MOX-Report No. 62/2025

Real-World Effectiveness of Influenza Vaccination in Preventing Influenza and Influenza-Like Illness in Children

Rigamonti, V.; Torri, V.; Morris, S. K.; Ieva, F.; Giaquinto, C.; Donà, D.; Di Chiara, C.; Cantarutti, A.; CARICE study group

MOX, Dipartimento di Matematica
Politecnico di Milano, Via Bonardi 9 - 20133 Milano (Italy)

mox-dmat@polimi.it https://mox.polimi.it

Real-World Effectiveness of Influenza Vaccination in Preventing Influenza and Influenza-Like Illness in Children

Vera Rigamonti (MSc)[1], Vittorio Torri (MSc)[2], Shaun K Morris (MD, MPH, FRCPC, Prof)[3,4,5,6], Francesca Ieva (Prof)[2,7], Carlo Giaquinto (Prof)[8], Daniele Donà (MD, PhD)[8] , Costanza Di Chiara (MD, PhD)[3,4,8*], Anna Cantarutti (PhD)[1*] on behalf of the CARICE study group

*contributed as co-senior authors

Affiliations:

1 Laboratory of Healthcare Research and Pharmacoepidemiology, Department of Statistic and Quantitative Methods, Division of Biostatistics, Epidemiology and Public Health, University of Milano-Bicocca, Milano, Italy

2 MOX – Modelling and Scientific Computing Lab, Department of Mathematics, Politecnico di Milano, Milano, Italy

3 Division of Infectious Diseases, The Hospital for Sick Children, Toronto, ON, Canada

4 Center for Global Child Health, The Hospital for Sick Children, Toronto, ON, Canada

5 Department of Pediatrics, Faculty of Medicine, University of Toronto, Toronto, ON, Canada

6 Division of Clinical Public Health and Centre for Vaccine Preventable Diseases, Dalla Lana School of Public Health, Toronto, ON, Canada

7 HDS - Health Data Science Centre, Human Technopole, Milano, Italy

8 Department of Women's and Children's Health, University of Padova, Padova, Italy

Address correspondence to: Costanza Di Chiara MD, Division of Pediatric Infectious Diseases, Department for Women's and Children's Health, University of Padua, Italy. Via Giustiniani 3, Padua, Italy. Contact: Phone: 0498213585, E-mail: costanza.dichiara@phd.unipd.it

Abbreviations:

IIV, inactivated influenza vaccine

LAIV, live attenuated influenza vaccine

LAIV-4, quadrivalent LAIV

ILI, influenza-like illness

FP, family pediatrician

VE, vaccine effectiveness

HR, hazard ratio

CI, confidence interval

PPIP, special professional commitment service

Abstract

Background and objectives: Quadrivalent live attenuated influenza vaccines (LAIV-4) offer an alternative to inactivated influenza vaccines (IIV) for children aged 2–17 years, but data on their comparative effectiveness are limited. This study assessed vaccination rates and real-world effectiveness of LAIV-4 and IIV in preventing influenza and influenza-like illness (ILI) in Italian children during the 2022–2023 and 2023–2024 seasons.
Methods: We conducted a population-based cohort study of children aged 2–14 years from September 2022 to April 2024, using data from Pedianet, a pediatric primary care database of anonymized records from family pediatricians. Children vaccinated with LAIV-4 or IIV were compared to unvaccinated children. The primary outcome was any first influenza or ILI episode. Monthly vaccination incidence rates per 1000 person-months were calculated for each vaccine type. Hazard ratios (HRs) and their 95 % confidence intervals (CIs) for vaccine effectiveness (VE) were estimated using adjusted mixed-effects Cox models.
Results: A total of 65,545 (472,173 person-months) and 72,377 (527,348 person-months) children were included for the 2022–2023 and 2023–2024 seasons, respectively. Vaccination rates were 12.71 and 12.85 per 1000 person-months, respectively. Compared to unvaccinated children, LAIV-4 had an overall effectiveness of 43 % (95 % CI, 32 %–53 %), while IIV effectiveness was 54 % (95 % CI, 46 %–61 %). In 2022–2023, LAIV-4 (38 % [95 % CI, 12 %–56 %]) and IIV (49 % [95 % CI, 37 %–58 %]) had comparable effectiveness. In 2023–2024, LAIV-4 (40 % [95 % CI, 25 %–52 %]) was slightly less effective than IIV (58 % [95 % CI, 44 %–68 %])($p = 0.048$).
Conclusions: An overall moderate, comparable effectiveness of LAIV-4 and IIV in preventing influenza/ILI among Italian children was observed.

Keywords: Influenza; Influenza vaccine; Vaccine effectiveness; Real-world data; Population-based study; Children

Background

Influenza causes seasonal epidemics and occasional pandemics, leading to significant morbidity and mortality worldwide [1]. While children and adolescents generally face a lower risk of severe illness compared to infants and the elderly [2], they remain vulnerable to severe infections [3-5]. Moreover, they play a crucial role in the spread of the virus in the communities [3-8].

Vaccination is the most cost-effective strategy to prevent seasonal influenza, reducing morbidity and reducing community transmission, thus protecting vulnerable groups [9,10]. However, the prevalence of children vaccinated against influenza remains low and, in Italy, ranged from 7% to 15% during the influenza seasons from 2009 to 2018 [10].

Inactivated influenza vaccines (IIV) have been the cornerstone of influenza prevention for decades. Live attenuated influenza vaccines (LAIV), administered as a nasal spray, have only recently started being extensively used as an alternative to intramuscular IIV for children aged 2-17 years. Both vaccines are currently quadrivalent and updated annually based on national and international recommendations [11].

In Italy, influenza vaccination is offered free of charge to all children aged six months to six years, although it is recommended for all pediatric age groups [12]. Two-dose influenza vaccination is recommended in children younger than nine years who haven't received previous influenza vaccinations, regardless of the type of vaccine (LAIV or IIV); one-dose influenza vaccination is recommended for other children [12].

The immune responses elicited by these two vaccine types differ significantly, potentially impacting their effectiveness [13]. IIVs induce strong serum antibody responses, particularly IgG, but have limited capacity to induce mucosal IgA or T-cell responses. Conversely, LAIVs elicit a broader immune response, encompassing cellular, humoral, and mucosal components [14]. This broader response better mimics natural infection and may offer enhanced protection against a wider range of influenza strains, including those not closely matched to the vaccine, as well as reducing transmission [14].

Studies on the effectiveness of LAIV and IIV in children show inconsistent results [15-18]. Some comparative studies suggest superior efficacy of LAIV over IIV [3,19-21]. However, observational studies indicate mixed effectiveness of LAIVs depending on the setting and circulating strain [22-25].

This population-based cohort study aimed to describe the administration rate of LAIV-4 and IIV and assess the real-world effectiveness of LAIV-4 vs IIV in preventing influenza and influenza-like illness (ILI) episodes among Italian children and adolescents during the 2022-2023 and 2023-2024 influenza seasons when LAIV-4 became available in Italy. Specifically, the 2022-2023 season was characterized by the predominance of influenza virus A(H3N2) in both sentinel and non-sentinel specimens, although increased circulation of A(H1N1)pdm09 and type B viruses occurred from week 50 of 2022 and week 2 of 2023, respectively. Most characterized viruses aligned with the recommended vaccine clades, indicating a good vaccine match [26]. Conversely, the 2023-2024 season was characterized by the dominance of A(H1N1)pdm09 strain, followed by A(H3N2). While most characterized viruses matched the vaccine clades, some A(H3N2) viruses were antigenically distinct, potentially affecting vaccine effectiveness [27].

Materials and Methods

Setting

Publicly funded primary healthcare services for children in Italy are delivered free of charge by individual Family Pediatricians (FPs) within the National Health System. This study utilized data from Pedianet (http://www.pedianet.it), a well-established electronic health record database specifically designed for pediatric care covering around 4% of the annual pediatric population [28]. Pedianet encompasses data from over 200 FPs across Italy who utilize the Junior Bit® software in their practices, providing a representative coverage of the Italian pediatric population [28].

This comprehensive database includes anonymized patient-level information, including demographics, growth parameters, diagnoses and symptoms (both ICD-9-CM coded and free text entries), medication prescriptions, and disease-based healthcare exemptions — which cover the costs of essential medical services such as diagnostics, treatments, and medications required for managing chronic conditions— and vaccination history.

In Italy, influenza vaccination is administered by FPs who participate voluntarily in the influenza vaccination program. These FPs receive reimbursement through the Special Professional Commitment Services (PPIPs) registry. Participation in the influenza vaccination program is not mandatory for FPs in Italy. We defined FPs as participants if they vaccinated at least 1.5% of their patients [10].

Data anonymization is performed in accordance with Italian regulations. Each anonymized record is assigned a unique numerical identifier. The data is then transmitted monthly to a centralized database located in Padua, Italy, for validation purposes. Inclusion in the Pedianet database is voluntary, and parents/legal guardians must provide general consent for their children's anonymized data to be stored and used for research purposes. The Internal Scientific Committee of Società Serivizi Telematici Srl, the legal owner of Pedianet granted ethical approval of the study and access to the database.

