Discovery Session:
California IIS Data in Action–
Insights into Flu Vaccine Effectiveness

February 24, 2025
4 PM ET

Today's Presenter

- **Josh Quint, PhD, MPH,** Epidemiology Supervisor, California Department of Public Health

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

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

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/

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Quick Poll

- Over the past 10 years, what was the median estimated vaccine effectiveness for the seasonal influenza vaccine in the United States?
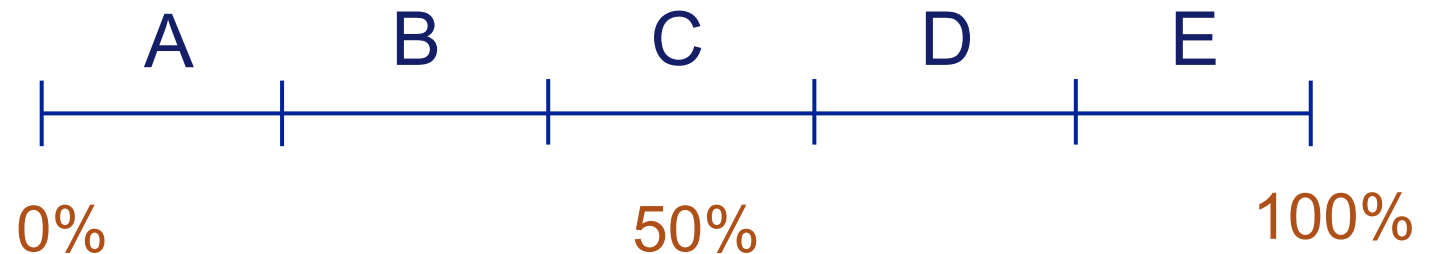
A.   0 - 19%

B. 20 - 39%

C. 40 - 59%

D. 60 - 79%

E. 80 - 99%

A   B   C   D   E

0%   50%   100%

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Overview

- Background

- Methods

- Results

- Discussion

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Background

Burden of Influenza in the United States

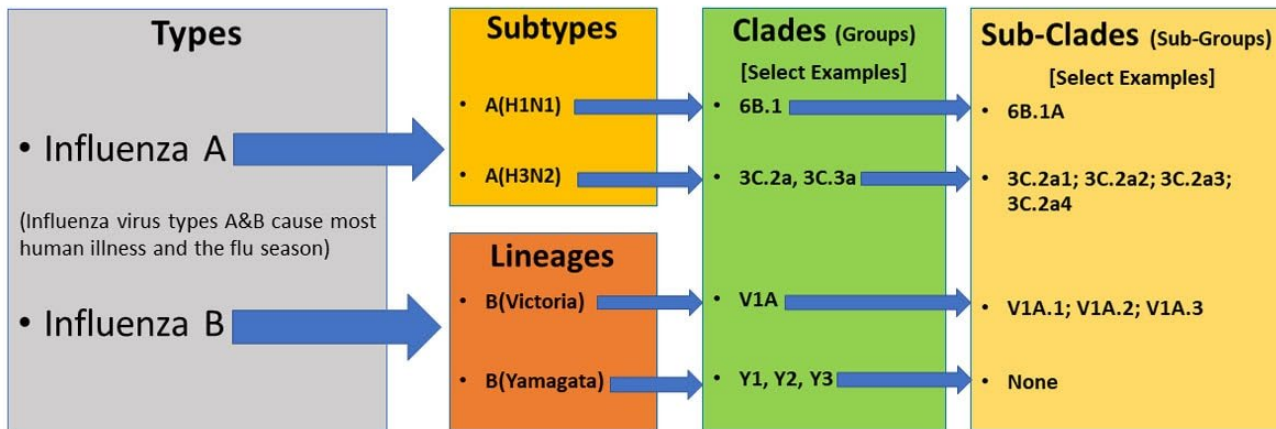- Flu vaccine prevents millions of illnesses and flu-related doctor's visits each year.

