SUPPLEMENTARY MATERIAL

Skowronski DM, Chambers C, Sabaiduc S, et al. Beyond antigenic match: possible agent-host and immuno-epidemiological influences on influenza vaccine effectiveness during the 2015-16 season in Canada. J Infect Dis 2017.

TABLE OF CONTENTS

SUPPLEMENT 1. Birth (immunological) cohorts defined by influenza A(H1N1) priming epochs

SUMMARY

In their recent publication, Linderman et al. [1] emphasize amino acid position 166 (based on the A(H3) numbering scheme) located within pivotal antigenic site Sa atop the hemagglutinin (HA) surface protein of influenza A(H1N1) viruses as potentially immuno-dominant and influential on original antigenic sin (OAS) responses. Position 166 based on A(H3) numbering corresponds with position 163 based on the A(H1) numbering scheme[2] to which we instead preferentially refer throughout here for A(H1N1) viruses.

Authors hypothesize that first (priming) exposure to an A(H1N1) virus with a particular amino acid at position 163 (e.g. x163) induces a robust imprint that determines immunity to subsequent A(H1N1) viruses with a different amino acid at x163. Conversely, glycans (i.e. sugar residues) present nearby on the viral HA can mask that epitope, preventing antibody focusing or re-focusing toward x163 specificity and enabling a broader immune response to include other Sa epitopes or HA antigenic sites (such as Sb or Ca1). Authors predict immunological cohort effects based on priming epochs defined by exposure to a specific amino acid at x163 and driven by alterations in the gain or loss of N-linked glycosylation sites for which glycans may potentially shield or expose, respectively, x163 [1].

In 2012-13, a new clade of A(H1N1)pdm09 virus called clade 6B emerged that has the amino acid glutamine (Q) at position 163 (i.e. Q163) and that became the dominant circulating strain during the subsequent 2013-14 A(H1N1)pdm09 epidemic in the northern hemisphere. All previous A(H1N1) viruses since at least 1977 instead bore lysine (K) at that position (i.e. K163) [1].

Linderman et al. [1] hypothesize that **individuals born between 1940 and 1984—notably between 1965 and 1979** (i.e. those aged between 37 and 51 years old in 2016)—and who were originally exposed to K163 viruses lacking glycan shielding would have mounted preferential K163-specific (but Q163-impaired) antibody responses. Authors also propose that annual administration of A/California/07/2009 A(H1N1)pdm09 vaccines that were consistently K163 since 2009 would have preferentially reinforced K163 specificity (as would A(H1N1)pdm09 infection prior to Q163 emergence in 2012-13).

In this Supplement, the priming epochs (or immunological cohort effects) proposed by Linderman et al. [1] are adapted for their potential effects on vaccine effectiveness (VE) during the 2015-16 season. Additional considerations related to lag time from birth or new variant emergence to priming exposure (ranging as much as 6-9 years [3-5]) as well as heterosubtypic exposures are also incorporated. Adjusted age groups (including children) are summarized in **S1 Table 1** and explained in more detail in the ensuing pages:

S1 Table 1. Adapted age groups for exploring the effects of potential K163 priming specificity on A(H1N1)pdm09 vaccine effectiveness (VE) against Q163 A(H1N1)pdm09 viruses in 2016[1]:

Age group, 2016[1] [Year of Birth]	Potential A(H1N1) K163-priming specificity	Commentary
1-16 years [2000 – 2015]	Various	A(H1N1): K163 masked by N125+N160 glycans[2] until 2008 A(H1N1)pdm09: K163 from 2009 until 2012-13, then Q163 without N162 glycan[2] shielding until 2015
17-30 years [1986-1999]	No	A(H1N1): K163 masked by N125+N160 glycan[2] shielding
31-39 years [1977-1985]	Yes, if A(H1N1) primed before 1986	A(H1N1): K163 without glycan[2] shielding 1977-1985
40-48 years [1968-1976][3]	Yes, A(H1N1)-specific priming beginning from 1977	A(H3N2) epoch. No A(H1N1) priming until 1977. Preceding heterosubtypic A(H3N2) priming likely.
49-59 years [1957-1967][4]	Yes, A(H1N1)-specific priming beginning from 1977	A(H2N2) epoch No A(H1N1) priming until 1977. Preceding heterosubtypic A(H2N2) priming likely.
≥60 years [before 1957]	Various	A(H1N1): various non-Q-163 specificity with/without glycan[2] shielding

[1] The 2015-16 epidemic was delayed; hence 2016 is used to derive age bands for the 2015-16 season. For the 2015 period of the 2015-16 influenza season, subtract 1 year from the specified age bands. For 2013-14, subtract 2 years from the specified age bands.
[2] Potential gain of N-linked glycosylation—gain of a sugar moiety often represented as +CHO.
[3] Period of no A(H1N1) circulation: A(H3N2) circulation following the 1968 pandemic.
[4] Period of no A(H1N1) circulation: A(H2N2) circulation following the 1957 pandemic.

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BACKGROUND

HA numbering scheme

Of note, the HA amino acid numbering cited in this Supplement corresponds with the H1 numbering scheme for A(H1N1) viruses and begins with the signal peptide removed. This should be taken into account when comparing with the H3 numbering scheme for A(H3N2) viruses used instead by Linderman et al. [1] to also describe A(H1N1) viruses. Relevant translations are shown in **S1 Table 2**:

S1 Table 2. Translation of H1 amino acid position according to numbering scheme used

H1 numbering scheme (used here) [2]	H3 numbering scheme (used by Linderman et al. [1])
125	129
127	131
155	158
160	163
162	165
163	166

x163 specificity

In 2012-13, A(H1N1)pdm09 viruses became Q163; prior to that, however, all A(H1N1) viruses were consistently non-Q at position 163 in so far as available archival sequences enable that determination. Influenza (H1N1) viruses had instead been consistently K163 since at least 1977 with more variability in the amino acid at that position (i.e. K/N/R/T/E) during the early to middle part of the last century (**S1 Table 3**).

In that context, preferential non-Q163 OAS responses could affect all birth cohorts prior to 2012-13, notably among those exposed to A(H1N1) viruses containing K163 after their reemergence in 1977. Variability by age in K163 specificity is hypothesized by Linderman et al. [1] to be driven by historic alterations in the location and efficiency of glycosylation sites potentially shielding K163.

Glycosylation: alterations and implications

A potential gain (or loss) of glycosylation is conferred to a protein whenever an amino acid change occurs that confers (or disrupts) the amino acid sequence "N-z-S/T", where N is the amino acid asparagine, z is any amino acid other than proline (non-P), and S/T is either serine or threonine [6-8]. The potential gain of a glycosylation site is often represented as +CHO; conversely loss of glycosylation is often represented as –CHO.

Glycosylation site alterations occur more often within the HA than the neuraminidase surface protein of influenza viruses and more frequently on the top of the HA head, proximal to the receptor binding site (RBS) and the pivotal antigenic site Sa of A(H1N1) viruses [6-8].

Few early A(H1N1) viral sequences exist, but historically, N-linked glycosylation sites affecting antigenic site Sa have involved amino acid positions 125 or 127, position 155, and positions 160 or 162 [6-8]. Potential glycosylation at position 155 (in the 1950s) has been debated but historic alterations and implications of N125/N127 and N160/N162 as emphasized by Linderman et al. [1] are outlined below:

<u>N125 or N127</u>

These two glycosylation sites have been emphasized for their differential effects in shielding or exposing x163. N125 is located at the centre of antigenic site Sa and may shield it more effectively than N127 located instead adjacent to the Sa.

N125 and N127 were variously present in A(H1N1) viruses during the 1930s; N127 became more prominent in the 1940s and 1950s and from 1977 to 1985; whereas N125 replaced N127 from 1986 to 2008. A(H1N1)pdm09 viruses since 2009 have had neither N125 nor N127. Linderman et al. [1] propose that, through more effective K163 shielding, the gain of the N125 glycosylation from 1986 to 2008 may have blocked the induction of K163-specific priming during that period.

N160 or N162

Both N160 and N162 are located within antigenic site Sa, but N160 is in a more central Sa position, whereas N162 is located at its edge. Both glycosylation sites may shield not only the Sa of the same HA monomer but also part of antigenic sites Sb and Ca2 on the adjacent monomer of the HA trimer.

N162 appeared in 1933 but was replaced by N160 from 1951 to 1957 and from 1977 to 2008. N160 accompanied N125 between 1986 and 2008, potentially contributing to more pronounced K163 shielding during this period.

A(H1N1)pdm09 viruses bore neither N160 nor N162 until 2015 when N162 re-appeared for the first time since the 1940s [1], accompanying Q163 in clade 6B viruses that were then further distinguished by N162 as sub-clade 6B.1 which dominated during the 2015-16 season [9,10].

IMMUNOLOGICAL COHORT EFFECTS

Glycan shielding of K163 between 1986 and 2008

As outlined above, glycan shielding of x163 likely became more efficient between 1986 and 2008. As per Linderman et al. [1] shift in the glycosylation site to position 125 located at the centre of the Sa, combined with the established glycosylation site at position 160 also at the Sa centre (i.e. N125 + N160), will have prominently masked the K163 epitope, preventing K163-specific priming. With the Sa site maximally shielded, antibodies might then also be directed toward other sites such as Sb.

Delay from birth to first influenza priming exposure

Potential x163-specific priming epochs determined by variation in the gain or loss of glycan shielding are shown in **S1 Table 3** by birth cohort, translated into age (in years) for 2016. A lag from birth to first influenza priming exposure should also be taken into account in considering priming epochs and potential immunological cohort effects.

In a cross-sectional sero-prevalence study conducted in the Netherlands in 2006 and 2007 among children 1-7 years old, the proportion of children with detectable antibodies (titre ≥10) against influenza gradually increased with age until they reached 6-years old, when they all had antibodies to at least one influenza A virus[3]. However, sero-prevalence was higher for A(H3N2) than A(H1N1), consistent with A(H3N2) dominant epidemics between 1999 and 2006, with about three-quarters of children 7-years-old having detectable antibody to A(H1N1) strains. For children receiving influenza vaccine for the first time, expert recommendations in both Canada and the United States are to provide two spaced doses to children <9-years old but a single dose to previously unvaccinated children ≥9-years old for whom prior influenza priming is otherwise assumed[4,5]. The interval from birth to first influenza priming exposure may thus range by as much as 6-9 years around a particular birth annum and potentially longer in relation to a specific subtype or variant. We have chosen a 9-year lag to more clearly delineate distinct priming epochs as explained below.

Re-defining age groups based on potential K163-specificity, accounting for possible priming delay

Allowing as much as a 6-9-year lag to the first influenza infection, those within the birth cohort specified by the earliest YOB in a given column of **S1 Table 3** minus 6-9 years may have had the subsequent epoch's priming experience. Where there may be evolution in a particular priming epitope, younger individuals (e.g. 6-year lag from birth) are less likely than older individuals (e.g. 9-year lag) to have their own predicted priming epoch based on birth year alone.

For example, the A(H1N1) priming epoch of 1986-2008 (*without* K163-specificity) may have also been the priming experience of individuals born 1977-1985 (i.e. 31-39 years old in 2016) given a 9-year lag or of those born 1980-1985 (i.e. 31 to 36 years old in 2016) given a 6-year lag, otherwise predicted to be *with* K163-specificity. Accordingly, as per **S1 Table 3** we may have stronger expectation of first A(H1N1) exposure that is K163-specific in those born 1957-1976 (i.e. 40-59 years old in 2016) but less certainty in K163-specificity for those 31-39 years old (9-year lag) or 31-36 years old (6-year lag). Assuming a 9-year (vs. 6-year) lag to

priming exposure allows for an extended period of uncertainty in classifying cohorts based on those likely *with* vs. *without* K163-specificity.

Similarly the priming epoch of 2009-12 (*with* K163-specificity) may have also been the priming experience of individuals born 2000-2008 (i.e. 8-16 years old in 2016) given a 9-year lag or of those born 2003-2008 (i.e. 8-13 years old in 2016) given a 6-year lag, otherwise predicted to be *without* K163-specificity. Accordingly, we may have stronger expectation that those born 1986-1999 (i.e. 17-30 years old) will be *without* K163-specificity but less certainty for those 8-16 years old (9-year lag) or 8-13 years old (6-year lag).

Variable K163-specificity is already predicted among those <8 years old (and >60 years old) owing to changes in glycan shielding or amino acid substitutions associated with those birth years. As per above, K163-specificity is also variably anticipated among those 31-39 years old in 2016 (born 1977-1985) conditional upon the actual lag from birth to first influenza exposure, whereas those 40-59 years old will have had first A(H1N1) exposure *with* K163-specificity.

The choice of a 6- vs. 9-year lag interval is particularly relevant to the Linderman et al. [1] hypothesis in defining further age sub-strata among those born after 1985 (i.e. <31 years old), notably those born before 2009 (*without* K163-specificity) or since 2009 (variably *with/without* K163-specificity)(see **S1 Table 3**).

We used a 9-year (rather than 6-year or less) lag time in order to exclude those potentially *with* K163-specificity (i.e. those <17 years old) from the group *without* such priming (i.e. those 17-30 years old) after 1985. We further explored based on a 6-year lag (i.e. using age categories <14 years old and 14-30 years old) although this may have increased misclassification by including individuals potentially *with* K163-specificity in the group otherwise predicted to be *without* K163-specificity (potentially lowering VE). Ultimately, however, we had limited precision to discern differences by choice of 9- or 6-year lag interval (see footnotes 7 and 8 in **Supplement 15**).

Accordingly, in 2016[1,2] (and as summarized in S1 Table 1 and detailed in S1 Table 3):

1. **K163 priming specificity should not be evident in people born between 1986 and 1999[3] (i.e. 17-30 years old)** because of effective glycan shielding by N125 + N160 among A(H1N1) viruses to which they were earlier primed in childhood. K163 specificity may be variously expressed in those <17 years old depending upon actual age of priming. Immunity to a broader array of A(H1N1) epitopes may be anticipated vs. older cohorts.

2. **K163 priming specificity may be evident in people born before 1986 (i.e. ≥31 years old)** due to absent or less effective glycan shielding among A(H1N1) viruses to which they were earlier primed in childhood. K163 specificity may be prominent in those born between 1957 and 1976 (i.e. middle-age approximately 40-59 years) but also variously expressed in those 31-39 years and in older adults depending upon the actual age of A(H1N1) priming.

These effects on age-related risk were originally proposed by Linderman et al. [1] for 2013-14 but may be more pronounced in 2015 if additional doses of annual K163-containing A/California/07/2009 vaccine further reinforced K163 specificity. The re-appearance of N162 glycosylation in clade 6B.1 viruses in 2015 may have also partially shielded the Sa, potentially reducing 2015-16 VE against A(H1N1)pdm09 overall but especially in adults ≥31 years old with a greater dependency on antibody directed toward that site. Immunity to other epitopes (non-x163 directed) in younger individuals may provide compensatory protection.

