A Sentinel Platform to Evaluate Influenza Vaccine Effectiveness and New Variant Circulation, Canada 2010–2011 Season

Danuta M. Skowronski,1,2 Naveed Z. Janjua,1,2 Gaston De Serres,3,5 Anne-Luise Winter,7 James A. Dickinson,8,9 Jennifer L. Gardy,1,3 Jonathan Gubbay,7,11 Kevin Fonseca,10,12 Hugues Charest,5 Natasha S. Crowcroft,7,11,14 Monique Douville Fradet,5 Nathalie Bastien,15 Yan Li,15,16 Mel Krajden,1,4 Suzana Sabaiduc,1 and Martin Petric1,4

1British Columbia Centre for Disease Control, Provincial Health Services Authority, Vancouver; 2School of Population and Public Health, 3Department of Microbiology and Immunology, and 4Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver; 5Institut national de santé publique du Québec; 6Department of Social and Preventive Medicine, Faculty of Medicine, Laval University, Québec; 7Public Health Ontario, Toronto; 8Department of Family Medicine, 9Department of Community Health Sciences, and 10Department of Microbiology, Immunology and Infectious Diseases, University of Calgary, Alberta; 11Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto; 12Alberta Provincial Laboratory, Calgary; 13Department of Laboratory Medicine and Pathobiology, and 14Dalla Lana School of Public Health, University of Toronto, Ontario; 15National Microbiology Laboratory, Public Health Agency of Canada, Winnipeg; and 16Department of Medical Microbiology, University of Manitoba, Canada

Background. During the 2010–2011 winter, a large number of outbreaks due to influenza A/H3N2 at long-term care facilities, including higher-than-expected attack rates among vaccinated staff, were reported in some regions of Canada. Interim analysis from the community-based sentinel surveillance system showed circulating H3N2 variants and suboptimal vaccine effectiveness (VE), assessed here for the entire season’s data set.

Methods. Nasal/nasopharyngeal swabs and epidemiologic details were collected from patients presenting to sentinel sites within 7 days of onset of influenza-like illness. Cases tested positive for influenza by real-time reverse-transcription polymerase chain reaction; controls tested negative. Odds ratios for medically attended, laboratory-confirmed influenza in vaccinated vs nonvaccinated participants were used to derive adjusted VE. Viruses were characterized by hemagglutination inhibition (HI), and the viruses were matched to the vaccine.

Results. Final 2010–2011 VE analysis included 1718 participants (half aged 20–49 years), 93 with A(H1N1)pdm09, 408 with A/H3N2, and 199 with influenza B. Among adults aged 20–49 years, adjusted VE was 65% (95% confidence interval [CI], 8%–87%) for A(H1N1)pdm09 and 66% (95% CI, 10%–87%) for influenza B. Vaccine effectiveness was substantially lower for A/H3N2, at 39% (95% CI, 0%–63%). Phylogenetic analysis identified 2 circulating H3N2 variant clades, A/HongKong/2121/2010 (87%) and A/Victoria/208/2009 (11%), bearing multiple amino acid substitutions at antigenic sites (12 and 8, respectively) compared with the H3N2 vaccine component used in Canada (A/Victoria/210/2009[NYMC X-187]). However, HI characterized all H3N2 isolates as well matched to the vaccine.

Conclusions. Public health observations of increased facility H3N2 outbreaks were consistent with the sentinel network’s detection of genetic variants and suboptimal VE but not with conventional HI characterization. We highlight the utility of a multicomponent sentinel surveillance platform that incorporates genotypic, phenotypic, and epidemiologic indicators into the assessment of influenza virus, new variant circulation, vaccine relatedness, and VE.
provinces (British Columbia [BC], Alberta, Ontario, Quebec), which together are home to >85% of the Canadian population. In comparison with other VE monitoring approaches, including randomized controlled trials, the test-negative design applied to the Canadian surveillance system has proven robust and reliable, with annual VE estimates within the range of recent meta-analyses [2–4, 7–12]. As a surveillance approach, the platform is efficient and sustainable, permits trend analysis and signal detection, and leverages the input of public health partners for context, interpretation, and action.

