Surveillance and outbreak report

Interim estimates of 2015/16 vaccine effectiveness against influenza A(H1N1)pdm09, Canada, February 2016

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Using a test-negative design, the Canadian Sentinel Practitioner Surveillance Network (SPSN) assessed interim 2015/16 vaccine effectiveness (VE) against influenza A(H1N1)pdm09 viruses. Adjusted VE showed significant protection of 64% (95% confidence interval (CI): 44–77%) overall and 56% (95%CI: 26–73%) for adults between 20 and 64 years-old against medically attended, laboratory-confirmed A(H1N1)pdm09 illness. Among the 67 A(H1N1)pdm09-positive specimens that were successfully sequenced, 62 (>90%) belonged to the emerging genetic 6B.1 subclade, defined by S162N (potential gain of glycosylation) and I216T mutations in the haemagglutinin protein. Findings from the Canadian SPSN indicate that the 2015/16 northern hemisphere vaccine provided significant protection against A(H1N1)pdm09 illness despite genetic evolution in circulating viruses.

Introduction

In contrast to the early and intense 2014/15 influenza season dominated by A(H3N2) viruses that were mismatched to vaccine [1,2], the beginning of the 2015/16 northern hemisphere season had low-level, mixed circulation of influenza A and B viruses. Notable influenza activity in North America and some European countries did not start until December 2015 and A(H1N1)pdm09 viruses predominated among influenza A detections, with some regional variation observed [3-5]. An increasing proportion of A(H1N1)pdm09 viruses belonging to the newly emerging 6B.1 subclade, defined by S162N (conferring a potential gain of glycosylation) and I216T mutations in the haemagglutinin (HA) protein, has been identified since October 2015 [5-7].

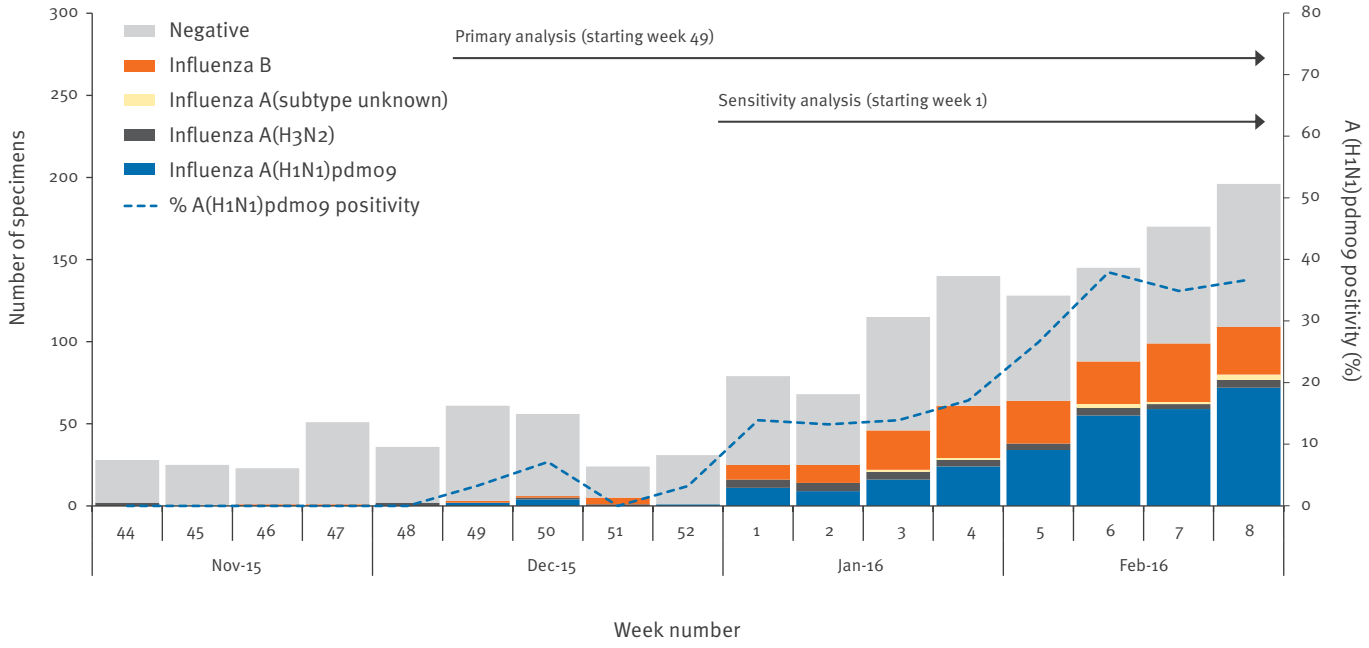
In February 2016, the Influenza – Monitoring Vaccine Effectiveness in Europe (I-MOVE) multicentre case–control study was published reporting early estimates of 2015/16 vaccine effectiveness (VE) against A(H1N1)pdm09 of<50% based on a test-negative study design [8]. This finding raised possible concerns about reduced protection conferred by the A/California/07/2009(H1N1)pdm09 vaccine component that has been recommended for the northern hemisphere seasonal influenza vaccine since the 2009 pandemic, including for the forthcoming 2016/17 season [7,9,10]. Here we present interim VE findings for A(H1N1)pdm09 viruses collected through the Canadian Sentinel Practitioner Surveillance Network (SPSN) also using a test-negative study design. Detailed genetic characterisation of sentinel viruses was undertaken to assess the contribution of the emerging 6B.1 subclade in Canada and its potential impact on measured VE.