[1] The 2015-16 epidemic was delayed; hence 2016 is used to derive age bands for the 2015-16 season. For the 2015 period of the 2015-16 influenza season, subtract 1 year from the specified age bands. For 2013, subtract 2 years from the specified age bands.
[2] For the K163-bearing A/California/07/2009-like vaccine strain used for the 2015-16 season.
[3] Allowing a 9-year lag to priming; 1986-2002 if applying a 6-year lag (i.e. 14-30 years old)

S1 Table 3. Potential N-linked glycosylation effects on x163 epitope priming by birth cohort and age in 2016

Cohorts	x163 priming epochs									
Year of birth (YOB)	1918-29	1930-39	1940-49	1950-56	1957-76	1977-85	1986-2008	2009-12	2013-14	2015-16
Age cohort (years) in 2016[1]	87-98	77-86	67-76	60-66	40-59	31-39	8-30	4-7	2-3	<1
x163 priming and H1 glycan[2] shielding considerations										
X163, where x is predominantly[3]	K	N	K and N	K; some R/N/T/E	No A(H1N1) circulation A(H2N2) epoch: 1957-67 A(H3N2) epoch: 1968-76	K	K	K	Q	
N125 (Sa, centre) or N127 (adjacent to Sa)	Neither	Variably Neither or N125 or N127 or N162	Variably Neither or N127 or N160 or N162 or N127 + N160 or N127 + N162	Variably N127 or N160 or N160 + N125 or N160 + N127		N127	N125	Neither		
N160 (Sa, centre) or N162 (Sa, edge)	Neither					N160	N160	Neither		N162
Glycan shielding of x163[4]	No	Variable				No[5]	Yes	No		Yes, likely[6]
Predicted x163 priming specificity	Yes	Variable			Yes per 1977-85[7]	Yes[5]	No	Yes - K	Yes - Q	No, unlikely[6]

N= asparagine – conferring N-linked glycosylation through the amino acid codon "N-z-S/T "where "z" is any amino acid other than proline and S/T is either one of serine or threonine; K= lysine; R= arginine; T= threonine; E=glutamic acid; Q=glutamine

[1] The 2015-16 epidemic was delayed; hence 2016 is used to derive age bands for the 2015-16 season. For the 2015 period of the 2015-16 influenza season, subtract 1 year from the specified age bands. For 2013, subtract 2 years from the specified age bands.
[2] Potential gain of N-linked glycosylation—gain of a sugar moiety is often represented as +CHO.
[3] H1 sequences with collection dates from 1918-1957 were obtained from the NIAID Influenza Research Database (IRD) [Zhang Y, et al. (2017), http://www.fludb.org] and aligned in Geneious [Version 7.1, Biomatters Ltd] to A/California/07/2009. Sequences lacking coverage of the Sa antigenic site were removed from the alignment.
[4] Assumes per Linderman et al. [1] that shielding effects from N125 are more prominent in combination with N160 both located centrally in the Sa; shielding by other glycosylation sites alone or in combination less certain.
[5] According to Linderman et al. [1]; however, as per footnote [4], the independent shielding of x163 by N160 is uncertain and was not specifically explored by Linderman et al. [1]
[6] Shielding of x163 by adjacent N162 uncertain but considered likely given proximity.
[7] Owing to absence of A(H1N1) circulation after 1957, those born between 1957 and 1976 (i.e. between 40 and 59 years old in 2016) will have shared the same A(H1N1)-specific priming epoch as those with YOB 1977-85, although heterosubtypic priming to A(H2N2) or A(H3N2) is likely to have preceded this.

CAVEATS

Linderman et al. [1] report greater K163 specificity in sera from middle-aged adults born between 1940 and 1984 (notably 1965 to 1979) compared to adults born after 1985. This interpretation is based on two-fold differences in hemagglutination inhibition (HI) assay titres to K163 vs. Q163 viruses (reinforced through further mouse/ferret investigations). Heterotypic effects or other potential contributors to immunity, alone or in combination were not considered although, as authors highlight, other variation even in nearby positions may affect HI findings. Heterosubtypic effects, particularly among birth cohorts 1957-1976, were not considered at all. As also acknowledged, differences of two-fold dilution may be considered within the margin of error for the HI assay, and only individuals with ≥2-fold differences on all three triplicate assay repeats were considered to have K163-specific responses. Authors indicated (but did not show) similar pattern based on 4-fold or 8-fold titre differences. More generally, however, the limitations of the HI assay in predicting immunity are well recognized. The human sera used in this study were collected from <200 adults across birth cohorts ranging from 1940 to 1997 as surrogates for possible x163 priming epochs; however, limited methodological details (e.g. sampling frame) or epidemiological characteristics (e.g. beyond age) were provided for interpretation and children were not included. Sequencing is available for only a small subset of viruses historically so that the timing of potential gain/loss of glycosylation or x163-specificity are difficult to conclude. Viral sequences submitted to public databases are limited, and may not be representative, particularly in defining more distant epochs. Finally, influenza priming infection may vary several years—assumed by as much as 6-9 years around a birth annum but likely shorter but potentially longer in relation to a particular subtype or variant or in adults with less social contacts or exposure opportunities. Such lag may obscure the precise demarcation of priming epochs or immunological cohort effects within the population. We have explored the influence of K163-specific priming epochs on A(H1N1)pdm09 VE estimates given the Linderman et al. [1] report and influence, but underscore this remains a hypothesis only.

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SUPPLEMENT 2. Influenza diagnosis and characterization methods

Influenza diagnosis

Specimens were tested for influenza viruses using RT-PCR assays validated for use at participating provincial reference laboratories. This includes in-house assays in Alberta [1], and in Ontario where targets included the M gene of influenza A and NS1 gene of influenza B, with influenza A(H1N1)pdm09 and A(H3N2) subtyping by real-time RT-PCR targeting the HA gene (CDC protocol) or an in-house assay targeting the NA gene of A(H1N1)pdm09 [2-4]. In British Columbia a combination of in-house and commercial assays were used [5-7] and in Quebec a commercial assay was used supplemented by in-house assay for confirmatory testing when results were inconclusive by commercial assay [2,7].

Antigenic characterization

A subset of RT-PCR-positive specimens was inoculated into Madin-Darby Canine or Rhesus Monkey Kidney cell cultures for virus isolation by provincial public health reference laboratories. Aliquots of virus isolates were submitted to Canada's National Microbiology Laboratory (NML) for antigenic characterization by HI assay using turkey or guinea pig erythrocytes and post-infection ferret anti-sera raised against egg- and/or cell-passaged reference strains, as specified [8]. For A(H3N2) viruses, HI assays were conducted in the presence of 20nM oseltamivir following re-growth in SIAT cells [9-11]. A ≥8-fold reduction in post-infection ferret HI-antibody titre raised to a given reference strain and tested against a field isolate was interpreted as antigenic distinction [8].

Sequence analysis

Sequencing was attempted on HA1 genes for influenza A and HA1/HA2 genes for influenza B viruses from original patient specimens included in VE analysis. Phylogenetic analysis using the approximate-likelihood method determined clade distribution. Deduced amino acids of HA1 were aligned in FastTree[12] and visualized in FigTree[13]. Global reference sequences, including vaccine and clade reference viruses, were obtained from the Global Initiative on Sharing All Influenza Data (GISAID) (www.gisaid.org).

Amino acid differences from the egg-adapted vaccine strain at key antigenic sites were interpreted according to previously published maps labelled A-E for A(H3N2) and Sa, Sb, Ca1, Ca2, and Cb for A(H1N1)pdm09 [14-17]. The antigenic site map for influenza B is shown below in **S2 Table 4** based on B(Victoria) numbering with the signal peptide removed [16]. Subtraction of one amino acid where appropriate is required for the corresponding B(Yamagata) antigenic site map (as previously published in [17]).

Amino acid substitutions close to the receptor-binding site (RBS) and involving antigenic site A and immunodominant site B of A(H3N2) viruses or their equivalents for H1 (Sa and Sb) and influenza B (160 loop and 190 helix) are considered most relevant to antigenicity or immunogenicity [9,14,17]. Substitutions associated with potential gain/loss of N-linked glycosylation are also emphasized for their potential effects in masking/uncovering antibody epitopes [18].

S2 Table 4. Influenza B(Victoria) map (n=73 residues) shown as amino acid number of the HA1 domain, with signal peptide (n=15 residues) removed [16]

Antigenic site (n=total number of residues)	**Residue number(s)**
120 loop (n=29)	73-79; 116-137
150 loop (n=10)	141-150
160 loop (n=9)	162-170
190 helix (n=9)	197-205
230 region (n=16)	229-244

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SUPPLEMENT 3. Influenza vaccination and ascertainment details and vaccine effectiveness estimation methods

Vaccine products

Vaccines used in participating provinces of the Canadian Sentinel Practitioner Surveillance Network (SPSN) for the 2015-16 season were mostly non-adjuvanted, trivalent inactivated, split (~50%) or subunit (~30%). An MF59-adjuvanted trivalent subunit vaccine was also publicly funded for elderly adults ≥65 years old in Alberta and British Columbia, including community-based, but comprised <10% of total doses distributed in SPSN provinces. Quadrivalent formulations of inactivated split vaccine and live attenuated influenza vaccine (LAIV) were also available in participating provinces primarily for pediatric use but each also comprised <10% of total doses distributed (<15% combined) in SPSN provinces. Quadrivalent LAIV was approved for individuals aged 2–59 years, preferentially recommended for children 2-17 years old in Alberta and Quebec, 2-8 years old in British Columbia and 2-5 years old in Ontario.

Vaccine components

For the 2015-16 northern hemisphere trivalent vaccine, the World Health Organization (WHO) recommended the same A(H1N1)pdm09 antigen, but a clade-level change for the influenza A(H3N2) and influenza B(Yamagata) components (**S3 Table 5**).

For influenza A, the egg-adapted high-growth reassortant (HGR) strains used by manufacturers were A/California/7/2009(H1N1)pdm09[NYMC X-179A/X-181] and A/Switzerland/9715293/2013(H3N2)[NIB-88], the latter belonging to clade 3C.3a, antigenically distinct from the prior season's clade 3C.1 vaccine strain (A/Texas/50/2012[X-223A]).

A switch was made to clade 3 B/Phuket/3073/2013-like (Yamagata lineage) antigen from the clade 2 B/Massachusetts/2/2012-like (Yamagata lineage) antigen used in 2013-14 and 2014-15, although the egg-adapted vaccine antigens are considered antigenically related. Quadrivalent vaccine included the same clade 1A B/Brisbane/60/2008-like (Victoria lineage) strain recommended by the WHO since the 2009-10 season.

Vaccine status ascertainment

Patients enrolled by the Canadian SPSN received 2015-16 influenza vaccine as part of the regular vaccination campaign, typically commencing in October and publicly-funded for all residents in Alberta and Ontario, and for high-risk groups and their close contacts in British Columbia and Quebec. Vaccination status was based on patient or guardian self-report and sentinel provider documentation, recorded at the time of specimen collection prior to influenza testing. Age-appropriate one- or two-dose influenza vaccine receipt was not further queried for children.

Vaccine effectiveness estimation

Primary analysis

Owing to the late 2015-16 epidemic start (**Supplement 4**), vaccine effectiveness (VE) analyses were limited to specimens collected from January 3 to April 30, 2016 (week 1—17), but also explored for additional calendar subsets beginning from November 1 (week 44) or December 6 (week 49) of 2015 to April 30 (week 17) of 2016.

VE was derived by TND: cases tested influenza-positive and controls tested negative for any influenza. Patients who self-reported receiving at least one 2015-16 influenza vaccine dose ≥2 weeks before onset of influenza-like illness (ILI) were considered vaccinated. Patients were excluded if they were: <1-year-old; not meeting the ILI case definition; vaccinated <2 weeks before ILI onset; presenting >7 days since ILI onset; otherwise missing covariate information or with indeterminate RT-PCR results. Logistic regression models derived odds ratios (OR) for medically-attended, laboratory-confirmed influenza in vaccinated versus unvaccinated participants, adjusted for recognized potential confounders, as specified for each model. VE was derived as (1-OR) X 100%.

Serial/repeat vaccination effects

Serial/repeat vaccination effects were assessed among participants ≥9-years-old through indicator-variable analyses based on current (2015-16) and up to two prior (2014-15 and/or 2013-14) seasons' vaccine history using participants unvaccinated in the current and prior season(s) as the reference group for VE estimation, with adjustment as per primary analysis. The odds ratio for influenza test-positivity was also assessed among participants

vaccinated both current and prior season(s) or prior season(s) alone relative to current season only as the reference group. The effect of prior 2009 monovalent A(H1N1)pdm09 vaccination was also explored—about 95% of monovalent A(H1N1)pdm09 doses distributed in Canada in 2009 were an AS03-adjuvanted formulation[1].

Stratified and exploratory cohort analyses

Stratified analyses were primarily conducted using an interaction term for vaccination status by the stratification variable, including standard age grouping (children: 1-19 years; non-elderly adults: 20-64 years; elderly adults: ≥65 years old), month (January-April), or epidemic-period defined as early (January-February) or late (March-April).

Age re-grouping was also undertaken for A(H1N1)pdm09 based on predicted priming epochs in order to explore potential immunological cohort effects, as defined in **Supplement 1**. Adjusted VE was explored for these regrouped age strata modeled using an interaction term for age group*vaccination status, and also by deriving separate adjusted VE estimates for subsets of data based on the stratification variable (i.e. age group).

To further explore these effects, VE by age in years was also modeled for A(H1N1)pdm09 with age smoothed as a restricted cubic-spline function using 5 knots based on percentiles (as per [2]) and an interaction term for single year of age by vaccination status. The model with 5 knots had slightly improved fit (i.e. lower Akaike Information Criterion (AIC) values) than with 3 or 7 knots, the latter also presented in sensitivity analyses (see **Supplement 16**). Year of birth (YOB) was derived based on recorded age in years in 2016. Owing to sparse data in the very old, additional age-based evaluations were subset to participants 1-76-years-old in 2016 (i.e. YOB=1940-2015).

All analyses were performed using SAS version 9.4 (SAS Inc., Cary, NC).

S3 References:

1. Skowronski DM, Janjua NZ, De Serres G, et al. Effectiveness of AS03-adjuvanted pandemic H1N1 vaccine: case-control evaluation based on sentinel surveillance system in Canada, autumn 2009. BMJ 2011; 342:c7297.

2. McLean HQ, Thompson MG, Sundaram ME, et al. Influenza vaccine effectiveness in the United States during 2012-2013: variable protection by age and virus type. Clin Infect Dis. 2015;211:1529-40.

