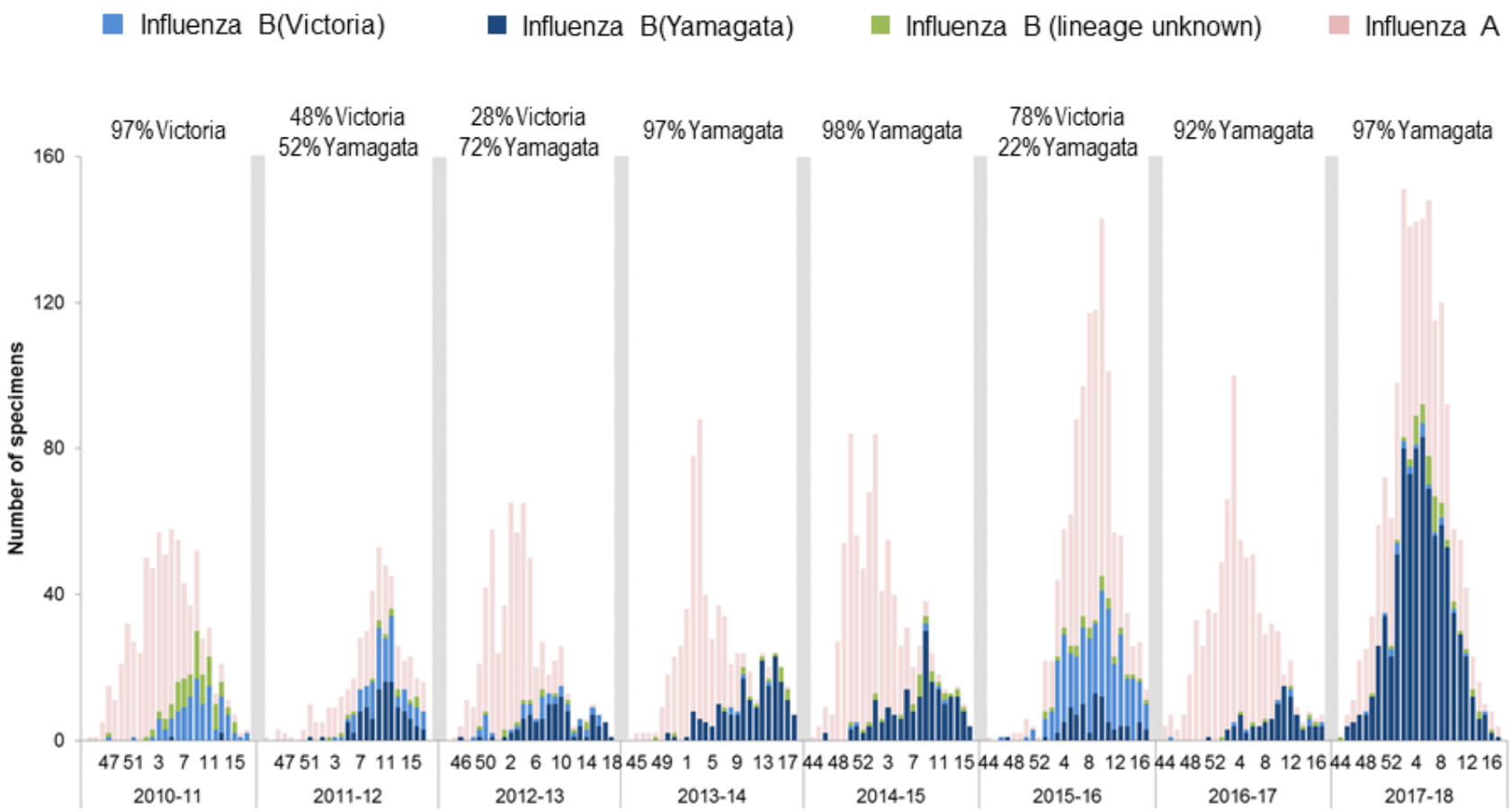
SUPPLEMENTARY MATERIAL

Additional References

Figure 1 Epidemic curves of influenza detection, October-April, by week and season[1]



[1] Influenza case detection by type (A or B) and influenza B lineage (Yamagata or Victoria) by week with overall percentage mix of lineages among characterized viruses that contributed to vaccine effectiveness (VE) analyses each season. The same inclusion/exclusion criteria were applied as for VE analyses, but spanning October to April. Details related to virological characterization are provided in **Supplement Table 1**.

Table 1. Virological diagnosis and characterization – methods and details

Influenza B was diagnosed by real-time reverse transcription polymerase chain reaction (rRT-PCR) at provincial public health reference laboratories in participating provinces of the Canadian Sentinel Practitioner Surveillance Network (SPSN), including Alberta, British Columbia, Ontario and Quebec [24-29]. As context for vaccine effectiveness (VE) estimates displayed in the current report, a subset of sentinel virus isolates was further characterized antigenically by hemagglutination inhibition (HI) assay at Canada's National Microbiology Laboratory (NML) using turkey erythrocytes and ferret anti-sera raised against egg- (until 2013-14) and/or cell-passaged (after 2013-14) versions of the vaccine reference strain [12, 24-29]. Influenza B lineage was determined by a combination of HI assay findings, RT-PCR-based methods[1,2] and, beginning in 2013-14, sequencing of the hemagglutinin (HA) gene from primary patient specimens.

Because only a subset (59%) of influenza B viruses were lineage-characterized in 2010-11, 97% of which were B(Victoria)-lineage [24], viruses of unknown lineage were re-classified as B(Victoria) and included in VE analysis that season. For all other seasons, most (>90%) of influenza B viruses were lineage-characterized and cases of alternate or unknown lineage were excluded from lineage-specific VE derivation.

Prior to 2013-14 the clade of circulating viruses by season was inferred from HI characterization of SPSN viruses using cell-culture isolates, turkey erythrocytes and post-infection ferret antisera raised against egg-passaged vaccine reference strains [24-26], and was further informed by national and global surveillance reports as indicated in **Table 1A** below. Beginning in 2013-14, genetic clade designation was based on phylogenetic analysis of viral HA sequencing data obtained directly from primary specimens provided by SPSN participants [associated Genbank accession numbers provided in **Table 1B** below].

Similar to influenza A vaccine strains of both subtypes [13-19], candidate influenza B vaccine strains of both lineages [18-23], can acquire *in vitro* mutations with adaptation for egg-based manufacturing, including loss of N-linked glycosylation sites that can variably affect their antigenicity and immunogenicity assessment [15, 17, 18-22].

Victoria lineage viruses detected by the SPSN between 2010-11 and 2012-13 that were characterized by HI assay at Canada's NML were considered antigenically related to the egg-passaged clade 1A vaccine reference strain [24-26]. Globally, circulating viruses of the Victoria lineage were also considered antigenically related to the cell-passaged clade 1A vaccine reference strain, but with more variable antigenic distinction in relation to the egg-adapted vaccine strain [18,19]. Prior to the 2015-16 season, Victoria clade 1A viruses sequenced by the SPSN had acquired I117V and N129D antigenic site substitutions, defining a major sub-cluster (along with V146I) within clade 1A. Relevance of these mutations is uncertain: characterized SPSN viruses were still considered antigenically similar to the cell-passaged vaccine reference virus but with more variability in relation to the egg-passaged vaccine virus [29]. Thereafter in 2016-17, viruses of the clade 1A group were shown elsewhere (notably the United States) to

[1] In 2012-13, the WHO one-step conventional RT-PCR protocol for the detection of influenza B lineage was used [WHO information for the molecular detection of influenza viruses, August 2011 version].
[2] In 2017-18, the United States Centers for Disease Control and Prevention RT-PCR protocol was used [US CDC Real-time RT-PCR (rRT-PCR) Protocol for Detection and Characterization of Influenza – B Genotyping, LP-339,R-0D].

have acquired a double amino acid deletion (Δ) in HA1 antigenic site positions 162-163 (Δ162-163) distinguishing them antigenically from the cell-passaged clade 1A vaccine reference virus [18, 19, 30]; however Victoria viruses did not contribute to lineage-specific VE analyses presented here for 2016-17 or 2017-18.

Yamagata lineage viruses detected by the SPSN and elsewhere during the study period clustered phylogenetically into clades 2 and 3. Many but not all anti-sera were able to antigenically differentiate viruses falling in the alternate clade. In general, anti-sera raised against clade 2 viruses better recognized clade 2 than clade 3 test viruses, and anti-sera raised against clade 3 viruses better recognized clade 3 viruses than did the anti-sera raised against clade 2 viruses. Yamagata clade 2 and clade 3 viruses can likely be considered antigenically distinct, but with some variation in cross-reactivity based on anti-sera used [18, 19].

We interpret VE findings foremost in the context of phylogenetic clade- and/or lineage-level relationship between vaccine and epidemic strains.

