International Journal of Infectious Diseases 125 (2022) 164–169

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Relative effectiveness of the adjuvanted vs non-adjuvanted seasonal influenza vaccines against severe laboratory-confirmed influenza among hospitalized Italian older adults

Alexander Domnich [1,*], Donatella Panatto [2,3], Elena Pariani [3,4], Christian Napoli [5], Maria Chironna [6], Ilaria Manini [3,7], Caterina Rizzo [8], Andrea Orsi [1,2,3], Giancarlo Icardi [1,2,3], on behalf of the IT-BIVE-HOSP Network Study Group

[1] *Hygiene Unit, San Martino Policlinico Hospital - IRCCS for Oncology and Neurosciences, Genoa, Italy*
[2] *Department of Health Sciences, University of Genoa, Genoa, Italy*
[3] *Interuniversity Research Center on Influenza and Other Transmissible Infections (CIRI-IT), Genoa, Italy*
[4] *Department of Biomedical Sciences for Health, University of Milan, Milan, Italy*
[5] *Sant'Andrea Hospital, University La Sapienza, Rome, Italy*
[6] *Interdisciplinary Department of Medicine, University of Bari, Bari, Italy*
[7] *Department of Molecular and Developmental Medicine, University of Siena, Siena, Italy*
[8] *Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy*

A R T I C L E I N F O

Article history:
Received 16 September 2022
Revised 17 October 2022
Accepted 27 October 2022

Keywords:
Influenza
Influenza vaccines
Adjuvanted influenza vaccine
Vaccine effectiveness
Older adults

A B S T R A C T

Objectives: In this study, we aimed to investigate the relative vaccine effectiveness (rVE) of the MF59-adjuvanted trivalent (aTIV) and non-adjuvanted quadrivalent (QIVe) egg-based standard-dose vaccines against severe laboratory-confirmed influenza.
Methods: This test-negative case-control study was conducted in a hospital setting during four recent Italian influenza seasons (from 2018/19 to 2021/22). The clinical outcome was severe acute respiratory infection (SARI) with laboratory confirmation diagnosed among subjects aged ≥65 years. rVE of aTIV versus QIVe was estimated through propensity score matching followed by logistic regression.
Results: The influenza virus circulated to a significant extent only during the 2018/19 and 2019/20 seasons. The final population included 512 vaccinated older adults, of which 83 were cases and 429 were test-negative controls. aTIV and QIVe users differed substantially from the point of view of several baseline characteristics. The propensity score adjusted rVE of aTIV vs QIVe was 59.2% (95% CI: 14.6%, 80.5%), 54.7% (95% CI: -28.7%, 84.0%) and 56.9% (95% CI: -7.8%, 82.8%) against any influenza, A(H1N1)pdm09 and A(H3N2), respectively.
Conclusion: aTIV was more effective than QIVe in preventing laboratory-confirmed SARI. The benefits of aTIV may be obscured by confounding indication.

Introduction

Worldwide seasonal influenza carries a large socioeconomic burden, and most influenza-related deaths are registered among older adults. Seasonal influenza vaccination (SIV) is the most effective means able to reduce this burden, and older adults are considered the primary target population for SIV (Cassini et al., 2018; World Health Organization, 2012).

Despite clear advantages of annual SIV at the population level, older adults are subject to age-related dysregulation and an overall decline of the innate and adaptive immune system compartments (i.e., immunosenescence) (Crooke *et al.*, 2019), which may lead to a significant reduction in terms of SIV-induced immune response (Seidman *et al.*, 2012).

To address the unmet need for suboptimal immune response among older adults, the MF59-adjuvanted egg-based standard-dose trivalent influenza vaccine (aTIV) was developed and licensed in Italy in 1997 (O'Hagan *et al.*, 2013). The mechanism of action of the MF59 adjuvant is complex and can be succinctly described as follows. For instance, the MF59 adjuvant induces a higher re-

* Corresponding author.
E-mail address: alexander.domnich@hsanmartino.it (A. Domnich).

https://doi.org/10.1016/j.ijid.2022.10.041

cruitment of key immune cells, promoting a more efficient antigen uptake and transport to local lymph nodes (O'Hagan *et al.*, 2012, 2013). This immune cascade typically results in both higher and wider immune responses in aTIV recipients, as compared with non-adjuvanted standard-dose SIVs (Ansaldi *et al.*, 2010; Nicolay *et al.*, 2019).

Several systematic reviews and/or meta-analyses of vaccine effectiveness (VE) studies have highlighted the potential benefits of the aTIV over standard-dose egg-based trivalent (TIVe) and/or quadrivalent (QIVe) vaccines (Coleman *et al.*, 2021; Domnich *et al.*, 2017; Gärtner *et al.*, 2022). For instance, a recent review by Coleman *et al.* (2021) has reported a pooled relative VE (rVE) in preventing influenza-related medical encounters of aTIV vs TIVe and aTIV vs QIVe of 13.9% (95% CI: 4.2%, 23.5%) and 13.7% (95% CI: 3.1%, 24.2%), respectively. However, the main drawback of the available evidence is that most published rVE studies relied on non-laboratory-confirmed proxy influenza measures. In contrast, very few data with laboratory-confirmed endpoints are available and date back several years. Thus, a study conducted during the 2011/12 season dominated by the A(H3N2) subtype in Canada showed an rVE of aTIV vs TIVe of 63% (95% CI: 4%, 86%) (Van Buynder *et al.*, 2013).

