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Real-world comparison of live attenuated and inactivated influenza vaccine effectiveness in Italian children

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ABSTRACT

Background: Live attenuated (LAIV) and inactivated (IIV) influenza vaccines provide comparable protection in children, but differences in the timing of protection during the influenza season remain poorly characterized in real-world settings.
Methods: Using data from a large Italian primary care database, we conducted a retrospective population-based comparative effectiveness study comparing quadrivalent LAIV (LAIV-4) and IIV among children aged 2–14 years vaccinated during the 2023–2024 and 2024–2025 influenza seasons. Clinically diagnosed influenza and influenza-like illness (ILI) episodes were identified from clinical records. Vaccine effectiveness was assessed using time-to-event analyses based on restricted mean survival time (RMST).
Results: Overall effectiveness against influenza/ILI was similar between LAIV-4 and IIV across both seasons. However, temporal patterns differed, with LAIV-4 showing a trend toward earlier protection and IIV greater effectiveness during the 2023–2024 seasonal-peak.
Conclusions: LAIV-4 and IIV showed comparable overall effectiveness, although temporal patterns of protection varied across influenza seasons.

1. Introduction

Influenza is one of the most common respiratory infections in children, with high transmissibility and substantial morbidity each year [1–3]. Vaccination remains the most effective preventive strategy [4], and both live attenuated influenza vaccines (LAIV) and inactivated influenza vaccines (IIV) are recommended for pediatric use in many countries, including Italy [5]. Available evidence indicates that LAIV and IIV provide broadly comparable overall protection against influenza-related clinical outcomes in children, supporting their use as alternative options within routine immunization programs [6–9]. However, less is known about how protection unfolds over time within the influenza season, particularly in real-world settings. This aspect may be especially relevant for vaccines with distinct immunologic mechanisms. While IIV primarily induces systemic humoral immunity, LAIV also elicits mucosal and

Abbreviations: LAIV, live attenuated influenza vaccine; IIV, inactivated influenza vaccine; LAIV-4, quadrivalent LAIV; NPL, natural language processing; ADI, area deprivation index; TTE, target trial emulation; RMST, restricted mean survival time; ICD-9-CM, international classification of diseases, ninth revision, clinical modification.

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cellular immune responses, which could influence the timing of protection under real-world conditions [10,11].

These questions are particularly relevant in the post-COVID-19 period, during which influenza epidemiology has changed substantially, including shift in epidemic peak timing and more frequent co-circulation with other respiratory viruses. In Italy, the 2023–2024 and 2024–2025 influenza seasons were characterized by differing virologic and epidemiologic patterns [12,13], providing a contemporary setting to examine vaccine performance under heterogeneous conditions.

Building on our previous population-based analysis comparing each vaccine with no vaccination [14], the present study applied design principles inspired by target trial emulation to compare quadrivalent LAIV (LAIV-4) and IIV in a real-world setting. Rather than assessing vaccine superiority, we aimed to examine whether vaccines with distinct immunologic profiles exhibit different temporal patterns of effectiveness across recent influenza seasons.

2. Methods

2.1. Study design and data source

We conducted a population-based observational study using data from the Pedianet primary care database (http://www.pedianet.it), a nationwide network of community-based pediatricians across Italy. Pedianet collects longitudinal, individual-level clinical data, including demographics, diagnoses, prescriptions, and vaccinations, and has been widely used for pharmacoepidemiologic and vaccine effectiveness research.

The study applied selected design principles inspired by target trial emulation by aligning key elements of the observational design with those of a hypothetical randomized comparison between LAIV-4 and IIV in children [15]. A detailed mapping of the target trial components and their observational analogues is provided in **eMethods 1**.

2.2. Study population

We included children aged 2–14 years who received influenza vaccination during the 2023–2024 and 2024–2025 influenza seasons. The age range was selected based on national recommendations, as LAIV-4 is approved for use in children aged ≥2 years in Italy, and because children are routinely followed by family pediatricians up to 14 years of age within the Italian healthcare system, ensuring homogeneous follow-up within the same primary care setting [5]. Children with chronic comorbidities were excluded.

To ensure complete capture of exposures and outcomes, we included only children who adhered to the recommended well-child visit schedule and were followed by pediatricians adhering to the national influenza vaccination program [14].

