HUMAN VACCINES & IMMUNOTHERAPEUTICS
2023, VOL. 19, NO. 1, 2177461
https://doi.org/10.1080/21645515.2023.2177461

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RESEARCH ARTICLE

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Vaccine effectiveness of recombinant and standard dose influenza vaccines against outpatient illness during 2018–2019 and 2019–2020 calculated using a retrospective test-negative design

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ABSTRACT

Newer influenza vaccine formulations have entered the market, but real-world effectiveness studies are not widely conducted until there is sufficient uptake. We conducted a retrospective test-negative case-control study to determine relative vaccine effectiveness (rVE) of recombinant influenza vaccine or RIV4, compared with standard dose vaccines (SD) in a health system with significant RIV4 uptake. Using the electronic medical record (EMR) and the Pennsylvania state immunization registry to confirm influenza vaccination, VE against outpatient medically attended visits was calculated. Immunocompetent outpatients ages 18–64 years seen in hospital-based clinics or emergency departments who were tested for influenza using reverse transcription polymerase chain reaction (RT-PCR) assays during the 2018–2019 and 2019–2020 influenza seasons were included. Propensity scores with inverse probability weighting were used to adjust for potential confounders and determine rVE. Among this mostly white and female cohort of 5,515 individuals, 510 were vaccinated with RIV4 and 557 were vaccinated with SD, with the balance of 4,448 (81%) being unvaccinated. Adjusted influenza VE estimates were 37% overall (95% CI = 27, 46), 40% (95% CI = 25, 51) for RIV4 and 35% (95% CI = 20, 47) for standard dose vaccines. Overall, rVE of RIV4 compared to SD was not significantly higher (11%; 95% CI = −20, 33). Influenza vaccines were moderately protective against medically attended outpatient influenza during the 2018–2019 and 2019–2020 seasons. Although the point estimates are higher for RIV4, the large confidence intervals around VE estimates suggest this study was underpowered to detect significant rVE of individual vaccine formulations.

ARTICLE HISTORY
Received 8 December 2022
Revised 16 January 2023
Accepted 3 February 2023

KEYWORDS
Influenza; vaccine effectiveness; recombinant influenza vaccine; relative vaccine effectiveness

Introduction

In recent influenza seasons, influenza vaccine effectiveness (VE) has been moderate at best ranging from 19% to 52% from 2009–2010 to 2019–2020 (pre-COVID-19 pandemic) in the US,[1] and vaccination is often ineffective against the A (H3N2) strain. The A(H3N2) strain is more likely to mutate, thus evading vaccine-induced immunity and resulting in lower VE. In addition, A(H3N2) is more sensitive to genetic substitutions that occur during the production of egg-based influenza vaccines. Thus, new influenza vaccines are being developed and manufactured to avoid these mutations, in an effort to improve influenza VE. One newer vaccine formulation, recombinant influenza vaccine (RIV4), is not produced in egg culture, thereby lowering the possibility for mutations; it contains three times the amount of antigen as standard dose (SD) vaccines and has been shown to be effective against influenza in a RCT in healthy adults,[2] and to be more effective than SD to prevent influenza cases in a RCT in adults aged 50 years and over.[3] Therefore, RIV4 may be more effective for those with reduced immune function such as the elderly, and people with high-risk conditions, than other vaccine formulations.[3] VE studies of specific vaccine types and relative VE studies among various vaccine types are generally limited until uptake of specific vaccines reaches sufficient numbers for comparative analyses. This constraint has been especially evident among younger adults whose overall influenza vaccine uptake is generally lower than that of older populations.[4] While there are numerous studies of the rVE of cell-cultured influenza vaccine,[5–7] there are relatively few involving RIV4 VE against outpatient influenza illness, and that include non-elderly adults. We conducted a retrospective test-negative case-control study of influenza VE against medically attended outpatient illness using data from electronic medical records (EMR) of a large health system to determine the VE of influenza vaccines and relative VE (rVE) of RIV4 among persons 18–64 years of age in the 2018–2019 and 2019–2020 seasons.

Patients and methods

The University of Pittsburgh Institutional Review Board approved this retrospective study using EMR databases. A test-negative case-control study estimates VE by comparing the odds of vaccination among confirmed influenza cases to the odds of vaccination among controls.

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Patients

Participants were outpatients 18 through 64 years of age as of August 1 each season who had a test for influenza at a UPMC hospital-based clinic or Emergency Department at any time between 11/01/2018 and 04/30/2020. UPMC Health System has a 44–45% market share in the state, and the local county. The Theradoc® infection control database was used to identify those tested for influenza using reverse transcription polymerase chain reaction (RT-PCR) assays. Influenza cases were those who tested positive for influenza and controls were those who tested negative for influenza, regardless of any other identified viral infection. Both the EMR and Pennsylvania Statewide Immunization Information System (PA-SIIS) were queried for influenza vaccines given between August 1 and the date of illness/PCR testing. Incomplete vaccination information was considered to be missing and these patients were not included in analyses. Patients with no influenza vaccine record in PA-SIIS or the EMR were assumed to be unvaccinated. Exclusion criteria were testing within 2 weeks of vaccination, having two different types of influenza vaccine in a season, receiving a high dose or adjuvanted influenza vaccine, missing vaccination data, and having an immunocompromising condition. High-risk conditions were based on the list found in Appendix 1 and included chronic cardiovascular and respiratory diseases.

Statistical methods

For analysis, patients were grouped into recombinant vs. other standard dose vaccine recipients. Descriptions of variables for each group were summarized as frequencies and percentages for categorical data. Baseline characteristics between the vaccination groups were compared using chi-square or the Fisher's exact tests for categorical variables. Using adjusted odds ratios (aOR) obtained from multivariable logistic regression models, VE estimates were calculated as (1-aOR) × 100. The dependent variable of interest was influenza status. The primary exposure of interest was vaccine type (recombinant vs. standard dose vaccines). Vaccinated individuals with no information about type of vaccine received were not included in the rVE analyses. The independent variables were age, influenza season (2018–2019 and 2019–2020), sex, race and presence of one or more high-risk conditions. Relative VE (rVE) was calculated as 1 minus the ratio of adjusted VE for recombinant and standard dose vaccine times 100%.

We conducted propensity adjustment analyses to reduce the potential impact of selection effects (i.e., confounding) on baseline characteristics – age (18–64 years, continuous), race (white, nonwhite), sex (male, female), presence of ≥1 high-risk condition (yes, no), season (2018–2019, 2019–2020). Number of high-risk conditions was not equally distributed among vaccine recipient groups (see Appendix 2).

We estimated the propensity scores using the Generalized Boosted Regression Models (GBM) approach, which is a nonparametric model that allows for nonlinear relationships with a maximum number of iterations set to the default (i.e.,10,000) that minimized the balance statistics of interest. We used the balance statistic based on absolute standardized bias (also referred as the effect size or absolute standardized mean difference) and summarized across variables. We allowed a maximum of three splits for each tree in the model, allowing for three-way interactions among all covariates to be considered. The shrinkage parameter was set to 0.0005 to ensure a smooth fit.

We also checked the balance of all the variables included in the model to assess the quality of the propensity score and overlap in the range of propensity scores across treatment and comparison groups using a value under 0.25 as indicative of good balance. We also used the balance plots to compare the propensity score distributions and to evaluate the common support. We used five plot methods to determine the balance of each covariate used in the propensity score model: 1) optimization using the estimated mean average treatment effect; 2) box plot of the propensity of the vaccine; 3) the standardized effect size of the unweighted and weighted values; 4) t-test p-values of the group mean of the covariate; and 5) K-S p-values of the covariates. We also checked that there were no extreme values in the estimated weights using the GBM method. In all, the weights were stable and balanced. See an example in Appendix 3.

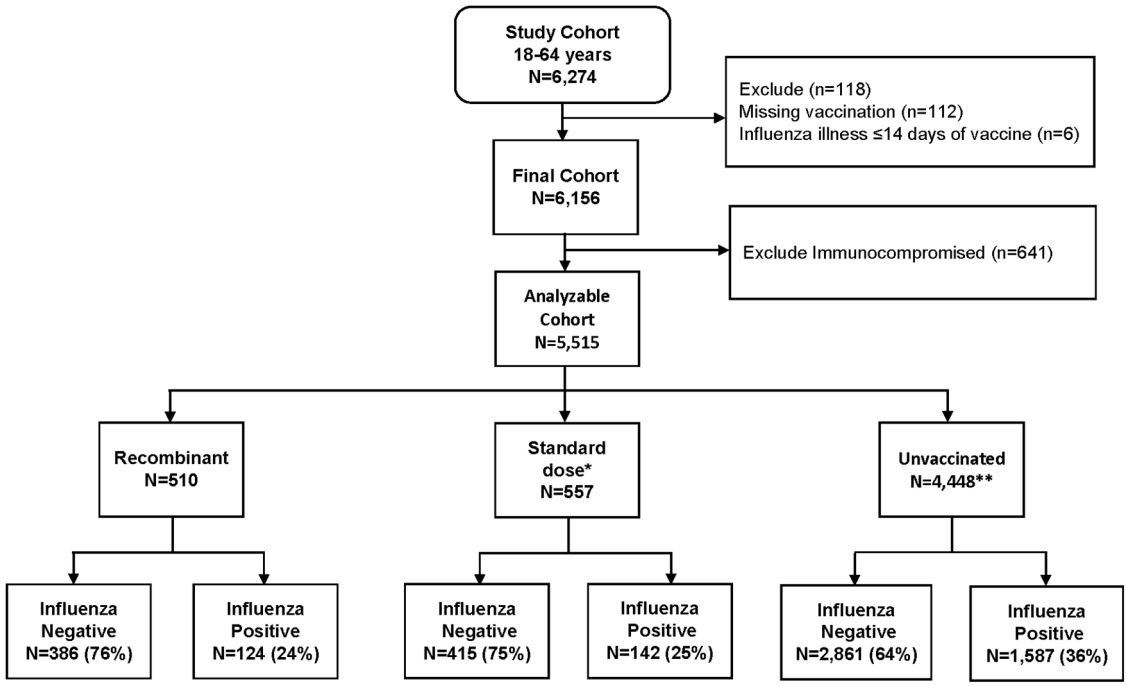
Using the propensity score, we calculated the inverse probability of receiving standard dose vaccine weighting. In this approach, for an individual receiving standard dose vaccine t, the weight equals $1/p_t(x)$, where $p_t(x)$ is the propensity score (probability that an individual with characteristic x receives standard dose vaccine t). A propensity score weighted logistic regression with influenza status as the dependent variable was fitted to estimate the effect of vaccine (standard dose vs. recombinant vaccine) on outcome and also used inverse probability weighting to estimate VE and its 95% confidence intervals. Because all the covariates are balanced using the weighted method, we fit the model with propensity weights and the inverse probability weight to estimate the rVE.