Methods

Patients ≥ 1-year-old presenting within seven days of influenza-like illness (ILI) onset to community-based sentinel sites in four provinces (Alberta, British Columbia, Ontario, and Quebec) were eligible for study inclusion. ILI was defined as acute onset of respiratory illness with fever (based on physician's assessment

Figure 1

Influenza detections by type/subtype and week of specimen collection, Canadian Sentinel Practitioner Surveillance Network (SPSN), 1 November 2015–27 February 2016 (n = 1,375)[a]



[a] Includes specimens collected from week 44 2015 (starting 1 November) to week 8 2016 (ending 27 February). Specimens were included in the epidemic curve if the patient met the influenza-like illness case definition, had specimen collection within 7 days of illness onset, was ≥1 year-old at time of illness onset, had valid laboratory results, and had known information for all covariates assessed in vaccine effectiveness analysis (age, comorbidity, influenza-like illness onset date, province, and specimen collection date); specimens were included regardless of the patient's vaccination status or timing of vaccination. Missing collection dates were imputed as the laboratory accession date minus two days.

or self reported by the patient) and cough and one or more of the following symptoms: arthralgia, myalgia, prostration or sore throat. Fever was not required for patients ≥ 65-years-old. Epidemiological information was collected from consenting patients/guardians using a standard questionnaire at the time of specimen collection. Ethics review boards in each participating province provided study approval.

Nasal/nasopharyngeal specimens were tested for influenza viruses by real-time, reverse-transcription polymerase chain reaction (RT-PCR) at provincial reference laboratories.

Sequencing of the HA1 region was attempted on a subset of original patient specimens that tested RT-PCR-positive for A(H1N1)pdm09 and contributed to VE analysis to identify mutations in established antigenic sites (Sa, Sb, Ca1, Ca2, and Cb) [11,12].

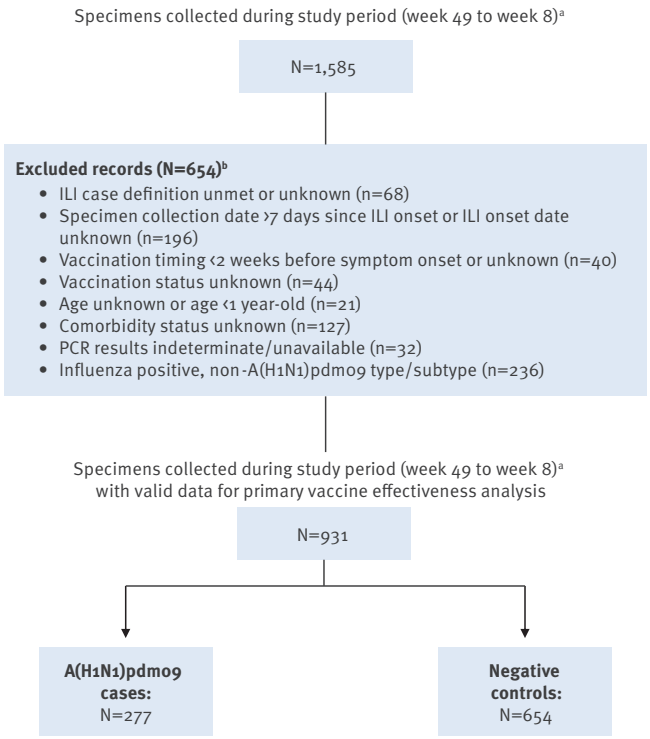
A subset of A(H1N1)pdm09-positive specimens were cultured in Madin-Darby canine kidney (MDCK) or rhesus monkey kidney cells and submitted to Canada's National Microbiology Laboratory for antigenic characterisation by haemagglutination inhibition (HI) assay using turkey erythrocytes, as previously described [12-14].

