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Estimating Influenza Vaccine Effectiveness Against Laboratory-Confirmed Influenza Using Linked Public Health Information Systems, California, 2023–2024 Season

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Abstract

Background. Mandatory public health reporting of influenza laboratory results and vaccine doses administered in the state of California can provide estimates of seasonal influenza vaccine effectiveness (VE).

Methods. We analyzed linked influenza immunization registry and laboratory reporting data among California residents aged ≥ 6 months tested for influenza during the 2023–24 influenza season (October 2023–June 2024). Individually linked laboratory reporting included influenza molecular or viral culture test result. Odds Ratios (OR) and 95% confidence intervals (CI) contrasted odds of documented 2023–2024 vaccination among persons with influenza-positive tests versus persons with negative influenza tests. VE was calculated as $(1 - \text{adjusted OR}) \times 100$ using logistic regression, adjusting for patient age, race, ethnicity, week of specimen collection, and county of residence.

Results. Among 1,382,142 laboratory reports, 129,253 persons (9%) (129,253) had a positive influenza test result, of whom 415,390 (30%) had documented influenza vaccination ≥ 14 days before test date. VE against laboratory-confirmed influenza was 41% (95% CI, 40%–42%). VE

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was 32% (95% CI, 31%–33%) against influenza A, 68% (95% CI, 66%–69%) against influenza B, and 26% (95% CI, 24%–29%) among adults aged ≥ 65 years.

Conclusions. Influenza vaccination was associated with prevention of laboratory-confirmed influenza. Results demonstrated feasibility of assessing seasonal influenza vaccine effectiveness using linked immunization and laboratory data from public health surveillance systems.

Summary. Influenza vaccines provided protection against laboratory-confirmed influenza in California during the 2023–2024 season. Interim and final season estimates were consistent. Linked public health information systems can be used to calculate timely influenza vaccine effectiveness estimates.

Keywords

Influenza; vaccine effectiveness; surveillance; immunization registry; case control

INTRODUCTION

During 2010–2019, seasonal influenza caused an estimated 9.4–41 million symptomatic illnesses, 100,000–710,000 hospitalizations, and 4,900–52,000 deaths annually in the United States [1]. Influenza vaccination provides protection against influenza-associated illness, hospitalization, and death, with estimated effectiveness of 40 to 60 percent during most seasons when circulating influenza viruses are similar to vaccine components [2]. The U.S. Centers for Disease Control and Prevention (CDC) provides both interim and final estimates of influenza vaccine effectiveness (VE) to assess effects of vaccination each season [2–5]. Evaluation of vaccine effectiveness informs immunization recommendations, policies surrounding vaccination timing, and communications regarding prevention of influenza, antiviral treatment and nonpharmaceutical interventions. VE platforms also document effects of intra-season influenza viral genetic changes and waning immunity [6–8]. Surveillance systems that link individual patient influenza test results and immunization records can provide early season indication of vaccine protection.

Multiple information systems support influenza surveillance in California, including laboratory reports, ambulatory consultations, hospitalizations, and influenza-associated deaths [9]. Influenza-positive laboratory test results became reportable October 1, 2019, including all influenza test results since June 15, 2023 [10]. Mandatory influenza vaccine reporting to the state immunization information system began January 1, 2023. These influenza reporting improvements were made for improved geographic coverage for respiratory virus surveillance and pandemic preparedness. To assess use of linked laboratory reporting and immunization records, the California Department of Public Health (CDPH) conducted an analysis of VE against laboratory-confirmed influenza during October 2023–June 2024, including VE against influenza A and B by age group and time since vaccination.

METHODS

Population and Setting

Electronic laboratory reporting data were extracted from the California Reportable Disease Information Exchange (CalREDIE) for all persons aged ≥ 6 months tested for influenza during October 1, 2023–June 30, 2024. Laboratory results for influenza tests are submitted to CalREDIE by electronic data exchange according to Health Level 7 (HL7) message standards; these results include test description, virus type, specimen collection date, patient identifiers, demographic characteristics, and facility information. Influenza laboratory results are available in CalREDIE within two weeks of testing; $>95\%$ of results are submitted within seven days of testing. CDPH de-duplicates data based on last name, first name, date of birth, specimen collection date, influenza type, and influenza A subtype. Information regarding testing facility, patient clinical presentation, and indication for testing were not available. All persons who received a polymerase chain reaction (PCR) test or viral culture for influenza at laboratory, hospital, pharmacy, ambulatory, or community-based testing facilities during this period were included in the analysis.