During the 2010–2011 influenza season, public health laboratories in Ontario detected an early upswing in A/H3N2 activity. Local public health units also notified provincial epidemiologists of a heightened number of outbreaks at long-term care facilities (LTCFs), including greater-than-expected attack rates among vaccinated staff. This signal of possible vaccine mismatch prompted Ontario to request interim analysis of VE in January 2011 through Canada’s community-based sentinel surveillance network. Interim analysis showed significant amino acid (AA) mutations in dominant A/H3N2 isolates and suboptimal VE estimates.

Midseason findings, based on limited sample size, were conveyed to health authorities. At season’s end, we used the full sentinel surveillance data set, based on nearly 3-fold more participants, to characterize circulating influenza variants and their impact on VE through genotypic, phenotypic, and epidemiologic measures. Here we summarize VE of the 2010–2011 trivalent inactivated influenza vaccine (TIV) during the first postpandemic influenza season in Canada and demonstrate the utility of a multicomponent influenza surveillance platform.

MATERIALS AND METHODS

Our methods have been described previously [1–6]. Briefly, participating sentinel sites are provided test kits and instructed to offer influenza testing through nasal/nasopharyngeal specimen collection to all patients presenting within 7 days of onset of influenza-like illness (ILI), defined as acute onset of fever and cough ≥1 of the following symptoms: sore throat, arthralgia, myalgia, or prostration. Specimens are submitted to provincial public health laboratories for respiratory virus testing. Epidemiologic information is collected from consenting patients at the time of specimen collection using a standardized questionnaire. The approval of institutional ethics boards in each province is obtained.

A patient with a specimen testing positive for any influenza virus is considered a case; patients testing negative for influenza are considered controls. Participants are considered immunized if vaccine was given ≥2 weeks prior to ILI onset; subjects vaccinated <2 weeks prior to ILI onset are excluded but assessed in sensitivity analyses. The VE analysis period for 2010–2011 spanned from 1 November 2010 (week 44) to 30 April 2011 (week 17). The odds ratio (OR) for medically attended, laboratory-confirmed influenza in vaccinated vs nonvaccinated participants was estimated by logistic regression with adjustment for relevant confounders. The VE was calculated as [1 – OR] × 100.

Immunization

Participants received the split (nonadjuvanted) 2010–2011 TIV during the regular fall immunization campaign [13]. In BC and Quebec, the TIV is provided free of charge to individuals at higher risk of influenza-related complications [13]. Others are encouraged to receive the vaccine but must purchase it. The TIV is provided free of charge to all citizens aged ≥6 months in Ontario (since 2000) and Alberta (since 2009). Vaccine status is based on self/parental/guardian report; further detail related to special pediatric dosing requirements is not sought [13]. Per the World Health Organization (WHO) recommendation, the 2010–2011 TIV components included A/California/7/2009(H1N1)-like (hereafter A(H1N1)pdm09), A/Perth/16/2009(H3N2)-like, and B/Brisbane/60/2008(Victoria)-like strains [13]. For the A/Perth/16/2009(H3N2)-like component, manufacturers for the public program in Canada (GlaxoSmithKline and Sanofi Pasteur) used A/Victoria/210/2009(NYMC X-187) as the antigenically equivalent strain.