S3 Table 5. Vaccine strains recommended by the World Health Organization[1] and corresponding egg-adapted high-growth reassortant viruses used for production of vaccine components, 2009-10 to 2015-16

Season	Influenza A(H1N1)pdm09		Influenza A(H3N2)		Influenza B(Yamagata) [TIV]		Influenza B(Victoria) [TIV or QIV]	
	WHO-recommended	Egg-adapted HGR*	WHO-recommended	Egg-adapted HGR	WHO-recommended	Egg-adapted HGR	WHO-recommended	Egg-adapted HGR
2009-10	California/7/2009	X-179A / X-181	Brisbane/10/2007	Uruguay/716/2007 X-175C	—	—	Brisbane/60/2008 (clade 1A)	Brisbane/60/2008
2010-11	California/7/2009	X-179A / X-181	Perth/16/2009	Victoria/210/2009 X-187 (clade 1)	—	—	Brisbane/60/2008 (clade 1A)	Brisbane/60/2008
2011-12	California/7/2009	X-179A / X-181	Perth/16/2009	Victoria/10/2009 X-187 (clade 1)	—	—	Brisbane/60/2008 (clade 1A)	Brisbane/60/2008
2012-13	California/7/2009	X-179A / X-181	Victoria/361/2011** (clade 3C)	IVR-165	Wisconsin/1/2010 (clade 3)[Ŧ]	Hubei-Wujiagang/158/2009 BX-39[Ω]	Brisbane/60/2008 (clade 1A)	Brisbane/60/2008
2013-14	California/7/2009	X-179A / X-181	Texas/50/2012** (clade 3C.1)	X-223A	Massachusetts/2/2012 (clade 2)[Ŧ]	BX-51B[Ω]	Brisbane/60/2008 (clade 1A)	Brisbane/60/2008
2014-15	California/7/2009	X-179A / X-181	Texas/50/2012 (clade 3C.1)	X-223A	Massachusetts/2/2012 (clade 2)[Ŧ]	BX-51B[Ω]	Brisbane/60/2008 (clade 1A)	Brisbane/60/2008
2015-16	California/7/2009	X-179A / X-181	Switzerland/9715293/2013 (clade 3C.3a)	NIB-88	Phuket/3073/2013 (clade 3)[Ŧ]	Phuket/3073/2013[Ω]	Brisbane/60/2008 (clade 1A)	Brisbane/60/2008

TIV= trivalent influenza vaccine; QIV=quadrivalent influenza vaccine; WHO=World Health Organization; HGR=high-growth reassortant
Where the strain name or clade is not specified for the HGR, it is the same as specified for the WHO-recommended vaccine strain

"—" indicates that the trivalent influenza vaccine contained no B(Yamagata)-lineage strain that season. Grey shading indicates that the specified B(Victoria)-lineage strain was included only as a component of the quadrivalent vaccine that season. Quadrivalent live attenuated influenza vaccine (LAIV) became available in Canada from 2014-15 and quadrivalent inactivated influenza vaccine also became available in Canada from the 2015-16 season, both primarily for pediatric use.

*Two egg-adapted A/California/07/2009 A(H1N1)pdm09 HGR strains, NYMC X-179A and X-181, have been used by manufacturers supplying influenza vaccine to Canada since 2009, the majority of which has been X-179A.

**These cross-season (and cross-clade) A(H3N2) viruses are considered antigenically related despite the change in strain name[2]

[Ŧ]Based on hemagglutination inhibition (HI) assay, cell propagated B(Yamagata) viruses within clade 3 are generally considered antigenically distinct from clade 2, with variation depending upon selected reference anti-sera and other conditions of HI assay[3]

[Ω]Based on HI assay, egg-adapted clade 3 and clade 2 B(Yamagata) viruses are generally considered antigenically related, with variation depending upon selected reference anti-sera and other conditions of HI assay[3]

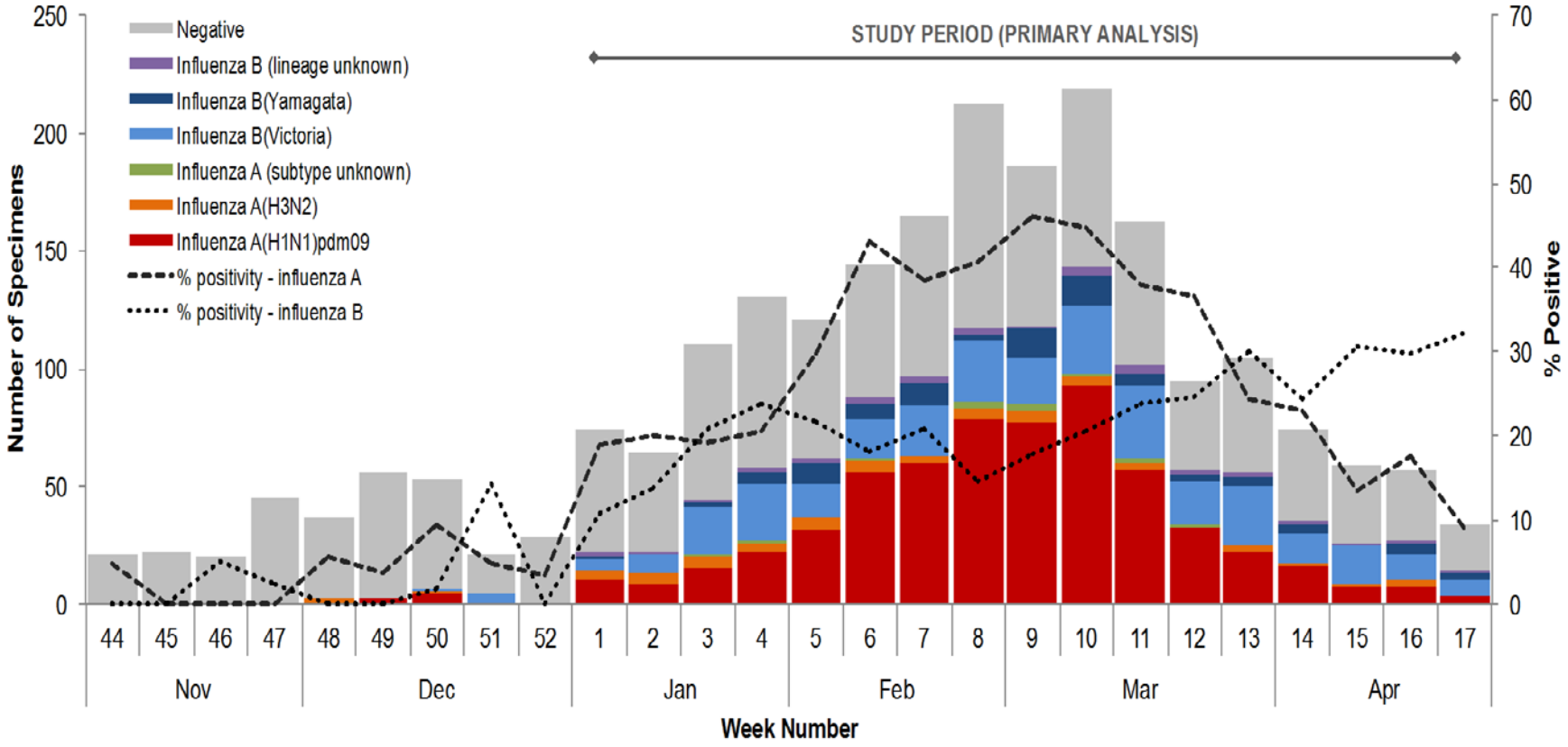
[1] World Health Organization. WHO recommendations on the composition of influenza virus vaccines. [Accessed 14 August 2017]. Available: http://www.who.int/influenza/vaccines/virus/recommendations/en/

[2] Skowronski DM, Chambers C, De Serres G, et al. Serial vaccination and the antigenic distance hypothesis: effects on influenza vaccine effectiveness during A(H3N2) epidemics in Canada, 2010-11 to 2014-15. J Infect Dis 2017;215:1059-99.

[3] The Francis Crick Institute, Worldwide Influenza Centre. Annual and interim reports. Accessed 14 August 2017]. Available at: https://www.crick.ac.uk/research/worldwide-influenza-centre/annual-and-interim-reports/

SUPPLEMENT 4. Epidemic curve, 2015-16 season

S4 Figure 1. Influenza detections by type/subtype and week of specimen collection, 2015-16 influenza vaccine effectiveness evaluation, Canadian Sentinel Practitioner Surveillance Network (SPSN)



Epidemic curve is based on the same exclusion criteria as the primary analysis. Study period for primary analysis from January 3 to April 30, 2016 (week 1-17) is indicated. Missing collection dates were imputed as the date the specimen was accessioned at the provincial laboratory minus two days, the average time between specimen collection and accession date among specimens with complete information for both values.

SUPPLEMENT 5. Antigenic site substitutions - influenza A(H1N1)pdm09, 2015-16

S5 Table 6. Antigenic map showing amino acid substitutions in sentinel A(H1N1)pdm09 viruses relative to the egg-adapted high-growth reassortant (HGR) vaccine strain, 2015-16 season, Canadian Sentinel Practitioner Surveillance Network (SPSN)

Antigenic Site			Cb			Sa	Ca2			Sa				Sb				Ca1			
HA1 Position	N	Clade	71	73	74	124	137	139	141	156	160	162	163	185	187	190	195	203	205	235	
A/California/07/2009 (cell-passaged)	-	-	S	A	S	P	P	A	A	N	K	S	K	S	D	S	A	S	R	E	Number of substitutions
HGR: A/California/07/2009 X-179A [HGR]	-	-	S	A	S	P	P	A	A	N	K	S	K	S	D	S	A	S	R	E	
A/Michigan/45/2015 (cell-passaged)	-	6B.1	S	A	S	P	P	A	A	N	K	**N**	**Q**	**T**	D	S	A	**T**	R	E	4
HGR: A/Michigan/45/2015 X-275 [HGR]	-	6B.1	S	A	S	P	P	A	A	N	K	**N**	**Q**	**T**	D	S	A	**T**	R	E	4
Alberta																					
A/Alberta/01/2016	74	6B.1										**N**	**Q**	**T**				**T**			4
A/Alberta/77/2016	1	6B.1	**P**									**N**	**Q**	**T**				**T**			5
A/Alberta/93/2016	1	6B.1								**K**		**N**	**Q**	**T**				**T**			5
A/Alberta/108/2016	1	6B.1						**T**				**N**	**Q**	**T**				**T**			5
A/Alberta/26/2016	1	6B.2											**Q**	**T**				**T**			3
British Columbia																					
A/British Columbia/01/2016	60	6B.1										**N**	**Q**	**T**				**T**			4
A/British Columbia/92/2016	3	6B.1										**N**	**Q**	**T**				**T**	**K**		5
A/British Columbia/15/2016	2	6B.2											**Q**	**T**				**T**			3
A/British Columbia/40/2016	2	6B											**Q**	**T**				**T**			3
Ontario																					
A/Ontario/002/2016	167	6B.1										**N**	**Q**	**T**				**T**			4
A/Ontario/001/2016	3	6B.1										**N**	**Q**	**I**				**T**			4
A/Ontario/009/2016	1	6B.1				**A**						**N**	**Q**	**T**				**T**			5
A/Ontario/010/2016	1	6B.1					**T**					**N**	**Q**	**T**				**T**			5
A/Ontario/092/2016	1	6B.1										**N**	**Q**	**T**			**V**	**T**			5
A/Ontario/112/2016	3	6B.1									**R**	**N**	**Q**	**T**				**T**			5
A/Ontario/142/2016	2	6B.1		**T**								**N**	**Q**	**T**				**T**			5
A/Ontario/147/2016	3	6B.1										**N**	**Q**	**T**				**T**	**K**		5
A/Ontario/183/2016	1	6B.1										**N**	**Q**	**T**	**G**			**T**			5
A/Ontario/192/2016	1	6B.1			**N**							**N**	**Q**	**T**				**T**			5
A/Ontario/194/2016	3	6B.1					**S**					**N**	**Q**	**T**				**T**			5
A/Ontario/204/2016	1	6B.1			**I**							**N**	**Q**	**T**				**T**			5
A/Ontario/214/2016	1	6B.1					**S**					**N**	**Q**	**T**		**G**		**T**			6
A/Ontario/230/2016	1	6B.1										**N**	**Q**	**T**				**T**		**D**	5
A/Ontario/003/2016	3	6B											**Q**	**T**				**T**			3
A/Ontario/188/2016	1	6B.2											**Q**	**T**				**T**			3
Quebec																					
A/Quebec/01/2016	114	6B.1										**N**	**Q**	**T**				**T**			4
A/Quebec/18/2016	2	6B.1										**N**	**Q**	**T**			**V**	**T**			5
A/Quebec/19/2016	1	6B.1										**N**	**R**	**T**				**T**			4
A/Quebec/20/2016	1	6B.1							**E**			**N**	**Q**	**T**				**T**			5
A/Quebec/111/2016	1	6B.1										**N**		**T**				**T**			3
A/Quebec/06/2016	4	6B											**Q**	**T**				**T**			3
A/Quebec/138/2016	1	6B.2											**Q**	**T**				**T**			3
Total*	462																				

HA = hemagglutinin; HGR = egg-adapted high-growth reassortant

* Total number of viruses shown in antigenic map excludes five viruses (1 clade 6B, 4 clade 6B.1) where clade could be determined but had insufficient quality for antigenic map (i.e. incomplete antigenic site coverage).

Two egg-adapted A/California/07/2009 HGR strains, NYMC X-179A and X-181, have been used by manufacturers supplying influenza vaccine to Canada since 2009, both identical in their antigenic site amino acid sequence to the WHO-recommended A/California/07/2009 reference strain. Non-antigenic site HA1substitutions distinguishing X-179A and X-181 from the WHO-recommended A/California/07/2009 reference strain include T209K and R223Q with a third non-antigenic site substitution (N129D) in X-181. The majority of vaccine doses distributed in Canada were based on X-179A.

Antigenic site substitutions in sentinel viruses are based on sequencing of viral HA1 in original patient specimens collected through the Canadian SPSN during the 2015-16 season. These are shown in bold by province relative to the sequence for X-179A (also shown in bold). Only positions with HA1 antigenic site substitutions in sentinel viruses or other reference viruses relative to X-179A are shown.