Table 1A Trivalent influenza vaccine (TIV) influenza B component and epidemic strain (lineage and clade) by season and scenario, with supporting documentation and details, Canadian Sentinel Practitioner Surveillance Network (SPSN), 2010-11 to 2017-18

Lineage-specific Scenario	Season [Reference]	TIV strain Lineage, Clade	Epidemic strain		
			Lineage (%)	Clade (%)	Supporting documentation and details[1]
1	**2010-11** [24]	Victoria Clade 1A[2]	97% Victoria	Clade 1A	Only a subset (59%) of influenza B viruses was lineage-level characterized, of which 97% were Victoria lineage. SPSN viruses of the Victoria lineage were characterized by hemagglutination inhibition (HI) assay as antigenically similar to egg-propagated B/Brisbane/60/2008, a clade 1A virus [24].
2	**2011-12** [25]	Victoria Clade 1A[2]	48% Victoria	Clade 1A	SPSN viruses of the Victoria lineage were characterized by HI assay as antigenically similar to egg-propagated B/Brisbane/60/2008, a clade 1A virus [25].
3			52% Yamagata	Clade 2/3	SPSN viruses belonging to the Yamagata lineage were characterized by HI assay as similar to egg-propagated B/Wisconsin/1/2010, a clade 3 virus; however, viruses belonging to clades 2 and 3 co-circulated globally with many but not all anti-sera able to antigenically differentiate viruses falling in the alternate clade [18, 19, 25].
4	**2012-13** [26]	Yamagata Clade 3[3]	28% Victoria	Clade 1A	SPSN viruses of the Victoria lineage were characterized by HI assay as antigenically similar to egg-propagated B/Brisbane/60/2008, a clade 1A virus [26].
5			72% Yamagata	Clade 2/3	SPSN viruses belonging to the Yamagata lineage that were characterized by HI assay were considered similar to egg-propagated B/Wisconsin/1/2010, a clade 3 virus. However, viruses belonging to clades 2 and 3 co-circulated globally with many but not all anti-sera able to antigenically differentiate viruses falling in the alternate clade [18, 19, 26].
6	**2013-14** [27]	Yamagata Clade 2[4]	97% Yamagata	82% Clade 3; 18% Clade 2	Per phylogenetic analysis of SPSN viruses [27]. A small proportion of clade 3 viruses bore an L172Q substitution, with few also bearing M251V, both in non-antigenic sites [27]. Among characterized SPSN viruses and more generally, anti-sera raised against clade 2 viruses better recognized clade 2 than clade 3 test viruses [18, 19, 27].
7	**2014-15** [28]	Yamagata Clade 2[4]	98% Yamagata	100% Clade 3	Per phylogenetic analysis of SPSN viruses [28]. Virtually all of the sequenced SPSN clade 3 viruses bore the L172Q substitution and a substantial proportion also bore M251V, both in non-antigenic sites and generally not considered to have conferred antigenic drift. SPSN viruses belonging to clade 3 that were HI-characterized were considered antigenically related to the cell-passaged clade 2 vaccine strain [28]. In general elsewhere, however, anti-sera raised against the clade 2 vaccine strain (cell- or egg-passaged) did not recognize clade 3 test viruses as well as anti-sera raised against a clade 3 reference strain (cell- or egg-passaged) [18, 19]. Clade 2 and clade 3 viruses can likely be considered antigenically distinct but with some variation in cross-reactivity based on anti-sera used [18, 19].
8	**2015-16** [29]	Yamagata Clade 3[5]	78% Victoria	100% Clade 1A	Per phylogenetic analysis of SPSN viruses [29]. Prior to the 2015-16 season, Victoria clade 1A viruses sequenced by the SPSN had acquired I117V and N129D antigenic site substitutions, defining a major sub-cluster (along with V146I). SPSN viruses were considered antigenically similar to the cell-passaged vaccine reference virus with more variability in relation to the egg-passaged vaccine virus [29]. Thereafter in 2016-17, clade 1A viruses were shown elsewhere (notably the United States) to have acquired a double amino acid deletion in HA1 antigenic sites 162-163 (Δ162-163) distinguishing them antigenically from the cell-passaged clade 1A vaccine reference virus [18, 19, 30]; however Victoria viruses did not contribute to lineage-specific VE analyses here for 2016-17 or 2017-18.
9			22% Yamagata	100% Clade 3	Per phylogenetic analysis of SPSN viruses [29]. All sequenced clade 3 SPSN viruses bore the L172Q substitution and 90% (64/71) also bore M251V, both in non-antigenic sites. Six of seven viruses without M251V fell within a sub-cluster defined by L172Q with 3 other antigenic site substitutions reported elsewhere to be associated with re-assorted B(Victoria) neuraminidase [18,19]. In general, clade 3 viruses characterized by the SPSN and elsewhere were not considered antigenically drifted in their HA [18, 19, 27].
10	**2016-17**	Victoria Clade 1A[2]	92% Yamagata	100% Clade 3	Per phylogenetic analysis of SPSN viruses. Virtually all sequenced SPSN clade 3 viruses fell in the major subgroup defined by L172Q and M251V non-antigenic site substitutions without conferring antigenic drift. In general, clade 3 viruses characterized by the SPSN and elsewhere were not considered antigenically drifted in their HA [18,19].
11	**2017-18**	Victoria Clade 1A[2]	97% Yamagata	100% Clade 3	Per phylogenetic analysis of SPSN viruses. All sequenced clade 3 viruses fell in the major subgroup defined by L172Q and M251V non-antigenic site substitutions. A subset bore other substitutions (e.g. V73M (120-loop) + Q122K (120-loop) + T181A in 11/194 (6%)). In general, clade 3 viruses characterized by the SPSN and elsewhere were not considered antigenically drifted in their HA [18,19].

[1] Sequencing of SPSN viruses was not undertaken prior to the 2013-14 season. Genbank accession numbers of sequences since 2013-14 are shown in **Table 1B** below.
[2] Throughout the study period (and since 2009-10), the World Health Organization (WHO) selected B/Brisbane/60/2008, a clade 1A virus, as the representative B(Victoria) vaccine strain [10].
[3] For the 2012-13 season, the WHO selected B/Wisconsin/1/2010, a clade 3 virus, as the representative B(Yamagata) TIV strain [10].
[4] For the 2013-14 and 2014-15 seasons, the WHO selected B/Massachusetts/2/2012, a clade 2 virus, as the representative B(Yamagata) TIV strain [10].
[5] For the 2015-16 season, the WHO selected B/Phuket/3073/2013, a clade 3 virus, as the representative B(Yamagata) TIV strain (i.e. same clade but different representative strain as in 2012-13 [10].

Table 1B Genbank accession numbers

Genbank accession numbers are specified below for SPSN viruses that were: sequenced to establish clade and/or lineage during the 2013-14 to 2017-18 seasons; were collected between the January and April study period each season; and contributed to vaccine effectiveness (VE) analyses presented in the current manuscript.

Case summary profiles are provided in **Supplement Tables 3f-j, 3l**

Season (Table)	Lineage	Number of cases in VE analyses, N	Sequence information unavailable or insufficient, N	VE study sequences deposited in Genbank, N	Genbank accession numbers, SPSN viruses	
					Range (N)	Sequences in the range that were deposited in Genbank but not included in VE analyses presented here[1] (N)
2013-14 (Table 3f)	Yamagata	186	22	164	KP864148-KP864310; MH613834-MH613836 (166)	KP864266, KP864273 (2)
2014-15 (Table 3g)	Yamagata	182	26	156	KU729495-KU729659 (165)	KU729512, KU729513, KU729527, KU729530, KU729539, KU729561, KU729581, KU729619, KU729627 (9)
2015-16 (Tables 3h, 3i)	Victoria	305	28	348	MF195744-MF196091 (348)	Not applicable
	Yamagata	85	14			
2016-17 (Table 3j)	Yamagata	94	2	92	MH216551-MH216662 (112)	MH216552, MH216558, MH216576, MH216577, MH216612, MH216613, MH216616, MH216617, MH216618, MH216620, MH216622, MH216623, MH216627, MH216629, MH216631, MH216632, MH216636, MH216642, MH216657, MH216659 (20)
2017-18 (Table 3l)	Yamagata[2]	718	1	194	MG910749-MG910761; MG910826-MG910870; MG910907-MG910945; MG910969-MG910975; MH603701-MH603806 (210)	MG910758; MG910829, MG910846; MG910922, MG910929, MG910937; MG910973; MH603711, MH603726, MH603731, MH603733, MH603742, MH603753, MH603781, MH603791, MH603803 (16)

[1] Specimens were collected outside the January to April vaccine effectiveness (VE) analysis period or did not meet other eligibility criteria specified for the current study.
[2] Given the number of detections, lineage was foremost determined by alternative (rRT-PCR or hemagglutination inhibition (HI) assay) methods.

Supplement 2 Influenza vaccine and vaccine effectiveness (VE) – methods and details

Influenza vaccines

Among participating provinces (Alberta, British Columbia (BC), Ontario and Quebec) of the Canadian Sentinel Practitioner Surveillance Network (SPSN), influenza vaccine was available free of charge across the study period (2010-11 to 2017-18) to all citizens ≥ 6 months of age in Alberta and Ontario. In BC and Quebec the vaccine was provided free of charge to individuals considered to be at high risk of serious influenza complications, as well as to their close contacts and care givers [24-29].

Most influenza vaccines used in SPSN provinces across the study period were split, unadjuvanted, inactivated formulations; however, other available vaccine products were subunit, including MF59-adjuvanted subunit vaccine for elderly adults ≥ 65-years-old, or live attenuated influenza vaccine (LAIV), primarily for children. Prior to 2014-15, only trivalent influenza vaccines (TIV) were authorized for use in Canada. Quadrivalent influenza vaccine (QIV) first became authorized for use in Canada in 2014-15 as LAIV and in 2015-16 as inactivated formulation, both primarily for children. As shown below in **Table 2A**, TIV comprised the majority (>70%) of all publicly funded influenza vaccine doses purchased for the annual influenza immunization campaign by SPSN provinces overall across the study period. However, in 2016-17 and 2017-18 most doses in Alberta were QIV (>75% and >95% of doses, respectively) while QIV remained limited (primarily for children) in the other SPSN provinces both seasons (<15% and <25% of doses, respectively).

