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Vaccine Effectiveness of non-adjuvanted and adjuvanted trivalent inactivated influenza vaccines in the prevention of influenza-related hospitalization in older adults: A pooled analysis from the Serious Outcomes Surveillance (SOS) Network of the Canadian Immunization Research Network (CIRN)

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ABSTRACT

Background: Influenza vaccines prevent influenza-related morbidity and mortality; however, suboptimal vaccine effectiveness (VE) of non-adjuvanted trivalent inactivated influenza vaccine (naTIV) or quadrivalent formulations in older adults prompted the use of enhanced products such as adjuvanted TIV (aTIV). Here, the VE of aTIV is compared to naTIV for preventing influenza-associated hospitalization among older adults.

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Frailty
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Methods: A test-negative design study was used with pooled data from the 2012 to 2015 influenza seasons. An inverse probability of treatment (IPT)-weighted logistic regression estimated the Odds Ratio (OR) for laboratory-confirmed influenza-associated hospitalization. VE was calculated as (1-OR)*100% with accompanying 95% confidence intervals (CI).

Results: Of 7,101 adults aged ≥ 65, 3,364 received naTIV and 526 received aTIV. The overall VE against influenza hospitalization was 45.9% (95% CI: 40.2%–51.1%) for naTIV and 53.5% (42.8%–62.3%) for aTIV. No statistically significant differences in VE were found between aTIV and naTIV by age group or influenza season, though a trend favoring aTIV over naTIV was noted. Frailty may have impacted VE in aTIV recipients compared to those receiving naTIV, according to an exploratory analysis; VE adjusted by frailty was 59.1% (49.6%–66.8%) for aTIV and 44.8% (39.1%–50.0%) for naTIV. The overall relative VE of aTIV to naTIV against laboratory-confirmed influenza hospital admission was 25% (OR 0.75; 0.61–0.92), demonstrating statistically significant benefit favoring aTIV.

Conclusions: Adjusting for frailty, aTIV showed statistically significantly better protection than naTIV against influenza-associated hospitalizations in older adults. In future studies, it is important to consider frailty as a significant confounder of VE.

1. Introduction

Influenza vaccination continues to be essential in preventing severe influenza-related outcomes, particularly among older adults. In Canada, the National Advisory Committee on Immunization (NACI) recommends influenza vaccination, particularly for adults ≥ 65 years of age when the burden of influenza disease and the occurrence of adverse clinical outcomes is higher [1]. Older adults ≥ 65 years represent approximately 16% of the Canadian population; estimates from the U.S. have suggested that 54–70% of influenza-related hospitalizations and 71–85% of influenza-related deaths occur in patients ≥ 65 years [2]. Unfortunately, while older adults are at heightened influenza risk, a combination of factors, including immunosenescence, increased comorbidities, and frailty, are hypothesized to contribute to a decreased immune response which usually translates into a suboptimal influenza vaccine effectiveness (VE) observed as compared to VE in adults < 65 years [3–6].

Many influenza vaccine products are available, but each jurisdiction decides which of the authorized vaccines is distributed and administered to their population. As of 2010, there were five trivalent inactivated influenza vaccines (TIV) authorized for use in Canada [7]; in 2011, three new vaccines were approved for use, including an enhanced vaccine targeted to older adults, adjuvanted TIV (aTIV) [8]. The aTIV contains MF-59, an oil-in-water adjuvant containing oil, squalene, polysorbate 80 (Tween 80), and sorbitan triolate in citrate buffer (Span 85) [9]. In older adults, the MF-59 adjuvanted vaccine has demonstrated more robust immune responses than the non-adjuvanted vaccine against vaccine-matched strains and has also been assumed to be beneficial against drifted influenza strains that are vaccine mismatched [10–16]. However, the adjuvanted vaccine has not been demonstrated to elicit significantly higher cellular immune responses in older adults [17].

Despite immunological evidence suggesting benefit, compelling real-world evidence demonstrating improved effectiveness of aTIV over standard-dose non-adjuvanted TIV (naTIV) in older adults continues to be of interest.[4] Due to the absence of consistent evidence and logistical constraints, Canada's NACI does not preferentially recommend aTIV in older adults [1]. Additionally, because each Canadian provincial and territorial health care system operates autonomously, not all provinces/territories publicly fund aTIV, and even those that do may not fund it yearly. More data on the aTIV VE is required to support policy-making decisions. Notably, the United States Advisory Committee on Immunization Practices (ACIP) has a preferential recommendation for several enhanced products, including aTIV, high-dose inactivated vaccine, and recombinant influenza vaccine [18]. These agree with the World Health Organization (WHO)'s position recommending high-dose, recombinant, and adjuvant influenza vaccines as long as they do not compromise the country's ability to provide influenza vaccination [19].