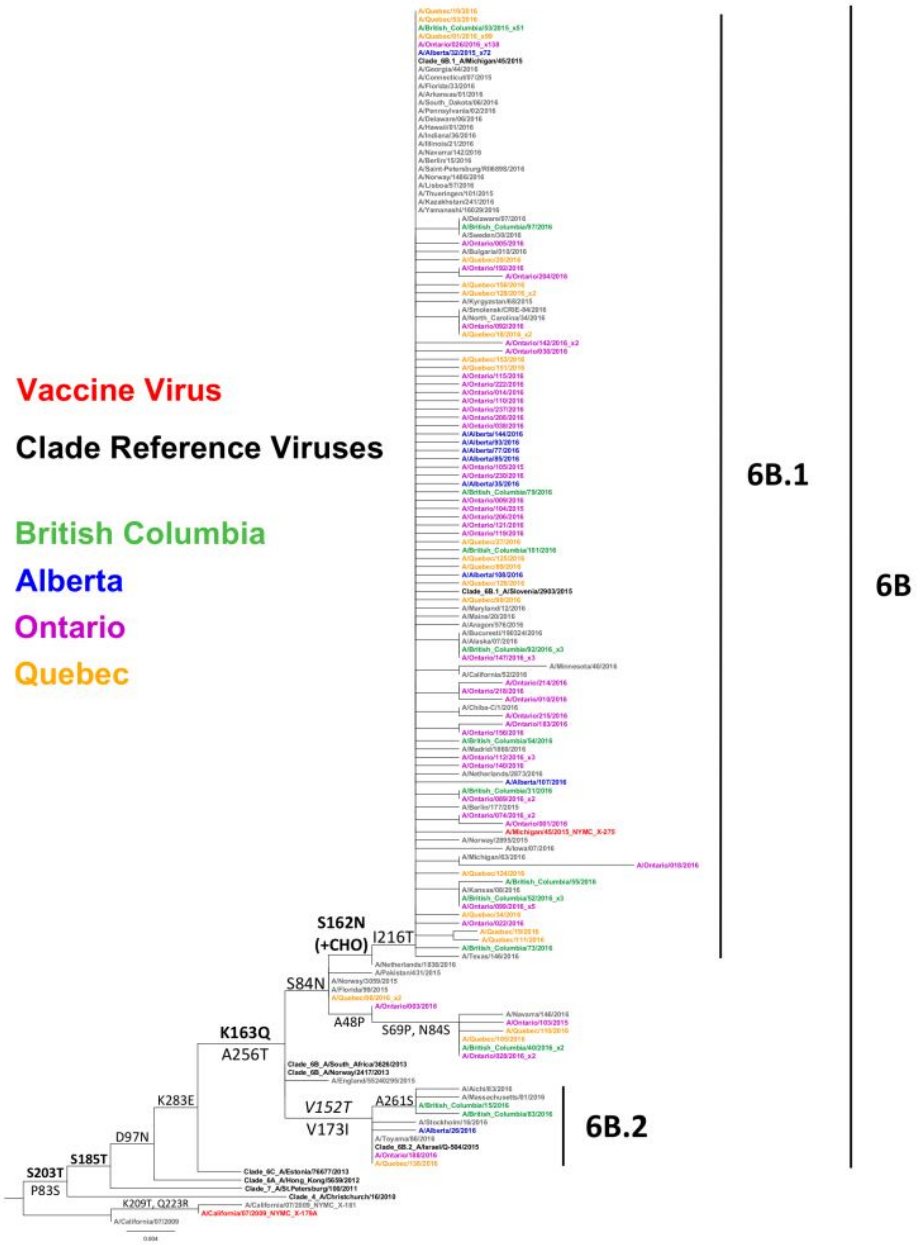
Corresponding sequences (cell- and egg-passaged HGR) for the A/Michigan/45/2015 A(H1N1)pdm09 vaccine strain recommended by the WHO for the southern hemisphere's 2017 and northern hemisphere's 2017-18 season are also displayed for interest[1]. All vaccine reference sequences were obtained from the Global Initiative on Sharing All Influenza Data (GISAID) (www.gisaid.org). Note that amino acid numbering is based on the H1 scheme and begins with the signal peptide removed. This should be taken into account when comparing with other analyses for which the H3 numbering scheme has instead been used in describing H1[2]. Accordingly, positions 162 and 163 displayed here correspond with positions 165 and 166 displayed elsewhere.

[1] World Health Organization. WHO recommendations on the composition of influenza virus vaccines. [Accessed 14 August 2017]. Available: http://www.who.int/influenza/vaccines/virus/recommendations/en/

[2] Linderman SL, Chambers BS, Zost SJ, et al. Potential antigenic explanation for atypical H1N1 infections among middle-aged adults during the 2013-2014 influenza season. Proc Natl Acad Sci U S A 2014;111:15798-803.

SUPPLEMENT 6. Phylogenetic tree – influenza A(H1N1)pdm09, 2015-16 season

S6 Figure 2. Phylogenetic tree of sentinel influenza A(H1N1)pdm09 viruses contributing to 2015-16 vaccine effectiveness analysis by the Canadian Sentinel Practitioner Surveillance Network (SPSN)



Deduced amino acids of hemaggultinin (HA1) were aligned in FastTree[1] and visualized in FigTree[2]. Substitutions in bold are located in antigenic sites; those in italics are located in the receptor binding site. Vaccine virus and clade reference virus sequences were obtained from the Global Initiative on Sharing All Influenza Data (GISAID) (www.gisaid.org).

[1] Price MN, Dehal PS, Arkin AP. FastTree 2--approximately maximum-likelihood trees for large alignments. PLoS ONE. 2010;5(3):e9490.
[2] Rambaut A. FigTree v1.4.0, a graphical viewer of phylogenetic trees. Edinburgh: University of Edinburgh. [Accessed 14 August 2017]. Available from: http://tree.bio.ed.ac.uk/software/figtree/.

SUPPLEMENT 7. Antigenic site substitutions – influenza A(H3N2), 2015-16 season

S7 Table 7. Antigenic map showing amino acid substitutions in sentinel A(H3N2) viruses relative to the egg-adapted high-growth reassortant (HGR) vaccine strain, 2015-16 season, Canadian Sentinel Practitioner Surveillance Network (SPSN)

Antigenic Site			C		E	D		B	A				B		D	B					D	E		C		Number of
HA1 Position	N	Clade	46	48	94	96	121	128	138	140	142	144	159	160	171	186	188	194	197	198	219	261	262	311	312	substitutions
A/Switzerland/9715293/2013 (cell-passaged)	-	3C.3a	S	I	Y	N	N	A	S	I	G	N	S	K	N	G	D	L	Q	S	S	R	S	Q	S	3
HGR: A/Switzerland/9715293/2013_NIB-88 (HGR)	-	3C.3a	S	I	Y	N	N	A	S	R	G	N	S	K	N	V	D	L	Q	S	Y	R	S	Q	S	-
A/Hong Kong/4801/2014 (cell-passaged)	-	3C.2a	S	I	Y	N	N	T	A	I	R	S	Y	T	N	G	D	L	Q	S	S	R	S	H	S	10
HGR: A/Hong Kong/4801/2014_X-263B (HGR)	-	3C.2a	S	I	Y	S	N	T	A	I	R	S	Y	K	N	G	D	P	Q	S	S	R	S	H	S	11
Alberta																										
A/Alberta/52/2016	2	3C.2a					K	T	A	I	R	S	Y	T	K	G					S			H		12
A/Alberta/96/2016	1	3C.2a						T	A	I	R	S	Y	T	K	G					S			H		11
British Columbia																										
A/British Columbia/02/2016	12	3C.2a						T	A	I	R	S	Y	T	K	G					S			H		11
A/British Columbia/03/2016	2	3C.2a						T	A	I	R	S	Y	T		G					S		G	H		11
A/British Columbia/07/2016	1	3C.2a						T	A	I	R	S	Y	T		G			K		S	Q		H		12
A/British Columbia/23/2016	1	3C.2a						T	A	M	R	S	Y	T		G			K		S	Q		H		12
A/British Columbia/62/2016	1	3C.2a						T	A	I	K	S	Y	T		G					S			H		10
A/British Columbia/64/2016	2	3C.3a								I						G			K	P	S				N	6
A/British Columbia/08/2016	1	3C.3a	F		H					I						G					S					5
Ontario																										
A/Ontario/031/2016	1	3C.2a					K	T	A	M	R	S	Y	T	K	G					S			H		12
A/Ontario/040/2016	7	3C.2a					K	T	A	I	R	S	Y	T	K	G					S			H		12
A/Ontario/047/2016	1	3C.2a						T	A	I	R	S	Y	T	K	G	E				S			H		12
A/Ontario/196/2016	1	3C.2a						T	A	I	R	S	Y	T		G					S			H		10
A/Ontario/231/2016	1	3C.2a		M			K	T	A	I		S	Y	T	K	G					S			H		12
A/Ontario/144/2016	1	3C.3a								I						G				P	S				N	5
Quebec																										
A/Quebec/95/2016	1	3C.2a						T	A	I	R	S	Y	T		G					S			H		10
A/Quebec/152/2016	2	3C.2a					K	T	A	I	R	S	Y	T	K	G					S			H		12
A/Quebec/65/2016	1	3C.3a								M						G				P	S					4
Total	39																									

HA = hemagglutinin; HGR = egg-adapted high-growth reassortant

Antigenic site substitutions in sentinel viruses are based on sequencing of viral HA1 in original patient specimens collected through the Canadian SPSN during the 2015-16 season. These are shown in bold by province relative to the egg-adapted clade 3C.3a A/Switzerland/9715293/2013 HGR (NIB-88) (also shown in bold) used in vaccine manufacturing. Only positions with HA1 antigenic site substitutions in sentinel viruses or other reference viruses relative to NIB-88 are shown. The antigenic map excludes four clade 3C.2a viruses sequenced from cultured isolates at the National Microbiology Laboratory included in **Table 1** of the manuscript.

Corresponding sequences (cell- and egg-passaged HGR) for the clade 3C.2a A/Hong Kong/4801/2014 vaccine strain recommended by the World Health Organization for the southern hemisphere's 2017 and northern hemisphere's 2017-18 season are also displayed for interest[1].

[1] World Health Organization. WHO recommendations on the composition of influenza virus vaccines. [Accessed 14 August 2017]. Available: http://www.who.int/influenza/vaccines/virus/recommendations/en/

SUPPLEMENT 8. Antigenic site substitutions – influenza B(Victoria), 2015-16 season

S8 Table 8. Antigenic map showing amino mino acid substitutions in sentinel B(Victoria) viruses relative to the egg-adapted quadrivalent B(Victoria) vaccine strain, 2015-16 season, Canadian Sentinel Practitioner Surveillance Network (SPSN)

Antigenic site	N	Clade	120 loop						150 loop			160 loop	190 helix		230 region		Number of
Amino acid number HA1			73	117	123	126	127	129	144	149	150	165	197	199	230	235	substitutions
B/Brisbane/60/2008 (cell-passaged)	-	1A	T	I	N	N	A	N	P	G	N	K	**N**	T	G	T	1
B/Brisbane/60/2008 (egg-passaged)	-	1A	T	I	N	N	A	N	P	G	N	K	S	T	G	T	-
B/Brisbane/60/2008_BX-31 (HGR)	-	1A	T	I	N	N	A	N	P	G	N	K	**N**	**I**	G	T	2
B/Brisbane/60/2008_BX-31B (HGR)	-	1A	T	I	N	N	A	N	P	G	N	K	**D**	T	G	T	1
B/Brisbane/60/2008_BX-33B (HGR)	-	1A	T	I	N	N	A	N	P	G	N	K	**D**	T	G	T	1
B/Brisbane/60/2008_BX-35 (HGR)	-	1A	T	I	N	N	A	N	P	G	N	K	**D**	T	G	T	1
Alberta																	
B/Alberta/001/2016	50	1A		**V**				**D**					**N**				3
B/Alberta/004/2016	16	1A		**V**		**D**		**D**					**N**				4
B/Alberta/058/2016	1	1A		**V**				**D**			**K**		**N**				4
British Columbia																	
B/British Columbia/002/2016	79	1A		**V**				**D**					**N**				3
B/British Columbia/011/2016	4	1A		**V**		**D**		**D**					**N**				4
B/British Columbia/012/2016	2	1A		**V**				**D**					**N**		**S**		4
B/British Columbia/057/2016	3	1A	**I**	**V**				**D**					**N**				4
B/British Columbia/058/2016	1	1A		**V**				**D**			**K**		**N**				4
B/British Columbia/118/2016	1	1A		**V**				**D**				**E**	**N**				4
B/British Columbia/137/2016	1	1A		**V**				**D**	**L**				**N**				4
Ontario																	
B/Ontario/003/2016	71	1A		**V**				**D**					**N**				3
B/Ontario/014/2016	1	1A		**V**				**D**		**E**			**N**				4
B/Ontario/019/2016	1	1A		**V**				**D**					**N**			**I**	4
B/Ontario/032/2016	1	1A		**V**			**T**	**D**					**N**				4
B/Ontario/103/2019	1	1A		**V**		**D**		**D**					**N**				4
B/Ontario/127/2043	1	1A						**D**					**N**				2
Quebec																	
B/Quebec/002/2016	41	1A		**V**				**D**					**N**				3
B/Quebec/043/2016	1	1A		**V**	**D**			**D**					**N**				4
B/Quebec/066/2016	1	1A		**V**				**G**					**N**				3
Total	277																

HA = hemagglutinin; HGR = egg-adapted high-growth reassortant

Antigenic site substitutions in sentinel viruses are based on sequencing of viral HA1 in original patient specimens collected through the Canadian SPSN during the 2015-16 season. These are shown in bold by province relative to the egg-passaged B/Brisbane/60/2008 reference strain (also shown in bold) used in quadrivalent vaccine manufacturing; however the specific HGR was not available from public sources. Only positions with HA1 antigenic site substitutions in sentinel viruses or other reference viruses relative to the egg-passaged B/Brisbane/60/2008 reference strain are shown.

Note that the cell-passaged B/Brisbane/60/2008 consensus sequence and all sentinel viruses have a potential glycosylation site at 197-198-199 because of the N-z-T amino acid motif. The egg-passaged B/Brisbane/60/2008 and all displayed HGRs have lost the glycosylation motif either through N197S in the egg-passaged reference displayed, or through T199I in BX-31 or through N197D in BX-31B, BX-33B or BX-35.

SUPPLEMENT 9. Antigenic site substitutions – influenza B(Yamagata), 2015-16 season

S9 Table 9. Antigenic map showing amino acid substitutions in sentinel B(Yamagata) viruses relative to the egg-adapted trivalent B(Yamagata) vaccine strain, 2015-16 season, Canadian Sentinel Practitioner Surveillance Network (SPSN)

Antigenic site	N	Clade	120 loop			150 loop	160 loop	190 helix			230 region	Number of
Amino acid number HA1			116	122	123	150	165	196	198	202	234	substitutions
B/Wisconsin/01/2010 (cell-passaged)	-	3	**N**	Q	N	I	Y	**N**	T	S	T	2
B/Hubei-Wujiagang/158/2009 _BX-39 (HGR)	-	3	**N**	Q	N	I	Y	**N**	**N**	S	T	3
B/Massachusetts/02/2012 (cell-passaged)	-	2	**N**	Q	N	**S**	**N**	**N**	T	**N**	T	5
B/Massachusetts/02/2012 _BX-51B (HGR)	-	2	**N**	Q	N	**S**	**N**	D	T	**N**	T	4
B/Phuket/3073/2013 (cell-passaged)	-	3	K	Q	N	I	Y	**N**	T	S	T	1
B/Phuket/3073/2013 (egg-passaged)	**-**	3	K	Q	N	I	Y	D	T	S	T	-
Alberta												
B/Alberta/008/2016	5	3						**N**				1
B/Alberta/041/2016	1	3	**R**					**N**			**K**	3
British Columbia												
B/British Columbia/017/2016	24	3						**N**				1
B/British Columbia/060/2016	5	3	**R**					**N**			**K**	3
B/British Columbia/061/2016	3	3		**K**				**N**				2
B/British Columbia/139/2016	1	3						**N**			**K**	2
Ontario												
B/Ontario/008/2016	27	3						**N**				1
B/Ontario/042/2016	1	3			**D**			**N**				2
Quebec												
B/Quebec/021/2016	4	3						**N**				1
Total	71											

HA = hemagglutinin; HGR = egg-adapted high-growth reassortant

Antigenic site substitutions in sentinel viruses are based on sequencing of viral HA1 in original patient specimens collected through the Canadian SPSN during the 2015-16 season. These are shown in bold by province relative to the clade 3 egg-passaged B/Phuket/3073/2013 reference strain (also shown in bold) used in trivalent vaccine manufacturing for the 2015-16 season; however the specific HGR was not available from public sources. Only positions with HA1 antigenic site substitutions in sentinel viruses or other reference viruses relative to the egg-adapted reference strain are shown. Owing to partially indeterminate residues, the antigenic map excludes two clade 3 viruses shown in **Table 1** of the manuscript.