Specimens collected from week 49 2015 (starting 6 December), corresponding to the first week of A(H1N1)pdm09 detection (Figure 1), to week 8 2016 (ending 27 February) were included in the primary VE analysis. In sensitivity analyses, the study period was restricted to specimens collected from week 1 2016 (starting 3 January) onwards, corresponding to the first week when A(H1N1)pdm09 positivity exceeded 10% (Figure 1).

Patients received 2015/16 influenza vaccine as part of the seasonal vaccination campaign, typically commencing in October in each province. Patients who self-reported receiving at least one dose of influenza vaccine ≥ 2 weeks before ILI onset were considered vaccinated; those vaccinated < 2 weeks before ILI onset were excluded. Odds ratios (OR) for laboratory-confirmed, medically attended A(H1N1)pdm09 illness in vaccinated compared to unvaccinated participants were derived using logisitic regression. VE (expressed as a percentage) was calculated as 1 – OR. ORs were adjusted for age group, comorbidity, province, interval from specimen collection to ILI onset, and calendar time (based on 2-week interval for specimen collection). All analyses were conducted using SAS version 9.3 (SAS Inc., Cary, NC).

Figure 2

Study exclusions, interim influenza A(H1N1)pdm09 vaccine effectiveness (VE) evaluation, Canadian Sentinel Practitioner Surveillance Network (SPSN), 6 December 2015–27 February 2016 (n = 1,585)



ILI: influenza-like illness; PCR: polymerase chain reaction.

[a] Includes specimens collected from week 49 2015 (starting 6 December) to week 8 2016 (ending 27 February).

[b] Exclusions are not mutually exclusive; specimens may have >1 exclusion criterion that applies. Counts for each criterion will sum to more than the total number of specimens excluded.

Results

From 6 December 2015 to 27 February 2016, 1,585 specimens were collected, of which 1,167 (74%) met study inclusion criteria (Figure 2). Influenza viruses were detected in 513 (44%) specimens, including 321 (63%) influenza A, 191 (37%) influenza B, and one influenza A/B co-infection. Of the 314 of 322 (98%) influenza A viruses with known subtype, 277 (88%) were A(H1N1) pdm09.

Overall 14% (n=40) of cases and 31% (n=200) of controls were considered vaccinated (p < 0.01) (Table 1).

Among vaccinated participants who had available data for prior vaccination history, 89% (198/222) of participants ≥ 2 years-old had also received the prior season's 2014/15 vaccine, 83% (172/207) ≥ 3 years-old had received both the 2014/15 and 2013/14 seasonal vaccines, and 79% (132/168) ≥ 7 years-old had received the 2009 monovalent A(H1N1)pdm09 pandemic vaccine, for which ca 95% of the product distributed in Canada was AS03-adjuvanted [15]. Among the 38 vaccinated cases with available data, 37 (97%) had received prior 2014/15 vaccine, 95% (35/37) had received both 2014/15 and 2013/14 vaccines, and 81% (22/27) had received 2009 monovalent A(H1N1)pdm09 vaccine.

After adjustment for relevant covariates, VE against A(H1N1)pdm09 was 64% (95% confidence interval (CI): 44–77%) for the primary analysis and 62% (95%CI: 41–76%) when restricted to specimens collected from week 1 2016 onwards (Table 2). Adjusted VE was 56% (95%CI: 26–73%) and 59% (95%CI: 21–79%) among adults between 20 and 64 years-old, and 20 and 49 years-old, respectively.

Sequencing was attempted on 102 A(H1N1)pdm09-positive specimens collected up to 15 February 2016. Amplification was successful for 67 (66%) of these viruses. All 67 sequenced viruses (100%) had the antigenic site mutation K163Q (Sa) and the non-antigenic site mutations A256T and K283E in HA1 associated with clade 6B, along with antigenic site mutations S185T (Sb) and S203T (Ca1) present in all clade 6 viruses [6]. Sixty-two (93%) viruses had the additional mutations S162N (Sa), conferring a potential gain of glycosylation at residues 162–164, and I216T (non-antigenic) defining the emerging 6B.1 subclade. Two (3%) viruses had the additional mutation V152T within the receptor binding site (RBS) associated with the emerging 6B.2 subclade. One 6B.1 subclade virus had a V152I mutation in addition to S162N and I216T mutations.

