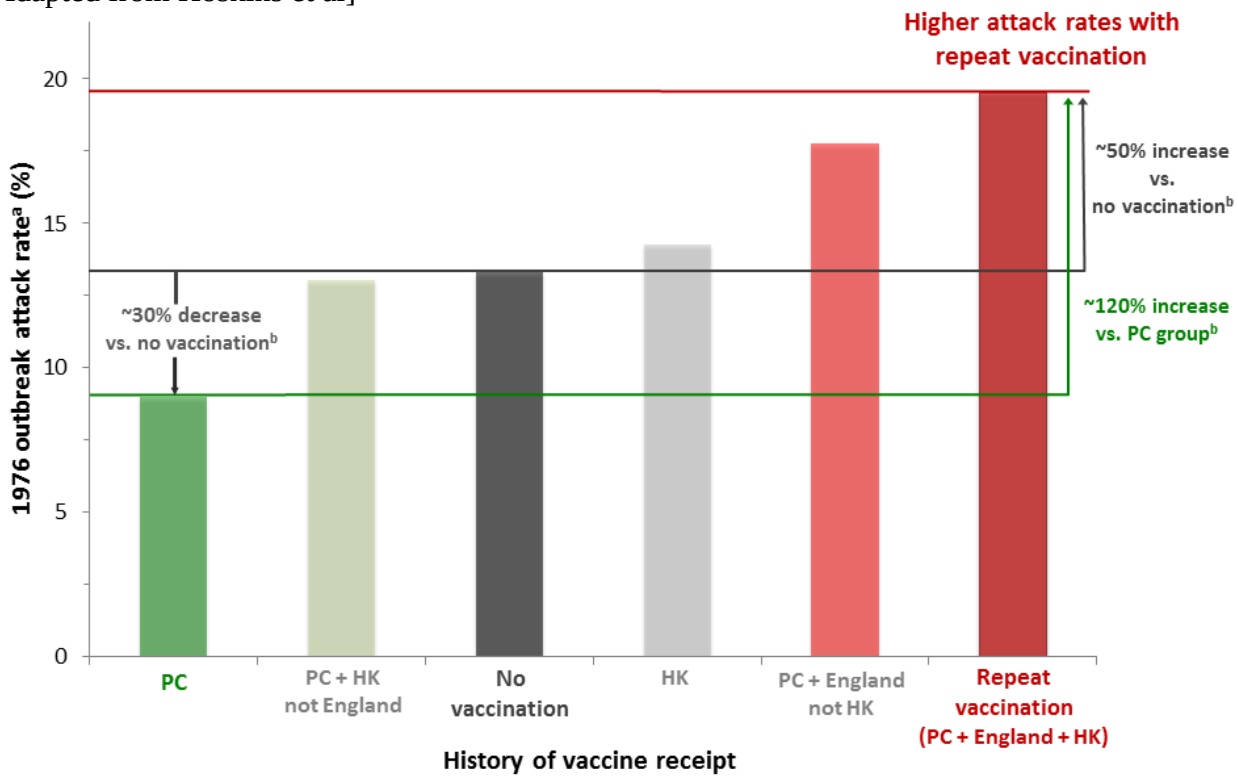
Supplement 1. Student attack rates during the final 1976 influenza A(H3N2) outbreak according to influenza vaccine receipt before boarding school outbreaks in 1976, 1974 and 1972 [Adapted from Hoskins et al][1]



[a] Attack rates based on virologic and serologic confirmation of infection; [b] $p > 0.05$

VACCINE RECEIPT DETAILS:

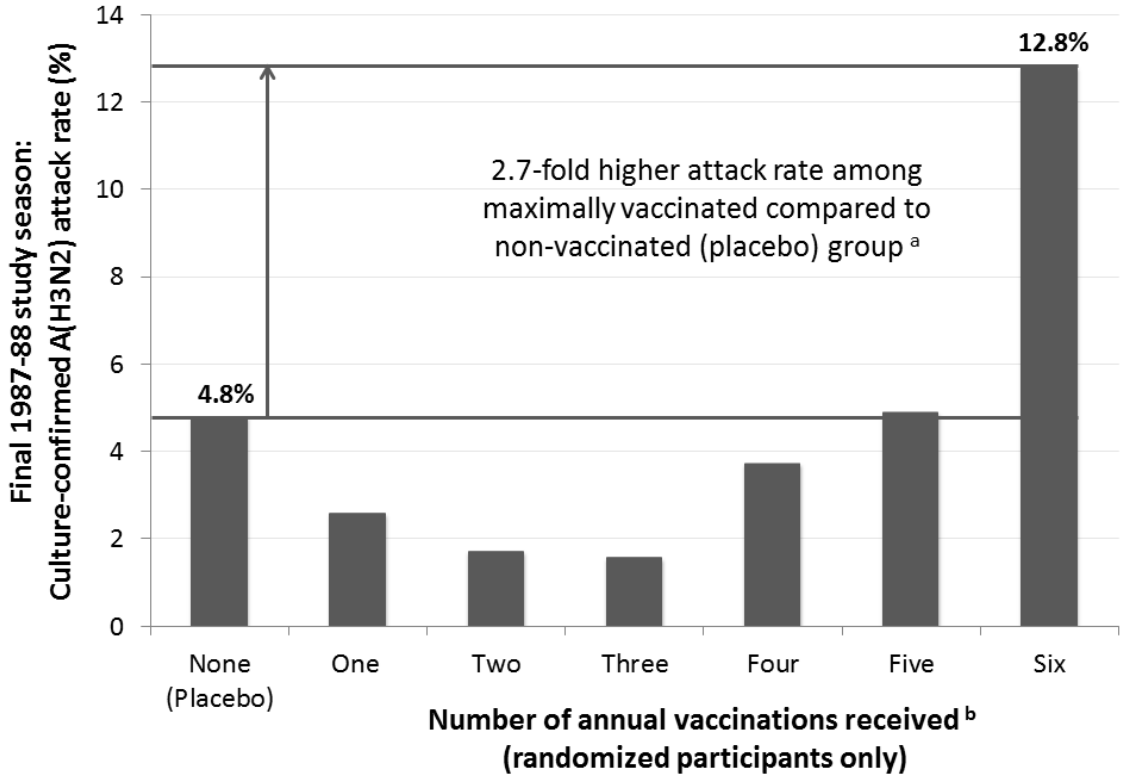
PC (1975-76, 1974-75 vaccines)
Two-thirds of PC recipients had received the A/Port Chalmers/1/73 vaccine in both 1975-76 (combined with A/Scotland/840/74 (H3N2); 400 I.U. each) as well as 1974-75 (300 I.U. combined with 100 I.U. of A/England/42/72 (H3N2)) before the spring 1976 outbreak due to A/Victoria/3/75 (H3N2). One-third received A/Port Chalmers/1/73 vaccine in 1974-75 only.

