JAMA Network Open

Research Letter | Infectious Diseases

Influenza Vaccine Effectiveness, 2004 to 2024
A Meta-Analysis

Matthew D. Wolpert, MD; Yuanyuan Liang, PhD; Meagan C. Fitzpatrick, PhD; Justin R. Ortiz, MD

Introduction

Since 2004, the US Centers for Disease Control and Prevention (CDC) has estimated seasonal influenza vaccine effectiveness (VE) through the US Influenza Vaccine Effectiveness (Flu VE) Network, a coordinated network of observational studies of medically attended influenza.[1] Influenza VE is often described as 40% to 60% when vaccine strains are well matched to circulating viruses.[2-4] This qualified range is a widely used benchmark for expected vaccine performance. However, restricting expectations to biologically favorable conditions may not reflect typical year-to-year performance. We therefore evaluated whether the 40% to 60% heuristic accurately reflects influenza vaccine performance across historical US seasonal conditions represented in the Flu VE Network.

Methods

We conducted a meta-analysis of all overall, end-of-season VE estimates generated by the Flu VE Network, indexed by CDC,[5] and reported in peer-reviewed publications for the 2004 to 2005 through 2023 to 2024 influenza seasons, covering all ages and any influenza type and subtype (eTable in Supplement 1). We followed applicable Meta-Analysis of Observational Studies in Epidemiology (MOOSE) reporting guideline and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines. Multiseason analyses of Flu VE Network data are well established.[6] Because the evidence set was the complete series of network end-of-season reports, no database search was performed. M.D.W. and J.R.O. abstracted the data independently, and Y.L. verified it. We abstracted VE estimates with 95% CIs, predominant circulating virus type and subtype, and antigenic mismatch. A season was classified as mismatched when authors reported antigenic differences between circulating viruses and at least 1 vaccine component, including differences related to egg adaptation. All used the network's standardized test-negative design; formal quality scoring was not performed given the single-source design.

We pooled VE estimates using a random-effects inverse-variance model, following previously described methods.[7] Between-season heterogeneity was assessed using Cochran Q test and the I^2 statistic. We calculated 95% CIs for pooled VE estimates and 95% prediction intervals (PIs) to quantify the expected range of VE in a future season. A 95% CI or PI excluding 0 was considered evidence that VE differed significantly from 0. In subgroup analyses, we pooled VE for seasons with and without reported antigenic mismatch and tested the difference between subgroups. All statistical tests were 2-sided with a significance level of .05. Analyses were performed using Stata/SE version 19.0 (StataCorp). The University of Maryland, Baltimore institutional review board (IRB) determined that this project did not meet the definition of human participants research and did not require IRB review; consent was not applicable. Further methods are in the eMethods in Supplement 1.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Open Access. This is an open access article distributed under the terms of the CC-BY-NC-ND License, which does not permit alteration or commercial use, including those for text and data mining, AI training, and similar technologies.

jamanetwork/2026/jno/11_10_2026/zld260275 PAGE: 1 SESS: 14 OUTPUT: Oct 13 19:59 2026

Results

This aggregate-data meta-analysis pooled 18 season-level VE estimates (**Table**) derived from 96 335 participants; participant-level characteristics were not available. Two seasons did not contribute estimates: 2008 to 2009 lacked a peer-reviewed estimate, and 2020 to 2021 was not estimated. No final estimate was published after 2023 to 2024. Season-specific VE ranged from 10% (95% CI, −36% to 40%) in 2004 to 2005 to 60% (95% CI, 53% to 66%) in 2010 to 2011. Three seasons (17%) had CIs crossing the null. Eleven seasons (61%) had a mismatch in at least 1 vaccine component; in 10 of 11 (91%), the reported mismatch involved a predominant or codominant strain. Across the 18 seasons,

Table. Influenza Vaccine Effectiveness, US Influenza Vaccine Effectiveness Network, 2004 to 2005 Through 2023 to 2024