To address this knowledge gap, in this study we present data on the effectiveness of aTIV compared to naTIV for the prevention of laboratory-confirmed influenza-associated hospitalization among adults ≥ 65 years and explore how frailty influences VE.

2. Methods

2.1. Hospital-based surveillance

The Serious Outcomes Surveillance (SOS) Network of the Canadian Immunization Research Network (CIRN) is an active influenza surveillance network in Canadian hospitals [3,20,21]. Active surveillance for influenza began approximately November 15 of each year; SOS Network monitors reviewed all daily admissions of adult patients to medical wards and intensive care and coronary units to identify eligible patients. Patients ≥ 16 years admitted with an acute respiratory illness are eligible for enrollment.

2.2. Study design and participants

This study employed a test-negative design using pooled data from the CIRN SOS Network for the 2012/2013, 2013/2014, and 2014/2015 influenza seasons. We selected these influenza seasons because they consistently collected information on frailty using the Clinical Frailty Scale (CFS), and because in these seasons additional resources were applied to gather and validate the vaccine product received. Eligibility criteria were [1] available data on influenza vaccination status during the year of enrollment in the CIRN SOS Network database and, when vaccinated, on the type of influenza vaccine received, and [2] age ≥ 65 years. Exclusions were as follows: [1] participants not receiving a TIV formulated for intramuscular administration (such as intradermal); [2] those receiving a high-dose TIV (HD-TIV, which was only approved for use in Canada in 2015, so no individuals had actually received HD-TIV); and [3] individuals receiving a quadrivalent inactivated influenza vaccine (also not in general use at the time), or [4] receiving a live attenuated influenza vaccine.

The SOS study surveillance protocol was approved by the Research Ethics Board of the participating institutions (ClinicalTrials.gov Identifier: NCT01517191).

2.3. Measures

Demographic and clinical data collection followed a standardized CIRN SOS Network protocol, which has been described elsewhere [22]. Demographic data included sex, age, and location where the person lived before hospital admission. Health-related data included underlying comorbidities, smoking status, frailty, influenza vaccination status for the current season and the previous season, and whether the participant used antivirals before hospital admission. Comorbidity burden was assessed using Charlson Comorbidity Index (CCI) and was considered both as a score and as a dichotomous variable with a cut-off ≥ 4 (indicating a high comorbidity burden) [23]. Frailty was measured

using the Clinical Frailty Scale (CFS) and was considered both as the full ordinal scale and as a categorical variable: CFS score 1 – 4 (non-frail), CFS score 5 – 6 (mild-to-moderately frail), and CFS score ≥ 7 (severely frail). For further details on how to utilize the Clinical Frailty Scale, kindly consult the Supplemental Material.

2.4. Cases and controls

All participants had a nasopharyngeal (NP) swab test to assess influenza virus infection that was subjected to influenza A and B real-time RT-PCR, as well as subsequent reactions to characterize influenza A subtypes (H3 or H1) or influenza B lineages according to local or reference laboratories protocols [22]. Patients were classified as cases if they tested positive for influenza or controls if they tested negative for influenza. In order to control for exposure risk, test-negative controls were selected from the same hospital site (geographical location) as the case, with a date of admission within +/- 2 weeks. In all, cases and controls were matched based on location, time of admission, and age (>or < 65 years).

2.5. Influenza vaccination history

Vaccination history was assessed through registries where these existed, chart records, and self-report by participants or their responsible decision-makers. Vaccination status and product received were verified with the vaccination provider where necessary. To be classified as "Current season vaccination," individuals must have received the influenza vaccine for the year they enrolled in the CIRN SOS Network database at least 14 days prior to becoming ill.

2.6. Statistical analysis

Descriptive statistics were used to compare infection status (cases vs. controls) and vaccination status (unvaccinated vs. aTIV vs. naTIV). Standardized Mean Differences (SMD) and differences in proportions assessed imbalance between groups according to their vaccination status.

The primary outcome of interest was VE against laboratory-confirmed influenza-associated hospitalization among older adults, according to the vaccine type. The stabilized Inverse Probability of Treatment Weighting (IPTW) method was applied to the test-negative design to adjust imbalances between vaccination status groups before estimating VE [24]. A complete description of the methods used for balancing covariates via IPTW before assessing VE is presented in the Supplementary Material.

