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Effectiveness of Live Attenuated vs Inactivated Influenza Vaccines in Children During the 2012-2013 Through 2015-2016 Influenza Seasons in Alberta, Canada

A Canadian Immunization Research Network (CIRN) Study

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IMPORTANCE Recent observational studies report conflicting results regarding the effectiveness of live attenuated influenza vaccine (LAIV), particularly against influenza A(H1N1)pdm09.

OBJECTIVE To compare the effectiveness of LAIV and inactivated influenza vaccine (IIV) against laboratory-confirmed influenza.

DESIGN, SETTING, AND PARTICIPANTS A test-negative study to estimate influenza vaccine effectiveness (VE) using population-based, linked, individual-level laboratory, health administrative, and immunization data. Data were obtained from 10 169 children and adolescents aged 2 to 17 years (children) who were tested for influenza in inpatient or outpatient settings during periods when influenza was circulating based on a threshold level of 5% weekly test positivity for the province during the 4 influenza seasons spanning from November 11, 2012, to April 30, 2016, in Alberta, Canada. Logistic regression was used to estimate VE by vaccine type, influenza season, and influenza type and subtype. The relative effectiveness of each vaccine type was assessed by comparing the odds of laboratory-confirmed influenza infection for LAIV recipients with that for IIV recipients.

EXPOSURES The primary exposure was receipt of LAIV or IIV before testing for influenza.

MAIN OUTCOMES AND MEASURES The primary outcome was influenza case status as determined by reverse-transcriptase polymerase chain reaction testing.

RESULTS A total of 10 779 respiratory specimens (from 10 169 children) collected and tested for influenza during the 4 influenza seasons were included, with 53.4% from males; the mean (SD) age was 7.0 (4.6) years. Across the 4 influenza seasons, 3161 children tested positive for influenza. Combining the 4 influenza seasons, the adjusted VE against influenza A(H1N1)pdm09 was 69% (95% CI, 56%-78%) for LAIV compared with 79% (95% CI, 70%-86%) for IIV. Vaccine effectiveness against influenza A(H3N2) was 36% (95% CI, 14%-53%) for LAIV and 43% (95% CI, 22%-59%) for IIV. Against influenza B, VE was 74% (95% CI, 62%-82%) for LAIV and 56% (95% CI, 41%-66%) for IIV. There were no significant differences in the odds of influenza infection for LAIV recipients compared with IIV recipients except for influenza B during the 2015-2016 season, when LAIV recipients had lower odds of infection than IIV recipients (odds ratio, 0.36; 95% CI, 0.17-0.76).

CONCLUSIONS AND RELEVANCE There was no evidence to support the lack of effectiveness of LAIV against influenza A(H1N1)pdm09. These results support administration of either vaccine type in this age group.

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Supplemental content

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Children experience high rates of influenza-attributable illness. In some countries, live attenuated influenza vaccine (LAIV) and inactivated influenza vaccine (IIV) are both available and recommended for children and adolescents aged 2 to 17 years (hereinafter referred to as *children*).

The Canadian province of Alberta has universally funded influenza immunization since 2009, with LAIV becoming publicly funded for the 2012-2013 influenza season, expanding on a pilot program in the 2011-2012 season (before the 2012-2013 season, only IIV was publicly funded).[1] Based on results of randomized clinical trials demonstrating superior efficacy of LAIV compared with IIV,[2] national immunization technical advisory groups in the United States, Canada, the United Kingdom, and elsewhere[3] recommended LAIV over IIV for certain age groups and influenza seasons. These recommendations have varied by country, with the United States preferentially recommending LAIV for children aged 2 to 8 years (2014-2015 season)[4]; Canada, for children aged 2 to 17 (2011-2012 and 2012-2013 seasons) and 2 to 6 years (2013-2014 to 2015-2016 seasons)[5]; and the United Kingdom, for children aged 2 to 3 (2013-2014 season), 2 to 4 (2014-2015 season), and 2 to 6 years (2015-2016 season).[3]

Recent observational studies have reported conflicting results regarding the effectiveness of LAIV, specifically against influenza A(H1N1)pdm09.[6-8] Based on evidence from the US Flu Vaccine Effectiveness (VE) Network demonstrating that LAIV provided no protection against influenza A(H1N1)pdm09 during the 2013-2014 and 2015-2016 seasons, the US Advisory Committee on Immunization Practices made an interim recommendation that LAIV not be used for the 2016-2017 season and recommended against its use again for the 2017-2018 season.[9] However, in February 2018, the committee approved the use of LAIV for the 2018-2019 season.[10] Other countries, including Canada and the United Kingdom, continued to recommend LAIV, although Canada removed its preferential recommendation for LAIV in the 2016-2017 season.[11] The objective of this study was to compare the effectiveness of LAIV and IIV against laboratory-confirmed influenza.

Key Points

Question Does vaccine effectiveness differ between live attenuated influenza vaccine and inactivated influenza vaccine in children and adolescents?