England (1973-74 vaccine)
Received A/England/42/72 (H3N2) vaccine (180 or 200 I.U.) in 1973-74 before the spring 1974 outbreak of A/Port Chalmers/3/73 (H3N2).

HK (1970-71, 1971-72 and/or 1972-73 vaccines)
Received one to three doses of A/Hong Kong/1/68 (H3N2) vaccine (200 I.U.) in 1970-71, 1971-72 and/or 1972-73 before the December 1972 outbreak of A/England/42/72 (H3N2). A/Hong Kong/1/68 vaccine is believed to have partially protected against A/England/42/72 infection. Authors reported no significant difference in A/England/42/72 attack rates whether the student had received one, two or three seasonal doses of A/Hong Kong/1/68.

[1] Republished with modifications on permission of Elsevier Health Science Journals from Hoskins TW, Davies JR, Smith AJ, Miller CL, Allchin A. Assessment of inactivated influenza-A vaccine after three outbreaks of influenza A at Christ's Hospital. Lancet 1979;1:33-5.

Supplement 2. Influenza A(H3N2) attack rates (culture confirmed) during the final 1987-88 study season according to number of annual influenza vaccinations received among participants randomized to receive the number of indicated doses (or placebo) [Adapted from Keitel et al][1]



[a] p = 0.07 (based on chi-square for 7/145 (4.8%) placebo versus 5/39 (12.8%) six-dose recipients)
[b] Six doses possible across the five study seasons owing to a supplemental monovalent subvirion A/Taiwan/1/86 (H1N1) vaccine administered in addition to the trivalent whole inactivated vaccine during the 1986-87 season.

The 1987-88 A(H3N2) epidemic virus (represented by A/Sichuan/2/87) was characterized as antigenically different from previous reference strains, including the most recent vaccine strains A/Leningrad/360/86 (1987-88 vaccine), A/Mississippi/1/85 (1986-87 vaccine) and A/Christchurch/4/85 (1985-86 vaccine); conversely, the latter three sequential vaccine strains were characterized antigenically as closely related to each other.[2,3,4]

[1] Republished with modifications on permission of Elsevier Science and Technology Journals from Keitel WA, Cate TR, Couch RB, Huggins LL, Hess KR. Efficacy of repeated annual immunization with inactivated influenza virus vaccines over a five year period. Vaccine 1997;15:1114-22.
[2] World Health Organization. Recommended composition of influenza virus vaccines for use in the 1988-1989 season: Influenza activity, October 1987 – February 1988. Wkly Epidem Rec 1988;9: 57-60.
[3] World Health Organization. Recommended composition of influenza virus vaccines for use in the 1987-1988 season: Influenza activity, October 1986 – February 1987. Wkly Epidem Rec 1987;9: 54-57.
[4] World Health Organization. Recommended composition of influenza virus vaccines for use in the 1986-1987 season: Influenza activity, October 1985 – February 1986. Wkly Epidem Rec 1986;9: 61-64.

Supplement 3A. Methods and summary of homologous and heterologous hemagglutination inhibition (HI) titres and fold-differences between vaccine and epidemic reference viruses reported by the WHO Collaborating Centre for Reference and Research on Influenza (London) and used in antigenic distance derivations

As specified by Smith et al[1], antigenic distances (ADs) were derived based on $\log_2$ of the fold-difference between homologous and heterologous hemagglutination inhibition (HI) antibody titres for comparator strains representing prior season's vaccine (*v1*), current season's vaccine (*v2*) and the current season's epidemic strain (*e*), i.e. difference in the number of twofold dilutions in HI titre. For example, as shown in Supplemental Table 3B for *v1-v2* comparison, the first virus is the homologous strain (i.e. *v1*) and the second is the heterologous strain (i.e. *v2*).

For standardized approach, we relied on HI titres posted in bi-annual (February and September) reports of the WHO Collaborating Centre for Reference and Research on Influenza (London) [2] for which all HI assays for A(H3N2) characterization were conducted using guinea pig erythrocytes in the presence of 20nM oseltamivir added to circumvent neuraminidase-mediated binding of influenza A(H3N2) viruses to erythrocytes.

Where actual vaccine strains (i.e. egg-adapted WHO reference or egg-adapted high-growth reassortant (HGR) strains) were not included in posted antigenic comparisons, the nearest alternate egg-passaged reference virus based on phylogenetic tree analysis was used from the same report. Similarly, the nearest available cell-passaged reference virus representative of the dominant epidemic clade detected among SPSN study participants was based on phylogenetic tree analysis. For each season, multiple HI assay repeats conducted on different dates compared antigenic relatedness of reference viruses, sometimes under varying conditions of virus passage and/or ferret anti-sera. The most frequent combination of the same specific reference virus passage and ferret anti-sera was used to derive the average antigenic distances shown in Supplemental Table 3B; however, summary conclusions were similar when averaged across the broader range of assays conducted with guinea pig erythrocytes regardless of other assay conditions (explained in footnote for each season). ADs are average values rounded to a whole number but added potential variation in the representativeness of selected vaccine and epidemic reference strains and field isolates is acknowledged.

[1] Smith DJ, Forrest S, Ackley DH, Perelson AS. Variable efficacy of repeated annual influenza vaccination. Proc Natl Acad Sci U S A. 1999;96:14001-6.
[2] The Francis Crick Institute. Annual and interim reports. [Accessed November 13, 2016]. Available: https://www.crick.ac.uk/research/worldwide-influenza-centre/annual-and-interim-reports/

Supplement Table 3B: Reference viruses by season used in antigenic distance (AD) derivation

	2010-11[a]			2012-13[b]			2014-15[c]		
Prior season's vaccine (*v1*)									
Recommended by WHO	A/Brisbane/10/2007-like			A/Perth/16/2009-like			A/Texas/50/2012-like		
High-growth reassortant	A/Uruguay/716/2007 X-175C			A/Victoria/210/2009 X-187			A/Texas/50/2012 X-223A		
Clade	NA			1			3C.1		
Available reference virus	A/Brisbane/10/2007			A/Perth/16/2009			A/Texas/50/2012		
Date of collection	February 6, 2007			July 4, 2009			April 15, 2012		
Passage history	E2/E4			E3/E2			E5/E2		
Ferret anti-sera	F09/11			F35/11			F42/13		
Current season's vaccine (*v2*)									
Recommended by WHO	A/Perth/16/2009-like			A/Victoria/361/2011-like			A/Texas/50/2012-like		
High-growth reassortant	A/Victoria/210/2009 X-187			A/Victoria/361/2011 IVR-165			A/Texas/50/2012 X-223A		
Clade	1			3C			3C.1		
Available reference virus	A/Victoria/210/2009			A/Victoria/361/2011			A/Texas/50/2012		
Date of collection	June 2, 2009			October 24, 2011			April 15, 2012		
Passage history	E2/E3			E3/E2			E5/E2		
Ferret anti-sera	F10/11			F05/12			F42/13		
Epidemic strain (*e*)									
Clade	5			3C			3C.2a		
Available reference virus	A/Alabama/5/2010			A/Victoria/361/2011			A/Hong Kong/5738/2014		
Date of collection	July 13, 2010			October 24, 2011			April 30, 2014		
Passage history	MK1/M2/SIAT4			MDCK2/SIAT2			MDCK1/MDCK2/SIAT1		
Antigenic distance (AD)[d]	N	Sum	Average[e,f]	N	Sum	Average[g,h]	N	Sum	Average[i,j]
v1-v2	5	18	4	17	21	1	11	0	0
v1 - *e*	5	33	7	17	47	3	11	47	4
v2 - *e*	5	30	6	17	60	4	11	47	4