Study design and study cohort criteria

We conducted a retrospective observational cohort study on children aged 2 to 14 years enrolled in the Pedianet database and followed by FPs adhering to the influenza vaccination program during the observation period from September 1, 2022, to April 30, 2024. We worked on two subsequent flu seasons; the first went from September 1, 2022 to April 30, 2023, and the second from September 1, 2023 to April 30, 2024. To ensure complete data on exposure, outcomes, and covariates, we only included children who adhered to the recommended well-child visit

schedule with their FP, aligning with established protocols outlined in previous research [29], and with at least one year of follow-up before entry into the cohort.

Children who recorded any influenza/ILI episode from the day of influenza vaccination (day 0) to 14 days post-vaccination were excluded.

Exposure to influenza vaccine

Children were classified as vaccinated or unvaccinated to influenza vaccination for each season included in the study. Vaccinated children were further classified into those vaccinated with LAIV-4 and those vaccinated with IIV, based on whether they received a single dose of each respective vaccine type.

Unvaccinated children were considered the reference group.

Outcome and definitions

The primary outcome of the study was any influenza/ILI episode. Only the first seasonal influenza/ILI episode for each child was considered to mitigate the potential bias introduced by prior infections, which can influence susceptibility to subsequent infections through mechanisms such as cross-reactive immunity and transient immune modulation [30].

Influenza/ILI episodes were identified using an artificial intelligence-driven algorithm. This algorithm incorporated both structured clinical diagnoses (ICD-9-CM codes: 487, 487.0, 487.1, 487.8) and unstructured free text from medical charts. A custom-developed and validated Natural Language Processing (NLP) algorithm, trained on a comprehensive, gold-standard labeled dataset, was employed to ensure accurate case identification within our study population. The algorithm demonstrated excellent performance, achieving an accuracy of approximately 99% (**eMethods, eTable1, eTable2, eTable3**).

Covariates

Covariates used for confounding adjustment included demographic variables (sex, age at the start of each influenza season, Italian region of birth, and deprivation index [31]), comorbidities, and several variables measured in the previous epidemiological season, such as influenza vaccination status, number of influenza/ILI episodes, antibiotic therapies, and primary care visits .

Children were classified as having comorbidity if they had at least one disease-based healthcare exemption for chronic complex condition (i.e., cystic fibrosis, diabetes, chronic obstructive pulmonary disease, and asthma), immunodeficiency or immunosuppressive therapy, neurological and neurocognitive conditions (including Trisomy 21), prematurity (less than 37 weeks of gestation), renal failure, congenital cardiac disease (including heart failure), or chronic liver conditions (**eTable4**).

Statistical analysis

Administration rates of influenza vaccination stratified by vaccine type (LAIV-4 or IIV) were calculated per 1,000 person-months.

Descriptive statistics were provided, and the chi-squared test was used to assess differences between the groups of children who were unvaccinated, vaccinated with LAIV-4, and vaccinated with IIV.

Mixed-effect Cox proportional-hazards models were used to assess the effectiveness of LAIV-4 and IIV compared to unvaccinated children in preventing influenza/ILI, considering the FP as a random effect, overall and stratified by season. Hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) were independently estimated for each vaccine type relative to the unvaccinated group. Vaccine effectiveness (VE) was then calculated as VE = (1-HR) x 100.

Influenza vaccine exposure was considered a time-varying covariate to avoid immortal time bias. All models were adjusted for covariates of interest (sex, age at the start of each influenza season, Italian region of birth, deprivation index, comorbidities, and influenza vaccination status,

number of influenza/ILI episodes, antibiotic therapies, and primary care visits in the epidemiological season preceding the season of interest) and for correlation within children who contributed to more than one influenza season. Follow-up began on September 1st and ended upon death, migration, transfer to an FP outside the Pedianet network, occurrence of the incident outcome, or the end of the study period, which coincided with the end of the season evaluated (April 30).

Homogeneity between the LAIV-4 and IIV effectiveness was tested using the chi-squared test [32].

Finally, sensitivity analyses were performed stratifying the main models by influenza season and replicating the main analysis on children aged 2-5 years and those without any comorbidity.

All data analyses were performed using SAS statistical software, version 14.1 (SAS, College Station, TX, USA). Hypothesis tests were two-sided with a type I error of 0.05.

Results

Study cohort characteristics

A total of 65,545 (472,173 person-months) and 72,377 (527,348 person-months) children were included in the study for the 2022-2023 and 2023-2024 influenza seasons, respectively. The inclusion and exclusion flowchart is shown in **Figure 1**.

Table 1 (eTable5 and **eTable6)** presents the sociodemographic and clinical variables of the study population. Overall, this shows that 125,142 children were unvaccinated, 5,270 were vaccinated with LAIV-4, and 7,510 were vaccinated with IIV. Vaccinated children were younger, mostly born in southern Italy, and had fewer comorbidities. Comparing LAIV-4-vaccinated and IIV-vaccinated children, those in the LAIV-4 group were younger and had fewer comorbidities.

Influenza vaccine administration rates by season

A total of 6,003 (12.71 per 1,000 person-months) and 6,777 (12.85 per 1,000 person-months) children were vaccinated for influenza in the 2022-2023 and 2023-2024 seasons, respectively.

In the 2022-2023 influenza season, LAIV-4 administration rate (3.56 per 1,000 person-months) was lower than that of IIV (9.15 per 1,000 person-months). Interestingly, in the 2023-2024 season, the administration rate of LAIV-4 (6.80 per 1,000 person-months) appeared to converge with that of IIV (6.05 per 1,000 person-months) (**Figure 2**).

Effectiveness of LAIV-4 and IIV

Figure 3 shows the effectiveness of LAIV-4 and IIV against influenza/ILI. Overall, compared to unvaccinated children, the effectiveness of LAIV-4 (43%; 95% CI, 32%-53%) and that of IIV (54%; 95% CI, 46%-61%) were statistically similar in preventing influenza/ILI (p-value = 0.095), based on data from the two seasons. In the 2022-2023 season, characterized by the dominance of the A(H3N2) strain with a high virus-vaccine match, LAIV-4 (38% [95% CI, 12%-56%]) and IIV (49% [95% CI, 37%-58%]) showed comparable effectiveness (p-value = 0.374). In the 2023-2024 season, characterized by the dominance of A(H1N1)pdm09 but also the circulation of some A(H3N2) strains antigenically distinct from the seasonal vaccine, LAIV-4 (40% [95% CI, 25%-52%]) showed slightly but significantly lower effectiveness compared to IIV (58% [95% CI, 44%-68%]) (p-value = 0.048) (**Figure 3**).

To better evaluate the impact of age on VE, we replicated the main analysis on children aged 2-5 years, combining data from both seasons. Overall, the effectiveness of LAIV-4 against influenza/ILI (46% [95% CI, 32%-57%]) was comparable to that of IIV (55% [95% CI, 43%-64%]) (p-value = 0.266). Furthermore, the sensitivity analysis restricted to children without any comorbidities showed similar VE between LAIV-4 (45% [95% CI, 33%-55%]) and IIV (53% [95% CI, 44%-61%]) (p-value = 0.247), based on data from the two seasons.

Discussion

This nationwide study aimed to investigate the real-world effectiveness of the LAIV-4 vs IIV among children and adolescents across Italy. To the best of our knowledge, this is the first population-based study assessing the effectiveness of LAIV-4 against influenza/ILI in the Italian pediatric population using real-world data. It is also the first study in Italy to develop a Natural Language Processing algorithm for the identification of patients with influenza/ILI from free text records.

Our results strengthen and expand the evidence from other studies evaluating LAIV-4 effectiveness in the pediatric population [21,33]. We found moderate protection by LAIV-4 against influenza/ILI episodes, with VE of 38% and 40% in the 2022-2023 and 2023-2024 seasons, respectively. Previous studies evaluated the protection of LAIV-4 against influenza, observing a VE ranging from 0% to 50% in seasons 2014-2015 through 2018-2019 [17,23,24,34]. Furthermore, recent studies with microbiologically confirmed influenza/ILI have provided evidence of influenza vaccine effectiveness in the 2022-2023 and 2023-2024 seasons. In particular, Marron et al. [35] reported a LAIV-4 VE of 50% and 68% in preventing influenza/ILI among 2-7-year-old outpatients in Ireland during the 2022-2023 and 2023-2024 seasons, respectively. Differences in LAIV-4 effectiveness across studies might be due to several factors, including the age and immune status of recipients and antigenic similarity between the vaccine and circulating strains [21-24,33]. Moreover, differences in influenza VE could also be attributed to varying exposure and outcome definitions among studies [33], including the lack of microbiologically confirmed influenza/ILI, as seen in our study.

