Interim Influenza Vaccine Effectiveness Against Laboratory-Confirmed Influenza, California, October 2024 – January 2025

Joshua Quint, PhD, MPH

California Department of Public Health

American Immunization Registry Association Meeting

February 24, 2025

CDPHVaccineDataTeam@cdph.ca.gov

CDPH
California Department of Public Health

Disclaimer: The findings and conclusions in this presentation are those of the authors and do not necessarily represent the views or opinions of the California Department of Public Health or the California Health and Human Services Agency.

Conflicts of interest: None

Morbidity and Mortality Weekly Report

Interim Influenza Vaccine Effectiveness Against Laboratory-Confirmed Influenza — California, October 2023–January 2024

Sophie Zhu, PhD[1,2]; Joshua Quint, PhD[2]; Tomás M. León, PhD[2]; Monica Sun, MPH[2]; Nancy J. Li, MS[2]; Mark W. Tenforde, MD, PhD[3]; Seema Jain, MD[2]; Robert Schechter, MD[2]; Cora Hoover, MD[2]; Erin L. Murray, PhD[2]

---

https://pubmed.ncbi.nlm.nih.gov/38421946/

CDPH

Quick Poll

- Over the past 10 years, what was the median estimated vaccine effectiveness for the seasonal influenza vaccine in the United States?

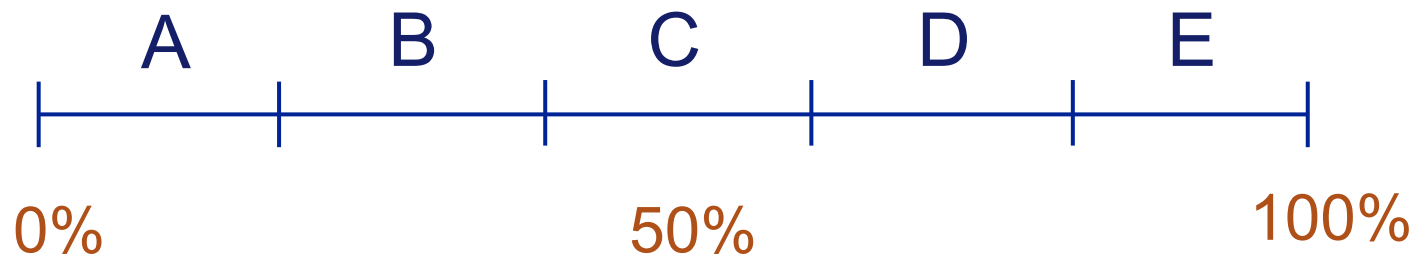
A. 0 - 19%

B. 20 - 39%

C. 40 - 59%

D. 60 - 79%

E. 80 - 99%



CDPH

Overview

- Background
- Methods
- Results
- Discussion

CDPH

Background

Burden of Influenza in the United States

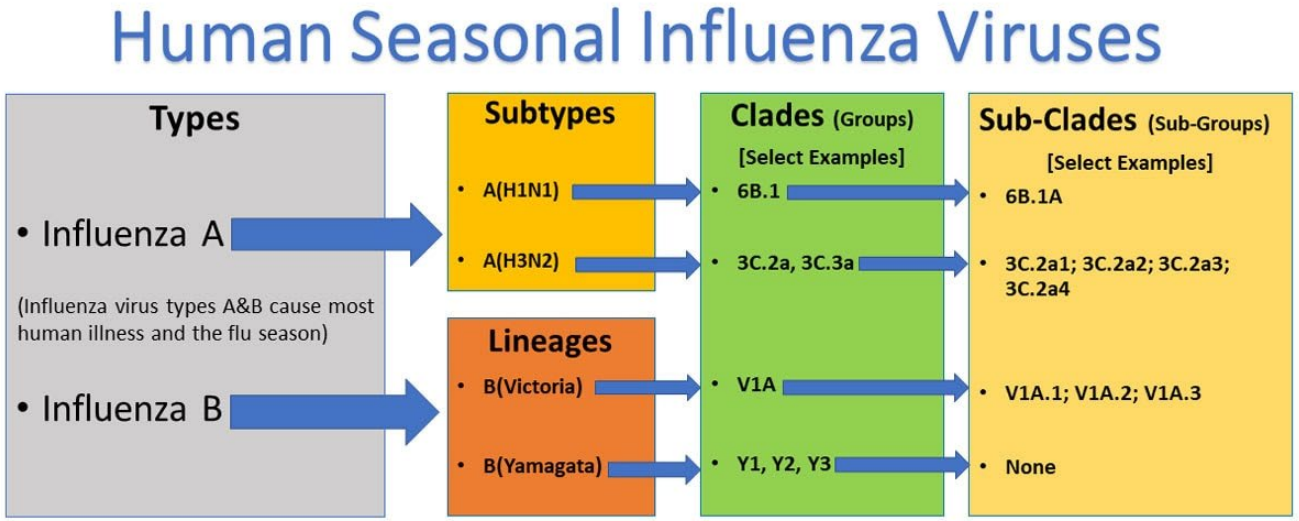
- Flu vaccine prevents millions of illnesses and flu-related doctor's visits each year.
- During 2019-2020, vaccination in the United States prevented an estimated:
  - 7 million influenza illnesses,
  - 3 million influenza-associated medical visits,
  - 100,000 influenza-associated hospitalizations, and
  - 7,000 influenza-associated deaths
- The Centers for Disease Control and Prevention (CDC) recommends that everyone age 6 months and older receive an annual influenza (flu) vaccine.
  - During seasons when flu vaccine viruses are similar to circulating flu viruses, flu vaccine has been shown to reduce the risk of having to go to the doctor with flu by 40% to 60%.

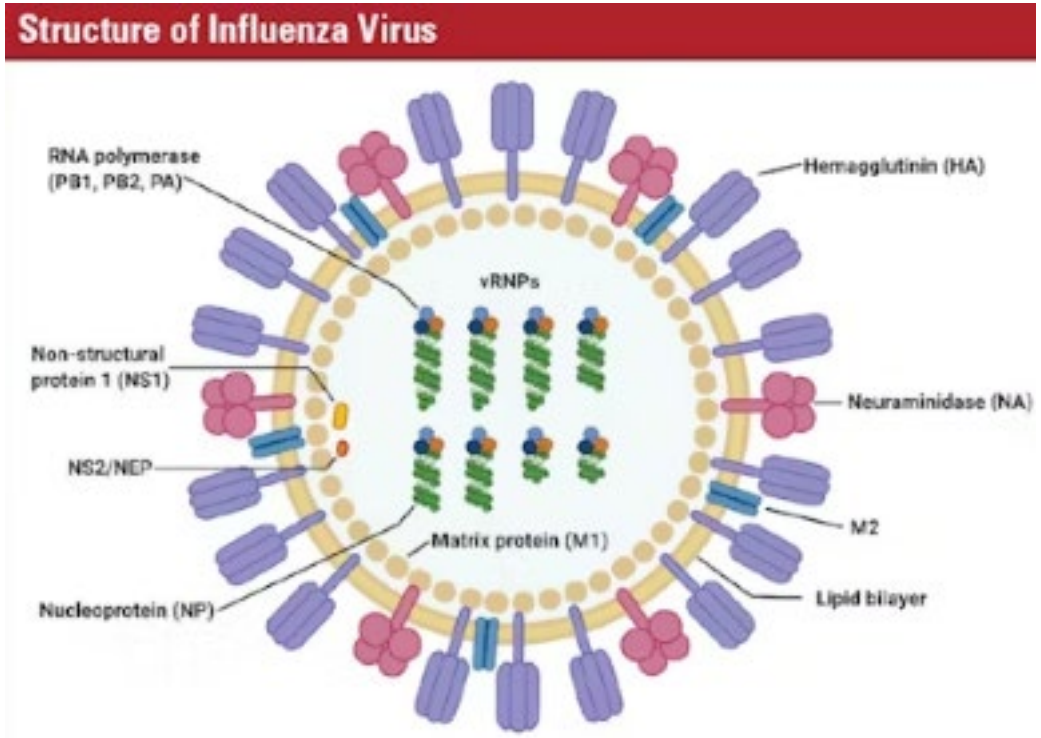
https://www.cdc.gov/flu/vaccines/index.html

Background

Why do we need a new vaccine every year?

- Influenza Types





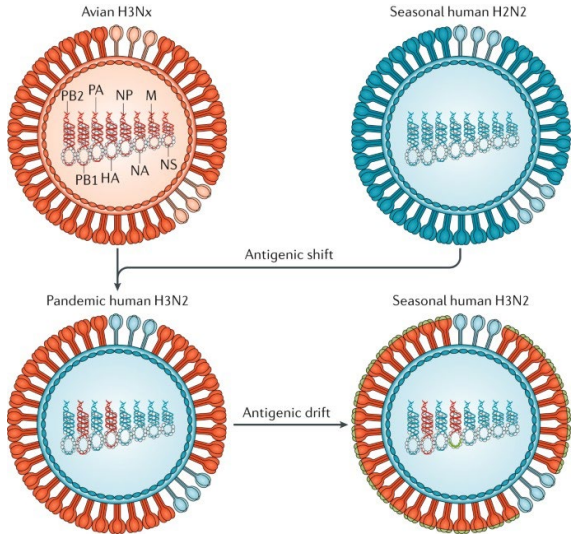
CDPH

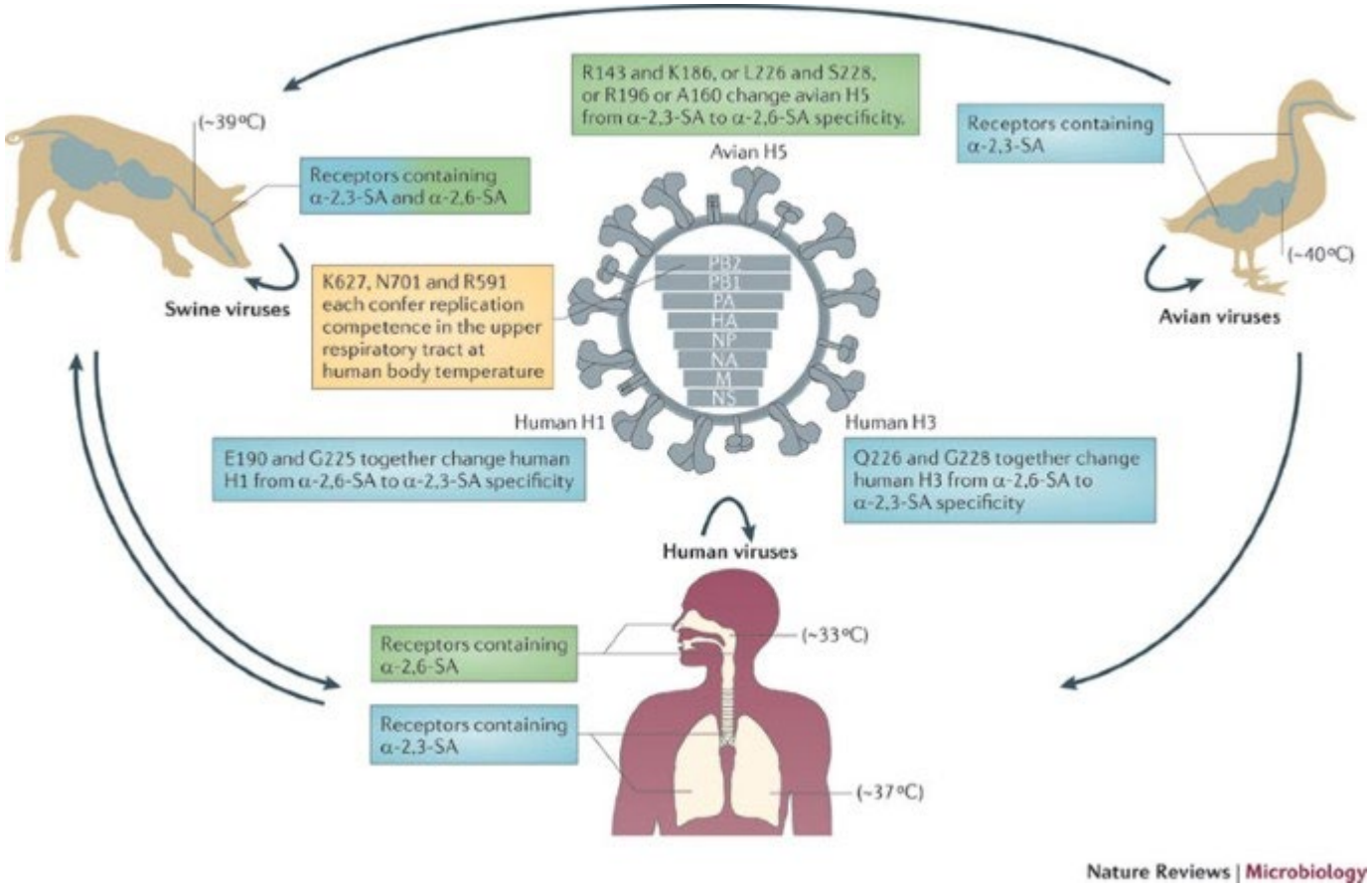
https://pmc.ncbi.nlm.nih.gov/articles/PMC3074182/
https://www.health.harvard.edu/staying-healthy/why-do-we-need-new-flu-shots-every-year
https://www.cdc.gov/flu/about/viruses-types.html

Background

Why do we need a new influenza vaccine every year?