Findings This test-negative study compared health administrative data and laboratory test results on respiratory specimens from 10 169 children and adolescents across 4 influenza seasons and found no significant differences in the odds of influenza infection between children who received live attenuated and those who received inactivated influenza vaccine. The only exception was influenza B during the 2015-2016 season, for which live attenuated influenza vaccine provided better protection than inactivated influenza vaccine.

Meaning These results support receipt of either live attenuated influenza vaccine or inactivated influenza vaccine in this age group.

Methods

Study Population, Setting, and Design

We studied children aged 2 to 17 years who received medical attention and were tested for influenza during the 2012-2013 to 2015-2016 influenza seasons in Alberta (2016 population: 4.3 million), where health care is publicly funded. We deterministically linked individual-level laboratory data to health administrative and immunization data at the Alberta Ministry of Health using personal health numbers, which act as unique lifetime identifiers. By using the test-negative design,[12] children with laboratory-confirmed influenza served as cases and those who tested negative served as controls. The study was restricted to periods when influenza was circulating, which was based on a threshold level of 5% weekly test positivity for the province overall from November 11, 2012, to April 30, 2016 (eTable 1 in the Supplement).

This study was approved by the Conjoint Health Research Ethics Board of the University of Calgary, Calgary, Alberta, Canada, and the University of Alberta (Health Panel), Edmonton, Alberta, Canada, which also waived the need for informed patient consent because data were deidentified. The study was supported by the Canadian Immunization Research Network (CIRN).

Data Sources and Definitions

Laboratory Testing

Laboratory data were obtained from Alberta Health Services' Provincial Laboratory for Public Health, which tests all respiratory samples for the province. All specimens had been tested using a real-time reverse-transcriptase polymerase chain reaction assay designed by the Centers for Disease Control and Prevention during the study period.[13] Influenza A–positive specimens were also analyzed by real-time reverse-transcriptase polymerase chain reaction for H3 subtypes using an assay developed by the Centers for Disease Control and Prevention and for A(H1N1)pdm09 using a test developed by the Provincial Laboratory for Public Health.[13,14] Influenza A–positive specimens that had a low viral load and could not be typed by these assays were considered untypable. Lineage information was not available for influenza B infections. Symptom onset date was not available; therefore, we used the specimen collection date as the index date. Testing algorithms varied across time and settings, but many specimens were also tested for other respiratory viruses using real-time reverse-transcriptase polymerase chain reaction.

Setting

We included children tested for influenza in hospitals, emergency departments, and physician offices using data provided by Alberta Health. We identified hospitalizations using the Discharge Abstract Database, emergency department visits using the Ambulatory Care Database, and office visits using physician billing claims data captured in the Supplemental Enhanced Service Event system. We assigned a health care setting for each child based on the testing date corresponding with 1 or more records in the aforementioned data sets. When children had more than 1 health care record for a given date, we

assigned the setting based on a hierarchy of clinical severity (hospital > emergency department > physician office). To exclude hospital-acquired infections, we excluded records of children tested more than 3 days after admission (n = 557). We excluded duplicate specimens collected for an individual child in a single season (n = 1275); we included the first specimen with a positive test result for influenza (cases) or the first specimen if all specimens collected during the season had negative test results (controls).

Influenza Vaccination

To ascertain vaccination status, we used data from several sources that capture vaccines administered through public health clinics (Immunization and Adverse Reaction to Immunization repository), pharmacies (Pharmaceutical Information Network and Alberta Blue Cross databases), and physician offices (Supplemental Enhanced Service Event system) (details can be found in eTable 2 in the Supplement).

Influenza vaccines for children are administered primarily through public health nurses in community-based clinics. Pharmacists are authorized to provide influenza vaccines to children 9 years or older. Live attenuated influenza vaccine and IIV were distributed equally across the province during the study years.

Children were considered vaccinated if they were fully vaccinated 14 days or more before the specimen collection date (ie, 1 dose of influenza vaccine for those aged ≥9 years or 2 doses spaced 28 days apart for those <9 years in their first vaccination season). Children vaccinated after specimen collection were considered unvaccinated. We excluded children with missing vaccination criteria data (ie, missing vaccine type), partially vaccinated children (those aged <9 years in their first vaccination season who had received 1 dose of vaccine or who received both doses at an interval of <28 days), and those vaccinated less than 14 days before testing (combined number of children, 216). Alberta switched from trivalent IIV (IIV3) to quadrivalent IIV (IIV4) in the 2015-2016 influenza season. Live attenuated influenza vaccine was trivalent (LAIV3) for the 2012-2013 and 2013-2014 influenza seasons and quadrivalent (LAIV4) for the 2015-2016 seasons; LAIV3 and LAIV4 were both used in the 2014-2015 season.[1]

Covariates

We used health administrative data to identify characteristics of the study population. We used hospitalization data to assign complex chronic condition status, using a definition adapted for Canadian data,[15] and provincial disease registries to identify asthma and diabetes status.[16] We used the postal code of residence at the time of laboratory testing linked to Statistics Canada Census 2011 data for Alberta to assign neighborhood income quintile based on mean household incomes and rurality based on location in relation to metropolitan centers in Alberta.