Corresponding sequences (cell- and egg-passaged HGR) for the clade 3 B/Wisconsin/01/2010 vaccine strain recommended by the World Health Organization for the northern hemisphere's 2012-13 season and the clade 2 B/Massachusetts/02/2012 recommended by the World Health Organization for the northern hemisphere's 2013-14 and 2014-15 seasons are also displayed for interest[1].

[1] World Health Organization. WHO recommendations on the composition of influenza virus vaccines. [Accessed 14 August 2017]. Available: http://www.who.int/influenza/vaccines/virus/recommendations/en/

SUPPLEMENT 10. Participant characteristics by age, vaccination status and influenza type/subtype/lineage, 2015-16 season

S10 Table 10. Distribution by influenza type/subtype/lineage and age group

Age group (years)	Negative controls	Any influenza	Influenza A	A(H1N1)pdm09	A(H3N2)	Influenza B	B(Victoria)	B(Yamagata)
	n (column %)	n (column %)	n (column %)	n (column %)	n (column %)	n (column %)	n (column %)	n (column %)
Overall	**926**	**1082**	**664**	**596**	**55**	**423**	**305**	**85**
1-8	112 (12)	169 (16)	85 (13)	83 (14)	1 (2)	86 (20)	75 (25)	7 (8)
9-19	115 (12)	145 (13)	50 (8)	40 (7)	10 (18)	95 (22)	79 (26)	12 (14)
20-49	400 (43)	502 (46)	331 (50)	298 (50)	25 (45)	173 (41)	116 (38)	38 (45)
50-64	188 (20)	194 (18)	151 (23)	135 (23)	12 (22)	44 (10)	21 (7)	19 (22)
≥65	111 (12)	72 (7)	47 (7)	40 (7)	7 (13)	25 (6)	14 (5)	9 (11)
Median age (years)	**37**	**33**	**38**	**38**	**39**	**23**	**19**	**39**

S10 Table 11. Distribution by influenza type/subtype/lineage and age group and vaccination status

Age group (years)	Negative controls	Any influenza	Influenza A	A(H1N1)pdm09	A(H3N2)	Influenza B	B(Victoria)	B(Yamagata)
	n/N (row %)	n/N (row %)	n/N (row %)	n/N (row %)	n/N (row %)	n/N (row %)	n/N (row %)	n/N (row %)
Overall	**306/926 (33)**	**204/1082 (19)**	**134/664 (20)**	**120/596 (20)**	**10/55 (18)**	**70/423 (17)**	**45/305 (15)**	**17/85 (20)**
1-8	23/112 (21)	16/169 (9)	12/85 (14)	11/83 (13)	0/1 (0)	4/86 (5)	4/75 (5)	0/7 (0)
9-19	24/115 (21)	16/145 (11)	1/50 (2)	0/40 (0)	1/10 (10)	15/95 (16)	11/79 (14)	4/12 (33)
20-49	101/400 (25)	73/502 (15)	49/331 (15)	43/298 (14)	4/25 (16)	24/173 (14)	13/116 (11)	6/38 (16)
50-64	81/188 (43)	57/194 (29)	46/151 (30)	44/135 (33)	1/12 (8)	11/44 (25)	6/21 (29)	3/19 (16)
≥65	77/111 (69)	42/72 (58)	26/47 (55)	22/40 (55)	4/7 (57)	16/25 (64)	11/14 (79)	4/9 (44)

S10 Table 12. Distribution of test-negative controls and A(H1N1)pdm09 cases by redefined age group based on potential priming epochs[1] and month of specimen collection and epidemic period

Age group (years) (as per priming epoch[1])	Month of specimen collection n (column %, row %)				Epidemic period n (column %, row %)		Overall n (column %)
	January	February	March	April	January-February	March-April	
Negative controls	N=233	N=273	N=269	N=120	N=506	N=389	N=895
1-16	50 (21, 27)	59 (22, 32)	53 (20, 29)	21 (18, 11)	109 (22, 60)	74 (19, 40)	183 (20)
17-30	52 (22, 27)	61 (22, 32)	47 (17, 25)	30 (25, 16)	113 (22, 59)	77 (20, 41)	190 (21)
31-39	26 (11, 21)	44 (16, 35)	42 (16, 34)	13 (11, 10)	70 (14, 56)	55 (14, 44)	125 (14)
40-48	29 (12, 25)	32 (12, 27)	38 (14, 32)	18 (15, 15)	61 (12, 52)	56 (14, 48)	117 (13)
49-59	34 (15, 24)	42 (15, 30)	48 (18, 34)	18 (15, 13)	76 (15, 54)	66 (17, 46)	142 16)
60-76	42 (18, 30)	35 (13, 25)	41 (15, 30)	20 (17, 14)	77 (15, 56)	61 (16, 44)	138 (15)
A(H1N1)pdm09	N=54	N=248	N=251	N=34	N=302	N=285	N=587
1-16	16 (30, 15)	46 (19, 43)	45 (18, 42)	1 (3, 1)	62 (21, 57)	46 (16, 43)	108 (18)
17-30	12 (22, 13)	36 (15, 38)	43 (17, 45)	4 (12, 4)	48 (16, 51)	47 (16, 49)	95 (16)
31-39	13 (24, 12)	45 (18, 41)	44 (18, 40)	7 (21, 6)	58 (19, 53)	51 (18, 47)	109 (19)
40-48	8 (15, 8)	46 (19, 45)	42 (17, 41)	7 (21, 7)	54 (18, 52)	49 (17, 48)	103 (18)
49-59	3 (6, 3)	48 (19, 43)	50 (20, 45)	10 (29, 9)	51 (17, 46)	60 (21, 54)	111 (19)
60-76	2 (4, 3)	27 (11, 44)	27 (11, 44)	5 (15, 8)	29 (10, 48)	32 (11, 52)	61 (10)

[1] As defined in **Supplement 1**

SUPPLEMENT 11. Vaccine effectiveness estimates by influenza type and subtype or lineage, 2015-16 season

S11 Table 13. Unadjusted and adjusted vaccine effectiveness (VE) estimates by influenza type and subtype or lineage, 2015-16 season, Canadian Sentinel Practitioner Surveillance Network (SPSN)

	VE (95% CI)						
	Any influenza	Influenza A	A(H1N1)pdm09	A(H3N2)	Influenza B	B(Victoria)	B(Yamagata)
N	2008	1590	1522	981	1349	1231	1011
n case (% vac)	1082 (19)	664 (20)	596 (20)	55 (18)	423 (17)	305 (15)	85 (20)
n control (% vac)	926 (33)	926 (33)	926 (33)	926 (33)	926 (33)	926 (33)	926 (33)
Primary analysis[1]							
Unadjusted	53 (42-62)	49 (35-59)	49 (35-60)	55 (9-78)	60 (46-70)	65 (50-75)	49 (12-71)
Age group (1-8, 9-19, 20-49, 50-64, ≥65 years)	49 (36-59)	48 (34-60)	48 (33-60)	61 (18-81)	51 (34-64)	53 (32-68)	53 (16-73)
Sex (Female, Male)	53 (42-61)	48 (35-59)	48 (34-60)	54 (7-77)	59 (46-70)	65 (50-75)	49 (12-71)
Comorbidity (No, Yes)	49 (37-59)	46 (31-58)	47 (31-58)	50 (-1-76)	55 (40-67)	61 (45-73)	46 (6-69)
Province (Alberta, British Columbia, Ontario, Quebec)	52 (40-61)	47 (32-58)	46 (32-58)	54 (6-77)	59 (45-69)	65 (50-75)	50 (12-71)
Specimen collection interval from ILI onset (≤4 or 5-7 days)	53 (42-62)	49 (35-59)	49 (34-60)	55 (8-77)	60 (46-70)	65 (50-75)	49 (12-71)
Calendar time (week of specimen collection)[2]	54 (43-63)	49 (35-60)	49 (34-60)	54 (8-77)	60 (47-70)	65 (51-75)	51 (15-72)
Fully adjusted[3]	46 (32-57)	44 (27-57)	43 (25-57)	NE	50 (31-63)	54 (32-68)	NE
Sensitivity analysis – study period							
Subset to specimens collected from week 49 (starting December 6, 2015) to week 17							
n case (% vac)	1095 (19)	673 (20)	603 (20)	57 (19)	427 (16)	309 (15)	85 (20)
n control (% vac)	1072 (32)	1072 (32)	1072 (32)	1072 (32)	1072 (32)	1072 (32)	1072 (32)
Unadjusted	51 (41-60)	47 (33-58)	47 (33-59)	49 (1-74)	59 (45-69)	64 (49-74)	47 (9-69)
Fully adjusted[3]	47 (33-57)	44 (28-57)	45 (27-58)	NE	50 (32-64)	54 (33-68)	NE
Subset to specimens collected from week 44 (starting November 1, 2015) to week 17 (usual SPSN analysis period)							
n case (% vac)	1100 (19)	676 (20)	603 (20)	60 (18)	429 (16)	310 (15)	86 (20)
n control (% vac)	1211 (31)	1211 (31)	1211 (31)	1211 (31)	1211 (31)	1211 (31)	1211 (31)
Unadjusted	49 (38-58)	44 (30-56)	45 (30-56)	50 (3-74)	57 (42-67)	62 (47-73)	45 (5-68)
Fully adjusted[3]	47 (34-58)	45 (28-57)	45 (27-58)	NE	50 (32-64)	54 (33-68)	NE

CI=confidence interval; NE = not estimated owing to insufficient sample size; VE=vaccine effectiveness; % vacc=% vaccinated

[1] Patients <1year-old (or age unknown) at specimen collection, those who did not meet the ILI case definition, those with specimen collection >7 days since ILI onset or ILI onset date unknown, those vaccinated <2weeks before onset or with unknown vaccination status or timing, with indeterminate RT-PCR results or missing sex or comorbidity information were excluded from primary analysis (and all other analyses except where otherwise specified).

[2] Calendar time was modeled by week of specimen collection using cubic B-spline functions with 3 equally spaced knots.

[3] Fully adjusted model includes age group, sex, comorbidity, province, collection interval and calendar time (week of specimen collection using cubic B-spline with 3 equally spaced knots) except where otherwise specified

S11 Table 13 Cont'd.

	VE (95% CI)						
	Any influenza	Influenza A	A(H1N1)pdm09	A(H3N2)	Influenza B	B(Victoria)	B(Yamagata)
N	2008	1590	1522	981	1349	1231	1011
n case (% vac)	1082 (19)	664 (20)	596 (20)	55 (18)	423 (17)	305 (15)	85 (20)
n control (% vac)	926 (33)	926 (33)	926 (33)	926 (33)	926 (33)	926 (33)	926 (33)
Stratified analyses – interaction model							
By month of specimen collection							
Main effects and interaction							
January	58 (28-75)	67 (30-85)	65 (19-85)	NE	47 (-3-73)	50 (-5-76)	NE
February	67 (53-77)	69 (54-80)	70 (54-80)	NE	62 (36-78)	68 (38-84)	NE
March	35 (8-53)	22 (-14-46)	26 (-7-50)	NE	56 (29-73)	65 (37-80)	NE
April	59 (26-78)	24 (-63-65)	7 (-105-58)	NE	75 (45-89)	74 (38-89)	NE
Fully adjusted[1]							
January	50 (14-71)	65 (24-84)	61 (9-83)	NE	28 (-44-63)	29 (-54-67)	NE
February	62 (45-74)	66 (47-78)	66 (47-79)	NE	54 (19-73)	60 (21-80)	NE
March	22 (-11-45)	13 (-28-41)	19 (-22-46)	NE	44 (7-67)	53 (12-75)	NE
April	52 (11-74)	18 (-79-63)	0 (-126-55)	NE	68 (29-86)	63 (10-85)	NE
By epidemic period							
Main effects and interaction							
Early period (January-February)	63 (50-73)	67 (53-77)	67 (52-77)	68 (16-88)	56 (34-71)	61 (37-76)	36 (-37-71)
Late period (March-April)	42 (23-57)	25 (-3-46)	28 (-1-48)	23 (-120-73)	63 (44-75)	68 (48-80)	59 (10-81)
Fully adjusted[2]							
Early period (January-February)	57 (42-69)	63 (46-74)	62 (44-74)	NE	44 (14-64)	49 (14-70)	NE
Late period (March-April)	31 (7-49)	17 (-17-41)	19 (-15-44)	NE	53 (27-69)	56 (27-74)	NE
By 3-level age grouping							
Main effects and interaction							
1-19 y	57 (29-73)	59 (21-79)	62 (24-81)	62 (-207-95)	55 (20-75)	59 (23-78)	-2 (-222-68)
20-64 y	49 (34-60)	45 (27-59)	44 (25-58)	65 (9-87)	57 (36-71)	64 (40-79)	58 (13-80)
≥65 y	38 (-15-67)	45 (-10-73)	46 (-13-74)	41 (-177-88)	22 (-95-68)	-62 (-518-58)	65 (-40-91)
Fully adjusted[3]							
1-19 y	58 (31-75)	63 (27-81)	67 (31-84)	NE	53 (16-74)	57 (20-77)	NE
20-64 y	44 (26-57)	36 (13-53)	35 (10-52)	NE	55 (32-70)	64 (39-79)	NE
≥65 y	36 (-22-66)	45 (-15-74)	43 (-26-74)	NE	12 (-123-66)	-66 (-547-57)	NE

CI=confidence interval; NE = not estimated owing to insufficient sample size; VE=vaccine effectiveness; % vacc=% vaccinated

[1] Adjusted for age group, sex, comorbidity, province, collection interval, month of specimen collection and vaccine*month interaction.
[2] Adjusted for age group, sex, comorbidity, province, collection interval, epidemic period and vaccine*epidemic period interaction
[3] Adjusted for age group (3-level), sex, comorbidity, province, collection interval, calendar time (week of specimen collection using cubic B-spline with 3 equally spaced knots) and vaccine*age group interaction.