WHO=World Health Organization; *v1*=prior season's vaccine; *v2*=current season's vaccine; *e*=current season's epidemic strain

[a] Original assay results available at https://www.crick.ac.uk/media/221917/interim-report-feb-2011.pdf (14-17 February 2011; pp 34-35) and https://www.crick.ac.uk/media/222077/interim-report-sep-2011.pdf (26-30 September 2011; pp 33-38).

[b] Original assay results available at https://www.crick.ac.uk/media/221869/interim_report_february_2013.pdf (18-20 February 2013; pp 36-44) and https://www.crick.ac.uk/media/221859/nimr-report-sep2013final.pdf (23-25 September 2013; pp 44-59). Because titres in relation to the egg-passaged A/Victoria/210/2009 vaccine strain actually used were not presented, the egg-passaged A/Perth/16/2009 reference virus was instead selected as the next best alternate. Accordingly, *v1*-*v2* and *v1*-*e* distances may be greater than displayed.

[c] Original assay results available at https://www.crick.ac.uk/media/221813/nimr-report-feb2015-web.pdf (23-25 February 2015; pp 41-50) and https://www.crick.ac.uk/media/273950/crick_sep2015_vcm_report_to_post.pdf (21-23 September 2015; pp 45-58)

[d] Antigenic distances (ADs) are displayed for the single most frequent combination of reference virus passage history and ferret anti-sera used in repeat hemagglutination inhibition (HI) assays across the season. N is the number of assay repeats; sum is the total of ADs across those repeats and average is the sum/N.

[e] ADs are identical if averaged across all assay repeats using guinea pig erythrocytes but regardless of other assay conditions (N=11). Using guinea pig erythrocytes but regardless of other assay conditions where *e* is a range of global cell-passaged clade 5 field isolates tested by the WHO Collaborating Centre for Reference and Research on Influenza (London), respective ADs for *v1*-*v2*, *v1*-*e* and *v2*-*e* are: 4, 6, 5 (N=15).

[f] If an egg-passaged A/Perth/16/2009 virus is instead used as *v2* reference, the corresponding ADs for *v1*-*v2*, *v1*-*e* and *v2*-*e* are: 5, 7, 3, whether based on all assay repeats (N=11) or the single most frequent combination of assay conditions (N=4). ADs where *e* is a range of global clade 5 field isolates tested by the WHO Collaborating Centre for Reference and Research on Influenza (London) are then 5, 6, 3, respectively (N=15).

[g] ADs are identical if averaged across all assay repeats using guinea pig erythrocytes but regardless of other assay conditions (N=25). ADs are also identical using guinea pig erythrocytes where *e* is the A/Berlin/93/2011 (NVD3/SIAT6) reference virus (N=15). ADs are also identical using guinea pig erythrocytes but regardless of other assay conditions for a range of other global cell-passaged clade 3C.1 field isolates tested (N=8).

[h] An egg-passaged A/Victoria/210/2009 reference virus and a cell-passaged A/Hong Kong/3969/2011 (clade 3C) virus closely related phylogenetically to *e* (A/Victoria/361/2011) was presented in the February 2012 interim report (see https://www.crick.ac.uk/media/221907/interim-report-feb-2012.pdf ; pp 27-31). Using guinea pig erythrocytes averaged across all assay repeats regardless of assay conditions, the AD using these specific viruses for v1-e comparison was 4 (N=5).

[i] A/Hong Kong/5738/2014 shows partial loss of the potential glycosylation motif at position 158-160 present in the consensus sequence of clade 3C.2a viruses. This may have affected HI characterization data and derived *v1*/*v2*-*e* ADs. For discussion of the effects of this glycosylation motif on the ability to antigenically characterize clade 3C.2a viruses, see: Skowronski D, Sabaiduc S, Chambers C et al. Mutations acquired during cell culture isolation may affect antigenic characterisation of influenza A(H3N2) clade 3C.2a viruses. Euro Surveill. 2016;21(3):pii=30112. http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=21355

[j] Using guinea pig erythrocytes but averaged across all assay repeats regardless of assay conditions, ADs for *v1*/*v2*-*e* are 5 (N=24) or where *e* is a range of global cell-passaged clade 3C.2a field isolates tested by the WHO Collaborating Centre (London), ADs for *v1*/*v2*-*e* are 6 (N=100).

Supplement 4a. Participant profile by influenza A(H3N2) case and one season's prior vaccination status among Canadian SPSN patients aged ≥9 years, 2010-11 season