Statistical Analysis

We used multivariable logistic regression to estimate VE by comparing the odds of influenza in vaccinated vs unvaccinated children. Vaccine effectiveness was calculated as follows:

$$(1 - \text{Adjusted Odds Ratio [AOR]}) \times 100\%.$$

We estimated VE for LAIV and IIV separately but also for all health care settings combined because estimates from outpatient and inpatient settings tend to be similar.[17] We decided a priori to control for age, influenza season, presence of any comorbidity, and calendar month within influenza season (relative to the peak month of influenza activity) in adjusted analyses.[18,19] We performed subgroup analyses by influenza season, influenza type and subtype, age group, health care setting, and presence of a comorbidity and included an interaction term with vaccine type to examine differences in outcomes among these groups. We also estimated VE by influenza subtype and age group.

To compare the relative effectiveness of the 2 vaccine types, we restricted the sample to vaccinated children and compared the odds of laboratory-confirmed influenza infection in LAIV recipients to IIV recipients. We performed logistic regression using IIV recipients as the reference group to calculate ORs and 95% CIs, with ORs greater than 1 favoring IIV with regard to VE. We did this regression by type and subtype for each influenza season, as well as by type and subtype for all seasons combined, and by type and subtype and season for the dominant type and subtypes for a given season. We performed several sensitivity analyses: restricting the analysis to children who had specimens collected during a hospitalization or emergency department visit with an acute respiratory infection diagnostic code (eTable 3 in the Supplement); adjusting for health care setting; using those who tested positive for another respiratory virus as controls; and removing LAIV-ineligible children (ie, those with asthma or a hematologic or immunodeficiency condition) from the analysis.

We also explored the association between repeatedly receiving a particular vaccine type with VE. We first considered 2 consecutive influenza seasons, restricting the sample to those eligible for provincial health insurance during the earlier season and estimating subtype-specific VE for the latter season, taking into account all possible combinations of vaccination and vaccine type across the 2 seasons. We extended the analysis further by taking into account the type of vaccine received across 3 consecutive seasons, restricted to children who were eligible (based on age and Alberta Health Care Insurance Plan coverage) to receive LAIV during 3 consecutive seasons after it was introduced in Alberta.

All analyses were conducted using SAS, version 9.4 (SAS Institute, Inc). All tests were 2-sided and used $P < .05$ as the level of statistical significance.

Results

A total of 10 779 respiratory specimens (from 10 169 children) collected and tested for influenza during the 4 influenza seasons were included, with 53.4% from males; the mean (SD) age of participants was 7.0 (4.6). Five hundred five children (5.0%) were included in more than 1 season. A total of 3161 children tested positive for influenza. During the 4 seasons, 1948 children received at least 1 influenza vaccine 14 days or more before the specimen collection date: 858 received LAIV and 1090 received IIV. Of the 2098 children who tested positive for influenza A, 1053 were positive for A(H1N1)pdm09 only, 951 for A(H3N2) only, and the subtype was unknown for 77. An addi-

