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 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 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, outpatient visits, hospitalization, intensive care unit (ICU) admission, and death) across different influenza types (all types, 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 medically attended acute respiratory illness, 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 medically attended acute respiratory illness, 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 2,773 records and included 15 studies:
  - all 15 studies were test-negative case-control designs
  - nine studies were included for meta-analysis.
- The risk of bias (ROBINS-I) among 15 studies was assessed as the following:
  - low risk (n = 5)
  - moderate risk (n = 10).
- 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 age groups.

Key findings in relation to the research question

- The 15 included studies were conducted across diverse healthcare settings, including primary care and outpatient and inpatient facilities.
- The research spanned multiple geographic regions:
  - North America (United States and Canada)
  - Europe (multiple countries)
  - Asia (China, Japan, and South Korea).
- Our meta-analysis of nine studies showed that vaccine effectiveness (VE) estimates aligned with the individual study ranges of 40–60% across different healthcare settings:
  - mid-season estimates were 53% for medically attended acute respiratory illness (MAARI) and 50% for hospitalization
  - end-season estimates showed a decline (MAARI: 50%; hospitalization: 39%).
- Our meta-analysis showed age-related patterns:
  - 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:
  - influenza A:
    - mid-season: effectiveness ~50% for both MAARI and hospitalization, declined to ~37–39% by end-season
    - A(H1N1): effective (50–57%) during mid-season, maintained relatively good protection against hospitalization (37%) by end-season
    - A(H3N2): effective during mid-season (MAARI: 43%; hospitalization: 48%)
  - influenza B:
    - strong end-season effectiveness (MAARI: 63%; hospitalization: 60%)
    - limited mid-season data available.
- No studies were identified that evaluated VE in individuals with immunocompromising conditions, such as solid organ transplant recipients. Additionally, no studies assessed VE against severe outcomes like ICU admission or death.

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.

Box 1: Approach and supporting materials

We retrieved candidate studies by searching: 1) Medline; 2) Embase via OVID; 3) Preprint Citation Index (e.g., bioRiv, 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 1 January 2023 and 9 October 2024. 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, and 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. A PRISMA flow diagram is 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.

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 (medically attended acute respiratory illness, outpatient visits, hospitalization, ICU admission, and death) across different influenza types (all types, 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?

Our secondary research questions were:

1) What is the effectiveness of trivalent and quadrivalent influenza vaccines in preventing medically attended acute respiratory illness, 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 medically attended acute respiratory illness, 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 2,773 articles, and after removing 205 duplicates, we screened 2,568 titles and abstracts. We reviewed 133 full-text articles and included 15 single studies:

- All 15 studies were test-negative case-control studies and conducted across diverse healthcare settings, including primary care and outpatient and inpatient facilities.
- The 15 studies spanned multiple geographic regions:
  - North America (United States and Canada)
  - Europe (multiple countries)
  - Asia (China, Japan, and South Korea).
- Ten studies address the research questions about effectiveness and were included in the meta-analysis.

The risk of bias in the included studies was moderate in 10 studies and low in five studies.

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

Overall vaccine effectiveness

Mid-season effectiveness

Four studies evaluated VE against MAARI in outpatient and primary-care settings during mid-season (7-10). An analysis of eight cohorts demonstrated an overall VE of 53% (95% CI: 48–57, p<0.001) against medically attended acute respiratory illness during mid-season, with no heterogeneity (I^2 = 3.26%, Tau^2 = 0.00, p = 0.405) (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.

Two studies evaluated VE against hospitalization in inpatient settings during mid-season.(9; 10) For hospitalization outcomes during mid-season, the overall VE was 50% (95% CI: 41–57, p<0.001) across seven cohorts, with substantial heterogeneity (I^2 = 71%, Tau^2 = 0.03, p<0.002). 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

Four studies evaluated VE against MAARI in outpatient and primary care settings during the end of the 2023/24 season.(11-14) By end-season, analysis of seven cohorts showed an overall VE of 50% (95% CI: 47–52, p<0.001) against MAARI, with moderate heterogeneity (I^2 = 52%, p = 0.054). 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 4). 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.

Five studies evaluated VE against hospitalization in inpatient settings during the end of the 2023/24 season.(11; 13-16) For hospitalization outcomes during end-season, the overall VE was 39% (95% CI: 32–45, p<0.001) across eight cohorts, with low heterogeneity (I^2 = 24%, p = 0.234). 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 6).

Influenza subtype analysis

Influenza A

Mid-season effectiveness

Mid-season VE against influenza A was 54% (95% CI: 48–59, p<0.001) across nine cohorts for MAARI outcomes, with no heterogeneity (I^2 = 0%, p = 0.695) (Table 2). 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 3). For hospitalization outcomes, VE against influenza A was similar at 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).