Influenza cases were defined as illnesses with a positive influenza PCR result or culture test. Clinical laboratories provided $>95\%$ of laboratory reporting data. Test results were reported as type A, B, or indeterminate if virus type was unknown. Influenza A subtype (H1N1 or H3N2) is reported for approximately 5% of influenza A positive specimens from clinical or public health laboratories (PHLs). For cases with multiple tests, date of illness was defined as the first positive test result. For influenza-negative controls, reference date was the earliest influenza PCR or viral culture result. To account for underreporting of influenza negative test results from individual laboratories, we excluded test results from any week in which a laboratory reported $\geq 50\%$ influenza positivity ($\sim 5\%$ of all test results reported during the period) [11]. SARS-CoV-2 testing was not assessed; positive SARS-CoV-2 results were not explicitly excluded.

Current season influenza vaccination status, including date of vaccine administration and vaccine product, was determined from the California Immunization Registry (CAIR). The majority ($>90\%$) of data are submitted by electronic data exchange according to HL7 message standards; a limited proportion are manually entered into CAIR with a user interface. Influenza vaccination records are available in CAIR within two weeks of testing; $>95\%$ of results are submitted within five days of testing. Vaccine product information was available for 100% of CAIR records for persons aged ≥ 65 years. Persons were classified as vaccinated if they had one or more documented doses of 2023–2024 influenza vaccination received at least 14 days before the reference date; those with documented vaccination 0–13 days before the reference date were excluded from analysis. Persons with no record of 2023–2024 vaccination or documented vaccination after the reference date were considered unvaccinated. Influenza test results and vaccination records were linked with using a probabilistic algorithm with exact match for date of birth and fuzzy match with a 95% cutoff on first name, last name, and county of residence [12]. Date of birth, first name, last name, and county of residence were $>99\%$ complete for CalREDIE and CAIR data.

Statistical Analysis

Characteristics of influenza-positive or negative persons, including vaccination status, were described using counts and percentages. VE was estimated using case-control analysis contrasting odds of current season influenza vaccination among laboratory-confirmed cases vs influenza-negative controls. VE was calculated as $100\% \times (1 - \text{adjusted odds ratio [aOR]})$ of vaccination, in mixed-effects logistic regression models including patient race, ethnicity, and age (natural cubic spline, five knots, degrees of freedom=4) as fixed effects, and county of residence and specimen week as random effects. We included specimen week as a random effect because time was not a primary factor of interest, and we wanted to account for changing influenza activity and testing volume during the season. Unadjusted odds ratios were estimated from logistic regression models without covariates.

VE was estimated by age group against any influenza virus, by type and subtype, calendar month and time since vaccination. VE by interval between vaccination to test reference date was estimated for 14–29, 30–59, 60–89, 90–119, 120–149, 150–179, or ≥ 180 days. We estimated product-specific VE among adults aged ≥ 65 years, and VE for live attenuated influenza vaccine (LAIV) vs inactivated vaccines among children aged 2–17 years. Analyses were conducted using R software, version 4.3.1 (R Foundation for Statistical Computing).

Ethical Statement

This activity was reviewed by CDPH and CDC, deemed not research, and was conducted consistent with applicable federal law and CDC policy (see eg, 45 C.F.R. part 46, 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq).

RESULTS

Patient Characteristics

Influenza laboratory test positivity (7-day rolling average) ranged from 1% to 19% during the analysis period (Figure 1). During October 1, 2023–June 30, 2024, a total of 1,382,142 persons with influenza laboratory test results were reported to CDPH, met inclusion criteria, and were included in the analysis. Of these, 129,253 (9%) were influenza-positive cases and 1,252,889 (91%) were influenza negative controls. Over 99% of influenza tests were PCR ($n = 1,381,952$); 94,414 (73%) were influenza type A, 24,533 (19%) were type B, and 10,306 (8%) were indeterminate (Supplemental Figure 1). Of 7,981 influenza A results that were subtyped, 84% (6,700) were A(H1N1)pdm09 and 16% (1,281) were A(H3N2). The characteristics of case-patients and control-subjects are presented in Table 1. Median ages were 30 years (IQR = 10–51) among case-patients and 43 years (IQR = 19–67) among control subjects. Overall, 415,390 (25%) persons had documented receipt of 2023–2024 influenza vaccine ≥ 14 days before test result; 19% (24,374) of case-patients and 31% (391,016) of control subjects were vaccinated. Median time since vaccination was 92 days (IQR = 64–129) among case-patients versus 105 days (IQR = 63–158) among control subjects.

Vaccine Effectiveness

Adjusted VE against any influenza was 41% (95% confidence interval (CI) = 40%–42%), 32% (95% CI = 31%–33%) against influenza A and 68% (95% CI = 66%–69%) against influenza B viruses (Figure 2). Estimated VE against any influenza was higher among children aged <18 years (53%) than adults aged 18–49 (42%), 50–64 (30%), and ≥65 years (26%). Similar trends by age were observed for VE against influenza A, ranging from 43% among children aged <18 years to 23% among adults aged ≥65 years, and influenza B, ranging from 71% among children aged <18 years to 58% among adults aged ≥65 years (Figure 2). Among cases of known influenza A subtype compared to influenza-negative controls, overall VE was 44% (40%–47%) against influenza A(H1N1)pdm09 and 25% (15%–35%) against A(H3N2) (Table 2).