Table 1. Characteristics of the Study Population

Characteristic	No. (%)				
	All		Influenza Negative		
	Influenza Negative (n = 7618)	Influenza Positive (n = 3161)	Unvaccinated (n = 5974)	LAIV (n = 711)	IIV (n = 933)
Influenza season					
2012-2013	1820 (23.9)	660 (20.9)	1457 (24.4)	151 (21.2)	212 (22.7)
2013-2014	1902 (25.0)	543 (17.2)	1480 (24.8)	151 (21.2)	271 (29.1)
2014-2015	2291 (30.0)	788 (24.9)	1796 (30.0)	234 (32.9)	261 (28.0)
2015-2016	1605 (21.1)	1170 (37.0)	1241 (20.8)	175 (24.6)	189 (20.3)
Age group, y					
2-4	3663 (48.1)	1129 (35.7)	2820 (47.2)	374 (52.6)	469 (50.3)
5-8	1827 (24.0)	962 (30.4)	1407 (23.6)	215 (30.2)	205 (22.0)
9-17	2128 (27.9)	1070 (33.9)	1747 (29.2)	122 (17.2)	259 (27.8)
Male sex	4084 (53.6)	1677 (53.1)	3197 (53.5)	380 (53.4)	507 (54.3)
Rural residence	1546 (20.3)	766 (24.2)	1303 (21.8)	114 (16.0)	129 (13.8)
Neighborhood income quintile[a]					
1	1526 (20.0)	668 (21.1)	1229 (20.6)	118 (16.6)	179 (19.2)
2	1397 (18.3)	568 (18.0)	1121 (18.8)	121 (17.0)	155 (16.6)
3	1255 (16.5)	539 (17.0)	982 (16.4)	96 (13.5)	177 (19.0)
4	1528 (20.1)	614 (19.4)	1187 (19.9)	160 (22.5)	181 (19.4)
5	1689 (22.2)	657 (20.8)	1272 (21.3)	192 (27.0)	225 (24.1)
Unknown	223 (2.9)	115 (3.6)	183 (3.1)	24 (3.4)	16 (1.7)
Risk factors for influenza complications					
Any comorbidity	3377 (43.8)	1079 (34.1)	2441 (40.8)	286 (40.2)	620 (66.5)
Any complex chronic condition	2330 (30.6)	646 (20.4)	1626 (27.2)	198 (27.9)	506 (54.2)
Technology assistance	537 (7.1)	99 (3.1)	308 (5.2)	30 (4.2)	199 (21.3)
Diabetes	85 (1.1)	30 (1.0)	66 (1.1)	≤5 (≤1.0)	17 (1.8)
Asthma	1541 (20.2)	565 (17.9)	1177 (19.7)	134 (18.9)	230 (24.7)
Month of influenza test					
2 mo Before peak month	754 (9.9)	90 (2.9)	678 (11.4)	29 (4.1)	47 (5.0)
1 mo Before peak month	1281 (16.8)	648 (20.5)	1060 (17.7)	94 (13.2)	127 (13.6)
Peak month	1752 (23.0)	1238 (39.2)	1374 (23.0)	166 (23.4)	212 (22.7)
1 mo After peak month	1520 (20.0)	699 (22.1)	1144 (19.2)	174 (24.5)	202 (21.7)
2 mo After peak month	1143 (15.0)	280 (8.9)	838 (14.0)	138 (19.4)	167 (17.9)
3 mo After peak month	722 (9.5)	134 (4.2)	547 (9.22)	67 (9.4)	108 (11.6)
4 mo After peak month	446 (5.9)	72 (2.3)	333 (5.6)	43 (6.1)	70 (7.5)
Setting					
Hospital	2920 (38.3)	591 (18.7)	2221 (37.2)	262 (36.9)	437 (46.8)
Emergency department	2968 (39.0)	1546 (48.9)	2359 (39.5)	274 (38.5)	335 (35.9)
Physician office	1249 (16.4)	743 (23.5)	1010 (16.9)	129 (18.1)	110 (11.8)
Unknown	481 (6.3)	2818.9)	384 (6.4)	46 (6.5)	51 (5.5)
Vaccine received					
LAIV	711 (9.3)	147 (4.7)	NA	NA	NA
IIV	933 (12.3)	157 (5.0)	NA	NA	NA
Unvaccinated	5974 (78.4)	2857 (90.4)	NA	NA	NA

Abbreviations: IIV, inactivated influenza vaccine; LAIV, live attenuated influenza vaccine; NA, not applicable.

[a] Income quintiles are ranked from 1 (lowest income) to 5 (highest income).

tional 1080 children tested positive for influenza B, including 17 with influenza A/B coinfections. The numbers by case status, season, and influenza type and subtype are presented in eTable 4 in the Supplement. Among the study cohort, more specimens were collected in a hospital or emergency department than at a physician office.

A higher proportion of influenza cases were unvaccinated compared to influenza-negative controls (90% vs 78%) (**Table 1**). Among influenza-negative controls who received IIV, more than half were categorized as having any comorbidity; this proportion was lower for LAIV recipients and unvaccinated children.

For the 2012-2013 to 2015-2016 seasons combined, the adjusted VE against A(H1N1)pdm09 was 69% (95% CI, 56%-78%) for LAIV compared with 79% (95% CI, 70%-86%) for IIV (**Table 2**). Vaccine effectiveness against A(H3N2) was 36% (95% CI, 14%-53%) for LAIV and 43% (95% CI, 22%-59%) for IIV. Against influenza B, VE was 74% (95% CI, 62%-82%) for LAIV

Table 2. Adjusted Estimates of Vaccine Effectiveness by Selected Characteristics and Vaccine Type, 2012-2013 to 2015-2016 Seasons[a]