	By case status, n (column %)			By current (v2) and one season's prior (v1) vaccination n (column %)				
	Negative controls	Influenza A(H3N2) cases	p-value	Neither current nor prior	Prior, not current	Current, not prior	Current and prior	p-value
N	786	316		707	164	42	189	
Age group (years)			0.05					<0.01
9-19	124 (16)	37 (12)		109 (15)	25 (15)	7 (17)	20 (11)	
20-49	453 (58)	203 (64)		446 (63)	104 (63)	25 (60)	81 (43)	
50-64	164 (21)	52 (16)		132 (19)	27 (16)	7 (17)	50 (26)	
≥65	45 (6)	24 (8)		20 (3)	8 (5)	3 (7)	38 (20)	
Median (range)	37 (9-105)	38.5 (9-88)	0.17	35 (9-105)	38 (9-84)	39 (9-78)	47 (9-89)	<0.01
Female sex	487 (62)	181 (57)	0.15	415 (59)	108 (66)	26 (62)	119 (63)	0.33
Comorbidity	164 (21)	63 (20)	0.73	93 (13)	44 (27)	10 (24)	80 (42)	<0.01
Province			<0.01					0.01
Alberta	253 (32)	42 (13)		170 (24)	45 (27)	18 (43)	62 (33)	
British Columbia	134 (17)	17 (5)		109 (15)	15 (9)	2 (5)	25 (13)	
Ontario	278 (35)	195 (62)		298 (42)	80 (49)	15 (36)	80 (42)	
Quebec	121 (15)	62 (20)		130 (18)	24 (15)	7 (17)	22 (12)	
Interval from ILI onset to specimen collection			<0.01					0.04
0-4 days	590 (75)	276 (87)		567 (80)	128 (78)	26 (62)	145 (77)	
5-7 days	196 (25)	40 (13)		140 (20)	36 (22)	16 (38)	44 (23)	
Median (range)	3 (0-7)	3 (0-7)	<0.01	3 (0-7)	3 (0-7)	4 (0-6)	3 (0-7)	0.01
Month of enrolment			<0.01					<0.01
November	131 (17)	15 (5)		99 (14)	32 (20)	6 (14)	9 (5)	
December	102 (13)	78 (25)		114 (16)	32 (20)	6 (14)	28 (15)	
January	177 (23)	125 (40)		200 (28)	44 (27)	12 (29)	46 (24)	
February	153 (19)	71 (22)		140 (20)	31 (19)	11 (26)	42 (22)	
March	155 (20)	21 (7)		111 (16)	14 (9)	6 (14)	45 (24)	
April	68 (9)	6 (2)		43 (6)	11 (7)	1 (2)	19 (10)	
A(H3N2) status								0.02
Control	--	--		502 (71)	104 (63)	33 (79)	147 (78)	
Case	--	--		205 (29)	60 (37)	9 (21)	42 (22)	
Current vaccination								
Any	207/813 (25)	55/320 (17)	<0.01	--	--	--	--	
≥2 weeks before ILI onset	180 (23)	51 (16)	0.01	--	--	--	--	
Prior vaccination (v1)			0.02					
Neither current nor prior	502 (64)	205 (65)		--	--	--	--	
Prior, not current	104 (13)	60 (19)		--	--	--	--	
Current, not prior	33 (4)	9 (3)		--	--	--	--	
Current and prior	147 (19)	42 (13)		--	--	--	--	

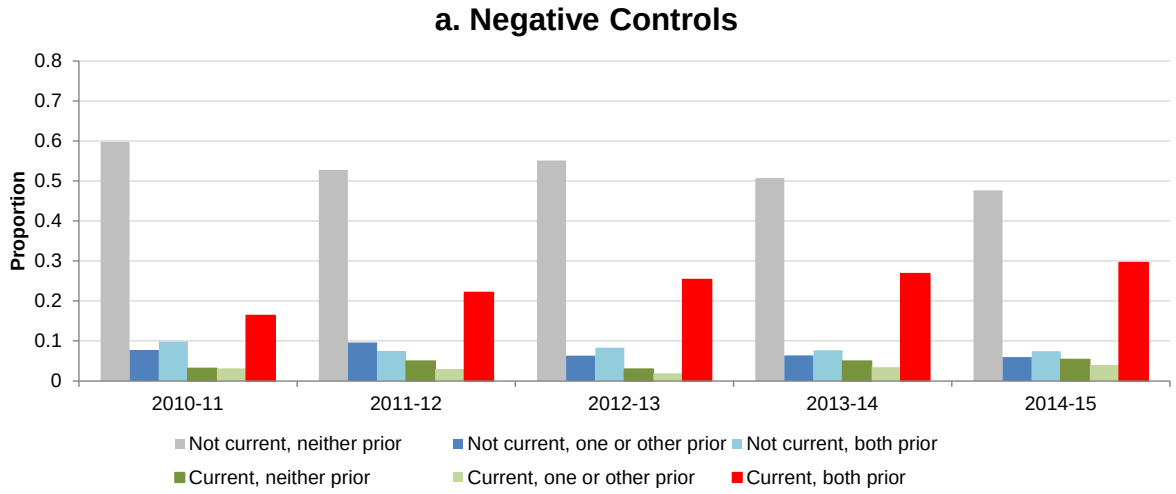
Supplement 4b. Participant profile by influenza A(H3N2) case and prior vaccination status among Canadian SPSN patients aged ≥9 years, 2012-13 season

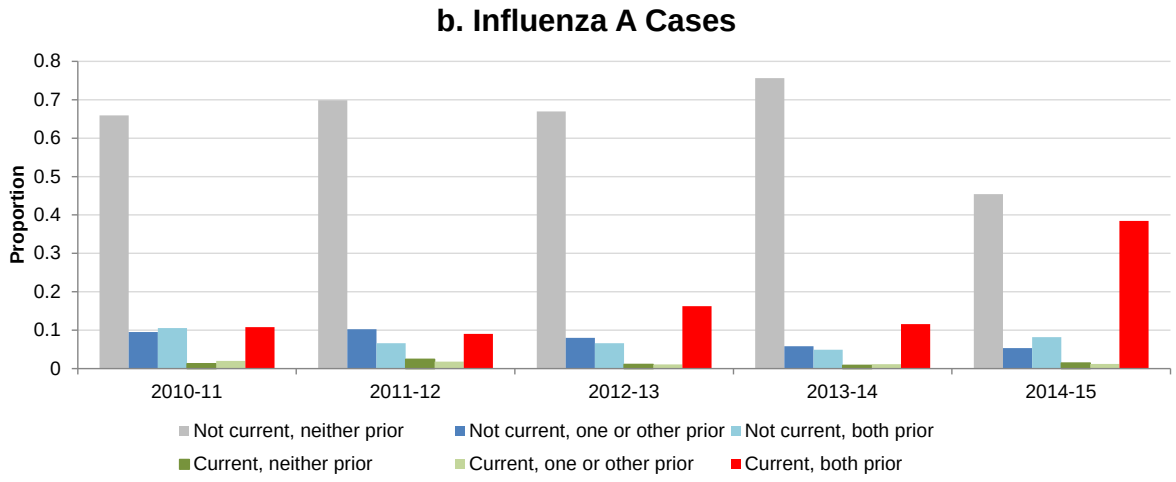
	By case status, n (column %)			By current (v2) and one season's prior (v1) vaccination n (column %)				
	Negative controls	Influenza A(H3N2) cases	p-value	Neither current nor prior	Prior, not current	Current, not prior	Current and prior	p-value
N	662	297		598	105	29	227	
Age group (years)			0.08					<0.01
9-19	71 (11)	49 (17)		98 (16)	12 (11)	3 (10)	7 (3)	
20-49	356 (54)	156 (53)		365 (61)	55 (52)	17 (59)	75 (33)	
50-64	152 (23)	61 (21)		113 (19)	29 (28)	6 (21)	65 (29)	
≥65	83 (13)	31 (10)		22 (4)	9 (9)	3 (10)	80 (35)	
Median (range)	40 (9-95)	39 (9-92)	0.15	34 (9-92)	44 (9-92)	39 (12-75)	58 (11-95)	<0.01
Female sex	403 (61)	178 (60)	0.78	350 (59)	66 (63)	17 (59)	148 (65)	0.34
Comorbidity	157 (24)	67 (23)	0.70	91 (15)	29 (28)	5 (17)	99 (44)	<0.01
Province			<0.01					<0.01
Alberta	234 (35)	72 (24)		170 (28)	44 (42)	10 (34)	82 (36)	
British Columbia	164 (25)	70 (24)		159 (27)	22 (21)	9 (31)	44 (19)	
Ontario	162 (24)	76 (26)		127 (21)	29 (28)	9 (31)	73 (32)	
Quebec	102 (15)	79 (27)		142 (24)	10 (10)	1 (3)	28 (12)	
Interval from ILI onset to specimen collection			<0.01					0.52
0-4 days	475 (72)	246 (83)		458 (77)	79 (75)	20 (69)	164 (72)	
5-7 days	187 (28)	51 (17)		140 (23)	26 (25)	9 (31)	63 (28)	
Median (range)	3 (0-7)	3 (0-7)	<0.01	3 (0-7)	3 (0-7)	3 (1-7)	3 (0-7)	0.16
Month of enrolment			<0.01					<0.01
November	52 (8)	16 (5)		52 (9)	9 (9)	0 (0)	7 (3)	
December	84 (13)	106 (36)		129 (22)	22 (21)	3 (10)	36 (16)	
January	213 (32)	144 (48)		218 (36)	39 (37)	12 (41)	88 (39)	
February	131 (20)	26 (9)		99 (17)	13 (12)	6 (21)	39 (17)	
March	110 (17)	4 (1)		59 (10)	18 (17)	7 (24)	30 (13)	
April	72 (11)	1 (0)		41 (7)	4 (4)	1 (3)	27 (12)	
A(H3N2) status								0.01
Control	--	--		394 (66)	71 (68)	24 (83)	173 (76)	
Case	--	--		204 (34)	34 (32)	5 (17)	54 (24)	
Current vaccination								
Any	210/675 (31)	61/299 (20)	<0.01	--	--	--	--	
≥2 weeks before ILI onset	197 (30)	59 (20)	<0.01	--	--	--	--	
Prior vaccination (v1)			0.01					
Neither current nor prior	394 (60)	204 (69)		--	--	--	--	
Prior, not current	71 (11)	34 (11)		--	--	--	--	
Current, not prior	24 (4)	5 (2)		--	--	--	--	
Current and prior	173 (26)	54 (18)		--	--	--	--	