- 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%.
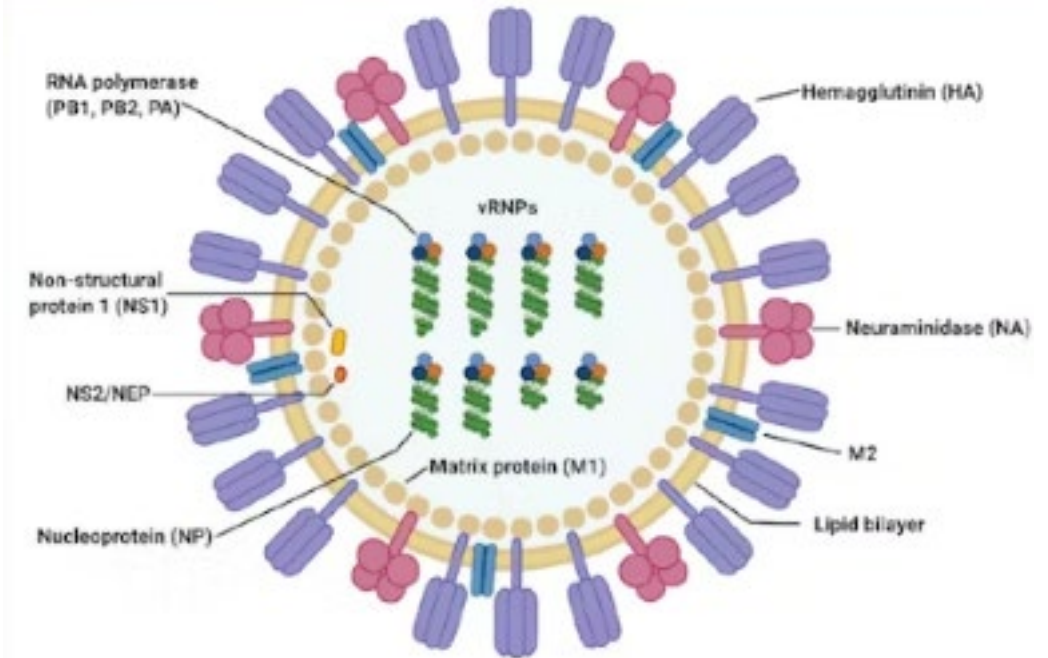
CDPH   https://www.cdc.gov/flu/vaccines/index.html

Background

Why do we need a new vaccine every year?