On the other hand, our study found similar protection of IIV against influenza/ILI compared to studies conducted in other regions during the same seasons. Specifically, studies in Japan involving pediatric outpatient cohorts reported a VE of IIV of 34% and 54% against microbiologically confirmed influenza during the 2022-2023 [36] and 2023-2024 [37] seasons,

respectively. Similarly, Lei et al. [38] observed a VE of 53% for IIV-4 against medically attended influenza in a cohort of outpatient children.

We observed similar effectiveness of LAIV-4 and IIV in preventing influenza/ILI in children, in accordance with findings from previous studies [17]. However, a trend emerged when analyzing by influenza season. Although VE was confirmed for both LAIV-4 and IIV in the two study seasons, during the 2023-2024 season, IIV appeared to offer slightly greater protection compared to LAIV-4. Previous analyses have yielded conflicting results due to variations in study populations and influenza strains. While some evidence showed a reduced effectiveness of LAIV compared to IIV against influenza A/H1N1pdm09 in children aged 2 to 17 years during the 2013–2014 and 2015–2016 seasons [14], other research on healthy children aged 6 to 59 months indicated that LAIV were more effective than IIV during the 2004-2005 influenza season [39]. However, our results appear to be in contrast with previous evidence suggesting greater cross-protective immunity of LAIV compared to IIV, likely due to the enhanced mucosal immunity induced by LAIV. This would have been expected to result in a higher VE of LAIV versus IIV during the 2023-2024 season, when antigenic differences existed between the circulating strains and the vaccine [13].

The study also documented an increase in LAIV-4 administration rates between the 2022-2023 and 2023-2024 seasons during the implementation of a new type of vaccine in Italy. These results predict a promising higher influenza vaccine uptake among children and adolescents, driven by vaccination campaigns based on less invasive vaccine administration. This aligns with previous research showing caregivers were more likely to accept nasal spray vaccines than injectable ones [40,41].

This study has several strengths. The use of data from Pedianet, a large population-based dataset, allowed us to assess the real-world effectiveness of LAIV-4 in Italian children. While randomized clinical trials remain the gold standard for demonstrating vaccine safety and efficacy, real-world evidence has become crucial for ongoing VE monitoring, given the influenza virus's dynamics. Furthermore, due to the Italian-wide coverage of Pedianet, which collects all

sociodemographic and clinical information, we obtained complete medical information for enrolled children, thus accounting for the impact of influenza/ILI episodes and influenza vaccination in the previous season. Moreover, the high quality of data on the influenza vaccination provided by FPs adhering to the influenza vaccination program, which reimbursed FPs for every dose of administered influenza vaccine minimizing exposure misclassification.

However, this study has several limitations. Children receiving influenza vaccination may differ from unvaccinated children in some unmeasured covariates, which results in residual confounding. The exclusion of children followed by FPs not adhering to the influenza vaccination program could also affect the study. Moreover, Pedianet only includes influenza vaccinations registered by FPs, leading to a small underreporting of vaccine coverage. Furthermore, defining full vaccination based on a single dose may have introduced misclassification, as a two-dose regimen is recommended for children under 9 years receiving their first influenza vaccination. However, in our dataset, fewer than 8% of children were potentially misclassified as fully vaccinated, which could have biased our estimates towards the null. Additionally, since influenza/ILI cases were defined clinically rather than confirmed by laboratory testing, outcome misclassification cannot be excluded, especially given that in Italy, the 2022–2023 and 2023–2024 influenza seasons coincided with similar surges in RSV and COVID-19. Furthermore, due to the lack of hospitalization data, we were unable to assess the effectiveness of IIV and LAIV-4 against hospitalization and severe outcomes, which are the primary goals for vaccinating children. Lastly, the 2022–2024 period was characterized by low pre-existing influenza immunity in the population following the COVID-19 pandemic. While this setting provided a unique opportunity for a more direct assessment of real-world influenza VE, it also raises questions about the generalizability of our findings to seasons with higher pre-existing immunity. However, several studies suggest that pre-existing immunity may not prevent infection but does reduce illness severity [42], supporting that the absence of pre-existing immunity should not significantly affect the generalizability of our results.

In conclusion, this population-based analysis provides real-world evidence on the moderate, comparable effectiveness of LAIV-4 and IIV against influenza/ILI among children across Italy. Further studies are needed to confirm our findings in future influenza seasons and investigate the effectiveness of LAIV-4 in preventing severe influenza/ILI in children and adolescents. Research focusing on the effectiveness of the LAIV-4 in the pediatric population is crucial for optimizing pediatric influenza vaccination campaigns to increase vaccination acceptance and uptake among children.

Acknowledgments

The authors thank all the family paediatricians collaborating in Pedianet. Eva Alfieri, Michela Alfiero Bordigato, Angelo Alongi, Biagio Amoroso, Rosaria Ancarola, Barbara Andreola, Giampaolo Anese, Roberta Angelini, Maria Grazia Apostolo, Giovanna Argo, Giovanni Avarello, Lucia Azzoni, Maria Carolina Barbazza, Patrizia Barbieri, Gabriele Belluzzi, Eleonora Benetti, Filippo Biasci, Franca Boe, Stefano Bollettini, Francesco Bonaiuto, Anna Maria Bontempelli, Matteo Bonza, Sara Bozzetto, Andrea Bruna, Ivana Brusaterra, Massimo Caccini, Laura Calì, Sonia Camposilvan, Laura Cantalupi, Luigi Cantarutti, Chiara Cardarelli, Giovanna Carli, Sylvia Carnazza, Massimo Castaldo, Stefano Castelli, Monica Cavedagni, Giuseppe Egidio Cera, Chiara Chillemi, Francesca Cichello, Giuseppe Cicione, Carla Ciscato, Mariangela Clerici Schoeller, Samuele Cocchiola, Giuseppe Collacciani, Valeria Conte, Roberta Corro', Rosaria Costagliola, Nicola Costanzo, Sandra Cozzani, Giancarlo Cuboni, Giorgia Curia, Caterina D'alia, Vito Francesco D'Amanti, Antonio D'Avino, Roberto De Clara, Lorenzo De Giovanni, Annamaria De Marchi, Gigliola Del Ponte, Tiziana Di Giampietro, Giuseppe Di Mauro, Giuseppe Di Santo, Piero Di Saverio, Mattea Dieli, Marco Dolci, Mattia Doria, Dania El Mazloum, Maria Carmen Fadda, Pietro Falco, Mario Fama, Marco Faraci, Maria Immacolata Farina, Tania Favilli, Mariagrazia Federico, Michele Felice, Maurizio Ferraiuolo, Michele Ferretti, Mauro Gabriele Ferretti, Paolo Forcina, Patrizia Foti, Luisa Freo, Ezio Frison, Fabrizio Fusco, Giovanni Gallo, Roberto Gallo,

Andrea Galvagno, Alberta Gentili, Pierfrancesco Gentilucci, Giuliana Giampaolo, Francesco Gianfredi, Isabella Giuseppin, Laura Gnesi, Costantino Gobbi, Renza Granzon, Mauro Grelloni, Mirco Grugnetti, Antonina Isca, Urania Elisabetta Lagrasta, Maria Rosaria Letta, Giuseppe Lietti, Cinzia Lista, Ricciardo Lucantonio, Francesco Luise, Enrico Marano, Francesca Marine, Lorenzo Mariniello, Gabriella Marostica, Sergio Masotti, Stefano Meneghetti, Massimo Milani, Stella Vittoria Milone, Donatella Moggia, Angela Maria Monteleone, Pierangela Mussinu, Anna Naccari, Immacolata Naso, Flavia Nicoloso, Cristina Novarini, Laura Maria Olimpi, Riccardo Ongaro, Maria Maddalena Palma, Angela Pasinato, Andrea Passarella, Pasquale Pazzola, Monica Perin, Danilo Perri, Silvana Rosa Pescosolido, Giovanni Petrazzuoli, Giuseppe Petrotto, Patrizia Picco, Ambrogina Pirola, Lorena Pisanello, Daniele Pittarello, Elena Porro, Antonino Puma, Maria Paola Puocci, Andrea Righetti, Rosaria Rizzari, Cristiano Rosafio, Paolo Rosas, Bruno Ruffato, Lucia Ruggieri, Annamaria Ruscitti, Annarita Russo, Pietro Salamone, Daniela Sambugaro, Luigi Saretta, Vittoria Sarno, Valentina Savio, Nico Maria Sciolla, Rossella Semenzato, Paolo Senesi, Carla Silvan, Giorgia Soldà, Valter Spanevello, Sabrina Spedale, Francesco Speranza, Sara Stefani, Francesco Storelli, Paolo Tambaro, Giacomo Toffol, Gabriele Tonelli, Silvia Tulone, Angelo Giuseppe Tummarello, Cristina Vallongo, Sergio Venditti, Maria Grazia Vitale, Concetta Volpe, Francesco Paolo Volpe, Aldo Vozzi, Giulia Zanon, Maria Luisa Zuccolo.