Cumulative VE by calendar month showed consistent estimates of approximately 41% and 44% during December 2023–June 2024 (Figure 3); stratification by month of test showed lower VE estimates during April–June 2024 than during November 2023–March 2024 (Supplemental Table 1). Overall, VE was highest among persons with an influenza test result 14–29 days after vaccination (59%; 95% CI = 56%–61%). Estimated VE was lower with increasing interval between vaccination and testing: 30–59 days (52%; 95% CI = 50%–53%), 60–89 days (39%; 95% CI = 38%–41%), 90–119 days (34%; 95% CI = 32%–36%), 120–149 days (35%; 95% CI = 32%–37%), 150–179 days (34%; 95% CI = 30%–37%), and ≥180 days (23%; 95% CI = 20%–27%) (Figure 4).

Among 172,846 vaccinated adults aged ≥65 years, 150,958 (87%) received high-dose, adjuvanted, or recombinant influenza vaccine (Table 1). (CDC's Advisory Committee on Immunization Practices recommends that adults aged ≥65 years preferentially receive a high-dose, adjuvanted, or recombinant influenza vaccine [13].) All products were associated with protection, from 38% (95% CI = 17%–54%) for recombinant vaccine to 21% (95% CI = 14%–27%) for standard-dose inactivated vaccines (Supplemental Table 2). Among children aged 2–17 years, VE for LAIV was 45% (95% CI = 35%–54%) and 52% (95% CI = 51%–53%) for inactivated vaccines (Supplemental Table 3).

DISCUSSION

Our findings demonstrated feasibility of monitoring effectiveness of seasonal influenza vaccination using public health information systems that linked influenza vaccination records to influenza laboratory test results (including negative results) [11]. Influenza vaccination reduced the odds of laboratory-confirmed influenza by 41%. Although we were unable to assess effectiveness by illness severity, estimates from these information systems were consistent with those from U.S. and Canadian estimates for the 2023–2024 season, especially those from ambulatory settings [3, 14]. Previous studies have documented feasibility of assessing vaccine effectiveness using routinely reported public health data and compared results to traditional test-negative design studies [15]. However, consistency of VE estimated from surveillance data depends on data completeness and linkages between information systems [16]. Influenza test positivity and distribution of circulating influenza virus types in laboratory testing data were similar to overall influenza activity in California (Supplemental Figure 1), but lower compared with other multi-center U.S. studies [17, 18].

California's laboratory reporting system includes all influenza test results rather than only tests among patients with influenza-like illness. While most influenza testing occurred in outpatient settings, laboratory reporting did not indicate whether tests were ordered for ambulatory or hospitalized patients.

Mandatory reporting requirements in California contributed to data completeness for both influenza testing and immunization data, with a high degree of matching between information systems. Although not all influenza immunizations were reported to CAIR, coverage estimates for children aged <18 years and adults aged ≥65 years in CAIR were similar to estimates from the National Immunization Survey and the Behavioral Risk Factor Surveillance System [19, 20]. Linkage between California's state immunization information system and laboratory reporting can help assess vaccine effectiveness during future seasons and has the potential to provide early season estimates.

Lower estimates of vaccine effectiveness with increasing patient age are consistent with findings of a meta-analysis of test-negative studies conducted during 2004–2015 [21]. Age-related factors that contribute to lower VE might include diminished adaptive immune response, increased prevalence of comorbidities, and frailty [22]. Influenza VE estimates may inform strategies to communicate benefits of vaccination to persons at higher risk, in addition to importance of early influenza antiviral treatment to reduce the risk for severe influenza-related complications [23]. Demonstrated effectiveness among children inform providers and parents to increase influenza vaccination rates in children. Our findings should be examined alongside VE studies that assess clinical outcomes such as hospitalization and death; vaccination is likely to reduce the risk for severe influenza outcomes, even when not preventing infection [24].