For the VE analysis, IPT-weighted Odds Ratio (OR) were obtained for laboratory-confirmed influenza-associated hospitalization from the odds of vaccination among cases vs. controls. IPT-weighted ORs were converted to VE using the formula VE = 100%*(1-OR). A sandwich method was used to estimate robust standard errors and 95% confidence intervals (95% CI). Next, samples were filtered to include only vaccinated persons and used logistic regression to compare the odds of laboratory-confirmed influenza-associated hospitalization among those receiving aTIV to naTIV; an OR greater than 1 favors naTIV.

To ascertain the impact of clinical frailty on the VE estimated of both vaccines, the changes in VE between the unadjusted and the frailty-adjusted estimates was explored. As there was about 13% of missingness in frailty assessment, a Multiple Imputation by Chained Equations (MICE) methodology was used to deal with incomplete data on the CFS before analyzing its effects on VE estimates. Rubin's rules were used to pool parameter estimates and to derive confidence intervals and p-values [25]. Supplemental Material presents a complete description of the methods applied for data imputation. VE calculation was the same as previously described.

The statistical significance was assessed at a two-sided p-value < 0.05. All analyses were conducted using was performed in R (version 4.2.1) using RStudio IDE (RStudio 2022.02.1 + 461 "Prairie Trillium" Release).

3. Results

3.1. Characteristics of cases and controls

This analysis included 3,441 cases and 3,660 controls aged ≥ 65 years (Fig. 1). A total of 1,578 (45.9%) influenza-positive patients were immunized in the current season with any TIV, compared to 2,312 (63.2%) for influenza-negative controls. Influenza A represented 78.1% of all strains identified; H3N2 was the most common subtype, accounting for 37.5% of all influenza A-positive tests, but it is likely that this proportion was underestimated since 32.9% of the strains were not subtyped. The numbers by case status and vaccination status are presented in Table 1.

Of those individuals immunized with any TIV in the current season, the bulk of vaccines received were naTIV (86.5%), while 526 patients had received aTIV. Frailty was higher among the aTIV recipients. Among non-frail patients, 15.2% had received aTIV, and 55.4% had received naTIV, whereas more aTIV receipt was reported for severely frail patients, with 33.3% having received aTIV vs. 5.6% naTIV (Table 1). Given the significant numerical imbalance between the vaccine status groups (unvaccinated vs. aTIV vs. naTIV), IPT weighting was used to balance the baseline characteristics and reduce the influence of possible confounders. Supplementary Material – Tables 1 and 2 show the results of IPT-weighted covariates before estimating VE.

3.2. Vaccination effectiveness

The overall IPT-weighted VE against hospitalization for laboratory-confirmed influenza was 45.9% (95%CI: 40.2–51.1) for naTIV compared with 53.5% (42.8–62.3) for aTIV before adjusting for frailty. No significant differences were observed in VE estimated between aTIV and naTIV by sex, age group, and influenza season, though there was a trend toward favoring aTIV over naTIV. The estimates for VE varied significantly based on the influenza strain. aTIV showed higher VE

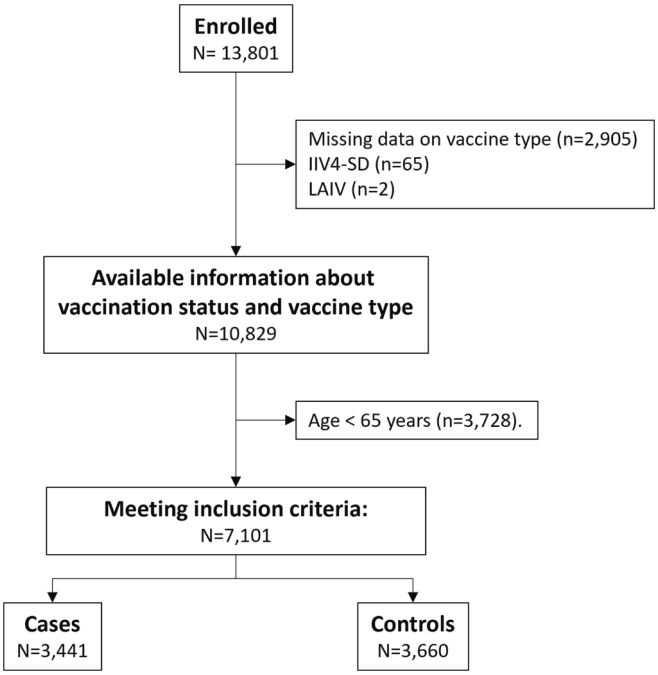

Fig. 1. Study participants flow diagram. Abbreviation: IIV4-SD, Standard-dose Quadrivalent Inactivated Influenza Vaccine; LAIV, Live attenuated Influenza Vaccine.