Virus Detection and Characterization

Specimens were tested for influenza A (to subtype) and influenza B at provincial reference laboratories by real-time reverse-transcription polymerase chain reaction (RT-PCR) according to provincially determined procedures (Supplementary Data 1, Laboratory Methods). The RT-PCR–positive specimens from across the season were inoculated into cell culture for virus isolation (Supplementary Data 1, Laboratory Methods). An aliquot of each isolate was submitted to the National Microbiology Laboratory for hemagglutination inhibition (HI) characterization, which was performed with post-infection ferret antisera against specific strains using guinea pig erythrocytes for H3 and turkey erythrocytes for H1 and B. Isolates were identified as antigenically most similar to a prototype strain according to the reciprocal of the highest HI titer. Sequencing and phylogenetic analysis of the hemagglutinin gene of A/H3N2 isolates spanning the season from each province were undertaken to identify AA substitutions potentially contributing to suboptimal VE [14]. Methods related to sequencing and phylogenetic analysis and corresponding GenBank accession numbers are provided in Supplementary Data (Supplementary Data 2, Hemagglutinin Sequencing and Phylogenetic Analysis).

RESULTS

Participant Profile

After applying exclusion criteria, 1718 participants contributed to VE analysis for the 2010–2011 season (Supplementary
Table 1). As in previous years, adults aged 20–49 years comprised the greatest proportion (49%) of sentinel study participants (Table 1). The proportion with comorbidity in 2010–2011 was comparable among controls and cases (19% vs 16%) and to previous estimates from the sentinel system (14%–23%) and the Canadian Community Health Survey (CCHS) (15%–20%) [3–6, 15].

The proportion of participants vaccinated was 16% among cases and 24% among controls. This latter figure is lower than previous years’ reports of control vaccination rates from both
the sentinel system (approximately 33%) [3–5] and CCHS (approximately 30%) [16], although vaccination among controls aged 20–49 years was comparable with previous reports. Of vaccinated participants in 2010, >70% had also received the TIV in both 2008–2009 and 2009–2010. The 2010–2011 participants reported receipt of the 2008–2009 TIV and the 2009–2010 TIV at rates comparable with those reported by controls during those seasons (approximately 30%); reported rates of pandemic vaccination (43%) were also comparable with those estimated through separate surveys in Canada in 2009 (41%) [17].

**Influenza Identification**

The temporal distribution of influenza detections is shown in Figure 1. Overall, influenza was detected in 709 of 1718 (41%) participants (Table 2). Of the 700 influenza viruses characterized, 13% were A(H1N1)pdm09, 58% were A/H3N2, and 28% were influenza B. In the adjacent eastern provinces of Ontario and Quebec, influenza A dominated (approximately 80%), whereas influenza B made a greater contribution in the adjacent western provinces of BC and Alberta (approximately 50%). Influenza A subtype distribution also varied by province, with a greater proportion of H3N2 in Ontario and Quebec (86% and 98%, respectively) but a greater proportion of A(H1N1)pdm09 in BC and Alberta (59% and 33%, respectively) (Table 2).

Detection of influenza also varied by age (Supplementary Table 2). The majority (56%) of influenza B detections were in children <20 years of age, with the highest proportion of specimens positive among schoolchildren 9–19 years of age (28%). Conversely, detection of A/H3N2 was lowest in the 9–19 years age group (16%) and highest in the elderly (31%), with the majority of A/H3N2 detection in adults ≥20 years of age (73%). A(H1N1)pdm09 was detected in <10% of participants across all ages, which is substantially different from sentinel findings during the 2009 fall pandemic wave, when this virus was detected in >50% of those <20 years old, 40% of those 20–49 years of age, 30% of those 50–64 years of age, and 10% of those ≥65 years old. A higher proportion of pandemic detection occurred among adults ≥20 years of age in 2010–2011 (86%) than in 2009 (57%).

**Influenza Genetic and Antigenic Characterization**

Sufficient virus for HI characterization was isolated from 233 specimens, which were collected mid-November 2010 to the
end of April 2011 (Table 2). All 62 A/H3N2 isolates showed <4-fold reduction in HI titers with reference antibody to the vaccine strain and were designated A/Perth/16/2009-like. Of the 51 A(H1N1)pdm09 isolates, all were designated A/California/7/2009-like, with 1 showing 4-fold and 1 showing 8-fold reduction in titers with reference antibody. Of the 120 influenza B isolates characterized by HI, 117 belonged to B/Brisbane/60/2008(Victoria-lineage), and 3 belonged to B/Wisconsin/01/2010(Yamagata-lineage) (Table 2).