- Antigenic drift and shift





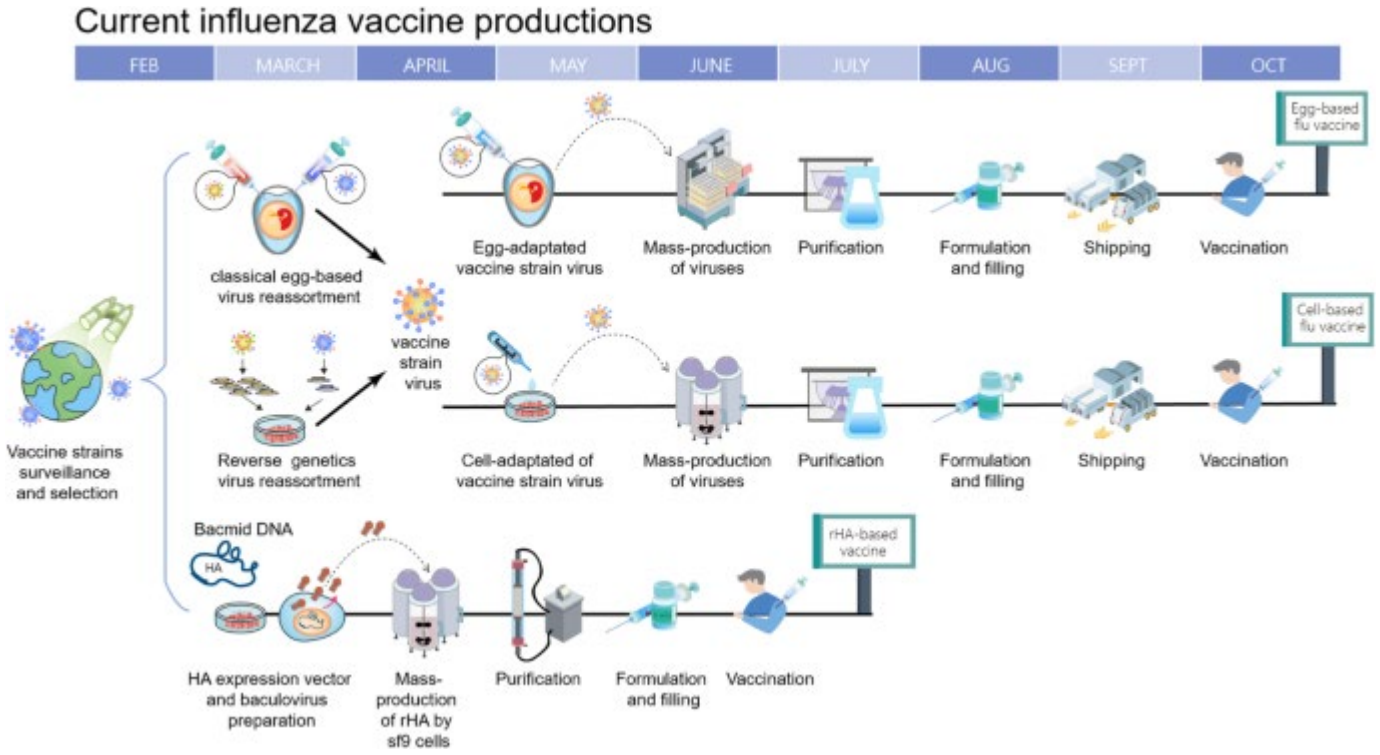
CDPH

https://www.nature.com/articles/s41572-018-0002-y
https://www.nature.com/articles/nrmicro2613

Vaccine Formula

How is the seasonal vaccine formula selected?

- To obtain the best possible match between the vaccine and the circulating viruses, the FDA, WHO, CDC and other partners review data on the circulating flu strains from around the world
- In late February, the FDA convenes its vaccines advisory committee to review data and recommend which flu virus strains to include in the vaccines for the upcoming U.S. flu season
- Once the strains are selected, vaccine manufacturers begin the process to include the newly selected flu strains in their FDA-approved vaccines

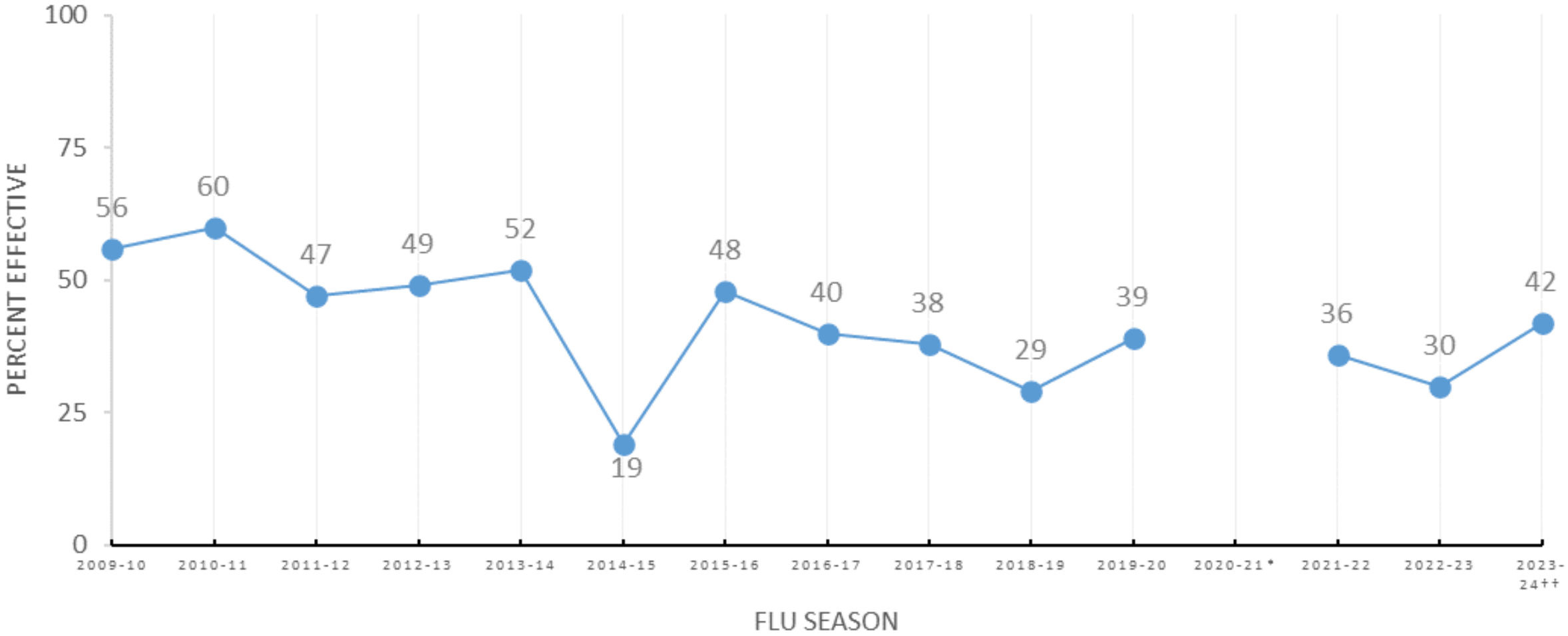


CDPH

https://www.fda.gov/consumers/consumer-updates/fdas-critical-role-ensuring-safe-and-effective-flu-vaccines
https://jbiomedsci.biomedcentral.com/articles/10.1186/s12929-020-0626-6

SEASONAL FLU VACCINE EFFECTIVENESS

UNITED STATES 2009-2024



CDPH

https://www.cdc.gov/flu-vaccines-work/php/effectiveness-studies/index.html

Quick Poll

- Over the past 10 years, what was the median estimated vaccine effectiveness for the seasonal influenza vaccine in the United States?

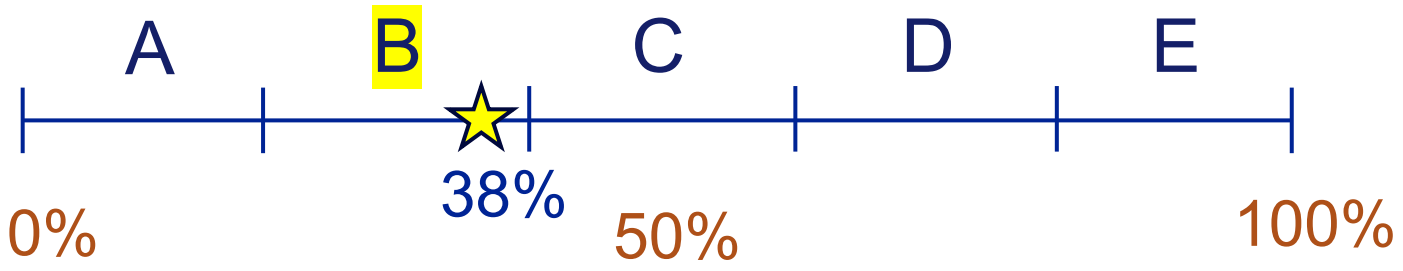
A. 0 - 19%

B. 20 - 39%

C. 40 - 59%

D. 60 - 79%

E. 80 - 99%



CDPH

Background

Why calculate vaccine effectiveness?

- Having information about vaccine effectiveness is important to:

    1. Understand how well the previous vaccine composition selection performed

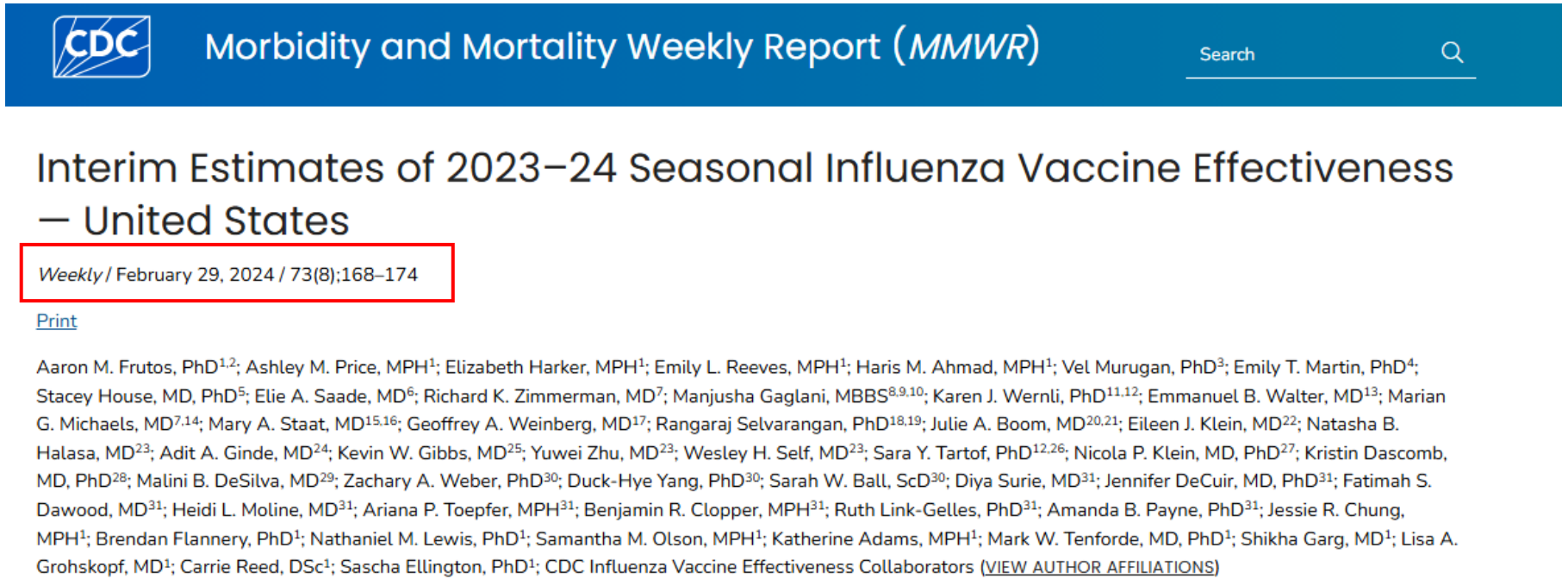
    2. Understand the relative importance of other (non-pharmaceutical) interventions

Evaluation of influenza vaccine effectiveness - A guide to the design and interpretation of observational studies (World Health Organization)

Background

Why calculate vaccine effectiveness?