Characteristic	Vaccine Effectiveness (95% CI)			*P* Value[b]	Relative Odds (95% CI) of Influenza, LAIV vs IIV[c]
	Cases/Total	LAIV	IIV		
Overall	3161/10779	59 (50 to 66)	60 (52 to 67)		1.09 (0.83 to 1.42)
By influenza season					
2012-2013	660/2480	45 (18 to 63)	59 (40 to 73)	.04	1.62 (0.91 to 2.89)
2013-2014	543/2445	60 (34 to 76)	69 (52 to 80)		1.22 (0.62 to 2.39)
2014-2015	788/3079	53 (34 to 66)	52 (32 to 66)		0.90 (0.53 to 1.54)
2015-2016	1170/2775	75 (64 to 83)	62 (48 to 73)		0.76 (0.46 to 1.27)
By influenza subtype[d]					
A(H1N1)pdm09	1065/8683	69 (56 to 78)	79 (70 to 86)		1.50 (0.86 to 2.60)
2013-2014	443/2345	76 (52 to 88)	85 (71 to 92)	.76	1.43 (0.53 to 3.87)
2015-2016	573/2178	65 (46 to 77)	72 (54 to 83)		1.44 (0.73 to 2.87)
A(H3N2)	953/8571	36 (14 to 53)	43 (22 to 59)		1.23 (0.78 to 1.96)
2012-2013	303/2123	56 (14 to 77)	51 (14 to 72)	.23	1.39 (0.56 to 3.46)
2014-2015	625/2916	40 (13 to 58)	45 (17 to 63)		1.04 (0.58 to 1.86)
Influenza B	1080/8698	74 (62 to 82)	56 (41 to 66)		0.67 (0.42 to 1.05)
2012-2013	292/2112	39 (-2 to 64)	56 (23 to 74)	.004	1.52 (0.71 to 3.26)
2015-2016	583/2188	86 (74 to 93)	52 (29 to 68)		0.36 (0.17 to 0.76)
By age group, y					
2-4	1129/4792	63 (50 to 72)	61 (48 to 71)	.17	1.03 (0.67 to 1.58)
5-8	962/2789	62 (48 to 72)	70 (56 to 79)		1.41 (0.85 to 2.35)
9-17	1070/3198	47 (22 to 64)	49 (31 to 62)		0.97 (0.58 to 1.60)
By health care setting					
Hospital[e]	591/3511	41 (15 to 59)	53 (35 to 66)	.06	1.30 (0.80 to 2.13)
Emergency department[e]	1546/4514	66 (54 to 75)	68 (57 to 76)		1.12 (0.73 to 1.74)
Physician office	743/1992	62 (43 to 74)	40 (10 to 60)		0.59 (0.32 to 1.09)
Unknown	281/762	61 (24 to 80)	66 (33 to 82)		1.35 (0.42 to 4.39)
By comorbidity status					
Yes	1079/4456	55 (38 to 67)	58 (48 to 67)	.52	1.07 (0.74 to 1.56)
No	2082/6323	61 (51 to 70)	62 (49 to 72)		1.06 (0.72 to 1.58)

Abbreviations: IIV, inactivated influenza vaccine; LAIV, live attenuated influenza vaccine.

[a] Adjusted for age (in groups for overall estimates and months or years for age-group estimates), calendar month within season, presence of any comorbidity, and influenza season where applicable.

[b] Two-sided *P* value for interaction between vaccine type and subgroup.

[c] Analysis limited to vaccinated children, comparing odds of laboratory-confirmed influenza in LAIV recipients to IIV recipients.

[d] Season-specific estimates are provided for a given subtype when it was a dominant circulating strain.

[e] In sensitivity analyses restricted to acute respiratory infection–coded hospitalizations (70% of visits) or emergency department visits (68% of visits), vaccine effectiveness remained similar. For the hospital setting, vaccine effectiveness was 44% (95% CI, 18%-62%) for LAIV and 52% (95% CI, 32%-66%) for IIV. In emergency departments, vaccine effectiveness was 64% (95% CI, 50%-75%) for LAIV and 72% (95% CI, 60%-82%) for IIV.

and 56% (95% CI, 41%-66%) for IIV. We observed similar VE estimates between LAIV and IIV for any influenza strain for all seasons combined, by age group, and by comorbidity status. Differences in VE estimates were inconsistent by influenza season, by influenza type and subtype and season, and by health care setting, but confidence intervals generally overlapped.

Restricting our analysis to vaccine recipients only, we observed no significant differences in the odds of influenza infection for LAIV recipients compared with IIV recipients except for influenza B during the 2015-2016 season (Table 2). Vaccine effectiveness estimates by vaccine type, influenza type and subtype, and age group are presented in eTable 5 in the Supplement and unadjusted VE estimates in eTable 6 in the Supplement.

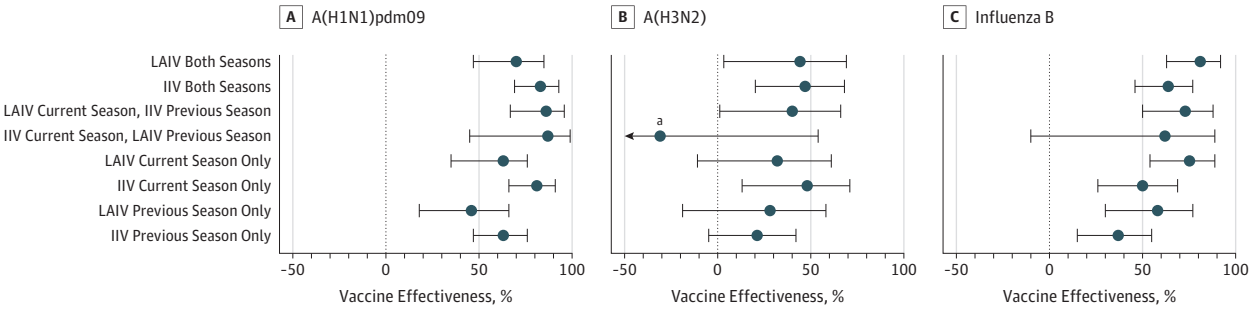
Our results were generally unchanged when we restricted our analysis to acute respiratory infection–coded hospitalizations or emergency department visits (Table 2) and when we included health care setting in our model (eTable 7 in the Supplement). We also observed similar VE estimates using children who tested positive for other respiratory viruses as controls, although some estimates for IIV increased, and we no longer found significantly reduced odds of influenza B infection for those receiving LAIV relative to IIV in the 2015-2016 influenza season (eTable 8 in the Supplement). This finding was more pronounced in an alternate sensitivity analysis when we excluded LAIV-ineligible children (eTable 9 in the Supplement).