End-season effectiveness

By end-season, the overall VE against influenza A for MAARI decreased to 39% (95% CI: 33–44, p<0.001) across eight cohorts, with substantial heterogeneity (I^2 = 71%, p = 0.001) (Table 2). There were insufficient data for the age-stratified analysis. For hospitalization outcomes, end-season VE against influenza A was 37% (95% CI: 31–41, p<0.001) across nine cohorts, with no heterogeneity (I^2 = 0%, p = 0.953). 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

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 (six cohorts). End-season VE remained high for MAARI at 77% (95% CI: 56–88, p<0.001, one cohort) but decreased for hospitalization to 37% (95% CI: 23–49, p<0.001, three cohorts) (Table 2).

Influenza A/H3N2 subtype

Mid-season VE against influenza A/H3N2 was 43% (95% CI: 30–54, p<0.001) for MAARI (five cohorts) and 48% (95% CI: 25–65, p<0.001) for hospitalization (seven cohorts) (Table 2).

Influenza B

Mid-season data for influenza B were not available. End-season VE against influenza B was 63% (95% CI: 57–68, p<0.001) for MAARI (six cohorts) and 60% (95% CI: 45–72, p<0.001) for hospitalization (two cohorts) (Table 2).

Out of 15 included studies, five were excluded from the meta-analysis (17-21): three did not provide specific vaccine information,(18-20) and two did not differentiate between inpatient and outpatient data.(17; 21) No studies were identified that evaluated VE in individuals with immunocompromising conditions, such as solid organ transplant recipients. Additionally, we found no studies assessing VE against severe outcomes like ICU admission or death.

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.
- 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.
- 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 (author year), with URL	Research question addressed	Geographical location	Design	Population	Analysis	Type of vaccine	Risk of Bias	Included in meta-analysis
Lei 2024	• Vaccine effectiveness (VE) against hospital-attended influenza infection • VE by vaccine type (IIV3, IIV4, LAIV3), influenza type (A and B), age group, and vaccination timing	China (Hangzhou)	Test-negative case-control	Patients (n = 157,291) with influenza-like illness across all age groups (from 6 months to 70+ years)	VE was estimated using multivariate logistic regression models, adjusted for sex, age, influenza detection methods, and influenza testing timing	• Trivalent inactivated influenza vaccine (IIV3) • Quadrivalent inactivated influenza vaccine (IIV4) • Trivalent live attenuated vaccine (LAIV3)	Mod-erate	Yes
Costantino 2024	• VE against influenza strain A(H1N1)pdm09 • VE against influenza strain A(H1N1)pdm09 by age group	Italy (Sicily)	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	Mod-erate	Yes
Frutos 2024	• VE against influenza-associated outpatients visits and hospitalizations by age group	United States	Test-negative case-control	Patients who received medical care in outpatient settings or in hospital for acute respiratory illness and were tested for influenza	VE was estimated to compare the odds ratio of vaccination against acute respiratory illness 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
Zhu 2024	• Interim VE against influenza between 1 October 2023 and 31 January 2024 by age group	United States (California)	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	• High-dose, adjuvanted, or recombinant vaccine	Low	No

Reference (author year), with URL	Research question addressed	Geographical location	Design	Population	Analysis	Type of vaccine	Risk of Bias	Included in meta-analysis
					positive influenza laboratory-confirmed test result (case patients) and patients who 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	• Interim VE of influenza vaccine during November to December 2023	South Korea	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	Mod-erate	No
Whitaker 2024	• Seasonal influenza VE by age group	England, Scotland, Wales	Test-negative case-control	The GB-PC study included 1,193 cases and 12,098 controls for A(H1N1)pdm09, A(H3N2), influenza A (untyped), influenza B, and 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	• VE against influenza strain A(H1N1)pdm09, influenza strain A(H3N2), and influenza strain B	Canada (Alberta)	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

Reference (author year), with URL	Research question addressed	Geographical location	Design	Population	Analysis	Type of vaccine	Risk of Bias	Included in meta-analysis
	• VE against influenza strain A(H1N1)pdm09 by age group							
Shinjoh 2024	• VE against hospitalization or influenza infection in outpatient settings • VE by age, presence of underlying disease, one dose vs. two dose regimen, influenza strain, and method of testing	Japan	Test-negative case-control	Patients (n = 1,832) aged 6 months to 15 years old presenting with fever who were tested for influenza	VE was estimated using an adjusted odds ratio formula and adjusted for sex, age, comorbidity, area, month of onset, and diagnostic methods	• Quadrivalent inactivated influenza vaccine (IIV4)	Mod-erate	Yes
Pérez-Gimeno 2024	• VE against acute respiratory illness (ARI) in primary care settings or severe acute respiratory illness (SARI) in hospital • VE by influenza type, subtype, and clade	Spain	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	• Interim VE against influenza between 4 September 2024 to 25 March 2024 by age group	China (Yinzhou)	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 VE 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)	Mod-erate	Yes
Mi 2024	• VE against influenza infection between 1	China (Ili, Xinjiang)	Test-negative case-control	1,094 patients across all age groups (6 months and older) were	VE against influenza infection by influenza type between 1	• Not specified	Mod-erate	No