We performed two sensitivity analyses using 1) for all adults ≥18 years including the immunocompromised, excluding recipients of other advanced vaccines (Flucelvax, HD Fluzone, and Fluad) in the analytic dataset; and 2) non-immunocompromised adults 18–64 years, excluding age ≥65 years, and recipients of other advanced vaccine (Flucelvax). The final dataset included non-immunocompromised adults 18–64 years, including recipients of other (non-RIV4) advanced vaccines (Flucelvax) in the standard dose group.

All analyses were two-sided and the alpha level was set to 0.05. All analyses were conducted using SAS, version 9.4 statistical software (SAS Institute Inc., Cary, NC). We used the Toolkit for Weighting and Analysis of Nonequivalent Groups (TWANG) software package and the SAS Macros (available at http://www.rand.org/statistics/twang/downloads.html) to calculate the propensity scores.

Results

The total number of influenza test results among outpatients was 6,274, of which 112 were excluded because of missing vaccination information (see Appendixes 4 and 5) or vaccination <14 days before illness, and 641 were excluded because patients were immunocompromised, leaving 5,515 for analysis



*Standard dose: Afluria (n=49), Fluarix (n=91), FluLaval (n=81), SD Fluzone (n=114), FlucelVax (n=222)
**185 subjects were vaccinated after they became ill and were classified as unvaccinated

Figure 1. Flow chart.

(Figure 1). Of these, 510 were vaccinated with recombinant and 557 were vaccinated with standard dose vaccines, with the balance of 4,448 being unvaccinated.

Demographic characteristics of the population are shown in Table 1; most participants were white (73.3%) and female (62.9%) and less than half (40.7%) had a high-risk condition. Patients who received RIV4 were significantly less often white ($p < .001$), but did not otherwise differ from those who received SD. There were significant demographic and health differences ($p < .001$) between vaccinated and unvaccinated individuals with whites, females, older and healthier individuals more often vaccinated against influenza.

Overall, influenza vaccines (including SD) were moderately effective against outpatient illness (37%; 95% CI = 27, 46) during 2018–2019 and 2019–2020 seasons. Influenza vaccines were effective against both influenza A and B, but VE was higher for influenza B (52%; 95%CI = 36, 64) than for influenza A (31%; 95%CI = 17, 42). With the exception of patients 50–64 years of age, adjusted VEs were significant, ranging from 33% to 46% across age, sex, and risk groups (Table 2).

When estimating VE overall and for each age and risk group adjusting for the other variables and stratifying by vaccine type, both recombinant and standard dose vaccines were significantly effective compared with no vaccination,

Table 1. Characteristics of patients.

		Vaccine Received			Vaccination Status		
Measures	Total N = 5,515	Recombinant n = 510	Standard dose n = 557	*P*-value Recombinant vs. SD	Vaccinated* n = 1,067	Unvaccinated n = 4,448	*p*-value Vaccinated vs. Unvaccinated
Age, Mean (SD)	38.5 (13.4)	41.5 (13.4)	41.2 (13.9)	0.736	37.8 (13.2)	37.8 (13.2)	**<0.001**
White race, ref. = nonwhite, n (%)	4,045 (73.3)	374 (73.3)	459 (82.4)	**<0.001**	833 (78.1)	3,212 (72.2)	**<0.001**
Female sex, ref. = male, n (%)	3,471 (62.9)	373 (73.1)	381 (68.4)	0.089	754 (70.7)	2,717 (61.1)	**<0.001**
Season, n (%)				0.798			**<0.001**
2018–2019	1,189 (21.6)	142 (27.8)	159 (28.5)		301 (28.2)	888 (20.0)	
2019–2020	4,326 (78.4)	368 (72.2)	398 (71.5)		766 (71.8)	3,560 (80.0)	
Age Group, n (%)				0.743			**<0.001**
18–49 years	4,086 (74.1)	333 (65.3)	369 (66.2)		702 (65.8)	3,384 (76.1)	
50–64 years	1,429 (25.9)	177 (34.7)	188 (33.8)		365 (34.2)	1,064 (23.9)	
Influenza case, ref. = non-case, n (%)	1,853 (33.6)	124 (24.3)	142 (25.5)	0.656	621 (58.2)	1,623 (36.5)	**<0.001**
High-risk condition[†] ref. = no, n (%)	2,244 (40.7)	356 (69.8)	265 (47.6)	<0.001	621 (58.2)	1,623 (36.5)	**<0.001**

*Vaccinated=Flublok and standard dose vaccines (Afluria, Fluarix, FluLaval, SD Fluzone and FlucelVax).
[†]High-risk conditions include chronic cardiovascular, respiratory disease, among others. See Appendix 1.

with few exceptions (Table 3, columns a and b). Significant adjusted VE estimates ranged from 29% to 47%. Standard dose vaccines were not significantly effective for those with one or more high-risk conditions (VE = 20%; 95%CI = −8, 40); whereas, recombinant vaccine was significantly effective for those with high-risk conditions (45%; 95%CI = 25, 56).

Relative VE of recombinant compared with standard dose vaccines overall was insignificant even when adjusted for propensity scores with inverse probability weights (rVE = 11; 95% CI = −20, 33) (Table 3, columns d-f). Subgroup analyses by age and risk group identified no significant rVE for recombinant influenza vaccine. Although the point estimate for rVE for those with a high-risk condition was 26%, the 95%CI was −8 to 50.

Sensitivity analyses were conducted using different patient groups including a cohort for all adults ≥18 years including the immunocompromised and excluding recipients of other advanced and high-dose vaccines (Appendix 6) and adults 18–64 years, excluding the immunocompromised and those who received other advanced (non-RIV4) vaccines (Appendix 7). Results were similar to the primary analyses in that recombinant and standard dose vaccines were generally effective, except standard dose vaccine among older age and high risk/immunocompromised groups. Relative VE of recombinant vaccine was not significant for any subgroup after adjustments using inverse probability weights.

Discussion

The Advisory Committee on Immunization Practices and U.S. Centers for Disease Control and Prevention have completed literature reviews, GRADE analyses and Evidence-to-Recommendations processes on influenza vaccines in seniors and voted that seniors should receive high-dose, adjuvanted or recombinant influenza vaccine.[8] An outstanding question involves VE in those younger than 65 years, which was addressed in this analysis by testing rVE of RIV4 (high dose and adjuvanted vaccines are not licensed for use in persons <65 years of age).

Previous research, including retrospective test-negative case-control study during 2019–2020[9] and a RCT during 2014–2015,[3] has demonstrated significant rVEs for RIV4

Table 2. Overall influenza vaccine effectiveness (all vaccines combined*) during the 2018–2019 and 2019–2020 influenza seasons.

Group	Influenza Positive %	Influenza Negative %	Vaccine Effectiveness	
			Unadjusted % (95% CI)	Adjusted** % (95% CI)
Overall	14	22	**40 (30, 49)**	**37 (27, 46)**
Influenza A	17	22	**26 (13, 38)**	**31 (17, 42)**
Influenza B	9	22	**63 (51, 72)**	**52 (36, 64)**
Age 18–49 years	12	20	**48 (37, 57)**	**46 (35, 56)**
Age 50–64 years	24	26	13 (−13, 34)	13 (−14, 34)
Female sex	17	24	**37 (24, 47)**	**33 (19, 44)**
Male sex	11	18	**46 (29, 59)**	**46 (28, 59)**
High-risk condition†	22	30	**34 (19, 47)**	**33 (18, 46)**
No high-risk condition	10	16	**44 (29, 55)**	**42 (26, 54)**
2018–2019 season	19	29	**40 (20, 55)**	**41 (21, 56)**
2019–2020 season	13	20	**41 (30, 51)**	**36 (23, 47)**

Bold indicates non-overlapping intervals. *Vaccinated: Recombinant and Standard dose egg-based vaccines (Afluria, Fluarix, FluLaval, SD Fluzone, and FlucelVax).
**Multivariable logistic regression model adjusted for age, race, sex, season, and high-risk conditions, except that the stratified variable is not included as an adjustment in its own analysis.
†High-risk conditions include chronic cardiovascular, respiratory disease, among others. See Appendix 1.

Table 3. Effectiveness and relative effectiveness of recombinant and standard dose influenza vaccines against RT-PCR-confirmed influenza during the 2018–2019 and 2019–2020 influenza seasons.