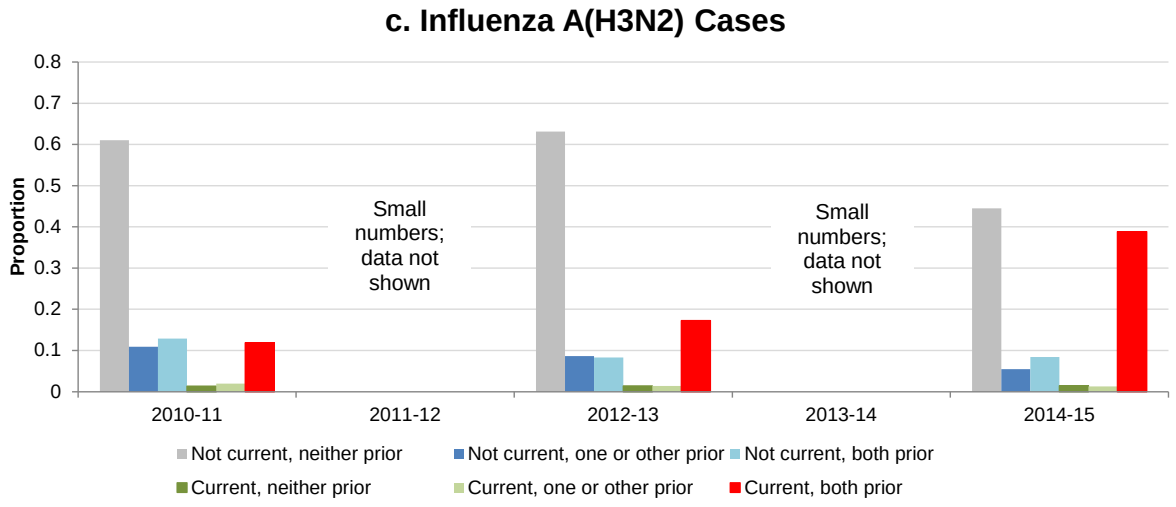
Supplement 4c. Participant profile by influenza A(H3N2) case and prior vaccination status among Canadian SPSN patients aged ≥9 years, 2014-15 season

	By case status, n (column %)			By current (v2) and one season's prior (v1) vaccination n (column %)				
	Negative controls	Influenza A(H3N2) cases	p-value	Neither current nor prior	Prior, not current	Current, not prior	Current and prior	p-value
N	926	490		698	158	71	489	
Age group (years)			0.06					<0.01
9-19	121 (13)	80 (16)		139 (20)	24 (15)	11 (15)	27 (6)	
20-49	437 (47)	204 (42)		367 (53)	85 (54)	33 (46)	156 (32)	
50-64	235 (25)	118 (24)		155 (22)	37 (23)	20 (28)	141 (29)	
≥65	133 (14)	88 (18)		37 (5)	12 (8)	7 (10)	165 (34)	
Median (range)	43 (9-94)	44 (9-103)	0.69	35 (9-94)	40 (9-83)	39 (9-93)	56 (9-103)	<0.01
Female sex	610 (66)	278 (57)	<0.01	422 (60)	92 (58)	49 (69)	325 (66)	0.07
Comorbidity	229 (25)	128 (26)	0.57	115 (16)	33 (21)	14 (20)	195 (40)	<0.01
Province			0.12					<0.01
Alberta	277 (30)	135 (28)		182 (26)	49 (31)	20 (28)	161 (33)	
British Columbia	167 (18)	71 (14)		132 (19)	30 (19)	15 (21)	61 (12)	
Ontario	316 (34)	178 (36)		211 (30)	53 (34)	24 (34)	206 (42)	
Quebec	166 (18)	106 (22)		173 (25)	26 (16)	12 (17)	61 (12)	
Interval from ILI onset to specimen collection			<0.01					0.07
0-4 days	628 (68)	400 (82)		510 (73)	118 (75)	42 (59)	358 (73)	
5-7 days	298 (32)	90 (18)		188 (27)	40 (25)	29 (41)	131 (27)	
Median (range)	4 (0-7)	3 (0-7)	<0.01	3 (0-7)	3 (0-7)	3 (0-7)	3 (0-7)	0.15
Month of enrolment			<0.01					<0.01
November	78 (8)	17 (3)		54 (8)	20 (13)	4 (6)	17 (3)	
December	168 (18)	213 (43)		177 (25)	56 (35)	12 (17)	136 (28)	
January	276 (30)	182 (37)		223 (32)	40 (25)	20 (28)	175 (36)	
February	198 (21)	63 (13)		122 (17)	21 (13)	17 (24)	101 (21)	
March	129 (14)	13 (3)		72 (10)	15 (9)	15 (21)	40 (8)	
April	77 (8)	2 (0)		50 (7)	6 (4)	3 (4)	20 (4)	
A(H3N2) status								<0.01
Control	--	--		468 (67)	101 (64)	62 (87)	295 (60)	
Case	--	--		230 (33)	57 (36)	9 (13)	194 (40)	
Current vaccination								
Any	382/951 (40)	214/501 (43)	0.35	--	--	--	--	
≥2 weeks before ILI onset	357 (39)	203 (41)	0.29	--	--	--	--	
Prior vaccination (v1)			<0.01					
Neither current nor prior	468 (51)	230 (47)		--	--	--	--	
Prior, not current	101 (11)	57 (12)		--	--	--	--	
Current, not prior	62 (7)	9 (2)		--	--	--	--	
Current and prior	295 (32)	194 (40)		--	--	--	--	