Contributors Statement Page

Dr. Vera Rigamonti performed the statistical analysis, interpreted the results, and drafted the initial manuscript;

Dr. Vittorio Torri conceptualized and designed the artificial intelligence algorithms;

Dr. Daniele Donà contributed to data interpretation;

Drs Anna Cantarutti and Costanza Di Chiara, designed the study, contributed to the analysis plan, interpreted the results, supervised the project, and contributed to the manuscript writing;

Profs. Shaun K Morris, Francesca Ieva, and Carlo Giaquinto interpreted the results and critically reviewed the manuscript for important intellectual content.

All authors reviewed, edited, and approved the final version of the manuscript, authorized its submission for publication, and agree to be accountable for all aspects of the work.

Funding/Support

This work is partially supported by CARICE (COVID-19 and Acute Respiratory Infections: the Clinical and Epidemiological changes in the pediatric population) project, which is funded by the Ministry of University and Research within the PRIN 2022 PNRR.

Conflict of Interest Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Centers for Disease Control and Prevention. Estimated US Flu Disease Burden. Published on November 26, 2024. Available at: https://www.cdc.gov/flu-burden/php/data-vis/index.html.

[2] Wang X, Li Y, O'Brien KL, et al. Global burden of respiratory infections associated with seasonal influenza in children under 5 years in 2018: a systematic review and modelling study. Lancet Glob Health 2020; 8: e497–510.

[3] Smith KJ, Raviotta JM, DePasse JV, Brown ST, Shim E, Patricia Nowalk M, et al. Cost effectiveness of influenza vaccine choices in children aged 2–8 years in the U.S. Am J Prev Med. 2016;50(5):600–8. https://doi.org/10.1016/j.amepre.2015.12.010.

[4] Gregg M, Blackhouse G, Loeb M, Goeree R. Economic evaluation of an influenza immunization strategy of healthy children. Int J Technol Assess Health Care. 2014;30(4):394–9. https://doi.org/10.1017/S0266462314000397.

[5] Pebody RG, Green HK, Andrews N, Boddington NL, Zhao H, Yonova I, et al. Uptake and impact of vaccinating school age children against influenza during a season with circulation of drifted influenza a and B strains, England, 2014/15. Eurosurveillance. 2015;20:39. https://doi.org/10.2807/1560-7917.ES.2015.20.39.30029.

[6] Grijalva CG, Zhu Y, Simonsen L, Mitchel E, Griffin MR. The Population Impact of a Large School-Based Influenza Vaccination Campaign. Poon LLM, editor. PLoS One. 2010;5(11):e15097.

[7] King JC. A pilot study of the effectiveness of a school-based influenza vaccination program. Pediatrics. 2005;116(6):e868–73. https://doi.org/10.1542/peds.2005-1301.

[8] King JC, Lichenstein R, Cummings GE, Magder LS. Impact of influenza vaccination of schoolchildren on medical outcomes among all residents of Maryland. Vaccine. 2010 Nov;28(49):7737–42. https://doi.org/10.1016/j.vaccine.2010.09.064.

[9] Tsang TK, Fang VJ, Ip DKM, et al. Indirect protection from vaccinating children against influenza in households. Nat Commun 2019; 10: 106.

[10] Cantarutti A, Barbieri E, Didonè F, Scamarcia A, Giaquinto C, Corrao G. Influenza Vaccination Effectiveness in Paediatric 'Healthy' Patients: A Population-Based Study in Italy. Vaccines (Basel). 2022 Apr 10;10(4):582. doi: 10.3390/vaccines10040582.

[11] Centers for Disease Control and Prevention (CDC). Key Facts About Influenza (Flu). Published on August 13, 2024. Available at: https://www.cdc.gov/flu/about/index.html.

[12] Ministero della salute. Direzione generale della prevenzione sanitaria. Circolare 21 aprile 2023. Prevenzione e controllo dell'influenza: raccomandazioni per la stagione 2023-2024. Published on April 21, 2023. Accessed on March 20, 2024. Available at: https://www.salute.gov.it/portale/news/p3_2_1_1_1.jsp?lingua=italiano&menu=notizie&p=dalministero&id=6229

[13] Mohn KG, Smith I, Sjursen H, Cox RJ. Immune responses after live attenuated influenza vaccination. Hum Vaccin Immunother. 2018 Mar 4;14(3):571-578. doi: 10.1080/21645515.2017.1377376. Epub 2018 Jan 3. PMID: 28933664; PMCID: PMC5861782.

[14] Hoft DF, Babusis E, Worku S, et al. Live and inactivated influenza vaccines induce similar humoral responses, but only live vaccines induce diverse T-cell responses in young children. J Infect Dis 2011;204: 845–53.

[15] Chung, J. R., Flannery, B., Ambrose, C. S., Bégué, R. E., Caspard, H., DeMarcus, L., Fowlkes, A. L., Kersellius, G., Steffens, A., Fry, A. M., Influenza Clinical Investigation for Children Study Team, Influenza Incidence Surveillance Project, & US Influenza Vaccine Effectiveness Network (2019). Live Attenuated and Inactivated Influenza Vaccine Effectiveness. Pediatrics, 143(2), e20182094. https://doi.org/10.1542/peds.2018-2094.

[16] Caspard H, Gaglani M, Clipper L, et al. Effectiveness of live attenuated influenza vaccine and inactivated influenza vaccine in children 2-17 years of age in 2013-2014 in the United States. Vaccine. 2016;34(1):77-82. doi:10.1016/j.vaccine.2015.11.010.

[17] Price, A. M., Flannery, B., Talbot, H. K., Grijalva, C. G., Wernli, K. J., Phillips, C. H., Monto, A. S., Martin, E. T., Belongia, E. A., McLean, H. Q., Gaglani, M., Mutnal, M., Geffel, K. M.,

Nowalk, M. P., Tartof, S. Y., Florea, A., McLean, C., Kim, S. S., Patel, M. M., & Chung, J. R. (2023). Influenza Vaccine Effectiveness Against Influenza A(H3N2)-Related Illness in the United States During the 2021-2022 Influenza Season. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, 76(8), 1358–1363. https://doi.org/10.1093/cid/ciac941

[18] Buchan SA, Booth S, Scott AN, et al. Effectiveness of Live Attenuated vs Inactivated Influenza Vaccines in Children During the 2012-2013 Through 2015-2016 Influenza Seasons in Alberta, Canada: A Canadian Immunization Research Network (CIRN) Study. JAMA Pediatr. 2018;172(9):e181514. doi:10.1001/jamapediatrics.2018.1514.

[19] Minozzi S, Lytras T, Gianola S, et al. Comparative efficacy and safety of vaccines to prevent seasonal influenza: a systematic review and network meta-analysis. EClinicalMedicine 2022;46: 101331.

[20] Jefferson T, Rivetti A, Di Pietrantonj C, Demicheli V. Vaccines for preventing influenza in healthy children. Cochrane Database Syst Rev 2018; 2: CD004879.

[21] Shim E, Brown ST, DePasse J, Nowalk MP, Raviotta JM, Smith KJ, et al. Cost effectiveness of influenza vaccine for U.S. children. Am J Prev Med. 2016 Sep;51(3):309–17. https://doi.org/10.1016/j.amepre.2016.02.027.

[22] Kildegaard H, Lund LC, Pottegård A, Stensballe LG. Effectiveness of the quadrivalent live attenuated influenza vaccine against influenza-related hospitalisations and morbidity among children aged 2 to 6 years in Denmark: a nationwide cohort study emulating a target trial. Lancet Child Adolesc Health. 2023 Dec;7(12):852-862. doi: 10.1016/S2352-4642(23)00225-0. Epub 2023 Oct 25. PMID: 37898144.

[23] Boddington NL, Pearson I, Whitaker H, Mangtani P, Pebody RG. Effectiveness of influenza vaccination in preventing hospitalization due to influenza in children: a systematic review and meta-analysis. Clin Infect Dis 2021; 73: 1722–32.

[24] Baum U, Kulathinal S, Auranen K, Nohynek H. Effectiveness of 2 influenza vaccines in nationwide cohorts of Finnish 2-year-old children in the seasons 2015-2016 through 2017-2018. Clin Infect Dis 2020; 71: e255–61.

[25] Pebody R, Djennad A, Ellis J, et al. End of season influenza vaccine effectiveness in adults and children in the United Kingdom in 2017/18. Euro Surveill 2019; 24: 1800488.

[26] ECDC SURVEILLANCE REPORT Seasonal influenza, 2022−2023. Annual Epidemiological Report for 2023. Available at: https://www.ecdc.europa.eu/sites/default/files/documents/seasonal-influenza-annual-epidemiological-report-2022-2023.pdf . Last accessed on January 31, 2025.

[27] ECDC SURVEILLANCE REPORT Seasonal influenza, 2023−2024. Annual Epidemiological Report for 2023. Available at: https://www.ecdc.europa.eu/sites/default/files/documents/seasonal-influenza-annual-epidemiological-report-2023-2024.pdf. Last accessed on January 31, 2025

[28] Cantarutti A, Gaquinto C. Pedianet database. In: Sturkenboom M, Schink T, editors. Databases for pharmacoepidemiological research. Springer series on epidemiology and public health. Springer International Publishing (2021). p. 159–64. doi: 10.1007/978-3-030-51455-6_13.

