Dealing with the End of B/Yamagata Transmission

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Influenza B viruses

- **Circulate globally every year. Drift but no Shift**
- **Subdivided into two lineages; currently co-circulate annually. Difficult to predict which ones will circulate.**
  - B/Yamagata
  - B/Victoria
  - How much cross protection? Is this age specific?
- **On average, fewer severe complications and deaths than A (H3N2) virus**
  - Severe complications and deaths caused by influenza B do occur in all age groups
  - Children appear to have higher rates of infection

Options in an era of excess capacity
Option: Move forward on QIV

- **Pro**
  - Prevention or mitigation of some severe morbidity and mortality associated with influenza B
  - Public and provider enthusiasm for vaccine that might offer better prevention
  - Puts excess manufacturing capacity to potential public health benefit

- **Con**
  - Public health impact of adding 2nd B strain are modest, especially if predominant lineage matches
  - Increased costs
  - Immunogenicity data more difficult to interpret for B strains
  - More data needed

Table 2

Characteristics of influenza seasons and vaccine coverage [13,15]

Season	Influenza A			Influenza B			Vaccine coverage		B Lineage in TIV
	Total A	A H1N1	A H3N2	Total B	B Yamagata	B Victoria	Israel	Meuhedet, *n* (%)	
2014–2015	90.8%	6.4% of A	92.3% of A	9.2%	95.5% of B	4.5% of B	20.8%	200 218 (18%)	Yamagata
2015–2016	44.2%	98.4% of A	1.6% of A	57.1%	12.8% of B	87.2% of B	20.9%	190 415 (16.5%)	Yamagata
2016–2017	97.9%	0.2% of A	99.8% of A	2.1%	–	Majority	21.0%	192 799 (16.2%)	Victoria
2017–2018	30.6%	56.2% of A	43.8% of A	69.4%	98.7% of B	1.3% of B	20.0%	209 670 (17.3%)	Victoria

Shasha, D Clin Microbiol Infect. 2020 Jan;26(1):101-106

Original article

Quadrivalent versus trivalent influenza vaccine: clinical outcomes in two influenza seasons, historical cohort study

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ABSTRACT

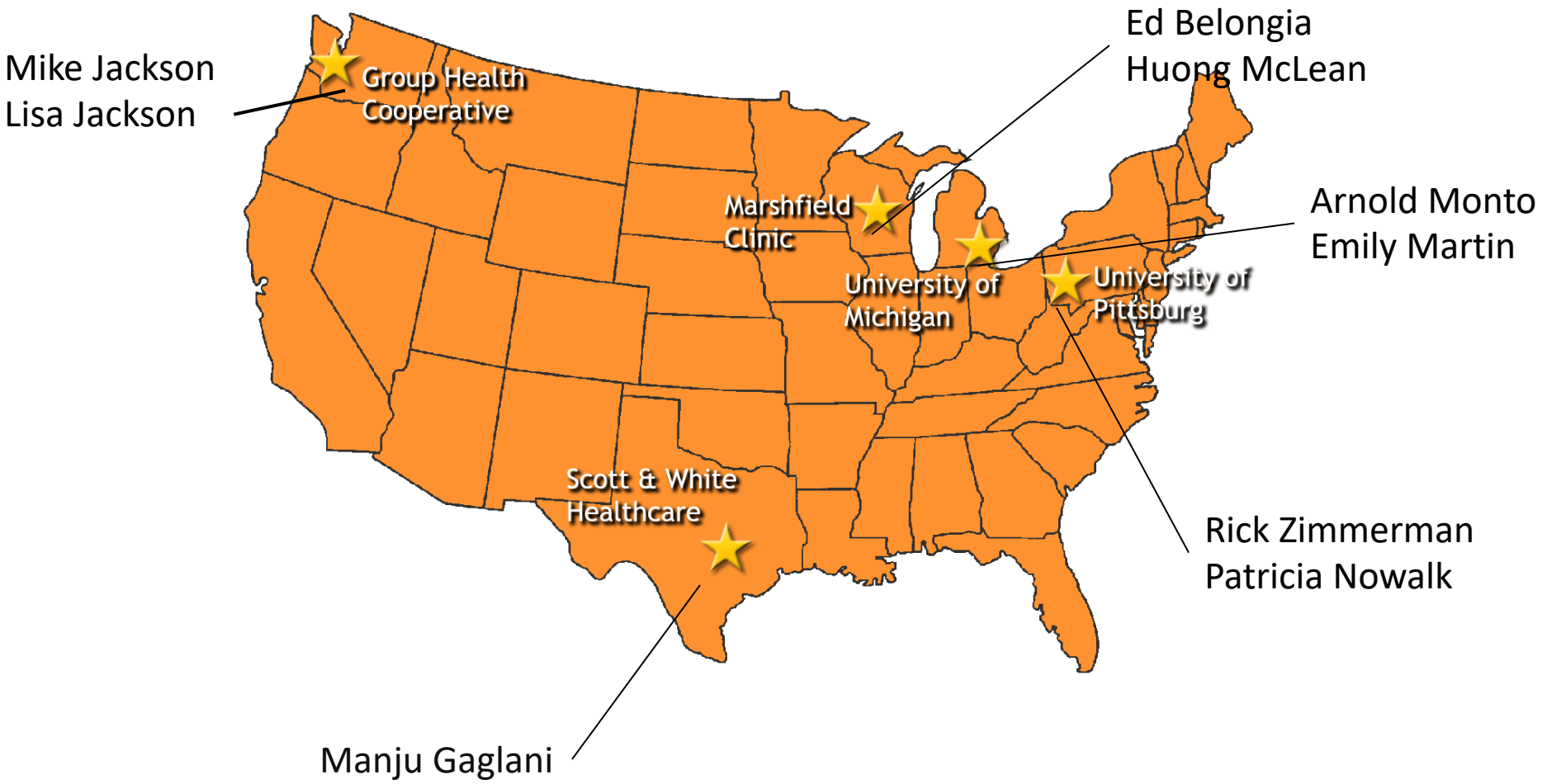
Objectives: The quadrivalent influenza vaccine (QIV) contains two influenza B antigens (one of each B lineage), while the trivalent vaccine (TIV) contains solely one. As a result, a mismatch between the circulating B lineage and the lineage in the TIV occurs frequently. We aimed to compare the frequency of clinically significant outcomes in a large cohort of vaccinees receiving either TIV or QIV.