Study year[a]	VE (95% CI), %[b]	Predominant type or subtype	Mismatch reported[c]	Basis for mismatch classification (as characterized by the source study)
2004-2005	10 (−36 to 40)	H3N2	Yes	A total of 95% of Influenza viruses isolated from study participants were A/California/7/2004-like viruses, which "were antigenically different from the vaccine strains."
2005-2006	21 (−52 to 59)	B/Victoria	Yes	A total of 95% of Influenza viruses isolated from study participants were either A/Wisconsin/67/2005-like or B/Victoria/2/87-like, both of which "were antigenically different from the vaccine strains."
2006-2007[d]	52 (22 to 70)	H1N1	No	NA
2007-2008	37 (22 to 49)	H3N2	Yes	"There was a lineage mismatch with the vaccine strain for all 39 characterized influenza B viruses."
2008-2009	Not included	NA	NA	NA
2009-2010[d]	56 (23 to 75)	H1N1	No	NA
2010-2011[d]	60 (53 to 66)	H3N2, H1N1, B codominant[e]	No	NA
2011-2012[d]	47 (36 to 56)	H3N2	Yes	The authors reported reduced VE against A(H3N2): "In 2011-2012, a year of modest influenza activity, there was reduced VE against type A (H3N2). Although there was drift in the A (H3N2) viruses, we also demonstrated an apparent negative effect of repeated annual vaccination on effectiveness."
2012-2013[d]	49 (43 to 55)	H3N2	Yes	Egg-propagated A/Victoria/361/2011 reassortant "acquired 3 amino acid changes in the antigenic region of HA which altered its antigenicity significantly."
2013-2014[d]	52 (44 to 59)	H1N1	No	NA
2014-2015	19 (10 to 27)	H3N2	Yes	Adjusted VE against A/H3N2 was 6%, which the authors reported as "consistent with a mismatch between the vaccine and circulating viruses."
2015-2016[d]	48 (41 to 55)	H1N1	No	NA
2016-2017[d]	40 (32 to 46)	H3N2	Yes	While 97% of H3N2 viruses were similar to the cell-propagated strain, "only 24 (38%) of the 63 A(H3N2) viruses tested were antigenically similar to the egg-propagated A/Hong Kong/4801/2014(H3N2) vaccine reference strain."
2017-2018	38 (31 to 43)	H3N2	Yes	"[M]any circulating A(H3N2) viruses were poorly inhibited by antisera raised against egg-adapted viruses used for production of the majority of influenza vaccines."
2018-2019	29 (21 to 35)	H3N2, H1N1 codominant[e]	Yes	"Most" A(H3N2) clade 3C.3a viruses "reacted poorly (≥8-fold reduction in titer compared with homologous virus) with ferret antisera to cell culture-propagated A/Singapore/INFIMH-16-0019/2016."
2019-2020	39 (32 to 44)	H1N1, B/Victoria codominant[e]	Yes	"Vaccination offered no protection against A(H1N1)pdm09 viruses with antigenically drifted clade 6B.1A 183P-5A+156K HA genes"; "Antigenically characterized B/Victoria viruses during 2019-2020 showed reduced reactivity by ferret antisera to the vaccine component."
2020-2021	Not estimated	NA	NA	NA
2021-2022	36 (21 to 48)	H3N2	Yes	"All 206 sequenced A(H3N2) viruses were characterized as belonging to genetic group 3C.2a1b subclade 2a.2, which has antigenic differences from the 2021-2022 season A(H3N2) vaccine component that belongs to clade 3C.2a1b subclade 2a.1."
2022-2023	30 (−9 to 54)	H1N1	No	NA
2023-2024[d]	44 (36 to 51)	H1N1	No	NA

Abbreviation: NA, not applicable.

[a] The 2008 to 2009 estimate was not published in a peer-reviewed source and did not meet the inclusion criteria; no estimate was produced for 2020 to 2021 because of minimal influenza circulation during the COVID-19 pandemic. No final estimate was published after 2023 to 2024. Study citations appear in the eTable in Supplement 1.