2.3. Exposure and follow-up

Exposure was defined as receipt of LAIV-4 or IIV, as recorded in the Pedianet vaccination registry. The vaccination date was used as time zero. Follow-up continued until the first occurrence of an influenza/ILI episode, loss to follow-up (disenrollment from the pediatrician), or the end of the influenza season (April 30), whichever occurred first.

To account for differences in the onset of vaccine-induced immunity, observations were excluded if follow-up ended before the expected effectiveness period, defined as ≥7 days after vaccination for LAIV-4 and ≥ 14 days for IIV, based on prior evidence [16,17].

2.4. Outcome definition

The primary outcome was the occurrence of clinically diagnosed influenza/ILI. Events were identified using a validated algorithm leveraging both structured diagnostic codes and unstructured clinical notes through natural language processing (NLP) [14]. A detailed description of the outcome identification algorithm is provided in **eMethods 2**.

Influenza-related hospitalization was also evaluated; however, the number of events was very limited in both seasons (2023–2024: 4 [0.15%] in the LAIV group vs 6 [0.22%] in the IIV group; 2024–2025: 1 [0.03%] vs 2 [0.06%], respectively), precluding meaningful comparative analyses.

2.5. Matching and statistical analysis

Children vaccinated with LAIV-4 were matched 1:1 with children vaccinated with IIV using pre-specified matching criteria, including sex, age, geographic area of residence (North, Center, and South and Islands), area deprivation index (ADI), and vaccination date (±3 days, time zero). ADI was used as an area-level proxy of socioeconomic deprivation and categorized as low versus high deprivation [18,19].

Vaccine effectiveness was compared using restricted mean survival time (RMST), which does not rely on proportional hazards assumptions, to estimate differences in time to influenza/ILI between vaccine groups.

A sensitivity analysis was conducted by restricting the outcome to influenza/ILI episodes occurring during the seasonal influenza peak, when clinical diagnoses are more likely to represent true influenza infections. The peak period was defined as December–January for the 2023–2024 season and January–February for the 2024–2025 season, based on national surveillance data [12,13]. For this analysis, only matched pairs in which vaccination was administered before the seasonal peak began were included.

Additionally, we performed an exploratory subgroup analysis restricted to matched pairs in which neither child had experienced influenza/ILI before the seasonal peak, to evaluate vaccine effectiveness during peak circulation among children still at risk at the beginning of the peak period.

Ethics approval and consent to participate.

This study was conducted in accordance with the principles of the Declaration of Helsinki. Data were encrypted and anonymized before use in compliance with Italian law and the General Data Protection Regulation. Participation in the Pedianet database required voluntary informed consent from parents or legal guardians.

3. Results

The matched cohorts included 2745 and 3385 children per group in the 2023–2024 and 2024–2025 influenza seasons, respectively. In both seasons, the sex distribution was approximately 47% female and 53% male. Median age was 5 years (IQR: 3–8) in both seasons, and the largest age group was 2–5 years, representing 59% and 51% of participants in the two seasons, respectively. Geographic area of residence and ADI distributions were similar across seasons, with most children residing in the North (approximately 55%) and in high-deprivation areas (43%) (**eTable 1**).

In both seasons, the proportion of children with an influenza/ILI episode before the vaccination date did not differ significantly between

Table 1
Number and percentage of children diagnosed with influenza/ILI in the LAIV-4 and IIV groups stratified by influenza season. Matched cohorts.

	LAIV-4	IIV	*P*-value [a]
2023–2024	*N* = 2745	N = 2745	
Influenza/ILI previous time zero – N (%)	3 (0.11)	2 (0.07)	1.000
Influenza/ILI (outcome) – N (%)	82 (2.99)	74 (2.70)	0.516
2024–2025	*N* = 3385	N = 3385	
Influenza/ILI previous time zero – N (%)	2 (0.06)	6 (0.18)	0.289
Influenza/ILI (outcome) – N (%)	101 (2.98)	123 (3.63)	0.135

[a] Chi-square or Fisher's exact test, as appropriate; ILI: Influenza-Like Illness; LAIV-4: Live Attenuated Influenza Vaccine; IIV: Inactivated Influenza Vaccine.

