McMaster University | Health Forum

Living Evidence Synthesis

Effectiveness of trivalent and quadrivalent influenza vaccines in preventing infection, hospitalization, and severe outcomes in the 2023–2024 season onwards

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Context

- Seasonal influenza (the flu) is a globally common respiratory virus that spreads easily when someone with the flu coughs or sneezes.(1)
- Vaccination is considered the best method to prevent serious outcomes associated with influenza infection.(1)
- In Canada, influenza and pneumonia are ranked among the top 10 leading causes of death.
  - While most people recover from the flu in 7 to 10 days, some population groups are at increased risk of severe influenza illness.(2)
  - Each year, influenza causes an estimated 3,500 deaths and 12,200 hospital stays.(3)
  - Adults aged 65 years and older account for 46% of the reported hospitalizations.(4)
- Influenza viruses constantly evolve, requiring continuous global monitoring and frequent reformulation of vaccines.(5)
- Given this, the effectiveness of influenza vaccines can vary from season to season, depending on factors such as the match between vaccine strains and circulating viruses, as well as the age and health status of vaccinated individuals.(6)
- Monitoring vaccine performance is crucial for understanding and improving vaccination benefits.
- This monitoring can be done through vaccine effectiveness (VE) studies that evaluate how circulating and evolving influenza viruses affect vaccine performance in real-world conditions, considering factors such as outcome, season, and population.
- The Public Health Agency of Canada (PHAC) aims to monitor the effectiveness and impact of influenza vaccines over time to support vaccine policy, enhance situational awareness, inform routine briefings, and ultimately protect Canadians from severe illness, and this living evidence synthesis has been requested to inform those efforts.

Questions

Primary research question

1) What is the effectiveness of trivalent and quadrivalent influenza vaccines in preventing influenza-associated outcomes (medically attended acute respiratory illness (MAARI), outpatient visits, hospitalization, intensive care unit (ICU) admission, and death) across different influenza types and subtypes (all types and subtypes, A, A(H1N1)pdm09, A(H3N2), and B) in the following populations: a) general population (all ages); b) older adults aged ≥65 years; c) adults aged 18–64 years; and d) children aged 6 months–17 years ?

Secondary research questions

1) What is the effectiveness of trivalent and quadrivalent influenza vaccines in preventing MAARI (outpatient visits), hospitalization, ICU admission, and death among individuals with immunocompromising conditions (e.g., solid organ transplant recipients)?

2) What is the efficacy and effectiveness of any pre-pandemic H5 vaccines and potential H5 vaccines made using existing candidate vaccine viruses (CVVs) authorized in Canada, in preventing MAARI (outpatient visits), hospitalization, ICU

admission, and death associated with highly pathogenic influenza A(H5N1) in the general population (all ages) and older adults aged ≥65 years (for future update)?

High-level summary of key findings

Evidence identified

- We identified 3,705 records and included 33 studies, of which 19 were newly identified in this version, and one study had progressed from a preprint to a peer-reviewed publication:
  - 27 studies were test-negative case-control designs (13 were newly identified in this version and one study had progressed from a preprint to a peer-reviewed publication)
  - 25 studies were included for meta-analysis (16 were newly identified in this version and one study had progressed from a preprint to a peer-reviewed publication).
- The risk of bias (ROBINS-I) among 32 studies was assessed as the following:
  - Low risk of Bias (n=6)
  - Moderate risk of Bias (n=26)
  - Serious Risk of Bias (n=1)
- Random-effects models were used to calculate pooled effects as we anticipated meaningful heterogeneity across studies and group comparisons.
- When data were available, subgroup analyses were computed to examine how findings varied according to different vaccine seasons and age groups.

Key findings in relation to the research question

- Of the 33 included studies, 27 used a test-negative case-control design, and the studies were conducted across diverse healthcare settings, including primary care, outpatient clinics, emergency departments, and inpatient hospital facilities.
- The research spanned multiple geographic regions:
  - North America (United States and Canada)
  - Europe (Italy, U.K., Spain, France, Ireland, Denmark, and other European countries)
  - Asia (China, Japan, South Korea, and Israel)
  - South America (Argentina, Brazil, Chile, Paraguay, and Uruguay)
- The expanded meta-analysis of 25 studies corroborated our initial findings from nine studies while enhancing precision of effect estimates and external validity through broader geographic and healthcare setting representation, with the notable addition of preliminary 2024/25 season data not available in the previous review.
- Our meta-analysis of multiple studies showed that VE estimates consistently ranged between 40–60% across different healthcare settings:
  - Mid-season estimates were 54% for MAARI and 47% for hospitalization
  - End-season estimates showed a decline (MAARI: 45%, hospitalization: 45%).
- Our meta-analysis showed age-related patterns (no new studies were added to the age-related meta-analysis):
  - consistently higher effectiveness in children (<18 years) across all analyses
    - mid-season MAARI: children (65%) > older adults (55%) > adults (51%)
    - mid-season hospitalization: children (64%) > older adults (47%) ≈ adults (46%)
  - effectiveness declined more substantially in older adults by end-season.
- Our meta-analysis confirmed patterns seen in individual studies (findings for influenza A and B subtypes were substantiated with additional data):
  - influenza A:
    - mid-season: effectiveness ~53% for both MAARI and hospitalization, declined to ~34–39% by end-season
    - A(H1N1): maintained protection (50–57% mid-season), relatively consistent hospitalization effectiveness (44–50%)

        - A(H3N2): mid-season effectiveness (MAARI: 43%, hospitalization: 48%), declined to 28–38% by end-season
    - influenza B:
        - strong early and end-season effectiveness (early-season: MAARI 63%, hospitalization 74%, end-season: MAARI 58%, hospitalization 62%)
        - limited mid-season data available.
- Preliminary 2024/25 season data showed no notable changes in VE patterns:
    - overall mid-season
        - MAARI effectiveness: 48%
        - hospitalization effectiveness: 49%
    - overall end-season
        - MAARI effectiveness: 50%
        - hospitalization effectiveness: 56%.
- Limitations include absence of studies on VE in immunocompromised populations, sparse data on severe outcomes (ICU admission, mortality), and substantial heterogeneity across analyses, indicating significant variability in vaccine performance.

Box 1: Approach and supporting materials

We retrieved candidate studies by searching: 1) Medline, 2) Embase via OVID, 3) Preprint Citation Index (e.g. bioRxiv, medRxiv), and 4) ClinicalTrials.gov. We also included studies identified by subject-matter experts who reviewed the protocols and final report. Searches were conducted for studies reported in English, French, Spanish, Portuguese, Arabic, and Chinese conducted with humans and published between January 2023 and 10 March 2025. Our detailed search strategy is included in Appendix 1.

For efficacy/effectiveness outcomes, any experimental design such as interventional trials or observational designs including cohort, case-control, before-after studies, interrupted time-series, and case series were considered for inclusion. For all outcomes, evidence syntheses were tracked, and any relevant primary studies from them were pulled out for our analysis. A full list of included studies is provided in Appendix 2. Studies excluded at the last stages of reviewing are provided in Appendix 3.

Population of interest: General population (all ages), adults aged 18–64 years, older adults aged ≥65 years, children aged 6 months to 17 years, individuals with immunocompromising conditions (e.g., solid organ transplant recipients for secondary question 1.

Intervention: Vaccination with trivalent or quadrivalent influenza vaccines.

Control: Unvaccinated individuals or individuals receiving placebo.

Primary outcomes: Any of the following outcomes associated with any influenza, influenza A, influenza A(H1N1) pdm09, influenza A(H3N2), and influenza B): 1) medically attended acute respiratory illness; 2) outpatient visits; 3) hospitalization; 4) ICU admission; and 5) death.

Data extraction: Data extraction was conducted by one team member.

Critical appraisal: The risk of bias (ROB) of individual studies was assessed using validated ROB tools. For randomized controlled trials we used ROB-2, and for observational studies we used ROBINS-I. Judgements for the domains within these tools were decided by one reviewer and details are provided in Appendix 4. PRISMA flow diagram are provided in Appendix 5.

Summaries: We summarized the evidence by presenting narrative evidence profiles across studies by outcome measure. When appropriate, statistical pooling of results was performed using random effects methods. The presence of heterogeneity was measured with the I^2 estimator. When heterogeneity was higher than 50%, we suppressed the meta-analysis and reported the findings only narratively.