Table 2A Proportion of publicly-funded influenza vaccine doses purchased that were TIV versus QIV, by SPSN province and season, 2014-15 to 2017-18[1]

SPSN Province, Season	SPSN provinces combined		Alberta		British Columbia		Ontario		Quebec	
	% TIV	% QIV	% TIV	% QIV	% TIV	% QIV	% TIV	% QIV	% TIV	% QIV
2010-11	100	0	100	0	100	0	100	0	100	0
2011-12	100	0	100	0	100	0	100	0	100	0
2012-13	100	0	100	0	100	0	100	0	100	0
2013-14	100	0	100	0	100	0	100	0	100	0
2014-15	96	4	91	9	96	4	100	0	94	6
2015-16	86	14	78	22	87	13	86	14	91	9
2016-17	77	23	21	79	86	14	86	14	91	9
2017-18	71	29	3	97	78	22	84	16	89	11

[1]Proportions are based upon influenza vaccine doses purchased for the publicly funded influenza immunization campaign which provides the vast majority of influenza vaccine doses administered each year in Canada. By way of illustration, vaccine purchase per capita for Canada through the publicly funded program corresponds well with other sources of immunization coverage data for Canada [31, 32], including the proportion self-reporting vaccination among test-negative controls displayed for the current study (in **Supplement Table 3**), each indicating that about 30-40% of the Canadian population (including across SPSN provinces) receive influenza vaccine annually. Information on privately purchased vaccines is not otherwise available but is not anticipated to much alter the above proportionate distributions. Although QIV was primarily targeted to children (except in the province of Alberta in 2016-17 and 2017-18), information is not available for TIV vs. QIV distribution by age and is summarized based on overall publicly-funded doses distributed.

Influenza vaccine manufacturing for Canada was egg-based throughout the study period. Vaccine strains recommended each season by the World Health Organization (WHO) as TIV and QIV components are displayed in **Table 2B** below, including cell-passaged prototype reference and egg-adapted high-growth reassortant (HGR) strains.

Table 2B Summary of influenza B cell-passaged prototype and egg-adapted high-growth reassortant (HGR) vaccine viruses recommended by the WHO, by season[1]

Season	Influenza B(Yamagata)		Influenza B(Victoria)	
	WHO-recommended	Egg-adapted HGR	WHO-recommended	Egg-adapted HGR
2009-10 [10]	—	—	**Brisbane/60/2008 (clade 1A)**	**Brisbane/60/2008 (clade 1A)**
2010-11 [10, 24]	—	—	**Brisbane/60/2008 (clade 1A)**	**Brisbane/60/2008 (clade 1A)**
2011-12 [10, 25]	—	—	**Brisbane/60/2008 (clade 1A)**	**Brisbane/60/2008 (clade 1A)**
2012-13 [10, 26]	**Wisconsin/1/2010 (clade 3)**	**Hubei-Wujiagang/158/2009 BX-39 (clade 3)**	Brisbane/60/2008 (clade 1A)	Brisbane/60/2008 (clade 1A)
2013-14 [10, 27]	**Massachusetts/2/2012 (clade 2)**	**Massachusetts/2/2012 BX-51B (clade 2)**	Brisbane/60/2008 (clade 1A)	Brisbane/60/2008 (clade 1A)
2014-15 [10, 28]	**Massachusetts/2/2012 (clade 2)**	**Massachusetts/2/2012 BX-51B (clade 2)**	Brisbane/60/2008 (clade 1A)	Brisbane/60/2008 (clade 1A)
2015-16 [10, 29]	**Phuket/3073/2013 (clade 3)**	**Phuket/3073/2013 (clade 3)**	Brisbane/60/2008 (clade 1A)	Brisbane/60/2008 (clade 1A)
2016-17 [10]	Phuket/3073/2013 (clade 3)	Phuket/3073/2013 (clade 3)	**Brisbane/60/2008 (clade 1A)**	**Brisbane/60/2008 (clade 1A)**
2017-18 [10]	Phuket/3073/2013 (clade 3)	Phuket/3073/2013 (clade 3)	**Brisbane/60/2008 (clade 1A)**	**Brisbane/60/2008 (clade 1A)**

[1] TIV components are displayed in unshaded cells and bold font. Grey shading indicates that the specified strain was included only as a component of QIV that season. "—" indicates no Yamagata-containing TIV or QIV was recommended that season.

Vaccine effectiveness (VE) estimation

Participants were outpatients ≥1-year-old presenting to community-based sentinel practitioner sites in Alberta, BC, Ontario and Quebec within 7 days of onset of influenza-like illness (ILI) with specimen collection between January and April each season. ILI was defined by fever and cough and one or more of sore throat, myalgia, arthralgia or prostration. After the 2010-11 season, fever was not required for elderly adults ≥65-years-old.

Patient data, including vaccination status, were recorded on the laboratory requisition questionnaire by the sentinel practitioner at the time of nasal/nasopharyngeal specimen collection, prior to influenza diagnosis. Vaccination status was based on patient (or guardian) report but may have also been documented in the physician's records. Patients were considered vaccinated if they received seasonal influenza vaccine ≥2 weeks before symptom onset. Age-appropriate one- or two-dose influenza vaccine receipt was not further queried for children.

Cases tested positive for the specified influenza B lineage; controls tested negative for any influenza virus. Odds ratios (ORs) for influenza test positivity (by influenza B lineage) comparing vaccinated to unvaccinated patients were derived using logistic regression according to a test-negative study design. VE was derived as (1 - OR) X 100%. Patients were excluded from VE analyses if their specimens were collected outside the January – April analysis period, if they were <1-year-old, did not meet the ILI case definition or presented > 7 days since ILI onset, were vaccinated <2 weeks before ILI onset or were missing vaccination status, timing or covariate information. Except where specifically indicated otherwise, all analyses were adjusted for the following covariates: age group (1-8; 9-19; 20-49; 50-64; ≥65 years), sex (male/female), comorbidity (yes/no), province (Alberta, British Columbia, Ontario, Quebec), specimen collection interval (0-4 or 5-7 days from ILI onset) and calendar time based on week of specimen collection (cubic B-spline with 3 equally spaced knots) or else month where specified.

Negative interference was explored during seasons for which the TIV component was unchanged and lineage- or clade-mismatched to circulating viruses (i.e. 2011-12, 2014-15 and 2017-18). These secondary VE analyses were additionally restricted to patients ≥9-years-old with complete information for both current and prior season's vaccination. To derive VE by current and/or prior season's vaccination, vaccine status was specified in the model as an indicator variable, classified into four mutually exclusive groups: (1) unvaccinated both seasons (reference); (2) vaccinated prior but not current season; (3) vaccinated current but not prior season; and (4) vaccinated both current and prior season. Odds ratios for lineage-specific influenza B illness for each of these vaccination subgroups were also separately derived relative to current season only vaccine recipients as the reference group. These secondary vaccination subgroup analyses were adjusted as for the primary VE analysis, except where otherwise specified, and with the same exclusion criteria but with patients <9-years-old and missing information for prior season's vaccination status additionally excluded.

Table 3a Participant profile by influenza B(Victoria) case status among Canadian Sentinel Practitioner Surveillance Network (SPSN) patients, 2010-11[1,2]

	Total N (column %)	Case status, n (column %)		
		Cases	Controls	p-value
N	879 (100)	190 (100)	689 (100)	
Age group (years)				
1-8	142 (16)	36 (19)	106 (15)	<0.01
9-19	155 (18)	71 (37)	84 (12)	
20-49	403 (46)	67 (35)	336 (49)	
50-64	138 (16)	11 (6)	127 (18)	
≥65	41 (5)	5 (3)	36 (5)	
Median (range)	29 (1-93)	17 (1-73)	33 (1-93)	<0.01
Female sex	514 (58)	105 (55)	409 (59)	0.31
Comorbidity	150 (17)	20 (11)	130 (19)	<0.01
Province				
Alberta	272 (31)	65 (34)	207 (30)	0.02
British Columbia	174 (20)	47 (25)	127 (18)	
Ontario	282 (32)	57 (30)	225 (33)	
Quebec	151 (17)	21 (11)	130 (19)	
Interval to specimen collection				
0-4 days	686 (78)	153 (81)	533 (77)	0.35
5-7 days	193 (22)	37 (19)	156 (23)	
Median (range)	3 (0-7)	3 (0-7)	3 (0-7)	0.50
Month of specimen collection				
January	233 (27)	20 (11)	213 (31)	<0.01
February	258 (29)	62 (33)	196 (28)	
March	283 (32)	89 (47)	194 (28)	
April	105 (12)	19 (10)	86 (12)	
Vaccinated the current season (≥2 weeks before ILI onset)[3]	201 (23)	28 (15)	173 (25)	<0.01
Also vaccinated the prior season[4]	144/187 (77)	17/26 (65)	127/161 (79)	0.13

[1] Analyses restricted to specimens collected from January to April each season.

[2] A subset only of 114/193 (59%) of influenza B viruses were lineage-level characterized in 2010-11, of which 111/114 (97%) meeting inclusion criteria for the current study were B(Victoria)-lineage [24]. Influenza B positive specimens of unknown lineage were therefore re-categorized as B(Victoria) that season. Influenza B positive specimens of the alternate lineage were excluded. Other virological details are provided in **Supplement Table 1**.

[3] Patients reporting current season's vaccination ≥2 weeks before influenza-like illness (ILI) onset were considered vaccinated; those with missing information for vaccination status or timing, or vaccinated <2 weeks before ILI onset were excluded from VE analyses.

[4] Among participants ≥1 year of age considered vaccinated the current season and with complete information for both current and prior season's vaccination, the number (%) also vaccinated the prior season.