We noted substantial overlap of CIs of VE estimates when we considered the outcomes associated with repeated receipt of a particular vaccine type (**Figure 1**). Although receiving one vaccine type repeatedly did not result in substantially higher or lower VE than repeated receipt of the other vaccine type, the patterns for the VE point estimates by influenza type and subtype were similar to the original analysis, whether we evaluated receipt of a particular vaccine type for both current and previous seasons, the current season only, or the previous season only. Results were similar when children received the same vaccine type for 3 consecutive seasons (**Figure 2**). Influenza type and subtype and season-specific results showing data from repeated vaccination across 2 seasons are presented in the eFigure in the Supplement.

Discussion

We found LAIV and IIV both to be effective against medically attended, laboratory-confirmed influenza among children aged 2 to 17 years during the 2012-2013 through 2015-2016

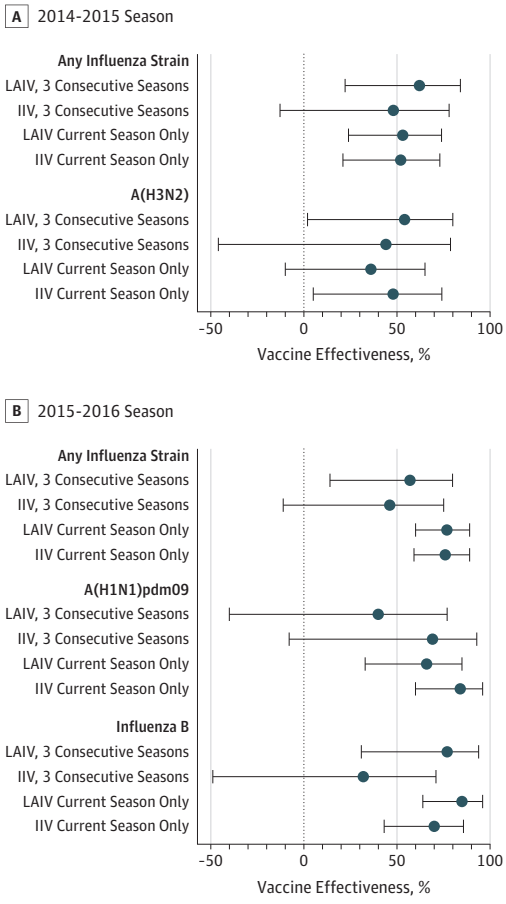
Figure 1. Effectiveness of Vaccines Received During Current and Previous Influenza Seasons by Influenza Subtype



Vaccine effectiveness was calculated as (1 − adjusted odds ratio) × 100%. IIV indicates inactivated influenza vaccine; LAIV, live attenuated influenza vaccine. Error bars indicate 95% CIs.

[a] The lower confidence limit for the A(H3N2) vaccine effectiveness estimate is −253.

Figure 2. Vaccine Effectiveness by 3-Year History of Vaccination by Influenza Season