The next update to this document is to be determined.

Background

Seasonal influenza presents a significant and variable public-health challenge in Canada, with case numbers and rates fluctuating annually. Recent data from the 2023/24 influenza season (27 August 2023 to 13 April 2024) highlight the scope of this issue:

- A total of 94,394 influenza detections were reported, with influenza A accounting for 82% (77,249) of these cases.
- Among adults, those over 65 years had the highest detection rate at 28%, followed by similar rates in the 45–64 (22%) and 20–44 (19%) age groups.
- Participating provinces and territories reported 4,205 influenza-associated hospitalizations, with older adults aged ≥65 years representing 46% of these cases.
- The highest cumulative hospitalization rates were observed in older adults ≥65 years (131 per 100,000) and children under 5 years (91 per 100,000).

This growing public-health concern has intensified focus on more effective influenza prevention strategies, particularly for high-risk and disproportionately affected groups. Vaccination remains the primary means of reducing influenza-related

mortality and morbidity in communities. However, the constantly evolving nature of influenza viruses necessitates continuous global monitoring and frequent vaccine reformulation.

While trivalent and quadrivalent vaccines show potential for influenza prevention, uncertainty persists about their effectiveness across different populations and influenza types.(7) Factors such as age, health status, and the match between vaccine strains and circulating viruses can all influence vaccine efficacy and effectiveness.

To inform ongoing efforts to update and refine vaccine recommendations, there is a critical need for high-quality, routinely updated syntheses of the best-available evidence. This is why this living evidence synthesis has been requested. In synthesizing evidence about the effectiveness of trivalent and quadrivalent vaccines in preventing influenza, it is important to focus on effects at a population level, with particular emphasis on groups disproportionately affected by or at higher risk of contracting influenza. Such evidence is crucial for supporting vaccine policy, enhancing situational awareness, and ultimately protecting vulnerable populations from severe influenza-related outcomes.

Our primary research question was:

1) What is the effectiveness of trivalent and quadrivalent influenza vaccines in preventing influenza-associated outcomes (MAARI/outpatient visits, hospitalization, ICU admission, and death) across different influenza types and subtypes (all types and subtypes, A, A(H1N1)pdm09, A(H3N2), and B) in the following populations: a) the general population (all ages); b) older adults aged ≥65 years; c) adults aged 18–64 years; and d) children aged 6 months–17 years ?

Our secondary research questions were:

1) What is the effectiveness of trivalent and quadrivalent influenza vaccines in preventing MAARI, outpatient visits, hospitalization, ICU admission, and death among individuals with immunocompromising conditions (e.g., solid organ transplant recipients)?

2) What is the efficacy and effectiveness of any pre-pandemic H5 vaccines and potential H5 vaccines (made using existing candidate vaccine viruses (CVVs) authorized in Canada) in preventing MAARI, outpatient visits, hospitalization, ICU admission, and death associated with highly pathogenic influenza A(H5N1) in the general population (all ages) and older adults aged ≥65 years (for future update)?

What we found

We identified 3,705 articles, and after removing 237 duplicates, we screened 3,468 titles and abstracts. We reviewed 156 full-text articles and included 33 single studies, of which 19 were newly identified in this version, and one study had progressed from a preprint to a peer-reviewed publication:

- Of the 33 included studies, 27 studies (13 were newly identified in this version, and one study had progressed from a preprint to a peer-reviewed publication) used a test-negative case-control design, and the studies were conducted across diverse healthcare settings, including primary care, outpatient clinics, emergency departments, and inpatient hospital facilities.
- The 33 studies spanned multiple geographic regions:
  - North America (United States and Canada)
  - Europe (Italy, UK, Spain, France, Ireland, Denmark, and other European countries)
  - Asia (China, Japan, South Korea, and Israel)
  - South America (Argentina, Brazil, Chile, Paraguay, and Uruguay)
- Two studies (8; 9) that were previously included as a preprint has now been published, and the preprint versions have been replaced by the new publication (10; 11)
- 25 studies address the research questions about effectiveness and were included in the meta-analysis (16 were newly identified in this version).

- The expanded meta-analysis of 25 studies corroborated our initial findings from nine studies while enhancing precision of effect estimates and external validity through broader geographic and healthcare setting representation, with the notable addition of preliminary 2024/25 season data not available in the previous review.

The risk of bias in the included studies was moderate in 26 studies, low in six studies, and serious in one study.

Random-effects models were used to calculate pooled effects, as we anticipated meaningful heterogeneity across studies and group comparisons. When data were available, subgroup analyses were computed to examine how patterns of findings varied according to different age groups. All estimates, and their corresponding confidence intervals (CIs), were converted to risk ratios (RRs). RRs were then log-transformed for use in meta-analytic models, and the CIs were used to derive a standard error for each effect size. If a study only reported VE for each single influenza season, age group or influenza subtype/lineage without an overall estimate, we considered each season, age group, or influenza subtype/lineage as a separate cohort in the meta-analysis.

Key findings in relation to influenza vaccine effectiveness

Our comprehensive meta-analysis examined influenza VE across two consecutive seasons, providing a detailed assessment of protection against MAARI, hospitalization, and other severe outcomes.

Overall vaccine effectiveness in the 2023/24 season

Early-season effectiveness

In early-season, the vaccine demonstrated promising overall effectiveness. Against MAARI, an analysis of two cohorts (one study) demonstrated an overall VE of 53% (95% CI: 41–62%, p<0.001),(12) with substantial heterogeneity (I^2=98%, Tau^2=0.03, p<0.001). Hospitalization protection was similarly robust, with an overall effectiveness of 49% (95% CI: 39–57%, p<0.001) across four cohorts (two studies) with substantial heterogeneity (I^2=84%, Tau^2=0.08, p<0.001).(12; 13) The vaccine also showed potential in preventing critical outcomes, with a VE of 55% (95% CI: 35–69%, p<0.001) against ICU admissions across four cohorts (two studies)(12; 13), with moderate heterogeneity (I^2=63%, Tau^2=0.04, p<0.001) (Table 2). One study evaluated VE against death during the 2023/24 early-season among adults ≥18 years and reported VE of 50% (95% CI: 31–65%).(12) We did not find any studies assessing VE against any outcomes of interest in the 2024/25 early-season. There is insufficient data for a subgroup analysis by age group.

Mid-season effectiveness

The mid-season of 2023/24 revealed more consistent protection. Four studies evaluated VE against MAARI in outpatient and primary-care settings during the 2023/24 mid-season (7; 14-16). An analysis of six cohorts demonstrated an overall VE of 54% (95% CI: 49–97%, p<0.001) against MAARI during mid-season, with no heterogeneity (I^2=0 Tau^2=0.00, p=0.61) (Table 2). The age-stratified analysis revealed VE estimates of 65% (95% CI: 54–73%, p<0.001) in children and adolescents <18 years (eight cohorts), 51% (95% CI: 44–56%, p<0.001) in adults 18–64 years (eight cohorts), and 55% (95% CI: 45–63%, p<0.001) in older adults ≥65 years (eight cohorts) (Table 3). The test for age group differences was not statistically significant (Q=5.25, df=2, p=0.072), with between-group variance (Tau^2) of 0.02.

For hospitalization outcomes, the overall VE was 47% (95% CI: 39–54%, p<0.001) across nine cohorts, with substantial heterogeneity (I^2=66%, Tau^2=0.03, p<0.001). The age-stratified analysis showed VE estimates of 64% (95% CI: 54–72%, p<0.001) in children <18 years (two cohorts), 46% (95% CI: 24–62%, p<0.001) in adults 18–64 years (two cohorts), and 47% (95% CI: 32–58%, p<0.001) in older adults ≥65 years (two cohorts) (Table 5). Age group differences were statistically significant (Q=6.21, df=2, p=0.045).