- CDC publishes interim estimates from their hospital network platforms in late February



Morbidity and Mortality Weekly Report (*MMWR*)

Search

Interim Estimates of 2023–24 Seasonal Influenza Vaccine Effectiveness — United States

Weekly / February 29, 2024 / 73(8);168–174

Print

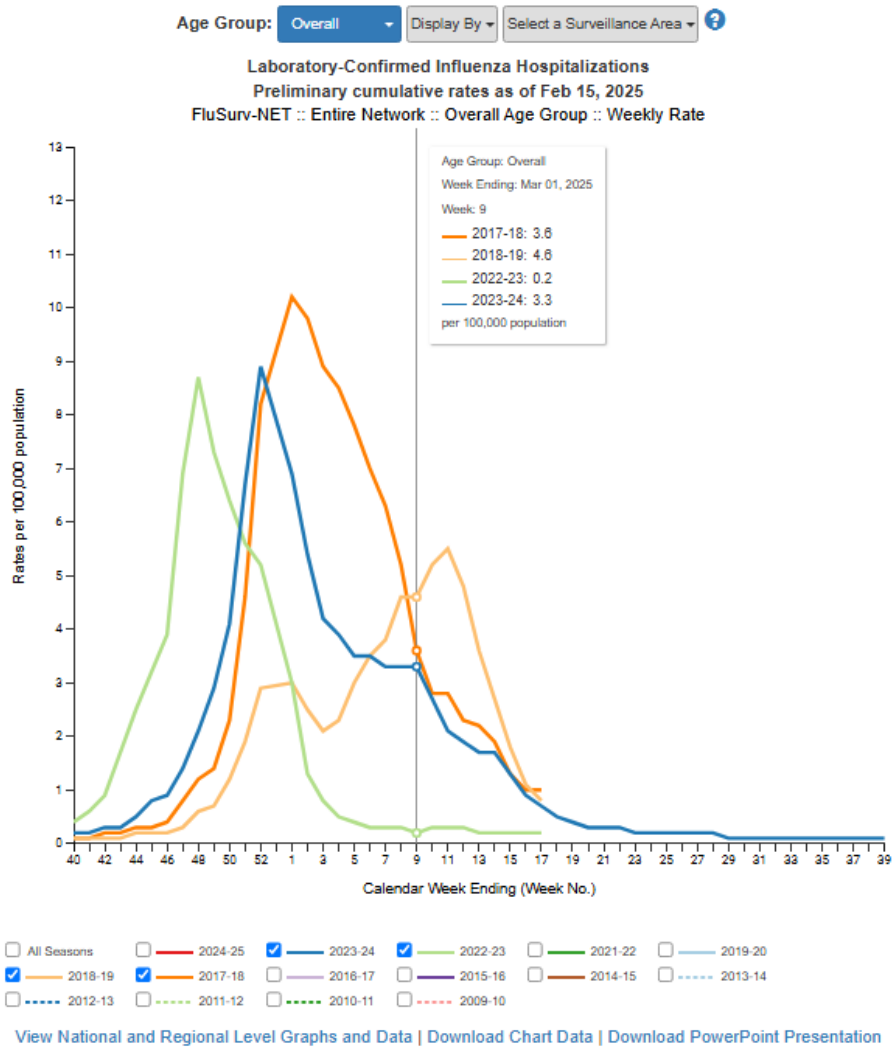
Aaron M. Frutos, PhD[1,2]; Ashley M. Price, MPH[1]; Elizabeth Harker, MPH[1]; Emily L. Reeves, MPH[1]; Haris M. Ahmad, MPH[1]; Vel Murugan, PhD[3]; Emily T. Martin, PhD[4]; Stacey House, MD, PhD[5]; Elie A. Saade, MD[6]; Richard K. Zimmerman, MD[7]; Manjusha Gaglani, MBBS[8,9,10]; Karen J. Wernli, PhD[11,12]; Emmanuel B. Walter, MD[13]; Marian G. Michaels, MD[7,14]; Mary A. Staat, MD[15,16]; Geoffrey A. Weinberg, MD[17]; Rangaraj Selvarangan, PhD[18,19]; Julie A. Boom, MD[20,21]; Eileen J. Klein, MD[22]; Natasha B. Halasa, MD[23]; Adit A. Ginde, MD[24]; Kevin W. Gibbs, MD[25]; Yuwei Zhu, MD[23]; Wesley H. Self, MD[23]; Sara Y. Tartof, PhD[12,26]; Nicola P. Klein, MD, PhD[27]; Kristin Dascomb, MD, PhD[28]; Malini B. DeSilva, MD[29]; Zachary A. Weber, PhD[30]; Duck-Hye Yang, PhD[30]; Sarah W. Ball, ScD[30]; Diya Surie, MD[31]; Jennifer DeCuir, MD, PhD[31]; Fatimah S. Dawood, MD[31]; Heidi L. Moline, MD[31]; Ariana P. Toepfer, MPH[31]; Benjamin R. Clopper, MPH[31]; Ruth Link-Gelles, PhD[31]; Amanda B. Payne, PhD[31]; Jessie R. Chung, MPH[1]; Brendan Flannery, PhD[1]; Nathaniel M. Lewis, PhD[1]; Samantha M. Olson, MPH[1]; Katherine Adams, MPH[1]; Mark W. Tenforde, MD, PhD[1]; Shikha Garg, MD[1]; Lisa A. Grohskopf, MD[1]; Carrie Reed, DSc[1]; Sascha Ellington, PhD[1]; CDC Influenza Vaccine Effectiveness Collaborators (VIEW AUTHOR AFFILIATIONS)

https://www.cdc.gov/mmwr/volumes/73/wr/mm7308a3.htm

Background

Why calculate vaccine effectiveness?

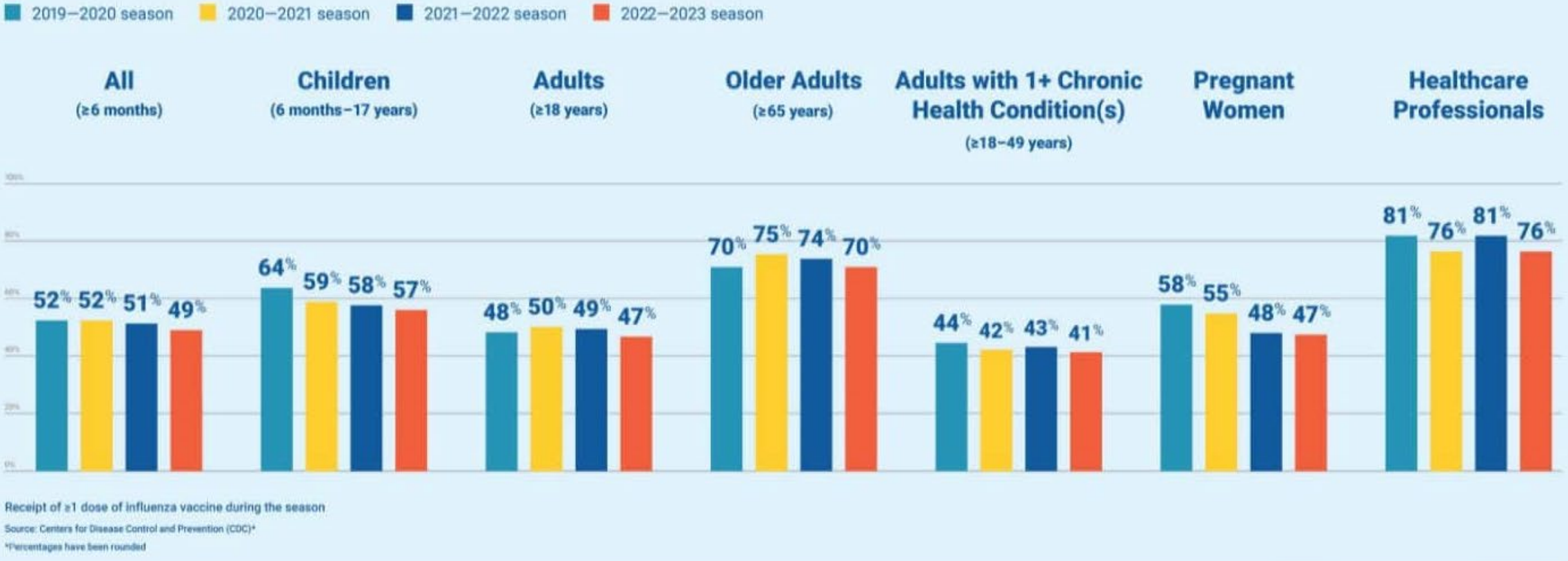
- CDC publishes interim estimates from their hospital network platforms in late February
- Flu activity for most seasons peaks before the end of February



CDPH

https://www.cdc.gov/fluview/surveillance/2025-week-07.html

Influenza Vaccination Coverage by Population



Receipt of ≥1 dose of influenza vaccine during the season

Source: Centers for Disease Control and Prevention (CDC)*

*Percentages have been rounded

Annual vaccination is the best way to help protect against flu and potentially serious complications
Visit www.nfid.org/flu to learn more about how you can help #FightFlu

https://www.nfid.org/resource/influenza-vaccination-coverage-by-population/

National Foundation for Infectious Diseases

www.nfid.org

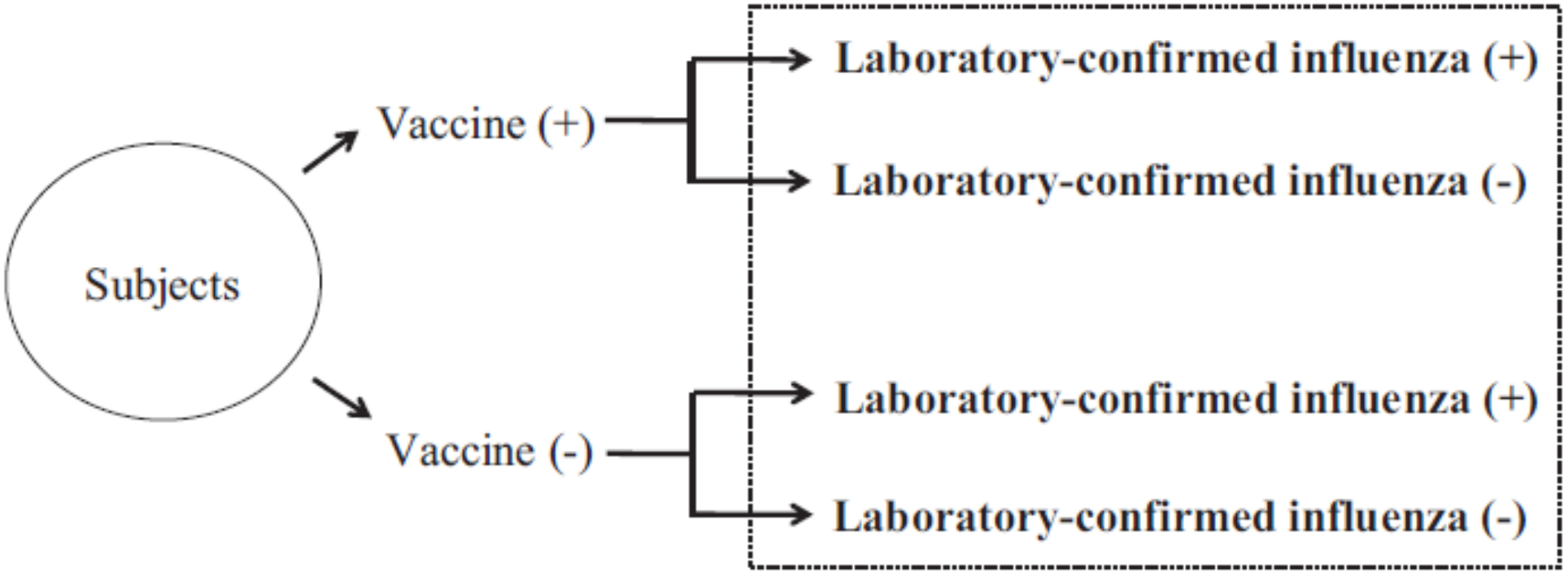
Background

How could earlier vaccine effectiveness estimates be useful?

- Inform messaging regarding importance of vaccination
- Inform messaging about importance of non-pharmaceutical preventive measures (masks, distancing)
- Support resource planning for a potential high-severity, low effectiveness scenario (anti-viral availability, hospital capacity)

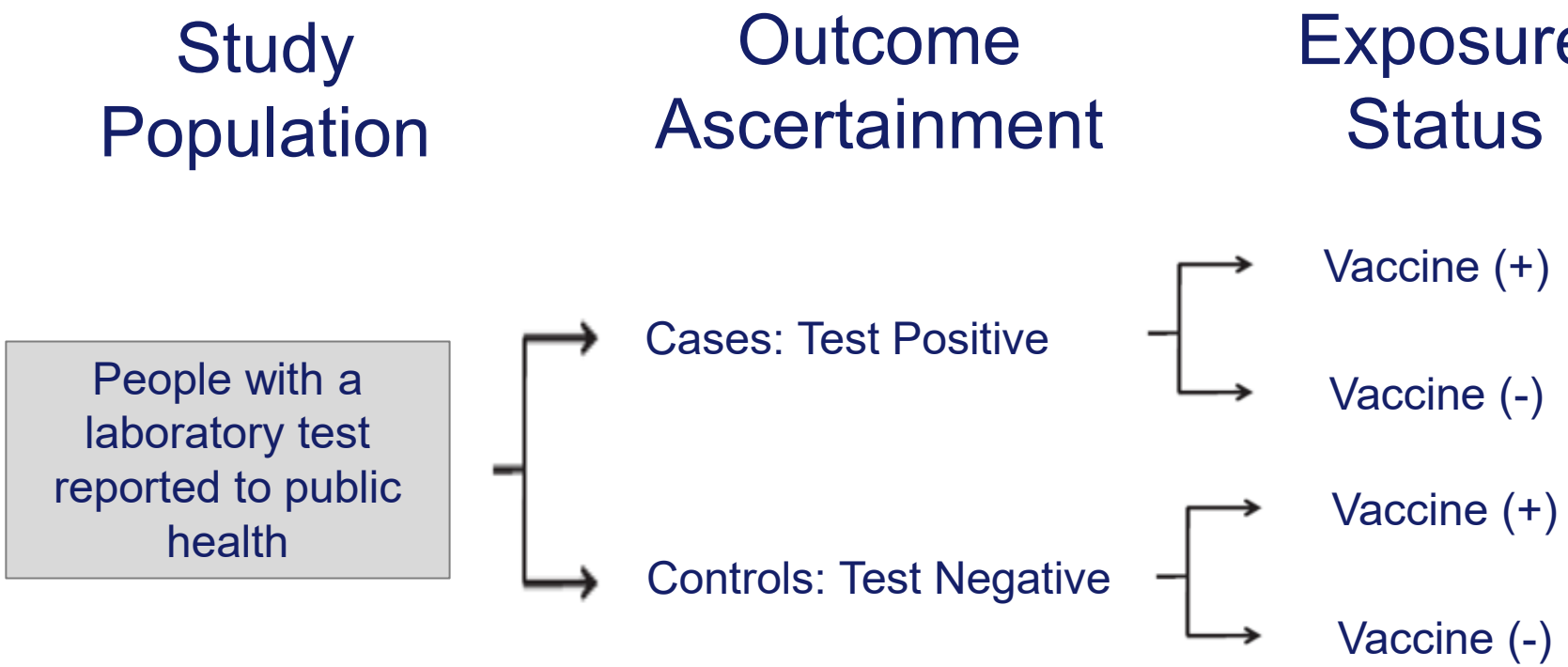
Randomized Control Trial (RCT)