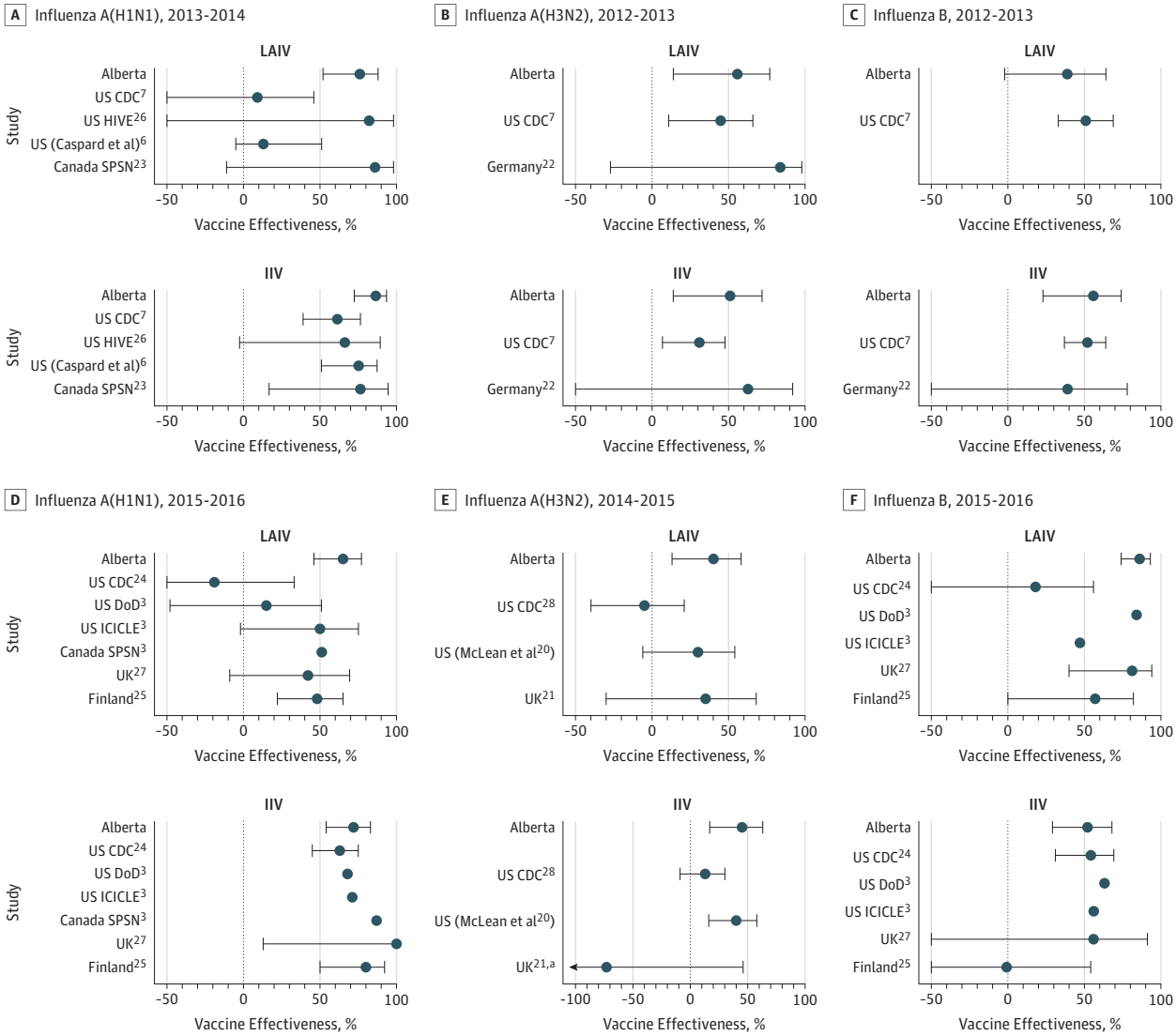
Vaccine effectiveness was calculated as (1 − adjusted odds ratio) × 100%. IIV indicates inactivated influenza vaccine; LAIV, live attenuated influenza vaccine. Error bars indicate 95% CIs.

influenza seasons. We found no significant differences in VE for those receiving LAIV vs IIV except for influenza B during the 2015-2016 season, for which LAIV provided better protection than IIV.

All of our VE estimates were within the 95% CIs of estimates from most previous studies (**Figure 3**).[3,6-8,20-28] None of our estimates were outliers given the substantial variability in previous estimates. We found no evidence indicating a lack of effectiveness of LAIV against A(H1N1)pdm09 in Alberta, which is in contrast to reports from the United States for the 2013-2014 and 2015-2016 influenza seasons.[6-8] A recent meta-analysis found significant protection of LAIV against A(H1N1)pdm09, but VE was relatively low (32%; 95% CI, 16%-44%).[29] Our VE estimate for LAIV against A(H1N1)pdm09 in the 2013-2014 season had a point estimate similar to that of another Canadian study of children aged 2 to 19 years (VE, 86%; 95% CI, −11% to 98%)[23] and the US Household Influenza Vaccine Effectiveness study of children aged 2 to 8 years (VE, 82%; 95% CI, −65% to 98%).[26] Both of those studies found nonsignificant VE, whereas our larger study had greater power. A cluster randomized clinical trial involving Hutterite colonies in 2 Canadian provinces also looked at the relative effectiveness of LAIV vs IIV across 3 influenza seasons and found no significant differences between the 2 vaccine types in preventing laboratory-confirmed influenza in the community.[30] In one of our sensitivity analyses, the relative odds of influenza comparing LAIV with IIV appeared more pronounced when we excluded LAIV-ineligible children (ie, the relative odds of influenza in this group was higher when comparing LAIV with IIV than for the total cohort). This result may be because influenza vaccines provide less protection for children with comorbidities, a group that is overrepresented among those receiving IIV, thus underestimating VE for IIV in our original analysis.