Hemagglutinin in genes from 91 A/H3N2 viruses isolated between mid-November 2010 and mid-April 2011 were sequenced and subjected to phylogenetic analysis (Figures 1 and 2; Supplementary Figure 1). Of these, 60 were also characterized by HI, and all were considered A/Perth/16/2009-like. Based on phylogenetic analysis, however, only 2 isolates belonged to the A/Perth/16/2009 vaccine clade, with the majority (79; 87%) belonging to a clade distinguished as the A/HongKong/2121/2010 variant. Dominance of this clade was observed among A/H3N2 viruses in all provinces (Alberta: 14 of 20; BC: 11 of 12; Ontario: 23 of 24; Quebec: 31 of 35). Ten sequenced A/H3N2 viruses (11%) belonged to the A/Victoria/208/2009 clade.

Pairwise identity between antigenic regions of the 2010–2011 WHO-recommended A/Perth/16/2009 vaccine strain and the A/HongKong/2121/2010 variant circulating in Canada was 93.8%, with 8 AA substitutions across the 130 residues comprising antigenic sites (Figure 2B; Supplementary Table 3) [14]. The A/Victoria/210/2009(NYMC X-187) strain actually used by manufacturers for Canada was 90.8% identical to the A/HongKong/2121 variant, with 12 AA changes. The A/Perth/16/2009 strain and the A/Victoria/208/2009 variant were 96.9% identical across these residues, with 4 AA substitutions (Figure 2B; Supplementary Table 3). The A/Victoria/210/2009 (NYMC X-187) vaccine strain used in Canada was 93.8% identical to the A/Victoria/208/2009 variant, with 8 AA changes.

By way of context, the corresponding pairwise identity between antigenic regions of the successive A/Brisbane/10/2007 (2008–2009 TIV) and A/Perth/16/2009 (2009–2010 TIV) H3N2 vaccine strains was 95.4%, with 6 AA substitutions. The notorious antigenic drifts A/Sydney/5/1997 and A/Fujian/411/2002 had antigenic site pairwise identities of 92.3% (10 AA changes) and 87.7% (16 AA changes) relative to their respective 1997 and 2004 H3N2 vaccine predecessor strains.

Vaccine Effectiveness Estimates
Crude and adjusted VE estimates are shown in Table 3. There was little change with adjustment for most covariates except age. Fully adjusted VE estimates for any influenza were 37%. The VE estimates by type/subtype were 43% for influenza A, 59% for A(H1N1)pdm09, 39% for A/H3N2, and 25% for influenza B.
Figure 2. A. Phylogenetic tree of influenza A/H3N2 isolates, sentinel system 2010–2011. A maximum-likelihood phylogeny of the 91 sentinel isolates in the context of globally isolated 2010–2011 H3N2 viruses (n = 177) based on alignment of the full-length HA protein sequence (566 amino acids) is shown. The major clades A/Perth/16/2009, A/Victoria/208/2009, and A/Hong Kong 2121/2010 are colored in shades of green and blue. Eastern Canadian (Ontario/Quebec) sentinel system viruses are shown in orange; western Canadian (British Columbia/Alberta) sentinel viruses are shown in purple. Sentinel H3N2 viruses were collected from specimens spanning mid-November 2010 to mid-April 2011. Vaccine strains are labeled in black, with the exception of the 2012–2013 northern hemisphere H3N2 vaccine component A/Victoria/361/2011. Star symbols denote the clade markers A/Perth/16/2009, A/Victoria/208/2009, and A/Hong Kong/2121/2010; a circle symbol denotes the 2012–2013 H3N2 vaccine strain A/Victoria/361/2011. Shimodar-Hasegawa likelihood ratio test local support values are shown at major bifurcation points. A fully labeled phylogeny is provided as Supplementary Figure 1.
When restricted to adults aged 20–49 years, the VE estimates were substantially improved for A(H1N1)pdm09 (65%) and influenza B (66%) but not A/H3N2 (39%) (Table 3). Point estimates of VE for A/H3N2 were consistently low for young adults with stratification by eastern (39%; 95% confidence interval [CI], −9% to 66%) and western (41%; 95% CI, −63% to 79%) provinces and in other sensitivity analyses (Table 3).