Cohort Design (Observational)



CDPH

Case Control Design (Observational)

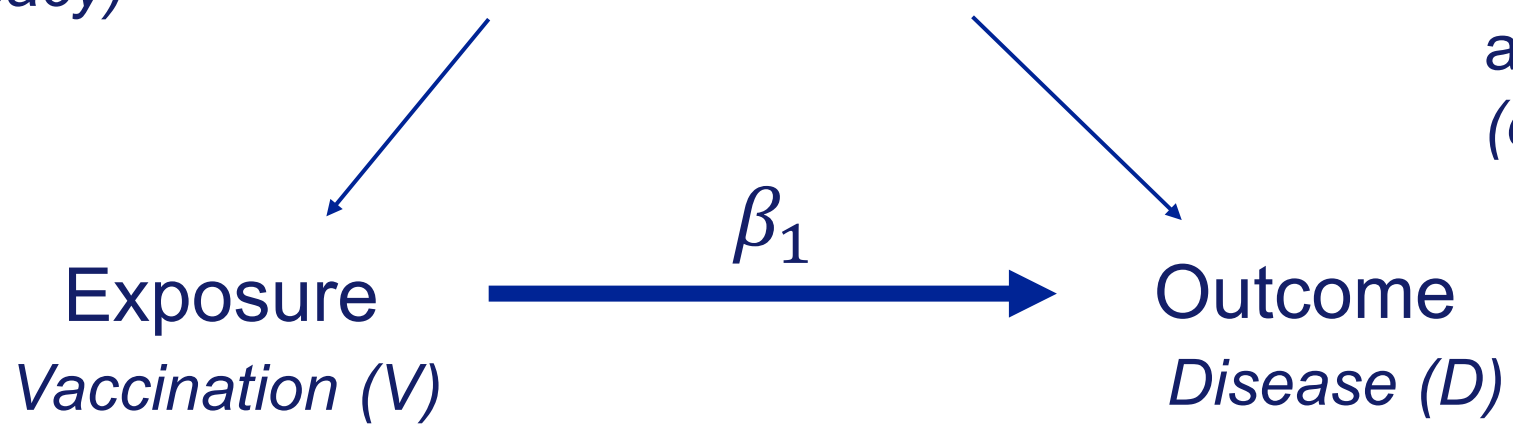


CDPH

Target Parameter

$\beta_1 =$ **causal effect** of vaccine on disease *(efficacy)*

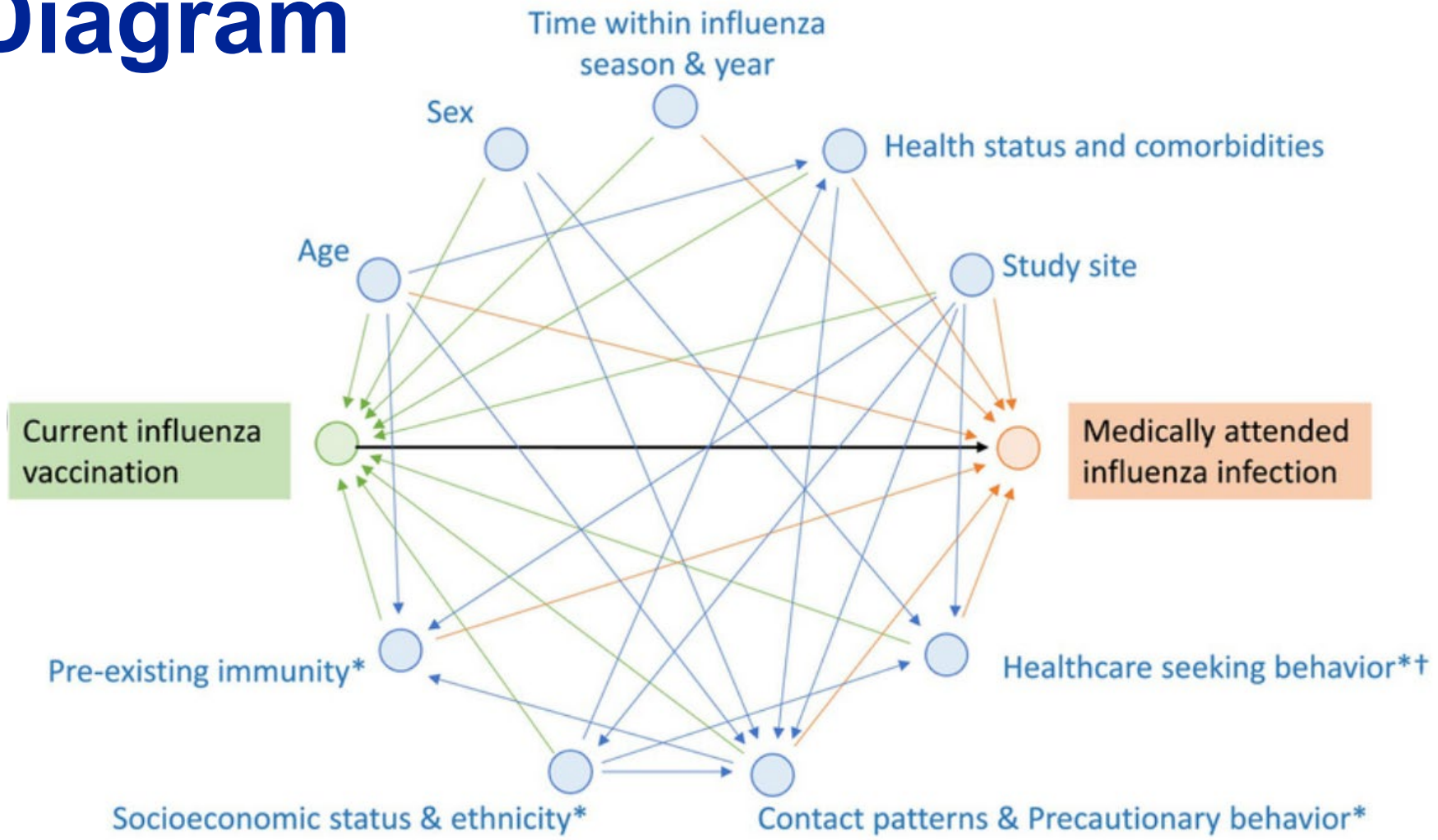
$\beta_1' =$ **statistical association** between vaccine and disease *(effectiveness)*



$$\ln\big(odds(D=1)\big) = \beta_0 + \boldsymbol{\beta_1} * V + \beta_n C_n$$

CDPH

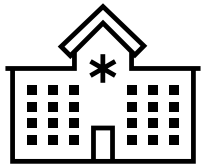
Causal Diagram



CDPH

Stuurman AL, et al. **Investigating confounding in network-based test-negative design influenza vaccine effectiveness studies.** Influenza Other Respir Viruses. 2023 Jan;17(1):e13087. doi: 10.1111/irv.13087. https://pubmed.ncbi.nlm.nih.gov/36550627/

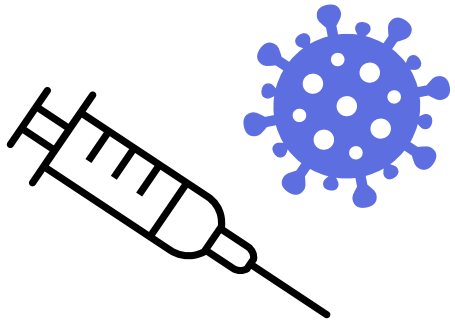
Considerations



Setting:
Inpatient, Outpatient

Data Sources:
Hospital networks
Public health surveillance

Population:
Pediatric, Adult

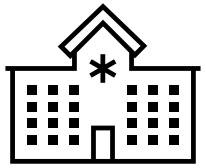


Data Type:
Electronic health/lab records, patient interviews

Influenza VE

CDPH

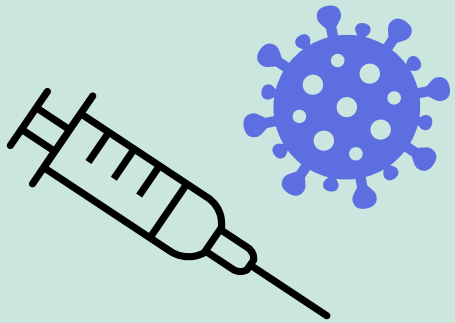
Considerations



Setting:
Inpatient, Outpatient

Data Sources:
Hospital networks
Public health surveillance

Population:
Pediatric, Adult



Influenza VE

Data Type:
Electronic health**/lab records,**
patient interviews

CDPH

New California Data Reporting Requirements

- January 1, 2023
  - **All vaccination records** must be reported to the California Immunization Registry (CAIR)
  - Previously, only certain types of providers were required to report
- June 15, 2023:
  - **All influenza test results** must be reported to California Reportable Disease Information Exchange (CalREDIE)
  - Previously only positive results were reported

CAIR California Immunization Registry

CalREDIE California Reportable Disease Information Exchange

CDPH

New California Data Reporting Requirements

CalREDIE
California Reportable Disease Information Exchange

- **All influenza test results must be reported (06/2023)**

CAIR California Immunization Registry

- All vaccination records must be reported (01/2023)

	Test Positive	Test Negative
Vaccinated		
Unvaccinated		

CDPH

New California Data Reporting Requirements

CalREDIE
California Reportable Disease Information Exchange

- All influenza test results must be reported (06/2023)

CAIR California Immunization Registry

- **All vaccination records must be reported (01/2023)**

	Test Positive	Test Negative
Vaccinated		
Unvaccinated		

CDPH

Vaccine Effectiveness Formula

Vaccine Effectiveness (VE)

$$VE = \frac{\text{unvaccinated rate - vaccinated rate}}{\text{unvaccinated rate}} \quad \text{or} \quad = 1 - \frac{1}{RR}$$

Simulated Cohort

	Positive	Negative	Total
Vaccinated	5	95	100
Unvaccinated	50	50	100
Total	55	145	200

CDPH

Vaccine Effectiveness Formula

Vaccine efficacy (VE)

$$VE = 1 - \text{Relative Risk} = 1 - \frac{\text{Risk in vaccinated arm}}{\text{Risk in unvaccinated arm}}$$

Simulated Cohort

	Positive	Negative	Total	Rel Risk
Vaccinated	5	95	100	0.05
Unvaccinated	50	50	100	0.50
Total	55	145	200	

$$\text{VE} = \left(1 - \frac{0.05}{0.50}\right) x100$$

$$= (1 - 0.10)x100$$

$$= \mathbf{90\%}$$

CDPH

Covariates

- Age
- Race
- Ethnicity
- Week of Test
- County of Test

Background

Can we generate sufficiently reliable early-season VE estimates using public health surveillance data?

- 2023-2024 Influenza VE study
  - First attempt
  - Pilot
  - Feasibility
  - Accuracy

CDPH

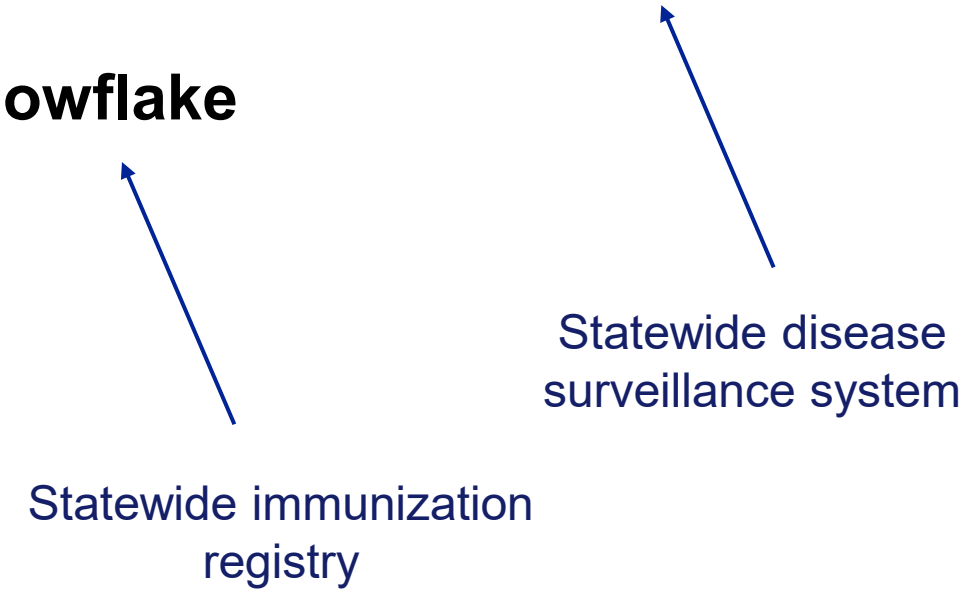
Methods

Case-control study (test negative design, unmatched)