Because vaccine effectiveness varies by influenza virus type and antigenic difference between vaccine components and circulating viruses [25, 26], vaccine effectiveness requires monitoring every season. Based on observed VE for influenza A and B, vaccines were protective during the 2023–24 respiratory season when vaccine components were antigenically similar to circulating viruses [27]. In California, approximately 85% of positive influenza specimens tested at Respiratory Laboratory Network facilities were influenza A viruses, of which 73% were A(H1N1)pdm09 viruses [28]. Because most clinical laboratory tests identify influenza A and B, and influenza A subtyping is not routine, virus subtype was only available for 5% of results. VE against influenza A subtypes, including A(H1N1)pdm09- and A(H3N2)-specific estimates should be interpreted with caution. Influenza A positive specimens from more severe or hospitalized cases may have been more likely to be submitted to public health laboratories for subtyping and be less representative of tests performed. We also observed higher VE against influenza B late in the influenza season in contrast to lower estimates observed against influenza A. Differences in viral evolution may contribute to waning vaccine effectiveness or immune escape [29].

Documentation of vaccine product in California's immunization information system allowed estimation of VE by vaccine type, which may inform specific vaccine recommendations. CDC's Advisory Committee for Immunization Practices preferentially recommends that adults aged ≥65 years receive a high-dose, recombinant, or adjuvanted influenza vaccine

[13]. While all products were associated with protection, confidence intervals were wide and differences between product-specific estimates were not statistically significant among adults aged ≥ 65 or children aged 6 months to 17 years.

The 2023–2024 season was the first since mandatory submission of influenza immunizations to California’s state information system and reporting of laboratory results, including negative results of influenza testing. Substantial increases in influenza test positivity during December 2023 and January 2024 coincided with indicators of influenza activity from other surveillance systems in California [28]. During January–June 2024, cumulative estimates of VE for the season were unchanged, whereas influenza activity decreased. However, we observed lower estimated VE against both influenza A and B beginning 60 to 89 days after vaccination, with the lowest estimates (including null estimates) occurring ≥ 180 days after vaccination. With most vaccinations occurring during September or October, protection was highest during peak influenza activity. After peak influenza activity, VE estimates might be lower late in the season due to higher attack rates among unvaccinated persons, referred to as differential depletion of susceptible persons [30, 31]. Cumulative VE estimates provide a better indication of protection during a season than when stratified by period [31].

The main strengths of this analysis were data timeliness and the substantial sample size to calculate VE for specific populations (i.e., those receiving a specific vaccine). We reported interim estimates of 2023–2024 influenza vaccine effectiveness in California in February 2024, when interim U.S. estimates were reported [3,11]. Depending on timing of influenza activity in California, surveillance data may provide early estimates due to the timeliness of reporting and large numbers of influenza tests performed. During 2023–2024, the number of influenza tests reported during October–January represented 53% of the total number for the season. The majority ($>95\%$) of influenza laboratory results and influenza vaccination records are available in CalREDIE and CAIR, respectively, within one week, allowing for near real time VE calculations. The captured population is also diverse, allowing for representativeness of California’s population. Mandatory reporting of laboratory and vaccine data in real time allows public health agencies to evaluate vaccine protection early during the influenza season, when developing communication strategies is crucial. The large population of California and these information systems might provide information about effectiveness of specific or new products recommended for children or older adults aged ≥ 65 years.

This analysis is subject to multiple limitations. First, incomplete influenza test results and influenza vaccinations during the first year of mandatory reporting may have resulted in misclassification of unvaccinated persons, under ascertainment of cases (i.e. unreported positive tests) and bias due to under reporting of negative test results. Second, laboratory data did not include influenza-associated symptoms, care setting, or illness outcomes. VE against medically attended acute respiratory infection, hospitalization, or death could not be calculated. Estimates of VE might have been biased if case-patients and control subjects were tested in different clinical settings, such that persons without influenza had less severe illness than persons who tested positive. Third, differences among preexisting conditions associated with likelihood of severe influenza, healthcare seeking, testing behavior, vaccination history, and prior influenza infection could not be assessed. Fourth, this analysis did not exclude persons who tested positive for SARS-CoV-2 infection. While

associations between influenza and COVID-19 vaccination can lead to underestimation of VE estimates [32], updated COVID-19 vaccination coverage was lower than 2023–2024 influenza vaccine coverage in California. Finally, this approach might be limited if patterns of clinical influenza testing, indications for testing, or use of rapid antigen tests versus molecular tests change over time.

CONCLUSIONS

During the 2023–2024 influenza season in California, data from influenza laboratory test results and vaccination information systems allowed health officials to assess VE. Influenza vaccination was protective against laboratory-confirmed influenza, though with heterogeneity across population subgroups and influenza type. Interim and final season estimates were consistent. Public health information systems can provide timely assessment of influenza vaccine effectiveness during the influenza season.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Disclaimer.

The findings and conclusions of this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the California Department of Public Health.