Group	Adjusted Vaccine Effectiveness,* % (95% CI)		Relative Vaccine Effectiveness of Recombinant vs. Standard Dose Influenza Vaccine, % (95% CI)			
	Recombinant (a)	Standard dose (b)	Unadjusted (c)	Adjusted using *a priori* variables** (d)	Adjusted using propensity score (e)	Adjusted using inverse probability weights (f)
Overall	**40 (25, 51)**	**35 (20, 47)**	6 (−24, 29)	11 (−19, 34)	13 (−19, 37)	11 (−20, 33)
Age 18–49 years	**50 (33, 61)**	**44 (28, 56)**	8 (−30, 35)	15 (−24, 40)	11 (−29, 38)	9 (−31, 36)
Age 50–64 years	14 (−25, 40)	13 (−23, 39)	3 (−54, 39)	6 (−52, 42)	4 (−56, 41)	−2 (−66, 36)
Female sex	**37 (18, 51)**	**29 (10, 45)**	6 (−31, 32)	11 (−25, 37)	10 (−28, 37)	8 (−31, 35)
Male sex	**48 (20, 65)**	**44 (20, 61)**	9 (−54, 46)	9 (−62, 49)	3 (−76, 47)	6 (−64, 46)
High-risk condition	**43 (25, 56)**	20 (−8, 40)	27 (−6, 49)	30 (−1, 52)	32 (−1, 54)	26 (−8, 50)
No high-risk condition	**31 (1, 52)**	**47 (30, 60)**	−34 (−109, 14)	−35 (−115, 15)	−22 (−95, 24)	−25 (−98, 20)
2018–2019 season	**43 (15, 62)**	**40 (13, 59)**	5 (−59, 43)	8 (−57, 46)	9 (−58, 48)	7 (−60, 46)
2019–2020 season	**38 (20, 52)**	**33 (15, 48)**	7 (−30, 33)	9 (−30, 36)	11 (−28, 38)	9 (−30, 35)

Bold indicates non-overlapping confidence intervals.
*Adjusted vaccine effectiveness for recombinant and standard dose vaccines vs. no vaccination.
**Multivariable logistic regression model adjusted for age, race, sex, season, and high-risk conditions, except that the stratified variable is not included as an adjustment in its own analysis.
Propensity score: Generalized Boosted Regression Method was used to calculate the propensity score using TWANG (Toolkit for Weighting and Analysis of Nonequivalent Groups).

vs. standard dose vaccines of 13% among adults ≥65 years of age against hospital encounters and 30% among adults ≥50 years of age against PCR-confirmed influenza-like illness, respectively. Using a health system's EMR database, we found that the use of influenza vaccine was moderately effective against outpatient visits to the Emergency Department and hospital-based outpatient clinics with higher point estimates for effectiveness against influenza B (52%) than influenza A (31%) over the 2018–2019 through 2019–2020 seasons. These VE estimates are comparable to VE reported in the US Flu VE Network ranging from 34% to 45% for influenza B compared to 26–43% for influenza A among 18–64-year-olds in these seasons.[1] Our relative VE estimates for RIV4 vs. SD favored RIV4 by 11% but were not significant, with wide confidence intervals.

We speculate that the study was underpowered because less than 20% of the analyzable cohort had documented influenza vaccination, despite our inquiry of both the medical record and the state immunization information system. Influenza vaccine uptake estimates for Pennsylvania adults 18–49 years old range from 39% to 43% and for adults 50–64 years range from 59% to 68%.[10] We suspected that some community pharmacies and employer vaccination sites did not report to the state system during this time period. Thus, these findings should be interpreted with caution.

In recent years, typical influenza seasons have been exemplified by an influenza A wave that is primarily A(H1N1) or A(H3N2) with a smaller influenza B wave starting later in the season. The 2018–2019 and 2019–2020 influenza seasons were atypical in that 2018–2019 influenza A(H1N1) and A(H3N2) co-circulated and in 2019–2020 influenza A(H1N1) and influenza B co-circulated. Thus, without a predominant strain causing a significant majority of influenza cases, rVE estimates necessarily included protection against all vaccine strains combined and rVE of different vaccine formulations against specific strains was not conducted.

Strengths and limitations

The vaccination rate of the final analytic cohort of working age adults was only 19%. Failure to capture vaccination status biased VE toward the null. Despite the initial large size of this database, it was underpowered because of the limited number of recorded recombinant and standard dose vaccinees. Our assumptions for sample size calculations were based on the entire population of adults. This analysis was restricted to 18–64-year-olds who have lower vaccine uptake.

While there are other ways to estimate rVE,[11] we compared RIV4 and SD using propensity and inverse probability weighting methods. Both methods produce similar results.

A strength of the study is confirmation of influenza by RT-PCR testing; case definition, high-risk conditions and vaccination status were based on EMR-documented data, while symptoms and demographics were self-reported. A further strength is the large number of tests performed. Moreover, this study uses the best observational design, i.e., the test-negative design, but all observational studies are subject to biases of undetected confounders.[12,13]

Conclusions

Influenza vaccines were moderately protective. Although the point estimates are higher for RIV4, the large, overlapping confidence intervals around VE estimates suggest this study was underpowered to detect significant rVE of individual vaccine formulations. Larger, better powered studies are warranted to achieve more precise estimates for individual influenza strains, population subgroups, and virus subtypes.

Disclosure statement

Drs. Zimmerman, Raviotta, Nowalk, and Balasubramani received investigator-initiated grant funding from Sanofi for this project. Drs. Nowalk and Balasubramani, have grant funding from Merck & Co., Inc. for an unrelated project. Ms. Dauer and Mr. Clarke have no conflicts to report.

Funding

This work was supported by Sanofi through an investigator-initiated grant (SP-2021-13463). This work represents the views of the authors and not Sanofi.

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References

1. Centers for Disease Control and Prevention. Past seasons' vaccine effectiveness estimates. 2022 Oct 6 [accessed 2022 Oct 26]. https://www.cdc.gov/flu/vaccines-work/past-seasons-estimates.html.
2. Treanor JJ, El Sahly H, King J, Graham I, Izikson R, Kohberger R, Patriarca P, Cox M. Protective efficacy of a trivalent recombinant hemagglutinin protein vaccine (FluBlok®) against influenza in healthy adults: a randomized, placebo-controlled trial. Vaccine. 2011;29(44):7733–39. doi:10.1016/j.vaccine.2011.07.128.
3. Dunkle LM, Izikson R, Patriarca P, Goldenthal KL, Muse D, Callahan J, Cox MMJ. Efficacy of recombinant influenza vaccine in adults 50 years of age or older. N Engl J Med. 2017;376(25):2427–36. doi:10.1056/NEJMoa1608862.
4. Centers for Disease Control and Prevention. Flu vaccination coverage, United States, 2021–22 influenza season. 2022 Oct 18 [accessed 2022 Nov 30]. https://www.cdc.gov/flu/fluvaxview/coverage-2022estimates.htm.
5. Izurieta HS, Chillarige Y, Kelman J, Wei Y, Lu Y, Xu W, Lu M, Pratt D, Chu S, Wernecke M, et al. Relative effectiveness of cell-cultured and egg-based influenza vaccines among elderly persons in the United States, 2017–2018. J Infect Dis. 2018 Dec 18;220(8):1255–64. doi:10.1093/infdis/jiy716.
6. Bruxvoort KJ, Luo Y, Ackerson B, Tanenbaum HC, Sy LS, Gandhi A, Tseng HF. Comparison of vaccine effectiveness against influenza hospitalization of cell-based and egg-based influenza vaccines, 2017–2018. Vaccine. 2019;37(39):5807–11. doi:10.1016/j.vaccine.2019.08.024.
7. Puig-Barberà J, Tamames-Gómez S, Plans-Rubio P, Eiros-Bouza JM. Relative effectiveness of cell-cultured versus egg-based seasonal influenza vaccines in preventing influenza-related outcomes in subjects 18 years old or older: a systematic review and meta-analysis. Int J Environ Res Public Health. 2022;19(2):818. doi:10.3390/ijerph19020818.
8. Grohskopf LA, Blanton LH, Ferdinands JM, Chung JR, Broder KR, Talbot HK, Morgan RL, Fry AM. Prevention and control of

seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices—United States, 2022–23 influenza season. MMWR Recomm Rep. 2022;71 (1):1–28. doi:10.15585/mmwr.rr7101a1.
9. Izurieta HS, Lu M, Kelman J, Lu Y, Lindaas A, Loc J, Pratt D, Wei Y, Chillarige Y, Wernecke M, et al. Comparative effectiveness of influenza vaccines among US medicare beneficiaries ages 65 years and older during the 2019–2020 season. Clin Infect Dis. 2021;73(11):e4251–59. doi:10.1093/cid/ciaa1727.
10. Centers for Disease Control and Prevention. Flu vaccination coverage by jurisdiction: data collection period: 05/01/2022-05/28/2022 Pennsylvania. 2022 Sep 29. https://www.cdc.gov/flu/fluvaxview/dashboard/vaccination-adult-coverage.html.
11. Lewis NM, Chung JR, Uyeki TM, Grohskopf L, Ferdinands JM, Patel MM. Interpretation of relative efficacy and effectiveness for influenza vaccines. Clin Infect Dis. 2022;75(1):170–75. doi:10.1093/cid/ciab1016.
12. Sullivan SG, Tchetgen Tchetgen EJ, Cowling BJ. Theoretical basis of the test-negative study design for assessment of influenza vaccine effectiveness. Am J Epidemiol. 2016;184(5):345–53. doi:10.1093/aje/kww064.
13. De Serres G, Skowronski D, Wu X, Ambrose C. The test-negative design: validity, accuracy and precision of vaccine efficacy estimates compared to the gold standard of randomised placebo-controlled clinical trials. Eurosurveillance. 2013;18 (37):20585. doi:10.2807/1560-7917.ES2013.18.37.20585.