[b] VE estimates are the overall, end-of-season influenza vaccine effectiveness values (all ages combined; any influenza type and subtype) from the peer-reviewed Influenza Vaccine Effectiveness Network reports indexed by the US Centers for Disease Control and Prevention.

[c] Antigenic mismatch as reported by the individual study authors; we did not independently adjudicate antigenic mismatch. Basis descriptions incorporate verbatim quotations from the source manuscripts.

[d] Indicates seasons with a point-estimate VE within 40% to 60% range (bounds inclusive).

[e] Codominant denotes comparable case share across the season among the listed types and subtypes.

jamanetwork/2026/jno/11_10_2026/zld260275 PAGE: 2 SESS: 14 OUTPUT: Oct 13 19:59 2026

VE was 40% to 60% in 9, less than 40% in 9, and greater than 60% in none. The median season-specific VE was 39.5%, and the unweighted mean was 39.3%. The 95% PI for a single future season was 15.6% to 59.3%.

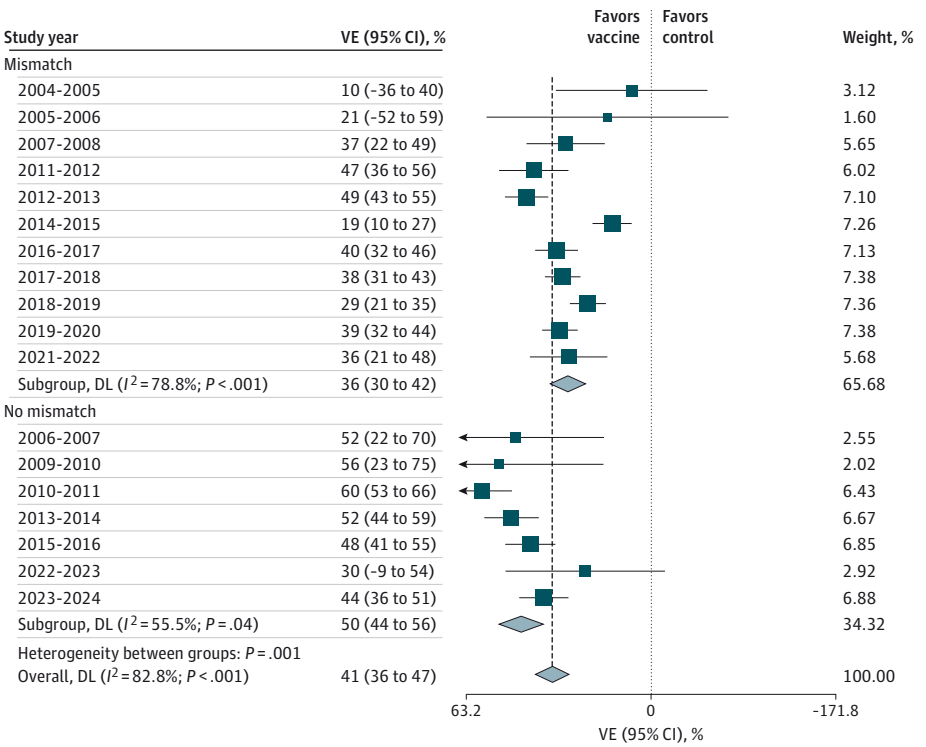
The pooled VE was 41.3% (95% CI, 35.6%-46.5%) (**Figure**). Substantial between-season heterogeneity was observed (I^2 = 82.8%; Cochran Q P < .001). In subgroup analyses, pooled VE was 36.2% (95% CI, 29.9%-42.0%) in seasons with any reported antigenic mismatch (I^2 = 78.8%) and 50.4% (95% CI, 44.2%-56.0%) in seasons without reported mismatch (I^2 = 55.5%); the between-subgroup difference was significant (P = .001).