End-season effectiveness

By the end of the 2023/24 season, VE began to wane. Twelve studies evaluated VE against MAARI in outpatient and primary care settings.(8; 11; 17-26) An analysis of 13 cohorts showed an overall VE of 45% (95% CI: 40–50%, p<0.001) against MAARI, with substantial heterogeneity (I^2=73%, Tau^2=0.01, p<0.001). The age-stratified analysis revealed VE estimates of 52% (95% CI: 44–59%, p<0.001) in children <18 years (seven cohorts), 64% (95% CI: 32–81%, p=0.002) in adults 18–64 years (two cohorts), and 28% (95% CI: 7–44%, p=0.012) in older adults ≥65 years (one cohort) (Table 5). The test for age group differences was statistically significant (Q=8.60, df=2, p=0.014), with between-group variance (Tau^2) of 0.03.

Eight studies evaluated VE against hospitalization in inpatient settings.(10; 17-20; 23; 27; 28). The overall VE was 45% (95% CI: 37–53%, p<0.001) across 11 cohorts, with moderate heterogeneity (I^2=50%, p=0.02). The age-stratified analysis showed VE estimates of 42% (95% CI: 33–50%, p<0.001) in children <18 years (five cohorts) and 34% (95% CI: 25–41%, p<0.001) in adults 18–64 years (six cohorts), with insufficient data for the older adult population (Table 7). One study evaluated VE against ICU admission during 2023/24 end-season among adults ≥18 years and reported VE of 50% (95% CI: 31–65%).(20)

Influenza type and subtype analysis

Influenza A

2023/24 early-season VE against influenza A was 40% (95% CI: 31–48%, p<0.001) across three cohorts for MAARI outcomes, with substantial heterogeneity (I^2=93%, p<0.001) (Table 2). Mid-season protection improved to 53% (95% CI: 45–60%, p<0.001) across nine cohorts, with low heterogeneity (I^2=17%, p=0.3). The age-stratified analysis revealed the highest effectiveness in children under 18 years at 65% (95% CI: 52–74%, p<0.001) based on seven cohorts, while both adults aged 18–64 years and the older adult population (≥65 years) showed comparable effectiveness of 49% (95% CI: 42–56%, p<0.001) and 56% (95% CI: 43–65%, p<0.001), respectively, each supported by seven cohorts (Table 4). For hospitalization outcomes, VE against influenza A was similar at 53% (95% CI: 45–60%, p<0.001) across fourteen cohorts, though with low heterogeneity (I^2=17%, p=0.30). Hospitalization effectiveness followed similar patterns, with 47% (95% CI: 38–55%, p<0.001) across 14 cohorts, though with moderate heterogeneity (I^2=46%, p=0.030) (Table 2). The age-stratified analysis of hospitalization outcomes showed the highest effectiveness in children under 18 years at 71% (95% CI: 54–81%, p<0.001) from three cohorts, while the VE in adults aged 18–64 years and older adults was 46% (95% CI: 29–60%, p<0.001) from six cohorts and 43% (95% CI: 32–51%, p<0.001) from seven cohorts, respectively (Table 5). The difference between age groups was statistically significant (Q=7.67, df=2, p=0.022).

By 2023/24 end-season, the overall VE against influenza A for MAARI decreased to 34% (95% CI: 28–40%, p<0.001) across 11 cohorts, with substantial heterogeneity (I^2=68%, p<0.001) (Table 2). There were insufficient data for the age-stratified analysis. For hospitalization outcomes, end-season VE against influenza A was 39% (95% CI: 34–45%, p<0.001) across nine cohorts, with no heterogeneity (I^2=0%, p=0.47). The age-specific analysis showed VE estimates of 37% (95% CI: 28–45%, p<0.001) for children under 18 years (six cohorts) and 32% (95% CI: 24–39%, p<0.001) for adults aged 18–64 years (five cohorts), while data for the older adult population were insufficient for analysis (Table 6).

Influenza A (H1N1 subtype)

2023/24 mid-season VE against influenza A(H1N1) was 57% (95% CI: 51–63%, p<0.001) for MAARI (six cohorts) and 50% (95% CI: 37–60%, p<0.001) for hospitalization (three cohorts). End-season VE slightly declined to 47% (95% CI: 14–67%, p<0.001, four cohorts) for MAARI and to 44% (95% CI: 35–52%, p<0.001, six cohorts) for hospitalization (Table 2).

Influenza A (H3N2 subtype)

Influenza A(H3N2) showed lower effectiveness, with mid-season protection at 43% (95% CI: 30–54%, p<0.001) for MAARI and 48% (95% CI: 25–65%, p<0.001) for hospitalization. End-season effectiveness further decreased to 28% (95% CI: 11–42%) for MAARI and 38% (95% CI: 27–48%) for hospitalization.

Influenza B

The highest effectiveness was demonstrated against influenza B. Early-season protection reached 63% (95% CI: 33–79%, p<0.001) for MAARI and 74% (95% CI: 55–85%, p<0.001) for hospitalization. End-season effectiveness remained strong at 58% (95% CI: 51–63%, p<0.001) for MAARI and 62% (95% CI: 50–71%, p<0.001) for hospitalization.

Overall vaccine effectiveness in the 2024/25 season

Preliminary mid-season data for 2024/25 revealed nuanced VE across different influenza types and outcomes. Three studies evaluated VE against MAARI in outpatient and primary-care settings.(29-31) An analysis of six cohorts demonstrated an overall VE of 48% (95% CI: 44–53%, p<0.001) against MAARI during mid-season, with low heterogeneity (I^2=21%, Tau^2=0.002, p=0.28) (Table 3). There is insufficient data for a subgroup analysis by age group. For hospitalization outcomes, the overall VE was 49% (95% CI: 39–57%, p<0.001) across five cohorts, with substantial heterogeneity (I^2=87%, Tau^2=0.03, p<0.001) (Table 3). There are insufficient data for a subgroup analysis by age group.

2024/25 mid-season VE against influenza A was 49% (95% CI: 39–57%, p<0.001) across nine cohorts for MAARI outcomes, with moderate heterogeneity (I^2=58%, p=0.695) (Table 2). For hospitalization outcomes, VE against influenza A was similar at 49% (95% CI: 42–55%, p<0.001) across six cohorts, though with no heterogeneity (I^2=0%, p=0.74) (Table 3). There were insufficient data for the age-stratified analysis.

2024/25 mid-season VE against influenza A(H1N1) was 50% (95% CI: 38–60%, p<0.001) for MAARI (five cohorts) and 50% (95% CI: 43–56%, p<0.001) for hospitalization (three cohorts). VE against influenza A(H3N2) was 47% (95% CI: 34–57%, p<0.001) for MAARI (four cohorts) and 37% (95% CI: 10–56%, p<0.001) for hospitalization (three cohorts).

2024/25 mid-season VE against influenza B was 66% (95% CI: 54–75%, p<0.001) for MAARI (three cohorts), with low heterogeneity (I^2=9%, Tau^2=0.006, p=0.34) and 76% (95% CI: 67–73%, p<0.001) for hospitalization (four cohorts), with no heterogeneity (I^2=0%, Tau^2=0.00, p=0.764).

End-season effectiveness

There was limited end-season data for 2024/25. Two studies evaluated VE against MAARI in primary care settings and reported VE of 50% (95% CI: 42-57) among participants of all ages.(32; 33) One study evaluated VE against influenza A for hospitalization and reported VE of 56% (95% CI: 43-66) among participants of all ages. No studies were identified that evaluated VE against severe outcomes like ICU admission or death.

2024/25 end-season VE against influenza A(H1N1) was 59% (95% CI: 31–75%, p<0.001) for MAARI (three cohorts) and 52% (95% CI: 22–71%, p<0.001) for hospitalization (two cohorts). VE against influenza A(H3N2) was 32% (95% CI: 15–46%, p<0.001) for MAARI (three cohorts) and 52% (95% CI: 30–67%, p<0.001) for hospitalization (two cohorts).

Out of 33 included studies, seven were excluded from the meta-analysis (34-40): five did not provide specific vaccine information,(35-37; 39; 40) and two did not differentiate between inpatient and outpatient data.(34; 38) One study compared high-dose (HD) and standard-dose (SD) influenza vaccines among older adults in Israel, finding limited incremental benefit with the HD vaccine, with non-significant relative VE of 27% and 7%, respectively. The researchers also found high numbers needed to vaccinate to prevent one influenza hospitalization, even among the highest-risk subgroups.(41) No studies were identified that evaluated VE in individuals with immunocompromising conditions, such as solid organ transplant recipients.