- Influenza Types

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
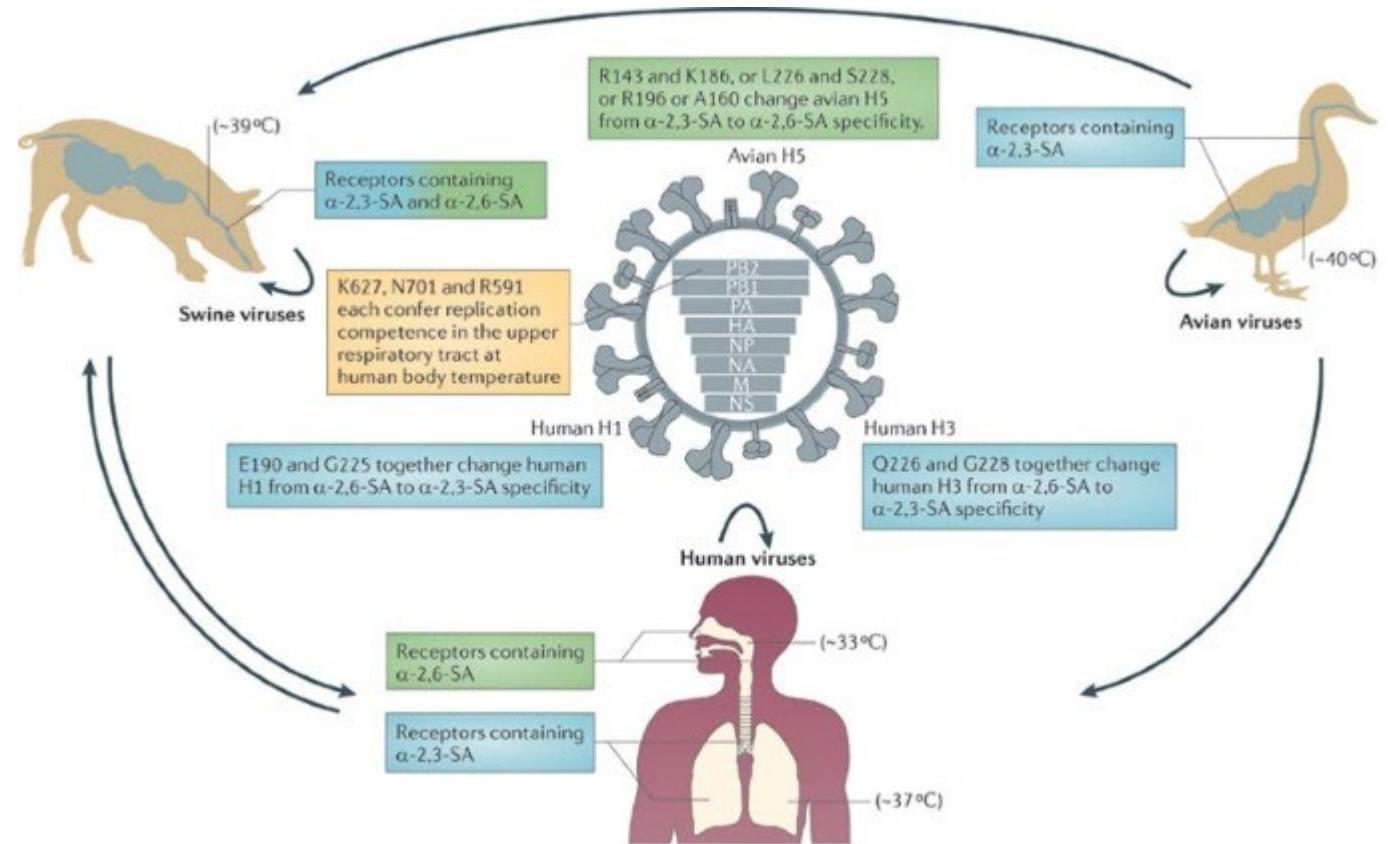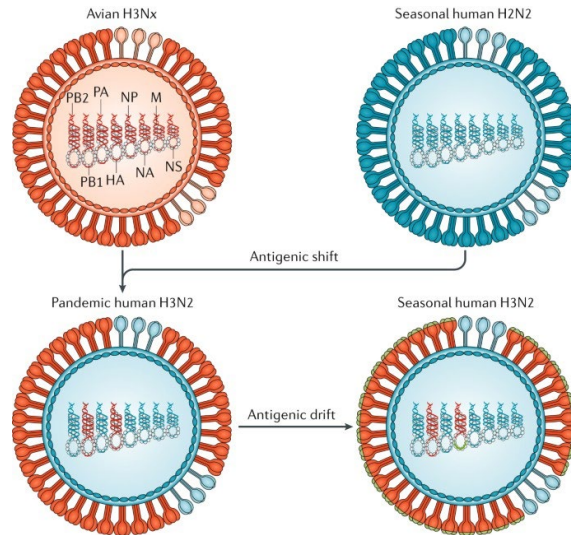
Nature Reviews | Microbiology