Table 3b Participant profile by influenza B(Victoria) case status among Canadian Sentinel Practitioner Surveillance Network (SPSN) patients, 2011-12[1,2]

	Total N (column %)	Case status, n (column %)		
		Cases	Controls	p-value
N	768 (100)	100 (100)	668 (100)	
Age group (years)				
1-8	83 (11)	13 (13)	70 (10)	<0.01
9-19	116 (15)	30 (30)	86 (13)	
20-49	345 (45)	41 (41)	304 (46)	
50-64	145 (19)	12 (12)	133 (20)	
≥65	79 (10)	4 (4)	75 (11)	
Median (range)	34 (1-90)	23 (1-83)	37 (1-90)	<0.01
Female sex	434 (57)	47 (47)	387 (58)	0.04
Comorbidity	137 (18)	14 (14)	123 (18)	0.28
Province				
Alberta	121 (16)	4 (4)	117 (18)	<0.01
British Columbia	112 (15)	8 (8)	104 (16)	
Ontario	414 (54)	57 (57)	357 (53)	
Quebec	121 (16)	31 (31)	90 (13)	
Interval to specimen collection				
0-4 days	596 (78)	79 (79)	517 (77)	0.72
5-7 days	172 (22)	21 (21)	151 (23)	
Median (range)	3 (0-7)	3 (0-7)	3 (0-7)	0.50
Month of specimen collection				
January	222 (29)	3 (3)	219 (33)	<0.01
February	199 (26)	26 (26)	173 (26)	
March	209 (27)	51 (51)	158 (24)	
April	138 (18)	20 (20)	118 (18)	
Vaccinated the current season (≥2 weeks before ILI onset)[3]	221 (29)	10 (10)	211 (32)	<0.01
Also vaccinated the prior season[4]	173/213 (81)	9/10 (90)	164/203 (81)	0.69

[1] Analyses restricted to specimens collected from January to April each season.

[2] Most (207/223; 93%) influenza B viruses were lineage characterized in 2011-12, of which 100/207 (48%) meeting inclusion criteria for the current study were influenza B(Victoria)-lineage [25]. Influenza B positive specimens of the alternate or unknown lineage were excluded. Other virological details are provided in **Supplement Table 1**.

[3] Patients reporting current season's vaccination ≥2 weeks before influenza-like illness (ILI) onset were considered vaccinated; those with missing information for vaccination status or timing, or vaccinated <2 weeks before ILI onset were excluded from VE analyses.

[4] Among participants ≥1 year of age considered vaccinated the current season and with complete information for both current and prior season's vaccination, the number (%) also vaccinated the prior season.

Table 3c Participant profile by influenza B(Yamagata) case status among Canadian Sentinel Practitioner Surveillance Network (SPSN) patients, 2011-12[1,2]

	Total N (column %)	Case status, n (column %)		
		Cases	Controls	p-value
N	775 (100)	107 (100)	668 (100)	
Age group (years)				
1-8	80 (10)	10 (9)	70 (10)	0.07
9-19	110 (14)	24 (22)	86 (13)	
20-49	345 (45)	41 (38)	304 (46)	
50-64	157 (20)	24 (22)	133 (20)	
≥65	83 (11)	8 (7)	75 (11)	
Median (range)	37 (1-90)	40 (3-81)	37 (1-90)	0.88
Female sex	445 (57)	58 (54)	387 (58)	0.47
Comorbidity	134 (17)	11 (10)	123 (18)	0.04
Province				
Alberta	121 (16)	4 (4)	117 (18)	<0.01
British Columbia	109 (14)	5 (5)	104 (16)	
Ontario	453 (58)	96 (90)	357 (53)	
Quebec	92 (12)	2 (2)	90 (13)	
Interval to specimen collection				
0-4 days	599 (77)	82 (77)	517 (77)	0.86
5-7 days	176 (23)	25 (23)	151 (23)	
Median (range)	3 (0-7)	3 (0-7)	3 (0-7)	0.49
Month of specimen collection				
January	223 (29)	4 (4)	219 (33)	<0.01
February	199 (26)	26 (24)	173 (26)	
March	214 (28)	56 (52)	158 (24)	
April	139 (18)	21 (20)	118 (18)	
Vaccinated the current season (≥2 weeks before ILI onset)[3]	238 (31)	27 (25)	211 (32)	0.19
Also vaccinated the prior season[4]	181/226 (80)	17/23 (74)	164/203 (81)	0.42

[1] Analyses restricted to specimens collected from January to April each season.

[2] Most (207/223; 93%) influenza B viruses were lineage characterized in 2011-12, of which 107/207 (52%) meeting inclusion criteria for the current study were influenza B(Yamagata)-lineage [25]. Influenza B positive specimens of the alternate or unknown lineage were excluded. Other virological details are provided in **Supplement Table 1**.

[3] Patients reporting current season's vaccination ≥2 weeks before influenza-like illness (ILI) onset were considered vaccinated; those with missing information for vaccination status or timing, or vaccinated <2 weeks before ILI onset were excluded from VE analyses.

[4] Among participants ≥1 year of age considered vaccinated the current season and with complete information for both current and prior season's vaccination, the number (%) also vaccinated the prior season.

Table 3d Participant profile by influenza B(Victoria) case status among Canadian Sentinel Practitioner Surveillance Network (SPSN) patients, 2012-13[1,2]

	Total N (column %)	Case status, n (column %)		
		Cases	Controls	p-value
N	647 (100)	36 (100)	611 (100)	
Age group (years)				
1-8	61 (9)	2 (6)	59 (10)	<0.01
9-19	69 (11)	11 (31)	58 (9)	
20-49	319 (49)	17 (47)	302 (49)	
50-64	121 (19)	2 (6)	119 (19)	
≥65	77 (12)	4 (11)	73 (12)	
Median (range)	37 (1-95)	25.5 (7-71)	38 (1-95)	<0.01
Female sex	383 (59)	22 (61)	361 (59)	0.81
Comorbidity	139 (21)	4 (11)	135 (22)	0.12
Province				
Alberta	220 (34)	16 (44)	204 (33)	0.01
British Columbia	154 (24)	14 (39)	140 (23)	
Ontario	179 (28)	3 (8)	176 (29)	
Quebec	94 (15)	3 (8)	91 (15)	
Interval to specimen collection				
0-4 days	469 (72)	26 (72)	443 (73)	0.97
5-7 days	178 (28)	10 (28)	168 (27)	
Median (range)	3 (0-7)	3 (0-7)	3 (0-7)	0.75
Month of specimen collection				
January	254 (39)	9 (25)	245 (40)	0.32
February	176 (27)	12 (33)	164 (27)	
March	128 (20)	8 (22)	120 (20)	
April	89 (14)	7 (19)	82 (13)	
Vaccinated the current season (≥2 weeks before ILI onset)[3]	188 (29)	4 (11)	184 (30)	0.01
Also vaccinated the prior season[4]	156/181 (86)	3/4 (75)	153/177 (86)	0.45

[1] Analyses restricted to specimens collected from January to April each season.

[2] Most (129/141; 91%) influenza B viruses were lineage characterized in 2012-13, of which 36/129 (28%) meeting inclusion criteria for the current study were influenza B(Victoria)-lineage [26]. Influenza B positive specimens of the alternate or unknown lineage were excluded. Other virological details are provided in **Supplement Table 1**.

[3] Patients reporting current season's vaccination ≥2 weeks before influenza-like illness (ILI) onset were considered vaccinated; those with missing information for vaccination status or timing, or vaccinated <2 weeks before ILI onset were excluded from VE analyses.

[4] Among participants ≥1 year of age considered vaccinated the current season and with complete information for both current and prior season's vaccination, the number (%) also vaccinated the prior season.

Table 3e Participant profile by influenza B(Yamagata) case status among Canadian Sentinel Practitioner Surveillance Network (SPSN) patients, 2012-13[1,2]

	Total N (column %)	Case status, n (column %)		
		Cases	Controls	p-value
N	704 (100)	93 (100)	611 (100)	
Age group (years)				
1-8	83 (12)	24 (26)	59 (10)	<0.01
9-19	78 (11)	20 (22)	58 (9)	
20-49	329 (47)	27 (29)	302 (49)	
50-64	138 (20)	19 (20)	119 (19)	
≥65	76 (11)	3 (3)	73 (12)	
Median (range)	37 (1-95)	28 (1-87)	38 (1-95)	<0.01
Female sex	402 (57)	41 (44)	361 (59)	<0.01
Comorbidity	148 (21)	13 (14)	135 (22)	0.07
Province				
Alberta	229 (33)	25 (27)	204 (33)	<0.01
British Columbia	154 (22)	14 (15)	140 (23)	
Ontario	201 (29)	25 (27)	176 (29)	
Quebec	120 (17)	29 (31)	91 (15)	
Interval to specimen collection				
0-4 days	513 (73)	70 (75)	443 (73)	0.58
5-7 days	191 (27)	23 (25)	168 (27)	
Median (range)	3 (0-7)	3 (0-7)	3 (0-7)	0.47
Month of specimen collection				
January	264 (38)	19 (20)	245 (40)	<0.01
February	194 (28)	30 (32)	164 (27)	
March	146 (21)	26 (28)	120 (20)	
April	100 (14)	18 (19)	82 (13)	
Vaccinated the current season (≥2 weeks before ILI onset)[3]	193 (27)	9 (10)	184 (30)	<0.01
Also vaccinated the prior season[4]	159/185 (86)	6/8 (75)	153/177 (86)	0.31

[1] Analyses restricted to specimens collected from January to April each season.

[2] Most (129/141; 91%) influenza B viruses were lineage characterized in 2012-13, of which 93/129 (72%) meeting inclusion criteria for the current study were influenza B(Victoria)-lineage [26]. Influenza B positive specimens of the alternate or unknown lineage were excluded. Other virological details are provided in **Supplement Table 1**.

[3] Patients reporting current season's vaccination ≥2 weeks before influenza-like illness (ILI) onset were considered vaccinated; those with missing information for vaccination status or timing, or vaccinated <2 weeks before ILI onset were excluded from VE analyses.