Appendix 1. ICD10 codes for high risk

ICD10	Description
I60*	Nontraumatic subarachnoid hemorrhage
I61*	Nontraumatic intracerebral hemorrhage
I62*	Other and unspecified nontraumatic intracranial hemorrhage
I63*	Cerebral infarction
I68*	Cerebrovascular disorders in diseases classified elsewhere
I69*	Sequelae of cerebrovascular disease
A52.0*	Cardiovascular syphilis
I01*	Rheumatic fever with heart involvement
I02*	Rheumatic chorea
I05*	Rheumatic mitral valve diseases
I06*	Rheumatic aortic valve diseases
I07*	Rheumatic tricuspid valve diseases
I08*	Multiple valve diseases
I09*	Other rheumatic heart diseases
I11*	Hypertensive heart disease
I13*	Hypertensive heart and chronic kidney disease
I20*	Angina pectoris
I21*	ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction
I22*	Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction
I23*	Certain current complications following ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardialinfarction (within the 28 day period)
I24*	Other acute ischemic heart diseases
I25*	Chronic ischemic heart disease
I26*	Pulmonary embolism
I27*	Other pulmonary heart diseases
I28*	Other diseases of pulmonary vessels
I31*	Other diseases of pericardium
I33*	Acute and subacute endocarditis
I34*	Nonrheumatic mitral valve disorders
I35*	Nonrheumatic aortic valve disorders
I36*	Nonrheumatic tricuspid valve disorders
I37*	Nonrheumatic pulmonary valve disorders
I38*	Endocarditis, valve unspecified
I39*	Endocarditis and heart valve disorders in diseases classified elsewhere
I40*	Acute myocarditis
I41*	Myocarditis in diseases classified elsewhere
I42*	Cardiomyopathy
I43*	Cardiomyopathy in diseases classified elsewhere
I44*	Atrioventricular and left bundle-branch block
I46*	Cardiac arrest
I48*	Atrial fibrillation and flutter
I50*	Heart failure
I51*	Complications and ill-defined descriptions of heart disease
I52*	Other heart disorders in diseases classified elsewhere
I97.0*	Postcardiotomy syndrome
I97.1*	Other postprocedural cardiac functional disturbances
M31*	Other necrotizing vasculopathies
Q20*	Congenital malformations of cardiac chambers and connections
Q21*	Congenital malformations of cardiac septa
Q22*	Congenital malformations of pulmonary and tricuspid valves
Q23*	Congenital malformations of aortic and mitral valves
Q24*	Other congenital malformations of heart
Q25*	Congenital malformations of great arteries
Q26*	Congenital malformations of great veins
Q27*	Other congenital malformations of peripheral vascular system
Q28*	Other congenital malformations of circulatory system
Q89.3*	Situs inversus
R00.1*	Bradycardia, unspecified
Z94.1*	Heart transplant status
Z95*	Presence of cardiac and vascular implants and grafts
Z98.61*	Coronary angioplasty status
A15*	Respiratory tuberculosis
A31.0*	Pulmonary mycobacterial infection
B39*	Histoplasmosis
B40*	Blastomycosis
B41*	Paracoccidioimycosis
B44*	Aspergillosis
B45*	Cryptococcosis
B46.0*	Pulmonary mucormycosis
D86.0*	Sarcoidosis of lung
E84*	Cystic fibrosis
E88.01*	Alpha-1-antitrypsin deficiency
J18.2*	Hypostatic pneumonia, unspecified organism
J41*	Simple and mucopurulent chronic bronchitis
J42*	Unspecified chronic bronchitis
J43*	Emphysema
J44*	Other chronic obstructive pulmonary disease
J45*	Asthma
J47*	Bronchiectasis
J60*	Coalworker's pneumoconiosis
J61*	Pneumoconiosis due to asbestos and other mineral fibers
J62*	Pneumoconiosis due to dust containing silica
J63*	Pneumoconiosis due to other inorganic dusts
J64*	Unspecified pneumoconiosis
J65*	Pneumoconiosis associated with tuberculosis
J66*	Airway disease due to specific organic dust
J67*	Hypersensitivity pneumonitis due to organic dust
J68*	Respiratory conditions due to inhalation of chemicals, gases, fumes and vapors
J69*	Pneumonitis due to solids and liquids
J70*	Respiratory conditions due to other external agents
J80*	Acute respiratory distress syndrome
J81*	Pulmonary edema
J82*	Pulmonary eosinophilia, not elsewhere classified
J84*	Other interstitial pulmonary diseases
J85*	Abscess of lung and mediastinum
J86*	Pyothorax
J95.0*	Tracheostomy complications
J96*	Respiratory failure, not elsewhere classified
J98.1*	Pulmonary collapse
J99*	Respiratory disorders in diseases classified elsewhere
P25*	Interstitial emphysema and related conditions originating in the perinatal period
P26*	Pulmonary hemorrhage originating in perinatal period
P27*	Chronic respiratory disease originating in the perinatal period
P28*	Other respiratory conditions originating in perinatal period
Q33*	Congenital malformations of lung
T86.3*	Complications of heart-lung transplant
T86.8*	Complications of lung transplant
Z94.2*	Lung transplant status
I12*	Hypertensive chronic kidney disease
N01*	Rapidly progressive nephritic syndrome
N02*	Recurrent and persistent hematuria
N03*	Chronic nephritic syndrome
N04*	Nephrotic syndrome
N05*	Unspecified nephritic syndrome
N06*	Isolated proteinuria with specified morphological lesion
N07*	Hereditary nephropathy, not elsewhere defined
N08*	Glomerular disorders in diseases classified elsewhere
N11*	Chronic tubulo-interstitial nephritis
N14*	Drug- and heavy-metal-induced tubulo-interstitial and tubular conditions
N15*	Other renal tubulo-interstitial diseases
N16*	Renal tubulo-interstitial disorders in diseases classified elsewhere
N17*	Acute kidney failure
N18*	Chronic kidney disease
N25*	Disorders resulting from impaired renal tubular function
N26*	Unspecified contracted kidney
N28*	Other disorders of kidney and ureter, not elsewhere classified
Q60*	Renal agenesis and other reduction defects of kidney
Z49*	Encounter for care involving renal dialysis
Z91.15*	Patient's noncompliance with renal dialysis
Z94.0*	Kidney transplant status
Z99.2*	Dependence on renal dialysis
E08*	Diabetes mellitus due to underlying condition
E09*	Drug or chemical induced diabetes mellitus
E10*	Type 1 diabetes mellitus
E11*	Type 2 diabetes mellitus
E13*	Other specified diabetes mellitus
O24*	Diabetes mellitus in pregnancy, childbirth, and the puerperium

(Continued).

ICD10	Description
I71*	Aortic aneurysm and dissection
I72*	Other aneurysm
I73*	Other peripheral vascular diseases
I74*	Arterial embolism and thrombosis
I75*	Atheroembolism
I76*	Septic arterial embolism
I79*	Disorders of arteries, arterioles and capillaries in diseases classified elsewhere
E00*	Congenital iodine-deficiency syndrome
E01*	Iodine-deficiency related thyroid disorders and allied conditions
E03*	Other hypothyroidism
E05*	Thyrotoxicosis [hyperthyroidism]
E06*	Thyroiditis
E15*	Other disorders of glucose regulation and pancreatic internal secretion
E16*	Other disorders of pancreatic internal secretion
E20*	Hypoparathyroidism
E21*	Hyperparathyroidism and other disorders of parathyroid gland
E22*	Hyperfunction of pituitary gland
E23*	Hypofunction and other disorders of the pituitary gland
E24*	Cushing's syndrome
E25*	Adrenogenital disorders
E26*	Hyperaldosteronism
E27*	Other disorders of adrenal gland
E28*	Ovarian dysfunction
E29*	Testicular dysfunction
E31*	Polyglandular dysfunction
E32*	Diseases of thymus
E34*	Other endocrine disorders
D55*	Anemia due to enzyme disorders
D56.0*	Alpha thalassemia
D56.1*	Beta thalassemia
D56.2*	Delta-beta thalassemia
D56.4*	Hereditary persistence of fetal hemoglobin [HPFH]
D56.5*	Hemoglobin E-beta thalassemia
D56.9*	Thalassemia, unspecified
D57.0*	Hb-SS disease with crisis
D57.1*	Sickle-cell disease without crisis
D57.2*	Sickle-cell/Hb-C disease
D57.4*	Sickle-cell thalassemia
D57.8*	Other sickle-cell disorders
D58*	Other hereditary hemolytic anemias
D59*	Acquired hemolytic anemia
D60*	Acquired pure red cell aplasia [erythroblastopenia]
D61*	Other aplastic anemias and other bone marrow failure syndromes
D64.0*	Hereditary sideroblastic anemia
D64.1*	Secondary sideroblastic anemia due to disease
D64.2*	Secondary sideroblastic anemia due to drugs and toxins
D64.3*	Other sideroblastic anemias
D64.4*	Congenital dyserythropoietic anemia
D64.8*	Other specified anemias
D65*	Disseminated intravascular coagulation [defibrination syndrome]
D66*	Hereditary factor VIII deficiency
D67*	Hereditary factor IX deficiency
D68*	Other coagulation defects
B20*	Human immunodeficiency virus (HIV) disease
B59*	Pneumocystosis
B97.3*	Retrovirus as the cause of diseases classified elsewhere
D47.Z1*	Post-transplant lymphoproliferative disorder (PTLD)
D70*	Neutropenia (including agranulocytosis)
D71*	Functional disorders of polymorphonuclear neutrophils
D72*	Other disorders of white blood cells
D73*	Diseases of spleen
D76*	Other specified diseases with participation of lymphoreticular and reticulohistiocytic tissue
D80*	Immunodeficiency with predominantly antibody defects
D81*	Combined immunodeficiencies
D82*	Immunodeficiency associated with other major defects
D83*	Common variable immunodeficiency
D84*	Other immunodeficiencies
D89*	Other disorders involving the immune mechanism, not elsewhere classified
M05*	Rheumatoid arthritis with rheumatoid factor
M06*	Other rheumatoid arthritis