Next steps based on the identified evidence

The following recommended actions, synthesized from a comprehensive review of the evidence, address critical knowledge gaps in influenza VE. They provide a structured framework to enhance research and public-health responses to seasonal influenza outbreaks. These recommendations aim to strengthen our understanding of vaccine performance across different populations while improving outbreak management strategies.

- Research priorities
  - Examine reasons for effectiveness decline in older adult populations, particularly by end-season
  - Develop strategies to enhance vaccine response in adults and older adults where effectiveness is consistently lower
  - Study the impact of viral evolution on VE
  - Conduct targeted research on populations with limited current data, including individuals with immunocompromising conditions and those with complex medical conditions
- Vaccine strategies
  - Develop specific approaches for populations showing lower vaccine protection
  - Evaluate optimal timing of vaccination to maximize protection throughout the season
  - Strengthen vaccination campaigns in children (<18 years) given consistently higher effectiveness in this population group across outcomes
  - Consider the appropriate timing of vaccination campaigns given the observed decrease in effectiveness from mid-season to end-season
  - Develop strategies to maintain vaccine protection through end-season
  - Explore potential booster or supplementary vaccination approaches for populations with lower protection
- Policy implications
  - Develop protocols for managing end-season vulnerability across different population groups
  - Strengthen healthcare capacity during periods of lower VE
  - Support the development of enhanced vaccines for populations with lower effectiveness
  - Encourage research into factors affecting end-season VE decline

Table 1: Characteristics of all included studies

Reference and author year with URL	Research question addressed	Geographical location and trial name	Design	Population (add age of population)	Analysis	Type of vaccine	Risk of bias	Included in meta-analysis
Costantino 2024 (14)	• Vaccine effectiveness (VE) against influenza strain A(H1N1)pdm09 • VE against influenza strain A(H1N1)pdm09 by age group	Sicily, Italy Trial Name: Italian RespiVirNet network	Test-negative case-control	• Patients (n=1,230) with influenza-like illness across all age groups	VE was estimated by comparing the odds ratio of vaccination between cases and controls and using a logistic regression model to estimate crude VE and VE adjusted by sex and at least one comorbidity overall and by age group	• Quadrivalent inactivated influenza vaccine (IIV4) • Live attenuated quadrivalent influenza vaccine	Moderate	Yes
Frutos 2024 (35)	• VE against influenza-associated outpatients visits and hospitalizations by age group	United States Trial Name: 1) Investigating Respiratory Viruses in the Acutely Ill (IVY) 2) New Vaccine Surveillance Network (NVSN) 3) U.S. Flu Vaccine Effectiveness (US Flu VE) 4) Virtual SARS-CoV-2, Influenza, and Other respiratory viruses Network (VISION)	Test-negative case-control	• Patients who received medical care in outpatient settings or in hospital for acute respiratory illness (ARI) and were tested for influenza	VE was estimated to compare the odds ratio of vaccination against ARI in different settings between cases and controls; a multivariable logistic regression model was used and adjusted for age, geographic region, and calendar time of illness	• Not specified	Low	No
Frutos 2025 (33)	• VE against medically attended influenza outpatient visits or influenza-associated hospitalizations	United States Trial Name: 1) Investigating Respiratory Viruses in the Acutely Ill (IVY)	Test-negative case-control	• 3,175 adult participants were included from the IVY network • 4,611 participants <18 years were included from NVSN; 2,969 were outpatients and 1,642 were hospitalized • 3,344 participants were included from the U.S. Flu VE network;	Multivariable logistic regression adjusted for geographic region, age, and calendar time of illness was used; VE was calculated using the following equation: VE = (1 – adjusted odds ratio) x 100%	• Trivalent inactivated influenza vaccine (IIV3) • Trivalent live attenuated vaccine (LAIV3)	Low	Yes

Reference and author year with URL	Research question addressed	Geographical location and trial name	Design	Population (add age of population)	Analysis	Type of vaccine	Risk of bias	Included in meta-analysis
		2) New Vaccine Surveillance Network (NVSN) 3) U.S. Flu Vaccine Effectiveness (U.S. Flu VE) 4) Virtual SARS-CoV-2, Influenza, and Other respiratory viruses Network (VISION)		1,134 were <18 years and 2,210 were adults • 139,558 outpatients were included from the VISION network; 36, 919 were patients <18 years and 102, 639 were adults • 32,671 hospitalized patients were included from the VISION network; 1,638 were <18 years, 31,033 were adults • Among control patients <18 years proportion of outpatients vaccinated against influenza ranged from 22% in the VISION network to 34% in the NVSN network; in hospitalized patients 27% (VISION) to 40% (NVSN) were vaccinated • Among adult controls 34% of outpatients were vaccinated against influenza; 35% (IVY) to 39% (VISION) of hospitalized patients were vaccinated • Among controls 65 years or older 54% (VISION) to 59% (U.S. Flu VE) of outpatients were vaccinated against influenza; 45% (IVY) to 46% (VISION) of hospitalized patients were vaccinated		• Other (Trivalent recombinant influenza vaccine)		
Zhu 2024 (38)	• Interim VE against influenza between 1 October 2023 and 31 January 2024 by age group	California, United States Trial Name: Not reported	Test-negative case-control	• Patients (n=678,422) with influenza laboratory-confirmed test results across all age groups	Interim VE against influenza between 1 October 2023 and 31 January 2024 was estimated by comparing the odds of vaccination amongst patients who received a positive influenza laboratory-confirmed test result (case patients) and patients who	• High-dose, adjuvanted, or recombinant vaccine	Low	No

Reference and author year with URL	Research question addressed	Geographical location and trial name	Design	Population (add age of population)	Analysis	Type of vaccine	Risk of bias	Included in meta-analysis
					received a negative influenza test result (control patients); a mixed effects logistic regression model was used and adjusted for age, race and ethnicity			
Choi 2024 (34)	• Interim VE of influenza vaccine during the November to December 2023	South Korea Trial Name: Not Reported	Test-negative case-control	• This study included 2,632 participants (F=1,497 and M=1,135)	VE was estimated using multivariate logistic and odds ratio, adjusted for age, sex, and underlying comorbidities	• Quadrivalent inactivated influenza v	Moderate	No
Whitaker 2024 (16)	• Seasonal influenza VE by age group	England, Scotland, Wales Trial Name: Not reported	Test-negative case-control	• The GB-PC study included 1,193 case and 12,098 controls for A(H1N1)pdm09, A(H3N2), influenza A (untyped), influenza B, dual infections • The EN-H study included 1,359 cases and 22,539 controls with cases of influenza A (untyped), influenza B, and dual infections • The SC-H study included 1,977 cases and 34,476 controls with influenza A (untyped), influenza A(H1N1)pdm09, influenza A(H3N2), and influenza B	VE was estimated using multivariate logistic regression models, adjusted for age, region, clinical risk status, sex, calendar time as week, setting (community or hospital), and deprivation quintile	• Live-attenuated influenza vaccine (for ages 2–17) via nasal spray • Quadrivalent cell-based vaccine (for ages 18–64 years) • Adjuvanted egg-based vaccine (for ages 65 years and older)	Low	Yes
Smolarchuk 2024 (37)	• VE against influenza strain A(H1N1)pdm09, influenza strain A(H3N2), and influenza strain B • VE against influenza strain A(H1N1)pdm09 by age group	Alberta, Canada Trial Name: Canada's Sentinel Practitioner Surveillance Network (SPSN)	Test-negative case-control	• Patients (n=38,136) with influenza-like illness across all age groups	VE by influenza type and age group was estimated using multivariate logistic regression models, adjusted for age, gender, calendar time, hospitalization status, and presence of comorbidities	• Not specified	Low	No
Shinjoh 2024 (19)	• VE against hospitalization or	Japan	Test-negative case-control	• Patients (n=1,832) aged 6 months to 15 years old	VE was estimated using an adjusted odds ratio formula	• Quadrivalent inactivated	Moderate	Yes