[4] Among participants ≥1 year of age considered vaccinated the current season and with complete information for both current and prior season's vaccination, the number (%) also vaccinated the prior season.

Table 3f Participant profile by influenza B(Yamagata) case status among Canadian Sentinel Practitioner Surveillance Network (SPSN) patients, 2013-14[1,2]

	Total N (column %)	Case status, n (column %)		
		Cases	Controls	p-value
N	946 (100)	186 (100)	760 (100)	
Age group (years)				
1-8	104 (11)	15 (8)	89 (12)	0.01
9-19	111 (12)	26 (14)	85 (11)	
20-49	439 (46)	76 (41)	363 (48)	
50-64	198 (21)	54 (29)	144 (19)	
≥65	94 (10)	15 (8)	79 (10)	
Median (range)	38 (1-94)	42.5 (2-81)	36 (1-94)	0.02
Female sex	574 (61)	105 (56)	469 (62)	0.19
Comorbidity	197 (21)	36 (19)	161 (21)	0.58
Province				
Alberta	245 (26)	15 (8)	230 (30)	<0.01
British Columbia	154 (16)	15 (8)	139 (18)	
Ontario	341 (36)	87 (47)	254 (33)	
Quebec	206 (22)	69 (37)	137 (18)	
Interval to specimen collection				
0-4 days	679 (72)	138 (74)	541 (71)	0.41
5-7 days	267 (28)	48 (26)	219 (29)	
Median (range)	3 (0-7)	4 (0-7)	3 (0-7)	0.78
Month of specimen collection				
January	329 (35)	23 (12)	306 (40)	<0.01
February	261 (28)	32 (17)	229 (30)	
March	188 (20)	61 (33)	127 (17)	
April	168 (18)	70 (38)	98 (13)	
Vaccinated the current season (≥2 weeks before ILI onset)[3]	313 (33)	31 (17)	282 (37)	<0.01
Also vaccinated the prior season[4]	240/294 (82)	29/31 (94)	211/263 (80)	0.07

[1] Analyses restricted to specimens collected from January to April each season.

[2] Most (191/206; 93%) influenza B viruses were lineage characterized in 2013-14, of which 186/191 (97%) meeting inclusion criteria for the current study were influenza B(Yamagata)-lineage [27]. Influenza B positive specimens of the alternate or unknown lineage were excluded. Other virological details are provided in **Supplement Table 1**.

[3] Patients reporting current season's vaccination ≥2 weeks before influenza-like illness (ILI) onset were considered vaccinated; those with missing information for vaccination status or timing, or vaccinated <2 weeks before ILI onset were excluded from VE analyses.

[4] Among participants ≥1 year of age considered vaccinated the current season and with complete information for both current and prior season's vaccination, the number (%) also vaccinated the prior season.

Table 3g Participant profile by influenza B(Yamagata) case status among Canadian Sentinel Practitioner Surveillance Network (SPSN) patients, 2014-15[1,2]

	Total N (column %)	Case status, n (column %)		
		Cases	Controls	p-value
N	1001 (100)	182 (100)	819 (100)	
Age group (years)				
1-8	111 (11)	15 (8)	96 (12)	0.08
9-19	116 (12)	21 (12)	95 (12)	
20-49	419 (42)	72 (40)	347 (42)	
50-64	243 (24)	58 (32)	185 (23)	
≥65	112 (11)	16 (9)	96 (12)	
Median (range)	39 (1-94)	43 (1-92)	38 (1-94)	0.02
Female sex	632 (63)	116 (64)	516 (63)	0.85
Comorbidity	223 (22)	31 (17)	192 (23)	0.06
Province				
Alberta	284 (28)	40 (22)	244 (30)	<0.01
British Columbia	147 (15)	12 (7)	135 (16)	
Ontario	357 (36)	49 (27)	308 (38)	
Quebec	213 (21)	81 (45)	132 (16)	
Interval to specimen collection				
0-4 days	719 (72)	139 (76)	580 (71)	0.13
5-7 days	282 (28)	43 (24)	239 (29)	
Median (range)	3 (0-7)	3 (0-7)	3 (0-7)	0.95
Month of specimen collection				
January	366 (37)	29 (16)	337 (41)	<0.01
February	269 (27)	35 (19)	234 (29)	
March	232 (23)	78 (43)	154 (19)	
April	134 (13)	40 (22)	94 (11)	
Vaccinated the current season (≥2 weeks before ILI onset)[3]	359 (36)	44 (24)	315 (38)	<0.01
Also vaccinated the prior season[4]	274/341 (80)	38/44 (86)	236/297 (79)	0.28

[1] Analyses restricted to specimens collected from January to April each season.

[2] Most (186/211; 88%) influenza B viruses were lineage characterized in 2014-15, of which 182/186 (98%) were B(Yamagata)-lineage [28]. Influenza B positive specimens of the alternate or unknown lineage were excluded. Other virological details are provided in **Supplement Table 1**.

[3] Patients reporting current season's vaccination ≥2 weeks before influenza-like illness (ILI) onset were considered vaccinated; those with missing information for vaccination status or timing, or vaccinated <2 weeks before ILI onset were excluded from VE analyses.

[4] Among participants ≥1 year of age considered vaccinated the current season and with complete information for both current and prior season's vaccination, the number (%) also vaccinated the prior season.

Table 3h Participant profile by influenza B(Victoria) case status among Canadian Sentinel Practitioner Surveillance Network (SPSN) patients, 2015-16[1,2]

	Total N (column %)	Case status, n (column %)		
		Cases	Controls	p-value
N	1234 (100)	305 (100)	929 (100)	
Age group (years)				
1-8	187 (15)	75 (25)	112 (12)	<0.01
9-19	195 (16)	79 (26)	116 (12)	
20-49	516 (42)	116 (38)	400 (43)	
50-64	211 (17)	21 (7)	190 (20)	
≥65	125 (10)	14 (5)	111 (12)	
Median (range)	32 (1-92)	19 (1-78)	37 (1-92)	<0.01
Female sex	778 (63)	175 (57)	603 (65)	0.02
Comorbidity	240 (19)	36 (12)	204 (22)	<0.01
Province				
Alberta	309 (25)	73 (24)	236 (25)	0.06
British Columbia	334 (27)	93 (30)	241 (26)	
Ontario	404 (33)	84 (28)	320 (34)	
Quebec	187 (15)	55 (18)	132 (14)	
Interval to specimen collection				
0-4 days	911 (74)	252 (83)	659 (71)	<0.01
5-7 days	323 (26)	53 (17)	270 (29)	
Median (range)	3 (0-7)	3 (0-7)	3 (0-7)	0.03
Month of specimen collection				
January	296 (24)	58 (19)	238 (26)	<0.01
February	369 (30)	80 (26)	289 (31)	
March	389 (32)	114 (37)	275 (30)	
April	180 (15)	53 (17)	127 (14)	
Vaccinated the current season (≥2 weeks before ILI onset)[3]	352 (29)	45 (15)	307 (33)	<0.01
Also vaccinated the prior season[4]	278/334 (83)	35/43 (81)	243/291 (84)	0.73

[1] Analyses restricted to specimens collected from January to April each season.

[2] Most (390/423; 92%) influenza B viruses were lineage characterized in 2015-16, of which 305/390 (78%) were B(Victoria)-lineage [29]. Influenza B positive specimens of the alternate or unknown lineage were excluded. Other virological details are provided in **Supplement Table 1**.

[3] Patients reporting current season's vaccination ≥2 weeks before influenza-like illness (ILI) onset were considered vaccinated; those with missing information for vaccination status or timing, or vaccinated <2 weeks before ILI onset were excluded from VE analyses.

[4] Among participants ≥1 year of age considered vaccinated the current season and with complete information for both current and prior season's vaccination, the number (%) also vaccinated the prior season.

Table 3i Participant profile by influenza B(Yamagata) case status among Canadian Sentinel Practitioner Surveillance Network (SPSN) patients, 2015-16[1,2]

	Total N (column %)	Case status, n (column %)		
		Cases	Controls	p-value
N	1014 (100)	85 (100)	929 (100)	
Age group (years)				
1-8	119 (12)	7 (8)	112 (12)	0.84
9-19	128 (13)	12 (14)	116 (12)	
20-49	438 (43)	38 (45)	400 (43)	
50-64	209 (21)	19 (22)	190 (20)	
≥65	120 (12)	9 (11)	111 (12)	
Median (range)	37 (1-92)	39 (2-92)	37 (1-92)	0.44
Female sex	655 (65)	52 (61)	603 (65)	0.49
Comorbidity	217 (21)	13 (15)	204 (22)	0.15
Province				
Alberta	242 (24)	6 (7)	236 (25)	<0.01
British Columbia	276 (27)	35 (41)	241 (26)	
Ontario	358 (35)	38 (45)	320 (34)	
Quebec	138 (14)	6 (7)	132 (14)	
Interval to specimen collection				
0-4 days	722 (71)	63 (74)	659 (71)	0.54
5-7 days	292 (29)	22 (26)	270 (29)	
Median (range)	3 (0-7)	3 (0-7)	3 (0-7)	0.64
Month of specimen collection				
January	246 (24)	8 (9)	238 (26)	<0.01
February	319 (31)	30 (35)	289 (31)	
March	309 (30)	34 (40)	275 (30)	
April	140 (14)	13 (15)	127 (14)	
Vaccinated the current season (≥2 weeks before ILI onset)[3]	324 (32)	17 (20)	307 (33)	0.01
Also vaccinated the prior season[4]	256/306 (84)	13/15 (87)	243/291 (84)	1.00

[1] Analyses restricted to specimens collected from January to April each season.