With additional adjustment for prior receipt of the 2009 adjuvanted pandemic vaccine, the VE of the 2010–2011 TIV against A(H1N1)pdm09 was reduced (40%; 95% CI, −54% to 76%), including the VE among young adults (25%; 95% CI, −117% to 74%). A category indicator variable based on receipt of 2009 adjuvanted pandemic vaccine alone, 2010–2011 TIV alone, or both vaccines relative to neither was created to explore this relationship. The adjusted VE for prior 2009 adjuvanted pandemic vaccine alone was 69% (95% CI, 38%–85%) overall and 76% (95% CI, 42%–90%) among young adults. Among those who received both the 2009 and 2010 vaccines, the VE was 75% (95% CI, 40%–90%) overall and 82% (95% CI, 40%–95%) among young adults. The VE for 2010–2011 TIV alone was much lower (47%; 95%, CI −136% to 88% overall; and 22%; 95% CI, −270% to 83% among young adults), but confidence intervals were wide.

DISCUSSION

In January 2011, Public Health Ontario alerted sentinel investigators of an unusual number of outbreaks of A/H3N2 at Ontario LTCFs. Ontario ultimately reported a 3-fold increase in institutional outbreaks in 2010–2011 relative to the historical average since 2005 (428 vs 118), and the adjacent province of Quebec reported a 5-fold increase (149 vs 29). This triggered interim investigation of VE using the established community-based sentinel system, which indicated that 2 variant A/H3N2 strains, designated A/Hong Kong/2121/2010-like and A/Victoria/208/2009-like, were circulating in the population and that VE estimates against A/H3N2 were suboptimal.

As reported here, interim observations were borne out when the entire season’s data set was analyzed. Component-specific estimates of VE for the A/H3N2 strain were low in all age groups, including young adults. In prior seasons during which H3N2-specific VE was similarly derived, point estimates for mismatched strains ranged 40%–60% in the Canadian sentinel system, consistent with our current findings and with findings from recent meta-analysis [2–4, 12]. Estimates of the 2010–2011 VE for the A/H3N2 component are not yet widely available from elsewhere, but suggestion of suboptimal protection has also been reported in interim estimates from the US military, although not as low as reported here [18]. Public health officials in Canada also reported lower immunization rates among LTCF staff in 2010–2011 compared with 2008–2009 in Ontario (58% vs 77%), Quebec (not available), BC (56% vs 64%) and Alberta (66% vs 69%) but more stable rates among LTCF residents (93% in Ontario, 84% in Quebec, 90% in BC, and 90% in Alberta). A combination of reduced vaccine coverage and low VE may account for the increase in outbreaks at LTCFs where H3N2 viruses dominated in 2010–2011.

Despite meeting genetic variation criteria for possible antigenic drift [14], neither the A/Victoria/208/2009 variant nor the A/Hong Kong/2121/2010 H3N2 variant met conventional HI criteria to be considered antigenically distinct from the vaccine [19]. This is consistent with WHO conclusions, based on postinfection ferret antisera and vaccine immunogenicity trials [20, 21] but is inconsistent with our observations based on phylogenetic and epidemiologic analysis as well as public health field experience. In vitro assessment of vaccine match based on postinfection ferret antisera may not accurately predict protection in humans, whose prior infection- or vaccine-induced immunity is likely to be more complex and to influence—positively or negatively—current vaccine protection [22]. There are also recognized issues in the use of human vaccine immunogenicity findings to predict vaccine protection [23]. If provided as timely, reliable, and representative estimates, the incorporation of epidemiologic VE measures could enhance the process of vaccine strain selection, and systems to achieve this warrant further evaluation and development.