Considering the paucity of data on laboratory-confirmed influenza, which is the "gold standard" for VE research (World Health Organization, 2017), the objective of this study was to investigate the comparative effectiveness of aTIV vs QIVe against laboratory-confirmed severe influenza observed among Italian older adults during the recent seasons.

Methods

Data source and study population

Data used for this study came from the DRIVE (Development of Robust and Innovative Vaccine Effectiveness) project, whose primary aim was to assess the brand-specific VE of SIVs available across European countries. The Italian network IT-BIVE-HOSP participated in projects in all four seasons (from 2018/19 to 2021/22) and was composed of four to five (depending on the season) referring hospitals located in Liguria, Lazio, Tuscany, and Apulia regions that each year performed test-negative case-control studies. A full description of the objectives and methods of the DRIVE project is available in previously published papers (Carmona *et al.*, 2021; Rizzo *et al.*, 2020; Stuurman *et al.*, 2020) and at https://www.drive-eu.org/.

For the present *post hoc* analysis, raw data collected by the IT-BIVE-HOSP network were extracted. In line with both the study objective and age indication of aTIV, all available records of older adults aged ≥65 years and vaccinated with any available SIV were potentially eligible. However, during the 2020/21 and 2021/22 seasons, which overlapped with the COVID-19 pandemic, only two influenza virus detections (one in each season) occurred in the vaccinated older adults. The analysis was therefore restricted to seasons 2018/19 and 2019/20.

Before inclusion in the study, all subjects provided written informed consent. Each seasonal study was approved by the relevant Ethics Committees: the Ethics Committee of the Bambino Gesù Children's Hospital in Rome (protocol # 1633_OPBG_2018) for the 2018/19 season and the Ethics Committee of the Liguria Region (protocols ## 245/2019, 429/2020 and 566/2021 for the 2019/20, 2020/21, and 2021/22 seasons, respectively).

Study setting and clinical endpoint

The study clinical endpoint and the dependent variable was severe acute respiratory infection (SARI) diagnosed in a hospital setting. All SARI cases were potentially eligible. SARI was defined as an individual presenting at the emergency department with at least one systemic symptom (fever or feverishness, malaise, headache, or myalgia), or deterioration of general conditions, and at least one respiratory symptom (cough, sore throat, or shortness of breath) at admission or within 48 hours following admission. The following were exclusion criteria: (i) any contraindication for SIV receipt; (ii) previous (<48 hours) hospitalization before SARI onset or SARI onset ≥48 hours after hospital encounter; (iii) no respiratory sample or sample taken >7 days after SARI onset; (iv) known positivity for influenza before the onset of symptoms leading to the current hospital encounter; (v) SIV administered ≤14 days before SARI onset, no SIV record for the current season, or ambiguous vaccination status; (vi) institutionalized individuals.

All naso-/oropharyngeal swabs underwent real-time reverse-transcription polymerase chain reaction. Subjects who tested positive were defined as cases, while those who tested negative were designated as controls.

Study variables

Only vaccinated individuals were included in the study. The independent variable of interest was the type of SIV administered and coded as 1 for aTIV and 0 for QIVe. The following list of potential baseline confounders was considered: region (Liguria, Tuscany, Lazio, or Apulia); influenza season (1 = 2019/20; 0 = 2018/19); the month of SIV receipt (October, November, or December); sex (1 = male); age (continuous); previous season vaccination (yes, no, or unknown); presence (1 = yes) of diabetes mellitus, cardiovascular, lung, kidney, liver, rheumatic diseases, cancer, immunodeficiency, anemia, dementia, and obesity; counts of general practitioner (GP) office visits and hospitalizations in the past 12 months. Owing to a significant proportion of missing number of GP visits and hospitalizations, these two count variables were median split and analyzed as nominal variables with three levels (below median, on/above the median, and unknown).

The list of covariates was determined on the basis of different pre-vaccination probabilities of receiving either aTIV or QIVe. Indeed, while during the study period at the national level, aTIV was preferentially recommended for all subjects aged ≥75 years (Italian Ministry of Health, 2018, 2019), some regions may have adopted their own operational protocols or guidelines (Barbieri *et al.*, 2017; Boccalini et al., 2019; Bonanni *et al.*, 2018).

Data analysis

The study outcome was rVE of aTIV vs QIVe expressed as (1 – adjusted odds ratio) × 100%. Independent categorical and continuous variables among cases and controls were compared by means of Fisher's exact and Student's *t*-tests, respectively.