Table 1
Demographic and clinical characteristics of cases and controls enrolled in the CIRN SOS network in 2012–2015.

Variable	Parameter	Controls N = 3,660	Cases N = 3,441	Unvaccinated N = 3,211	aTIV[1] N = 526	naTIV[1] N = 3,364
Sex	Male	1,724 (47.1)	1,607 (46.7)	1,489 (46.4)	225 (42.8)	1,617 (48.1)
	Female	1,936 (52.9)	1,834 (53.3)	1,722 (53.6)	301 (57.2)	1,747 (51.9)
Age group	65–75	1,172 (32.0)	887 (25.8)	1,026 (32.0)	85 (16.2)	948 (28.2)
	75–85	1,424 (38.9)	1,263 (36.7)	1,190 (37.1)	167 (31.7)	1,330 (39.5)
	85+	1,064 (29.1)	1,291 (37.5)	995 (31.0)	274 (52.1)	1,086 (32.3)
Influenza season	2012/2013	1,210 (33.1)	1,216 (35.3)	1,056 (32.9)	156 (29.7)	1,214 (36.1)
	2013/2014	1,465 (40.0)	969 (28.2)	1,018 (31.7)	184 (35.0)	1,232 (36.6)
	2014/2015	985 (26.9)	1,256 (36.5)	1,137 (35.4)	186 (35.4)	918 (27.3)
Vaccination status	Never vaccinated	1,109 (30.3)	1,601 (46.5)	2,710 (84.4)	0 (0.0)	0 (0.0)
	Vaccination in prior seasons only	239 (6.5)	262 (7.6)	501 (15.6)	0 (0.0)	0 (0.0)
	Current season vaccination	2,312 (63.2)	1,578 (45.9)	0 (0.0)	526 (100.0)	3,364 (100.0)
Smoking status	Never smoked	1,269 (34.7)	1,327 (38.6)	1,158 (36.1)	234 (44.5)	1,204 (35.8)
	Former smoker	1,764 (48.2)	1,193 (34.7)	1,076 (33.5)	202 (38.4)	1,679 (49.9)
	Current smoker	558 (15.2)	672 (19.5)	738 (23.0)	71 (13.5)	421 (12.5)
	Smoking status unknown	69 (1.9)	249 (7.2)	239 (7.4)	19 (3.6)	60 (1.8)
Charlson Comorbidity Index, CCI	Overall score, median [1st, 3rd quartile]	2.00 [1.00, 3.00]	1.00 [1.00, 2.00]	1.00 [1.00,2.00]	2.00 [1.00,3.00]	2.00 [1.00,3.00]
	Estimated 10-year mortality risk ≥ 5% (CCI score ≥ 4)	388 (10.6)	321 (9.3)	284 (8.8)	71 (13.5)	354 (10.5)
Antiviral use before admission	Yes	51 (1.4)	116 (3.4)	73 (2.3)	17 (3.2)	77 (2.3)
Clinical Frailty Scale, CFS	Unknown	317 (8.7)	630 (18.3)	619 (19.3)	119 (22.6)	209 (6.2)
	Non-frail (CFS 1–4)	1,946 (53.2)	1,435 (41.7)	1,439 (44.8)	80 (15.2)	1,862 (55.4)
	Mild-to-moderately frail (CFS 5–6)	1,086 (29.7)	1,025 (29.8)	856 (26.7)	152 (28.9)	1,103 (32.8)
	Severely frail (CFS ≥ 7)	311 (8.5)	351 (10.2)	297 (9.2)	175 (33.3)	190 (5.6)
Laboratory-confirmed influenza infection	Negative	3,660 (100.0)	–	1,348 (42.0)	313 (59.5)	1,999 (59.4)
	Positive	–	3,441 (100.0)	1,863 (58.0)	213 (40.5)	1,365 (40.6)
Influenza type and strain	Influenza A	–	2,688 (78.1)	1,452 (45.2)	162 (30.8)	1,074 (31.9)
	A(H1N1)pdm09	–	266 (7.7)	146 (4.5)	7 (1.3)	113 (3.4)
	A(H3N2)	–	1,289 (37.5)	617 (19.2)	135 (25.7)	537 (16.0)
	A unsubtyped	–	1,133 (32.9)	689 (21.5)	20 (3.8)	424 (12.6)
	Influenza B	–	751 (21.8)	409 (12.7)	51 (9.7)	291 (8.7)
	Influenza A/B	–	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
	Influenza untyped	–	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)

