



Article

Influenza Vaccine Effectiveness Among Italian Adults: A Test-Negative Case–Control Study from an Italian Southern Province During the 2024/25 Winter Season

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Abstract

Background: In Italy, seasonal flu vaccination was recommended for all children aged 6 months to 6 years, all adults aged ≥ 60 years and specific at-risk groups. Influenza vaccine effectiveness (IVE) varies from season to season. It can be related to several factors: possible mismatches between circulating virus strains and vaccine composition, the host immune response and the interval between the vaccine administration and the epidemic peak. The present study aimed to estimate IVE against acute respiratory infections (ARIs) caused by influenza during the 2024/25 season in the Province of Pescara, Abruzzo Region, Southern Italy. **Methods:** A retrospective test-negative case–control study was conducted in the tertiary hospital of the province of Pescara, Abruzzo region, Southern Italy. The study considered all naso/oropharyngeal swabs performed between 15 October 2024 and 1 April 2025. **Results:** During the study period, 5452 tests were performed and met the inclusion criteria. Among them, 637 tested positive for influenza (11.68%) and 4815 (88.32%) were considered controls. The IVE estimated using the fully adjusted model showed an overall effectiveness of 41.36% (from 1.08 to 57.29%). Considering influenza type, IVE against influenza A was 37.23%, whereas IVE against influenza B was 77.28%. **Conclusions:** The 2024/2025 season was characterized in our Italian region by a delayed start in flu circulation, with a concomitant and prominent co-circulation of all virus types. Available vaccines provided a moderate protection against laboratory-confirmed influenza, with an estimated VE of 41%.

Keywords: vaccine; flu; effectiveness; Italy; influenza



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1. Introduction

Influenza imposes a substantial annual burden across all age groups. It is estimated that influenza led to 130,000 hospitalizations and more than 5500 deaths among

adults between the ages of 18 and 64 years [1]. Vaccination remains the most effective preventive measure against influenza. Annual vaccination campaigns are estimated to prevent 2.8 million influenza-related illnesses, 22,000 hospitalizations, and more than 1000 deaths among adults [1]. Annual vaccine reformulation is necessary both to improve the match with circulating strains and because strain-specific immunity wanes over time. The composition of Influenza Virus Vaccines recommended by WHO for the 2024/25 influenza season in the northern hemisphere was: A/Victoria/4897/2022 (H1N1) pdm09-like virus, A/Thailand/8/2022 (H3N2)-like virus, B/Austria/1359417/2021 (B/Victoria lineage)-like virus and B/Phuket/3073/2013 (B/Yamagata lineage)-like virus for tetravalent egg-based vaccines; and A/Wisconsin/67/2022 (H1N1)pdm09-like virus, A/Massachusetts/18/2022 (H3N2)-like virus, B/Austria/1359417/2021 (B/Victoria lineage)-like virus and B/Phuket/3073/2013 (B/Yamagata lineage)-like virus¹ for tetravalent cell-based vaccines [2].

In Italy, seasonal flu vaccination was recommended for all children aged 6 months to 6 years, all adults aged ≥ 60 years and for specific at-risk groups. Flu vaccination is free of charge for all those in the recommended groups, irrespective of the influenza vaccine used, including the live attenuated influenza vaccine (LAIV), recommended for all children aged 2–17 years, and inactivated quadrivalent influenza vaccines (QIVs): standard-dose non-adjuvanted IIV4 (sdIIV4, subunit egg-based vaccine (Influvac S Tetra, Viatris)); and the Split egg-based (Vaxigrip Tetra, Sanofi) and cell-based vaccine (Flucelvax Tetra, CSL Seqirus). Enhanced vaccines were similarly available in Italy, including the MF59-adjuvanted (aIIV4; Fluad Tetra, CSL Seqirus) and high-dose (hdIIV4; Eflueda, Sanofi) vaccines. In accordance with the guidelines of the Italian Ministry of Health, both aIIV4 and hdIIV4 were preferentially recommended for all older adults aged ≥ 65 years [3]. Influenza vaccine effectiveness (IVE) varies from season to season [4]. It can be related to several factors: possible mismatches between circulating virus strains and vaccine composition [5], host immunity response and the lag between the vaccine administration and epidemic peak. Evidence from systematic reviews and meta-analyses indicates that influenza vaccines provide moderate protection against laboratory-confirmed influenza, although effectiveness varies considerably according to season, population characteristics, clinical setting, vaccine formulation, and circulating viral type or subtype. In a meta-analysis of test-negative design studies, Belongia et al. [5] reported lower and more variable effectiveness against A(H3N2) viruses than against A(H1N1)pdm09 and influenza B viruses. Moreover, a systematic review and meta-analysis focusing on adults found that influenza vaccination was associated with a reduced risk of severe laboratory-confirmed influenza, although the magnitude of protection differed across seasons and study populations [6]. In addition, several reports in the literature acknowledged a lower IVE against A(H3N2) viruses compared to H1N1 strains during recent decades [7]. Furthermore, the 2024/25 season was the final season in which quadrivalent vaccine formulations were widely used across European countries, due to the apparent extinction of the B/Yamagata lineage during recent years.