To establish a causal inference, a propensity score matching (PSM) approach was adopted. The optimal full PSM with a propensity score estimated through logistic regression of receiving aTIV vs QIVe on the pre-vaccination covariates was used. This technique constructs strata consisting of either ≥1 subject vaccinated with aTIV and ≥1 control subject vaccinated with QIVe or *vice versa*, and therefore bias due to incomplete matching is avoided (Austin and Stuart, 2021). Indeed, different nearest neighbor matching specifications with or without calipers were unsuccessful in yielding an adequate balance. The overall balance was assessed by quantifying standardized mean differences (SMDs). Covariates with absolute SMDs of ≥0.2 were considered severely unbalanced (Austin, 2011). Once the balance was judged adequate, a weighted generalized linear model regressing the influenza positivity status on the SIV type with a logit link function was used to estimate the rVE of aTIV vs QIVe. To account for dependence between observations within clusters of matched pairs, cluster-robust standard errors were computed. The eventual residual imbalance was further reduced by applying double adjustment for those covariates showing absolute SMDs of 0.10-0.19 (Nguyen *et al.*, 2017). We planned *a priori* to perform subgroup analysis by the virus (sub)type and season.

Two types of sensitivity analysis were then conducted. First, the E-values for point estimates and 95% CIs were computed for statistically significant (P <0.05) rVE measures. These were defined as the minimum strength of association that an unmeasured confounder would need to have with both the SIV type and positivity to influenza to fully explain away the observed association, which is conditional on the measured covariates (VanderWeele and Ding, 2017). Second, to verify the potential impact of the sparse-data bias, Firth's penalized logistic regression was applied to the base-case models (Skowronski et al., 2020).

All analyses were performed using R stats packages v. 4.0.3 (The R Foundation for Statistical Computing).

Results

The initial study population was composed of 520 vaccinated SARI patients. Of these, two subjects were administered with an unknown SIV type and were excluded. Another six individuals developed SARI within the first 12 days following an SIV receipt and were also excluded. In summary, the final study population included 512 subjects and was composed of 83 cases and 429 test-negative controls. As shown in Table 1, most cases were registered during the 2018/19 season and were unevenly distributed among single regions. Compared with controls, cases had a higher prevalence of missing information on the number of GP visits and hospitalizations in the past year. Finally, aTIV was more frequently used among cases than among controls (Table 1).

Across both seasons, most cases (53.0%; 44/83) were due to the A(H3N2) subtype. The only type B (Yamagata lineage) detection occurred in the 2019/20 season, and therefore no rVE for virus B could be calculated (Table 2).

Regarding the type of SIV, about two-thirds (65.8%; 337/512) of subjects were vaccinated with aTIV. As shown by SMDs (Supplementary Table S1), aTIV and QIVe subgroups were severely unbalanced for several variables, suggesting an important confounding by indication. For instance, aTIV users were, on average older with an SMD of 0.34 (95% CI: 0.16, 0.53). Following the PSM procedure, the observed balance in the overall cohort was significantly improved (Supplementary Table S1).

As shown in Figure 1, the adjusted rVE estimates of aTIV vs QIVe against any influenza and any type A influenza were 59.2% (95% CI: 14.6%, 80.5%; P-value = 0.017) and 63.7% (95% CI: 22.8%, 82.9%; P-value = 0.008), respectively. The unmeasured confounding was unlikely to explain the observed effect sizes. In particular, the E-values for the point estimate (95% CI) were 2.51 (1.38) and 2.70 (1.54) for any influenza and type A influenza, respectively. The estimates for the virus A subtypes showed comparable point estimates but were not statistically significant (P-value = 0.14 and P-value = 0.072 for A(H1N1)pdm09 and A(H3N2), respectively) at α <0.05.

When Firth's penalized logistic regression was applied, the point estimates of rVE were very similar (Supplementary Figure S1), although a higher level of precision was achieved, and rVE estimates for both A(H1N1)pdm09 (53.0% [95% CI: 8.5%, 76.0%]) and A(H3N2) (55.2% [95% CI: 18.6%, 75.5%]) turned statistically significant (P <0.05).

A small number of cases (especially during the 2019/20 season) did not allow establishing the season-specific rVE; all matching attempts were unsuccessful.

Discussion

The present study, which analyzed patterns of severe influenza among vaccinated older adults, contributes to the body of available evidence (reviewed in Coleman *et al.*, 2021; Domnich *et al.*, 2017; Gärtner *et al.*,2022) on the advantage of the use of enhanced SIV formulations to reduce the burden of influenza in older adults in several ways. First, it is among the first studies to use a laboratory-confirmed influenza-related outcome, which is considered the "gold standard" endpoint for the evaluation of VE (World Health Organization, 2017). Analogously, no study evaluated the rVE of aTIV vs QIVe against laboratory-confirmed SARIs. This study also underlines that in countries where both standard and enhanced SIVs are used in older adults, rVE estimates may be hugely affected by confounding by indication.