Supplement 5. Prior vaccination (current and two prior seasons) by year and case status among Canadian SPSN patients aged ≥9 years, 2010-11 to 2014-15







Supplement 6. Overall odds ratios (OR) and vaccine effectiveness (VE) estimates against influenza A(H3N2) among Canadian SPSN patients aged ≥9 years, for current season's (v2) regardless of prior seasons' (v1 or v0) vaccination status, 2010-11, 2012-13, 2014-15 seasons[a]

Current season's vaccine (v2) status	Negative controls n (%)	Influenza A(H3N2) cases n (%)	*vs. participants not vaccinated*			
			Unadjusted OR (95% CI)	Adjusted OR (95% CI)[b]	Unadjusted VE (95% CI)[c]	Adjusted VE (95% CI)[b,c]
2010-11						
Not vaccinated	606 (77)	265 (84)	Ref	Ref	Ref	Ref
Vaccinated	180 (23)	51 (16)	0.65 (0.46-0.91)	0.60 (0.40-0.91)	35 (9-54)	40 (9-60)
2012-13						
Not vaccinated	465 (70)	238 (80)	Ref	Ref	Ref	Ref
Vaccinated	197 (30)	59 (20)	0.59 (0.42-0.81)	0.69 (0.45-1.04)	41 (19-58)	31 (-4-55)
2014-15						
Not vaccinated	569 (61)	287 (59)	Ref	Ref	Ref	Ref
Vaccinated	357 (39)	203 (41)	1.13 (0.90-1.41)	1.12 (0.85-1.47)	-13 (-41-10)	-12 (-47-15)

[a] Excluding 2011-12 and 2013-14 seasons due to small number of A(H3N2) cases.
[b] Analyses adjusted for age group, sex, comorbidity, province, collection interval, and week of specimen collection (cubic B-spline functions with 3 equal knots).
[c] VE derived as (1 – OR) x 100%.

Supplement 7. Odds ratios (OR) and vaccine effectiveness (VE) estimates against influenza A(H3N2) by current (v2) and/or one season's prior (v1) vaccination history among Canadian SPSN patients aged ≥9 years, 2010-11, 2012-13, 2014-15 seasons[a]

Current and one prior season's vaccination history	Influenza negative controls n (%)	Influenza A(H3N2) cases n (%)	*vs. neither current nor prior (i.e. unvaccinated both seasons)*				*vs. current only, not prior*	
			Unadjusted OR (95% CI)	Adjusted OR (95% CI)[b]	Unadjusted VE (95% CI)[c]	Adjusted VE (95% CI) [b,c]	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[b]
2010-11								
Neither current nor prior	502 (64)	205 (65)	Ref	Ref	Ref	Ref	1.50 (0.70-3.18)	1.51 (0.66-3.46)
Prior, not current	104 (13)	60 (19)	1.41 (0.99-2.02)	1.55 (1.03-2.34)	-41 (-102-1)	-55 (-134- -3)	2.11 (0.95-4.72)	2.35 (0.97-5.68)
Current, not prior	33 (4)	9 (3)	0.67 (0.31-1.42)	0.66 (0.29-1.51)	33 (-42-69)	34 (-51-71)	Ref	Ref
Current and prior	147 (19)	42 (13)	0.70 (0.48-1.02)	0.66 (0.42-1.05)	30 (-2-52)	34 (-5-58)	1.05 (0.46-2.36)	1.01 (0.41-2.46)
2012-13								
Neither current nor prior	394 (60)	204 (69)	Ref	Ref	Ref	Ref	2.49 (0.93-6.61)	1.98 (0.68-5.75)
Prior, not current	71 (11)	34 (11)	0.92 (0.59-1.44)	1.00 (0.61-1.66)	8 (-44-41)	0 (-66-39)	2.30 (0.81-6.55)	1.99 (0.64-6.21)
Current, not prior	24 (4)	5 (2)	0.40 (0.15-1.07)	0.51 (0.17-1.47)	60 (-7-85)	49 (-47-83)	Ref	Ref
Current and prior	173 (26)	54 (18)	0.60 (0.43-0.85)	0.72 (0.46-1.12)	40 (15-57)	28 (-12-54)	1.50 (0.55-4.12)	1.42 (0.47-4.32)
2014-15								
Neither current nor prior	468 (51)	230 (47)	Ref	Ref	Ref	Ref	3.38 (1.65-6.93)	2.84 (1.34-6.02)
Prior, not current	101 (11)	57 (12)	1.15 (0.80-1.65)	1.07 (0.72-1.59)	-15 (-65-20)	-7 (-59-28)	3.89 (1.80-8.40)	3.03 (1.34-6.83)
Current, not prior	62 (7)	9 (2)	0.30 (0.14-0.61)	0.35 (0.17-0.75)	70 (39-86)	65 (25-83)	Ref	Ref
Current and prior	295 (32)	194 (40)	1.34 (1.05-1.70)	1.33 (0.99-1.78)	-34 (-70--5)	-33 (-78-1)	4.53 (2.20-9.32)	3.76 (1.75-8.07)

VE= vaccine effectiveness; OR=odds ratio; 95%CI= 95% confidence interval; Ref=reference group

[a] Excludes 2011-12 and 2013-14 seasons due to small number of A(H3N2) cases.

[b] Analyses adjusted for age group, sex, comorbidity, province, collection interval, and week of specimen collection (cubic B-spline functions).