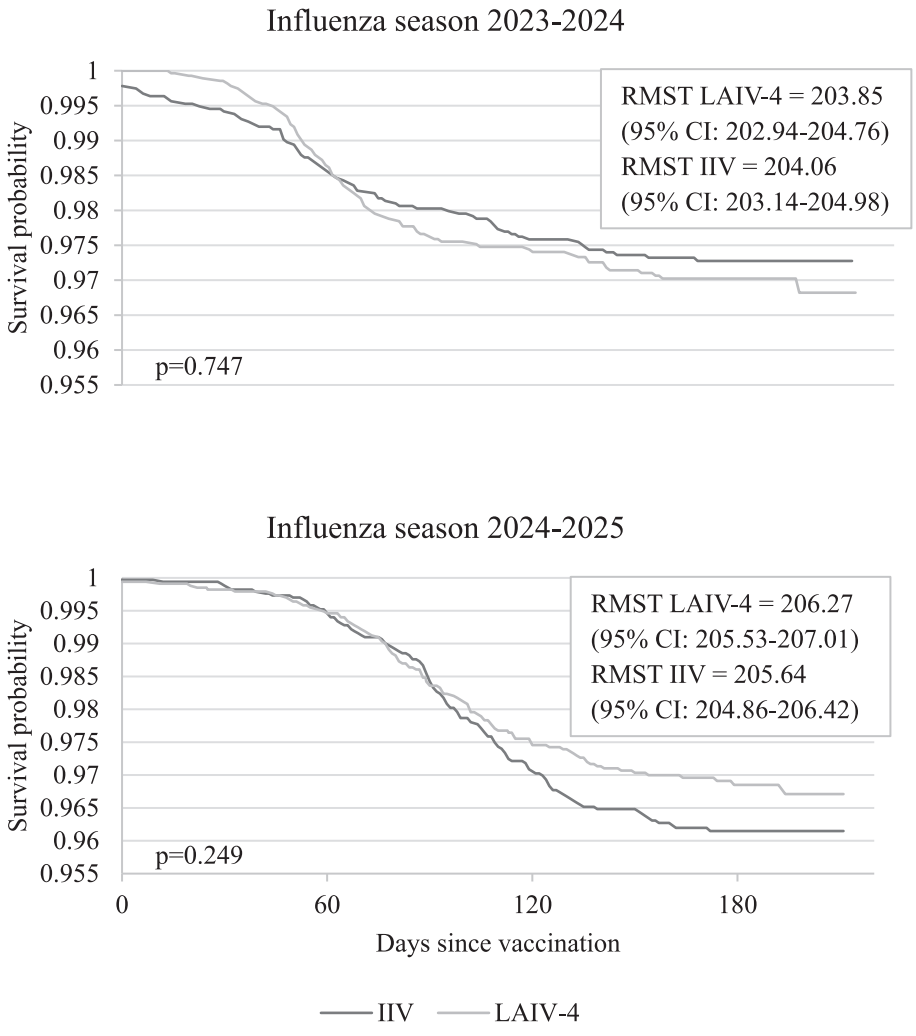
LAIV-4 and IIV groups (Table 1). Overall, areas under the survival curves were similar between groups ($p = 0.747$ for 2023–2024; $p = 0.249$ for 2024–2025), although a slight trend favoring the LAIV-4 group was observed within the first 60 days after vaccination date in the 2023–2024 season ($p = 0.037$; Fig. 1). Sensitivity analyses restricted to influenza/ILI episodes occurring during the influenza peak showed seasonal variations. Overall, areas under the curve differed significantly in the 2023–2024 influenza season in favor of the IIV group ($p = 0.034$), whereas no significant difference was observed in the 2024–2025 season ($p = 0.102$) (Fig. 2). The exploratory subgroup analysis led to the same conclusions as the sensitivity analysis (data not shown).

4. Discussion

In this real-world matched analysis, LAIV-4 and IIV demonstrated comparable overall effectiveness against influenza/ILI among Italian children across the influenza seasons considered. This finding is in line with our previous population-based analysis comparing each vaccine with no vaccination [6–10]. However, during the 2023–2024 influenza season, a trend toward greater protection in the LAIV-4 group was observed within the first 60 days following vaccination, whereas IIV appeared more effective during the seasonal peak.