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

Current influenza vaccine productions

CDPH
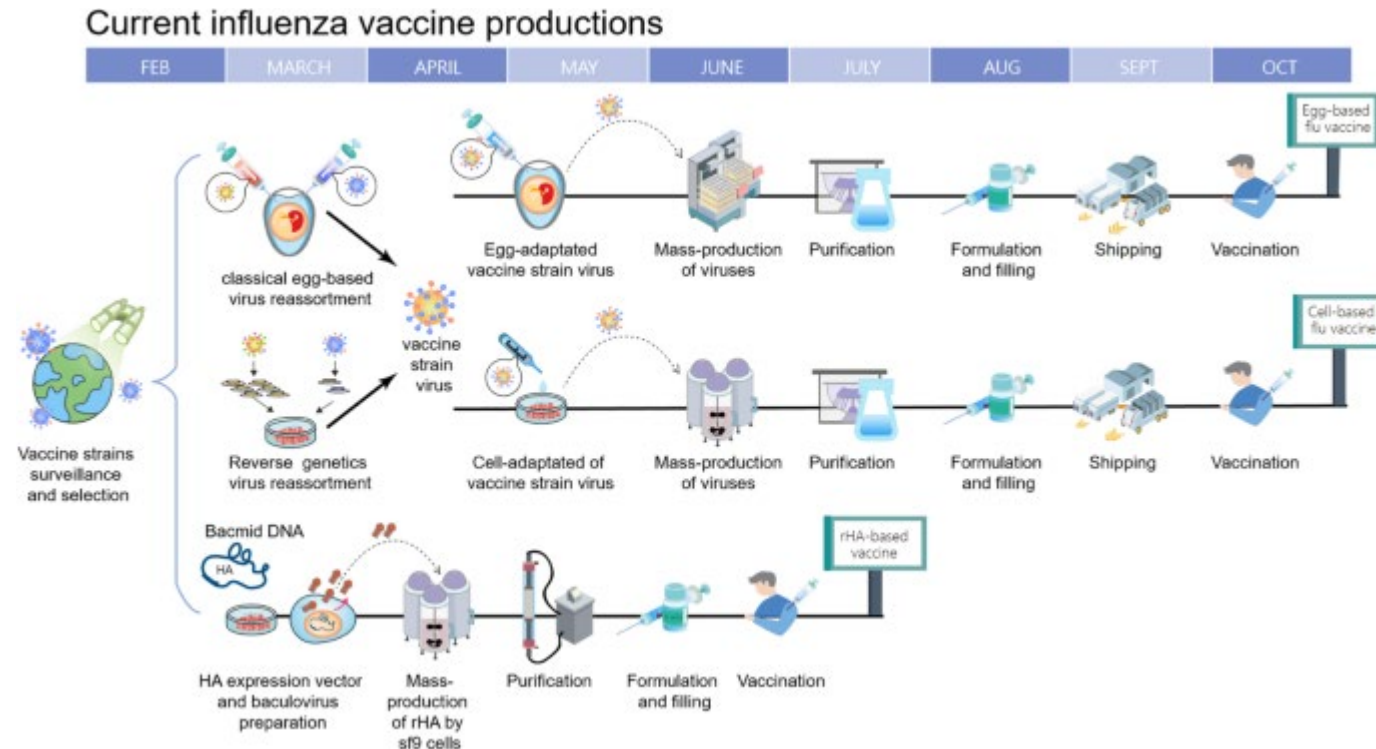
SEASONAL FLU VACCINE EFFECTIVENESS
UNITED STATES 2009-2024
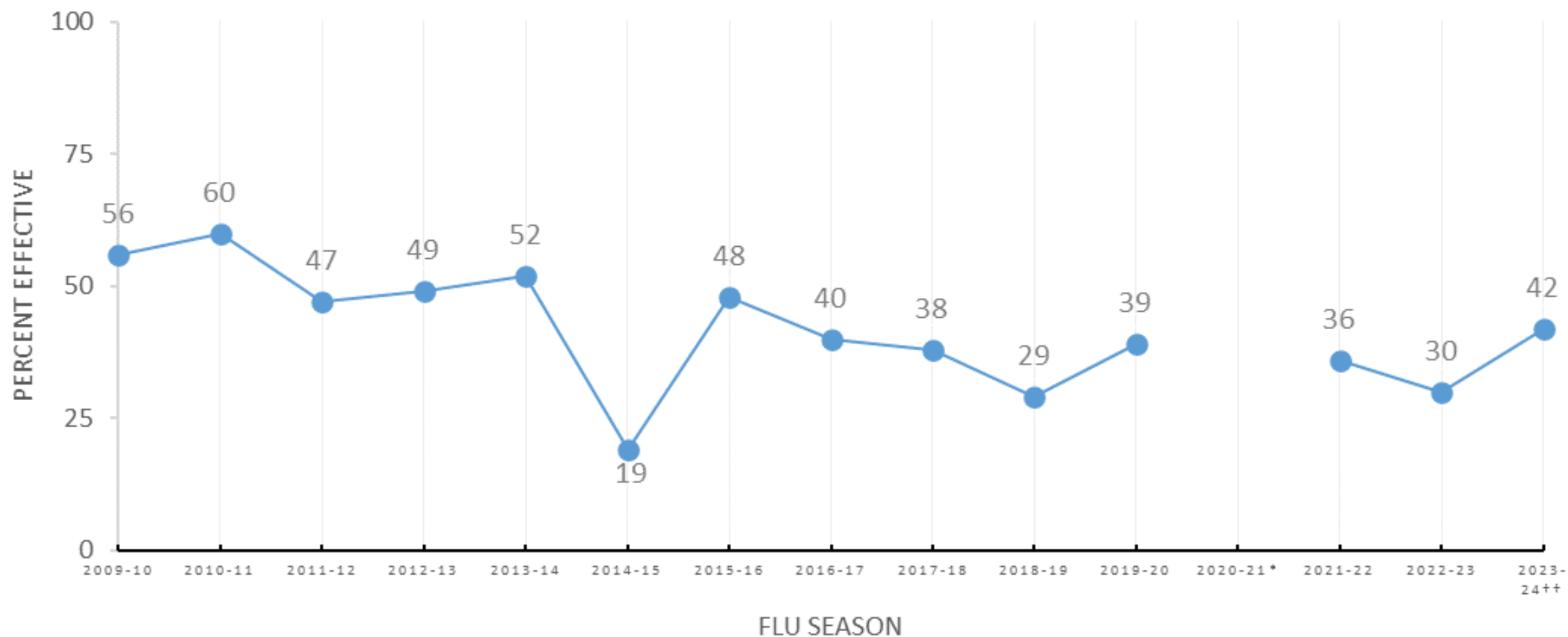
https://www.cdc.gov/flu-vaccines-work/php/effectiveness-studies/index.html