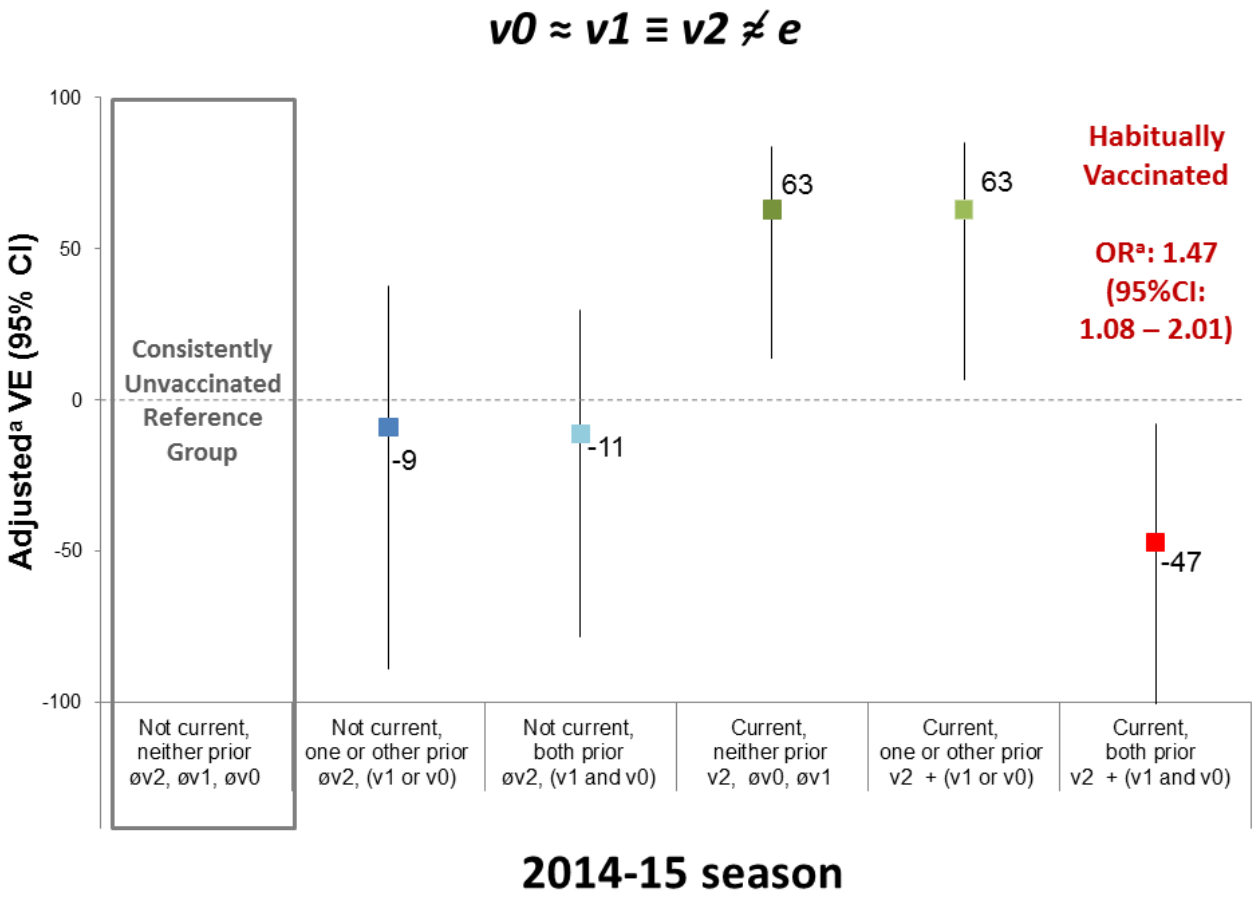
[c] VE derived as (1 – odds ratio) x 100%.

Supplement 8. Odds ratios (OR) and vaccine effectiveness (VE) estimates against influenza A(H3N2) by current (v2) and/or two prior seasons' (v1 and/or v0) vaccination history among Canadian SPSN patients aged ≥9 years, 2010-11, 2012-13, 2014-15 seasons[a]

Current and two prior seasons' vaccination history	Negative controls n (%)	A(H3N2) cases n (%)	*vs. not current, neither prior (i.e. unvaccinated all three seasons)*				*vs. current, neither prior*	
			Unadjusted OR (95% CI)	Adjusted OR (95% CI)[b]	Unadjusted VE (95% CI)[c]	Adjusted VE (95% CI)[b,c]	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[b]
2010-11								
Neither current, neither prior	456 (60)	185 (61)	Ref	Ref	Ref	Ref	2.43 (0.83-7.11)	2.37 (0.76-7.45)
Not current, one or other prior	59 (8)	33 (11)	1.38 (0.87-2.18)	1.56 (0.93-2.62)	-38 (-118-13)	-56 (-162-7)	3.36 (1.07-10.5)	3.71 (1.09-12.61)
Not current but both prior	75 (10)	39 (13)	1.28 (0.84-1.96)	1.25 (0.77-2.02)	-28 (-96-16)	-25 (-102-23)	3.12 (1.01-9.63)	2.96 (0.88-9.94)
Current only, neither prior	24 (3)	4 (1)	0.41 (0.14-1.20)	0.42 (0.13-1.32)	59 (-20-86)	58 (-32-87)	Ref	Ref
Current, one or other prior	24 (3)	6 (2)	0.62 (0.25-1.53)	0.81 (0.29-2.23)	38 (-53-75)	19 (-123-71)	1.50 (0.38-6.00)	1.92 (0.43-8.62)
Current and both prior	125 (16)	36 (12)	0.71 (0.47-1.07)	0.68 (0.42-1.11)	29 (-7-53)	32 (-11-58)	1.73 (0.56-5.30)	1.62 (0.48-5.41)
2012-13								
Neither current, neither prior	350 (55)	183 (63)	Ref	Ref	Ref	Ref	2.48 (0.83-7.41)	1.75 (0.53-5.76)
Not current, one or other prior	40 (6)	25 (9)	1.20 (0.70-2.03)	1.41 (0.77-2.61)	-20 (-103-30)	-41 (-161-23)	2.97 (0.90-9.74)	2.47 (0.67-9.06)
Not current but both prior	53 (8)	24 (8)	0.87 (0.52-1.45)	0.88 (0.49-1.57)	13 (-45-48)	12 (-57-51)	2.15 (0.66-7.01)	1.54 (0.42-5.59)
Current only, neither prior	19 (3)	4 (1)	0.40 (0.13-1.20)	0.57 (0.17-1.89)	60 (-20-87)	43 (-89-83)	Ref	Ref
Current, one or other prior	12 (2)	4 (1)	0.64 (0.20-2.00)	0.84 (0.23-3.07)	36 (-100-80)	16 (-207-77)	1.58 (0.33-7.56)	1.47 (0.26-8.27)
Current and both prior	161 (25)	50 (17)	0.59 (0.41-0.85)	0.71 (0.45-1.14)	41 (15-59)	29 (-14-55)	1.48 (0.48-4.54)	1.25 (0.36-4.35)
2014-15								
Neither current, neither prior	423 (48)	211 (45)	Ref	Ref	Ref	Ref	3.42 (1.52-7.68)	2.71 (1.16-6.35)
Not current, one or other prior	53 (6)	26 (5)	0.98 (0.60-1.62)	1.09 (0.62-1.89)	2 (-62-40)	-9 (-89-38)	3.36 (1.34-8.45)	2.95 (1.10-7.88)
Not current but both prior	66 (7)	40 (8)	1.21 (0.79-1.86)	1.11 (0.70-1.78)	-21 (-86-21)	-11 (-78-30)	4.15 (1.71-10.06)	3.02 (1.18-7.70)
Current only, neither prior	48 (5)	7 (1)	0.29 (0.13-0.66)	0.37 (0.16-0.86)	71 (34-87)	63 (14-84)	Ref	Ref
Current, one or other prior	35 (4)	6 (1)	0.34 (0.14-0.83)	0.37 (0.15-0.93)	66 (17-86)	63 (7-85)	1.18 (0.36-3.80)	1.00 (0.29-3.43)
Current and both prior	263 (30)	184 (39)	1.40 (1.09-1.80)	1.47 (1.08-2.01)	-40 (-80--9)	-47 (-101--8)	4.80 (2.12-10.83)	4.00 (1.69-9.48)