Recent estimates from several countries indicated moderate IVE during the 2024/25 season. However, the reported IVE varied significantly by country, age groups and vaccine type [8–11]. However, data from the Italian setting remain limited, and, in particular, no data from the Province of Pescara were available. The present study aimed to estimate IVE against acute respiratory infections (ARIs) caused by influenza during the 2024/25 season in the Province of Pescara, Abruzzo Region, Southern Italy.

2. Results

During the study period 5452 tests were performed and met the inclusion criteria. Among them, 637 tested positive for influenza (11.68%) and 4815 (88.32%) were considered as controls. The baseline characteristics of the included patients are presented in Table 1.

Table 1. Characteristics of included patients.

	Cases (<i>n</i> = 637)	Controls (<i>n</i> = 4815)	<i>p</i> -Value
Male gender	334 (53.43)	2608 (54.16)	0.410
Age	59.3 ± 22.98	69.69 ± 18.64	<0.001
Age > 80	51 (8.01)	1207 (25.07)	<0.001
Swab delay	2.4 (1.54)	2.5 (1.52)	0.119
Month of swab			<0.001
October	5 (0.78)	501 (10.40)	
November	6 (0.94)	809 (16.80)	
December	58 (9.11)	1118 (23.22)	
January	221 (34.69)	990 (20.56)	
February	208 (32.65)	656 (13.62)	
March	129 (20.25)	572 (11.88)	
April	10 (1.57)	169 (3.51)	
Vaccine type			<0.001
HD-IIV4	8 (1.26)	168 (3.49)	
aIIV4	17 (2.67)	370 (7.68)	
Standard dose-sdIIV			
cIIV4	1 (0.16)	70 (1.45)	
eIIV4	1 (0.16)	49 (1.02)	
2023/24 IV	205 (32.18)	2744 (56.9)	<0.001
Influenza subtypes			
AH3N2	61 (9.7)		
AH1N1	23 (3.7)		
A unsubtype	303 (47.6)		
B	250 (39.2)		

HD-IIV4: high dose quadrivalent inactivated influenza vaccine; aIIV4: adjuvanted quadrivalent inactivated influenza vaccine; sdIIV: standard dose inactivated influenza vaccine; cIIV4: cell-based quadrivalent inactivated influenza vaccine; eIIV4: egg-based quadrivalent inactivated influenza vaccine.

Cases were younger than controls, with a mean age of 59.3 ± 22.98 years compared with 69.6 ± 18.64 among controls ($p < 0.001$). The greatest proportion of tests were performed in December 2024 (1176, 21.57%) and January 2025 (1211, 22.21%). On the other hand, most flu diagnoses were observed between January and March 2025 (558 cases, 87.60%). Regarding vaccination status, 684 patients had received an influenza vaccine at least 14 days before testing. The most frequently administered vaccine was the aIIV4 with 387 doses administered (7.1% vaccine coverage among included patients).

As reported in Table 1, most influenza cases were caused by influenza A.

The IVE estimated using the fully adjusted model showed an overall effectiveness of 41.36% (from 1.08 to 57.29%). Considering influenza type, the IVE against the A-type was 37.23% and against the B-type 77.28%. The addition of calendar months did not substantially change the VE, as shown in Table 2. The sub-analysis of IVE by vaccine type showed a higher effectiveness of HD-IIV4 compared to aIIV4 (54.82% vs. 45.22%). Restricting the analysis to patients vaccinated in both seasons only, the overall effectiveness was similar, but not statistically significant (39.88%; −14.63 to 68.52). The point estimate of vaccine effectiveness was higher against influenza B than against influenza A. The Wald test comparing the vaccination coefficients yielded a p -value < 0.001, indicating evidence of heterogeneity between the type-specific estimates. The sub-analysis by gender showed

similar results: adjusting for age and week, the VE was 55.51% (11.90–77.23) among males and 51.55% (10.73–80.98) among females.

Table 2. Influenza vaccine effectiveness models.