[29] Cantarutti A, Barbiellini Amidei C, Valsecchi C, et al. Association of treated and untreated gastroesophageal reflux disease in the first year of life with the subsequent development of asthma. Int J Environ Res Public Health. 2021;18(18):9633.

[30] Piret, J., & Boivin, G. (2022). Viral Interference between Respiratory Viruses. Emerging infectious diseases, 28(2), 273–281. https://doi.org/10.3201/eid2802.211727

[31] Batzella E, Cantarutti A, Caranci N, Giaquinto C, Barbiellini Amidei C, Canova C. The Association Between Pediatric COVID-19 Vaccination and Socioeconomic Position: Nested Case-Control Study From the Pedianet Veneto Cohort. JMIR Public Health Surveill. 2023 Feb 1;9:e44234. doi: 10.2196/44234. PMID: 36645419; PMCID: PMC9897308.

[32] Newman, S.C. Biostatistical Methods in Epidemiology;Wiley Series in Probability and Statistics; JohnWiley & Sons: Hoboken, NJ, USA, 2002.

[33] Sridhar S, Brokstad KA, Cox RJ. Influenza Vaccination Strategies: Comparing Inactivated and Live Attenuated Influenza Vaccines. Vaccines (Basel). 2015 Apr 24;3(2):373-89. doi: 10.3390/vaccines3020373. PMID: 26343192; PMCID: PMC4494344.

[34] Boddington NL, Mangtani P, Zhao H, et al. Live-attenuated influenza vaccine effectiveness against hospitalization in children aged 2-6 years, the first three seasons of the childhood influenza vaccination program in England, 2013/14-2015/16. Influenza Other Respir Viruses 2022; 16: 897–905.

[35] Marron, L., McKenna, A., O'Donnell, J., Joyce, M., Bennett, C., Connell, J., & Domegan, L. (2024). Influenza Vaccine Effectiveness Against Symptomatic Influenza in Primary Care: A Test Negative Case Control Study Over Two Influenza Seasons 2022/2023 and 2023/2024 in Ireland. Influenza and other respiratory viruses, 18(12), e70023. https://doi.org/10.1111/irv.70023

[36] Shinjoh, M., Furuichi, M., Tsuzuki, S., Iqbal, A., Fukushima, N., Soen, S., Fukushima, H., Kobayashi, K., Yamada, G., Narabayashi, A., Tsunematsu, K., Maeda, N., Shimoyamada, M., Yoshida, M., Kuramochi, Y., Shibata, A., Yamaguchi, Y., Yaginuma, M., Takahashi, T., Ishikane, M., … Keio Pediatric Influenza Research Group (2023). Effectiveness of inactivated influenza and COVID-19 vaccines in hospitalized children in 2022/23 season in Japan - The first season of co-circulation of influenza and COVID-19. Vaccine, 41(33), 4777–4781. https://doi.org/10.1016/j.vaccine.2023.06.082

[37] Shinjoh, M., Yaginuma, M., Yamaguchi, Y., Tamura, K., Furuichi, M., Tsumura, Y., Itaki, R., Iqbal, A., Maeda, N., Narabayashi, A., Kamei, A., Shibata, A., Yamada, G., Nishida, M., Kenichiro, T., Chiga, M., Shimoyamada, M., Yoshida, M., Fukushima, N., Nakata, Y., … Keio Pediatric Influenza Research Group (2024). Effectiveness of inactivated influenza vaccine in children during the 2023/24 season: The first season after relaxation of intensive COVID-19 measures. Vaccine, 42(23), 126241. https://doi.org/10.1016/j.vaccine.2024.126241

[38] Lei, H., Niu, B., Sun, Z., Wang, Y., Che, X., Du, S., Liu, Y., Zhang, K., Zhao, S., Yang, S., Wang, Z., & Zhao, G. (2025). Influenza vaccine effectiveness against medically-attended influenza

infection in 2023/24 season in Hangzhou, China. Human vaccines & immunotherapeutics, 21(1), 2435156. https://doi.org/10.1080/21645515.2024.2435156

[39] Krishnan A, Dar L, Saha S, Narayan VV, Kumar R, Kumar R, Amarchand R, Dhakad S, Chokker R, Choudekar A, Gopal G, Choudhary A, Potdar V, Chadha M, Lafond KE, Lindstrom S, Widdowson MA, Jain S. Efficacy of live attenuated and inactivated influenza vaccines among children in rural India: A 2-year, randomized, triple-blind, placebo-controlled trial. PLoS Med. 2021 Apr 29;18(4):e1003609. doi: 10.1371/journal.pmed.1003609. PMID: 33914729; PMCID: PMC8118535.

[40] Belshe RB, Edwards KM, Vesikari T, Black SV, Walker RE, Hultquist M, Kemble G, Connor EM; CAIV-T Comparative Efficacy Study Group. Live attenuated versus inactivated influenza vaccine in infants and young children. N Engl J Med. 2007 Feb 15;356(7):685-96. doi: 10.1056/NEJMoa065368. Erratum in: N Engl J Med. 2007 Mar 22;356(12):1283. PMID: 17301299.

[41] Marien AG, Hochart A, Lagrée M, Diallo D, Martinot A, Dubos F. Parental acceptance of an intranasal vaccine: Example of influenza vaccine. Arch Pediatr. 2019 Feb;26(2):71-74. doi: 10.1016/j.arcped.2018.11.002. Epub 2019 Jan 15. PMID: 30658873.

[42] Rodgers L, Pabst LJ, Chaves SS. Increasing uptake of live attenuated influenza vaccine among children in the United States, 2008-2014. Vaccine. 2015 Jan 1;33(1):22-4. doi: 10.1016/j.vaccine.2014.11.006. Epub 2014 Nov 17. PMID: 25448098; PMCID: PMC5845854.

Legend of Figures and Table

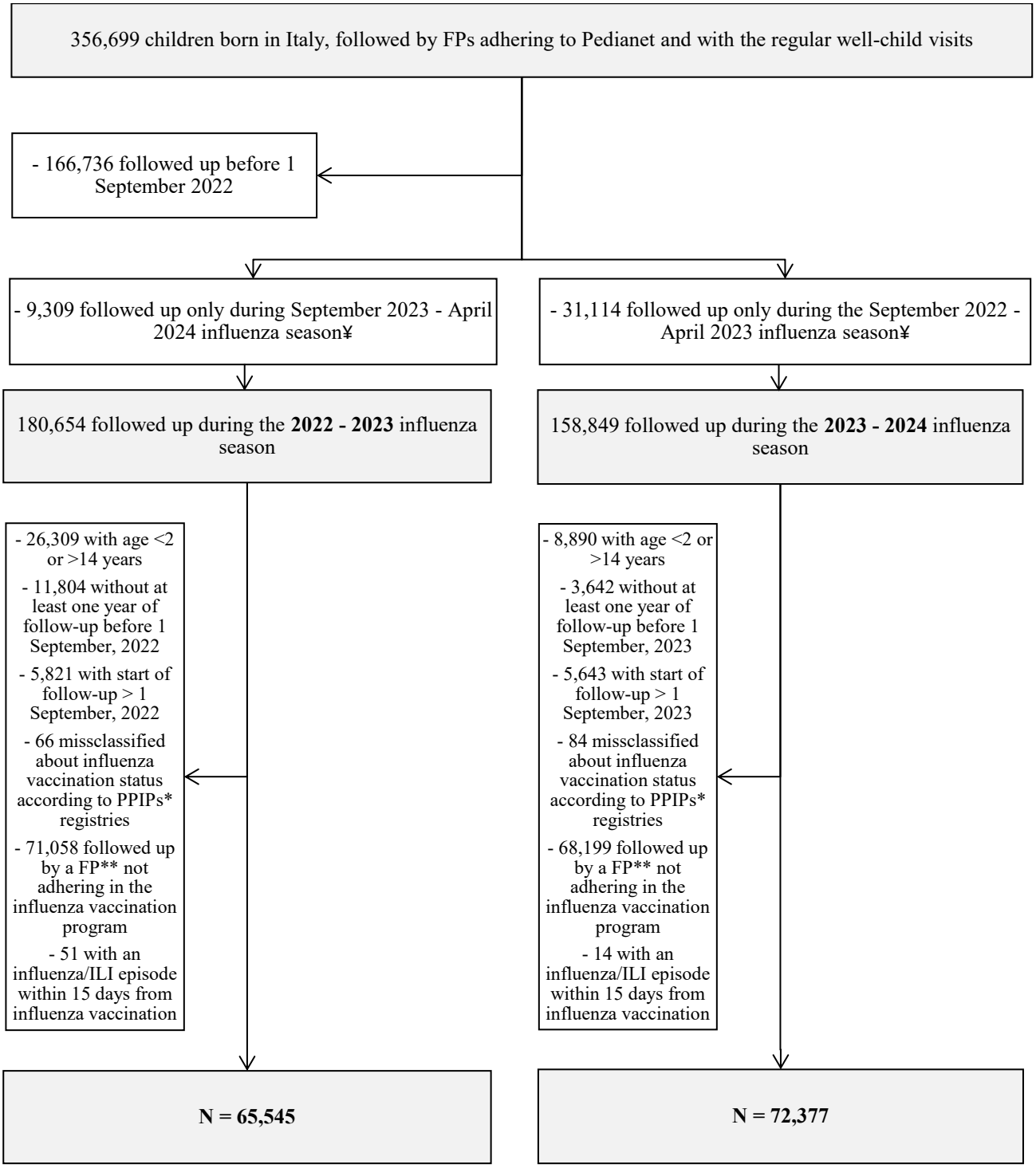
Figure 1. Flowchart of the study cohort. Pedianet dataset 2010-2024.