[a] Excluding 2011-12 and 2013-14 season due to small number of A(H3N2) cases. Same exclusion criteria as primary analysis; further restricted to participants with complete data for current and two prior season's vaccination status.
[b] Analyses adjusted for age group, sex, comorbidity, province, collection interval, and week of specimen collection (cubic B-spline functions with 3 equal knots).
[c] VE derived as (1 – OR) x 100%.

Supplement 9A. Adjusted odds ratios (OR) and vaccine effectiveness (VE) estimates **relative to consistently unvaccinated** for influenza A(H3N2) by current (v2) and/or two prior seasons' (v1 and/or v0) vaccination history among Canadian SPSN patients aged ≥9 years, 2014-15

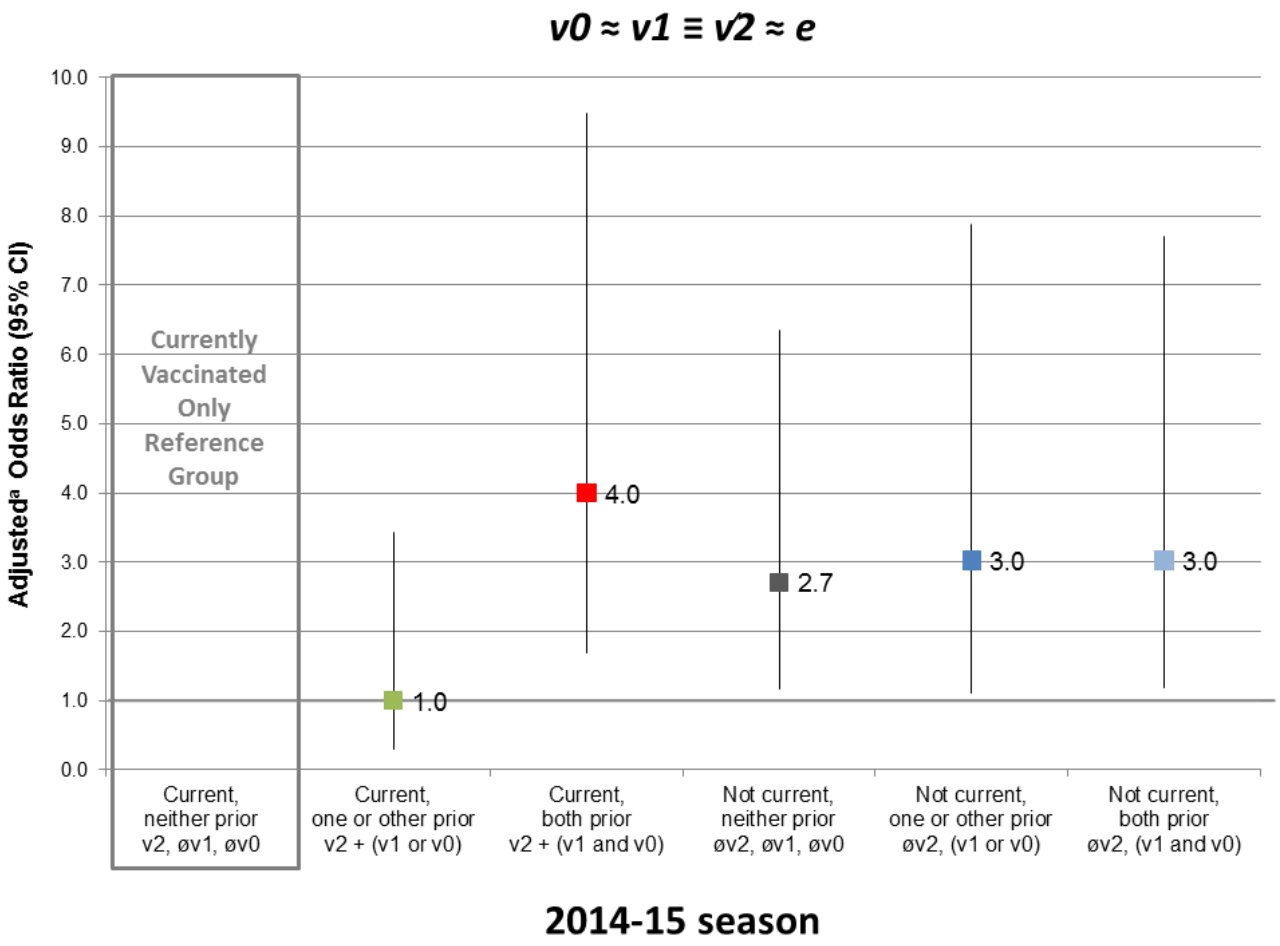


VE=vaccine effectiveness; 95% CI= 95% confidence interval; OR=odds ratio; *v2*=current season's vaccine; *v1*=prior season's vaccine; *v0*=vaccine of two prior season's ago;

≈ means antigenically related; ≠ means not antigenically related; ≡ means identical

[a]Adjusted for age group, sex, comorbidity, province, collection interval, and week of specimen collection (cubic B-spline functions with 3 equal knots).

Supplement 9B. Adjusted odds ratios (ORs) **relative to currently vaccinated only** for influenza A(H3N2) by current (v2) and/or two prior seasons' (v1 and/or v0) vaccination history among Canadian SPSN patients aged ≥9 years, 2014-15



OR=odds ratio; 95% CI= 95% confidence interval; *v2*=current season's vaccine; *v1*=prior season's vaccine; *v0*=vaccine of two prior season's ago;

≈ means antigenically related; ≠ means not antigenically related; ≡ means identical

[a]Adjusted for age group, sex, comorbidity, province, collection interval, and week of specimen collection (cubic B-spline functions with 3 equal knots).