SUPPLEMENT 12. Vaccine effectiveness estimates by type of influenza vaccine in children, 2015-16 season

S12 Table 14. Unadjusted vaccine effectiveness (VE) estimates by type of influenza vaccine (live attenuated or inactivated) in children 2-17 years old, 2015-16 season, Canadian Sentinel Practitioner Surveillance Network (SPSN)

Model[1]	Any influenza			Influenza A(H1N1)pdm09			Influenza B		
	Case n (%)	Control n (%)	Crude VE (95% CI)	Case n (%)	Control n (%)	Crude VE (95% CI)	Case n (%)	Control n (%)	Crude VE (95% CI)
2-17 years old									
Unvaccinated	259 (97)	154 (91)	74 (35-90)	99 (95)	154 (91)	51 (-37-83)	155 (99)	154 (91)	88 (45-97)
LAIV	7 (3)	16 (9)		5 (5)	16 (9)		2 (1)	16 (9)	
Unvaccinated	259 (95)	154 (87)	63 (27-81)	99 (98)	154 (87)	87 (44-97)	155 (93)	154 (87)	54 (4-78)
IIV	15 (5)	24 (13)		2 (2)	24 (13)		11 (7)	24 (13)	
Odds ratio LAIV vs. IIV[2]		0.70 (0.23-2.10)			3.75 (0.65-21.74)			0.27 (0.05-1.40)	
2-8 years old									
Unvaccinated	152 (97)	86 (92)	60 (-31-88)	68 (93)	86 (92)	10 (-197-73)	86 (100)	86 (92)	NE
LAIV	5 (3)	7 (8)		5 (7)	7 (8)		0 (0)	7 (8)	
Unvaccinated	152 (95)	86 (87)	65 (13-86)	68 (97)	86 (87)	81 (11-96)	86 (95)	86 (87)	62 (-13-87)
IIV	8 (5)	13 (13)		2 (3)	13 (13)		5 (5)	13 (13)	
9-17 years old									
Unvaccinated	107 (98)	68 (88)	86 (33-97)	31 (100)	68 (88)	NE	69 (97)	68 (88)	78 (-5-95)
LAIV	2 (2)	9 (12)		0 (0)	9 (12)		2 (3)	9 (12)	
Unvaccinated	107 (94)	68 (86)	60 (-9-85)	31 (100)	68 (86)	NE	69 (92)	68 (86)	46 (-54-81)
IIV	7 (6)	11 (14)		0 (0)	11 (14)		6 (8)	11 (14)	

VE=vaccine effectiveness; CI=confidence interval; LAIV=live attenuated influenza vaccine; IIV=inactivated influenza vaccine; NE= not estimated owing to insufficient sample size

[1] Unadjusted analysis; same exclusion criteria as primary analysis, except includes participants with unknown sex or comorbidity. LAIV analysis excludes participants who reported IIV receipt and those with unknown vaccine type; IIV analysis excludes participants who reported LAIV receipt and those with unknown vaccine type.
[2]Directly comparing the odds of influenza test-positivity (or vaccine failure) in children who received LAIV vs. children who received IIV

SUPPLEMENT 13. Current (2015-16) and/or one prior (2014-15) season's vaccine effectiveness

S13 Table 15. Effect of current and/or one prior season's influenza vaccine in participants ≥9 years old relative to participants vaccinated neither season or current season only, 2015-16 season, Canadian Sentinel Practitioner Surveillance Network (SPSN)

Outcome[1]	Influenza cases n (%)	Negative controls n (%)	Unadjusted OR (95% CI)	Adjusted OR[2] (95% CI)	Unadjusted VE (95% CI)	Adjusted VE[2] (95% CI)
A(H1N1)pdm09						
Participants unvaccinated both seasons as reference group						
Neither prior nor current	337 (69)	420 (54)	Referent	Referent	Referent	Referent
Prior not current	49 (10)	85 (11)	0.72 (0.49-1.05)	0.75 (0.49-1.13)	28 (-5-51)	25 (-13-51)
Current not prior	9 (2)	42 (5)	0.27 (0.13-0.56)	0.25 (0.12-0.55)	73 (44-87)	75 (45-88)
Current and prior	96 (20)	228 (29)	0.52 (0.40-0.69)	0.59 (0.43-0.82)	48 (31-60)	41 (18-57)
Participants vaccinated current season only as reference group						
Neither prior nor current	337 (69)	420 (54)	3.74 (1.80-7.80)	3.95 (1.82-8.58)	--	--
Prior not current	49 (10)	85 (11)	2.69 (1.21-5.99)	2.95 (1.26-6.89)	--	--
Current not prior	9 (2)	42 (5)	Referent	Referent	--	--
Current and prior	96 (20)	228 (29)	1.96 (0.92-4.19)	2.33 (1.04-5.21)	--	--
Influenza B						
Participants unvaccinated both seasons as reference group						
Neither prior nor current	220 (70)	420 (54)	Referent	Referent	Referent	Referent
Prior not current	33 (11)	85 (11)	0.74 (0.48-1.14)	0.82 (0.52-1.28)	26 (-14-52)	18 (-28-48)
Current not prior	11 (4)	42 (5)	0.50 (0.25-0.99)	0.48 (0.24-0.98)	50 (1-75)	52 (2-76)
Current and prior	50 (16)	228 (29)	0.42 (0.30-0.59)	0.54 (0.37-0.79)	58 (41-70)	46 (21-63)
Participants vaccinated current season only as reference group						
Neither prior nor current	220 (70)	420 (54)	2.00 (1.01-3.96)	2.08 (1.02-4.23)	--	--
Prior not current	33 (11)	85 (11)	1.48 (0.68-3.22)	1.69 (0.76-3.79)	--	--
Current not prior	11 (4)	42 (5)	Referent	Referent	--	--
Current and prior	50 (16)	228 (29)	0.84 (0.4-1.74)	1.12 (0.52-2.41)	--	--
Influenza B(Victoria)						
Participants unvaccinated both seasons as reference group						
Neither prior nor current	148 (70)	420 (54)	Referent	Referent	Referent	Referent
Prior not current	25 (12)	85 (11)	0.83 (0.51-1.35)	0.90 (0.54-1.51)	17 (-35-49)	10 (-51-46)
Current not prior	8 (4)	42 (5)	0.54 (0.25-1.18)	0.54 (0.24-1.21)	46 (-18-75)	46 (-21-76)
Current and prior	31 (15)	228 (29)	0.39 (0.25-0.59)	0.51 (0.32-0.82)	61 (41-75)	49 (18-68)
Participants vaccinated current season only as reference group						
Neither prior nor current	148 (70)	420 (54)	1.85 (0.85-4.03)	1.87 (0.82-4.24)	--	--
Prior not current	25 (12)	85 (11)	1.54 (0.64-3.71)	1.68 (0.67-4.24)	--	--
Current not prior	8 (4)	42 (5)	Referent	Referent	--	--
Current and prior	31 (15)	228 (29)	0.71 (0.31-1.66)	0.96 (0.39-2.35)	--	--

OR=odds ratio; VE=vaccine effectiveness; CI=confidence interval

[1] Same exclusion criteria as primary analysis but additionally subset to participants ≥9 years old and with complete data for 2014-15 and 2015-16 vaccine receipt.

[2] Adjusted for age group, sex, comorbidity, province, collection interval and calendar time (week of specimen collection using cubic B-spline with 3 equally spaced knots). VE derived as (1–OR)*100%.

SUPPLEMENT 14. Current (2015-16) and/or two prior (2014-15 and/or 2013-14) season's vaccine effectiveness

S14 Table 16. Effect of current and/or two prior season's influenza vaccine in participants ≥9 years old relative to participants vaccinated neither season or current season only, 2015-16 season, Canadian Sentinel Practitioner Surveillance Network (SPSN)

Outcome[1]	Influenza cases n (%)	Negative controls n (%)	Unadjusted OR (95% CI)	Adjusted OR[2] (95% CI)	Unadjusted VE (95% CI)	Adjusted VE[2] (95% CI)
A(H1N1)pdm09						
Participants unvaccinated all seasons as reference group						
Unvaccinated all 3 seasons	313 (66)	383 (51)	Ref	Ref	Ref	Ref
No current but one prior	26 (6)	46 (6)	0.69 (0.42-1.14)	0.79 (0.46-1.39)	31 (-14-58)	21 (-39-54)
No current but both prior	31 (7)	62 (8)	0.61 (0.39-0.97)	0.62 (0.38-1.03)	39 (3-61)	38 (-3-62)
Current season only	8 (2)	27 (4)	0.36 (0.16-0.81)	0.33 (0.14-0.77)	64 (19-84)	67 (23-86)
Current and one prior	4 (1)	28 (4)	0.17 (0.06-0.50)	0.21 (0.07-0.64)	83 (50-94)	79 (36-93)
Current and both prior	90 (19)	204 (27)	0.54 (0.40-0.72)	0.60 (0.43-0.85)	46 (28-60)	40 (15-57)
Participants vaccinated current season only as reference group						
Unvaccinated all 3 seasons	313 (66)	383 (51)	2.76 (1.24-6.16)	3.05 (1.30-7.16)	--	--
No current but one prior	26 (6)	46 (6)	1.91 (0.76-4.81)	2.43 (0.90-6.54)	--	--
No current but both prior	31 (7)	62 (8)	1.69 (0.69-4.15)	1.91 (0.73-4.96)	--	--
Current season only	8 (2)	27 (4)	Ref	Ref	--	--
Current and one prior	4 (1)	28 (4)	0.48 (0.13-1.79)	0.64 (0.16-2.54)	--	--
Current and both prior	90 (19)	204 (27)	1.49 (0.65-3.40)	1.84 (0.76-4.47)	--	--
Influenza B						
Participants unvaccinated all seasons as reference group						
Unvaccinated all 3 seasons	207 (69)	383 (51)	Ref	Ref	Ref	Ref
No current but one prior	13 (4)	46 (6)	0.52 (0.28-0.99)	0.54 (0.28-1.05)	48 (1-72)	46 (-5-72)
No current but both prior	23 (8)	62 (8)	0.69 (0.41-1.14)	0.73 (0.43-1.24)	31 (-14-59)	27 (-24-57)
Current season only	9 (3)	27 (4)	0.62 (0.28-1.34)	0.57 (0.26-1.29)	38 (-34-72)	43 (-29-74)
Current and one prior	2 (1)	28 (4)	0.13 (0.03-0.56)	0.15 (0.03-0.63)	87 (44-97)	85 (37-97)
Current and both prior	47 (16)	204 (27)	0.43 (0.30-0.61)	0.56 (0.37-0.83)	57 (39-70)	44 (17-63)
Participants vaccinated current season only as reference group						
Unvaccinated all 3 seasons	207 (69)	383 (51)	1.62 (0.75-3.51)	1.74 (0.78-3.92)	--	--
No current but one prior	13 (4)	46 (6)	0.85 (0.32-2.24)	0.94 (0.34-2.61)	--	--
No current but both prior	23 (8)	62 (8)	1.11 (0.46-2.72)	1.28 (0.50-3.24)	--	--
Current season only	9 (3)	27 (4)	Ref	Ref	--	--
Current and one prior	2 (1)	28 (4)	0.21 (0.04-1.08)	0.25 (0.05-1.34)	--	--
Current and both prior	47 (16)	204 (27)	0.69 (0.30-1.57)	0.97 (0.41-2.31)	--	--
Influenza B(Victoria)						
Participants unvaccinated all seasons as reference group						
Unvaccinated all 3 seasons	138 (69)	383 (51)	Ref	Ref	Ref	Ref
No current but one prior	8 (4)	46 (6)	0.48 (0.22-1.05)	0.53 (0.24-1.20)	52 (-5-78)	47 (-20-76)
No current but both prior	18 (9)	62 (8)	0.81 (0.46-1.41)	0.83 (0.46-1.50)	19 (-41-54)	17 (-50-54)
Current season only	6 (3)	27 (4)	0.62 (0.25-1.53)	0.60 (0.23-1.57)	38 (-53-75)	40 (-57-77)
Current and one prior	2 (1)	28 (4)	0.20 (0.05-0.84)	0.22 (0.05-0.97)	80 (16-95)	78 (3-95)
Current and both prior	28 (14)	204 (27)	0.38 (0.25-0.59)	0.53 (0.32-0.86)	62 (41-75)	47 (14-68)
Participants vaccinated current season only as reference group						
Unvaccinated all 3 seasons	138 (69)	383 (51)	1.62 (0.66-4.01)	1.67 (0.64-4.40)	--	--
No current but one prior	8 (4)	46 (6)	0.78 (0.25-2.50)	0.89 (0.26-3.06)	--	--
No current but both prior	18 (9)	62 (8)	1.31 (0.47-3.65)	1.38 (0.46-4.14)	--	--
Current season only	6 (3)	27 (4)	Ref	Ref	--	--
Current and one prior	2 (1)	28 (4)	0.32 (0.06-1.73)	0.37 (0.06-2.12)	--	--
Current and both prior	28 (14)	204 (27)	0.62 (0.23-1.63)	0.88 (0.31-2.51)	--	--

[1] Same exclusion criteria as primary analysis but additionally subset to participants ≥9 years old and with complete data for 2013-14, 2014-15 and 2015-16 vaccine receipt.

[2] Adjusted for age group, sex, comorbidity, province, collection interval and calendar time (week of specimen collection using cubic B-spline with 3 equally spaced knots). VE derived as (1–OR)*100%.