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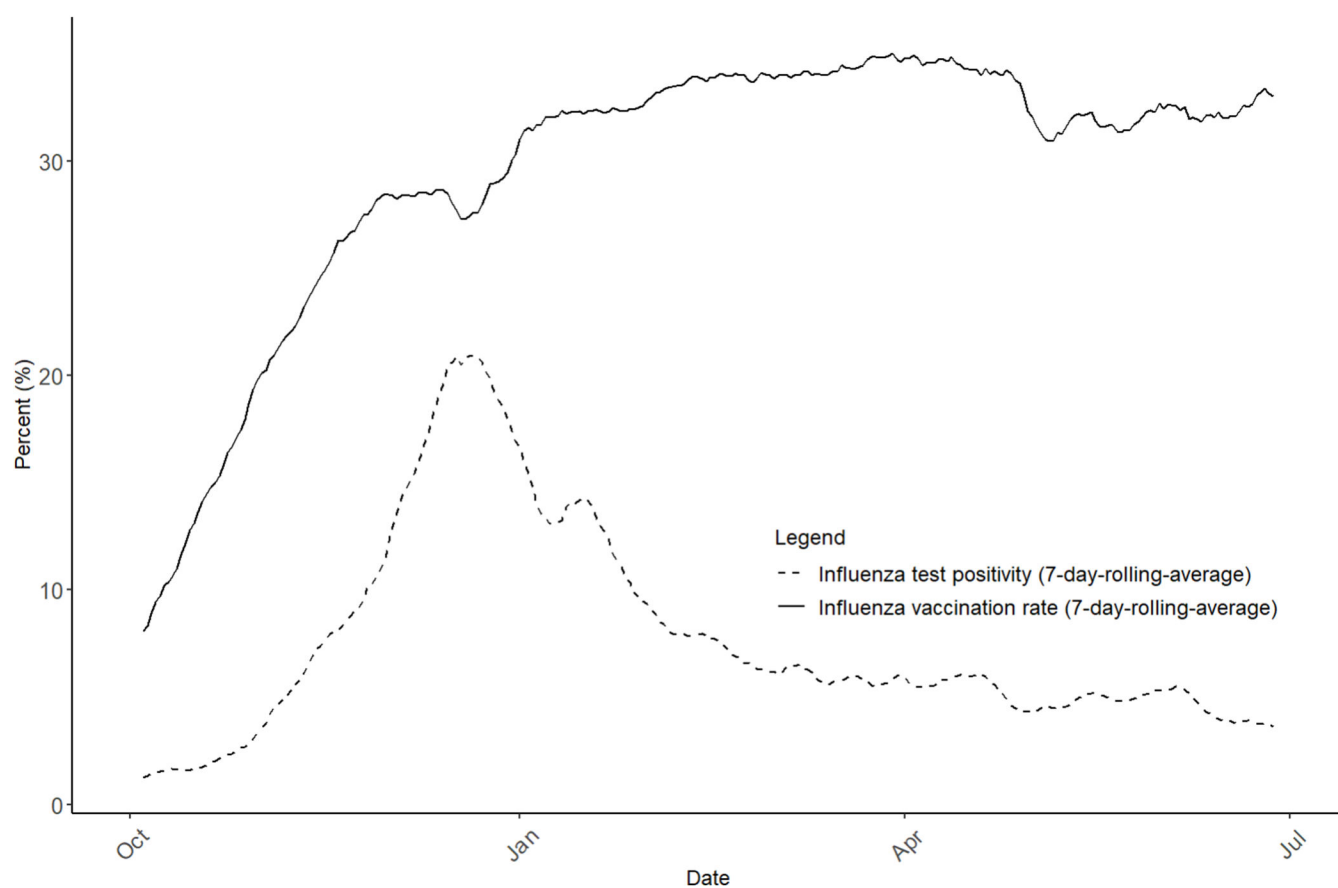
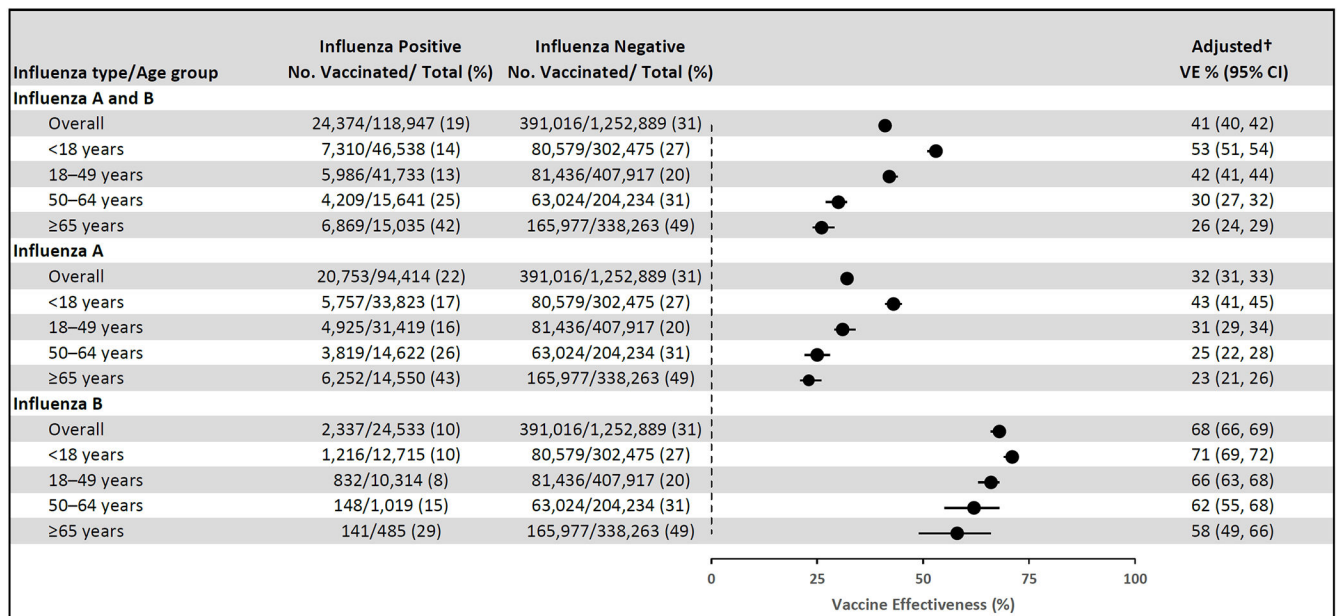