The observed rVE against any influenza (59.2%; P-value = 0.017) was very similar to that reported in Canada (63%; P-value = 0.04) for the 2011/12 season (Van Buynder *et al.*, 2013). Indeed, both studies were conducted during the seasons clearly predominated by type A influenza strains. In contrast, the 2011/12 season in Canada was characterized by a generally good match for both A(H1N1)pdm and A(H3N2), resulting in a relatively high SIV VE (Andrew *et al.*, 2017; Skowronski *et al.*, 2014). Conversely, during the Italian 2018/19 season (which most detections came from), SIV was ineffective against A(H3N2) (Rizzo *et al.*, 2020), likely as a consequence of a significant circulation of the 3C.3a clade, which was antigenically different from the 2018/19 A(H3N2) vaccine component (Glatman-Freedman *et al.*, 2020; Kissling *et al.*, 2019). In these mismatched seasons, the relative advantage of aTIV is biologically plausible, considering a well-documented superior to TIVe heterologous hemagglutination-inhibition and neutralizing antibody responses (Ansaldi *et al.*, 2008, 2010; Nicolay *et al.*, 2019). Finally, contrary to the Canadian study, which mainly enrolled community-dwelling adults (Van Buynder *et al.*, 2013), the present study was conducted in a hospital setting. It has been shown that inpatients and outpatients represent two distinct populations (Tenforde *et al.*, 2021), and SIV effectiveness may be higher against more severe outcomes, i.e., less effective against infection *per se*, but more effective against influenza disease (Godoy *et al.*, 2018). In summary, our study demonstrates that aTIV may be more effective than QIVe against severe influenza disease during seasons characterized by a substantial proportion of drifted circulating strains.

Our study demonstrated that in evaluating the rVE of enhanced SIVs, confounding by indication may play a crucial role. While the crude association would suggest that aTIV was less effective than QIVe, the adjusted estimate moved in the opposite direction. An analogous sign inversion has been recently reported by Lapi *et al.* (2022), who compared the all-cause mortality between vaccinated and unvaccinated Italian older adults across several seasons. For instance, while in the raw unadjusted model, vaccinated individuals would appear to have an increased risk of death (hazard ratio [HR] 1.36 [95% CI: 1.26-1.47]) during the 2018/19 season, the fully adjusted model highlighted the protective effect of SIV with an HR of 0.87 (95% CI: 0.80-0.95). Similarly, a large 3-season (2006-2009) study conducted in Lombardy by (Mannino *et al.*, 2012) reported that although the rate of hospitalization for influenza and/or pneumonia was roughly the same in older adults vaccinated with either aTIV or non-adjuvanted SIV, the PSM-adjusted estimate of rVE was 25% (95% CI: 2%; 43%) to the advantage of aTIV. Indeed, the difference between crude and adjusted estimates may show the degree of bias caused by confounding. In this regard, it has been recommended (Sullivan and Cowling, 2015) that the term "crude VE" is misleading and should not be reported because these estimates have no causal interpretation. We observed that compared with QIVe, aTIV users were significantly older. In countries like Italy, where different SIV types are available for subjects aged

Table 1
Characteristics of cases and controls.

Variable	Level	Cases (N = 83)	Controls (N = 429)	*P*-value
Sex, % (n)	Female	50.6 (42)	41.0 (176)	0.12
	Male	49.4 (41)	59.0 (253)	
Age, years	Mean (SD)	78.9 (7.5)	79.6 (7.6)	0.43
Region, % (n)	Liguria	30.1 (25)	49.0 (210)	<0.001
	Tuscany	3.6 (3)	2.6 (11)	
	Lazio	6.0 (5)	21.7 (93)	
	Apulia	60.2 (50)	26.8 (115)	
Season, % (n)	2018/19	73.5 (61)	48.0 (206)	<0.001
	2019/20	26.5 (22)	52.0 (223)	
Vaccine type, % (n)	Adjuvanted trivalent	77.1 (64)	63.6 (273)	0.022
	Unadjuvanted quadrivalent	22.9 (19)	36.4 (156)	
Month of vaccination, % (n)	October	2.4 (2)	6.5 (28)	0.21
	November	79.5 (66)	80.2 (344)	
	December	18.1 (15)	13.3 (57)	
Previous season vaccination, % (n)	Yes	90.4 (75)	86.0 (369)	0.30
	No	3.6 (3)	8.6 (37)	
	Unknown	6.0 (5)	5.4 (23)	
Diabetes mellitus, % (n)	Yes	22.9 (19)	34.3 (147)	0.054
	No	77.1 (64)	65.7 (282)	
Cardiovascular disease, % (n)	Yes	71.1 (59)	65.3 (280)	0.37
	No	28.9 (24)	34.7 (149)	
Lung disease, % (n)	Yes	49.4 (41)	52.0 (223)	0.72
	No	50.6 (42)	48.0 (206)	
Rheumatic disease, % (n)	Yes	1.2 (1)	5.6 (24)	0.10
	No	98.8 (82)	94.4 (405)	
Liver disease, % (n)	Yes	3.6 (3)	4.0 (17)	0.99
	No	96.4 (80)	96.0 (412)	
Renal disease, % (n)	Yes	7.2 (6)	15.6 (67)	0.058
	No	92.8 (77)	84.4 (362)	
Cancer, % (n)	Yes	12.0 (10)	14.7 (63)	0.61
	No	88.0 (73)	85.3 (366)	
Immunodeficiency, % (n)	Yes	2.4 (2)	2.6 (11)	0.99
	No	97.6 (81)	97.4 (418)	
Anemia, % (n)	Yes	6.0 (5)	5.8 (25)	0.99
	No	94.0 (78)	94.2 (404)	
Dementia, % (n)	Yes	9.6 (8)	8.4 (36)	0.67
	No	90.4 (75)	91.6 (393)	
Obesity, % (n)	Yes	2.4 (2)	8.4 (36)	0.066
	No	97.6 (81)	91.6 (393)	
General practitioner visits in the past year, % (n)	<2	19.3 (16)	28.7 (123)	<0.001
	≥2	26.5 (22)	47.6 (204)	
	Unknown	54.2 (45)	23.8 (102)	
Hospitalizations in the past year, % (n)	0	28.9 (24)	45.9 (197)	<0.001
	≥1	12.0 (10)	31.7 (136)	
	Unknown	59.0 (49)	22.4 (96)	