SUPPLEMENT 15. Vaccine effectiveness estimates by age groups based on potential priming epochs, 2015-16 season

S15 Table 17. VE estimates for A(H1N1)pdm09 stratified by age groups based on potential priming epochs[1] for participants 1-76 years old, 2015-16 season, Canadian Sentinel Practitioner Surveillance Network (SPSN) – interaction and subset models

	Sample size	Interaction model,[2] VE (95% CI)		Subset models[3], VE (95% CI)	
	N; n vac/n case (%); n vac/n control (%)	Unadjusted	Fully adjusted[4]	Unadjusted	Fully adjusted[5]
Overall	**1482; 113/587 (19); 282/895 (32)**				
Age groups (years) as per Linderman et al.[6,7]					
1-31 y	594; 21/212 (10); 76/382 (20)	56 (26-74)	58 (29-76)	56 (26-74)	61 (32-77)
32-76 y (YOB: 1940-1984)	**888; 92/375 (25); 206/513 (40)**	**52 (35-64)**	**41 (19-57)**	**52 (35-64)**	**41 (19-58)**
1-36 y	732; 29/274 (11); 96/458 (21)	55 (30-71)	55 (29-72)	55 (30-71)	58 (32-74)
37-51 y (YOB: 1965-1979)	**370; 30/172 (17); 61/198 (31)**	**53 (22-71)**	**43 (4-66)**	**53 (22-71)**	**41 (-4-66)**
52-76 y	380; 54/141 (38); 125/239 (52)	43 (14-63)	36 (0-60)	43 (14-63)	40 (1-63)
Finer age groups (years) as per potential priming epochs[1]					
1-16 y (YOB: 2000-2015)[8]	291; 11/108 (10); 41/183 (22)	61 (20-81)	65 (26-83)	61 (20-81)	NE
17-30 y (YOB: 1986-1999)[9]	285; 8/95 (8); 33/190 (17)	56 (1-81)	56 (-3-81)	56 (1-81)	63 (9-85)
31-39 y (YOB: 1977-1985)	234; 17/109 (16); 33/125 (26)	48 (1-73)	38 (-25-69)	48 (1-73)	41 (-21-71)
40-48 y (YOB: 1968-1976)[10]	**220; 17/103 (17); 37/117 (32)**	**57 (18-78)**	**45 (-11-72)**	**57 (18-78)**	**50 (-8-77)**
49-59 y (YOB: 1957-1967)[11]	**253; 34/111 (31); 50/142 (35)**	**19 (-38-52)**	**5 (-66-46)**	**19 (-38-52)**	**16 (-56-55)**
60-76 y (YOB: 1940-1956)	199; 26/61 (43); 88/138 (64)	58 (22-77)	58 (19-78)	58 (22-77)	58 (13-80)
1-16 y (YOB: 2000-2015)[8]	291; 11/108 (10); 41/183 (22)	61 (20-81)	65 (26-83)	61 (20-81)	NE
17-30 y (YOB: 1986-1999)[9]	285; 8/95 (8); 33/190 (17)	56 (1-81)	56 (-3-81)	56 (1-81)	63 (9-85)
31-39 y (YOB: 1977-1985)	234; 17/109 (16); 33/125 (26)	48 (1-73)	37 (-25-69)	48 (1-73)	41 (-21-71)
40-59 y (YOB: 1957-1976)[12]	**473; 51/214 (24); 87/259 (34)**	**38 (7-59)**	**25 (-16-51)**	**38 (7-59)**	**30 (-11-56)**
60-76 y (YOB: 1940-1956)	199; 26/61 (43); 88/138 (64)	58 (22-77)	58 (19-78)	58 (22-77)	58 (13-80)

VE= vaccine effectiveness; CI = confidence interval; YOB = year of birth; NE=not estimated

[1] As defined per **Supplement 1** with corresponding colour shading referring to potential A(H1N1) K163 specificity: gray=no K163 specificity; pink=conditional K163 specificity; orange=K163 specificity predicted

[2] Age-stratified estimates derived using interaction model based on entire analytic sample for A(H1N1)pdm09.

[3] Age-stratified estimates derived from subsets of data based on age group as specified.

[4] Adjusted for age group (per categories specified), sex, comorbidity, province, collection interval, calendar time (week of specimen collection using cubic B-spline with 3 equally spaced knots) and vaccine*age group interaction.

[5] Adjusted for sex, comorbidity, province, collection interval and calendar time (week of specimen collection using cubic B-spline with 3 equally spaced knots); not adjusted for age.

[6] Linderman SL, Chambers BS, Zost SJ, et al. Potential antigenic explanation for atypical H1N1 infections among middle-aged adults during the 2013-2014 influenza season. Proc Natl Acad Sci U S A 2014;111:15798-803.

[7] Linderman et al. hypothesize that individuals born between 1940 and 1984 (i.e. 32-76 years old in 2016)—notably those born between 1965 and 1979 (i.e. 37-51 years old in 2016) would have pronounced K163 specificity and impaired Q163 protection.

[8] In sensitivity analysis applying 6-year (vs. 9-year) lag to influenza priming in defining this cohort (see **Supplement 1**), adjusted VE for participants 1-13 y is 64% (95%CI=23-83) in the interaction model and not estimable in the subset model (crude subset estimate=59%;95%CI=16-80%).

[9] In sensitivity analysis applying 6-year (vs. 9-year) lag to influenza priming in defining this cohort (see **Supplement 1**), adjusted VE for participants 14-30 y is 60% (95%CI=7-83) in the interaction model and 66% (95%CI: 20-86%) in the subset model.

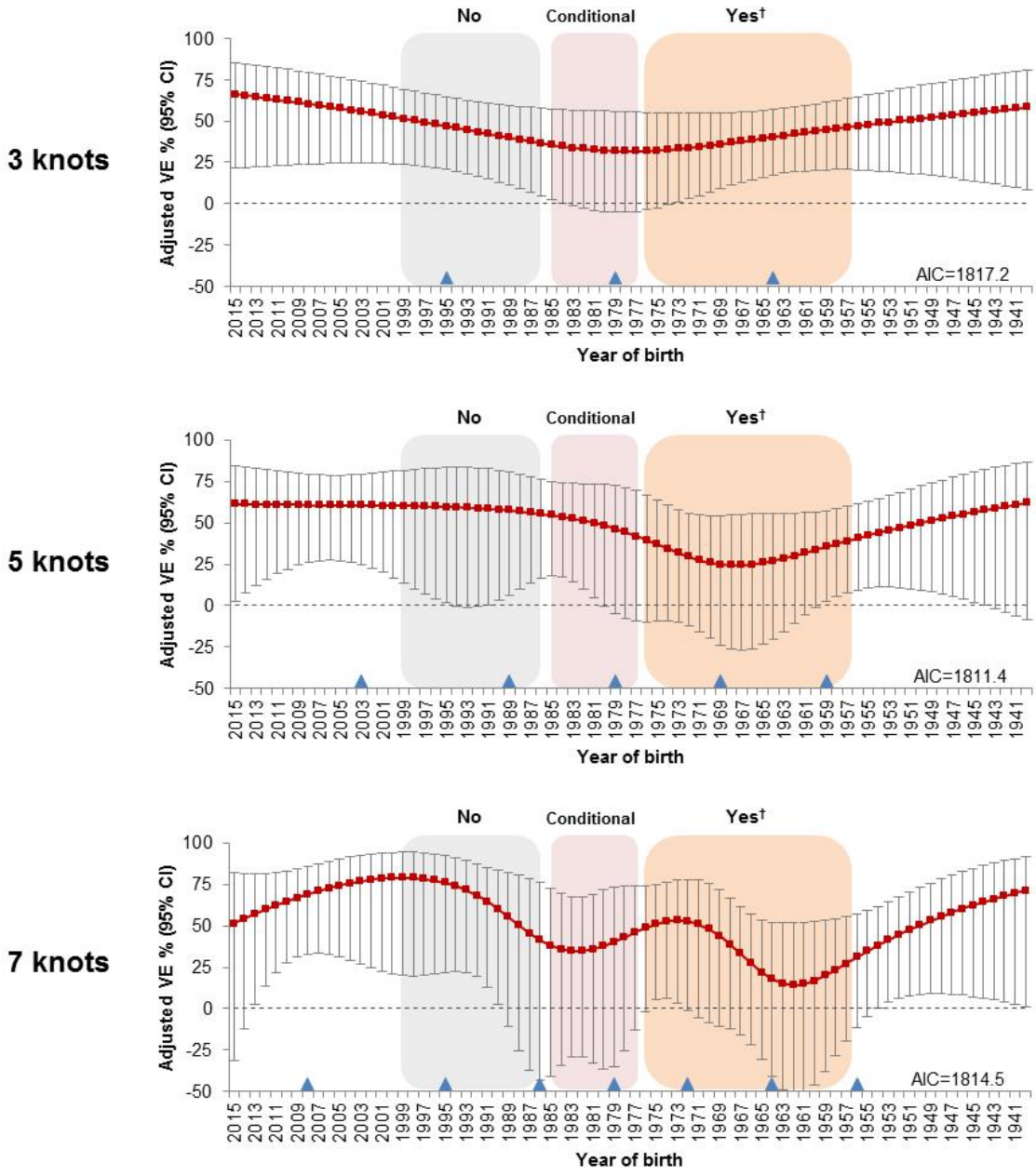
[10] Period of influenza A(H3N2) circulation; no A(H1N1) circulation.

[11] Period of influenza A(H2N2) circulation; no A(H1N1) circulation.

[12] Combining the age group 40-59 years (YOB: 1957-1976), and reflecting participants most likely heterosubtypically primed (with A(H2N2) and/or A(H3N2)) prior to A(H1N1) re-emergence in 1977.

SUPPLEMENT 16. Vaccine effectiveness estimation by year of birth – age smoothed as a restricted cubic spline function with varying (3, 5 or 7) knots, 2015-16 season

S16 Figure 3. Adjusted vaccine effectiveness (VE) against A(H1N1)pdm09 by year of birth (YOB) among Canadian Sentinel Practitioner Surveillance Network (SPSN) participants 1-76 years old during the 2015-16 season with varying number of knots in model with age as restricted cubic spline function*

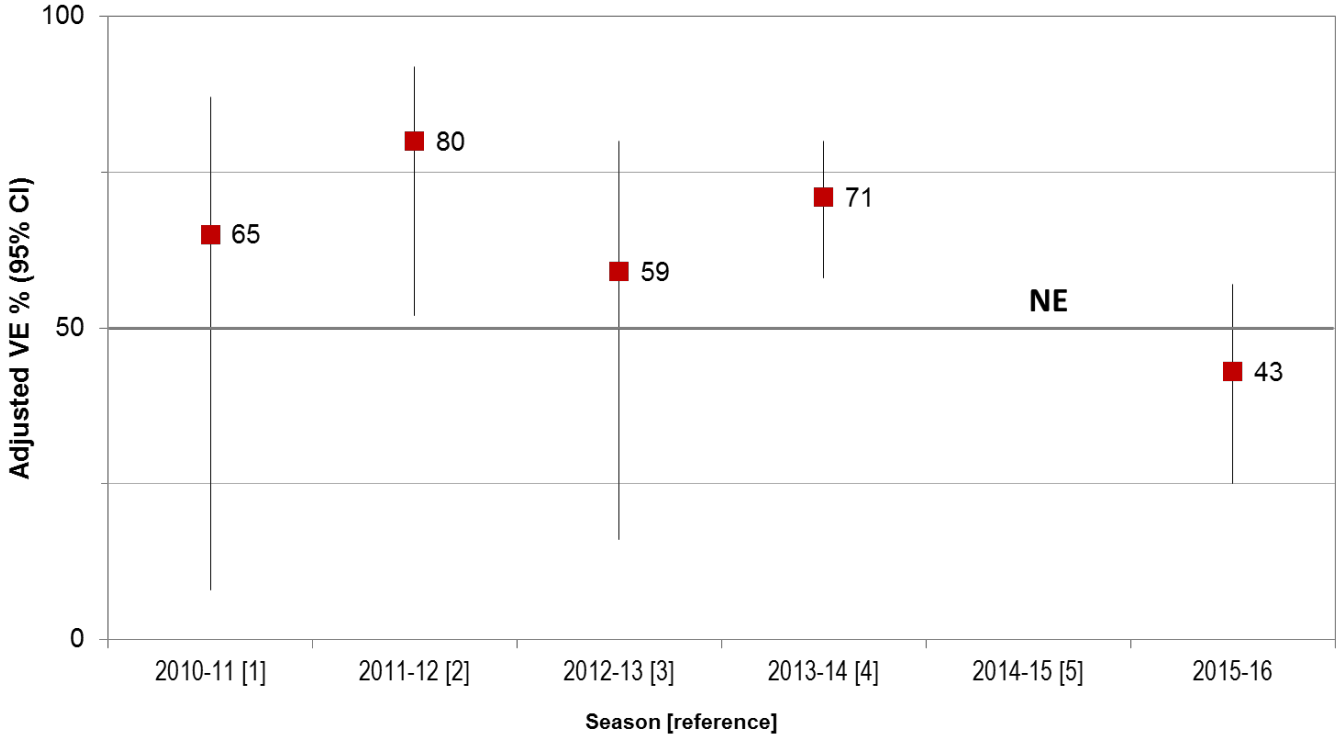


* Adjusted 2015-16 VE against A(H1N1)pdm09 by year of birth derived using age (in years) modeled as a restricted cubic spline function with number of knots based on percentiles set at 3 (top), 5 (middle) or 7 (bottom). Model includes an interaction term for age by vaccination status adjusted for age (modeled), sex, comorbidity, province, collection interval and calendar time (month of specimen collection). Blue triangles indicate position of the knots in each model. Akaike Information Criterion (AIC) values are provided as a measure of model fit for comparison purposes (i.e. minimization preferred) across models.

† Predicted K163 specificiy as per **Supplement 1** : gray=no K163 specificity; pink=conditional K163 specificity; orange=K163 specificity predicted. The 1957-76 epoch indicates period of no A(H1N1) circulation for which heterosubtypic priming with A(H2N2) (i.e. 1957-1967) and/or A(H3N2) (i.e. 1968-1976) is likely to have preceded exposure to K163-bearing A(H1N1) viruses (or vaccines) following re-emergence in 1977.