Of the 30 sentinel viruses collected in December and January characterised by HI assay, all were considered antigenically similar to the A/California/07/2009(H1N1) pdm09 reference strain.

Discussion

In this interim analysis, we measured statistically significant VE of 64% (95%CI: 44–77%) against circulating A(H1N1)pdm09 viruses largely belonging to the emerging 6B.1 subclade. This point estimate is slightly lower than but comparable to the significant VE measured by our network in 2013/14 mid-season (74%; 95%CI: 58–83%) [13] and end-of-season (71%; 95%CI: 58–80%) [12] analyses against dominant clade 6B A(H1N1)pdm09 viruses. In 2013/14, clade 6B viruses had the antigenic site K163Q mutation but had not yet acquired the adjacent S162N mutation associated with the newly emerging 6B.1 subclade. Despite some genetic evolution in A(H1N1)pdm09 viruses, our 2015/16 VE estimate remains closely aligned with a recent meta-analysis of test-negative studies globally for which pooled VE for seasonal vaccine against A(H1N1)pdm09 since 2010 was 61% (95%CI: 57–65%) [16].

Our point estimates of VE against A(H1N1)pdm09 are higher (but with overlapping confidence intervals) compared with those reported in similar mid-season analysis from the European I-MOVE multicentre case–control

Table 1

Characteristics of participants included in interim influenza A(H1N1)pdm09 vaccine effectiveness (VE) evaluation, Canadian Sentinel Practitioner Surveillance Network (SPSN), 6 December 2015–27 February 2016 (n = 931)

Characteristic	Overall n (column %)[a]	Distribution by case status n (column %)[a]			Vaccination coverage n (row %)	
		A(H1N1)pdm09 cases	Negative controls	P value[b]	Vaccinated	P value[b]
N (row %)	931 (100)	277 (30)	654 (70)	–	240 (26)	–
Age group in years						
1–8	132 (14)	35 (13)	97 (15)	<0.01	23 (17)	<0.01
9–19	113 (12)	25 (9)	88 (13)		14 (12)	
20–49	411 (44)	142 (51)	269 (41)		74 (18)	
50–64	179 (19)	57 (21)	122 (19)		64 (36)	
≥65	96 (10)	18 (7)	78 (12)		65 (68)	
Median (range)	36 (1–92)	37 (1–83)	35 (1–92)	0.62	53 (1–92)	<0.01
Sex[c]						
Female	571 (62)	164 (60)	407 (63)	0.37	156 (27)	0.19
Male	346 (38)	109 (40)	237 (37)		81 (23)	
Unknown	14	4	10		3	
Comorbidity[d]						
No	746 (80)	239 (86)	507 (78)	<0.01	152 (20)	<0.01
Yes	185 (20)	38 (14)	147 (22)		88 (48)	
Province						
Alberta	243 (26)	84 (30)	159 (24)	<0.01	70 (29)	0.14
British Columbia	241 (26)	47 (17)	194 (30)		65 (27)	
Ontario	323 (35)	95 (34)	228 (35)		83 (26)	
Quebec	124 (13)	51 (18)	73 (11)		22 (18)	
Collection interval in days						
≤4	697 (75)	229 (83)	468 (72)	<0.01	169 (24)	0.07
5–7	234 (25)	48 (17)	186 (28)		71 (30)	
Median (range)	3 (0–7)	3 (0–7)	3 (0–7)	<0.01	3 (0–7)	0.01
Month of specimen collection[e]						
December	152 (16)	7 (3)	145 (22)	<0.01	38 (25)	0.96
January	298 (32)	56 (20)	242 (37)		78 (26)	
February	481 (52)	214 (77)	267 (41)		124 (26)	
Vaccination status						
Any vaccination[f]	261/952 (27)	43/280 (15)	218/672 (32)	<0.01	NE	–
≥2 weeks before ILI onset	240 (26)	40 (14)	200 (31)	<0.01	NE	–
LAIV[g]	11/128 (9)	1/22 (5)	10/106 (9)	0.69	NE	–
QIV[h]	33/140 (24)	5/22 (23)	28/118 (24)	0.92	NE	–
Adjuvanted[i]	16/35 (46)	4/5 (80)	12/30 (40)	0.16	NE	–
Prior vaccination history						
2014/15 vaccine[j]	308/858 (36)	68/252 (27)	240/606 (40)	<0.01	198/308 (64)	<0.01
2013/14 vaccine[k]	301/811 (37)	74/240 (31)	227/571 (40)	0.02	185/301 (61)	<0.01
2009 monovalent vaccine[l]	296/673 (44)	79/199 (40)	217/474 (46)	0.15	132/296 (45)	<0.01