Methods: Historical cohort study of all inactivated influenza vaccinees (aged 3 years and older) in a Health Maintenance Organization insuring 1.2 million individuals, over two influenza seasons in which both vaccines were provided non-selectively. Primary outcome was hospital admissions during the influenza season. Multivariate analysis was performed using logistic regression to adjust for relevant covariates.

Results: Our cohort included 150 518 and 168 296 vaccinees in the first (S1) and second season (S2), respectively. The two influenza seasons were characterized by high Influenza B activity. Of those vaccinated with QIV, 2074 of 49 726 (4.2%) and 6563 of 121 741 (5.4%) were hospitalized compared with 7378 of 100 792 (7.3%) and 3372 of 46 555 (7.2%) of those vaccinated with TIV (S1 and S2, respectively). After multivariate analysis adjusting for several covariates (gender, age, socioeconomic status, chronic morbidity, timing of vaccination), compared with TIV recipients, QIV vaccinees had lower odds for hospitalization (OR = 0.92, 95% CI 0.87–0.98 and OR = 0.89, 95% CI 0.85–0.93) or emergency department visit (OR = 0.91, 95% CI 0.87–0.95 and OR = 0.84, 95% CI 0.81–0.87) in S1 and S2, respectively ($p < 0.001$). Lower odds of mortality and influenza-like illness were also observed in S2 (OR = 0.61, 95% CI 0.50–0.75 and OR = 0.92, 95% CI 0.90–0.95, respectively).

Conclusions: In seasons with relatively high influenza B activity, QIV appeared more protective than TIV in Israel. **D. Shasha, Clin Microbiol Infect 2020;26:101**

US Flu VE Network: Five Study Sites and Principal Investigators



US Flu VE Network 2011-12 Season: Crude and Adjusted VE by Influenza Type for All Ages

	CASES Number Immunized /Total (%)	CONTROLS Number Immunized /Total (%)	Unadjusted		Adjusted [a]	
			VE %	(95% CI)	VE %	(95% CI)
Influenza A	178/550 (32%)	1983/4090 (48%)	49	(39-58)	44	(31-55)
A(H1N1)	23/110 (21%)	1983/4090 (48%)	72	(55-82)	65	(44-79)
A(H3N2)	155/440 (35%)	1983/4090 (48%)	42	(29-53)	39	(23-52)
Influenza B	35/131 (27%)	1983/4090 (48%)	61	(43-74)	58	(35-73)
Victoria	16/64 (25%)	1983/4090 (48%)	65	(37-80)	52	(8-75)
Yamagata	18/64 (28%)	1983/4090 (48%)	58	(28-76)	66	(38-81)