[1] Patients considered immunized with adjuvanted trivalent inactivated influenza vaccine (aTIV) received Fluad (12%). Patients considered immunized with standard-dose trivalent inactivated influenza vaccine (naTIV) received either Agriflu (22.7%), Fluviral (44.9%), Influvac (2.7%), or Vaxigrip (17.7%).

values against influenza A(H1N1)pdm09 but lower VE values against A (H3N2) compared to naTIV. However, the analysis may have been compromised due to a large number of untyped influenza A strains (Table 2).

3.3. Exploratory analysis on the effect of clinical frailty on vaccine effectiveness

The overall VE against hospitalization adjusted for frailty was 59.1% (49.6–66.8) for aTIV compared with 44.8% (39.1–50.0) for naTIV. Table 3 shows the VE estimates by influenza type and strain, adjusted for frailty. Overall, the relative VE against laboratory-confirmed influenza was 25% (OR 0.75; 95%CI: 0.61–0.92), demonstrating a statistically significant benefit favoring aTIV. No significant differences were observed in VE estimated between aTIV and naTIV by age group and influenza season. There was a statistically significant difference in VE estimates according to sex and influenza strain: aTIV presented higher VE values among females and against influenza A (H1N1/pdm09 and untyped strains) compared to naTIV. Fig. 2 shows the effect of influenza vaccination on preventing hospitalization for laboratory-confirmed influenza adjusted for frailty, according to vaccine type and influenza type or subtype/lineage.

4. Discussion

Both aTIV and naTIV were effective against influenza-related hospitalizations, with VE estimates in the range of 45–54%. In the analysis that did not consider frailty, there were no statistically significant differences in VE for those receiving aTIV versus naTIV by age group and influenza season, though there was a trend favoring aTIV over naTIV. A statistically significant difference was observed in VE estimates by influenza A subtype, with aTIV showing higher VE against H1N1 vs. H3N2, though the high number of untyped influenza A strains may have compromised such analysis. After taking frailty into consideration as a potential confounding variable, the estimates of vaccine effectiveness were similar for naTIV and higher for aTIV. The relative VE against laboratory-confirmed influenza was 25%, indicating that aTIV was more effective compared to naTIV.

The magnitude of vaccination effect differed significantly between age categories, particularly for those receiving naTIV, with lower VE among those aged 85+ years: 49.8% (95% CI, 33.8–61.9) for aTIV, representing an increase of about 13% over naTIV VE of 36.8% (95% CI, 24.5–47.1), although this difference was not statistically significant. Still, there may be some plausible explanations for these findings. The first regards age distribution in each vaccine group: the aTIV group included a substantially higher proportion of the oldest adults aged 85+ than naTIV (52.1% vs. 32.3%). This unbalanced data is relevant as the immune system is continuously remodeled along with aging, presenting progressively fewer naïve cells and an increase in dysfunctional memory cells, in addition to the involution of primary lymphoid organs and altered innate immune response [26]. Our results showed that after IPT weighting but before adjusting for frailty, those receiving aTIV maintained numerically higher VE than naTIV values across age groups, although this remained statistically non-significant as confidence intervals overlapped. This suggests that adjuvants may improve VE among older adults aged 85+. However, the sample size limited this analysis, as VE calculation using the test-negative design depends on the proportion of immunized and non-immunized cases and controls. Further studies should consider assessing aTIV VE compared to standard products among those aged 85+ years.

It is likely that frailty influences how well older adults respond to influenza vaccination [3,27]. Our findings reinforce this idea by

Table 2
Vaccine effectiveness in preventing hospitalization for laboratory-confirmed influenza.