Figure 2. Monthly Administration Rates (AR) per 1,000 person-months of influenza vaccination among children in Italy by vaccine type.

Figure 3. Comparison between LAIV-4 and IIV vaccine effectiveness in preventing influenza/ILI in children in Italy.

Table 1. Sociodemographic and clinical characteristics of children stratified by vaccination exposure.

Figure 1

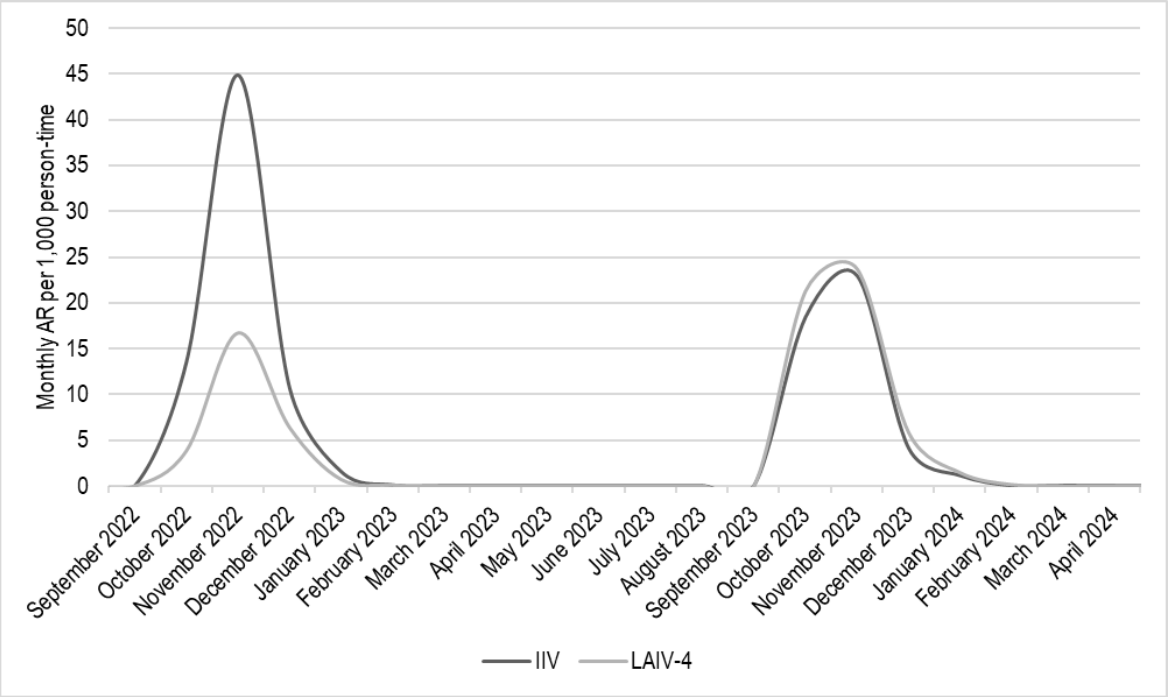


¥ 9,309 children were excluded from the 2022/2023 cohort as they were only followed during the 2023/2024 influenza season and 31,114 children were excluded from the 2023/2024 cohort as they were only followed during the 2022/2023 influenza season

* PPIPs, Special Professional Commitment Services

** FP, family pediatrician

Figure 2


Monthly AR per 1,000 person-time
50
45
40
35
30
25
20
15
10
5
0
September 2022
October 2022
November 2022
December 2022
January 2023
February 2023
March 2023
April 2023
May 2023
June 2023
July 2023
August 2023
September 2023
October 2023
November 2023
December 2023
January 2024
February 2024
March 2024
April 2024
IIV
LAIV-4

Type of vaccine	Influenza season	N of children		N of outcomes		HR (95% CI) *
		Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	
LAIV-4	2022/2024	5,270	125,142	154	6,212	0.57 (0.47 - 0.68)
IIV		7,510	125,142	245	6,212	0.46 (0.39 - 0.54)
LAIV-4	2022/2023	1,683	59,542	46	3,413	0.62 (0.44 - 0.88)
IIV		4,320	59,542	172	3,413	0.51 (0.42 - 0.63)
LAIV-4	2023/2024	3,587	65,600	108	2,799	0.60 (0.48 - 0.75)
IIV		3,190	65,600	73	2,799	0.42 (0.32 - 0.56)

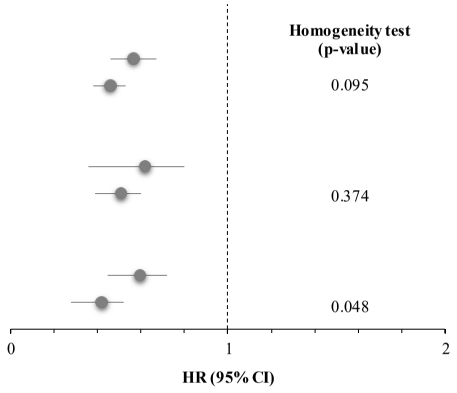


Figure 3

Table 1

	Unvaccinated (N = 125,142)	LAIV-4-vaccinated (N = 5,270)	IIV-vaccinated (N = 7,510)	P-value unvaccinated vs vaccinated (both LAIV-4 and IIV)*	P-value LAIV-4 vs. IIV*
Sex					
Male	64,439 (51.49%)	2,724 (51.69%)	3,937 (52.42%)	0.2866	0.4131
Female	60,703 (48.51%)	2,546 (48.31%)	3,573 (47.58%)		
Age					
2-5 years	32,011 (25.58%)	3,034 (57.57%)	2,757 (36.71%)	<.0001	<.0001
6-10 years	51,181 (40.90%)	1,754 (33.28%)	3,214 (42.80%)		
11-14 years	41,950 (33.52%)	482 (9.15%)	1,539 (20.49%)		
Region of birth in Italy					
North	83,518 (66.74%)	2,067 (39.22%)	3,857 (51.36%)	<.0001	<.0001
Center	18,546 (14.82%)	752 (14.27%)	1,752 (23.33%)		
South and islands	23,078 (18.44%)	2,451 (46.51%)	1,901 (25.31%)		
Deprivation index					
Low	42,872 (34.26%)	1,949 (36.98%)	2,740 (36.48%)	<.0001	<.0001
High	59,161 (47.28%)	2,720 (51.51%)	3,565 (47.47%)		
Missing	23,109 (18.47%)	601 (11.40%)	1,205 (16.05%)		
Comorbidity					
None	119,922 (95.83%)	4,909 (93.15%)	6,772 (90.17%)	<.0001	<.0001
At least one	5,220 (4.17%)	361 (6.85%)	738 (9.83%)		
Influenza vaccination status in the previous season				<.0001	<.0001
Unvaccinated	121,040 (96.72%)	2,026 (38.44%)	2,106 (28.04%)		
Vaccinated	4,102 (3.28%)	3,244 (61.65%)	5,404 (71.96%)		
Influenza/ILI episode(s) in the previous season				0.7772	0.4872
0	120,250 (96.09%)	5,058 (95.98%)	7,226 (96.22%)		
>=1	4,892 (3.91%)	212 (4.02%)	284 (3.78%)		
Drug prescription(s) in the previous season					
0	91,634 (73.22%)	2,130 (40.42%)	4,306 (57.34%)	<.0001	<.0001
1-2	26,039 (20.81%)	1,967 (37.32%)	2,259 (30.08%)		
>=3	7,469 (5.67%)	1,173 (22.26%)	945 (12.58%)		
Specialistic visit(s) in the previous season					
0-7	106,415 (85.04%)	3,013 (57.17%)	4,510 (60.05%)	<.0001	0.0011
>=8	18,727 (14.96%)	2,257 (42.83%)	3,000 (39.95%)		

* Chi-squared test.

Supplemental materials

1. **eMethods.** Description of influenza artificial intelligence algorithms
2. ***eTable1.*** Patterns that are verified by the methods called in the identify_influenza_sentence procedure.
3. ***eTable2.*** Validation of the algorithm for influenza identification on 2017-2018 gold-labelled data.
4. ***eTable3.*** Validation of the algorithm for influenza identification on 2022-2024 balanced sampled gold-labelled data.
5. ***eTable4.*** Comorbidities' exemption codes used.
6. ***eTable5.*** Children sociodemographic and clinical characteristics by exposure, flu season 2022-2023.
7. ***eTable6.*** Children sociodemographic and clinical characteristics by exposure, flu season 2023-2024.

eMethods. Description of influenza artificial intelligence algorithms

The algorithm for the identification of patients with influenza/ILI receives as input both the Pedianet database records, including free text fields, and, when available, discharge letters. Discharge letters are only available for children admitted to Emergency Rooms or hospitalized in the Veneto region, provided their hospitalization episode is reported in the Pedianet database.