Reference and author year with URL	Research question addressed	Geographical location and trial name	Design	Population (add age of population)	Analysis	Type of vaccine	Risk of bias	Included in meta-analysis
	influenza infection in outpatient settings • VE by age, presence of underlying disease, one dose vs. two dose regimen, influenza strain, and method of testing	Trial Name: Not reported		presenting with fever who were tested for influenza	and adjusted for sex, age, comorbidity, area, month of onset, and diagnostic methods	influenza vaccine (IIV4)		
Pérez-Gimeno 2024 (18)	• VE against ARI in primary care settings or severe acute respiratory illness (SARI) in hospital • VE by influenza type, subtype, and clade	Spain Trial Name: Surveillance System of Acute Respiratory Infections in Spain (SiVIRA)	Test-negative case-control	• Patients (n=1,666) aged 6 to 59 months with ARI or SARI	VE was estimated by comparing the odds of vaccination between influenza cases and controls using logistic regression and Firth's method; estimates were adjusted for sex, age, week, chronic conditions, and region/hospital for both ARI and SARI models	• Quadrivalent inactivated influenza vaccine (IIV4) • Intranasal live attenuated egg-based vaccine	Low	Yes
Gào 2024 (17)	• Interim VE against influenza between 4 September 2024 to 25 March 2024 by age group	Yinzhou, China Trial Name: Chinese Electronic health Records Research in Yinzhou (CHERRY)	Test-negative case-control	• Cases and controls (n=205, 028) across all age groups, including 96, 298 influenza cases and 108,730 influenza-negative controls (13.4% vaccinated)	Interim VE against influenza between 4 September 2024 to 25 March 2024 by age group was estimated by univariate and multivariate logistic regression for the IVE calculation; the multivariate model was adjusted for age, gender, calendar month of specimen collection, hospitalization status, and presence of chronic comorbidity	• Trivalent inactivated influenza vaccine (IIV3) • Quadrivalent inactivated influenza vaccine (IIV4) • Trivalent live attenuated vaccine (LAIV3)	Moderate	Yes
Mi 2024 (36)	• VE against influenza infection between 1 January and 7 April 2024 by age group	Ili, Xinjiang, China Trial Name: Not reported	Test-negative case-control	• 1,094 patients across all age groups (six months and older) were laboratory tested with nasopharyngeal specimens for influenza virus	VE against influenza infection by influenza type between 1 January to 7 April 2024 at four sentinel hospitals was estimated by using Bayesian logistic regression models, adjusted for age, gender, ethnicity, calendar year, and time interval, to compare	• Not specified	Moderate	No

Reference and author year with URL	Research question addressed	Geographical location and trial name	Design	Population (add age of population)	Analysis	Type of vaccine	Risk of bias	Included in meta-analysis
					vaccination amongst patients who tested positive (case patients) and negative (control patients) for influenza			
Domnich 2024 (27)	• VE against influenza between October 2023 and April 2024 by age group	Genoa, Italy Trial Name: Not reported	Test-negative case-control	• Patients (n=1664) ages 18 years and older at the San Martino Hospital were tested (RT-PCR) for influenza infection within five days of hospital referral	VE against influenza among patients was measured between 16 October 2023 and 14 April 2024 using logistic regression modelling, adjusted for age, sex, previous season vaccination, calendar week, and presence of comorbidities; vaccination amongst patients who tested positive for influenza (case patients) were compared to patients who tested negative for influenza (control patients)	• Quadrivalent inactivated influenza vaccine (IIV4)	Moderate	Yes
Zeno 2024 (28)	• VE against influenza in Southern hemisphere countries between March and July 2024 by age group and comorbidities	Argentina, Brazil, Chile, Paraguay, Uruguay Trial Name: 1) The Pan American Health Organization (PAHO) Network for the Evaluation of Vaccine Effectiveness in Latin America 2) Caribbean – influenza (Red para la Evaluación de Vacunas en Latino América y el Caribe – influenza [REVELAC-i]	Test-negative case-control	• Patients (n=11,751) 6 months and older with SARI from 2,535 hospitals in the target countries were identified through the SARInet Plus between 13 March 2024 and 19 July 2024 and tested for influenza using RT-PCR testing • VE against influenza-associated hospitalization was measured by comparing patients who tested positive for influenza (case patients) with patients who tested negative (control patients) for influenza and SARS-CoV-2	Interim VE was measured by comparing the odds of influenza vaccination between patients who tested positive for influenza (case patients) and patients who tested negative (control patients) for influenza and SARS-CoV-2 using multivariable logistic regression, adjusted for sex, age, country, week of symptom onset, and presence of at least one comorbidity	• Trivalent inactivated influenza vaccine (IIV3) • Quadrivalent inactivated influenza vaccine (IIV4) • Trivalent live attenuated vaccine (LAIV3)	Moderate	Yes

Reference and author year with URL	Research question addressed	Geographical location and trial name	Design	Population (add age of population)	Analysis	Type of vaccine	Risk of bias	Included in meta-analysis
Maurel 2024 (15)	• VE against medically attended acute respiratory illness (MAARI) (primary care by age group and hospitalization)	Europe Trial Name: 1) I-MOVE (Influenza – Monitoring Vaccine Effectiveness in Europe) 2) ECDC Vaccine Effectiveness, Burden and Impact Studies (VEBIS)	Test-negative case-control	• A total of 12,036 patients were collected between September 2024 to January 2024	VE was estimated using multivariate logistic regression models, adjusted for sex, age, presence of chronic conditions, and onset date	• Quadrivalent	Moderate	Yes
Skowronski 2024 (7)	• VE against MAARI and influenza-like illness	Canada Trial Name: Canadian Sentinel Practitioner Surveillance Network (SPSN)	Test-negative case-control	• 3,139 specimens were eligible for inclusion; 766 (24%) tested positive for influenza • 3,095 participants were included in the influenza A analysis; 722 (23%) tested positive for influenza A. 823 (27%) were vaccinated against influenza; 115 (16%) vaccinated individuals tested positive for influenza A, the remaining 708 (30%) were influenza controls	VE was calculated using the formula 1 – OR x 100%, adjusted for age group, province, and calendar time; Firth's penalized logistic regression was additionally used	• Egg-based inactivated vaccines	Moderate	Yes
Rigamonti 2024 (11)	• VE against influenza/influenza-like illness	Italy Trial name: Not reported	Retrospective observational cohort study	• A total of 65,545 children were included in the study for the 2022/23 season and 72,377 children were included in the study for the 2023/24 influenza season • 125,142 children were unvaccinated, 5,270 were exposed to LAIV-4, and 7,510 were exposed to IIV • A total of 6,003 and 6,777 children were vaccinated for	Mixed-effect Cox proportional-hazards model with VE calculated as VE = (1 – HR) x 100, which was adjusted for covariates (sex, age at the start of each influenza season, Italian region of birth, deprivation index, influenza vaccination status, number of influenza/influenza-like illness episodes, antibiotic therapies, primary care visits, and comorbidities)	• Quadrivalent inactivated influenza vaccine (IIV4) • Quadrivalent live attenuated influenza vaccine (LAIV-4)	Moderate	Yes

Reference and author year with URL	Research question addressed	Geographical location and trial name	Design	Population (add age of population)	Analysis	Type of vaccine	Risk of bias	Included in meta-analysis
				influenza in the 2022/23 and 2023/24 seasons, respectively • Children were aged 2 to 14				
Lee 2024 (10)	• Influenza VE against hospitalization	Hong Kong Trial name: Not reported	Test-negative	• 4,367 children aged 9 months to 17 years, 709 (16%) tested positive for influenza. • There were 2,311 children who reported receipt of influenza vaccination, including 2,247 (97%) who received quadrivalent inactivated influenza, vaccine and 51 (2%) that received quadrivalent live attenuated vaccine • Of the remaining 13 children, 8 received a trivalent vaccine and 5 received an unknown vaccination type • Children were aged 9 months to 17 years old	VE was estimated as (1 – OR) x 100 among vaccinated vs. unvaccinated persons from logistic regression models, and adjusted for covariates (age, sex, prior year's vaccination status, and presence of underlying conditions)	• Trivalent inactivated influenza vaccine (IIV3) • Quadrivalent inactivated influenza vaccine (IIV4) • Quadrivalent live attenuated vaccine	Moderate	Yes
Yaron 2025 (41)	• VE of high dose versus standard dose influenza vaccines against hospitalization	Israel Trial name: Not reported	Retrospective cohort	• 8,063 participants received the high dose vaccine in the 2023/24 season and were matched with 377,126 participants who received the standard dose vaccine in the 2023/24 season	Calculated VE using a 1:1 matching analysis	• Trivalent inactivated influenza vaccine (IIV3) • Quadrivalent inactivated influenza vaccine (IIV4) • Trivalent live attenuated vaccine (LAIV3)	Moderate	No
Gharpure 2025 (13)	• Evaluate VE against hospitalization and ICU admission for	Argentina, Australia, Brazil, Chile, New Zealand,	Test-negative design	• Data was analyzed from 12,609 patients; 4,388 (34.8%) were	A logistic regression model adjusted for age group, sex, underlying conditions, and week of symptom onset was	• Trivalent inactivated influenza	Moderate	Yes