(*Continued*)

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ICD10	Description
M07*	Enteropathic arthropathies
M08*	Juvenile arthritis
M30*	Polyarteritis nodosa and related conditions
M31*	Other necrotizing vasculopathies
M32*	Systemic lupus erythematosus (SLE)
M33*	Dermatopolymyositis
M34*	Systemic sclerosis [scleroderma]
M35.0*	Sicca syndrome [Sjögren]
M35.9*	Systemic involvement of connective tissue, unspecified
Q89.0*	Congenital absence and malformations of spleen
T45.1×1	Poisoning by antineoplastic and immunosuppressive drugs, accidental(unintentional)
Z21*	Asymptomatic human immunodeficiency virus [HIV] infection status
Z48.2*	Encounter for aftercare following organ transplant
Z51.0*	Encounter for antineoplastic radiation therapy
Z51.1*	Encounter for antineoplastic chemotherapy and immunotherapy
Z94*	Transplanted organ and tissue status
B18*	Chronic viral hepatitis
K70*	Alcoholic liver disease
K71*	Toxic liver disease
K72*	Hepatic failure, not elsewhere classified
K73*	Chronic hepatitis, not elsewhere classified
K74*	Fibrosis and cirrhosis of liver
K75*	Other inflammatory liver diseases
K76*	Other diseases of liver
K77*	Liver disorders in diseases classified elsewhere
I81*	Portal vein thrombosis
I85*	Esophageal varices
Z79.5*	Long term (current) use of steroids
Z79.82*	Long term (current) use of aspirin (*will only be used for those<19 years of age)
C00*	Malignant neoplasm of lip
C01*	Malignant neoplasm of base of tongue
C02*	Malignant neoplasm of other and unspecified parts of tongue
C03*	Malignant neoplasm of gum
C04*	Malignant neoplasm of floor of mouth
C05*	Malignant neoplasm of palate
C06*	Malignant neoplasm of other and unspecified parts of mouth
C07*	Malignant neoplasm of parotid gland
C08*	Malignant neoplasm of other and unspecified major salivary glands
C09*	Malignant neoplasm of tonsil
C10*	Malignant neoplasm of oropharynx
C11*	Malignant neoplasm of nasopharynx
C12*	Malignant neoplasm of pyriform sinus
C13*	Malignant neoplasm of hypopharynx
C14*	Malignant neoplasm of other and ill-defined sites in the lip, oral cavity and pharynx
C15*	Malignant neoplasm of esophagus
C16*	Malignant neoplasm of stomach
C17*	Malignant neoplasm of small intestine
C18*	Malignant neoplasm of colon
C19*	Malignant neoplasm of rectosigmoid junction
C20*	Malignant neoplasm of rectum
C21*	Malignant neoplasm of anus and anal canal
C22*	Malignant neoplasm of liver and intrahepatic bile ducts
C23*	Malignant neoplasm of gallbladder
C24*	Malignant neoplasm of other and unspecified parts of biliary tract
C25*	Malignant neoplasm of pancreas
C26*	Malignant neoplasm of other and ill-defined digestive organs
C30*	Malignant neoplasm of nasal cavity and middle ear
C31*	Malignant neoplasm of accessory sinuses
C32*	Malignant neoplasm of larynx
C33*	Malignant neoplasm of trachea
C34*	Malignant neoplasm of bronchus and lung
C37*	Malignant neoplasm of thymus
C38*	Malignant neoplasm of heart, mediastinum and pleura
C39*	Malignant neoplasm of other and ill-defined sites in the respiratory system and intrathoracic organs
C40*	Malignant neoplasm of bone and articular cartilage of limbs
C41*	Malignant neoplasm of bone and articular cartilage of other and unspecified sites
C43*	Malignant melanoma of skin
C44*	Other and unspecified malignant neoplasm of skin

(*Continued*)

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ICD10	Description
C45*	Mesothelioma
C46*	Kaposi's sarcoma
C47*	Malignant neoplasm of peripheral nerves and autonomic nervous system
C48*	Malignant neoplasm of retroperitoneum and peritoneum
C49*	Malignant neoplasm of other connective and soft tissue
C4A*	Merkel cell carcinoma
C50*	Malignant neoplasms of breast
C51*	Malignant neoplasm of vulva
C52*	Malignant neoplasm of vagina
C53*	Malignant neoplasm of cervix uteri
C54*	Malignant neoplasm of corpus uteri
C55*	Malignant neoplasm of uterus, part unspecified
C56*	Malignant neoplasm of ovary
C57*	Malignant neoplasm of other and unspecified female genital organs
C58*	Malignant neoplasm of placenta
C60*	Malignant neoplasm of penis
C61*	Malignant neoplasm of prostate
C62*	Malignant neoplasm of testis
C63*	Malignant neoplasm of other and unspecified male genital organs
C64*	Malignant neoplasm of kidney, except renal pelvis
C65*	Malignant neoplasm of renal pelvis
C66*	Malignant neoplasm of ureter
C67*	Malignant neoplasm of bladder
C68*	Malignant neoplasm of other and unspecified urinary organs
C69*	Malignant neoplasm of eye and adnexa
C70*	Malignant neoplasm of meninges
C71*	Malignant neoplasm of brain
C72*	Malignant neoplasm of spinal cord, cranial nerves and other parts of central nervous system
C73*	Malignant neoplasm of thyroid gland
C74*	Malignant neoplasm of adrenal gland
C75*	Malignant neoplasm of other endocrine glands and related structures
C76*	Malignant neoplasm of other and ill-defined sites
C77*	Secondary and unspecified malignant neoplasm of lymph nodes
C78*	Secondary malignant neoplasm of respiratory and digestive organs
C79*	Secondary malignant neoplasm of other and unspecified sites
C7A*	Malignant neuroendocrine tumors
C7B*	Secondary neuroendocrine tumors
C80*	Malignant neoplasm without specification of site
C81*	Hodgkin lymphoma
C82*	Follicular lymphoma
C83*	Non-follicular lymphoma
C84*	Mature T/NK-cell lymphomas
C85*	Other specified and unspecified types of non-Hodgkin lymphoma
C86*	Other specified types of T/NK-cell lymphoma
C88*	Malignant immunoproliferative diseases and certain other B-cell lymphomas
C90*	Multiple myeloma and malignant plasma cell neoplasms
C91*	Lymphoid leukemia
C92*	Myeloid leukemia
C93*	Monocytic leukemia
C94*	Other leukemias of specified cell type
C95*	Leukemia of unspecified cell type
C96*	Other and unspecified malignant neoplasms of lymphoid, hematopoietic and related tissue
D03*	Melanoma in situ
D46*	Myelodyplastic syndromes
Z85*	Personal history of malignant neoplasm
E70*	Disorders of aromatic amino-acid metabolism
E71*	Disorders of branched-chain amino-acid metabolism and fatty-acid metabolism
E72*	Other disorders of amino-acid metabolism
E74*	Other disorders of carbohydrate metabolism
E75.2*	Other sphingolipidosis
E76*	Disorders of glycosaminoglycan metabolism
E77*	Disorders of glycoprotein metabolism
E78*	Disorders of lipoprotein metabolism and other lipidemias
E79*	Disorders of purine and pyrimidine metabolism
E80*	Disorders of porphyrin and bilirubin metabolism
E83*	Disorders of mineral metabolism
E85*	Amyloidosis

(*Continued*)