This algorithm was originally developed using data from Pedianet between 2009 and 2020 (6'746'976 records from 283'817 unique patients). Discharge letters were available for patients hospitalized in the Veneto region from 2017 to 2020, comprising a total of 31'252 discharge letters for 15'539 patients. The subset of data related to influenza season 2017-2018 was manually annotated by clinicians and used to validate the algorithm. This subset includes 410'396 records for 117'694 unique patients, with 11'978 records positively labelled for influenza, corresponding to 10'904 unique patients. Among these, 2'646 records included a discharge letter, covering 1'364 patients, with 78 positively labelled for influenza. The remaining data were used to develop the algorithm.

To construct the algorithm, textual data were clustered, and the clusters with keywords associated with influenza were manually inspected to iteratively define the rules. In each iteration, a sample of 100 records was manually evaluated, until the number of false negatives and false positives resulted to be both lower than 5.

Below is a high-level pseudocode description of the algorithm:

Input:

r – pedianet record

dl – discharge letter from EHR (None if not available)

Procedure:

```
if icd_influenza(r.diagnosis_1.icd9) or icd_influenza(r.diagnosis_2.icd9) or
        icd_influenza(r.diagnosis_3.icd9):
  return True
if r.contact_reason == 'Vaccination':
  return False
pedianet_text = concat(r.diagnosis_1, r.diagnosis_2, r.diagnosis_3, r.discharge_diagnosis,
        r.admission_diagnosis,  r.hosp_reason, r.contact_reason, r.symptoms_1,
        r.symptoms_2, r.symptoms_3)
text = concat(pedianet_text, dl.text)
sentences = split_sentences(text)
for s in sentences:
```

```
        if identify_influenza_sentence(s):
            return True
    return False
```

In particular, the following pseudocode for the identify_influenza_sentence procedure describes the Natural Language Processing algorithm that analyzes a sentence to identify influenza/ILI:

Input:

s – a sentence extracted from the text

```
Procedure identify_influenza_sentence:
    s = remove_punctuation(s)
    s = lowercase(s)
    s = correct_typos(s) # corrects frequent typos related to influenza/ILI
    if is_vaccinazione(s):
        return False
    if mention_influenza(s):
        if intestinal_influenza(s) or influenza_verb(s) or emophilus_influenza(s) or
            another_subject_influenza(s) or influenza_contact(s) or
            in_case_influenza(s):
            return False
        if influenza_test(s):
            if positive_influenza_test(s):
                return True
            else(s):
                return False

        starting_word = find_starting_influenza_word(s)
        verb = get_verb(starting_word,s)
        if verb is not None:
            subj = get_subject(verb,s)
            if subj is None or not is_another_person(subj):
                return True
            return False
        return True
```

return False

The get_verb method extracts the verb for which the mention of influenza is the object, while the get_subject method extracts the subject of the verb. These methods are implemented using the dependency parser for the Italian language provided by the Spacy Python library.

The positive_influenza_test method checks for the presence of the keyword "positivo" (positive) in sentences where an influenza test is mentioned. It also verifies that this keyword is syntactically connected to the test mention and that it is not a hypothetical result.

Most of the other methods called by the identify_influenza_sentence procedure check for specific patterns in the text. They are detailed in **eTable1**.

This set of patterns is designed to exclude cases in which there is a mention of influenza/ILI, but the patient is not actually affected by influenza/ILI.

Some examples of these false positive sentences, along with their English translations:

- Familiari con influenza stagionale (*Family members with seasonal flu*)
- Ieri ha fatto vaccino per influenza (*Yesterday he had influenza vaccine*)
- L'orario è indicativo e la tempistica in cui verra effettuata la consulenza e influenzata dalle altre urgenze in atto (*The time is approximate and the timing at which counseling will be performed is affected by other ongoing emergencies* – the verb "influenzata" (affected) in Italian is the same as "having influenza")
- Influenzavirus A e B: negativa (*Influenzavirus A and B: negative*)

Algorithm validation

The algorithm was validated using gold-labelled data from the 2017-2018 influenza season.

Validation results, including true positives (TP), false positives (FP), true negatives (TN), false negatives (FN), sensitivity (TP / (TP+FN)), specificity (TN / (TN+FP)), precision (TP / (TP+FP)) and f1-score (2*precision*sensitivity / (precision + sensitivity)), are reported in e**Table2**.

The results are reported considering both the full 2017-2018 dataset and only the subset with discharge letters. For both datasets, we compared results computed considering labels derived from discharge letters, Pedianet and their combination. Considering the results on labels corresponding to the input data (i.e., discharge letters label with only discharge letters in input, Pedianet labels with only Pedianet data in input), the performance of the algorithm is excellent, both in identifying influenza from Pedianet records and in identifying it from discharge letters.

Adding the Pedianet labels to the evaluation of the algorithm with only discharge letters in input and vice-versa affects the sensitivity, demonstrating that the two sources are complementary: both allow the identification of cases of influenza that cannot be identified by the other data source.

The results with the highest number of TP are indeed those that combine Pedianet and discharge letters, and they maintain a limited number of FP and FN.

An additional validation was conducted using data from the 2022-2024 influenza seasons, to confirm the algorithm's performance on the current study cohort. In this case, Pedianet records were manually analysed up to the identification of 100 positive and 100 negative examples. The balance between the two classes is due to the need to assess the goodness of the algorithm without manually labelling another very large dataset. The same process has been repeated for the discharge letters of the 2022-2024 season (12'069 records in total).

The results, reported in **eTable3**, are consistent with those of the 2017-2018 full dataset. Due to the limited sample size and class balance, a direct comparison between Pedianet and discharge letter labels was not performed here.

eTable1. Patterns that are verified by the methods called in the identify_influenza_sentence procedure.

Method	Pattern*
is_vaccinazione	vaccin(o|azione|azioni|at)|profilassi vaccinale|vacc\b|vaccin\b | anti(-|\s*)?i?nfluenz | contro\s*(l'\s*)?influen?
mention_influenza	\b(sr|s|sdr|sindrome)\b\s*)?(((para|simil)(\s*-\s*|\s*)?)?influenz(?!(at|av)) | \binfluenza\b | \binfluenzavirus\b | (?<!non\s)(sintomi|sintomatologia) influenzal
intestinal_influenza	influenza intestinale
influenza_verb	influenzato da
emophilus_influenza	(emophilus|emofilo|influenzae|influenziae|haemoph) | h(aemophilus|emophilus|\.|\s) influ
another_subject_influenza	epidemi(a|e)\s*(d(i|') influenz|influenzal) | <mention_influenza> a scuola | <mention_influenza> in famiglia
influenza_contact	contatt(o|i) con persone con <mention_influenza>
influenza_test	(film array per virus e batteri su tampone nasale | \b(rna|anf|ricerca|antic|1-)\b) | (ricerca|tampon(e|i)|pcr|sierologi(a|e)) (virus)? influenza(le|li)? | (virus)? influenza (virus?) (tipo)? (A|B|A e B)?(negativ|positiv) | (negativ|positiv)(a|o) (a? virus)? influenza (virus?)
in_case_influenza	(in caso di | se comparsa) <mention_influenza>
is_another_person	madre | padre | mamma | pap(a|a\'|à) | genitor(e|i) | fratell(o|i|ino) | sorell(a|e|ina) | cugin(a|o|i|e|etta|etto) | zi(a|o) | nonn(i|a|o|e) | amic(a|i|o|) | parent(e|i) | famig?liar(e|i) | famiglia | compagn(i|a|o))

* Python regular expressions notation is used in pattern definitions. Single spaces are always to be intended as \s*, even when not reported for better readability.

eTable2. Validation of the algorithm for influenza identification on 2017-2018 gold-labelled data.

Dataset	Input data	Eval Labels	TP	FP	TN	FN	Sens.	Spec.	Prec.	F1-Score
2017-2018 with discharge letters	Discharge letters	Discharge letters only	34	0	2,612	0	100.00%	100.00%	100.00%	100.00%
2017-2018 with discharge letters	Discharge letters	Pedianet + Discharge letters	34	0	2,567	45	43.04%	100.00%	100.00%	60.18%
2017-2018 with discharge letters	Pedianet	Pedianet	51	0	2,595	0	100.00%	100.00%	100.00%	100.00%
2017-2018 with discharge letters	Pedianet	Pedianet + Discharge letters	51	0	2,567	28	64.56%	100.00%	100.00%	78.46%
2017-2018 with discharge letters	Pedianet + Discharge letters	Pedianet + Discharge letters	79	0	2,567	0	100.00%	100.00%	100.00%	100.00%
2017-2018 full	Pedianet	Pedianet	11,943	21	398,425	7	99.94%	99.99%	99.82%	99.88%
2017-2018 full	Pedianet	Pedianet + Discharge letters	11,943	21	398,397	35	99.71%	99.99%	99.82%	99.77%
2017-2018 full	Pedianet + discharge letters	Pedianet + Discharge letters	11,971	21	398,397	7	99.94%	99.99%	99.82%	99.88%

eTable3. Validation of the algorithm for influenza identification on 2022-2024 balanced sampled gold-labelled data.