Reference and author year with URL	Research question addressed	Geographical location and trial name	Design	Population (add age of population)	Analysis	Type of vaccine	Risk of bias	Included in meta-analysis
	severe acute respiratory infection	Paraguay, Thailand, and Uruguay Trial name: Not reported		influenza-positive and 8,221 (65.2%) were influenza-negative • 672 (15.3%) of cases and 2,858 (34.8%) of controls had received the influenza vaccine • Age 1 year and older	used; VE was calculated as (1 – OR) x 100%	vaccine (IIV3) • Quadrivalent inactivated influenza vaccine (IIV4)		
Separovic 2025 (31)	• VE of influenza VE against ARI	Canada Trial name: Canadian Sentinel Practitioner Surveillance Network (SPSN)	Test-negative design	• 4,421 participants were included; 609 (14%) were positive for Influenza A and 3,812 (86%) were controls • 1,004 (23%) of participants were vaccinated for influenza including 101 (17%) cases and 903 (24%) controls)	No analysis section provided	• Variety of inactivated, egg based, cell based	Moderate	Yes
Choi 2025 (20)	• Estimate influenza VE against infection, hospitalization, and ICU admission	Hospitals in South Korea Trial name: Not reported	Retrospective case-control	• 3,390 participants were included; 1,695 (50%) were influenza positive and 1,695 (50%) were influenza negative • 1,294 participants were vaccinated including 610 (36.0%) of the influenza-positive participants and 684 (40.4%) of the influenza-negative participants • Age ≥18 years	VE was calculated using logistic regression analysis adjusted for age, sex, and comorbidities	• Quadrivalent inactivated influenza vaccine (IIV4)	Moderate	Yes
Zhu 2025 (25)	• Estimate the effectiveness of the influenza vaccine against medically attended acute respiratory inllness	China Trial name: Not reported	Test-negative case-control	• A total of 27,670 patients were involved in this study • 16,540 patients were included in the 2023/24 season; 7,378 (66.3%) tested positive for influenza and 9, 162 (55.4%) tested negative • Participants were age 6 months to 17 years	VE was calculated using one minus odds ratio; an unconditional logistic regression model was used; covariates age, sex, and calendar month were accounted for	• Trivalent inactivated influenza vaccine (IIV3) • Quadrivalent inactivated influenza vaccine (IIV4) • Trivalent live attenuated vaccine (LAIV3)	Moderate	Yes

Reference and author year with URL	Research question addressed	Geographical location and trial name	Design	Population (add age of population)	Analysis	Type of vaccine	Risk of bias	Included in meta-analysis
Chung 2025 (21)	• Estimate VE against medically attended illness	United States Trial name: US Flu VE Network	Test-negative case-control	• A total of 9,061 participants were recruited; 6,629 were included in the final analysis Of the 6,629 included participants 1,780 (27%) were influenza-positive; 806 (45%) were positive for influenza A(H1N1)pdm09, 567 (32%) tested positive for influenza B/Victoria, 328 (18%) tested positive for influenza A(H3N2), 104 (6%) tested positive for Influenza A with undetermined subtype • 2,432 (37%) of participants were vaccinated against influenza • Participants were aged 8 months or older	VE was calculated using one minus odds ratio; odds ratio was estimated using logistic regression models adjusted for site, age, health condition, and month of onset	• Quadrivalent inactivated influenza vaccine (IIV4) • Other (egg-based, cell culture-based, or recombinant-based vaccines)	Moderate	Yes
Martínez-Baz 2025 (23)	• Estimate VE in preventing medical consultations and hospitalizations	Northern Spain Trial name: Not reported	Test-negative case-control	• Data from 3550 participants was collected from November 2023 to March 2024; 3,133 (88%) were hospitalized and 417 (12%) were treated in primary care centres • 529 (17%) of hospitalized patients were influenza positive, and 2,604 were influenza-negative (83%) • 314 (59%) of hospitalized cases were vaccinated in the current season and 53 (10%) were vaccinated in previous seasons but not the current one; 1,674 (64%) hospitalized controls were vaccinated in the current season • 146 (35%) of outpatients were influenza positive and 271 (65%) were influenza-negative • 18 (12%) of outpatient cases and 68 (25%) of outpatient	VE was calculated using one minus odds ratio; logistic regression was used to calculate the odds ratio and adjusted for sex, age, presence of chronic condition, nursing home residence, and month of sample collection	• Quadrivalent inactivated influenza vaccine (IIV4) • Other (quadrivalent live attenuated vaccine; cell culture vaccine)	Moderate	Yes

Reference and author year with URL	Research question addressed	Geographical location and trial name	Design	Population (add age of population)	Analysis	Type of vaccine	Risk of bias	Included in meta-analysis
				controls were vaccinated in the current season • Participants were all ages				
Zhang 2025 (40)	• VE against influenza A(H1N1)pdm09, A (H3N2) and influenza B (Victoria)	China Trial-name: Not reported	Test-negative case-control	• 18,665 individuals (all ages) with influenza-like illness between October 2023 to March 2024 participated in the study; the interval from influenza vaccination to onset of symptoms was ≥14 days, and samples were taken within seven days of symptom onset • Influenza positive and negative participants were identified using virological surveillance at 39 sentinel hospitals • 6,362 (34.1%) participants tested positive for influenza with 3,396 (53.38%) being infected with influenza A (H3N2) and 2,877 (45.22%) being infected with influenza B (Victoria); 83 (1.30%) were infected with A(H1N1)pdm09 and 6(0.10%) had mixed infection with influenza viruses • 342 (5.4%) of influenza positive patients and 1,291 (10.5%) influenza negative patients were vaccinated • All ages	VE was estimated using multivariate logistic regression models, adjusted for age, gender, region, month of onset, and chronic conditions	• Not reported	Moderate	No
Lei 2025 (22)	• VE against influenza infection	China Trial name: Not reported	Test-negative case-control	• Of the 157,291 patients (six months or older) with influenza-like illness who were tested between 1 October 2023 and 31 March 2024, 32,611 patients tested positive for influenza A, 24,030 tested positive for influenza B, and 63 had influenza A and B coinfections;	VE was calculated as (1 – OR) x 100%; OR was estimated using multivariate logistic regression models that were adjusted for age, sex, influenza detection methods, and testing timing	• Trivalent inactivated influenza vaccine (IIV3) • Quadrivalent inactivated influenza	Moderate	Yes

Reference and author year with URL	Research question addressed	Geographical location and trial name	Design	Population (add age of population)	Analysis	Type of vaccine	Risk of bias	Included in meta-analysis
				overall influenza positivity rate was 36% • Overall 11,148 (7.1%) participants were vaccinated against influenza including 8,603 (8.6%) influenza-negative participants, 1,473 (4.5%) influenza A participants 1,065 (4.4%) influenza B participants, and 7 (11.1%) participants with coinfections • All ages		vaccine (IIV4) • Trivalent live attenuated vaccine (LAIV3)		
Tenforde 2024 (12)	• VE against influenza-associated medical encounters	United States Trial name: Virtual Severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2], Influenza, and Other respiratory viruses Network (VISION)	Test-negative case-control	• 70,307 hospitalizations and 271,299 emergency department (ED)/urgent care (UC) encounters were analyzed • 340 (9.8%) of the 3,479 ARI-associated hospitalizations in children and adolescents were positive influenza patients; 1,270 (36.5%) of hospitalized pediatric patients were vaccinated against influenza (18.5% of cases and 38.5% of controls) • 17,493 (24.8%) of the 70,521 ARI-associated ED/UC encounters in children and adolescents tested positive for influenza; 19,728 (28.0%) were vaccinated against influenza (15.4% of cases and 32.1% of controls) • 5,721 (8.6%) of the 66,828 ARI-associated hospitalizations in adults were influenza positive; 32,455 (48.6%) were vaccinated (35.1% cases and 49.8% controls) • 40,893 (20.4%) of the 200,778 ARI-associated ED/UC	Logistic regression models adjusted for site, calendar day, age, sex, and race/ethnicity were used; VE was calculated as (1 – adjusted odds ratio) x 100	• Trivalent inactivated influenza vaccine (IIV3) • Trivalent live attenuated vaccine (LAIV3) • Other (cell-based/recombinant or adjuvanted influenza vaccines)	Moderate	Yes