Feature	Cases/ Total	Vaccine effectiveness (95% CI)		Relative odds (95% CI) of LCI[1]
		aTIV	naTIV	
Overall	3,441/ 7,101	53.5 (42.8–62.3)	45.9 (40.2–51.1)	0.86 (0.71–1.04)
Sex				
Female	1,834/ 3,770	53.0 (38.1–64.4)	42.6 (34.2–50.0)	0.82 (0.63–1.06)
Male	1,607/ 3,331	54.0 (36.9–66.5)	49.4 (41.5–56.3)	0.91 (0.68–1.20)
Age group				
65–74 years	887/ 2,059	55.6 (28.0–72.6)	48.4 (37.9–57.1)	0.86 (0.58–1.26)
75–84 years	1,263/ 2,687	55.2 (36.9–68.1)	52.6 (44.3–59.8)	0.95 (0.69–1.28)
85 and older	1,291/ 2,355	49.8 (33.8–61.9)	36.8 (24.5–47.1)	0.80 (0.57–1.10)
Influenza season				
2012/2013	1,216/ 2,426	50.7 (28.1–66.2)	44.9 (34.7–53.6)	0.90 (0.63–1.27)
2013/2014	969/ 2,434	62.1 (45.3–73.8)	52.9 (43.9–60.5)	0.80 (0.56–1.13)
2014/2015	1,256/ 2,241	46.6 (24.5–62.3)	33.3 (20.1–44.3)	0.80 (0.58–1.10)
Influenza type and strain				
Influenza A	2,688/ 6,348	53.9 (42.3–63.2)	44.9 (38.7–50.5)	0.84 (0.68–1.03)
A(H1N1) pdm09	266/ 3,926	77.6 (49.2–90.1)	40.6 (23.0–54.2)	0.38 (0.16–0.76)
A(H3N2)	1,289/ 4,949	13.8 (-10.2–32.6)	38.7 (29.6–46.5)	1.41 (1.11–1.76)
A unsubtyped	1,133/ 4,793	87.6 (79.2–87.6)	51.9 (44.5–58.3)	0.26 (0.15–0.41)
Influenza B	751/ 4,411	51.8 (31.3–66.2)	48.9 (39.6–56.8)	0.94 (0.67–1.31)

[1] To compare the relative effectiveness considering vaccine type, we filtered the sample to include only vaccinated persons and used logistic regression to compare the odds of laboratory-confirmed influenza infection among those receiving aTIV to naTIV; an OR greater than 1 favor naTIV persons concerning VE.

Table 3
Vaccine effectiveness in preventing hospitalization for laboratory-confirmed influenza, adjusted by the clinical frailty scale.

Feature	Cases/ Total	Vaccine effectiveness (95% CI)		Relative odds (95% CI) of LCI[1]
		aTIV	naTIV	
Overall	3,441/ 7,101	59.1 (49.6–66.8)	44.8 (39.1–50.0)	0.75 (0.61–0.92)
Sex				
Female	1,834/ 3,770	59.2 (45.8–69.2)	41.9 (33.5–49.3)	0.72 (0.54–0.94)
Male	1,607/ 3,331	58.8 (43.8–69.8)	48.2 (40.1–55.2)	0.81 (0.60–1.10)
Age group				
65–74 years	887/ 2,059	54.4 (32.2–69.3)	48.4 (37.9–57.2)	0.85 (0.57–1.28)
75–84 years	1,263/ 2,687	58.8 (42.0–70.7)	51.9 (43.4–59.1)	0.86 (0.62–1.20)
85 and older	1,291/ 2,355	57.0 (38.1–70.1)	33.9 (21.5–44.3)	0.73 (0.52–1.03)
Influenza season				
2012/2013	1,216/ 2,426	55.1 (34.0–69.4)	44.3 (34.2–52.8)	0.77 (0.53–1.12)
2013/2014	969/ 2,434	67.3 (52.2–77.7)	52.6 (43.7–60.1)	0.72 (0.49–1.04)
2014/2015	1,256/ 2,241	51.0 (30.9–65.2)	31.4 (17.8–42.7)	0.74 (0.53–1.03)
Influenza type and strain				
Influenza A	2,688/ 6,348	59.1 (48.7–67.4)	44.0 (37.8–49.6)	0.74 (0.60–0.93)
A(H1N1) pdm09	266/ 3,926	73.7 (39.4–88.6)	41.4 (24.1–54.8)	0.43 (0.19–0.96)
A(H3N2)	1,289/ 4,949	27.9 (7.5–43.7)	37.6 (28.7–45.5)	1.13 (0.88–1.44)
A unsubtyped	1,133/ 4,793	89.1 (81.7–93.5)	50.7 (43.2–57.1)	0.24 (0.15–0.40)
Influenza B	751/ 4,411	59.9 (42.3–72.0)	47.7 (38.2–55.8)	0.78 (0.54–1.11)

[1] To compare the relative effectiveness considering vaccine type, we filtered the sample to include only vaccinated persons and used logistic regression to compare the odds of laboratory-confirmed influenza infection among those receiving aTIV to naTIV; an OR greater than 1 favor naTIV persons concerning VE.