- **Dates:** October 1, 2024—December 31, 2024
- **Eligibility/inclusion criteria:** California residents aged ≥6 months with a test result reported through the state electronic laboratory reporting (ELR) system
- **Exclusions:** duplicate test results for persons with multiple records, laboratories with greater than 50% weekly positive results
- **Outcome (test result):** molecular (NAAT) or culture test results for influenza (A/B)
- **Exposure (vaccination status):** documented dose of seasonal influenza vaccine in CAIR at least 14 days prior to test date
- **Analysis:** VE = (1 – adjusted OR) x 100%
  - Mixed-effects logistic regression model
  - Adjusted for continuous age (natural cubic spline), categorical race and ethnicity; testing week and county as random effects

Data Sources and Tools

- *Primary* > **Test Result** > Electronic Laboratory Reporting > **CalREDIE**
- *Secondary* > **Vaccination Status** > CAIR > **Snowflake**
- *Tertiary* > **Covariates** > (from test data)
- *Data cleaning*: **SAS, R**
- *Data modeling*: **R**
- *Data viz*: **Excel, Tableau**



CDPH

Matching

```
p_load("RecordLinkage")
```

```
flu_pairs <-
  flu2024 %>%
  select(IncidentID, LastName, FirstName, DOB, DtLabCollect, County) %>%
  RLBigDataLinkage(FLU_recipient %>%
                     select(product, LastName, FirstName, DOB, admin_date, County),
                   blockfld = "DOB",
                   strcmp = c("LastName", "FirstName", "County"),
                   exclude = c("IncidentID", "DtLabCollect"))
```

Deterministic ("exact")

Probabilistic ("fuzzy")

CDPH

https://cran.r-project.org/web/packages/RecordLinkage/index.html

Matching

```
p_load("RecordLinkage")
```

```
flu_pairs <-
  flu2024 %>%
  select(IncidentID, LastName, FirstName, DOB, DtLabCollect, County) %>%
  RLBigDataLinkage(FLU_recipient %>%
                     select(product, LastName, FirstName, DOB, admin_date, County),
                   blockfld = "DOB",
                   strcmp = c("LastName", "FirstName", "County"),
                   exclude = c("IncidentID", "DtLabCollect"))
```

Deterministic ("exact")

Probabilistic ("fuzzy")

CDPH

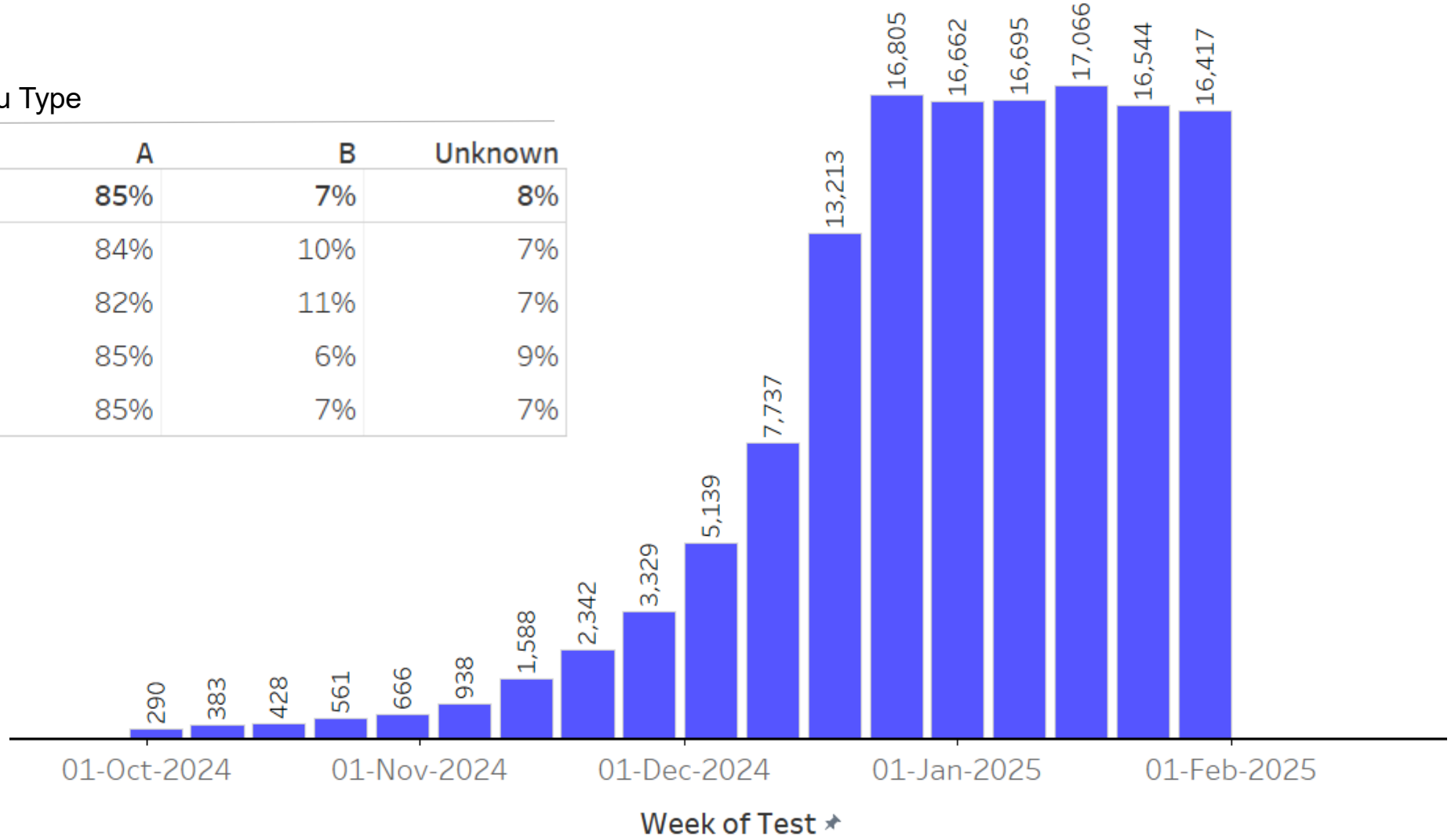
https://cran.r-project.org/web/packages/RecordLinkage/index.html

Results

Number of positive influenza detections by laboratories

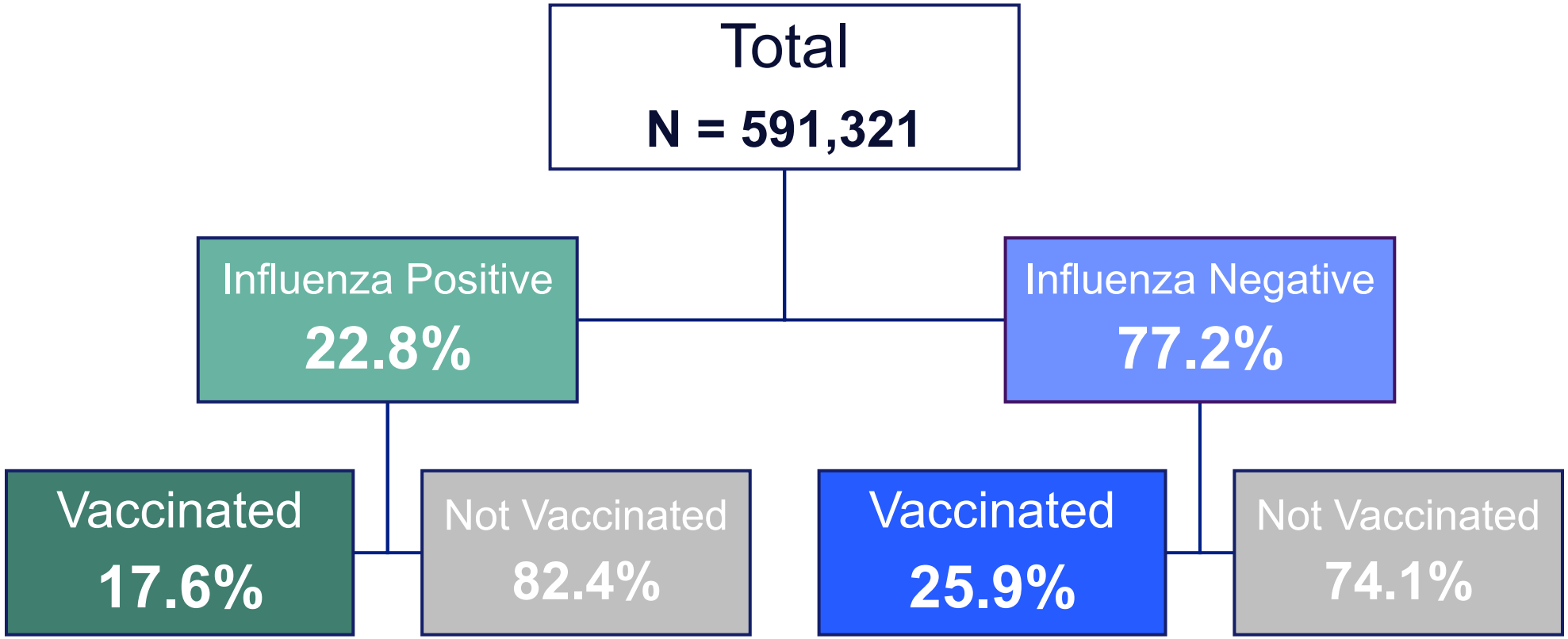
2024–2025 season to date

Flu Type	A	B	Unknown
Total	85%	7%	8%
October 2024	84%	10%	7%
November 2024	82%	11%	7%
December 2024	85%	6%	9%
January 2025	85%	7%	7%



CDPH

Study Population – Positivity and Vaccination



CDPH

Study Population - Demographics

	Test Negative	Test Positive
Total No.	456,437	134,884
Age (yrs) Median (IQR)	43 (20-67)	30 (11-55)
Ethnicity - Hispanic or Latino	24%	29%
Race		
White	46%	39%
Unknown	20%	22%
Other	19%	23%
Asian	8%	8%
Black	6%	6%
NHPI, AI/AN, or Multiple	<1%*	<1%*

CDPH

NHPI = Native Hawaiian or Pacific Islander; AI/AN = American Indian or Alaska Native; * <1% each

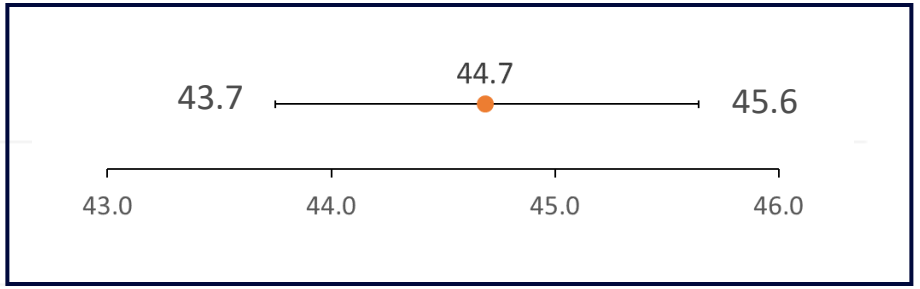
Results Overview

- Vaccine Effectiveness (%) by **Age Group** (all types)
- Vaccine Effectiveness (%) by **Type** (A/B) and **Age Group**
- **Cumulative** Vaccine Effectiveness (%) by **Week**
- Vaccine Effectiveness (%) by **Month**
- Vaccine Effectiveness (%) by **Month** and **Type**