Discussion

In this meta-analysis of influenza VE from the Flu VE Network across 18 seasons, we tested whether the 40% to 60% heuristic reflected expectations under routine seasonal conditions. The PI demonstrated substantial between-season variability, indicating that VE in a future season could fall well below the heuristic range. Most mismatch seasons involved a predominant or codominant strain, although mismatch with a nonpredominant strain can also lower overall VE when that virus accounts for a large share of cases. In seasons with reported antigenic mismatch, pooled VE was 36.2%, below the lower bound of the heuristic range and significantly lower than the 50.4% observed in seasons without reported mismatch. These findings were limited by design to VE estimates from a single US network. The mismatch comparison was associational; seasons also differed in population immunity, previous vaccination, and other factors.[8]

Influenza causes substantial morbidity and mortality annually,[9] and vaccination remains the best means for preventing influenza-associated illness, with evidence supporting protection against severe outcomes and population-level benefits from indirect vaccine effects.[7,10] Using the Flu VE Network as a test case, we found that the 40% to 60% heuristic describes performance under

Figure. Dot Plot Showing Pooled and Season-Specific Influenza Vaccine Effectiveness (VE), US Influenza Vaccine Effectiveness Network, 2004 to 2005 Through 2023 to 2024



Season-specific VE estimates were transformed to the log odds ratio scale, pooled using a DerSimonian-Laird (DL) random-effects inverse-variance model, and back-transformed to VE. Squares indicate season-specific VE estimates, sized in proportion to their weight in the pooled analysis, with horizontal lines denoting 95% CIs. Diamonds indicate subgroup and overall pooled estimates, with diamond width denoting 95% CIs. The solid vertical line marks the null and the dashed vertical line marks the overall pooled estimate. I^2 quantifies the proportion of total variability attributable to between-season heterogeneity; the accompanying P values are from Cochran Q.

jamanetwork/2026/jno/11_10_2026/zld260275 PAGE: 3 SESS: 14 OUTPUT: Oct 13 19:59 2026

biologically favorable conditions, but antigenic mismatch was reported in 61% of seasons. Communication of influenza VE should instead anchor expectations to historical performance across all seasons, not only the best ones. According to historical Flu VE Network estimates, influenza VE is about 40% in a typical season.

ARTICLE INFORMATION

Accepted for Publication: September 11, 2026.

Published: November 10, 2026. doi:10.1001/jamanetworkopen.2026.42906

Open Access: This is an open access article distributed under the terms of the CC-BY-NC-ND License, which does not permit alteration or commercial use, including those for text and data mining, AI training, and similar technologies. © 2026 Wolpert MD et al. *JAMA Network Open*.

Corresponding Author: Justin R. Ortiz, MD, Center for Vaccine Development & Global Health, University of Maryland School of Medicine, 685 W Baltimore St, Baltimore, MD 21201 (jortiz@som.umaryland.edu).

Author Affiliations: Internal Medicine Residency Program, University of Maryland Medical Center, Baltimore (Wolpert); Center for Vaccine Development and Global Health, University of Maryland School of Medicine, Baltimore (Wolpert, Fitzpatrick, Ortiz); Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore (Liang); Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, University of Maryland School of Medicine, Baltimore (Ortiz).

Author Contributions: Dr Ortiz had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Ortiz.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Fitzpatrick, Ortiz.

Critical review of the manuscript for important intellectual content: All authors.

Statistical analysis: Liang.

Obtained funding: Ortiz.

Administrative, technical, or material support: Ortiz.

Supervision: Ortiz.

Conflict of Interest Disclosures: Dr Liang reported receiving grants from the National Institutes of Health, the Bill and Melinda Gates Foundation, and Wellcome Trust outside the submitted work. Dr Fitzpatrick reported receiving personal fees from Sanofi Pasteur outside the submitted work. Dr Ortiz reported receiving personal fees from ENA Respiratory Pty Ltd, Moderna, Merck, and UpToDate; institutional research funding from ENA Respiratory Pty Ltd, BlueWillow Ltd, Vaccine Company Inc, and Pfizer outside the submitted work; and serving as cochair of the American Thoracic Society Vaccine and Immunization Advisory Group, Vaccine Guidance Review Panel, American Academy of Allergy, and Asthma & Immunology/American Thoracic Society/American College of Chest Physicians/Society of Critical Care Medicine. No other disclosures were reported.