[a] Adjusted for study site, age in months (natural cubic splines), self-rated health status, high risk medical condition, and days between illness onset and respiratory specimen collection

Ohmit et al. *Clin Inf Dis 2014;58:319-27*

Clinical Infectious Diseases

MAJOR ARTICLE

Effectiveness of Trivalent and Quadrivalent Inactivated Vaccines Against Influenza B in the United States, 2011–2012 to 2016–2017

Manjusha Gaglani,[1] Anupama Vasudevan,[1] Chandni Raiyani,[1] Kempapura Murthy,[1] Wencong Chen,[1] Michael Reis,[1] Edward A. Belongia,[2] Huong Q. McLean,[2] Michael L. Jackson,[3] Lisa A. Jackson,[3] Richard K. Zimmerman,[4] Mary Patricia Nowalk,[4] Arnold S. Monto,[5] Emily T. Martin,[5] Jessie R. Chung,[6] Sarah Spencer,[6] Alicia M. Fry,[6] and Brendan Flannery[6]

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Background. Since 2013, quadrivalent influenza vaccines containing 2 B viruses gradually replaced trivalent vaccines in the United States. We compared the vaccine effectiveness of quadrivalent to trivalent inactivated vaccines (IIV4 to IIV3, respectively) against illness due to influenza B during the transition, when IIV4 use increased rapidly.

Methods. The US Influenza Vaccine Effectiveness (Flu VE) Network analyzed 25 019 of 42 600 outpatients aged ≥6 months who enrolled within 7 days of illness onset during 6 seasons from 2011–2012. Upper respiratory specimens were tested for the influenza virus type and B lineage. Using logistic regression, we estimated IIV4 or IIV3 effectiveness by comparing the odds of an influenza B infection overall and the odds of B lineage among vaccinated versus unvaccinated participants. Over 4 seasons from 2013–2014, we compared the relative odds of an influenza B infection among IIV4 versus IIV3 recipients.

Results. Trivalent vaccines included the predominantly circulating B lineage in 4 of 6 seasons. During 4 influenza seasons when both IIV4 and IIV3 were widely used, the overall effectiveness against any influenza B was 53% (95% confidence interval [CI], 45–59) for IIV4 versus 45% (95% CI, 34–54) for IIV3. IIV4 was more effective than IIV3 against the B lineage not included in IIV3, but comparative effectiveness against illnesses related to any influenza B favored neither vaccine valency.

Conclusions. The uptake of quadrivalent inactivated influenza vaccines was not associated with increased protection against any influenza B illness, despite the higher effectiveness of quadrivalent vaccines against the added B virus lineage. Public health impact and cost-benefit analyses are needed globally.

Keywords. quadrivalent; trivalent; inactivated influenza vaccine; effectiveness; influenza B lineage.

FOOD AND DRUG ADMINISTRATION (FDA)
Center for Biologics Evaluation and Research (CBER)
180th Meeting of the Vaccines and Related Biological Products Advisory Committee
Silver Spring, MD
March 7, 2023
AGENDA

Topic: The Committee will meet in open session to discuss and make recommendations on the selection of strains to be included in the influenza virus vaccines for the 2023 – 2024 influenza season.

Time	Presentation/Presenter
9:00am – 9:10am	**Opening Remarks: Call to Order and Welcome (5 Min)** Hana El Sahly, M.D. Chair, VRBPAC Professor, Department of Molecular Virology and Microbiology Baylor College of Medicine
9:10am – 9:30am	**Administrative Announcements, Roll Call, Introduction of Committee, Conflict of Interest Statement (20 Min)** Sussan Paydar, Ph.D. Designated Federal Officer, VRBPAC Division Of Scientific Advisors and Consultants, CBER, FDA
9:30am – 9:45am	**Introduction (15 min)** **Jerry Weir, Ph.D. (10 Min)** Director Division of Viral Products (DVP) Office of Vaccines Research and Review (OVRR) CBER, FDA Q & A: 5 min
9:45am – 10:10am	**U.S. Surveillance (25 Min)** **Lisa Grohskopf, M.D., M.P.H. (20 Min)** Medical Officer Epidemiology & Prevention Branch, Influenza Division Centers for Disease Control and Prevention (CDC) Q & A: 5 min