demonstrating that the likelihood of hospitalization due to laboratory-confirmed influenza varies when considering frailty as a confounding factor. More than 60% of persons who received aTIV in our study had at least mild frailty, compared to 38% of persons who received naTIV. This raises the possibility of confounding by indication, in that there was a systematic difference in who received one product vs. the other based on clinicians' or vaccine programs' assessment of their vulnerability, and those who received aTIV would have been expected to have lower VE by these same vulnerability factors [3]. Even so, we observed greater VE among those receiving aTIV than naTIV after adjusting for frailty, at 59.1% vs. 44.8%, respectively; relative vaccine effectiveness of 25% (OR 0.75, 95%CI: 0.61–0.92) favoring aTIV. There are two significant implications of these results. Firstly, they emphasize the importance of considering frailty when evaluating VE. Secondly, the results suggest that adjuvants may have a potential role in enhancing influenza VE for individuals with even mild frailty.

We attempted to account for the imbalance between groups using IPTW and analysis broken down into subgroups; however, the relative benefit of aTIV over standard products is difficult in observational studies where underlying biases related to non-randomization of vaccination or vaccine type cannot be addressed. Randomized trials that can follow patients prospectively and investigate relative efficacy may provide a better understanding of the effectiveness of different vaccine products, such as the previously published cluster-randomized trial of adjuvanted versus nonadjuvanted trivalent influenza vaccine in U.S. nursing homes [28]. The study randomized 823 nursing homes housing 50,012 eligible residents to receive aTIV or naTIV, observing a 6% reduction for aTIV in the risk of all-cause hospitalizations ($p = 0.02$) and a non-significant 7% reduction in respiratory-related hospitalizations ($p = 0.19$). However, the authors observed a greater effect size of 21% for the secondary outcome of pneumonia and influenza-related hospitalizations ($p = 0.02$). It is noteworthy that the study used administratively collected diagnostic codes to define outcomes, so their results may have a residual bias, as administratively defined outcomes should not be interpreted as definitive clinical diagnoses. Despite this, the authors supported the use of adjuvanted influenza vaccines rather than standard-dose, non-adjuvanted, egg-based vaccines to prevent hospitalizations of nursing home residents.

Other observational studies of TIV have shown mixed benefits of aTIV over naTIV. A phase III clinical trial of MF-59 aTIV and naTIV in older adults ≥ 65y observed no increased clinical effectiveness of aTIV over naTIV in preventing influenza-like illness (ILI) [29]. In Italy, an observational study of TIV in long-term care facilities (LTCF) demonstrated that the aTIV, compared to a conventional TIV may provide increased clinical protection among elderly persons [30]. Another observational study conducted in 2011/2012 demonstrated the effectiveness of aTIV but not naTIV against laboratory-confirmed influenza-related outcomes [31]; however, the sample size was small, and the results should be interpreted cautiously. Nevertheless, a systematic review compared the VE of aTIV vs. naTIV and high-dose influenza vaccines regarding influenza-related outcomes in older adults [4], and found aTIV to be more effective than naTIV, although the magnitude of relative VE varied between influenza seasons and studies. A recent systematic review identified nine real-world evidence studies, with most

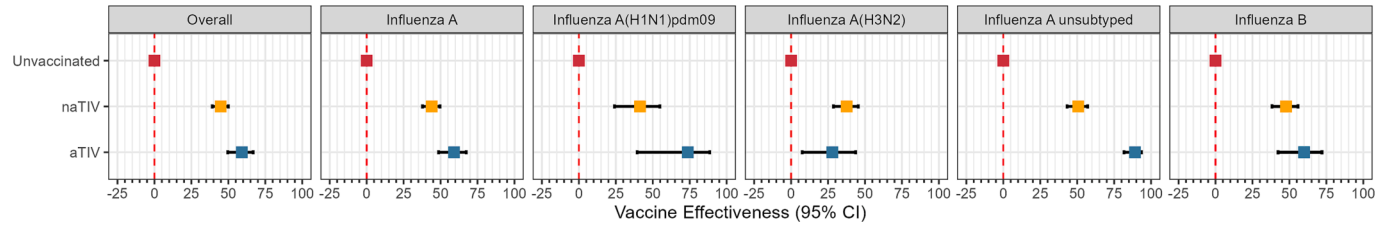

Fig. 2. Effectiveness of influenza vaccination in preventing hospitalization for laboratory-confirmed influenza, adjusted by Clinical Frailty Scale.

showing benefit of aTIV and rVE ranging from 7.5% to 25.6% for aTIV vs. TIV; notably frailty was not assessed in any of the identified studies. [4].