Dataset	TP	FP	TN	FN	Sens.	Spec.	Prec.	F1-Score
2022-2024 Pedianet sample	100	0	100	0	100.00%	100.00%	100.00%	100.00%
2022-2024 Discharge letters sample	96	4	100	0	100.00%	96.15%	96.00%	97.96%

eTable4. Comorbidities' exemption codes used.

Disease	Exemption Code
Cystic fibrosis	018
Diabetes mellitus	013
Chronic obstructive pulmonary disease	024, 057
Asthma	007
Congenital and acquired immunodeficiency (including HIV) and/or immunosuppressive therapy	003, 020, 048, 050, 052
Neurological and neurocognitive conditions (including Down syndrome)	011, 017, 038, 044, 065
Prematurity	040
Renal failure	023, 061
Congenital cardiac disease (including heart failure)	002, 021
Chronic liver conditions	008, 016

eTable5. Children sociodemographic and clinical characteristics by exposure, flu season 2022-2023.

	Unvaccinated (N = 59,542)	**LAIV-4-vaccinated (N = 1,683)**	**IIV-vaccinated (N = 4,320)**	**P-value***	**P-value LAIV-4 vs. IIV***
Sex					
Male	30,577 (51.35%)	854 (50.74%)	2,276 (52.69%)	0.2038	0.1760
Female	28,965 (48.65%)	829 (49.26%)	2,044 (47.31%)		
Age					
2-5 years	15,546 (26.11%)	1,012 (60.13%)	1,607 (37.20%)	<.0001	<.0001
6-10 years	25,153 (42.24%)	550 (32.68%)	1,886 (43.66%)		
11-14 years	18,843 (31.65%)	121 (7.19%)	827 (19.14%)		
Region of birth in Italy					
North	42,935 (72.11%)	481 (28.58%)	2,298 (53.19%)	<.0001	<.0001
Center	7,333 (12.32%)	298 (17.71%)	847 (19.61%)		
South and islands	9,274 (15.58%)	904 (53.71%)	1,175 (27.20%)		
Deprivation index					
Low	20,636 (34.66%)	585 (34.76%)	1,591 (36.83%)	<.0001	<.0001
High	27,888 (46.84%)	912 (54.19%)	2,058 (47.64%)		
Missing	11,018 (18.50%)	186 (11.05%)	671 (15.53%)		
Comorbidity					
None	57,011 (95.75%)	1,577 (93.70%)	3,898 (90.23%)	<.0001	<.0001
At least one	2,531 (4.25%)	106 (6.30%)	422 (9.77%)		
Influenza vaccination status in the previous season				<.0001	<.0001
Unvaccinated	57,452 (96.49%)	634 (37.67%)	1,193 (27.62%)		
Vaccinated	2,090 (3.51%)	1,049 (62.33%)	3,127 (72.38%)		
Influenza/ILI episode(s) in the previous season					
0	59,051 (99.18%)	1,676 (99.58%)	4,275 (98.96%)	0.0527	0.0188
>=1	491 (0.82%)	7 (0.42%)	45 (1.04%)		
Drug prescription(s) in the previous season					
0	47,393 (79.60%)	778 (46.23%)	2,829 (65.49%)	<.0001	<.0001
1-2	9,909 (16.64%)	591 (35.12%)	1,127 (26.09%)		
>=3	2,240 (3.76%)	314 (18.66%)	364 (8.43%)		
Specialistic visit(s) in the previous season					
0-7	49,962 (83.91%)	924 (54.90%)	2,524 (58.43%)	<.0001	0.0131
>=8	9,580 (16.09%)	759 (45.10%)	1,796 (41.57%)		

* Chi-squared test.

eTable6. Children sociodemographic and clinical characteristics by exposure, flu season 2023-2024.

	Unvaccinated (N = 65,600)	**LAIV-4-vaccinaed (N = 3,587)**	**IIV-vaccinated (N = 3,190)**	**P-value***	**P-value LAIV-4 vs. IIV***
Sex					
Male	33,862 (51.62%)	1,870 (52.13%)	1,661 (52.07%)	0.7488	0.9582
Female	31,738 (48.38%)	1,717 (47.87%)	1,529 (47.93%)		
Age					
2-5 years	16,465 (25.10%)	2,022 (56.37%)	1,150 (36.05%)	<.0001	<.0001
6-10 years	26,028 (39.68%)	1,204 (33.57%)	1,328 (41.63%)		
11-14 years	23,107 (35.22%)	361 (10.06%)	712 (22.32%)		
Region of birth in Italy					
North	40,583 (61.86%)	1,586 (44.22%)	1,559 (48.87%)	<.0001	<.0001
Center	11,213 (17.8092%)	454 (12.66%)	905 (28.37%)		
South and islands	13,804 (21.04%)	1,547 (43.13%)	726 (22.76%)		
Deprivation index					
Low	22,236 (33.90%)	1,364 (38.03%)	1,149 (36.02%)	<.0001	<.0001
High	31,273 (47.67%)	1,808 (50.40%)	1,507 (47.24%)		
Missing	12,091 (18.43%)	415 (11.57%)	534 (16.74%)		
Comorbidity					
None	62,911 (95.90%)	3,332 (92.89%)	2,874 (90.09%)	<.0001	<.0001
At least one	2,689 (4.10%)	255 (7.11%)	316 (9.91%)		
Influenza vaccination status in the previous season				<.0001	<.0001
Unvaccinated	63,588 (96.93%)	1,392 (38.81%)	913 (28.62%)		
Vaccinated	2,012 (3.07%)	2,195 (61.19%)	2,277 (71.38%)		
Influenza/ILI episode(s) in the previous season				0.0124	0.0032
0	61,119 (93.29%)	3,382 (94.28%)	2,951 (92.51%)		
>=1	4,401 (6.71%)	205 (5.72%)	139 (7.49%)		
Drug prescription(s) in the previous season					
0	44,241 (67.44%)	1,352 (37.69%)	1,477 (46.30%)	<.0001	<.0001
1-2	16,130 (24.59%)	1,376 (38.36%)	1,132 (35.49%)		
>=3	5,229 (7.97%)	859 (23.95%)	581 (18.21%)		
Specialistic visit(s) in the previous season					
0-7	56,453 (86.06%)	2,089 (58.24%)	1,986 (62.26%)	<.0001	0.0007
>=8	9,147 (13.94%)	1,498 (41.76%)	1,204 (37.74%)		

* Chi-squared test.

MOX Technical Reports, last issues

Dipartimento di Matematica
Politecnico di Milano, Via Bonardi 9 - 20133 Milano (Italy)

61/2025 Coclite, A; Montanelli Eccher, R.; Possenti, L.; Vitullo, P.; Zunino, P.
Mathematical modeling and sensitivity analysis of hypoxia-activated drugs

60/2025 Antonietti, P. F.; Caldana, M.; Gentile, L.; Verani M.
Deep Learning Accelerated Algebraic Multigrid Methods for Polytopal Discretizations of Second-Order Differential Problems

59/2025 Wolf, F.; Botteghi, N.; Fasel, U.; Manzoni, A.
Interpretable and efficient data-driven discovery and control of distributed systems

58/2025 Pivato, C.A.; Cozzi, O.; Fontana, N.; Ieva, F., et al.
Clinical outcomes of percutaneous coronary interventions after transcatheter aortic valve replacement

57/2025 Guagliardi, O.; Masci, C,; Breschi, V; Paganoni A, ; Tanelli, M.
A Novel DNA-Inspired Framework to Study University Dropout: Insights from Politecnico di Milano

56/2025 Tonini, A.; Bui-Thanh, T.; Regazzoni, F.; Dede', L; Quarteroni, A.
Improvements on uncertainty quantification with variational autoencoders

Tonini, A.; Bui-Thanh, T.; Regazzoni, F.; Dede', L; Quarteroni, A.
Improvements on uncertainty quantification with variational autoencoders

55/2025 Gimenez Zapiola, A.; Boselli, A.; Menafoglio, A.; Vantini, S.
Hyper-spectral Unmixing algorithms for remote compositional surface mapping: a review of the state of the art

53/2025 Zecchi, A. A.; Sanavio, C.; Perotto, S.; Succi, S.
Telescopic quantum simulation of the advection-diffusion-reaction dynamics

54/2025 Tomasetto, M.; Williams, J.P.; Braghin, F.; Manzoni, A.; Kutz, J.N.
Reduced order modeling with shallow recurrent decoder networks