Reference (author year), with URL	Research question addressed	Geographical location	Design	Population	Analysis	Type of vaccine	Risk of Bias	Included in meta-analysis
	January and 7 April 2024 by age group			laboratory tested with nasopharyngeal specimens for influenza virus	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 vaccination amongst patients who tested positive (case patients) and negative (control patients) for influenza			
Domnich 2024	• VE against influenza between October 2023 and April 2024 by age group	Italy (Genoa)	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)	Mod-erate	Yes
Zeno 2024	• VE against influenza in Southern hemisphere countries between March and July 2024 by age group and comorbidities	Argentina, Brazil, Chile, Paraguay, Uruguay	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)	Mod-erate	Yes

Reference (author year), with URL	Research question addressed	Geographical location	Design	Population	Analysis	Type of vaccine	Risk of Bias	Included in meta-analysis
Maurel 2024	• VE against medically attended acute respiratory illness (primary care) by age group and hospitalization	Europe	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		
Skowronski 2024	• VE against medically attended acute respiratory illness and influenza like illness	Canada	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, and 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	Mod-erate	Yes

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

Virus type	Pooled meta-analysis			Heterogeneity		
	No. of cohorts	VE (%)	p value	Tau^2	p value	I^2
Any type						
MAARI						
Mid-season	8	53 (48,57)	<0.001	0.00	0.404	3.26
End season	7	50 (47,52)	<0.001	0.002	0.054	52
Hospitalization						
Mid-season	7	50 (41,57)	<0.001	0.03	<0.002	71
End season	8	39 (32,45)	<0.001	0.005	0.234	24
Influenza A						
MAARI						
Mid-season	9	54 (48,59)	<0.001	0.01	0.695	0
End season	8	39 (33,44)	<0.001	0.006	0.001	71

Virus type	Pooled meta-analysis			Heterogeneity		
	No. of cohorts	VE (%)	p value	Tau^2	p value	I^2
Hospitalization						
Mid-season	14	47 (38,55)	<0.001	0.04	0.030	46
End season	9	37 (31,41)	<0.001	0.00	0.953	0
Influenza A/H1N1						
MAARI						
Mid-season	6	57 (51,63)	<0.001	0.00	0.435	0
End season	1	77 (56,88)	<0.001	0.00	1.000	0
Hospitalization						
Mid-season	6	50 (37,60)	<0.001	0.03	0.136	40
End season	3	37 (23,49)	<0.001	0.00	0.770	0
Influenza A/H3N2						
MAARI						
Mid-season	5	43 (30,54)	<0.001	0.00	0.552	0
End season	1	18 (–3233, 98)	0.916	0.00	1.000	0
Hospitalization						
Mid-season	7	48 (25,65)	<0.001	0.14	0.024	59
End season	2	36 (26,45)	<0.001	0.00	0.611	0
Influenza B						
MAARI						
Mid-season	–	–	–	–	–	–
End season	6	63 (57,68)	<0.001	0.02	<0.001	88
Hospitalization						
Mid-season	–	–	–	–	–	–
End season	2	60 (45,72)	<0.001	0.00	0.974	0

Table 3: 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	Age groups	No. of cohorts	Pooled VE (%)	p value for pooled VE	Tau² (within)	Tau² (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				
	<18 years	7	65 (52,74)	<0.001	0.08				
Influenza A	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				
	<18 years	4	67 (39,82)	<0.001	0.26				
Influenza A/H1N1	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				
Influenza B	<18 years	–	–	–	–				
	18–64 years	–	–	–	–	–	–	–	–
	≥65 years	–	–	–	–				

Table 4: 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	Age groups	No. of cohorts	Pooled VE (%)	p value for pooled VE	Tau² (within)	Tau² (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				
	<18 years	3	65 (39,80)	<0.001	0.09				
Influenza A	18–64 years	–	–	–	–	–	–	–	–
	≥65 years	–	–	–	–				
	<18 years	1	77 (56,88)	<0.001	0.00				
Influenza A/H1N1	18–64 years	–	–	–	–	–	–	–	–
	≥65 years	–	–	–	–				

Virus type	Age groups	No. of cohorts	Pooled VE (%)	p value for pooled VE	Tau² (within)	Tau² (between)	Q value	df	p value
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 5: Subgroup analysis of 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	Age groups	No. of cohorts	Pooled VE (%)	p value for pooled VE	Tau² (within)	Tau² (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				
	<18 years	3	71 (54,81)	<0.001	0.00				
Influenza A	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				
	<18 years	1	71 (44,85)	<0.001	0.00				
Influenza A/H1N1	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 6: Subgroup analysis of pooled effectiveness of influenza vaccination against hospitalization by virus type during end of season 2023/24 (between 1 October 2023 and 31 March 2024)

Virus type	Age groups	No. of cohorts	Pooled VE (%)	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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