ILI: influenza-like illness; LAIV: live attenuated influenza vaccine; NE: not estimated; QIV: quadrivalent influenza vaccine.

[a] Unless otherwise specified, the values presented in this column are the number of specimens per category and percentage relative to the total. Where the denominator for the percentages differs from the total, fractions supporting the calculation of percentages are shown.

[b] Differences between cases and controls and vaccinated and unvaccinated participants were compared using the chi-squared test, Fisher's exact test or Wilcoxon rank-sum test.

[c] The percentage was only calculated among the total patients whose sex was known.

[d] Includes chronic comorbidities that place individuals at higher risk of serious complications from influenza as defined by Canada's National Advisory Committee on Immunization (NACI) including: heart, pulmonary (including asthma), renal, metabolic (such as diabetes), blood, cancer, or immune comprising conditions; conditions that compromise management of respiratory secretions and increase risk of aspiration; or morbid obesity (body mass index ≥40) [29].

[e] Missing collection dates were imputed as the laboratory accession date minus two days.

[f] Participants who received seasonal 2015/16 influenza vaccine <2 weeks before ILI onset or for whom vaccination timing was unknown were excluded from the primary analysis. They were included for assessing 'any' vaccination, regardless of timing, for comparison with other sources of vaccination coverage.

[g] Among participants between two and 59 years-old who received 2015/16 influenza vaccine ≥2 weeks before ILI onset and had known information for type of vaccine. Among participants between two and 17 years-old for whom LAIV is recommended by NACI [29], 44% (11/25, including one case) with known information had received LAIV. Among participants between two and five years-old for whom LAIV is preferentially recommended by NACI [29], 36% (5/14, including one case) with known information had received LAIV.

[h] Among participants who had known information for trivalent vs. quadrivalent vaccine. QIV includes both inactivated influenza vaccine (IIV4) and live-attenuated influenza vaccine (LAIV4) products.

[i] Among participants ≥65 years-old who received 2015/16 influenza vaccine ≥2 weeks before ILI onset and had known information for adjuvanted vaccine receipt.

[j] Children <2 years-old in 2015/16 were excluded from 2014/15 vaccine uptake analysis as they may not have been eligible for vaccination during the autumn 2014 vaccination campaign.

[k] Children <3 years-old in 2015/16 were excluded from 2013/14 vaccine uptake analysis as they may not have been eligible for vaccination during the autumn 2013 vaccination campaign.

[l] Children <7 years-old in 2015/16 were excluded from 2009 monovalent A(H1N1)pdm09 vaccine uptake analysis as they may not have been eligible for vaccination during the autumn 2009 vaccination campaign.

Table 2

Interim vaccine effectiveness (VE) estimates against influenza A(H1N1)pdm09, Canadian Sentinel Practitioner Surveillance Network (SPSN), 6 December 2015–27 February 2016 (n = 931)