Quick Poll

- Over the past 10 years, what was the median estimated vaccine effectiveness for the seasonal influenza vaccine in the United States?
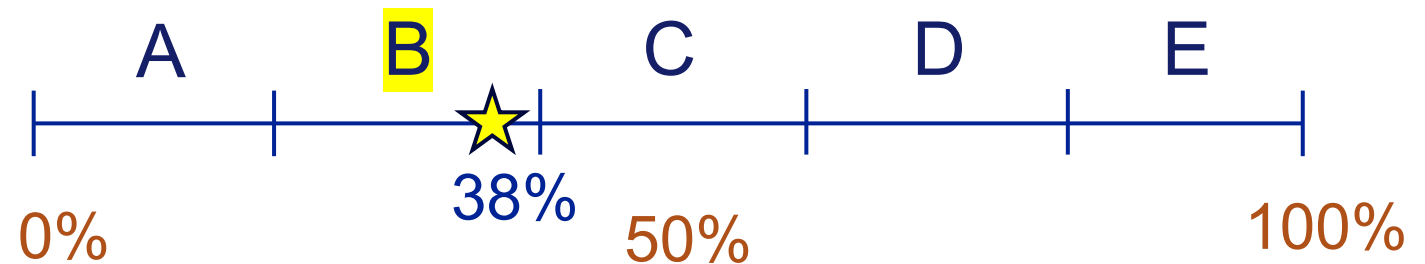
A.   0 - 19%

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A   B   C   D   E

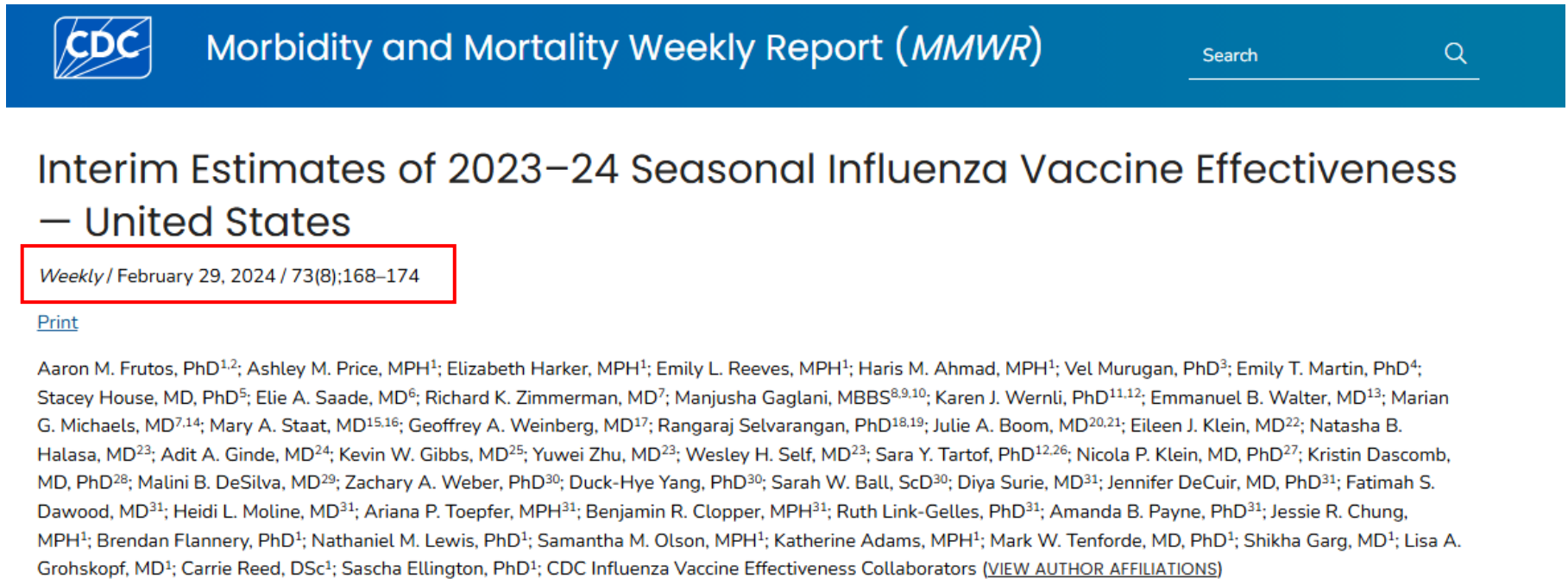0%   38%   50%   100%

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

Background

Why calculate vaccine effectiveness?