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ICD10	Description
E88*	Other and unspecified metabolic disorders
E89.1*	Postprocedural hypoinsulinemia
E89.6*	Postprocedural adrenocortical (−medullary) hypofunction
E66.01*	Morbid (severe) obesity due to excess calories
E66.2*	Morbid obesity with alveolar hypoventilation (pickwickian syndrome)
Z68.4*	Body mass index (BMI) 40 or greater, adult
H49.81*	Kearns-Sayre syndrome
M12.0*	Chronic postrheumatic arthropathy [Jaccoud]
M30*	Polyarteritis nodosa and related conditions
M36.0*	Dermato(poly)myositis in neoplastic disease
A17.0*	Tuberculosis meningitis
E75.02*	Tay-Sachs disease
E75.19*	Other gangliosidosis
E75.4*	Neuronal ceroid lipofuscinosis
F01*	Vascular dementia
F02*	Dementia in other diseases classified elsewhere
F03*	Unspecified dementia
F71*	Moderate intellectual disabilities
F72*	Severe intellectual disabilities
F73*	Profound intellectual disabilities
F84.2*	Rett's syndrome
G10*	Huntington's disease
G11*	Hereditary ataxia
G12*	Spinal muscular atrophy and related syndromes
G13*	Systemic atrophies primarily affecting central nervous system in diseases classified elsewhere
G14*	Postpolio syndrome
G20*	Parkinson's disease
G21*	Secondary parkinsonism
G23*	Other degenerative diseases of basal ganglia
G24*	Dystonia
G25*	Other extrapyramidal and movement disorders
G26*	Extrapyramidal and movement disorders in diseases classified elsewhere
G30*	Alzheimer's disease
G31*	Other degenerative diseases of nervous system, not elsewhere classified
G32*	Other degenerative disorders of nervous system in diseases classified elsewhere
G35*	Multiple sclerosis
G36*	Other acute disseminated demyelination
G37*	Other demyelinating diseases of central nervous system
G40*	Epilepsy and recurrent seizures
G45*	Transient cerebral ischemic attacks and related syndromes
G46*	Vascular syndromes of brain in cerebrovascular diseases
G60*	Hereditary and idiopathic neuropathy
G61*	Inflammatory polyneuropathy
G62*	Other and unspecified polyneuropathies
G63*	Polyneuropathy in diseases classified elsewhere
G64*	Other disorders of peripheral nervous system
G70*	Myasthenia gravis and other myoneural disorders
G71*	Primary disorders of muscles
G73*	Disorders of myoneural junction and muscle in diseases classified elsewhere
G80*	Cerebral palsy
G81*	Hemiplegia and hemiparesis
G82*	Paraplegia (paraperesis) and quadriplegia (quadriparesis)
G83*	Other paralytic syndromes
G90.3*	Multi-system degeneration of the autonomic nervous system
G91*	Hydrocephalus
G93*	Other disorders of brain
G94*	Other disorders of brain in diseases classified elsewhere
G95*	Other and unspecified diseases of spinal cord
G99.2*	Myelopathy in diseases classified elsewhere
P91*	Other disturbances of cerebral status of newborn
Q00*	Anencephaly and similar malformations
Q01*	Encephalocele
Q02*	Microcephaly
Q03*	Congenital hydrocephalus
Q04*	Other congenital malformations of brain
Q05*	Spina bifida
Q06*	Other congenital malformations of the spinal cord
Q07*	Other congenital malformations of nervous system

(*Continued*)

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ICD10	Description
Q76*	Congenital malformations of spine and bony thorax
Q77*	Osteochondrodysplasia with defects of growth of tubular bones and spine
Q78*	Other osteochondrodysplasias
Q79*	Congenital malformations of musculoskeletal system, not elsewhere classified
Q85*	Phakomatoses, not elsewhere classified
Q87.4*	Marfan's syndrome
Q90*	Down syndrome
Q91*	Trisomy 18 and Trisomy 13
Q92*	Other trisomies and partial trisomies of the autosomes, not elsewhere classified
Q93*	Monosomies and deletions from the autosomes, not elsewhere classified
Q96*	Turner's syndrome
R41*	Other symptoms and signs involving cognitive functions and awareness
R53.2*	Functional quadriplegia
R54*	Age-related physical debility/frailty
K55.1*	Chronic vascular disorders of intestine
K55.8*	Other vascular disorders of intestine
K55.9*	Vascular disorder of intestine, unspecified
I70*	Atherosclerosis
I77*	Other disorders of arteries and arterioles
Z95.8*	Presence of other cardiac and vascular implants and grafts
Z95.9*	Presence of cardiac and vascular implant and graft, unspecified
I64*	*Code may not exist in US version of ICD10

(*Continued*)

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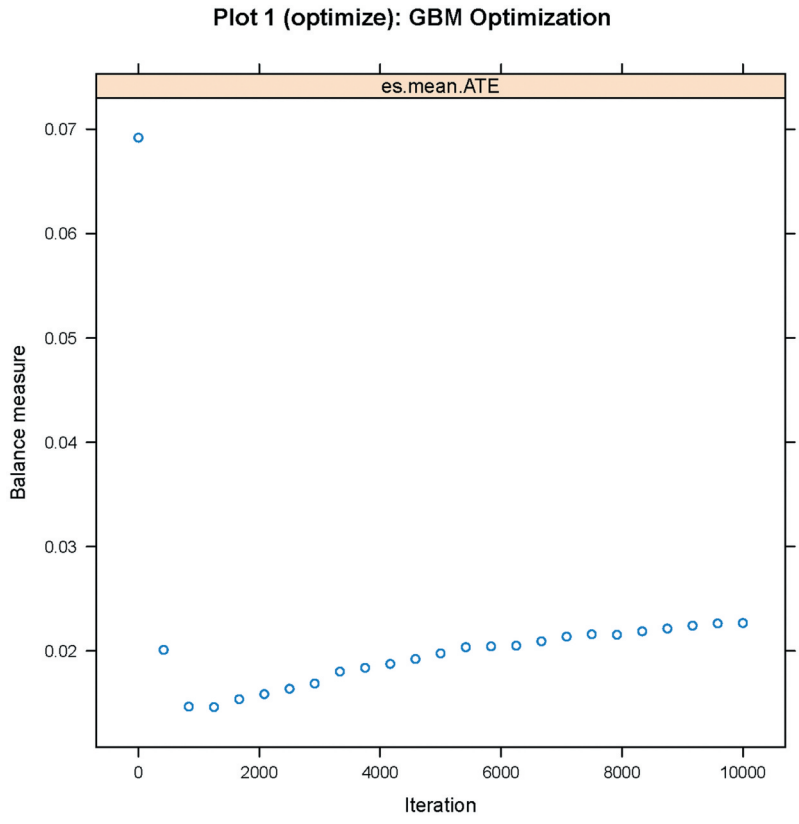
ICD10	Description
I65*	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
I66*	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
I67*	Other cerebrovascular diseases
H34.0*	Transient retinal artery occlusion
F00*	*Code may not exist in US version of ICD10
F05.1*	*Code may not exist in US version of ICD10
J40*	Bronchitis, not specified as acute or chronic
J46*	*Code may not exist in US version of ICD10
M35.1*	Other overlap syndromes
M35.3*	Polymyalgia rheumatica
K25*	Gastric ulcer
K26*	Duodenal ulcer
K27*	Peptic ulcer, site unspecified
K28*	Gastrojejunal ulcer
Z94.4*	Liver transplant status
E12*	*Code may not exist in US version of ICD10
E14*	*Code may not exist in US version of ICD10
G04.1*	Tropical spastic paraplegia
N19*	Unspecified kidney failure
C97*	*Code may not exist in US version of ICD10
I86.4*	Gastric varices
I98.2*	*Code may not exist in US version of ICD10
K79.9*	*Code may not exist in US version of ICD10
B21*	*Code may not exist in US version of ICD10
B22*	*Code may not exist in US version of ICD10
B24*	*Code may not exist in US version of ICD10
P29.0*	Neonatal cardiac failure

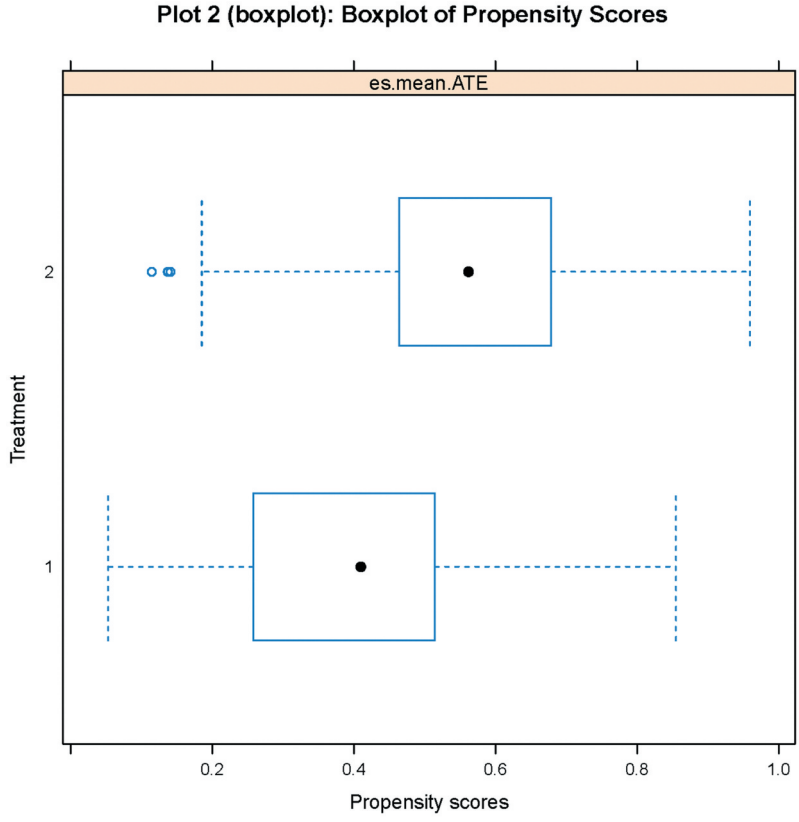
Appendix 2. Distribution of high-risk conditions between the two cohorts

Number of high-risk conditions	Total, N = 621	Recombinant, n = 356	Standard dose, N = 265
1	166 (26.73)	88 (24.72)	78 (29.43)
2	141 (22.73)	68 (19.10)	73 (27.55)
3	102 (16.43)	55 (15.45)	47 (17.74)
4	68 (10.95)	42 (11.8)	26 (9.81)
5	46 (7.41)	31 (8.71)	15 (5.66)
6	39 (6.28)	27 (7.58)	12 (4.53)
7	13 (2.09)	7 (1.97)	6 (2.26)
8	23 (3.70)	17 (4.78)	6 (2.26)
9	6 (0.97)	5 (1.40)	1 (0.38)
10	10 (1.61)	9 (2.53)	1 (0.38)
11	2 (0.32)	2 (0.56)	0
12	3 (0.48)	3 (0.84)	0
13	1 (0.16)	1 (0.28)	0
14	1 (0.16)	1 (0.28)	0