Our sentinel system findings and previous commentary by others [24] highlight substantial heterogeneity in influenza circulation (strains and their relative mix) by region. It is unclear to what extent the dominant A/Hong Kong/2121/2010 variant experienced in Canada contributed to the WHO assessment

Figure 2. Continued  Figure 2. B, Location of antigenic site mutations in A/Victoria/208/2009 (H3N2) and A/Hong Kong/2121/2010 (H3N2). Antigenic sites A–E (light green, dark green, light blue, dark blue, and purple, respectively) were mapped to a crystal structure of H3 hemagglutinin. The 4 substitutions differentiating both A/Victoria/208/2009 and A/Hong Kong/2121/2010 from the vaccine strain A/Perth/16/2009 are shown in red with bolded italic light blue labels. The additional 4 substitutions further differentiating A/Hong Kong/2121/2010 from A/Victoria/208/2009 are shown in red, with dark blue labels (the I246V substitution in A/Hong Kong/2121/2010 is not visible in these orientations). Residues are numbered from the N-terminal methionine. The Canadian antigenically equivalent vaccine strain A/Victoria/210/2009 is identical to the WHO-recommended A/Perth/16/2009 vaccine strain at its antigenic sites with the exception of the following substitutions: S61N, G202V, S230I (found also in A/Victoria/208/2009 and A/Hong Kong/2121/2010), S244T, I276M, and R277Q.
## Table 3. Component-Specific and Overall Influenza Vaccine Effectiveness Based on Sentinel System in Canada, 2010–2011 Season

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Vaccine Effectiveness (95% Confidence Interval) [N; Controls; Cases]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Influenza (N = 1718; Controls = 1009; Cases = 709)</td>
</tr>
<tr>
<td>Crude (unadjusted)</td>
<td>36 (17–51)</td>
</tr>
<tr>
<td>Adjusted for:</td>
<td></td>
</tr>
<tr>
<td>Age (1–8, 9–19, 20–49, 50–64, ≥65)</td>
<td>35 (15–50)</td>
</tr>
<tr>
<td>Comorbidity (yes/no)</td>
<td>34 (15–50)</td>
</tr>
<tr>
<td>Province (BC, AB, ON, QC)</td>
<td>36 (17–51)</td>
</tr>
<tr>
<td>Specimen collection interval (≤4 days or &gt;4 days)</td>
<td>35 (16–50)</td>
</tr>
<tr>
<td>Week of illness onset</td>
<td>38 (20–52)</td>
</tr>
<tr>
<td>Age and comorbidity</td>
<td>34 (14–50)</td>
</tr>
<tr>
<td>Age, comorbidity, and province</td>
<td>34 (14–50)</td>
</tr>
<tr>
<td>Age, comorbidity, province, interval</td>
<td>34 (13–50)</td>
</tr>
<tr>
<td>Age, comorbidity, province, interval, week</td>
<td>37 (17–52)</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
</tr>
<tr>
<td>Restricted to without comorbidity&lt;sup&gt;a&lt;/sup&gt;&lt;sup&gt;b&lt;/sup&gt;</td>
<td>38 (14–56) [1418; 820; 598]</td>
</tr>
<tr>
<td>Unknown comorbidity recoded “Yes”&lt;sup&gt;c&lt;/sup&gt;</td>
<td>36 (16–51)</td>
</tr>
<tr>
<td>Unknown comorbidity recoded “No”&lt;sup&gt;c&lt;/sup&gt;</td>
<td>35 (15–51) [1786; 1046; 740]</td>
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<tr>
<td>Vaccine receipt &lt; 2 weeks prior to ILL onset&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Considered immunized</td>
</tr>
<tr>
<td>Considered unimmunized</td>
<td>35 (14–50) [1765; 1046; 719]</td>
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<tr>
<td>Restricted to 20–49 years only</td>
<td>Crude (unadjusted)</td>
</tr>
<tr>
<td>Comorbidity, province, interval, week</td>
<td>49 (22–67) [838; 483; 355]</td>
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<tr>
<td>Restricted to &lt;20 years only</td>
<td>Crude (unadjusted)</td>
</tr>
<tr>
<td>Comorbidity, province, interval, week</td>
<td>27 (–23 to 57) [542; 304; 238]</td>
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<tr>
<td>Restricted to ≥50 years only</td>
<td>Crude (unadjusted)</td>
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<tr>
<td>Age (50–64, ≥65), comorbidity, province, interval, week</td>
<td>26 (–28 to 57) [338; 222; 116]</td>
</tr>
</tbody>
</table>