Figure 1. Rolling weekly influenza test positivity and vaccination rate from clinical specimens of 367 persons included in influenza vaccine effectiveness analysis — California, October 2023–July 2024.

**Figure 2.**

Influenza vaccine effectiveness against laboratory-confirmed influenza using case control 369 methodology — California, October 2023–June 2024. Error bars reflect 95% confidence intervals (CI). Note: VE for indeterminate influenza type was not calculated because of limited sample size. †Adjusted for age (natural cubic spline), race, ethnicity as fixed effects and specimen collection week and county of residence as random effects using mixed-effects logistic regression.

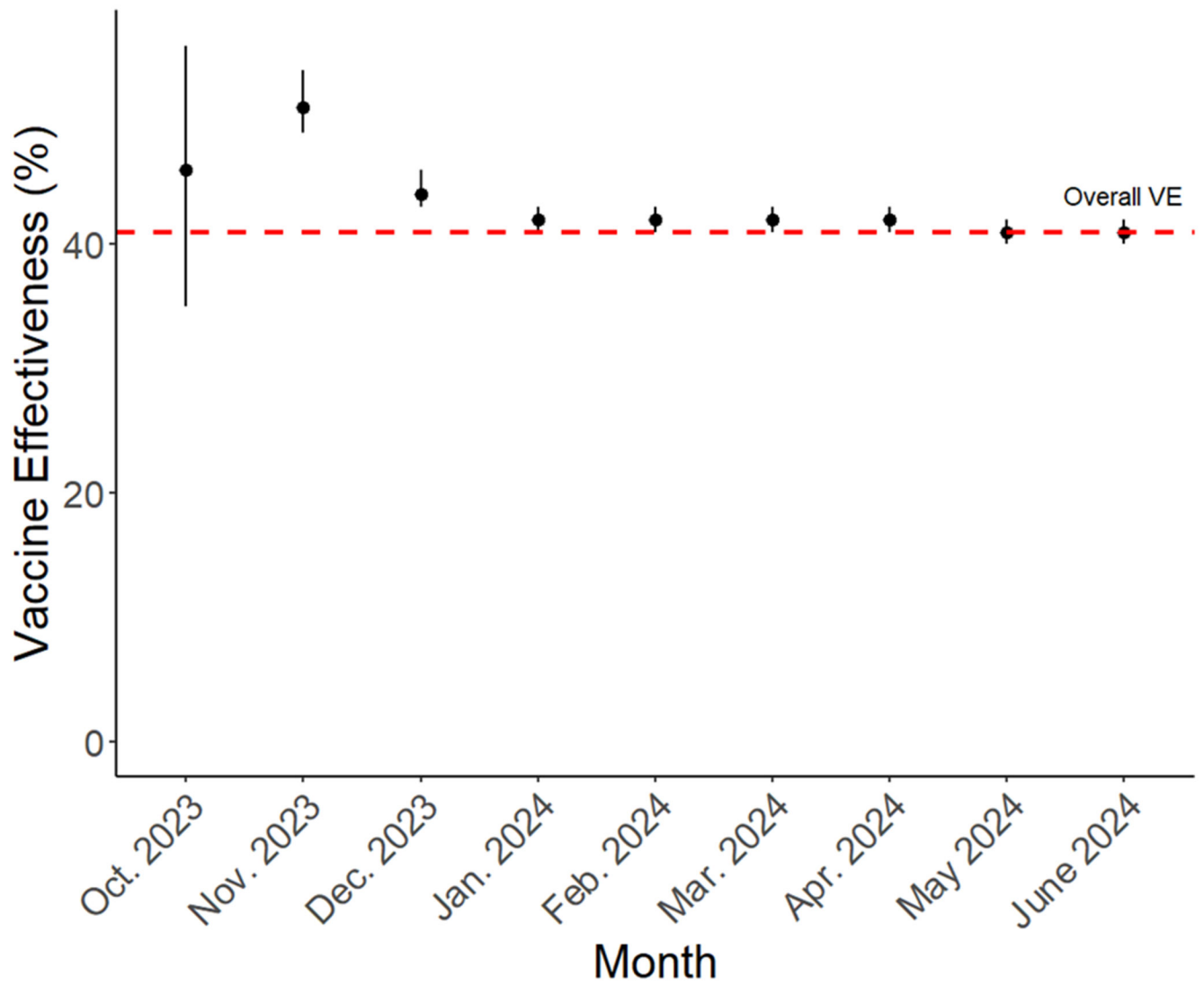
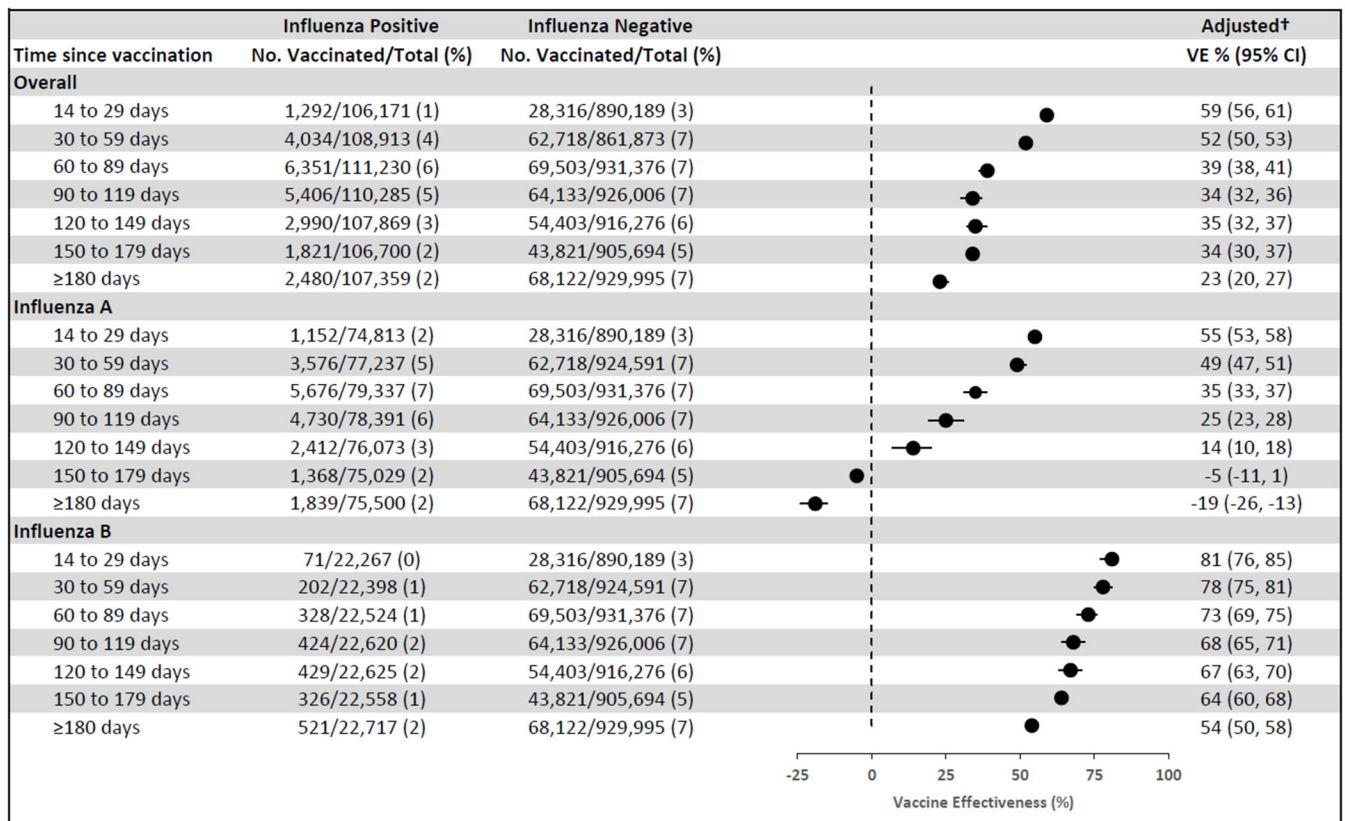


Figure 3. Cumulative influenza vaccine effectiveness over time against laboratory-confirmed influenza 375 using case control methodology — California, October 2023–June 2024. Error bars reflect 95% confidence intervals (CI).

