (for the TIV)

Reed et al. Vaccine 2012;30:1993-98

Circulating and vaccine influenza type B lineages in northern and southern hemisphere temperate/subtropical countries

Year	Vaccine lineage	% type B	Circulating lineage (%)		Degree of mismatch	% type B	Circulating lineage (%)		Degree of mismatch
			Victoria	Yamagata			Victoria	Yamagata	
Northern hemisphere countries			South Korea				Taiwan		
2007-08	Victoria	64.1	0	100	Complete	-	-	-	
2008-09	Yamagata	1.2	reported	Reported		-	-	-	
2009-10	Victoria	26.4	100	0		32	91	9	
2010-11	Victoria	0.9	reported	Reported		21	83	17	
2011-12	Victoria	48.5	73	27		76	14	86	Major
2012-13	Yamagata	5.6	65	35	Significant	2	13	87	
2013-14	Yamagata	53				25	81	19	Major
Southern hemisphere countries			Australia				New Zealand		
2005	Yamagata	23	51	49	Major	87	82	18	Major
2006	Victoria	35	94	6		1	60	40	
2007	Victoria	7	21	79	Major	23	1	99	Complete
2008	Yamagata	67	51	49	Major	58	77	23	Major
2009	Yamagata	1	-	-		0	0	0	
2010	Victoria	7	-	-		1	100	0	
2011	Victoria	38	-	-		50	98	2	
2012	Victoria	33	majority	-		14	16	84	Major
2013	Yamagata	37	7	93		40	1	99	

Mismatch years.

Low mismatch = <20% of circulating influenza type B strain was not the vaccine strain; **significant** mismatch >20-50%; **major** mismatch >50%; **complete** mismatch ≥95%
Shading indicates mismatch years

Jennings et al. A systematic review of the epidemiology and burden of Influenza B disease in 14 countries in the Asia-Pacific region. 2015

Circulating and vaccine influenza type B lineages in tropical countries

Year	Vaccine	Malaysia				Indonesia	Laos			Myanmar			Cambodia
	lineage	% type	Circulating lineage		Degree of mismatch	Circulating lineage	% type	Circulating lineage	Degree of mismatch	% type	Circulating lineage	% type	Circulating lineage
		B	Victoria	Yamagata			B	Victoria		B	Victoria	B	Victoria
2005	Yamagata	51	99%	1%	Complete	Predominant	-	-		42	Majority	-	-
2005-06	Yamagata												
2006	Victoria	43	94%	6%		Predominant	-	-		100	-	-	-
2006-07	Victoria												
2007	Victoria	30	27%	73%	Major	Predominant	-	-		67	Majority	-	-
2007-08	Victoria												
2008	Yamagata	18	0%	100%		-	66.7	-		-	-	-	-
2008-09	Yamagata												
2009	Yamagata	22	97%	3%	Complete	-	2.7	100%	Complete	-	-	12.6	All
2009-10	Victoria												
2010	Victoria	-	-	-		-	33.7	Majority		-	-	23.1	All
2010-11	Victoria												
2011	Victoria	-	-	-		-	-	-		-	-	64.8	All
2011-12	Victoria												

Mismatch years.
Low mismatch = <20% of circulating influenza type B strain was not the vaccine strain;
significant mismatch >20-50%;
major mismatch >50%;
complete mismatch ≥95%
Shading indicates mismatch years

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Influenza-associated mortality by influenza virus type

Country	Study year	Population	Influenza cases N	Case fatality rate (%)		
				Influenza B	Influenza A	All Influenza
South Korea	2011-12	Patients with ILI presenting to ER	7213	0.64	0.03	0.36
	2011-12	Hospitalized adults	79	2.9	0	2.5
Taiwan	2010-11	Patients with pulmonary complications	1751	9.5	2.4	7.3
	2011-12	Suspected influenza with complications	1704	7.6	10	9
	1997-2007	Patients with CNS dysfunction	74	-	-	4
Malaysia	2002-07	Hospitalized children with influenza	132	-	-	2.3
Thailand	2009-10	Hospitalized children with LRTI	902	0.5	0	0.4
	2010-11	Adults ≥ 50 hospitalized with LRTI	255	-	-	2
Philippines	2008-09	Hospitalized children with severe CAP	12	-	33.3	-
Australia	2010-11	Hospitalized adults with influenza	598	-	-	3

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Age distribution of confirmed influenza B cases

Age group	% of all influenza B									
(years)	Korea	Singapore	Thailand	Thailand	Vietnam	Vietnam	Australia	PNG	Laos	Myanmar
	Hospitalized patients with influenza	Respiratory specimens (71% inpatients)	Hospitalized with LRTI	Hospitalized Patients with pneumonia	Patients with ILI	Patients with ILI	Notified influenza cases	Patients with ILI	Patients with ILI	Patients with ILI
<5	48.7	45.3	25.8	26	22	68 (0-15)	6.4	76	25.4	43.2
5-9	18.4	10.5	43.8 (5-17)	34.7 (5-17)	41.5 (5-14)	11.8 (15-24)	25 (5-14)	24 (>5)	34.8 (5-17)	32.6
10-19	5.0	8.2								13.8
20-49	7.7	36.0 (≥ 20)	12.5 (18-49)	18.7 (18-49)	17.4 (25-)	18.0 (25-64)	46 (15-50)		39.8 (18-64)	2.2 (20-59)
50-64	6.5		15.6	20.7 (≥50)			10			
≥ 65	13.1		12.5		1.7	1.8	13		0	0 (≥ 60)

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Summary

- Given that the co-circulation globally of both B-lineages and the lack of significant vaccine cross-protection, TIV does not consistently provide adequate protection against influenza B disease
- QIV is expected to avert a substantial number of cases, hospitalisations & deaths each year; more than the current TIV, especially in years when influenza B is dominant and the B-lineage miss-matched.
- QIV will improve public confidence in influenza vaccines by reducing vaccine miss-match
- Although data are limited, there is no reason why all at-risk groups in Asia should not benefit from QIV

Thank you