These temporal differences may reflect the distinct immunological profiles induced by the two vaccines. LAIV-4 mimics natural infection and induces mucosal and cellular immune responses in addition to systemic humoral immunity, which may contribute to a faster onset of protection and broader early immune activation compared with IIV [10,11]. While this observation raises the hypothesis that LAIV-4 could offer advantages when vaccination is initiated after influenza circulation has already begun, our findings should be interpreted cautiously. The present study was not designed to evaluate vaccination strategies or inform changes in immunization policy, and further studies specifically addressing vaccination timing and clinical outcomes would be required before drawing implications for vaccination recommendations.

Differences between seasons may also be influenced by the broader respiratory viral landscape. The 2023–2024 influenza season was characterized by an earlier influenza peak occurring shortly after a SARS-CoV-2 wave, suggesting a more sequential pattern of viral circulation. In contrast, the 2024–2025 season showed greater overlap of influenza with other respiratory viruses [12,13]. Sequential exposure to respiratory viruses, including SARS-CoV-2, followed by influenza, may transiently modulate host immune responses and susceptibility to subsequent infections, potentially influencing observed vaccine effectiveness patterns. However, this interpretation remains speculative.



LAIV-4: Live Attenuated Influenza Vaccine; IIV: Inactivated Influenza Vaccine

Fig. 1. Survival curves, Restricted Mean Survival Times (RMSTs), and 95% Confidence Interval (95% CI) from vaccination date to the end of the influenza season (April 30) for the 2023–2024 and 2024–2025 influenza seasons. Matched cohorts.