Abbreviations: AB, Alberta; BC, British Columbia; IIL, influenza-like illness; ON, Ontario; QC, Quebec.

<sup>a</sup> Adjusted for age, province, interval, week.

<sup>b</sup> A/H1N1pdm09 without comorbidity age-adjusted as 1–8, 9–19, 20–49, ≥50 years due to sample size.

<sup>c</sup> Adjusted for age, comorbidity, province, interval, week.
of global virus circulation or to the field isolates selected for vaccine-relatedness or immunogenicity analysis in support of subsequent vaccine strain selection [20, 21]. Based on our phylogenetic tree, which included all 2010–2011 H3N2 sequences available at the National Center for Biotechnology Information, both A/Victoria/208/2009-like and A/Hong Kong/2121/2010-like viruses outnumbered A/Perth/16/2009-like viruses globally in 2010–2011 (53% and 32% of detections, respectively, vs 15%), although, unlike in Canada, the A/Victoria/208/2009-like variant predominated over the A/Hong Kong/2121/2010-like variant. For the 2011–2012 northern and 2012 southern hemispheres’ influenza seasons, the A/Perth/16/2009 vaccine strain was again selected as the H3N2 TIV component [20, 21] but was replaced for the 2012–2013 TIV by A/Victoria/361/2011 [25]. The latter belongs to the A/Victoria/208/2009 clade identified here but has accrued further mutations in antigenic sites, with 94.6% pairwise identity to A/Victoria/208/2009 (7 AA substitutions) and 91.5% to A/Perth/16/2009 (11 AA substitutions) (Figure 2; Supplementary Figure 1).

Although seasonal influenza strains dominated the 2010–2011 postpandemic season, a shift in the age distribution of pandemic detections toward adults was observed in the Canadian sentinel surveillance system. Such a shift had been predicted based on historic postpandemic observations [26], mathematical modeling [27], and sero-prevalence surveys [28] and was also reported by the UK Severe Influenza Surveillance System in 2010–2011 [29]. We additionally found that adults comprised the majority of sentinel A/H3N2 detections and had higher rates of positivity than schoolchildren. Heterosubtypic cross-immunity between A/H3N2 and pandemic A/H1N1 viruses has been observed experimentally, attributed to cross-protective T-cell responses [30]. The extent to which the substantial 2009 A/H1N1 pandemic affecting primarily young people may have also influenced the profile of A/H3N2 risk is intriguing to consider but remains speculative.

Whereas a monovalent AS03-adjuvanted pandemic vaccine was used for the 2009 immunization campaign in Canada, there was a return to the conventional nonadjuvanted TIV for 2010–2011. In 2009, adjuvanted pandemic VE estimates were consistently >85% in children and young adults, as measured through the sentinel system (93%) [6] and elsewhere [31–33]. Despite a vaccine that was still considered well matched to the circulating pandemic strain in 2010 [20, 21], our sentinel system estimated lower VE for that component (59% overall; 65% among young adults) compared with 2009 [6]. Our 2010–2011 A(H1N1)pdm09 estimate is comparable with or slightly higher than interim 2010–2011 VE estimates reported from the United Kingdom (51%) [34], Spain (49%) [35], and in a pooled analysis of 7 European countries (35%) [36]. These latter studies accounted for 2009 pandemic vaccine receipt; when we adjusted for that, we also observed a reduction in A(H1N1)pdm09 VE estimates. In further exploration, the adjuvanted vaccine administered in Canada in 2009 appeared to provide substantial protective effects >1 year later, whereas sentinel study participants given the 2010–2011 TIV alone appeared to derive less benefit.