Discussion Summary: There was general agreement among the committee members that the data presented was informative and convincing for the need to change the H1 components and to maintain the currently recommended H3 and B Victoria vaccine components. Committee members discussed the recommendation for a B Yamagata component for a quadrivalent influenza vaccine due to the absence of detectable B Yamagata viruses worldwide over the past 3 years. The majority of the committee agreed with the WHO recommendation to continue to include such a component in quadrivalent vaccines for the current North Hemisphere 2023 – 2024 influenza season because of the uncertainty as to whether the B Yamagata virus lineage was truly extinct; however, committee members noted that this issue would require further discussion at future VRBPAC influenza strain composition meetings.

Medicines & Healthcare products Regulatory Agency

36th Meeting between WHO ERLs, CCs and influenza vaccine manufacturers

11 to 13 July 2023

America Square Conference Centre, 1 America Square, 17 Crosswall, London EC3N 2LB, United Kingdom;

with online option

Version 3 July 2023

Day 1, 11 July 2023 (9:30 – 18:00 UK time)		
Registration/join online platform from 9:00		
1. Welcome and Introductions		*9:30-9:40*
2. Approval of Agenda		*9:40-9:45*
3. Review of action points from last meeting (unless separate agenda item)	*Othmar Engelhardt*	*9:45-9:55*
SEASONAL INFLUENZA		
4. Review of influenza in the world	*CC London (Nicola Lewis), CC Atlanta (tbc), CC Beijing (tbc), CC Melbourne (Ian Barr), CC Tokyo (Shinji Watanabe)*	*9:55-11:10*
Coffee break		*11:10-11:40*
5. Seasonal candidate vaccine viruses	*NYMC (Doris Bucher), MHRA (tbc), Seqirus (Christine Wadey), CBER (tbc), China CDC (tbc), Sanofi (Ray Schwartz)*	*11:40-12:20*
6. Seasonal reagents	*MHRA, CBER, TGA, NIID (no presentations, Q&A only)*	*12:20-12:30*
7. Review of northern hemisphere 2022-2023 production campaign	*IFPMA (Lauren Parker)*	*12:30-13:00*

Food and Drug Administration (FDA)
Center for Biologics Evaluation and Research (CBER)
Office of Vaccines Research and Review
183rd Meeting of the Vaccines and Related Biological Products Advisory Committee
October 5, 2023
AGENDA

Topic: Strain Selection for the Influenza Virus Vaccines for the 2024 Southern Hemisphere Influenza Season

Time	Presentation/Presenter
8:30 a.m.	**Opening Remarks: Call to Order (10 Min)** • Hana El Sahly, M.D. Chair, VRBPAC Professor, Department of Molecular Virology and Microbiology Baylor College of Medicine **Administrative Announcements, Roll Call, Conflict of Interest Statement (20 Min)** • Sussan Paydar, Ph.D. Designated Federal Officer, VRBPAC Division Of Scientific Advisors and Consultants, CBER, FDA
9:00 a.m.	**Introduction – 2024 Southern Hemisphere Influenza Virus Vaccine Strain Selection (15 Min total)** • Jerry Weir, Ph.D. (10 Min) Director Division of Viral Products Office of Vaccines Research and Review (OVRR) CBER, FDA