Reference and author year with URL	Research question addressed	Geographical location and trial name	Design	Population (add age of population)	Analysis	Type of vaccine	Risk of bias	Included in meta-analysis
				encounters in adults were also positive cases; 76,988 (38.3%) were vaccinated against influenza (23.5% cases vs. 42.1% controls) • Age 6 months and up				
Marron 2024 (26)	• VE against MAARI	Ireland Trial name: Vaccine Effectiveness Burden and Impact Studies (VEBIS) network	Test-negative case-control	• 2,399 patients were included in the 2023/24 dataset, 567 (24%) were influenza-positive and 1,832 (76%) were influenza-negative • 26.1% of controls were vaccinated compared to 16.9% of cases • Included ages 2 and older	Multivariable logistic regression adjusted for age, time of symptom onset, sex, and presence of a chronic condition were used to estimated adjusted odds ratios (aOR); VE was calculated using the following equation: VE = (1 – aOR) x 100	• Live attenuated influenza vaccine (Fluenz Tetra) • Quadrivalent inactivated influenza vaccine (IIV4), Influvac tetra	Moderate	Yes
Tian 2024 (24)	• Incidence rate and odds of influenza-like illness among vaccinated versus unvaccinated healthcare workers	China Trial name: Not reported	Prospective observational study	• 100 participants were included; 50 (50%) were vaccinated and 50 (50%) were unvaccinated • Included ages 20 to 60	Single-factor or multi-factor logistic regression adjusted for vaccination, age, and staff type	• Quadrivalent inactivated influenza vaccine (IIV4)	Moderate	Yes
Blanquart 2025 (32)	• VE against influenza infection	France Trial name: Not reported	Test-negative design	• 59,472 patients presented at RELAB community laboratories; 44,420 were influenza-negative and 15,052 were influenza-positive • Among influenza-negative patients 10,875 (24%) were vaccinated; among influenza-positive patients, 1,916 (13%) were vaccinated • All ages were included	A logistic (binomial) linear model was fitted to the test result as a function of sex, age category, PCR technique, week, and vaccination status; VE was estimated using the odds ratio of the vaccine effect on testing positive for influenza	• Quadrivalent inactivated influenza vaccine (IIV4)	Moderate	Yes
Sun 2025 (29)	• VE against influenza infection	China Trial name: Not reported	Test-negative design	• 8,775 patients were included; 6,741 (76.8%) were influenza-negative and 2,034 (23.2%) were influenza-positive • Of 8,442 patients with available immunization information, 6.2%	Logistic regression was used to estimate odds ratios for vaccination status; VE was calculated with the following formula: (1 – OR) x 100%	• Trivalent inactivated influenza vaccine (IIV3)	Moderate	Yes

Reference and author year with URL	Research question addressed	Geographical location and trial name	Design	Population (add age of population)	Analysis	Type of vaccine	Risk of bias	Included in meta-analysis
				of cases (124/1,998) and 15.5% (1,000/6,444) were vaccinated against influenza • All ages were included		• Quadrivalent inactivated influenza vaccine (IIV4)		
Rose 2025 (30)	• VE against MAARI and influenza-like illness	Denmark, the United Kingdom, the European Union, Northern Ireland, Scotland Trial/network name: U-PC (European Union VEBIS primary care network)	Test-negative case-control	• Participants presenting with influenza-like illness or ARI had specimens collected • Vaccinated participants were defined as having received the 2024/25 influenza vaccine at least 14 days before symptom onset • Number of participants was not reported • All ages	VE was calculated using the formula (1 – OR) x 100; logistic regression adjusted for measured potential cofounding variables was used	• Trivalent inactivated influenza virus (IIV3) • Quadrivalent inactivated influenza virus (IIV4)	Low	Yes
Martinez 2024 (39)	• Relationship between influenza vaccination and ICU admission or death for individuals hospitalized by influenza infection, measured by hazard ratios (HR)	Spain Trial name: not reported	Retrospective observational	• 238 patients; 101 (42.4%) were vaccinated • No age restrictions were indicated; mean age of patients was 72.89 ± 14.61 years	Cox regression adjusted for age, sex, cardiovascular disease, renal disease, and influenza vaccination status was used to examine the association between hospitalization for influenza and admission to the ICU and/or death for vaccinated/unvaccinated participants; Kaplan Meier survival analysis and log-rank test were additionally performed	• Not reported	Serious	No

Table 2: Pooled effectiveness of influenza vaccination against medically attended acute respiratory illness (MAARI) and hospitalization across all age groups during 2023/24 season

Virus type or subtype/outcome/season timing	Pooled meta-analysis			Heterogeneity		
	No. of cohorts	VE% (95% CI)	p value	Tau^2	p value	I^2
Any type						
MAARI						
Early season	2	53% (41,62)	<0.001	0.03	<0.001	98
Mid-season	6	54% (49,59)	<0.001	0.00	0.61	0
End season	13	45% (40,50)	<0.001	0.01	<0.001	73
Hospitalization						
Early season	4	54% (37,66)	<0.001	0.08	<0.001	84
Mid-season	9	47% (39,54)	<0.001	0.03	<0.001	66
End season	11	45% (37,53)	<0.001	0.02	0.03	50
ICU						
Early season	4	55% (35,69)	<0.001	0.09	0.04	63
End season	1	55% (–16,83)	0.10	0.00	1.00	0
Death						
Early season	1	50% (29,65)	<0.001	0.00	1.00	0
End season	–	–	–	–	–	–
Influenza A						
MAARI						
Early season	3	40% (31,48)	<0.001	0.01	<0.001	93
Mid–season	3	53% (45,60)	<0.001	0.00	0.30	17
End season	10	34% (28,40)	<0.001	0.01	<0.001	68
Hospitalization						
Early season	3	39% (32,46)	<0.001	0.00	0.31	15
Mid-season	1	38% (26,48)	<0.001	0.00	1.00	0
End season	11	39% (34,45)	<0.001	0.00	0.47	0
Influenza A(H1N1)						
MAARI						
Early season	–	–	–	–	–	–
Mid-season	6	57% (51,63)	<0.001	0.00	0.44	0
End season	4	47% (14,67)	0.01	0.16	0.01	72
Hospitalization						
Early season	1	52% (34,65)	<0.001	0.00	1.00	0
Mid-season	6	50% (37,60)	<0.001	0.03	0.14	40
End season	6	44% (35,52)	<0.001	0.00	0.68	0
Influenza A(H3N2)						
MAARI						
Early season	–	–	–	–	–	–

Virus type or subtype/outcome/season timing	Pooled meta-analysis			Heterogeneity		
	No. of cohorts	VE% (95% CI)	p value	Tau^2	p value	I^2
Mid-season	5	43% (30,54)	<0.001	0.00	0.70	0
End season	3	28% (11,42)	<0.001	0.00	0.95	0
Hospitalization						
Early season	1	72% (48,84)	<0.001	0.00	1.00	0
Mid-season	7	48% (25,65)	<0.001	0.14	0.02	59
End season	4	38% (27,48)	<0.001	0.00	0.37	4
Influenza B						
MAARI						
Early season	3	63% (33,79)	<0.001	0.26	<0.001	98
Mid-season	–	–	–	–	–	–
End season	7	58% (51,63)	<0.001	0.02	<0.001	80
Hospitalization						
Early season	3	74% (55,85)	<0.001	0.10	0.17	43
Mid-season	–	–	–	–	–	–
End season	3	62% (50,71)	<0.001	0.00	<0.001	0

Table 3: Pooled effectiveness of influenza vaccination against medically attended acute respiratory illness (MAARI) and hospitalization across all age groups during 2024/25 season