CDPH

Vaccine Effectiveness by Age Group

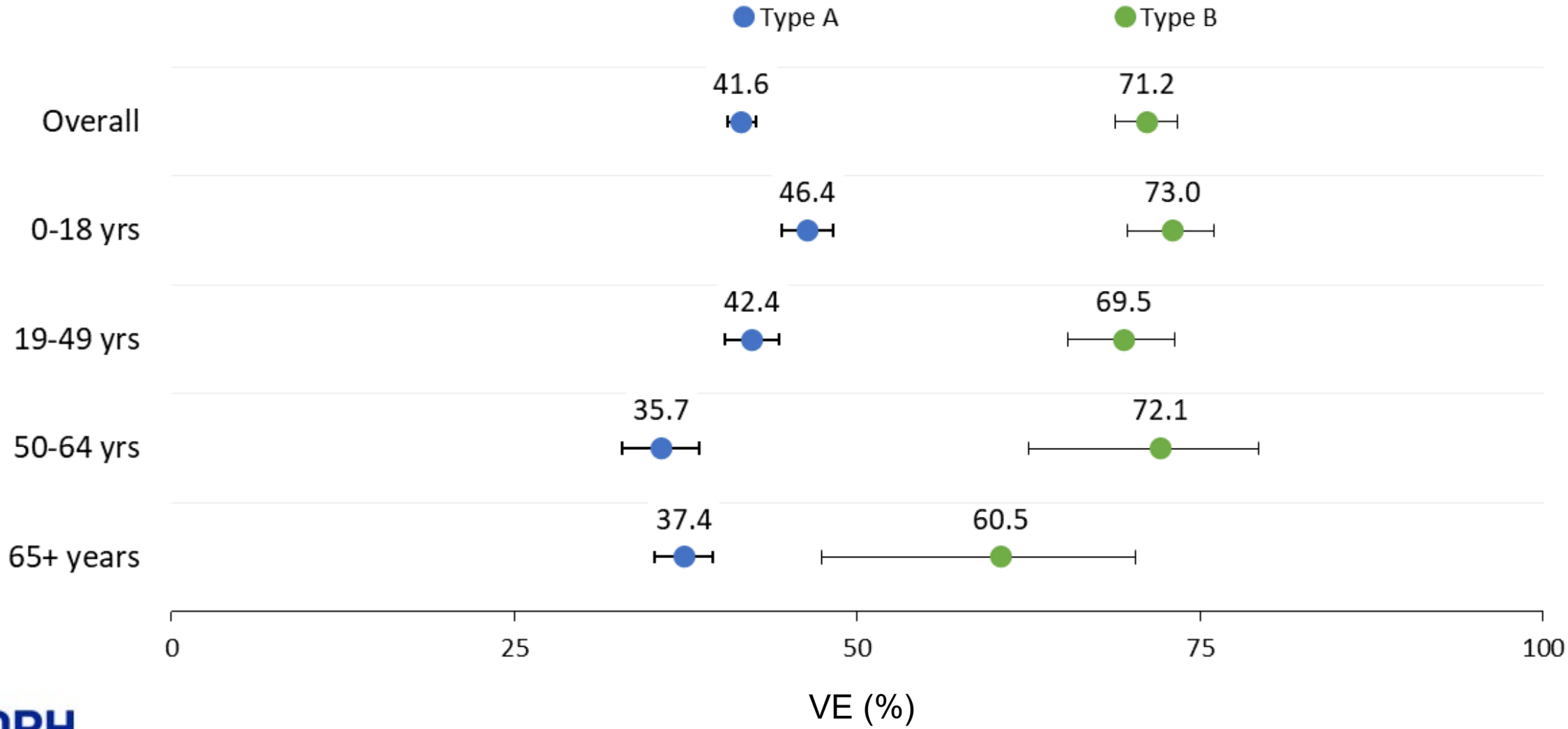
California October 2024 - January 2025



CDPH

Vaccine Effectiveness by Type and Age Group

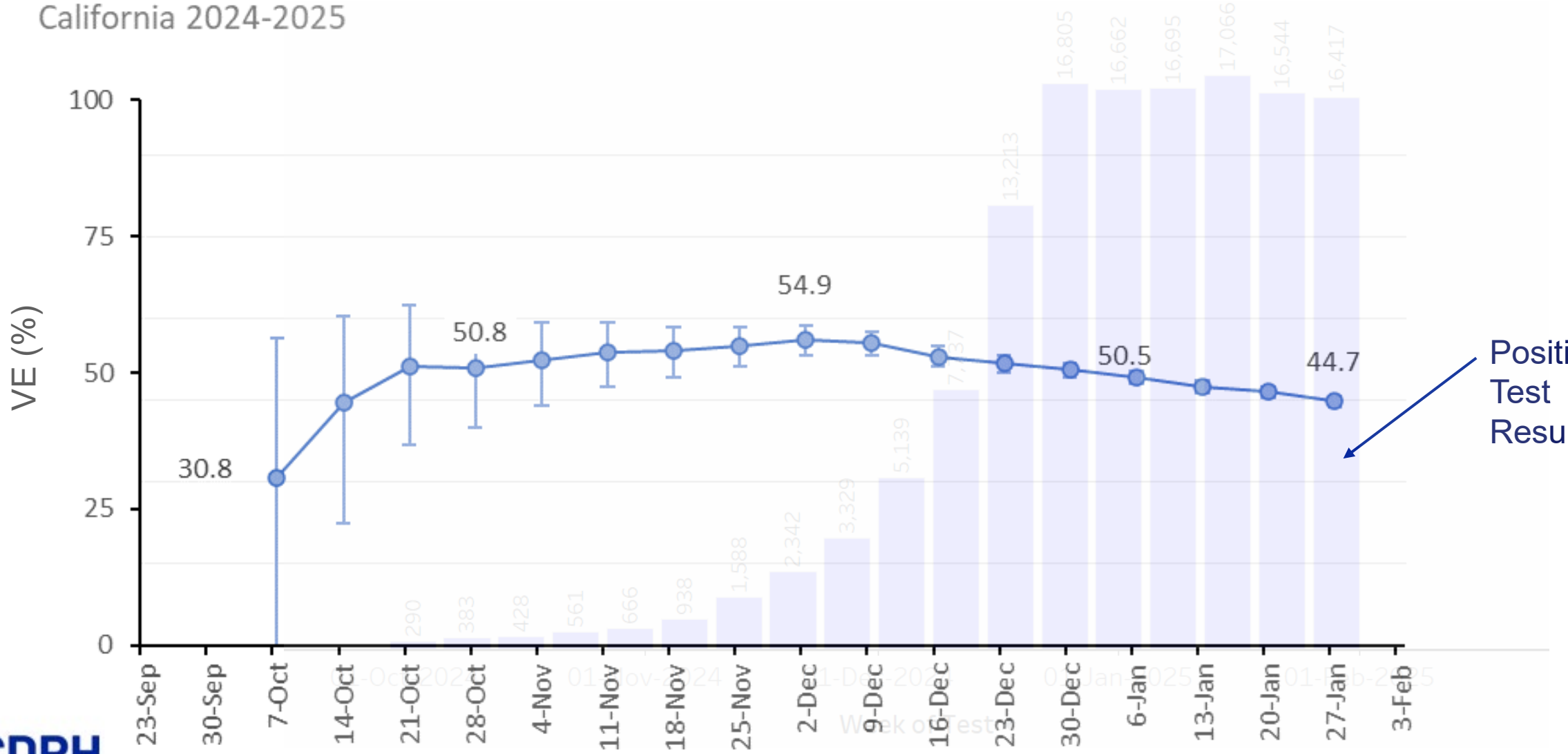
California 2024-2025



CDPH

Influenza VE Estimate (Cumulative)

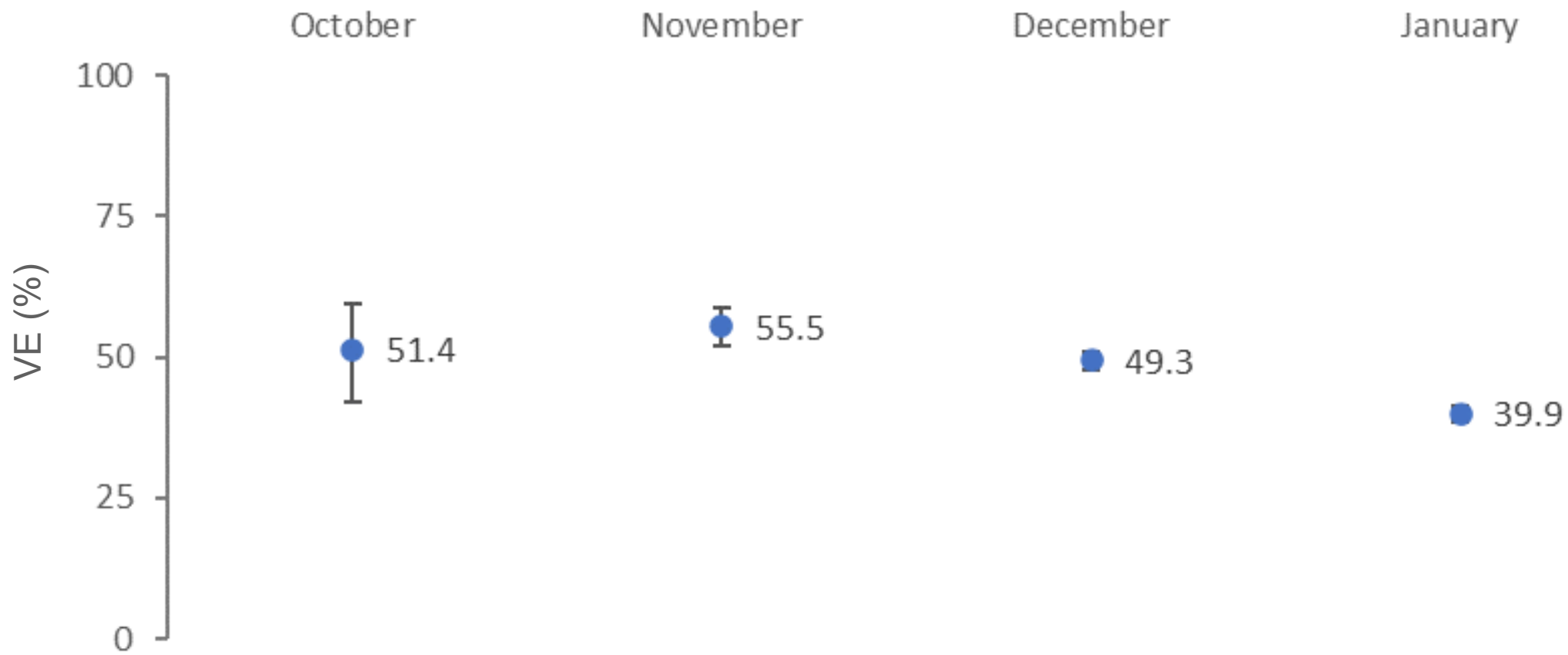
California 2024-2025



CDPH

Vaccine Effectiveness by Month

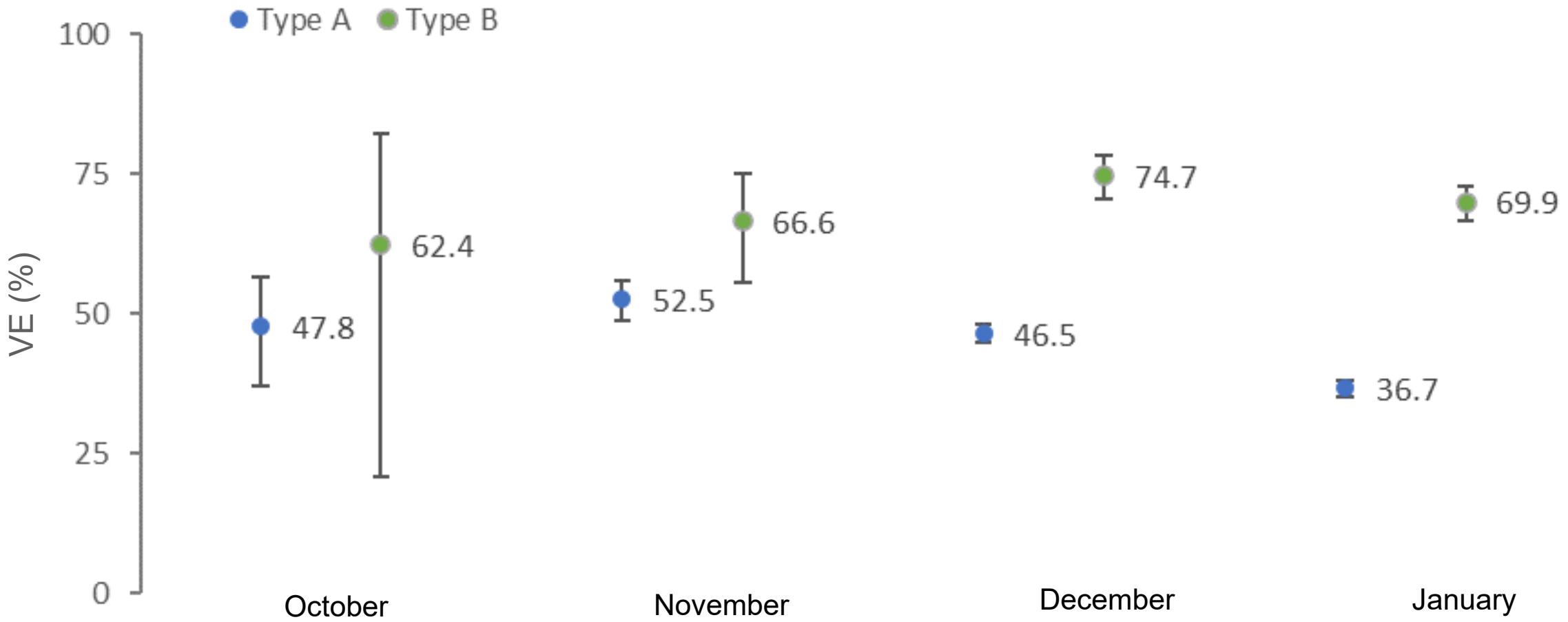
California 2024-2025



CDPH

Vaccine Effectiveness by Month and Type

California 2024-2025



CDPH

Limitations

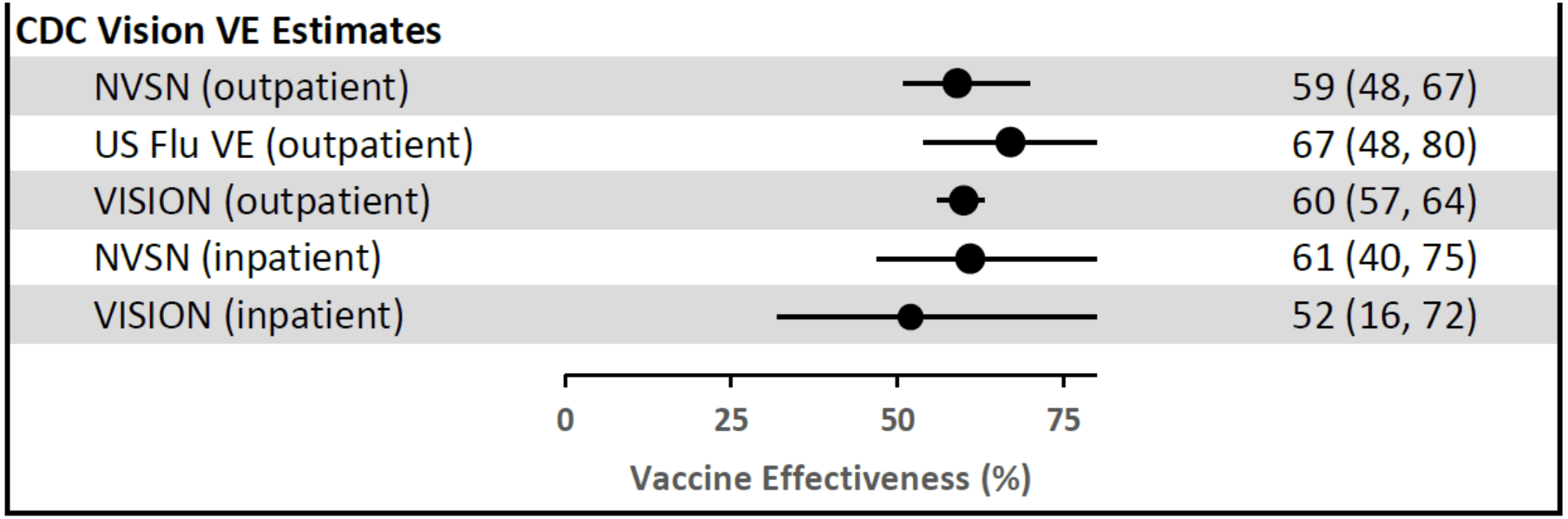
1. **Likely incomplete documentation and reporting of mandatory vaccination and testing**
2. Inability to assess partial/full vaccination status for children aged <9 years
3. **Lack of symptom information, test setting, and outcome status (illness, hospitalization, or death)**
4. Subtype information not available for all positive influenza results
5. Unable to control for other potential confounders (health seeking behavior, pre-existing conditions)

How did we do?