Table 2
Distribution of severe influenza cases, by (sub)type and season.

Influenza (sub)type	Both seasons	2018/19	2019/20
Any	100 (83)	100 (61)	100 (22)
Any A	98.8 (82)	100 (61)	95.5 (21)
A(H1N1)pdm09	38.6 (32)	36.1 (22)	45.5 (10)
A(H3N2)	53.0 (44)	57.4 (35)	40.9 (9)
A non-subtyped	7.2 (6)	6.6 (4)	9.1 (2)
B	1.2 (1)	0 (0)	4.5 (1)

≥65 years, older age and the presence of multiple comorbidities play an important role in choosing a more appropriate SIV type (Stuurman *et al.*, 2021). From the regulatory standpoint, during the study period, the Italian Ministry of Health (2018 and 2019) recommended the preferential use of aTIV for individuals aged ≥75 years. Moreover, the region of enrollment was among the most important sources of the baseline imbalance between aTIV and QIVe users. In the context of the Italian decentralized healthcare system, each region may fully adopt the Nation guidelines on SIV or issue its own circulars; this fact is on the basis of the "jeopardized" regional pattern of the procurement of single SIV types (Barbieri *et al.*, 2017; Boccalini et al., 2019; Bonanni *et al.*, 2018). To summarize, compared with register-based studies on influenza-related proxy outcomes, test-negative case-control studies typically have much smaller sample sizes and event occurrence rates. Traditionally used multivariable logistic regression models to establish VE or rVE usually adopt a parsimonious approach; indeed, as a rule-of-thumb, at least 10 influenza events per variable are needed to obtain consistent effect estimates (Peduzzi *et al.*, 1996). Conversely, the PSM approach allows for a non-parsimonious selection of covariates due to the non-random SIV type assignment (Benedetto *et al.*, 2018) even with very small sample sizes (Pirracchio *et al.*, 2012) and has become increasingly common in SIV rVE research (reviewed in Domnich and de Waure, 2022; Loiacono *et al.*, 2022).

The present *post hoc* analysis may suffer from some limitations. First, it was not explicitly designed to establish rVE and maybe, therefore, underpowered for this purpose. This shortcoming may explain the relatively large 95% CIs observed (especially for the single A subtypes). Analogously, no season-specific rVE estimates could be surely established. Second, although the calculated E-values were considerably large, which means that important unmeasured confounding would be needed to explain away the observed rVE, we cannot completely rule out some residual confounding. Finally, considering the low circulation of influenza B during the study period, no rVE estimate could be established