Covariates	VE % (95%CI)	N total Cases: n (n vac, % vac); Controls: n (n vac, % vac)
Primary analysis[a,b]		
Unadjusted	62 (44–74)	**Total: 931** Cases: 277 (40, 14%); Controls: 654 (200, 31%)
Age group (1–8, 9–19, 20–49, 50–64, ≥65 years)	62 (43–74)	
Comorbidity (no, yes)	58 (39–72)	
Province (AB, BC, ON, QC)	62 (44–74)	
Interval from specimen collection to ILI onset (≤4, 5–7 days)	61 (43–73)	
Calendar time (2-week interval)[c]	66 (49–77)	
Age group, comorbidity, province, interval, calendar time	64 (44–77)	
Restricted to specimens collected from week 1 to week 8, 2016[b]		
Unadjusted	63 (45–75)	**Total: 776** Cases: 270 (40, 15%); Controls: 506 (161, 32%)
Age group (1–8, 9–19, 20–49, 50–64, ≥65 years)	63 (44–75)	
Comorbidity (no, yes)	60 (40–73)	
Province (AB, BC, ON, QC)	62 (44–75)	
Interval from specimen collection to ILI onset (≤4, 5–7 days)	62 (44–74)	
Calendar time (2-week interval)[c]	65 (48–76)	
Age group, comorbidity, province, interval, calendar time	62 (41–76)	
Restricted to adults 20–64 years-old[a,b]		
Unadjusted	58 (34–73)	**Total: 590** Cases: 199 (28, 14%); Controls: 391 (110, 28%)
Age group (20–49, 50–64 years)	58 (34–74)	
Comorbidity (no, yes)	56 (30–72)	
Province (AB, BC, ON, QC)	58 (33–73)	
Interval from specimen collection to ILI onset (≤4, 5–7 days)	57 (33–73)	
Calendar time (2-week interval)[c]	56 (28–73)	
Age group, comorbidity, province, interval, calendar time	56 (26–73)	
Restricted to adults 20–49 years-old[a,b]		
Unadjusted	62 (29–80)	**Total: 411** Cases: 142 (14, 10%); Controls: 269 (60, 22%)
Comorbidity (no, yes)	61 (28–79)	
Province (AB, BC, ON, QC)	63 (31–80)	
Interval from specimen collection to ILI onset (≤4, 5–7 days)	61 (27–79)	
Calendar time (2-week interval)[c]	59 (23–79)	
Comorbidity, province, interval, calendar time	59 (21–79)	

AB: Alberta; BC: British Columbia; CI: confidence interval; ILI: influenza-like illness; ON: Ontario; QC: Quebec; vac: vaccinated; VE: vaccine effectiveness.

[a] Restricted to specimens collected from week 49 2015 (starting 6 December) to week 8 2016 (ending 27 February).

[b] Patient specimens were included in VE analysis if the patient met the ILI case definition, had specimen collection within 7 days of ILI onset, was ≥1 year-old at time of ILI onset (based on age eligibility of ≥6 months for influenza vaccine during the autumn 2015 vaccination campaign), received 2015/16 influenza vaccine ≥2 weeks before ILI onset, had valid laboratory results, and had known information for all covariates assessed in VE analysis (age, comorbidity, ILI onset date, province, and specimen collection date).

[c] Based on date of specimen collection; missing collection dates were imputed as the laboratory accession date minus two days.

study, which indicated VE against A(H1N1)pdm09 of 44% (95%CI: -3 to 70%) overall and 41% (95%CI: -25 to 72%) in adults between 18 and 64 years-old, although estimates were not statistically significant [8]. Because of the low vaccination coverage in Europe (<15% among controls) and late start to the 2015/16 influenza season, the I-MOVE study likely had limited statistical power to measure stable or significant VE in mid-season analysis [8]. Their findings are, however, comparable to their previously published estimates against A(H1N1)pdm09 from the 2013/14 and 2014/15 seasons (ranging from 48 to 54%) [17,18]. Our estimates are also slightly higher than the point estimate of 51% reported for A(H1N1)pdm09 by the United States (US) Flu VE Network for the current 2015/16 season [19], although this US estimate is also not substantially different from their recently published estimate of 54% (95%CI: 46–61%) for the A(H1N1)pdm09-dominant 2013/14 season [20]. The lack of further epidemiological and genomic detail in interim findings from elsewhere prevents direct comparison to our Canadian SPSN results. In addition to possible virologic differences in the mix of circulating strains contributing to VE analysis, differences in study methods, patient

populations, and vaccination programmes, including the use of AS03-adjuvanted vaccine during the 2009 pandemic in Canada [15], should be taken into account in comparing VE estimates across settings or seasons [16].

As seen in prior SPSN analyses [12-14], the largest proportion of specimens in the current analysis was collected from younger, non-elderly adults between 20 and 49 years-old (44%), more notable among cases than controls (51% vs 41%) (Table 1). Adjusted VE estimates in age-stratified analyses were comparable to, but slightly lower than, our primary analysis at 59% (95%CI: 21–79%) when restricted to adults aged between 20 and 49 years-old, and 56% (95%CI: 26–73%) when broadened to include all adults between 20 and 64 years-old. This may reflect random variation owing to the smaller sample size in age-stratified analyses or unmeasured residual confounding across patient age groups. Variation by age could also reflect cohort effects resulting from different immunological priming/boosting as well as varying responses to vaccination by age or other patient factors. Over 80% of vaccinated participants in our study had received prior 2014/15 and 2013/14 seasonal vaccines; however, repeat vaccination effects could not be assessed in interim analyses because of the small number of participants who were vaccinated in the current, but not prior, season. These considerations warrant further evaluation in end-of-season VE or serological analyses and should also be taken into account in comparing VE estimates across studies or seasons with different participant age-distribution or immunological profiles.