[2] Most (390/423; 92%) influenza B viruses were lineage characterized in 2015-16, of which 85/390 (22%) were B(Yamagata)-lineage [29]. Influenza B positive specimens of the alternate or unknown lineage were excluded. Other virological details are provided in **Supplement Table 1**.

[3] Patients reporting current season's vaccination ≥2 weeks before influenza-like illness (ILI) onset were considered vaccinated; those with missing information for vaccination status or timing, or vaccinated <2 weeks before ILI onset were excluded from VE analyses.

[4] Among participants ≥1 year of age considered vaccinated the current season and with complete information for both current and prior season's vaccination, the number (%) also vaccinated the prior season.

Table 3j Participant profile by influenza B(Yamagata) case status among Canadian Sentinel Practitioner Surveillance Network (SPSN) patients, 2016-17[1,2]

	Total N (column %)	Case status, n (column %)		
		Cases	Controls	p-value
N	950 (100)	94 (100)	856 (100)	
Age group (years)				
1-8	112 (12)	7 (7)	105 (12)	0.05
9-19	96 (10)	14 (15)	82 (10)	
20-49	375 (39)	40 (43)	335 (39)	
50-64	222 (23)	26 (28)	196 (23)	
≥65	145 (15)	7 (7)	138 (16)	
Median (range)	41 (1-97)	42 (4-91)	41 (1-97)	0.85
Female sex	595 (63)	59 (63)	536 (63)	0.98
Comorbidity	240 (25)	18 (19)	222 (26)	0.15
Province				
Alberta	185 (19)	10 (11)	175 (20)	<0.01
British Columbia	318 (33)	50 (53)	268 (31)	
Ontario	315 (33)	26 (28)	289 (34)	
Quebec	132 (14)	8 (9)	124 (14)	
Interval to specimen collection				
0-4 days	664 (70)	72 (77)	592 (69)	0.14
5-7 days	286 (30)	22 (23)	264 (31)	
Median (range)	3 (0-7)	4 (0-7)	3 (0-7)	0.92
Month of specimen collection				
January	335 (35)	16 (17)	319 (37)	<0.01
February	263 (28)	16 (17)	247 (29)	
March	252 (27)	47 (50)	205 (24)	
April	100 (11)	15 (16)	85 (10)	
Vaccinated the current season (≥2 weeks before ILI onset)[3]	334 (35)	15 (16)	319 (37)	<0.01
Also vaccinated the prior season[4]	272/317 (86)	12/14 (86)	260/303 (86)	1.00

[1] Analyses restricted to specimens collected from January to April each season.

[2] Most (102/110; 93%) influenza B viruses were lineage characterized in 2016-17, of which 94/102 (92%) were B(Yamagata)-lineage. Influenza B positive specimens of the alternate or unknown lineage were excluded. Other virological details are provided in **Supplement Table 1**.

[3] Patients reporting current season's vaccination ≥2 weeks before influenza-like illness (ILI) onset were considered vaccinated; those with missing information for vaccination status or timing, or vaccinated <2 weeks before ILI onset were excluded from VE analyses.

[4] Among participants ≥1 year of age considered vaccinated the current season and with complete information for both current and prior season's vaccination, the number (%) also vaccinated the prior season.

Table 3k Participant profile by influenza B(Yamagata) case status among Canadian Sentinel Practitioner Surveillance Network (SPSN) patients, 2016-17[1,2] EXCLUDING ALBERTA

	Total N (column %)	Case status, n (column %)		
		Cases	Controls	p-value
N	765 (100)	84 (100)	681 (100)	
Age group (years)				
1-8	99 (13)	7 (8)	92 (14)	0.14
9-19	78 (10)	11 (13)	67 (10)	
20-49	292 (38)	35 (42)	257 (38)	
50-64	178 (23)	24 (29)	154 (23)	
≥65	118 (15)	7 (8)	111 (16)	
Median (range)	41 (1-97)	42.5 (4-91)	41 (1-97)	0.63
Female sex	473 (62)	53 (63)	420 (62)	0.80
Comorbidity	185 (24)	16 (19)	169 (25)	0.24
Province				
British Columbia	318 (42)	50 (60)	268 (39)	<0.01
Ontario	315 (41)	26 (31)	289 (42)	
Quebec	132 (17)	8 (10)	124 (18)	
Interval to specimen collection				
0-4 days	533 (70)	65 (77)	468 (69)	0.10
5-7 days	232 (30)	19 (23)	213 (31)	
Median (range)	3 (0-7)	3 (0-7)	3 (0-7)	0.54
Month of specimen collection				
January	263 (34)	16 (19)	247 (36)	<0.01
February	216 (28)	15 (18)	201 (30)	
March	203 (27)	41 (49)	162 (24)	
April	83 (11)	12 (14)	71 (10)	
Vaccinated the current season (≥2 weeks before ILI onset)[3]	262 (34)	14 (17)	248 (36)	<0.01
Also vaccinated the prior season[4]	217/250 (87)	11/13 (85)	206/237 (87)	0.68

[1] Analyses restricted to specimens collected from January to April each season.

[2] In sensitivity analyses, cross-lineage VE was assessed excluding the province of Alberta where a greater proportion of influenza vaccine doses distributed through the public immunization program were the quadrivalent formulation that season. Excluding Alberta, most (90/98; 92%) influenza B viruses were lineage characterized in 2016-17, of which 84/90 (93%) were B(Yamagata)-lineage. Influenza B positive specimens of the alternate or unknown lineage were excluded. Other virological details are provided in **Supplement Table 1**.

[3] Patients reporting current season's vaccination ≥2 weeks before influenza-like illness (ILI) onset were considered vaccinated; those with missing information for vaccination status or timing, or vaccinated <2 weeks before ILI onset were excluded from VE analyses.

[4] Among participants ≥1 year of age considered vaccinated the current season and with complete information for both current and prior season's vaccination, the number (%) also vaccinated the prior season.

Table 3l Participant profile by influenza B(Yamagata) case status among Canadian Sentinel Practitioner Surveillance Network (SPSN) patients, 2017-18[1,2]

	Total N (column %)	Case status, n (column %)		
		Cases	Controls	p-value
N	1969	718	1251	
Age group (years)				
1-8	151 (8)	54 (8)	97 (8)	<0.01
9-19	223 (11)	92 (13)	131 (10)	
20-49	812 (41)	253 (35)	559 (45)	
50-64	485 (25)	217 (30)	268 (21)	
≥65	298 (15)	102 (14)	196 (16)	
Median (range)	43 (1-96)	46 (1-93)	41 (1-96)	0.02
Female sex	1200 (61)	439 (61)	761 (61)	0.89
Comorbidity	460 (23)	133 (19)	327 (26)	<0.01
Province				
Alberta	336 (17)	77 (11)	259 (21)	<0.01
British Columbia	493 (25)	178 (25)	315 (25)	
Ontario	787 (40)	300 (42)	487 (39)	
Quebec	353 (18)	163 (23)	190 (15)	
Interval to specimen collection				
0-4 days	1384 (70)	514 (72)	870 (70)	0.34
5-7 days	585 (30)	204 (28)	381 (30)	
Median (range)	3 (0-7)	4 (0-7)	3 (0-7)	0.15
Month of specimen collection				
January	843 (43)	333 (46)	510 (41)	<0.01
February	591 (30)	253 (35)	338 (27)	
March	386 (20)	116 (16)	270 (22)	
April	149 (8)	16 (2)	133 (11)	
Vaccinated the current season (≥2 weeks before ILI onset)[3]	622 (32)	176 (25)	446 (36)	<0.01
Also vaccinated the prior season[4]	500/586 (85)	144/172 (84)	356/414 (86)	0.48

[1] Analyses restricted to specimens collected from January to April each season.

[2] Most (737/787; 94%) influenza B viruses were lineage characterized in 2017-18, of which 718/737 (97%) were B(Yamagata)-lineage. Influenza B positive specimens of the alternate or unknown lineage were excluded. Other virological details are provided in **Supplement Table 1**.

[3] Patients reporting current season's vaccination ≥2 weeks before influenza-like illness (ILI) onset were considered vaccinated; those with missing information for vaccination status or timing, or vaccinated <2 weeks before ILI onset were excluded from VE analyses.

[4] Among participants ≥1 year of age considered vaccinated the current season and with complete information for both current and prior season's vaccination, the number (%) also vaccinated the prior season.

Table 3m Participant profile by influenza B(Yamagata) case status among Canadian Sentinel Practitioner Surveillance Network (SPSN) patients, 2017-18[1,2] EXCLUDING ALBERTA

	Total N (column %)	Case status, n (column %)		
		Cases	Controls	p-value
N	1633	641	992	
Age group (years)				
1-8	125 (8)	50 (8)	75 (8)	<0.01
9-19	200 (12)	87 (14)	113 (11)	
20-49	663 (41)	228 (36)	435 (44)	
50-64	385 (24)	182 (28)	203 (20)	
≥65	260 (16)	94 (15)	166 (17)	
Median (range)	42 (1-96)	45 (1-93)	40 (1-96)	0.11
Female sex	1009 (62)	402 (63)	607 (61)	0.54
Comorbidity	373 (23)	115 (18)	258 (26)	<0.01
Province				
British Columbia	493 (30)	178 (28)	315 (32)	<0.01
Ontario	787 (48)	300 (47)	487 (49)	
Quebec	353 (22)	163 (25)	190 (19)	
Interval to specimen collection				
0-4 days	1140 (70)	461 (72)	679 (68)	0.14
5-7 days	493 (30)	180 (28)	313 (32)	
Median (range)	4 (0-7)	4 (0-7)	3 (0-7)	0.39
Month of specimen collection				
January	700 (43)	291 (45)	409 (41)	<0.01
February	489 (30)	231 (36)	258 (26)	
March	326 (20)	105 (16)	221 (22)	
April	118 (7)	14 (2)	104 (10)	
Vaccinated the current season (≥2 weeks before ILI onset)[3]	503 (31)	157 (24)	346 (35)	<0.01
Also vaccinated the prior season[4]	395/471 (84)	128/154 (83)	267/317 (84)	0.76

[1] Analyses restricted to specimens collected from January to April each season.