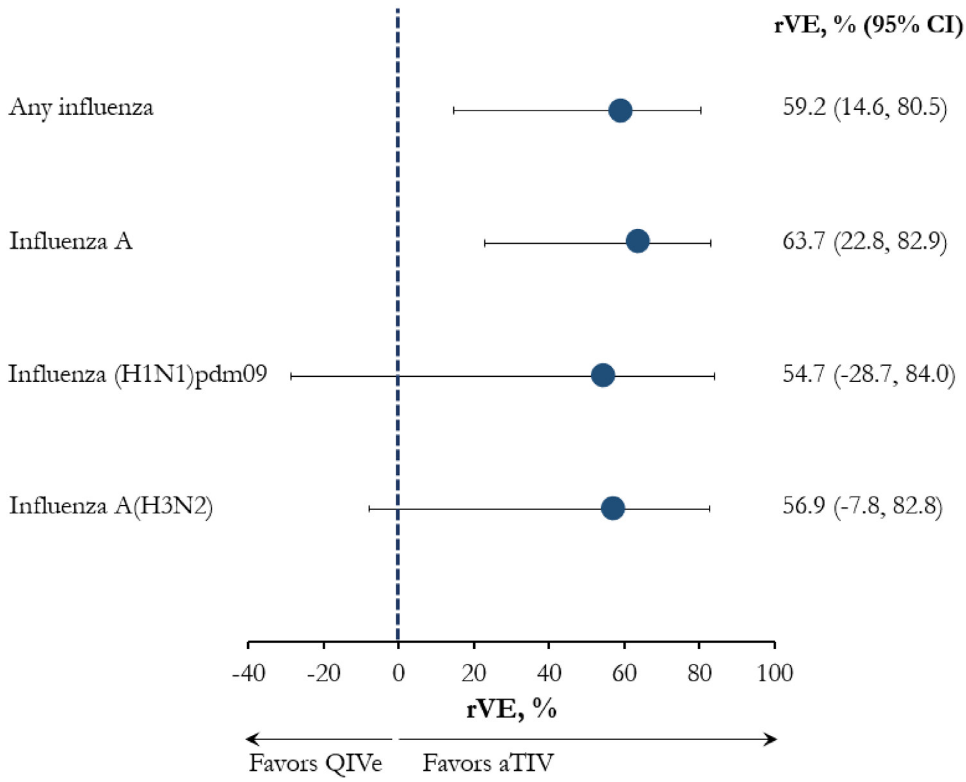

Figure 1. rVE of aTIV vs QIVe, by virus (sub)type.
aTIV, adjuvanted trivalent influenza vaccine; rVE, Relative vaccine effectiveness; QIVe, unadjuvanted quadrivalent influenza vaccine.

for this virus type. In this regard, it should also be considered that a trivalent formulation of the adjuvanted SIV containing a B strain belonging to the Victoria lineage was available during the study period. Although meta-regression modeling has suggested that the impact of B lineage mismatch has a limited impact on VE in older adults (Beyer *et al.*, 2017), in our study, the only B/Yamagata detection occurred in a subject vaccinated with aTIV. This explains an absolute increase in rVE estimate of aTIV vs QIVe by 4.5% when only type A virus was considered. It is, therefore, likely that a higher circulation of the B/Yamagata strains would significantly decrease rVE. However, a recent authorization of the quadrivalent MF59-adjuvanted SIV (Calabrò *et al.*, 2022) may decrease the negative impact of B lineage mismatch.

In conclusion, within its limitations, the present study showed that during the 2018/19 and 2019/20 seasons characterized by a predominance of influenza type A and with a likely high proportion of mismatched A(H3N2) strains, aTIV was more effective than QIVe in preventing laboratory-confirmed SARI among hospitalized older adults. Several baseline characteristics of older adults immunized with either aTIV or QIVe differed significantly. To reduce confounding by indication, researchers may consider adopting the PSM approach for future rVE studies.

Declaration of competing interests

Alexander Domnich was previously a permanent employee of Seqirus S.r.L., a pharmaceutical company that manufactures and commercializes influenza vaccines. The other authors have no competing interests to declare.

Funding

This report comes from the DRIVE project that has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 777363. This Joint Undertaking receives support from the European Union's Horizon 2020 Research and Innovation program and EFPIA.

Ethical approval

Each seasonal study was approved by the relevant Ethics Committees: the Ethics Committee of the Bambino Gesù Children's Hospital in Rome (protocol # 1633_OPBG_2018) for the 2018/19 season and the Ethics Committee of the Liguria Region (protocols ## 245/2019, 429/2020 and 566/2021 for the 2019/20, 2020/21 and 2021/22 seasons, respectively).

Acknowledgments

IT-BIVE-HOSP Network Study Group: Daniela Amicizia, Lavinia Bianco, Andrea Camarri, Pier Leopoldo Capecchi, Silvana Castaldi, Francesca Centrone, Ileana Croci, Cristina Galli, Piero Luigi Lai, Daniela Loconsole, Giovanna Milano, Emanuele Montomoli, Elisabetta Pandolfi, Laura Pellegrinelli, Luisa Russo, and Alessandra Torsello.

Author contributions

Conceptualization: AD and GI. Data collection: DP, EP, CN, MC, IM, and CR. Data analysis: AD, AO, and DP. Writing (original draft preparation): AD and DP. Writing (review and editing): EP, CN, MC, IM, CR, AO, and GI.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.10.041.

References

Andrew MK, Shinde V, Hatchette T, Ambrose A, Boivin G, Bowie W, et al. Influenza vaccine effectiveness against influenza-related hospitalization during a season with mixed outbreaks of four influenza viruses: a test-negative case-control study in adults in Canada. BMC Infect Dis 2017;17:805.

Ansaldi F, Bacilieri S, Durando P, Sticchi L, Valle L, Montomoli E, et al. Cross-protection by MF59-adjuvanted influenza vaccine: neutralizing and haemagglutination-inhibiting antibody activity against A(H3N2) drifted influenza viruses. Vaccine 2008;26:1525–9.

Ansaldi F, Zancolli M, Durando P, Montomoli E, Sticchi L, Del Giudice G, et al. Antibody response against heterogeneous circulating influenza virus strains elicited by MF59- and non-adjuvanted vaccines during seasons with good or partial matching between vaccine strain and clinical isolates. Vaccine 2010;28:4123–9.