Funding/Support: This work was supported by the University of Maryland, Baltimore Targeted Pivoting Programmatic Research Grant.

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 2.

Additional Contributions: We thank the University of Maryland Medical Center Internal Medicine Residency for supporting its trainee who collaborated with this study.

Additional Information: The authors used Claude Opus 5 (Anthropic) in August 2026 in preparing the Supplement to organize the MOOSE and PRISMA reporting checklists, to locate and insert page and line references, and to check the Supplement for internal consistency and completeness. The tool was not used to generate or format references and was not used to generate manuscript text. The authors reviewed and verified all AI-assisted output and take responsibility for the accuracy and integrity of the content.

REFERENCES

1. Centers for Disease Control and Prevention. US Flu VE Network. Accessed May 3, 2026, https://www.cdc.gov/flu-vaccines-work/php/vaccine-effectiveness/us-flu-ve-network.html

2. Dawood FS, Chung JR, Kim SS, et al. Interim estimates of 2019-20 seasonal influenza vaccine effectiveness—United States, February 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(7):177-182. doi:10.15585/mmwr.mm6907a1

3. Centers for Disease Control and Prevention. Benefits of the flu vaccine. Accessed May 3, 2026, https://www.cdc.gov/flu-vaccines-work/benefits/index.html

4. Balasubramani GK, Nowalk MP, Sax TM, et al. Influenza vaccine effectiveness among outpatients in the US Influenza Vaccine Effectiveness Network by study site 2011-2016. *Influenza Other Respir Viruses*. 2020;14(4):380-390. doi:10.1111/irv.12741

5. Centers for Disease Control and Prevention. CDC seasonal flu vaccine effectiveness studies. Accessed May 3, 2026, https://www.cdc.gov/flu-vaccines-work/php/effectiveness-studies/index.html

6. Gaglani M, Vasudevan A, Raiyani C, et al. Effectiveness of trivalent and quadrivalent inactivated vaccines against influenza B in the United States, 2011-2012 to 2016-2017. *Clin Infect Dis*. 2021;72(7):1147-1157. doi:10.1093/cid/ciaa102

7. Gilmore AC, Liang Y, Galbreath IM, et al. Indirect influenza vaccine effectiveness under randomized conditions: a systematic review and meta-analysis. *Clin Infect Dis*. 2026;83(2):303-311. doi:10.1093/cid/ciag138

8. Skowronski DM, Sabaiduc S, Leir S, et al. Paradoxical clade- and age-specific vaccine effectiveness during the 2018/19 influenza A(H3N2) epidemic in Canada: potential imprint-regulated effect of vaccine (I-REV). *Euro Surveill*. 2019;24(46):1900585. doi:10.2807/1560-7917.ES.2019.24.46.1900585

9. Rolfes MA, Foppa IM, Garg S, et al. Annual estimates of the burden of seasonal influenza in the United States: a tool for strengthening influenza surveillance and preparedness. *Influenza Other Respir Viruses*. 2018;12(1):132-137. doi:10.1111/irv.12486

10. Yegorov S, Patel OD, Sharma H, et al. Effectiveness of influenza vaccination to prevent severe disease: a systematic review and meta-analysis of test-negative design studies. *Clin Microbiol Infect*. 2026;32(2):219-229. doi:10.1016/j.cmi.2025.09.023

SUPPLEMENT 1.

eMethods. Evidence Set, Data Abstraction and Antigenic Mismatch Classification, Statistical Analysis, and Reporting Approach

eTable. Source Studies and Characteristics of the US Influenza Vaccine Effectivenzess (Flu VE) Network End-of-Season Estimates Included in the Meta-Analysis, 2004 to 2005 through 2023 to 2024

SUPPLEMENT 2.

Data Sharing Statement