	VE %	95%CI	<i>p</i> for Heterogeneity
Crude model			
Overall	72.53	59.31–81.48	
A	57.72	35.60–72.24	
B	92.08	75.22–97.47	<0.001
Adjusted for age and gender			
Overall	42.69	9.02–70.02	
A	38.11	–20.73–79.74	
B	78.38	31.39–93.19	<0.001
Adjusted for age, gender and week			
Overall	41.36	1.08–57.29	
A	37.23	–21.83–78.45	
B	77.28	30.91–90.98	<0.001

3. Discussion

The 2024/25 influenza season was characterized by a high burden of flu-related disease both in Italy and in other countries [12,13] associated with co-circulation of both A and B subtypes. Interim analyses from other countries showed results broadly consistent with our findings [8,10,11]. However, different IVE estimates were reported from countries with similar rates of subtype co-circulation [8,10,11]. Variability in IVE estimates across countries may be explained by differences in study design [10], while others included younger patients [11], and possible unreported differences in the co-circulation of influenza strains and other respiratory viruses, such as Metapneumovirus and Respiratory Syncytial virus, across countries [13,14]. An interim analysis from seven European countries [15] showed an IVE ranging from 40% to 53%. Such a study also confirmed higher effectiveness against type B (58–74%). In this regard, a population-based RT-PCR surveillance study conducted by Agustian et al. found marked age-related differences in influenza incidence, with young and school-age children experiencing a higher incidence than adults and older individuals. These findings highlight that influenza epidemiology and the population groups that may benefit most from vaccination can vary considerably across geographical and epidemiological settings. Therefore, differences in population structure and local circulation patterns should be considered when comparing vaccine effectiveness estimates and defining vaccination priorities. An interim analysis from eight European studies reported an influenza vaccine effectiveness ranging from 40% to 53% and similarly documented greater effectiveness against influenza B, ranging from 58% to 74% [16].

IVE was lower than that reported in previous seasons [17] and other countries [8,9]. It is well known that in an A (H3N2)-dominant season, a high proportion of enhanced vaccine users can experience an IVE decrease [5]. Patients vaccinated over three months prior to swab collection could experience a waning in IVE. Also, the effect of prior-season vaccination, compared with current-season vaccination alone, on IVE is a matter of debate. Valenciano et al. [18] reported that prior yearly vaccinations can have a highly favorable impact on AH3N2 immunity, although being vaccinated in that given season was always beneficial.

The transition from quadrivalent to trivalent influenza vaccines should also be considered when interpreting our findings. B/Yamagata-lineage viruses have not been confirmed to circulate widely since early 2020, leading WHO and EMA to recommend the removal of

the B/Yamagata component from seasonal influenza vaccines and the transition towards formulations containing A(H1N1)pdm09, A(H3N2), and B/Victoria-lineage antigens [19]. Accordingly, the relatively high effectiveness observed against influenza B in our study is unlikely to reflect a meaningful contribution from the B/Yamagata component of the quadrivalent vaccines administered during the 2024/25 season. Rather, it is likely to be mainly related to protection against circulating B/Victoria-lineage viruses. However, because influenza B-positive samples were not further characterized by lineage, this interpretation cannot be directly confirmed, and our estimate should be regarded as effectiveness against influenza B overall. The removal of a lineage that is no longer circulating is not expected to substantially reduce vaccine effectiveness and may simplify vaccine manufacturing and strain selection. Nevertheless, continued global surveillance remains essential to confirm the sustained absence of B/Yamagata viruses and to assess whether the transition affects lineage-specific and overall vaccine effectiveness in future seasons [20].

This study has several important limitations. Firstly, we enrolled only patients receiving naso/oropharyngeal swabs, which may result into an underestimation of influenza cases, particularly among patients aged <60 years. In addition, the study was performed in a single, relatively small region of Southern Italy, Abruzzo, which may limit the generalizability of the findings. In addition, the test-negative design of our study included all patients who underwent influenza testing, regardless of the available clinical information. Finally, the general lack of clinical information, including data on comorbidities and information on the time elapsed between IIV administration and swab collection, might have had an impact on the IVE evaluation. However, there is recognized evidence from previous studies that regression models adjusted for age, sex, and calendar time may provide sufficiently reliable and comparable IVE estimate [21]. Some secondary analyses may also have been affected by sparse-data bias. Although the total number of included participants was substantial, relatively few influenza-positive cases had received certain vaccine formulations, and some combinations of vaccination status, influenza type, and model covariates contained only a small number of observations. Under these conditions, conventional maximum-likelihood logistic regression may produce unstable or exaggerated odds-ratio estimates, large standard errors, and wide confidence intervals, and may be vulnerable to complete or quasi-complete separation [22]. Therefore, the type-specific and vaccine-specific effectiveness estimates, particularly those based on very few vaccinated cases, should be considered exploratory and interpreted cautiously. Larger multicenter studies are needed to provide more precise estimates for individual vaccine formulations.