It is notable that as vaccine programs weigh options for enhanced vaccines for older adults, there has been no head-to-head comparison of high dose vs. adjuvanted influenza vaccine in clinical trials. This, combined with the observation that frail older adults are not generally well represented in clinical trials, makes it even more important to consider evidence from other study designs and from real world settings. For context, the relative efficacy of HD-TIV has been found to be 24.2% compared with standard dose TIV in a randomized clinical trial.[32] A recent systematic review and *meta*-analysis found that the relative VE of aTIV was 13.9% compared with naTIV, and this rVE was comparable to that of High Dose vaccine.[33] Even as programmatic decisions are being made as to which products to procure and offer for older adults in different jurisdictions, it is important to emphasize that the primary message of public health should still be to promote the importance of annual influenza immunization with an indicated and available product, rather than to defer vaccination waiting for an optimal choice to become available. A recent study showed that delays or reductions in vaccination coverage could increase the burden of influenza [34]. Thus, it is crucial to have timely and adequate access to influenza vaccines and to use standard dose vaccines when enhanced products are not available.

Our study has several limitations. First, vaccine allocation was not randomized, and confounding by indication was likely. This was mitigated to the extent possible by conducting active surveillance with broad inclusion criteria and adjusting for clinical and demographic factors, including frailty. It is important to note that given the lack of vaccine registries and despite efforts to validate patient's vaccine history and the vaccine product received, a considerable number of participants had to be excluded from the anlayses due to incomplete information regarding the type of vaccine they received. This missing information could potentially impact our results, especially in relation to the smaller group of individuals who received an aTIV vaccine. Information on the brand of influenza vaccine administered to patients is challenging to ascertain systemically, given the lack of immunization registries in Canada. VE findings in this study represent a pooled average of the influenza seasons to accumulate enough persons immunized with aTIV since its use in Canada beginning in 2011. Even so, the number of persons who received aTIV was significantly lower than naTIV. The study was conducted before HD-TIV was in use, precluding head-to-head comparisons of enhanced vaccines. Moreover, it is worth noting that there was significant heterogeneity in strains circulating and vaccine match across the pooled seasons, which may account for diminished season-related VE. Nevertheless, the SOS Network continues to conduct active influenza surveillance with aims to further assess the VE of enhanced influenza vaccine products in older adults.

To summarize, after adjusting for frailty, our analysis indicated that aTIV was more favorable than naTIV in terms of relative VE. Frailty is an important factor modulating immune responses to vaccination and clinical illness and should be considered in future studies. As new influenza vaccine products come into use, continued monitoring of VE of all types of influenza vaccine types for important target populations, including older adults, is essential to inform influenza vaccination policy and provide evidence best to protect vulnerable populations from influenza-related adverse clinical outcomes.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: HP reports grant funding from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001. MKA reports grant funding from the GSK group of companies, Pfizer and Sanofi Pasteur and honoraria from Sanofi, Seqirus and Pfizer for past ad hoc advisory activities. TFH reports grants from Pfizer and GSK, outside the submitted work. AMcG reports payments to her institution from the GSK group of companies for the conduct of this study, and payments from GSK, Seqirus and Sanofi Pasteur, outside the submitted work. ML reports payments from Sanofi, Medicago, Sequirus, and Pfizer outside the submitted work. AP reports payments from Actelion, Sanofi-Pasteur, and Genentech outside the submitted work. JP reports payments from the GSK group of companies, Merck, Roche, and Synthetic Biologics, outside the submitted work. MS reports payments from the GSK group of companies and Pfizer during the study. SAM reports grants and payments from Pfizer, GSK, Merck, Novartis and Sanofi, outside the submitted work. outside the submitted work. ZS, MKN, JJL, ME, GB, WB, PL-W, LV, GT, LY, AA, JJ, KK, DR, DW, DS, GS, ST, SS, AMcC and KK report no conflicts of interest.

Data availability

The authors do not have permission to share data.

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Authors' contributions

SAM, MKA, MN and ZS conceived the study, along with SOS site investigators (GB, WB, JJ, KK, PL-W, ML, AM, AM, AP, JP, DR, MS, SS, DS, GS, GT, ST, LV, DW), who oversaw recruitment and data collection along with network manager AA and central laboratory leads JL, TH and ME. LY, MKN and HP were involved in data management and statistical analysis. HP, MKN, MKA, and SAM drafted the manuscript and interpreted the data. All authors had full access to the data, revised the manuscript critically for important intellectual content and reviewed and approved the final draft of the manuscript.

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Trademark statements

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2023.08.070.

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