CDPH

2023-2024 VE Platform Estimates

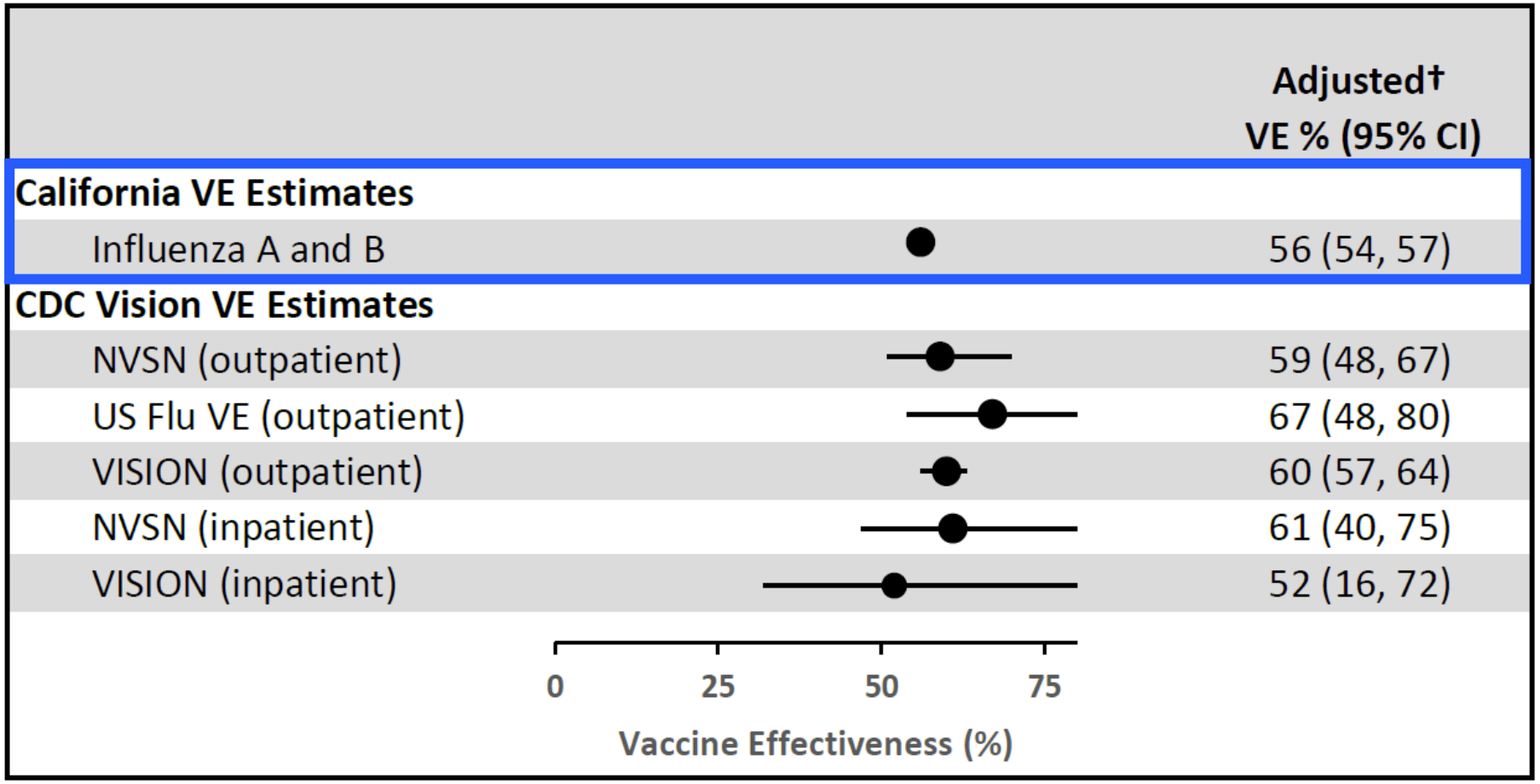
Pediatric: 0-18 yrs



CDPH

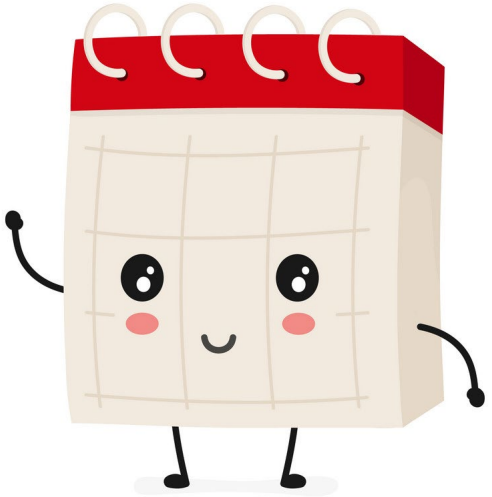
CA estimates similar to CDC VE platforms

Pediatric: 0-18 yrs



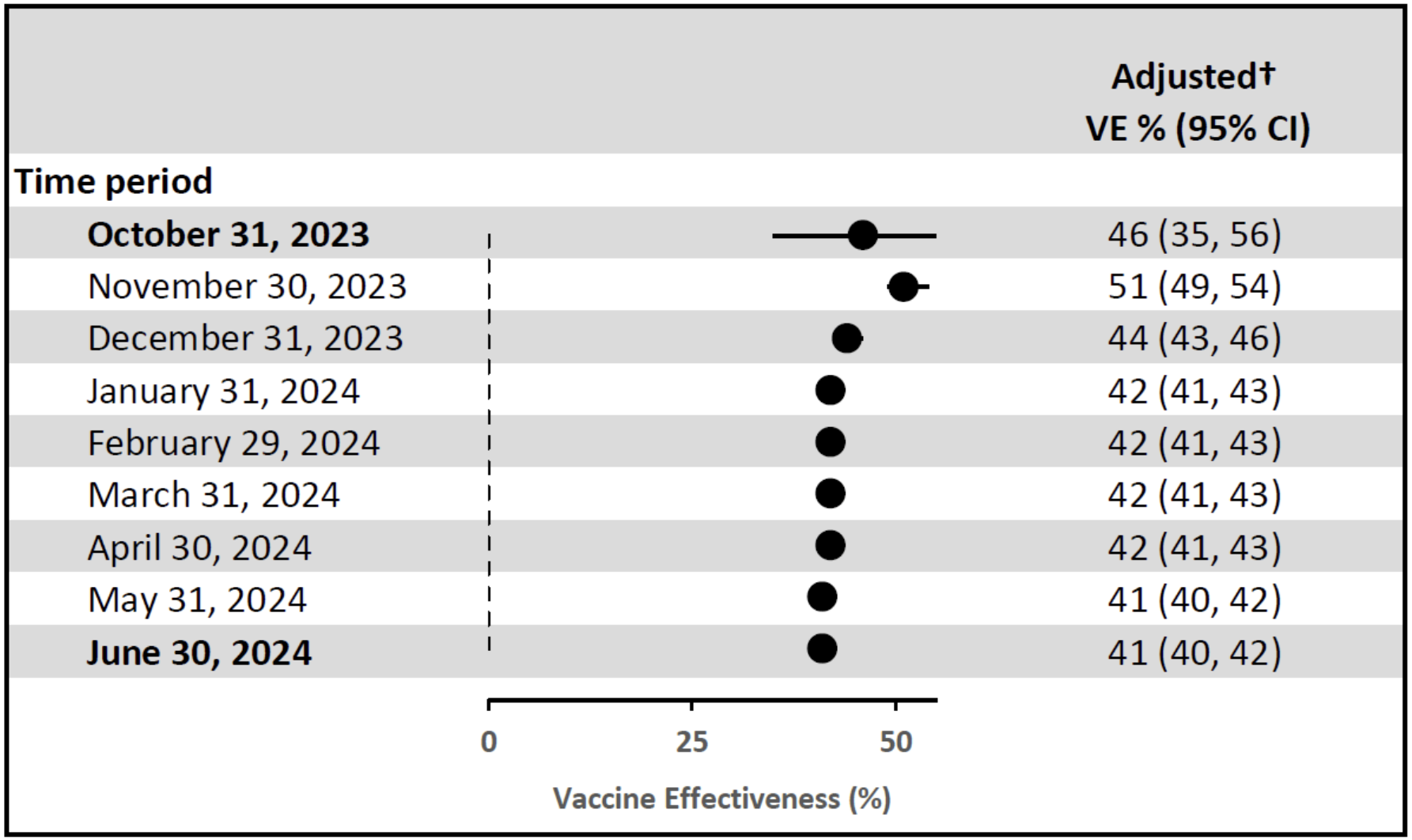
CDPH

What about timing?



CDPH

2023-2024 VE estimates stabilized by early January



CDPH

Conclusion

1. Current seasonal influenza vaccines provide protection against laboratory-confirmed influenza for persons aged ≥6 months
    - Higher VE for influenza B & younger age groups (<18 years, 18-49 years)
2. Increased reporting of public health data can be leveraged to calculate more timely influenza effectiveness
3. Earlier estimates of vaccine effectiveness can support influenza preparedness and prevention efforts including vaccination messaging
    - Promote highly effective vaccine in early phase of the peak
    - Emphasize importance of non-pharmaceutical measures during seasons with low VE
    - Prepare for increased hospital capacity during seasons with low VE

CDPH

Recipe for Surveillance-Based VE

Ingredients

- All influenza test results
- All vaccination records
- Covariate values for adjustment
- Data systems and software for management and processing
- Staff for analysis

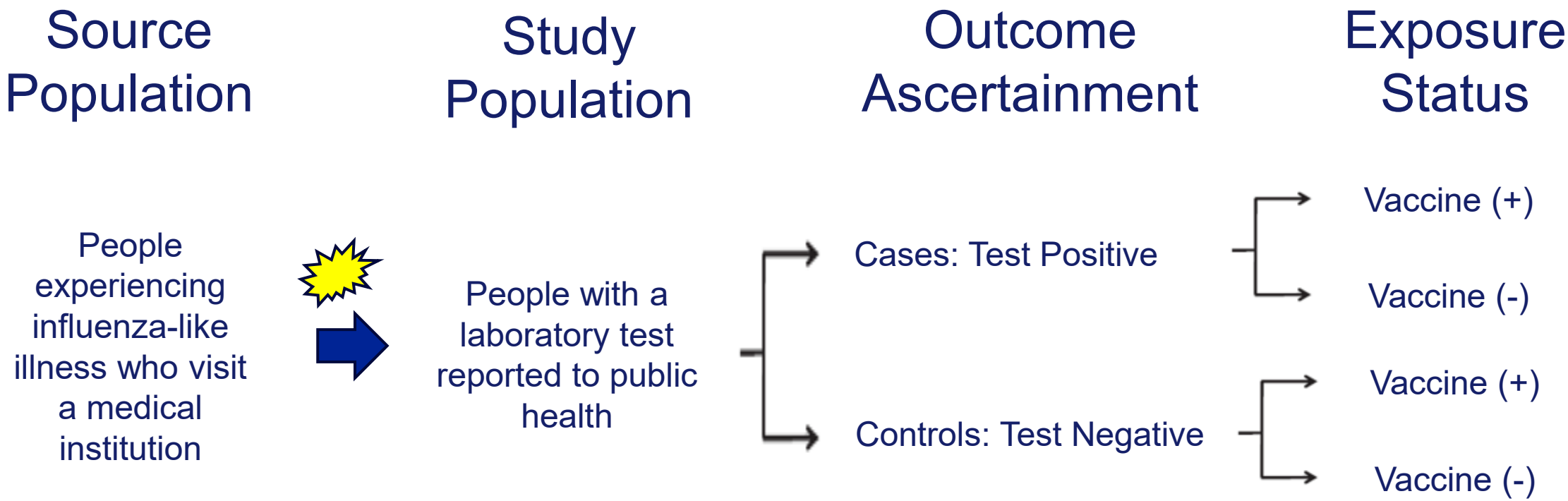
Steps

1. Clean testing data
2. Clean vaccination data
3. Match testing to vaccination records
4. Model selection
5. Tables and graphs