[2] In sensitivity analyses, cross-lineage VE was assessed excluding the province of Alberta where a greater proportion of influenza vaccine doses distributed through the public immunization program were the quadrivalent formulation that season. Excluding Alberta, most (659/703; 94%) influenza B viruses were lineage characterized in 2017-18, of which 641/659 (97%) were B(Yamagata)-lineage. Influenza B positive specimens of the alternate or unknown lineage were excluded. Other virological details are provided in **Supplement Table 1**.

[3] Patients reporting current season's vaccination ≥2 weeks before influenza-like illness (ILI) onset were considered vaccinated; those with missing information for vaccination status or timing, or vaccinated <2 weeks before ILI onset were excluded from VE analyses.

[4] Among participants ≥1 year of age considered vaccinated the current season and with complete information for both current and prior season's vaccination, the number (%) also vaccinated the prior season.

Table 4 Lineage-specific influenza B vaccine effectiveness (VE) estimates, including trivalent influenza vaccine (TIV) component and epidemic strain (lineage and clade) by season and scenario, Canadian Sentinel Practitioner Surveillance Network (SPSN), 2010-11 to 2017-18

Lineage-specific Scenario	Season [Reference]	TIV strain Lineage, Clade	Epidemic strain Lineage, Clade[1]	Lineage-specific influenza B VE (%) and 95% confidence intervals[2]	
				Unadjusted	Adjusted[3]
1	**2010-11** [24]	Victoria Clade 1A	Victoria Clade 1A	48 (20-67)	51 (20-70)
2	**2011-12** [25]	Victoria Clade 1A	Victoria Clade 1A	76 (53-88)	70 (37-86)
3			Yamagata Clade 2/3	27 (-16-54)	21 (-40-55)
4	**2012-13** [26]	Yamagata Clade 3	Victoria Clade 1A	71 (17-90)	78 (23-94)
5			Yamagata Clade 2/3	75 (49-88)	68 (31-85)
6	**2013-14** [27]	Yamagata Clade 2	Yamagata Clade 2/3[4]	66 (49-78)	74 (57-84)
7	**2014-15** [28]	Yamagata Clade 2	Yamagata Clade 3	49 (26-65)	39 (4-61)
8	**2015-16** [29]	Yamagata Clade 3	Victoria Clade 1A	65 (50-75)	54 (32-68)
9			Yamagata Clade 3	49 (12-71)	55 (18-75)
10	**2016-17**	Victoria Clade 1A	Yamagata Clade 3	68 (44-82)	73 (48-86)
11	**2017-18**	Victoria Clade 1A	Yamagata Clade 3	41 (28-52)	39 (23-52)

[1] Only a subset (59%) of influenza B viruses were lineage-characterized in 2010-11 of which 97% were Victoria lineage; viruses of unknown lineage were re-classified as Victoria and included in VE analysis that season. For all other seasons, >90% of influenza B viruses were lineage-characterized, and those of the alternate or unknown lineage were excluded from lineage-specific VE derivation. Prior to the 2013-14 season, sequencing of the hemagglutinin gene was not routinely undertaken and lineage and clade designation were based on alternative methods. See **Supplement Table 1** for details related to virological characterization.

[2] Analyses restricted to specimens collected from January to April each season. Sample size each season displayed in **Supplement Table 3.** Differences in inclusion criteria, analysis period and other model specifications should be taken into account when comparing to prior publications of season-specific VE estimates for influenza B [24-29].

[3] Adjusted for age group (1-8; 9-19; 20-49; 50-64; ≥65 years), sex (male/female), comorbidity (yes/no), province (Alberta, British Columbia, Ontario, Quebec), specimen collection interval (0-4 or 5-7 days from influenza-like illness (ILI) onset) and week of specimen collection (cubic B-spline with 3 equally spaced knots).

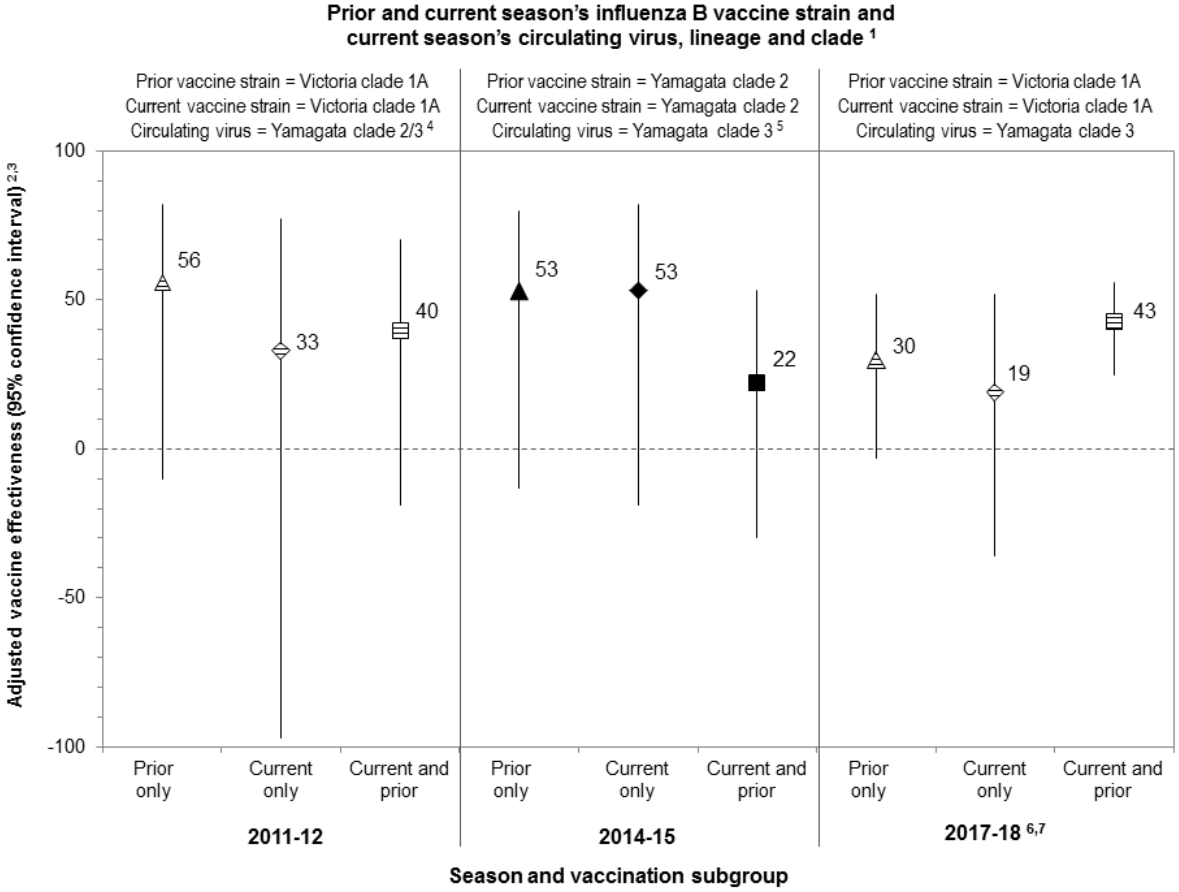
[4] In 2013-14, among Yamagata viruses that were sequenced 134/164 (82%) were clade 3 and 30/164 (18%) were clade 2. Yamagata clade 2 and clade 3 viruses can likely be considered antigenically distinct but with some variation in cross-reactivity based on anti-sera used [18, 19].

Table 5 Sensitivity analyses: lineage-specific influenza B vaccine effectiveness (VE) estimates, excluding children and/or the province of Alberta during seasons for which quadrivalent influenza vaccine (QIV) was available in Canada (2014-15 to 2017-18 seasons), and extended analysis of the early and prolonged 2017-18 epidemic

	Season (% TIV doses distributed across SPSN[1], with/without Alberta[2,3]) and lineage-specific VE with 95% confidence interval				
	2014-15 (96%/98%)	**2015-16 (86%/87%)**		**2016-17 (77%/88%)[2]**	**2017-18 (71%/84%)[3]**
TIV component	Victoria clade 1A	Yamagata clade 3		Victoria clade 1A	Victoria clade 1A
Epidemic strain	Yamagata clade 3	Victoria clade 1A	Yamagata clade 3	Yamagata clade 3	Yamagata clade 3
PRIMARY ANALYSIS					
Unadjusted	49 (26-65)	65 (50-75)	49 (12-71)	68 (44-82)	41 (28-52)
Adjusted[4]	39 (4-61)	54 (32-68)	55 (18-75)	73 (48-86)	39 (23-52)
SENSITIVITY ANALYSIS					
Age ≥ 20 years old[5]					
Unadjusted	48 (23-65)	58 (35-73)	58 (22-78)	70 (44-84)	39 (24-51)
Adjusted[6]	28 (-17-55)	52 (23-70)	60 (21-80)	72 (43-86)	38 (20-52)
Excluding Alberta[2,3]					
Unadjusted	Not applicable	Not applicable	Not applicable	65 (37-81)	39 (24-52)
Adjusted[7]				71 (43-85)	37 (18-51)
Age ≥ 20 years old and excluding Alberta					
Unadjusted	Not applicable	Not applicable	Not applicable	68 (38-83)	37 (19-50)
Adjusted[8]				70 (36-86)	35 (15-50)
Extended analysis of the early and prolonged 2017-18 epidemic (November 5, 2017—April 28, 2018)					
Unadjusted	Not applicable	Not applicable	Not applicable	Not applicable	42 (30-52)
Adjusted[4]					44 (30-55)
Extended analysis of the early and prolonged 2017-18 epidemic (November 5, 2017—April 28, 2018), excluding Alberta					
Unadjusted	Not applicable	Not applicable	Not applicable	Not applicable	37 (22-49)
Adjusted[7]					38 (22-51)