Austin PC. A tutorial and case study in propensity score analysis: an application to estimating the effect of in-hospital smoking cessation counseling on mortality. Multivariate Behav Res 2011;46:119–51.

Austin PC, Stuart EA. The effect of a constraint on the maximum number of controls matched to each treated subject on the performance of full matching on the propensity score when estimating risk differences. Stat Med 2021;40:101–18.

Barbieri M, Capri S, Waure C, Boccalini S, Panatto D. Age- and risk-related appropriateness of the use of available influenza vaccines in the Italian elderly population is advantageous: results from a budget impact analysis. J Prev Med Hyg 2017;58:E279–87.

Benedetto U, Head SJ, Angelini GD, Blackstone EH. Statistical primer: propensity score matching and its alternatives. Eur J Cardiothorac Surg 2018;53:1112–17.

Beyer WEP, Palache AM, Boulfich M, Osterhaus ADME. Rationale for two influenza B lineages in seasonal vaccines: a meta-regression study on immunogenicity and controlled field trials. Vaccine 2017;35:4167–76.

Boccalini S, Tacconi FM, Lai PL, Bechini A, Bonanni P, Panatto D. Appropriateness and preferential use of different seasonal influenza vaccines: a pilot study on the opinion of vaccinating physicians in Italy. Vaccine 2019;37:915–18.

Bonanni P, Boccalini S, Zanobini P, Dakka N, Lorini C, Santomauro F, et al. The appropriateness of the use of influenza vaccines: recommendations from the latest seasons in Italy. Hum Vaccin Immunother 2018;14:699–705.

Calabrò GE, Boccalini S, Panatto D, Rizzo C, Di Pietro ML, Abreha FM, et al. The new quadrivalent adjuvanted influenza vaccine for the Italian elderly: a health technology assessment. Int J Environ Res Public Health 2022;19:4166.

Carmona A, Muñoz-Quiles C, Stuurman A, Descamps A, Mira-Iglesias A, Torcel–Pagnon L, et al. Challenges and adaptation of a European influenza vaccine effectiveness study platform in response to the COVID-19 emergence: experience from the DRIVE project. Int J Environ Res Public Health 2021;18:1058.

Cassini A, Colzani E, Pini A, Mangen MJ, Plass D, McDonald SA, et al. Impact of infectious diseases on population health using incidence-based disability-adjusted life years (DALYs): results from the Burden of Communicable Diseases in Europe study, European Union and European Economic Area countries, 2009 to 2013. Euro Surveill 2018;23:17–00454.

Coleman BL, Sanderson R, Haag MDM, McGovern I. Effectiveness of the MF59-adjuvanted trivalent or quadrivalent seasonal influenza vaccine among adults 65 years of age or older, a systematic review and meta-analysis. Influenza Other Respir Viruses 2021;15:813–23.

Crooke SN, Ovsyannikova IG, Poland GA, Kennedy RB. Immunosenescence and human vaccine immune responses. Immun Ageing 2019;16:25.

Domnich A, Arata L, Amicizia D, Puig-Barberà J, Gasparini R, Panatto D. Effectiveness of MF59-adjuvanted seasonal influenza vaccine in the elderly: a systematic review and meta-analysis. Vaccine 2017;35:513–20.

Domnich A, de Waure C. Comparative effectiveness of adjuvanted versus high-dose seasonal influenza vaccines for older adults: a systematic review and meta-analysis. Int J Infect Dis 2022;122:855–63.

Gärtner BC, Weinke T, Wahle K, Kwetkat A, Beier D, Schmidt KJ, et al. Importance and value of adjuvanted influenza vaccine in the care of older adults from a European perspective - a systematic review of recently published literature on real-world data. Vaccine 2022;40:2999–3008.

Glatman-Freedman A, Pando R, Sefty H, Omer I, Rosenberg A, Drori Y, et al. Predominance of a drifted influenza A (H3N2) clade and its association with age-specific influenza vaccine effectiveness variations, Influenza Season 2018–2019. Vaccines (Basel) 2020;8:78.

Godoy P, Romero A, Soldevila N, Torner N, Jané M, Martínez A, et al. Influenza vaccine effectiveness in reducing severe outcomes over six influenza seasons, a case-case analysis, Spain, 2010/11 to 2015/16. Euro Surveill 2018;23.

Italian Ministry of Health. Prevention and control of influenza: recommendations for season 2018–2019. https://www.trovanorme.salute.gov.it/norme/renderNormsanPdf?anno=2018&codLeg=64381&parte=1%20&serie=null, 2018 (accessed 22 August 2022).

Italian Ministry of Health. Prevention and control of influenza: recommendations for season 2019–2020. https://www.trovanorme.salute.gov.it/norme/renderNormsanPdf?anno=2019&codLeg=70621&parte=1%20&serie=null, 2019 (accessed 22 August 2022).