Consistent with virus circulation globally [5,6], all sentinel A(H1N1)pdm09 viruses sequenced in our study belonged to clade 6B, with 62 of 67 (93%) more specifically falling within the emerging 6B.1 subclade. Information on genetic characterisation was not provided in the I-MOVE study [8], but separately published surveillance data for Europe report that about 80% of 6B viruses contain the S162N and I216T mutations [6]. The S162N mutation is located in antigenic site Sa close to the RBS and adjacent to the clade-defining K163Q mutation that other investigators have hypothesised to have facilitated resurgent A(H1N1) pdm09 activity disproportionately affecting middle-aged adults in 2013/14 [12,21]. The S162N mutation confers a potential gain of glycosylation at residues 162–164 that may mask K163Q and other epitopes relevant for neutralising antibody binding [6,22,23]. Despite genetic evolution, most circulating 6B viruses characterised globally, including the sentinel viruses assessed in this study, remain antigenically similar to the A/California/07/2009(H1N1)pdm09 reference strain (belonging to clade 1) based on HI and virus neutralisation assays [3-7]. Interim VE estimates from the Canadian SPSN were also not markedly affected by recent molecular changes in circulating A(H1N1) pdm09 viruses and are consistent with the recent World Health Organization (WHO) decision to retain the A/California/07/2009(H1N1)pdm09 vaccine strain for the forthcoming 2016/17 season [7]. Our interim VE estimates were submitted alongside other estimates from the Global Influenza Vaccine Effectiveness (GIVE) Collaboration and contributed to the February 2016 WHO consultation meeting on the composition of influenza vaccines for the 2016/17 northern hemisphere season [24].

Limitations of this analysis include the small number of cases available for interim analysis and resulting wide 95% CIs, particularly in stratified analyses. Although the validity of the test-negative design for deriving VE estimates has been demonstrated relative to randomised controlled trials and simulation studies [25-27], residual bias and confounding due to the observational study design cannot be ruled out. VE was measured against medically attended outpatient illness and may not be generalisable to more severe outcomes, although a recent meta-analysis suggests that VE estimates derived using the test-negative design do not substantially differ between outpatient and inpatient settings [28]. Interim estimates are only presented for A(H1N1)pdm09 viruses; where possible, VE for other types/subtypes, including clade- and lineage-specific estimates, will be explored in end-of-season analyses.

Interim VE analyses from the Canadian SPSN suggest that the 2015/16 northern hemisphere vaccine has provided significant protection against A(H1N1)pdm09 viruses belonging to the emerging 6B.1 subclade. Due to considerations such as the late start of the 2015/16 influenza season and smaller number of accrued cases, estimates may vary in end-of-season analyses and should be interpreted with caution. Further investigation into the impact of evolving antigenic site mutations, including the role of S162N and its potential glycosylation effects, on vaccine protection is required.

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l'Institut national de santé publique du Québec, and the Public Health Agency of Canada.

Conflict of interest

Within 36 months of manuscript submission, GDS received research grants and compensation for travel costs to attend an ad hoc advisory board meeting from GlaxoSmithKline (GSK), a research grant from Pfizer for unrelated studies, and separate compensation for participation as expert witness in a legal challenge of enforced healthcare worker influenza vaccination. JBG has received a research grant from Pfizer. MK has received research grants from Roche, Merck, Hologic, Boerhinger Ingelheim and Siemens. The other authors declare that they have no competing interests to report.

Authors' contributions

Principal investigators (epidemiological): DMS (National and British Columbia); JAD (Alberta); ALW (Ontario); and GDS (Québec). Principal investigator (laboratory): MK (British Columbia); SD (Alberta); JBG (Ontario); CM (Québec); and YL and NB (National Microbiology Laboratory). Virus sequencing: SS, JBG and AE. Data analysis: CC and DMS (epidemiological); SS (molecular). Preparation of first draft: CC and DMS. Draft revision and approval: all.

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