Virus type or subtype/outcome/season timing	Pooled meta-analysis			Heterogeneity		
	No. of cohorts	VE% (95% CI)	p value	Tau^2	p value	I^2
Any type						
MAARI						
Early season	–	–	–	–	–	–
Mid-season	6	48% (44,53)	<0.001	0.002	0.28	21
End season	6	50% (42,57)	<0.001	0.02	<0.001	89
Hospitalization						
Early season	–	–	–	–	–	–
Mid-season	5	49% (39,57)	<0.001	0.03	<0.001	87
End season	4	56% (43,66)	<0.001	0.04	0.01	73
Influenza A						
MAARI						
Early season	–	–	–	–	–	–
Mid-season	8	49% (39,57)	<0.001	0.03	0.02	58
End season	6	47% (35,57)	<0.001	0.06	<0.001	94
Hospitalization						
Early season	–	–	–	–	–	–
Mid-season	6	49% (42,55)	<0.001	0.00	0.74	0
End season	4	56% (43,66)	<0.001	0.04	0.01	73

Virus type or subtype/outcome/season timing	Pooled meta-analysis			Heterogeneity		
	No. of cohorts	VE% (95% CI)	p value	Tau^2	p value	I^2
Influenza A(H1N1)						
MAARI						
Early season	–	–	–	–	–	–
Mid-season	5	505 (38,60)	<0.001	0.04	0.003	74
End season	3	59% (31,75)	<0.001	0.13	0.06	65
Hospitalization						
Early season	–	–	–	–	–	–
Mid-season	3	50% (43,56)	<0.001	0.00	0.634	0
End season	2	52% (22,71)	<0.001	0.01	0.29	10
Influenza A(H3N2)						
MAARI						
Early season	–	–	–	–	–	–
Mid-season	4	47% (34,57)	<0.001	0.00	0.72	0
End season	3	32% (15,46)	<0.001	0.00	0.44	0
Hospitalization						
Early season	–	–	–	–	–	–
Mid-season	3	37% (10,56)	0.01	0.00	0.832	0
End season	2	52% (30,67)	<0.001	0.00	0.84	0
Influenza B						
MAARI						
Early season	–	–	–	–	–	–
Mid-season	3	66% (54,75)	<0.001	0.006	0.34	9
End season	1	75% (65,82)	<0.001	0.00	1.00	0
Hospitalization						
Early season	4	76% (67,83)	<0.001	0.00	0.764	0
Mid-season	4	76% (67,83)	<0.001	0.00	0.764	0
End season	–	–	–	–	–	–

Table 4: Subgroup analysis of pooled effectiveness of influenza vaccination against medically attended acute respiratory illness by virus type during mid-season 2023/24 (between 1 October 2023 and 31 January 2024)

Virus type/subtype	Age groups	No. of cohorts	Pooled VE% (95% CI)	p value for pooled VE	Tau^2 (within)	Tau^2 (between)	Q value	df	p value	
Any type	<18 years	8	65% (54,73)	<0.001	0.05					
	18–64 years	8	51% (44,56)	<0.001	0.00	0.02	5.25	2	0.072	
	≥65 years	8	55% (45,63)	<0.001	0.01					
Influenza A	<18 years	7	65% (52,74)	<0.001	0.08					

	18–64 years	7	49% (42,56)	<0.001	0.00	0.03	4.74	2	0.094	
	≥65 years	7	56% (43,65)	<0.001	0.02					
Influenza A(H1N1)	<18 years	4	67% (39,82)	<0.001	0.26					
	18–64 years	3	53% (39,64)	<0.001	0.02	0.06	1.14	2	0.566	
	≥65 years	4	58% (39,72)	<0.001	0.05					
Influenza A(H3N2)	<18 years	1	59% (18,80)	0.012	0.00					
	18–64 years	2	46% (25,61)	<0.001	0.00	0.00	0.58	2	0.749	
	≥65 years	1	44% (–5,70)	0.069	0.00					

Table 5: Subgroup analysis of pooled effectiveness of influenza vaccination against medically attended acute respiratory illness by virus type during end of season 2023/24 (between 1 October 2023 and March 31, 2024)

Virus type/subtype	Age groups	No. of cohorts	Pooled VE (95% CI)	p value for pooled VE	Tau^2 (within)	Tau^2 (between)	Q value	df	p value	
Any type	<18 years	7	52% (44,59)	<0.001	0.02					
	18–64 years	2	64% (32,81)	0.0017	0.17	0.03	8.60	2	0.014	
	≥65 years	1	28% (7,44)	0.012	0.00					
Influenza A	<18 years	3	65% (39,80)	<0.001	0.09					
	18–64 years	–	–	–	–	–	–	–	–	
	≥65 years	–	–	–	–					
Influenza A (H1N1)	<18 years	1	77% (56,88)	<0.001	0.00					
	18–64 years	–	–	–	–	–	–	–	–	
	≥65 years	–	–	–	–					
Influenza A(H3N2)	<18 years	1	18% (–3233,98)	0.916	0.00					
	18–64 years	–	–	–	–	–	–	–	–	
	≥65 years	–	–	–	–					
Influenza B	<18 years	1	56% (26,74)	0.002	0.00					
	18–64 years	–	–	–	–	–	–	–	–	
	≥65 years	–	–	–	–					

Table 6: Subgroup pooled effectiveness of influenza vaccination against hospitalization by virus type during mid-season 2023/24 (between 1 October 2023 and 31 January 2024)

Virus type/subtype	Age groups	No. of cohorts	Pooled VE (95% CI)	p value for pooled VE	Tau^2 (within)	Tau^2 (between)	Q value	df	p value	
Any type	<18 years	2	64% (54,72)	<0.001	0.00					
	18–64 years	2	46% (24,62)	<0.001	0.05	0.03	6.21	2	0.045	
	≥65 years	2	47% (32,58)	<0.001	0.02					
Influenza A	<18 years	3	71% (54,81)	<0.001	0.00					

	18–64 years	6	46% (29,60)	<0.001	0.05	0.00	7.67	2	0.022	
	≥65 years	7	43% (32,51)	<0.001	0.01					
Influenza A(H1N1)	<18 years	1	71% (44,85)	<0.001	0.00					
	18–64 years	3	49% (25,65)	<0.001	0.05	0.03	2.84	2	0.241	
	≥65 years	3	47% (32,59)	<0.001	0.00					
Influenza A(H3N2)	<18 years	2	70% (46,84)	<0.001	0.00					
	18–64 years	2	41% (–122,84)	0.437	0.65	0.13	3.13	2	0.209	
	≥65 years	3	43% (14,63)	0.007	0.07					
Influenza B	<18 years	–	–	–	–					
	18–64 years	–	–	–	–	–	–	–	–	
	≥65 years	–	–	–	–					

Table 7: Subgroup analysis of pooled effectiveness of influenza vaccination against hospitalization by virus type during end of season 2023/24 (between 1 October 2023 and March 31, 2024)

Virus type/subtype	Age groups	No. of cohorts	Pooled VE (95% CI)	p value for pooled VE	Tau^2 (within)	Tau^2 (between)	Q value	df	p value	
Any type	<18 years	5	42% (33,50)	<0.001	0.004					
	18–64 years	6	34% (25,41)	<0.001	0.00	0.00	1.95	1	0.162	
	≥65 years	–	–	–	–					
Influenza A	<18 years	6	37% (28,45)	<0.001	0.00					
	18–64 years	5	32% (24,39)	<0.001	0.00	0.00	0.67	1	0.411	
	≥65 years	–	–	–	–					
Influenza A(H1N1)	<18 years	2	29% (6,46)	0.015	0.00					
	18–64 years	2	33% (18,45)	<0.001	0.00	0.00	0.12	1	0.73	
	≥65 years	–	–	–	–					
Influenza A(H3N2)	<18 years	2	38% (17,53)	0.001	0.00					
	18–64 years	1	31% (14,44)	0.001	0.00	0.00	0.32	1	0.572	
	≥65 years	–	–	–	–					
Influenza B	<18 years	1	60% (22,79)	0.007	0.00					
	18–64 years	–	–	–	–	0.00	0.00	0	1.000	
	≥65 years	–	–	–	–					

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