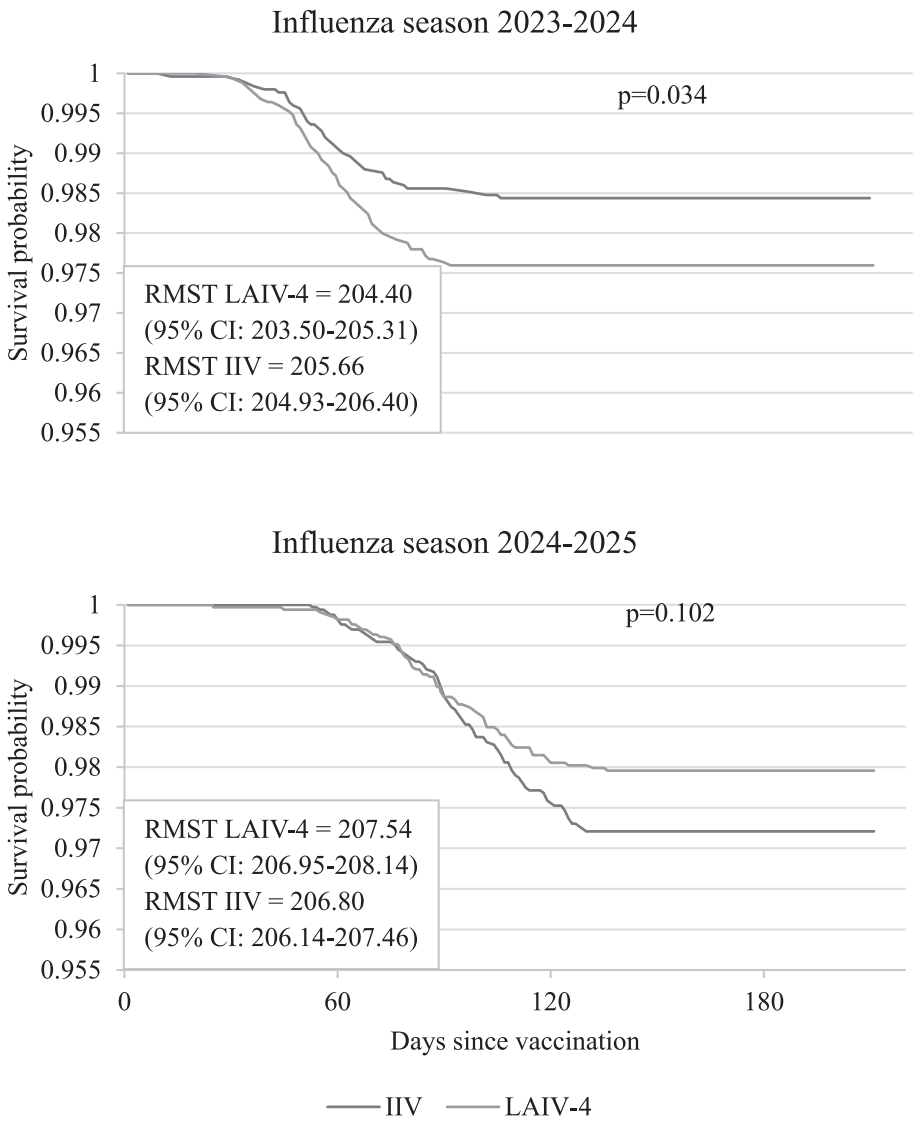


Fig. 2. Sensitivity analysis. Survival curves, Restricted Mean Survival Times (RMSTs), and 95% Confidence Interval (95% CI) from vaccination date to the end of the influenza season (April 30), restricted to influenza/ILI episodes occurring during the seasonal influenza peak (December–January for 2023–2024 and January–February for 2024–2025). Matched cohorts.

Although the Pedianet database captures clinically diagnosed respiratory infections, individual-level information on laboratory-confirmed SARS-CoV-2 infection preceding influenza was not available in a form that would allow a formal evaluation of infection-sequence effects.

The main limitation of this study is that influenza/ILI episodes were identified using clinical definitions rather than laboratory confirmation, reflecting routine pediatric primary care practice. Consequently, some degree of outcome misclassification is possible, particularly during periods of co-circulation of other respiratory viruses. Moreover, the temporal patterns observed across seasons were not fully consistent and should therefore be interpreted cautiously. However, sensitivity analyses restricted to the influenza peak yielded results broadly consistent with the primary analysis, supporting the robustness of the findings. In addition, despite the application of selected design principles inspired by target trial emulation and careful matching on vaccination timing and key covariates, the observational nature of the study inherently exposes the analysis to potential residual confounding and limits causal interpretation of the findings. Finally, the study population was restricted to children aged 2–14 years, reflecting the organization of pediatric primary care in Italy and limiting the generalizability of findings to older adolescents. Strengths include the use of a large population-based primary care database and the availability of longitudinal real-world clinical data collected under routine care conditions.

5. Conclusion

Overall, these findings support comparable effectiveness of LAIV-4 and IIV in pediatric populations while highlighting the importance of considering temporal patterns of protection and seasonal epidemiologic context when interpreting real-world influenza vaccine effectiveness.

Future studies should further investigate the duration and timing of vaccine-induced protection across influenza seasons and explore optimal vaccination strategies in pediatric populations.

Availability of data and materials

The data used in this study cannot be made publicly available due to Italian data protection laws. The anonymized datasets generated and/or analyzed during the current study can be provided upon request from the corresponding author, upon written approval from the Internal Scientific Committee (info@pedianet.it)

CRediT authorship contribution statement

Vera Rigamonti: Writing – original draft, Methodology, Formal analysis, Data curation. **Anna Cantarutti:** Writing – review & editing, Writing – original draft, Supervision, Software, Resources, Methodology, Investigation, Funding acquisition, Conceptualization. **Vittorio Torri:** Writing – review & editing, Formal analysis, Data curation. **Francesca Ieva:** Writing – review & editing, Methodology. **Carlo Giaquinto:** Writing – review & editing, Investigation. **Costanza Di Chiara:** Writing – review & editing, Writing – original draft, Supervision. **Daniele Donà:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **CARICE study group: Livia Antilici De Martini Di Valle Aperta, Alberto Argentiero, Riccardo Boracchini, Giulia Brigadoi, Beatrice Rita Campana, Susanna Maria Roberta Esposito, Valentina Fainardi, Hajrie Seferi, Alberto Villani, Anna Chiara Vittucci:** Writing – review & editing.

Consent for publication

The Internal Scientific Committee of Società Servizi Telematici Srl, the legal owner of Pedianet granted ethical approval and database access.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Anna Cantarutti reports financial support was provided by Italian Ministry of Education, University and Research. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jvacx.2026.100856.

Data availability

The authors do not have permission to share data.

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