Our study, indeed, was one of the first such studies performed in Italy, making the information provided rather relevant. Similar results were reported in a study conducted in the Liguria Region of Northern Italy [23]. A further strength of our study is its use of routinely collected data and a study design frequently employed to evaluate IVE [21].

4. Materials and Methods

4.1. Study Design

A retrospective test-negative case-control study design [24] was conducted in the tertiary hospital of the province of Pescara, Abruzzo region, Southern Italy. The hospital of Pescara hosts the Regional Clinical Microbiology and Virology Unit in charge of performing assays for influenza and other respiratory viruses on symptomatic patients. It represents the most advanced microbiology unit of the region, and it is the regional referral center for flu diagnosis. The study considered all naso/oropharyngeal swabs performed between 15 October 2024, and 1 April 2025. Only tests performed in symptomatic patients residing in the Province of Pescara were included. Subjects were enrolled among patients with flu-like symptoms (fever, asthenia, cold, bronchitis, pneumonia) admitted to the emergency

department of the hospital of Pescara, or among patients hospitalized in the same hospital that received the swab test for clinical diagnosis. Swabs performed in asymptomatic patients were excluded from the study. All consecutive assays performed on patients aged over 17 years were considered. Whenever patients performed multiple tests, only the first positive test was considered. Patients who tested positive for influenza were classified as cases, whereas those with negative results were classified as controls. Data on patients' identity were anonymized prior to statistical analyses, a unique identifier (UID) code being assigned to each patient. The study was conducted in conformity with the regulations of the Abruzzo Regional Health Authority and accordingly to the Italian privacy law (Art. 20-21 DL 196/2003) and GDPR (EU 2016/679). Current- and previous-season vaccination status was assessed by linking the laboratory results to the electronic vaccination record by the UID. Individuals were considered vaccinated if they received an IIV more than 14 days before the swab test. Due to the anonymous nature of the data, no information on chronic conditions could be retrieved. Real-time polymerase chain reaction (RT-PCR) was performed on the naso/oropharyngeal swab specimens. Influenza viruses and their subtypes were detected by RT-PCR. Samples with cycle threshold (Ct) values <40 were deemed positive. Samples positive for influenza B were not further characterized. When multiple RT-PCR tests were prescribed and one or more were positive, the first positive result was considered.

4.2. Statistical Analysis

Continuous variables were expressed as means with standard deviations (SD) and compared with Student's *t*-test. Categorical variables were expressed as frequencies and percentages, and compared with the Chi-square test or Fisher's exact test, as appropriate. Absolute IVE was estimated as $IVE = (1 - \text{odds ratio [OR] of vaccination between cases and controls}) \times 100$ using logistic regression. Both crude and adjusted logistic regression models were fitted and adjusted for age, gender and testing week.

The impact of potential confounders was assessed by progressively adding covariates to the crude model. Type-specific vaccine effectiveness estimates were obtained from separate logistic regression models comparing influenza A-positive cases and influenza B-positive cases, respectively, with test-negative controls. These analyses were stratified estimates and were not intended as formal tests of interaction. Differences between type-specific vaccine effectiveness estimates were therefore not inferred from the magnitude or overlap of their confidence intervals. As different IIV types were available for older adults, a subgroup analysis by vaccine type was also performed. While several studies suggest that vaccination in the prior season can reduce IVE in the current season [7,25] the vaccination in the 2023/24 season was also considered as covariate. Vaccine-specific IVE could not be estimated for individual standard-dose vaccines because of the small number of influenza cases among recipients of sdIIV formulations. Equality of the vaccination coefficients across the two outcome categories was assessed using a Wald test, and the corresponding *p*-value was interpreted as a test for heterogeneity between type-specific estimates. For all tests, a *p*-value less than 0.05 was considered significant. The statistical analysis was performed with STATA software v23 (StataCorp LLC, College Station, TX, USA).

5. Conclusions

The 2024/2025 season was characterized in our Italian region by a delayed start in flu circulation, with a concomitant and prominent co-circulation of all virus types. Available vaccines provided moderate protection against laboratory-confirmed influenza, with an estimated VE of 41%.

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Institutional Review Board Statement: The study was conducted in conformity with the regulations of the Abruzzo Regional Health Authority and accordingly to the Italian privacy law (Art. 20-21 DL 196/2003), published in the Official Journal, n. 190, on 14 August 2004, and GDPR (EU 2016/679). The data were encrypted prior to the analysis, when each patient was assigned a unique identifier. The identifiers eliminated the possibility of tracing the patients' identities. According to Italian legislation, the use of administrative data does not require any written informed consent from patients.

Informed Consent Statement: Not applicable.

Data Availability Statement: The datasets presented in this article are not readily available because data restriction. Requests to access the datasets should be directed to the Local Health Authority of Pescara.

Conflicts of Interest: The authors declare no conflicts of interest.

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