[1] Percentage of all publicly funded doses distributed across participating provinces of the Canadian Sentinel Practitioner Surveillance Network (SPSN) that were trivalent influenza vaccine (TIV). Although quadrivalent influenza vaccine (QIV) was primarily targeted to children (except in Alberta in 2016-17 and 2017-18), information is not available for TIV vs. QIV distribution by age and is summarized based on overall publicly-funded doses distributed.
[2] In Alberta, use of QIV was expanded in 2016-17 and comprised >75% of influenza vaccine doses distributed by the publicly funded immunization campaign. See **Supplement Table 2A**.
[3] In Alberta, use of QIV was expanded in 2017-18 and comprised >95% of influenza vaccine doses distributed by the publicly funded immunization campaign. See **Supplement Table 2A**.
[4] Adjusted for age group (1-8; 9-19; 20-49; 50-64; ≥65 years), sex (male/female), comorbidity (yes/no), province (Alberta, British Columbia, Ontario, Quebec), specimen collection interval (0-4 or 5-7 days from influenza-like illness (ILI) onset) and week of specimen collection (cubic B-spline with 3 equally spaced knots).
[5] QIV was targeted primarily to children when first introduced in Canada and thereafter in SPSN provinces outside of Alberta.
[6] Adjusted for age group (20-49; 50-64; ≥65 years), sex (male/female), comorbidity (yes/no), province (Alberta, British Columbia, Ontario, Quebec), specimen collection interval (0-4 or 5-7 days from influenza-like illness (ILI) onset) and week of specimen collection (cubic B-spline with 3 equally spaced knots).
[7] Adjusted for age group (1-8; 9-19; 20-49; 50-64; ≥65 years), sex (male/female), comorbidity (yes/no), province (British Columbia, Ontario, Quebec), specimen collection interval (0-4 or 5-7 days from influenza-like illness (ILI) onset) and week of specimen collection (cubic B-spline with 3 equally spaced knots).
[8] Adjusted for age group (20-49; 50-64; ≥65 years), sex (male/female), comorbidity (yes/no), province (British Columbia, Ontario, Quebec), specimen collection interval (0-4 or 5-7 days from influenza-like illness (ILI) onset) and week of specimen collection (cubic B-spline with 3 equally spaced knots).

Figure 2 Lineage-specific influenza B vaccine effectiveness (VE) by current and/or prior season's receipt of identical vaccine among Canadian Sentinel Practitioner Surveillance Network (SPSN) participants ≥9 years old, 2011-12, 2014-15, and 2017-18 seasons



[1] Where the trivalent influenza vaccine strain and circulating virus belong to different lineages, cross-lineage VE is shown as a hatched marker.

[2] Relative to participants unvaccinated both seasons. Analyses restricted to participants ≥9 years old with complete information for current and prior season's vaccination status. VE adjusted for age group (1-8; 9-19; 20-49; 50-64; ≥65 years), sex (male/female), comorbidity (yes/no), province (Alberta, British Columbia, Ontario, Quebec), specimen collection interval (0-4 or 5-7 days from influenza-like illness (ILI) onset) and week of specimen collection (cubic B-spline with 3 equally spaced knots) except for Yamagata-lineage estimates in 2011-12 for which calendar time adjustment was based on month of specimen collection owing to limited sample size.

[3] VE estimates presented here may not be directly comparable to overall VE estimates presented in the main manuscript or in prior publications [25, 28] owing to differences in the subset analyzed (participants ≥9 years old with complete information for current and prior season's vaccination status and restriction to the January to April period) as well as increased variability with reduced sample size, especially among those vaccinated current season only.

[4] Sequencing of circulating influenza B viruses was not undertaken prior to the 2013-14 season. See **Supplement Table 1** for details related to virological characterization in 2011-12.

[5] Yamagata clade 2 and clade 3 viruses can likely be considered antigenically distinct but with some variation in cross-reactivity based on anti-sera used [18, 19].

[6] Excluding the province of Alberta (owing to greater quadrivalent influenza vaccine (QIV) use in 2017-18), adjusted VE estimates were 28% (95%CI=-10-53%) for prior only, 22% (95%CI=-34-54%) for current only and 40% (95%CI=19-55%) for current and prior season's vaccine receipt.

[7] The 2017-18 B(Yamagata) epidemic was unusually early and prolonged. A similar pattern of VE estimates by vaccination subgroup was observed for the full-season's analysis (November 5, 2017 to April 28, 2018) [not displayed].

Table 6 Lineage-specific influenza B vaccine effectiveness (VE) by current and/or prior season's receipt of identical vaccine and odds ratios for lineage-specific influenza B illness relative to current season only vaccine recipients among Canadian Sentinel Practitioner Surveillance Network (SPSN) participants ≥9 years old, 2011-12, 2014-15, and 2017-18 seasons

Season: vaccine-virus relatedness conditions	Sample size n (%)		Vaccine effectiveness (VE)[1,2] (95% confidence interval)		Odds ratio [3] (95% confidence interval)	
	Cases	Controls	Unadjusted	Adjusted[4]	Unadjusted	Adjusted[4]
2011-12: Prior and current vaccine strain = Victoria clade 1A; Circulating virus =Yamagata clade 2/3 [5]						
Unvaccinated both current and prior season	61 (68)	312 (55)	Referent	Referent	1.45 (0.55-3.83)	1.49 (0.51-4.35)
Vaccinated prior season only	7 (8)	64 (11)	44 (-28-76)	56 (-10-82)	0.81 (0.24-2.73)	0.66 (0.18-2.49)
Vaccinated current season only	5 (6)	37 (7)	31 (-83-74)	33 (-97-77)	Referent	Referent
Vaccinated both current and prior season	17 (9)	154 (27)	44 (0-68)	40 (-19-70)	0.82 (0.28-2.36)	0.88 (0.28-2.78)
2014-15: Prior and current vaccine strain = Yamagata clade 2; Circulating virus = Yamagata clade 3 [5]						
Unvaccinated both current and prior season	113 (69)	346 (51)	Referent	Referent	2.78 (1.16-6.64)	2.13 (0.84-5.42)
Vaccinated prior season only	7 (4)	59 (9)	64 (18-84)	53 (-13-80)	1.01 (0.32-3.19)	1.00 (0.29-3.44)
Vaccinated current season only	6 (4)	51 (8)	64 (14-85)	53 (-19-82)	Referent	Referent
Vaccinated both current and prior season	38 (23)	224 (33)	48 (22-65)	22 (-30-53)	1.44 (0.58-3.59)	1.66 (0.61-4.49)
2017-18[6,7]: Prior and current vaccine strain = Victoria clade 1A; Circulating virus = Yamagata clade 3 [5]						
Unvaccinated both current and prior season	401 (65)	559 (53)	Referent	Referent	1.30 (0.79-2.13)	1.23 (0.73-2.08)
Vaccinated prior season only	49 (8)	102 (10)	33 (4-53)	30 (-3-52)	0.87 (0.48-1.56)	0.86 (0.47-1.60)
Vaccinated current season only	26 (4)	47 (4)	23 (-27-53)	19 (-36-52)	Referent	Referent
Vaccinated both current and prior season	139 (23)	346 (33)	44 (29-56)	43 (25-56)	0.73 (0.43-1.22)	0.71 (0.41-1.22)

[1] Relative to participants unvaccinated both seasons. Analyses restricted to participants ≥9 years old with complete information for current and prior season's vaccination status.

[2] VE estimates presented here may not be directly comparable to overall VE estimates presented in the main manuscript or in prior publications [25, 28] owing to differences in the subset analyzed (participants ≥9 years old with complete information for current and prior season's vaccination status and restriction to the January to April period) as well as increased variability with reduced sample size, especially among those vaccinated current season only.

[3] Relative to participants vaccinated the current season only. Analyses restricted to participants ≥9 years old with complete information for current and prior season's vaccination status.

[4] Analyses adjusted for age group, sex, comorbidity, province, specimen collection interval (0-4 or 5-7 days from influenza-like illness (ILI) onset) and week of specimen collection (cubic B-spline with 3 equally spaced knots) except for B(Yamagata) in 2011-12 for which calendar time adjustment was based on month of specimen collection.

[5] See **Supplement Table 1** for details related to virological characterization. Yamagata and Victoria lineages are antigenically distinct. Yamagata clade 2 and clade 3 viruses can likely be considered antigenically distinct but with some variation in cross-reactivity based on anti-sera used [18, 19].

[6] Excluding the province of Alberta (owing to greater quadrivalent influenza vaccine (QIV) use in 2017-18), adjusted VE estimates were 28% (95%CI=-10-53%) for prior only, 22% (95%CI=-34-54%) for current only and 40% (95%CI=19-55%) for current and prior season's vaccine receipt. Adjusted odds ratios relative to those vaccinated current season only were 1.28 (0.75-2.20) for unvaccinated both current and prior season, 0.92 (0.48-1.77) for vaccinated prior season only, and 0.77 (0.44-1.37) for vaccinated both current and prior season.

[7] The 2017-18 B(Yamagata) epidemic was unusually early and prolonged. A similar pattern of VE estimates by vaccination subgroup was observed for the full-season's analysis (November 5, 2017 to April 28, 2018) [not displayed].

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