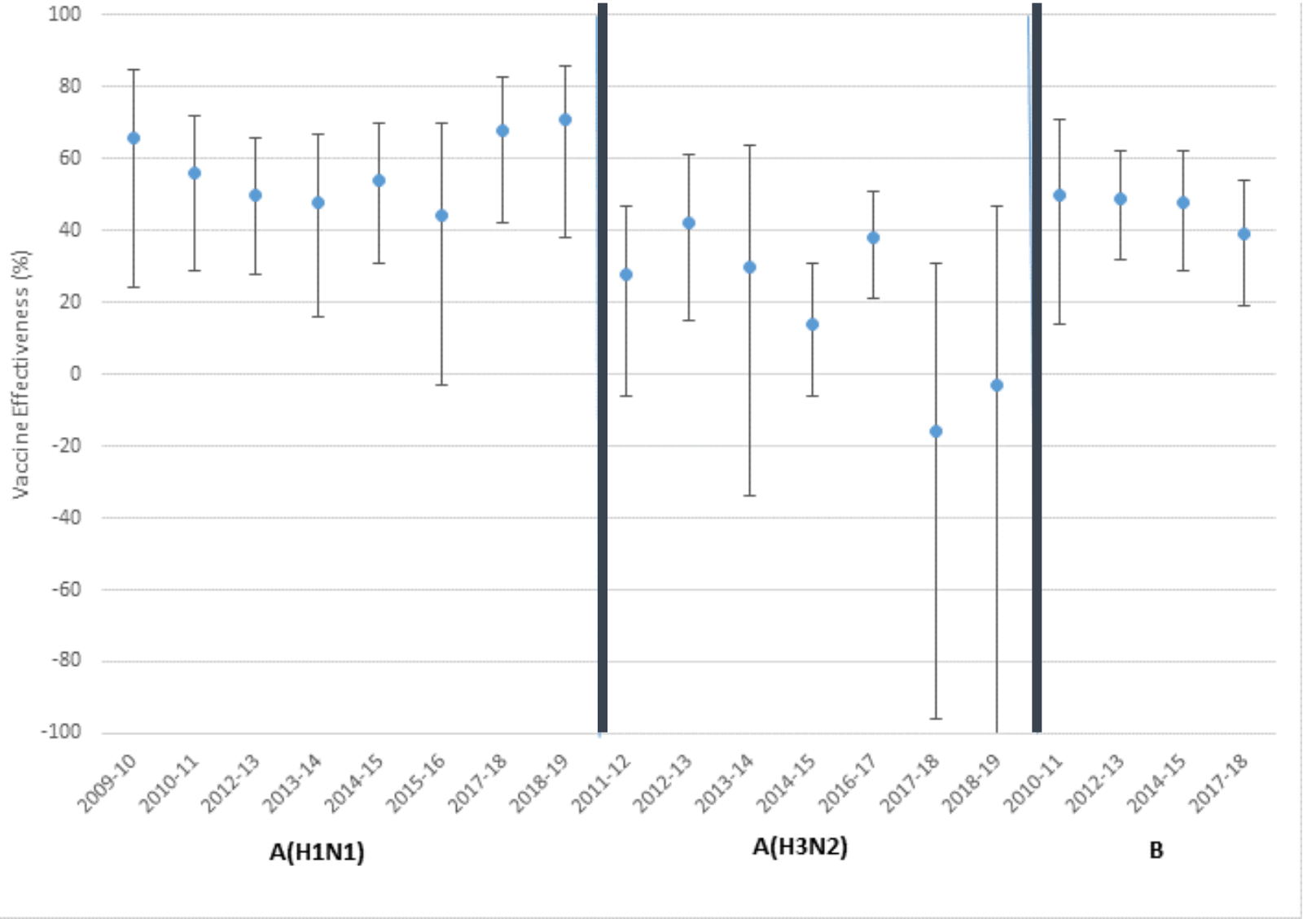
Voting Questions for the Committee

1. Does the committee recommend excluding the B/Yamagata lineage antigen component from quadrivalent influenza vaccines as soon as possible

2. For the composition of egg-based trivalent 2024 SH formulations of influenza vaccines, does the committee recommend:
   - Inclusion of an A/Victoria/4897/2022 (H1N1)pdm09-like virus;
   - Inclusion of an A/Thailand/8/2022 (H3N2)-like virus; and
   - Inclusion of a B/Austria/1359417/2021 (B/Victoria lineage)-like virus

3. For quadrivalent 2024 SH formulations of influenza vaccines, does the committee recommend:
   - Inclusion of a B/Phuket/3073/2013 (B/Yamagata lineage)-like virus as the 2nd influenza B strain in the vaccine

Influenza VE in Preventing Ambulatory Care Visits, I-MOVE 2009-19



Summary

- Historically, prediction of which B lineage was going to be prevalent was poor, and it was thought that vaccine protection might be sub-optimal with a lineage mis-match.
- Even then, there remained questions about how much need there was for a quadrivalent vaccine, especially given good VE, and the problems with H3N2.
- Once introduced, evidence for the need for the quadrivalent formulation has not been strong, although there are some supportive data. The need may only be in young children who have not had experience with both lineages.
- The view has been expressed that removal of the B/Yamagata component from the vaccine should be tied to a change in the formulation of the vaccine in general use. However, those formulations will be considered by regulators to be a new vaccine and have clinical data before approval.