**Figure 4.**

Influenza vaccine effectiveness against laboratory-confirmed influenza by number of days from vaccination to test result, California, October 2023–June 2024. Error bars reflect 95% confidence intervals (CI). †Adjusted for age (natural cubic spline), race, ethnicity as fixed effects and specimen collection week and county of residence as random effects using mixed-effects logistic regression.

Table 1.

Characteristics of Persons Tested for Influenza, With and Without Laboratory-Confirmed Influenza Infection
— California, October 2023–June 2024

	Test Result Status			
	Influenza Positive (n = 129,253; 9.4%)		Influenza Negative (n = 1,252,889; 90.6%)	
Characteristic	No.	(%)	No.	(%)
Median age, yrs (IQR)	29.5 (10–51)	—	43 (19–67)	—
Race				
American Indian or Alaska Native	624	0.5	8,315	0.7
Asian	10,580	8.2	98,621	7.9
Black or African American	7,266	5.6	72,435	5.8
Native Hawaiian or Pacific Islander	634	0.5	7,090	0.5
White	50,494	39.1	556,107	44.4
Multiple Races	230	0.2	2,286	0.2
Other	28,158	21.8	286,534	22.8
Unknown	31,267	24.1	221,501	17.7
Ethnicity				
Hispanic or Latino	36,214	28.0	319,301	25.5
Not Hispanic or Latino	65,642	50.8	687,389	54.9
Unknown	27,397	21.2	246,199	19.6
Sex (n=1,378,753)				
Female	69,115	53.5	679,540	54.4
Male	60,056	46.5	570,042	45.6
Influenza type				
A *	94,414	73.0	—	—
H1N1	6,700	83.9	—	—
H3N2	1,281	16.1	—	—
B	24,533	19.0	—	—
Indeterminate	10,306	8.0	—	—
Influenza vaccination status by test month				
Overall	24,374	18.9	391,016	31.2
Oct. 1–31	109	6.4	11,581	13.1
Nov. 1–30	1,536	12.6	38,370	25.9
Dec. 1–31	8,293	17.5	64,684	30.9
Jan. 1–31	6,275	21.2	67,219	33.7
Feb. 1–29	2,736	20.4	58,024	34.9
Mar. 1–31	2,175	20.2	59,601	35.2
Apr. 1–30	1,531	22.6	40,930	35.1

	Test Result Status			
	Influenza Positive (n = 129,253; 9.4%)		Influenza Negative (n = 1,252,889; 90.6%)	
Characteristic	No.	(%)	No.	(%)
May 1–31	890	21.2	26,467	32.2
Jun. 1–30	829	25.0	24,140	32.9
Influenza vaccination status by age group				
<18 years [†]	7,310	14.4	80,579	26.6
18–49 years	5,986	13.3	81,436	20.0
50–64 years	4,209	24.7	63,024	30.9
≥65 years	6,869	41.8	165,977	49.1
Median days from influenza vaccination to test result (IQR)	92 (64–129)	—	105 (63–158)	—
Adults aged ≥65 years who received high dose, adjuvanted, or recombinant influenza vaccine				
Yes	5,939	86.5	145,019	87.4
High-dose	3,395	57.6	81,344	56.1
Recombinant	47	0.4	1,213	0.8
Adjuvanted	2,497	42.0	62,462	43.1
No	930	13.5	20,958	12.6

Data are No. (%) except where indicated.

Abbreviation: IQR = interquartile range

* Subtyping was only performed on 8% of influenza A specimens.

[†] Children aged <6 months were excluded.

Table 2.

Influenza Vaccine Effectiveness Against Laboratory-Confirmed Influenza by Influenza A Subtype, Among All Ages, California, October 2023–June 2024

	Influenza Positive	Influenza Negative	Unadjusted	Adjusted [†]
Influenza A Subtype	No. Vaccinated/Total (%)	No. Vaccinated/Total (%)	VE (%) (95% CI)	VE (%) (95% CI)
H1N1	1184/6,700 (18)	391,016/1,252,889 (31)	53 (50–56)	44 (40–47)
H3N2	312/1,281 (24)	391,016/1,252,889 (31)	29 (19–38)	25 (15–35)

[†] Adjusted for age (natural cubic spline), race, ethnicity as fixed effects and specimen collection week and county of residence as random effects using mixed-effects logistic regression.