Influenza B showed the expected profile of greater positivity among children [37], and we observed a moderate VE of 66% in adults and a lower VE in children and older adults. Variability in VE estimates for influenza B has previously been recognized [2–4]. The alternate B/Yamagata-lineage virus was a minor contributor to sentinel surveillance detections and is unlikely to have substantially influenced suboptimal VE. However, lower immunogenicity to the 2010–2011 B/Brisbane/60/08(Victoria)-like antigen in young children primed with Yamagata-lineage antigen has recently been reported, and variable responses to the 2010–2011 influenza B component have also been shown in older children, based on prior immunization history [38, 39]. Young adults with greater cumulative experience and boosting to both influenza B lineages may achieve higher vaccine protection, but the reasons for variability in influenza B VE overall require better understanding and evaluation.

The limitations and strengths of our approach have been described previously [1–6]. Results are based primarily on the participation of working-age adults, and generalization to other age groups requires caution. In Canada, universal healthcare coverage addresses barriers to access that may exist in other countries, and the unrestricted offer of participation to all patients presenting to a sentinel site within 7 days of ILI onset helps to standardize in part for healthcare-seeking behavior. We also standardize for illness presentation and severity by including only those meeting a specified ILI definition. Although patient and clinician discretion is incorporated into the decision to test, the sentinel approach enables greater consistency (for example, in the likelihood of being ill with influenza) than other test-negative designs based on general laboratory submissions. Vaccine status in this study was self-reported but collected at the time of specimen submission, before the test result was known, minimizing differential recall bias. Studies in other settings have reported consistency between self-reported and registry-based influenza vaccine status, but we have not specifically assessed this in our system [40]. Component-specific analyses need substantial sample size for adequate precision, and this requires ongoing effort to enhance participation; we draw attention to wide confidence intervals, particularly for influenza B and in other stratified analyses, precluding definitive conclusions. Although we have scrutinized vaccine relatedness through gene sequencing and HI characterization of sentinel viruses from across the season, this ultimately represents only a proportion of all influenza detections. We cannot rule out systematic differences in viruses available for characterization—an issue for all laboratory-based influenza surveillance. Our estimates reflect vaccine performance in the context of a given mix of vaccine-related and variant
strains detected in the source population; overall VE results may not be generalizable to other regions with a different mix of viruses. We have illustrated how a complete package of surveillance observations, including molecular findings, can inform vaccine assessment, but further work is needed to strengthen that surveillance infrastructure and to correlate genetic/AA changes with impact on antigenicity, immunogenicity, and vaccine effectiveness. Finally as with any observational design, even with careful attention to measured and potentially important confounders and comparison against expected community profiles, we cannot rule out residual bias and confounding. We emphasize that our system is a surveillance approach intended for trend analysis and signal detection and for interpretation in the context of other indicators.

With further refinement to understand methodologic issues and expansion to include more regions, the surveillance system we describe—harnessing genotypic, phenotypic, and epidemiologic indicators—could help inform influenza virus evolution and annual vaccine protection. Differences across genotypic and phenotypic indicators may also point to opportunities for further immuno-epidemiologic evaluation and understanding. We thus encourage the development of linked sentinel surveillance networks as a core public health platform to monitor influenza virus, new variant circulation, vaccine-relatedness, and VE.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://www.oxfordjournals.org/our-journals/cid). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyrighted. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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