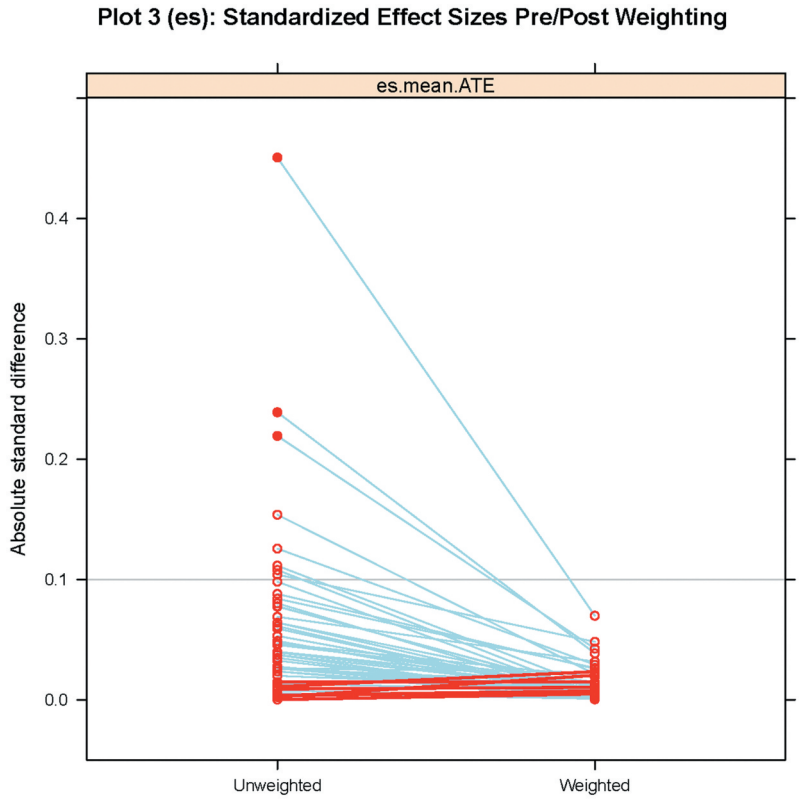
Appendix 3. Sample plots for Standardized Mean Difference (SMD) and balance plots between the two cohorts before and after weighting



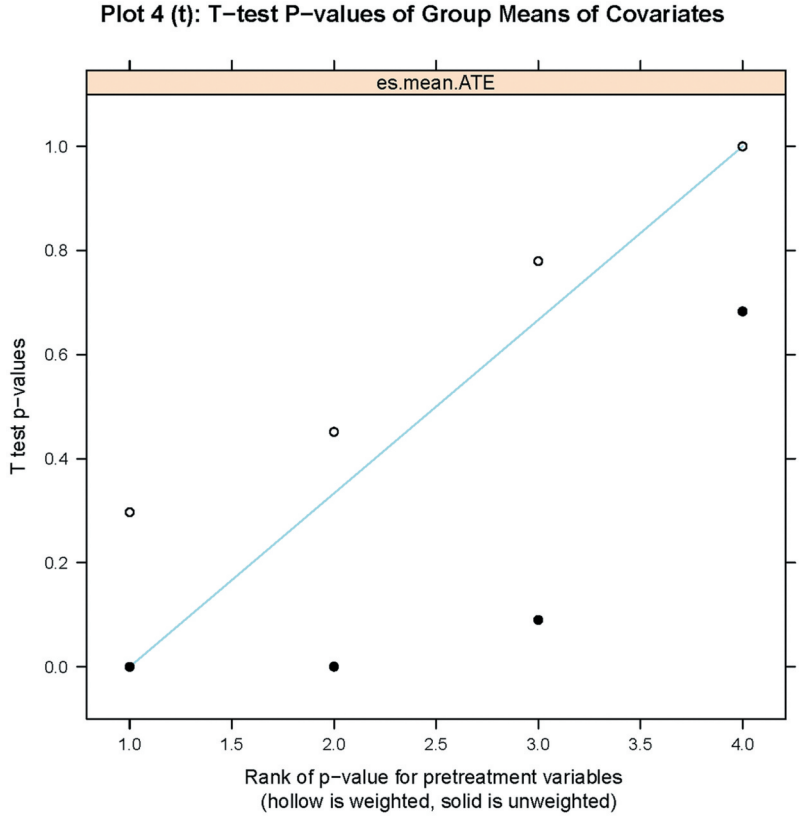
Plot 1 GBM Optimization_3.



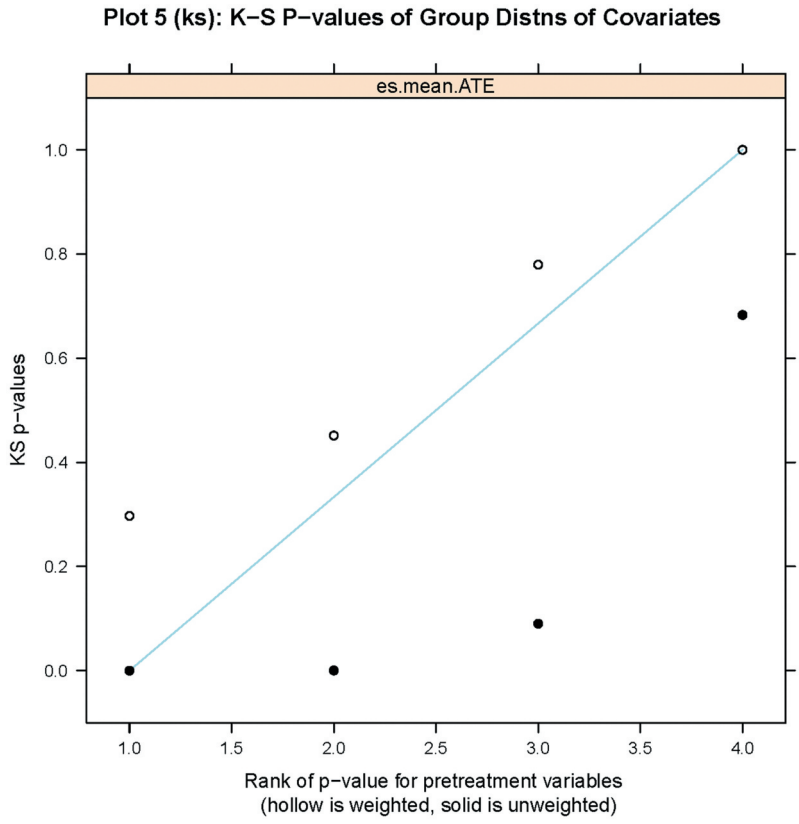
Plot 2 Boxplot of Propen_4.



Plot 3 Standardized Effect_5.



Plot 4 T test *p* values o_6.



Plot 5 Kolmogrov Simrnov_7.

Appendix 4. Patient characteristics by vaccination status (missing, recombinant, standard dose)

Measures	Missing vaccination, N = 95	Recombinant only, N = 510	Recombinant including missing vaccinations, N = 605	Standard dose only, N = 557	Standard Dose including missing vaccinations, N = 652
White race, ref. = nonwhite, n (%)	80 (84.2)	374 (73.3)	454 (75.0)	459 (82.4)	539 (82.7)
Female sex, ref. = male, n (%)	70 (73.7)	373 (73.1)	443 (73.2)	381 (68.4)	451 (69.2)
Season, n (%)					
2018–2019	31 (32.6)	142 (27.8)	173 (28.6)	159 (28.5)	190 (29.1)
2019–2020	64 (67.4)	368 (72.2)	432 (71.4)	398 (71.5)	462 (70.9)
Age Group, n (%)					
18–49 years	72 (75.8)	333 (65.3)	405 (66.9)	369 (66.2)	441 (67.6)
50–64 years	23 (24.2)	177 (34.7)	200 (33.1)	188 (33.8)	211 (32.4)
Influenza case, ref. = non-case, n (%)	17 (17.9)	124 (24.3)	141 (23.3)	142 (25.5)	159 (24.4)
High-risk condition, ref. = no, n (%)	41 (43.2)	356 (69.8)	397 (65.6)	265 (47.6)	306 (46.9)

Appendix 5. Effectiveness and relative effectiveness of recombinant and standard dose influenza vaccines including missing vaccination data

	Vaccine effectiveness		Relative Vaccine Effectiveness of Recombinant vs. Standard Dose Influenza Vaccine, % (95% CI)			
Group	Recombinant (a)	Standard dose (b)	Unadjusted (c)	Adjusted using *a priori* variables* (d)	Adjusted using Propensity score (e)	Adjusted using inverse probability weights (f)
Overall model	40 (25, 51)	35 (20, 47)	6 (−24, 29)	11 (−19, 34)	13 (−19, 37)	11 (−20, 33)
Overall model -including the missing	45 (34, 55)[1]	42 (30, 52)[2]	12 (−16, 32)[1]	10 (−20, 31)[1]	N/A	N/A
	42 (28, 52)[3]	38 (24, 49)[3]	1 (−30, 24)[2]	−4 (−39, 22)[2]	N/A	N/A

[1]Missing (unknown) vaccination subjects are included in the recombinant group.
[2]Missing (unknown) vaccination subjects are included in the standard dose group.
[3]Missing (unknown) vaccination subjects are included in the unvaccinated group.