What to watch for…

- **Selection bias**
  - Missing data from certain kinds of labs or vaccine providers
- **Confounding**
  - Missing data on important covariates
  - Model misspecification
- **Information bias**
  - Poor data quality (inaccurate values for exposure, outcome, or covariates)

Generalizability/Selection Bias



CDPH

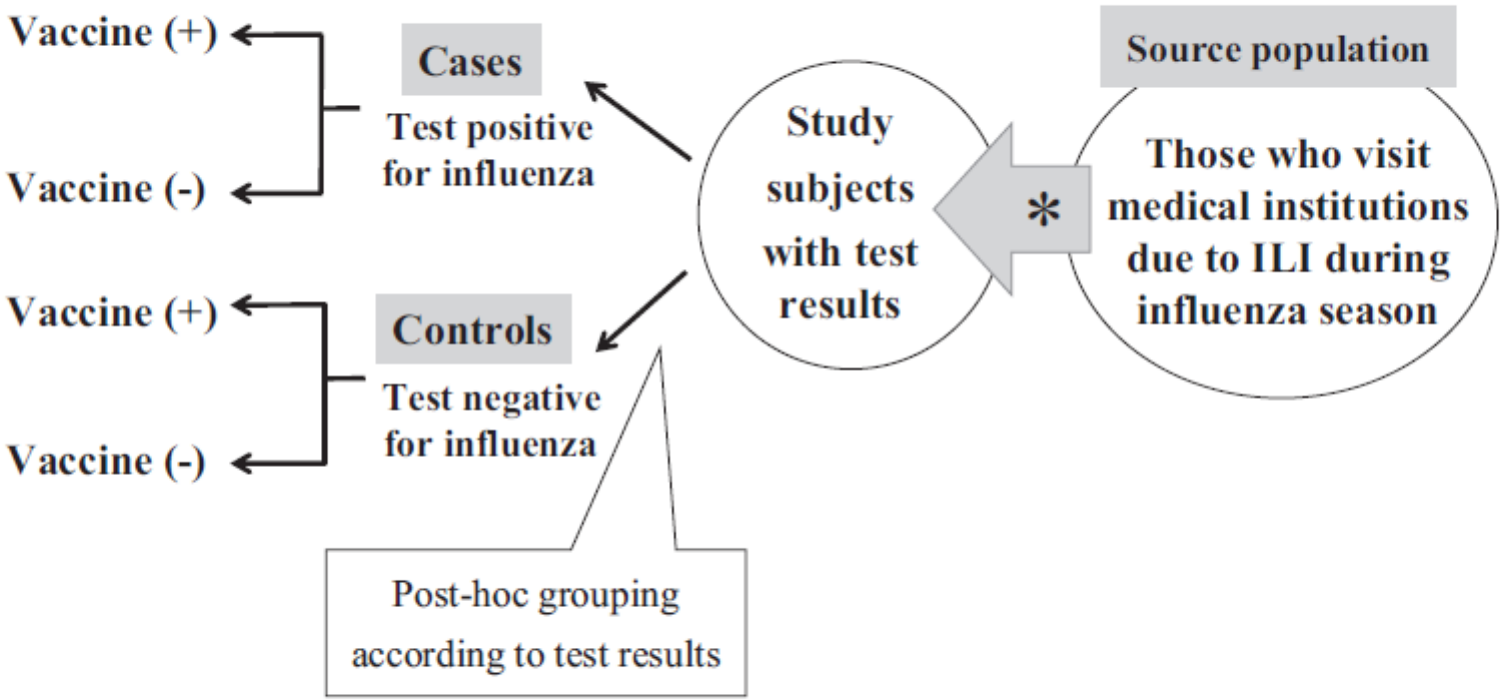


Fig. 3. A test-negative design to evaluate influenza vaccine effectiveness against laboratory-confirmed influenza. ILI denotes influenza-like illness. Asterisk (*) indicates a point where selection bias may occur. If the study subjects are limited to those who received the clinician-ordered test in the routine clinical setting, the application of the test would be related to (1) the likelihood of having influenza (outcome) or (2) influenza vaccination status (exposure), resulting in biased sampling (non-representativeness) of the study subjects from the source population.

CDPH

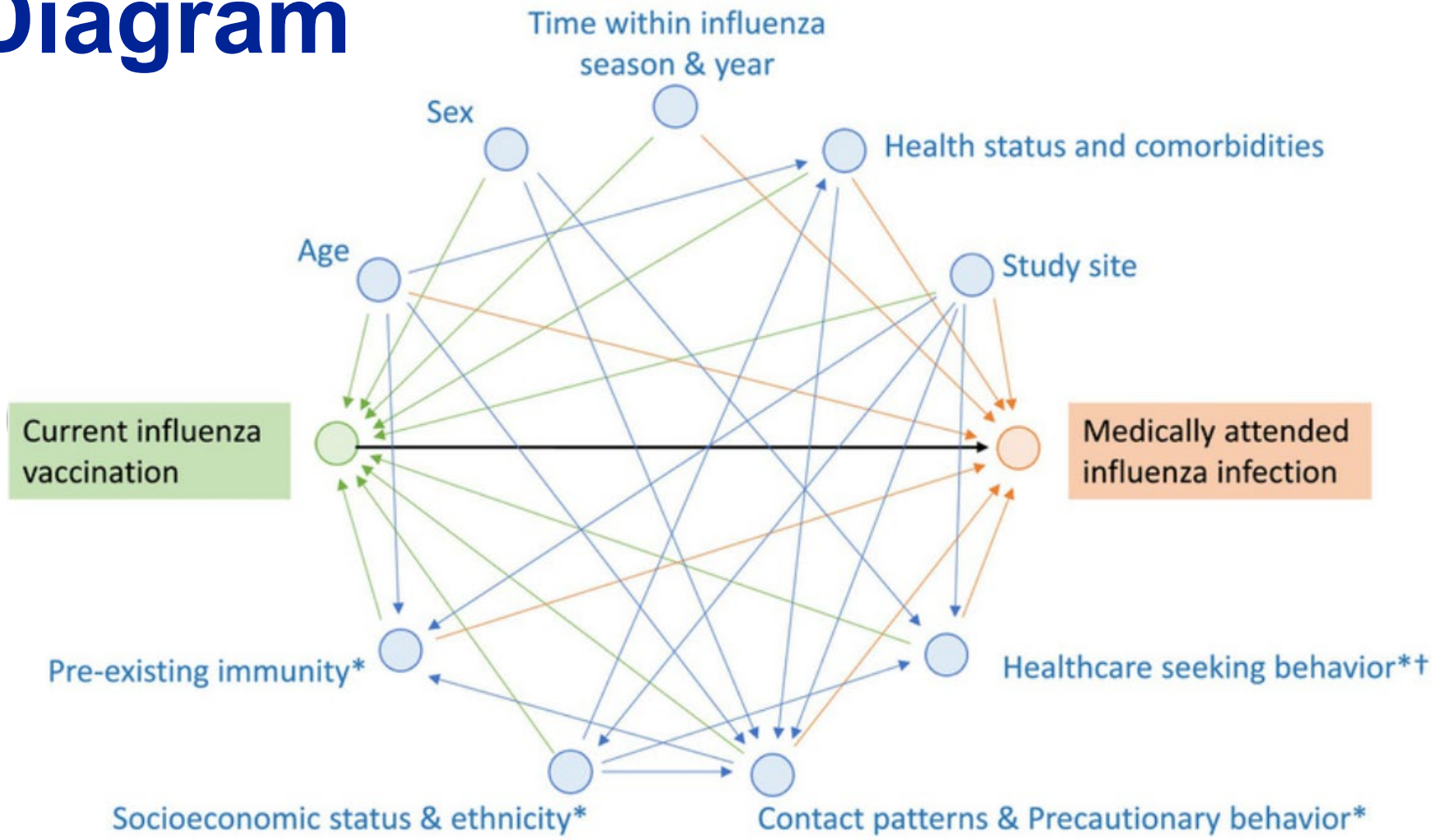
Conclusion

- 2023-2024
  - First attempt
  - Pilot
  - Feasibility
  - Accuracy
- 2024-2025
  - Did we get lucky last time?
  - Early indications that second season estimates are a close match to CDC

Future Work

- Modernize and optimize data pipeline
- Address limitations
  - Sub-analyses (e.g., subtype, disease severity, clinical setting)
  - Improve completeness and quality of reporting
- Communicating benefits of a vaccine with 40% effectiveness
- Pool with (or compare to) with other jurisdictions?

Causal Diagram

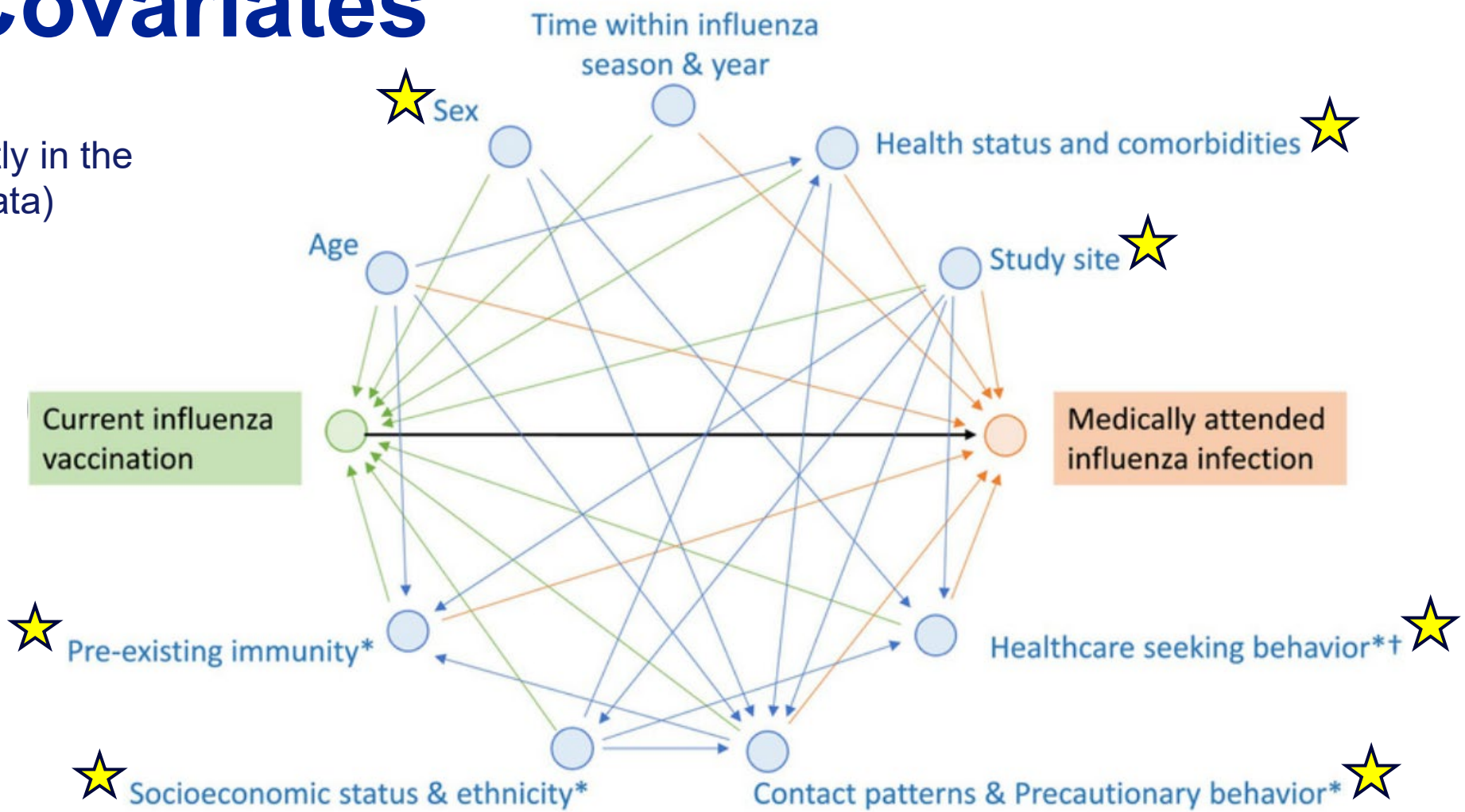


CDPH

Stuurman AL, et al. **Investigating confounding in network-based test-negative design influenza vaccine effectiveness studies.** Influenza Other Respir Viruses. 2023 Jan;17(1):e13087. doi: 10.1111/irv.13087. https://pubmed.ncbi.nlm.nih.gov/36550627/

Missing Covariates

= factors not currently in the model (missing data)



CDPH

Stuurman AL, et al. **Investigating confounding in network-based test-negative design influenza vaccine effectiveness studies.** Influenza Other Respir Viruses. 2023 Jan;17(1):e13087. doi: 10.1111/irv.13087. https://pubmed.ncbi.nlm.nih.gov/36550627/

References and Resources

Topic	Link
CDC MMWR	https://pubmed.ncbi.nlm.nih.gov/38421946/
Understanding VE	https://healthjournalism.org/blog/2020/10/know-the-nuances-of-vaccine-efficacy-when-covering-covid-19-vaccine-trials/
CDC VE Guide	https://www.cdc.gov/flu-vaccines-work/php/effectivenessqa/
WHO VE Guide	https://www.who.int/publications/i/item/9789241512121
Causal Diagram	https://pubmed.ncbi.nlm.nih.gov/36550627/
Test Negative Design	https://pubmed.ncbi.nlm.nih.gov/28818471/ https://pubmed.ncbi.nlm.nih.gov/31609860/ https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-017-2838-2
R matching	https://cran.r-project.org/web/packages/RecordLinkage/index.html