Live attenuated influenza virus and IIV both provided significant protection against A(H3N2) for the 2014-2015 influenza season in this study, a finding that differs from some published estimates that indicated no protection from either vaccine type that season.[21,28] However, our point estimates were similar to other estimates for that season. McLean et al[20] found significant protection for IIV (VE, 40%; 95% CI, 16%-58%), but the 95% CI for their LAIV VE estimate included zero (VE, 30%; 95% CI, −6% to 54%). In the United Kingdom, Pebody et al[21] estimated VE for LAIV to be 35% (95% CI, −30% to 68%). We included 2 times the number of children in the US study and 3 times the number of children in the UK study,

Figure 3. Comparison of Influenza Vaccine Effectiveness (VE) in Alberta With Other Published Estimates by Type/Subtype, Season, and Vaccine Type[3,6-8,20-28]



Vaccine effectiveness was calculated as (1 − adjusted odds ratio) × 100% for all studies except HIVE, where VE was calculated using the formula 1 − hazard ratio. All follow this formula except the results from the Household Influenza Vaccine Effectiveness Study (HIVE), where VE is calculated using the hazard ratio (HR); the formula is still (1 − HR). The threshold level of 5% weekly test positivity was used. CDC indicates Centers for Disease Control and Prevention; DoD, Department of Defense; ICICLE, Influenza Clinical Investigation for Children; IIV, inactivated influenza vaccine; LAIV, live attenuated influenza vaccine; and SPSN, Sentinel Practitioner Surveillance Network. Error bars indicate 95% CIs.

[a] The lower confidence limit for the vaccine effectiveness estimate from the UK study[21] is −457.

accounting for the greater power of the present study to show a significantly protective effect of LAIV.

Our VE estimates for influenza B were also similar to other studies, including those reported for the 2015-2016 influenza season in the United Kingdom, where VE was 81% (95% CI, 40%-94%) for LAIV and 56% (95% CI, −122% to 91%) for IIV.[27] Although our estimate for IIV in the 2015-2016 season was similar to those reported in the United States by the US Flu VE Network and a multiseason postmarketing observational study, our LAIV estimates differed.[24,31] However, our LAIV estimate was similar to that of another US-based study produced by the Department of Defense (VEs of 84% for LAIV and 63% for IIV).[11] Our finding that VE against influenza B in the 2015-2016 season was similar for those vaccinated in the current season only and those vaccinated in both the current and previous seasons aligned with results reported by the US Flu VE Network, but they only included children older than 9 years.[24]

Pebody et al[3] recently synthesized the literature on this issue, including a history of decisions made by various national technical advisory groups. Although reasons for the inconsistencies observed in different geographic settings are uncertain, they offered some hypotheses as to why LAIV may not have been protective against A(H1N1)pdm09 infection. One hypothesis is the existence of viral interference between the

A(H1N1)pdm09 vaccine strain and other vaccine viruses. In Alberta, LAIV3 was used for the 2013-2014 influenza season, whereas LAIV4 was used in the United States that season,[7] consistent with the possibility of viral interference for that season.[3,32] Another suggestion is that repeated vaccination with LAIV has resulted in long-term immunological changes.[3] Live attenuated influenza vaccine has been available for fewer seasons in Alberta than in the United States. As such, the Canadian cohort would have had less opportunity for multiple exposures to LAIV compared with American children. An additional hypothesis of diminished effectiveness of LAIV is associated with reduced thermostability of the A(H1N1) pdm09 vaccine strain.[9]

Strengths and Limitations

Because of our large sample size and the moderate vaccine coverage in this population, we generated some of the most precise VE estimates to date. We were also able to provide several stratified estimates of VE, an important contribution suggested by Pebody et al.[3] The available data allowed us to include all specimens tested for influenza in the province, to ascertain vaccination status using an immunization registry instead of parental recall, and to determine other important covariates using health administrative data.

A limitation of our study was the lack of a prespecified case definition for testing. However, we performed a sensitivity analysis in which we restricted the sample to children with an acute respiratory infection–coded encounter as a proxy for a case definition, and VE estimates did not change substantially. We also lacked symptom onset dates, but this omission is expected to be less of an issue in children because they shed high levels of virus for long periods.[33] To mitigate this issue, we repeated our analysis using children who tested positive for other respiratory viruses as controls, and VE estimates were generally unchanged. Using similar routinely collected clinical specimens and health administrative data in the province of Ontario, our group conducted a series of analyses suggesting the presence of minimal information and selection biases, confirming that such data can be used for estimating influenza VE (unpublished data, 2009-2014; J.C.K.; S.A.B.; Hannah Chung, MPH; Michael A. Campitelli, MPH; Kevin L. Schwartz, MD, MSc; N.S.C.; Michael L. Jackson, PhD; Timothy Karnauchow, PhD; Kevin Katz, MD; Allison J. McGeer, MD, MSc; J. Dayre McNally, MD, PhD; David Richardson, MD; Susan E Richardson, MD; Laura C. Rosella, PhD, MHSc; Andrew Simor, MD; Marek Smieja, MD, PhD; George Zahariadis, MD; Jonathan B. Gubbay, MBBS, MMedSc).

Conclusions

Our study demonstrates significant protection against influenza for children who received either IIV or LAIV. These results support receipt of either vaccine type in this age group.

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