Kissling E, Pozo F, Buda S, Vilcu AM, Gherasim A, Brytting M, et al. Low 2018/19 vaccine effectiveness against influenza A(H3N2) among 15–64-year-olds in Europe: exploration by birth cohort. Euro Surveill 2019;24.

Lapi F, Marconi E, Gualano MR, Vetrano DL, Grattagliano I, Rossi A, Cricelli C. A cohort study on influenza vaccine and all-cause mortality in older adults: methodological concerns and public health implications. Drugs Aging 2022;39:645–56.

Loiacono MM, Van Aalst R, Pokutnaya D, Mahmud SM, Nealon J. Methods to account for measured and unmeasured confounders in influenza relative vaccine effectiveness studies: a brief review of the literature. Influenza Other Respir Viruses 2022;16:846–50.

Mannino S, Villa M, Apolone G, Weiss NS, Groth N, Aquino I, et al. Effectiveness of adjuvanted influenza vaccination in elderly subjects in northern Italy. Am J Epidemiol 2012;176:527–33.

Nguyen TL, Collins GS, Spence J, Daurès JP, Devereaux PJ, Landais P, et al. Double-adjustment in propensity score matching analysis: choosing a threshold for considering residual imbalance. BMC Med Res Methodol 2017;17:78.

Nicolay U, Heijnen E, Nacci P, Patriarca PA, Leav B. Immunogenicity of aIIV3, MF59-adjuvanted seasonal trivalent influenza vaccine, in older adults ≥65 years of age: meta-analysis of cumulative clinical experience. Int J Infect Dis 2019;85S:S1–9.

O'Hagan DT, Ott GS, De Gregorio E, Seubert A. The mechanism of action of MF59 - an innately attractive adjuvant formulation. Vaccine 2012;30:4341–8.

O'Hagan DT, Ott GS, Nest GV, Rappuoli R, Giudice GD. The history of MF59(®) adjuvant: a phoenix that arose from the ashes. Expert Rev Vaccines 2013;12:13–30.

Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 1996;49:1373–9.

Pirracchio R, Resche-Rigon M, Chevret S. Evaluation of the propensity score methods for estimating marginal odds ratios in case of small sample size. BMC Med Res Methodol 2012;12:70.

Rizzo C, Gesualdo F, Loconsole D, Pandolfi E, Bella A, Orsi A, et al. Moderate vaccine effectiveness against severe acute respiratory infection caused by A(H1N1)pdm09 influenza virus and no effectiveness against A(H3N2) influenza virus in the 2018/2019 season in Italy. Vaccines (Basel) 2020;8:427.

Seidman JC, Richard SA, Viboud C, Miller MA. Quantitative review of antibody response to inactivated seasonal influenza vaccines. Influ Other Respir Viruses 2012;6:52–62.

Skowronski DM, Janjua NZ, Sabaiduc S, De Serres G, Winter AL, Gubbay JB, et al. Influenza A/subtype and B/lineage effectiveness estimates for the 2011–2012 trivalent vaccine: cross-season and cross-lineage protection with unchanged vaccine. J Infect Dis 2014;210:126–37.

Skowronski DM, Leir S, Sabaiduc S, Chambers C, Zou M, Rose C, et al. Influenza vaccine effectiveness by A(H3N2) phylogenetic sub-cluster and prior vaccination history: 2016–17 and 2017–18 epidemics in Canada. J Infect Dis 2020;225:1387–98.

Stuurman AL, Bollaerts K, Alexandridou M, Biccler J, Díez Domingo J, Nohynek H, et al. Vaccine effectiveness against laboratory-confirmed influenza in Europe - Results from the DRIVE network during season 2018/19. Vaccine 2020;38:6455–63.

Stuurman AL, Ciampini S, Vannacci A, Bella A, Rizzo C, Muñoz-Quiles C, et al. Factors driving choices between types and brands of influenza vaccines in general practice in Austria, Italy, Spain and the UK. PLoS One 2021;16.

Sullivan SG, Cowling BJ. Crude vaccine effectiveness" is a misleading term in test-negative studies of influenza vaccine effectiveness. Epidemiology 2015;26:e60.

Tenforde MW, Chung J, Smith ER, Talbot HK, Trabue CH, Zimmerman RK, et al. Influenza vaccine effectiveness in inpatient and outpatient settings in the United States, 2015–2018. Clin Infect Dis 2021;73:386–92.

Van Buynder PG, Konrad S, Van Buynder JL, Brodkin E, Krajden M, Ramler G, et al. The comparative effectiveness of adjuvanted and unadjuvanted trivalent inactivated influenza vaccine (TIV) in the elderly. Vaccine 2013;31:6122–8.

VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. Ann Intern Med 2017;167:268–74.

World Health Organization. Vaccines against influenza WHO position paper – November 2012. Wkly Epidemiol Rec 2012;87:461–76.

World Health Organization. Evaluation of influenza vaccine effectiveness: a guide to the design and interpretation of observational studies. https://apps.who.int/iris/bitstream/handle/10665/255203/9789241512121-eng.pdf, 2017 (accessed 22 August 2022).