Appendix 6. Sensitivity Analysis 1: Demographics and VE estimates

Baseline demographics all adults≥18 years old including immunocompromised, excluding recipients of other advanced (Flucelvax, FluAd) and high dose (High dose Fluzone) vaccines

	Vaccine received			Vaccination status		
Measures	Recombinant, n = 1,052	Standard Dose*, n = 501	*p* Value, recombinant vs. SD	Vaccinated, n = 1,553	Unvaccinated, n = 6,249	*p* Value, vaccinated vs. unvaccinated
Age, mean (SD)	54.2 (19.2)	45.9 (16.6)	<.001	51.5 (18.8)	46.7 (19.9)	<.001
White race, ref. = nonwhite, n (%)	841 (79.9)	417 (83.2)	0.113	1,258 (81.0)	4,817 (77.1)	<.001
Female sex, ref. = male, n (%)	712 (67.7)	307 (61.3)		1,019 (65.6)	3,782 (60.5)	
Season, n (%)			<.001			<.001
2018–2019	319 (30.3)	201 (40.1)		520 (33.5)	1,377 (22.0)	
2019–2020	733 (69.7)	300 (59.9)		1,033 (66.5)	4,872 (78.0)	
Age group, n (%)			<.001			<.001
18–49 years	296 (28.1)	199 (39.7)		495 (31.9)	2,806 (44.9)	
50–64 years	391 (37.2)	246 (49.1)		637 (41.0)	2,066 (33.1)	
≥65 years	365 (34.7)	56 (11.2)		421 (27.1)	1,377 (22.0)	
Influenza case, ref. = non-case, n (%)	197 (187)	108 (21.6)		305 (19.6)	1,928 (30.9)	
Immunocompromised, n (%)			<.001			<.001
No	769 (73.1)	419 (83.6)		1,188 (76.5)	5,638 (90.2)	
Yes	283 (26.9)	82 (16.4)		365 (23.5)	611 (9.8)	
High-risk condition, ref. = no, n (%)	880 (83.7)	283 (56.5)		1,163 (74.9)	2,958 (47.3)	

Effectiveness and relative effectiveness of recombinant and standard dose influenza vaccines against RT-PCR confirmed influenza for all adults≥18 years old including immunocompromised, excluding recipients of other advanced (Flucelvax, FluAd) and high dose (High dose Fluzone) vaccines

Influenza	Adjusted vaccine effectiveness,* % (95% CI)		Relative vaccine effectiveness of recombinant vs. standard dose influenza vaccine, % (95% CI)			
	Recombinant (a)	Standard Dose (b)	Unadjusted (c)	Adjusted using a priori variables** (d)	Adjusted using propensity score (e)	Adjusted using inverse probability weights (f)
Overall	**37 (25, 47)**	**42 (26, 54)**	13 (−15, 34)	1 (−34, 26)	3 (−31, 28)	−3 (−39, 22)
Age 18–49 years	**41 (22, 56)**	**50 (28, 65)**	−16 (−80, 25)	−7 (−70, 33)	−5 (−67, 33)	−10 (−73, 30)
Age 50–64 years	**36 (15, 52)**	**31 (2, 51)**	21 (−19, 48)	5 (−50, 40)	7 (−46, 40)	6 (−46, 39)
Age≥65 years	**30 (1, 51)**	63 (−6, 87)	−73 (−402, 40)	−76 (−427, 41)	−92 (−473, 36)	−112 (−517, 28)
Female sex	**39 (25, 51)**	**40 (18, 56)**	16 (−19, 40)	3 (−40, 33)	5 (−36, 34)	−2 (−46, 29)
Male sex	**33 (10, 51)**	**45 (17, 63)**	9 (−45, 43)	−8 (−84, 37)	−10 (−87, 35))	−4 (−72, 38)
High Risk Condition	**36 (21, 47)**	**29 (2, 49)**	22 (−10, 45)	12 (−27, 40)	14 (−24, 40)	10 (−28, 37)
No High-Risk Condition	**38 (11, 56)**	**54 (34, 68)**	−37 (−124, 17)	−33 (−122, 20)	−34 (−123, 20)	−31 (−117, 22)
2018–2019 Season	**39 (17, 56)**	**42 (16, 60)**	9 (−41, 42)	6 (−51, 42)	6 (−48, 40)	4 (−52, 39)
2019–2020 Season	**37 (22, 49)**	**40 (18, 57)**	14 (−24, 40)	−4 (−54, 30)	−3 (−52, 30)	−10 (−62, 25)
Immunocompromised	35 (−1, 59)†	53 (−13, 81)†	−36 (−241, 45)	−85 (−387, 30)†	−76 (−358, 32)†	–
Not Immunocompromised	**38 (25, 49)**	**41 (23, 54)**	9 (−41, 42)	6 (−51, 42)	9 (−25, 34)	4 (−32, 30)

Bold indicates non-overlapping confidence intervals. *Standard dose = Afluria, Fluarix, Flulaval and SD Fluzone.

*Adjusted vaccine effectiveness for recombinant and standard dose vaccines (Afluria, Fluarix, Flulaval and SD Fluzone) vs. no vaccination.

**Multivariable logistic regression model adjusted for age, race, sex, season, and high-risk conditions, except that the stratified variable is not included as an adjustment in its own analysis.

Propensity score: Generalized Boosted Regression Method was used to calculate the propensity score using TWANG (Toolkit for Weighting and Analysis of Nonequivalent Groups).

†High-risk not included.

Appendix 7. Sensitivity Analysis 2: Demographics and VE estimates

Baseline demographics for non-immunocompromised adults 18–64 years old, excluding recipients of other advanced (non-RIV4) vaccines

		Vaccine received			Vaccination status		
Measures	Total, N = 5,289	Recombinant, n = 509	Standard dose (SD), n = 332	*P* value recombinant vs. SD	Vaccinated, n = 841	Unvaccinated, n = 4,448	*p* Value vaccinated vs. unvaccinated
Age, Mean (SD)	38.4 (13.4)	41.4 (13.3)	41.6 (14.2)	0.853	41.5 (13.7)	37.8 (13.2)	**<.001**
White race, ref. = nonwhite, n (%)	3,853 (72.9)	373 (73.3)	268 (80.7)	**0.007**	641 (76.2)	3,212 (72.2)	**<.001**
Female sex, ref. = male, n (%)	3,307 (62.5)	372 (73.1)	218 (65.7)	**0.021**	590 (70.1)	2,717 (61.1)	**<.001**
Age Group, n (%)				0.918			**<.001**
18–49 years	3,063 (57.9)	245 (48.1)	161 (48.5)		406 (48.3)	2,657 (59.7)	
50–64 years	2,226 (42.1)	264 (51.9)	171 (51.5)		435 (51.7)	1,791 (40.3)	
Influenza case, ref. = non-case, n (%)	1,792 (33.9)	124 (24.4)	81 (24.4)	0.991	205 (24.4)	1,587 (35.7)	**<.001**
High-risk condition, ref. = no, n (%)	2,131 (40.3)	355 (69.7)	153 (46.1)	**<.001**	508 (60.4)	1,623 (36.5)	**<.001**
Season, n (%)				**<.001**			**<.001**
2018–2019	1,168 (22.1)	142 (27.9)	138 (41.6)		280 (33.3)	888 (20.0)	
2019–2020	4,121 (77.9)	367 (72.1)	194 (58.4)		561 (66.7)	3,560 (80.0)	

Effectiveness and relative effectiveness of recombinant and standard dose influenza vaccines against RT-PCR confirmed influenza for non-immunocompromised adults 18–64 years old, excluding recipients of other advanced (non-RIV4) vaccines

Influenza	Adjusted vaccine effectiveness,* % (95% CI)		Relative vaccine effectiveness of recombinant vs. standard dose influenza vaccine, % (95% CI)			
	Recombinant (a)	Standard Dose† (b)	Unadjusted (c)	Adjusted using a priori variables** (d)	Adjusted using propensity score (e)	Adjusted using inverse probability weights (f)
Overall	**40 (25, 51)**	**40 (22, 54)**	1 (−38, 28)	2 (−37, 31)	−8 (−56, 25)	−2 (−41, 27)
Age 18–49 years	**47 (27, 61)**	**51 (28, 67)**	−11 (−77, 30)	2 (−61, 40)	−5 (−71, 35)	−6 (−71, 35)
Age 50–64 years	**29 (3, 48)**	28 (−4, 50)	10 (−41, 42)	5 (−53, 41)	−1 (−64, 38)	−8 (−74, 34)
Female sex	**37 (18, 51)**	**34 (9, 52)**	1 (−47, 32)	5 (−42, 37)	−6 (−62, 31)	−5 (−58, 30)
Male sex	**46 (18, 65)**	**49 (21, 68)**	2 (−76, 45)	−13 (−121, 42)	−11 (−121, 45)	−6 (−100, 43)
High-risk condition	**42 (25, 56)**	21 (−15, 46)	28 (−11, 53)	29 (−11, 55)	26 (−21, 55)	28 (−15, 55)
No high-risk condition	**31 (1, 52)**	**55 (34, 69)**	−53 (−153, 7)	−67 (−185, 2)	−66 (−193, 6)	−61 (−174, 5)
2018–2019 season	**43 (15, 62)**	**47 (20, 65)**	−7 (−83, 37)	−5 (−84, 40)	−13 (−113, 40)	−9 (−98, 41)
2019–2020 season	**38 (20, 52)**	**37 (11, 55)**	2 (−48, 35)	0 (−55, 35)	−15 (−85, 28)	−7 (−67, 32)

Bold indicates non-overlapping confidence intervals. *Adjusted vaccine effectiveness for recombinant and standard dose vaccines vs. no vaccination.

**Multivariable logistic regression model adjusted for age, race, sex, season, and high-risk conditions, except that the stratified variable is not included as an adjustment in its own analysis.

†Standard dose = All standard dose egg-based; excludes other advanced (non-RIV4) vaccines Propensity score: Generalized Boosted Regression Method was used to calculate the propensity score using TWANG (Toolkit for Weighting and Analysis of Nonequivalent Groups).