SUPPLEMENT 17. Vaccine effectiveness against A(H1N1)pdm09, 2010-11 to 2015-16

S17 Figure 4. Adjusted seasonal influenza A(H1N1)pdm09 vaccine effectiveness (VE) estimates previously published by the Canadian Sentinel Practitioner Surveillance Network (SPSN), 2010-11 to 2014-15 seasons compared to 2015-16



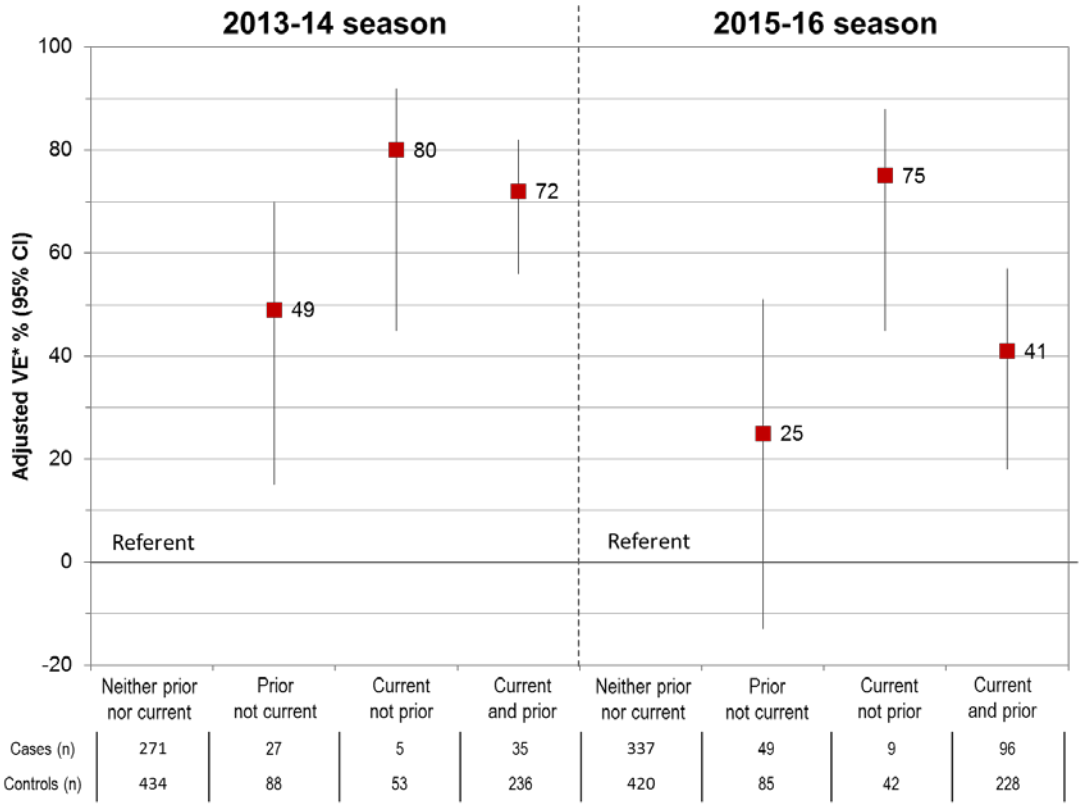
NE = not estimated owing to insufficient sample size

References

1. Skowronski DM, Janjua NZ, De Serres G, et al. A sentinel platform to evaluate influenza vaccine effectiveness and new variant circulation, Canada 2010-11 season. Clinical Infect Dis. 2012;55:332-42.
2. Skowronski DM, Janjua NZ, Sabaiduc S, et al. Influenza A/subtype and B/lineage effectiveness estimates for the 2011–12 trivalent vaccine: cross-season and cross-lineage protection with unchanged vaccine. J Infect Dis 2014; 210:126–37.
3. Skowronski DM, Janjua NZ, De Serres G, et al. Low 2012-13 influenza vaccine effectiveness associated with mutations in the egg-adapted H3N2 vaccine strain, not antigenic drift in circulating viruses. PLoS ONE. 2014;9(3):e92153.
4. Skowronski DM, Chambers C, Sabaiduc S, et al. Integrated sentinel surveillance linking genetic, antigenic and epidemiologic monitoring of influenza vaccine-virus relatedness and effectiveness during the 2013-2014 influenza season. J Infect Dis 2015;212:726-39.
5. Skowronski DM, Chambers C, Sabaiduc S, et al. A perfect storm: impact of genomic variation and serial vaccination on low influenza vaccine effectiveness during the 2014-2015 season. Clin Infect Dis 2016;63:21-32.

SUPPLEMENT 18. Current and/or prior season's vaccine effectiveness, 2013-14 and 2015-16 seasons

S18 Figure 5. Effect of prior and/or current season's influenza vaccine effectiveness (VE) against influenza A(H1N1)pdm09 in participants ≥9 years old relative to those who were vaccinated neither season, Canadian Sentinel Practitioner Surveillance Network (SPSN), 2013-14[1] and 2015-16 seasons



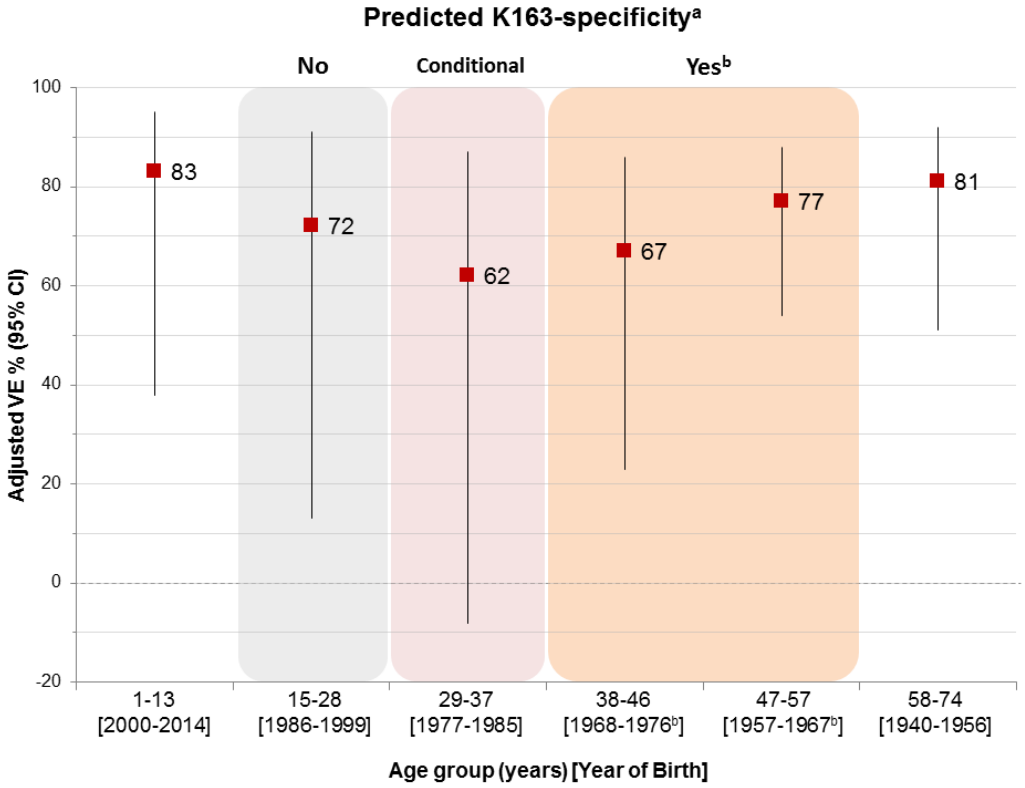
Exclusion criteria for both 2013-14 and 2015-16 are the same as specified for primary analysis in 2015-16 but subset to participants ≥9 years old and with complete information for current and prior season's vaccine receipt. Note that 2013-14 season's estimates span November-April whereas, owing to the delayed epidemic in 2015-16, estimates for the latter were subset to January-April.

*Adjusted for age group, sex, comorbidity, province, collection interval and calendar time (week of specimen collection using cubic B-spline with 3 equally spaced knots).

[1] Estimates displayed are updated from: Skowronski DM, Chambers C, Sabaiduc S, et al. Integrated sentinel surveillance linking genetic, antigenic and epidemiologic monitoring of influenza vaccine-virus relatedness and effectiveness during the 2013-2014 influenza season. J Infect Dis 2015;212:726-39. Note that previously published estimates for 2013-14 were subset to participants ≥2 years old, instead of ≥9 years old, and were not adjusted for sex as a covariate.

SUPPLEMENT 19. Exploration of potential cohort effects in vaccine effectiveness analysis against A(H1N1)pdm09, 2013-14 season

S19 Figure 6. Adjusted vaccine effectiveness (VE) against A(H1N1)pdm09 by age group (redefined based on potential K163-priming specificity)* and birth year among Canadian Sentinel Practitioner Surveillance Network (SPSN) participants 1-74 years old during the 2013-14 season[1]



Adjusted 2013-14 VE against A(H1N1)pdm09 by age groups adapted to reflect potential variation in K163 priming specificity as per **Supplement 1** but subtracting two years to reflect appropriate corresponding age ranges applicable in 2013-14 vs. 2015-16 (i.e. two years earlier). VE estimates were adjusted for the same covariates as for the 2015-16 season's primary VE analysis but with revised age categories as displayed and including an interaction term for age group by vaccination status.

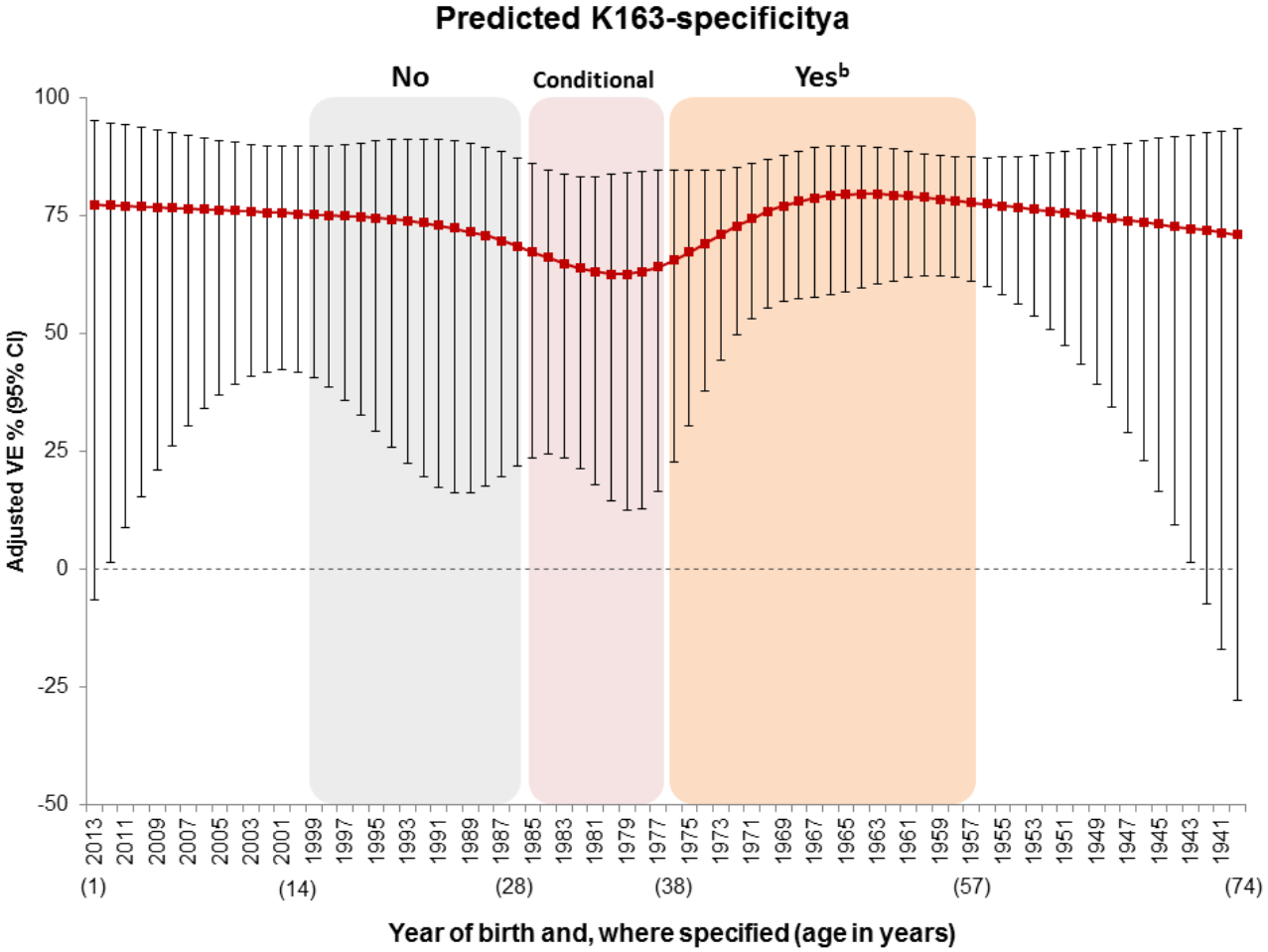
[a]Predicted K163 specificity as adapted from Linderman et al.[2] [**Supplement 1**]: orange shading indicates birth years (1957-1976) of participants for whom first exposure to K163-bearing A(H1N1) viruses (i.e. K163 priming specificity) is predicted to be pronounced; pink shading indicates birth years (1977-1985) of participants for whom K163 priming specificity is anticipated but conditional upon the age of first A(H1N1) exposure (i.e. whether before or after 1986); gray shading indicates birth years (1986-1999) of participants for whom K163 priming effects are not predicted. Estimates displayed without colour shading indicate birth years of children (2000-2013) or older adults (1940-1956) for whom priming in relation to position 163 is predicted to vary for additional reasons specified in **Supplement 1**.

[b]Indicates period of no A(H1N1) circulation (i.e. 1957-1976) for which heterosubtypic priming with A(H2N2) (i.e. 1957-1967) and/or A(H3N2) (i.e. 1968-1976) is likely to have preceded exposure to K163-bearing A(H1N1) viruses (or vaccines) following re-emergence in 1977. VE for birth cohorts 1957-1976 combined are 74% (95%CI: 57-84%)[unadjusted] and 73% (95%CI: 54-84%)[adjusted].

[1] Skowronski DM, Chambers C, Sabaiduc S, et al. Integrated sentinel surveillance linking genetic, antigenic and epidemiologic monitoring of influenza vaccine-virus relatedness and effectiveness during the 2013-2014 influenza season. J Infect Dis 2015;212:726-39.

[2] Linderman SL, Chambers BS, Zost SJ, et al. Potential antigenic explanation for atypical H1N1 infections among middle-aged adults during the 2013-2014 influenza season. Proc Natl Acad Sci U S A 2014;111:15798-803.

S19 Figure 7. Adjusted vaccine effectiveness (VE) against A(H1N1)pdm09 by birth year among Canadian Sentinel Practitioner Surveillance Network (SPSN) participants 1-74 years old during the 2013-14 season[1]



Adjusted 2013-14 VE against A(H1N1)pdm09 by birth year derived using age (in years) modeled as per McLean et al.[2] as a restricted cubic spline function with 5 knots based on percentiles and an interaction term for age by vaccination status adjusted for age (modeled), sex, comorbidity, province, collection interval and calendar time (month of specimen collection).

[a]Predicted K163 specificity as adapted from Linderman et al.[3] [Supplement 1]: orange shading indicates birth years (1957-1976) of participants for whom first exposure to K163-bearing A(H1N1) viruses (i.e. K163 priming specificity) is predicted to be pronounced; pink shading indicates birth years (1977-1985) of participants for whom K163 priming specificity is anticipated but conditional upon the age of first A(H1N1) exposure (i.e. whether before or after 1986); gray shading indicates birth years (1986-1999) of participants for whom K163 priming effects are not predicted. Estimates displayed without colour shading indicate birth years of children (2000-2013) or older adults (1940-1956) for whom priming in relation to position 163 is predicted to vary for several reasons as specified in Supplement 1.

[b]Indicates period of no A(H1N1) circulation (i.e. 1957-1976) for which heterosubtypic priming with A(H2N2) (i.e. 1957-1967) and/or A(H3N2) (i.e. 1968-1976) is more likely before the re-emergence of K163-bearing A(H1N1) viruses in 1977.

[1] Skowronski DM, Chambers C, Sabaiduc S, et al. Integrated sentinel surveillance linking genetic, antigenic and epidemiologic monitoring of influenza vaccine-virus relatedness and effectiveness during the 2013-2014 influenza season. J Infect Dis 2015;212:726-39.
[2] McLean HQ, Thompson MG, Sundaram ME, et al. Influenza vaccine effectiveness in the United States during 2012-2013: variable protection by age and virus type. Clin Infect Dis. 2015;211:1529-40.
[3] Linderman SL, Chambers BS, Zost SJ, et al. Potential antigenic explanation for atypical H1N1 infections among middle-aged adults during the 2013-2014 influenza season. Proc Natl Acad Sci U S A 2014;111:15798-803.