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

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
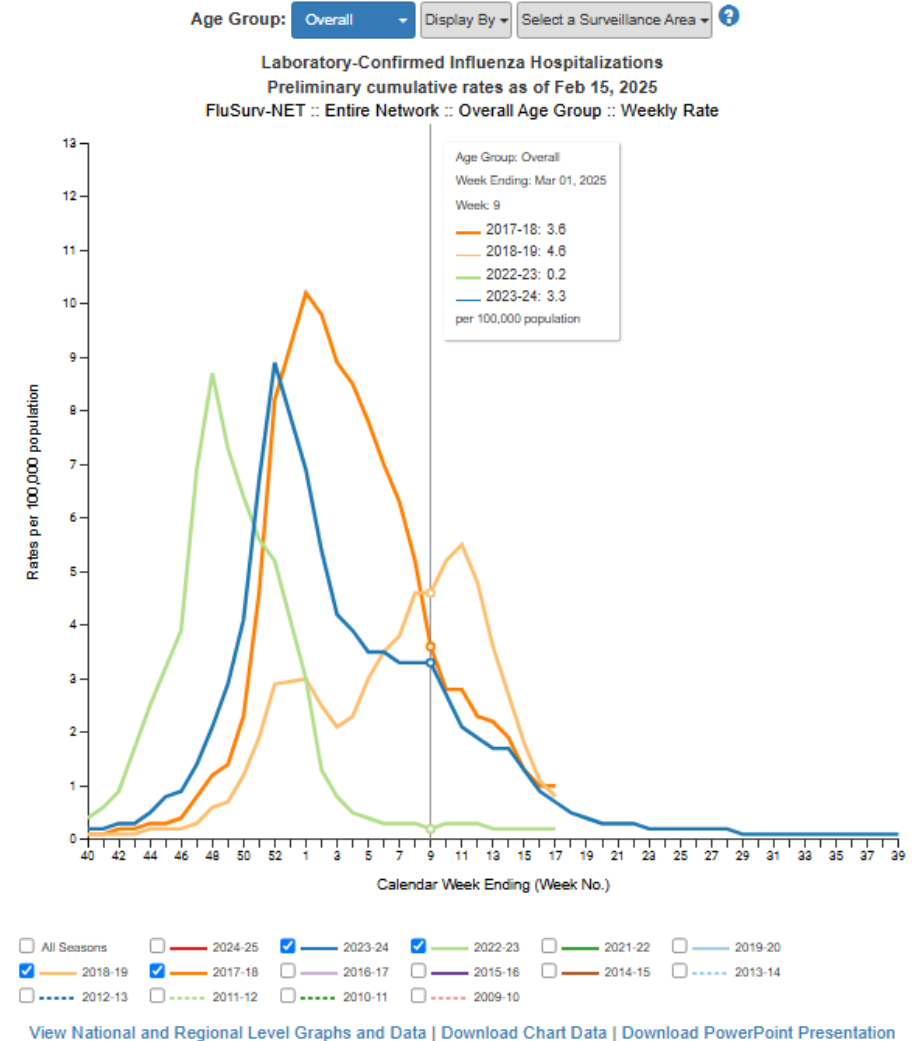
Influenza Vaccination Coverage by Population

Legend:
- 2019–2020 season
- 2020–2021 season
- 2021–2022 season
- 2022–2023 season

All (≥6 months)
- 52%
- 52%
- 51%
- 49%

Children (6 months–17 years)
- 64%
- 59%
- 58%
- 57%

Adults (≥18 years)
- 48%
- 50%
- 49%
- 47%

Older Adults (≥65 years)
- 70%
- 75%
- 74%
- 70%

Adults with 1+ Chronic Health Condition(s) (≥18–49 years)
- 44%
- 42%
- 43%
- 41%

Pregnant Women
- 58%
- 55%
- 48%
- 47%

Healthcare Professionals
- 81%
- 76%
- 81%
- 76%
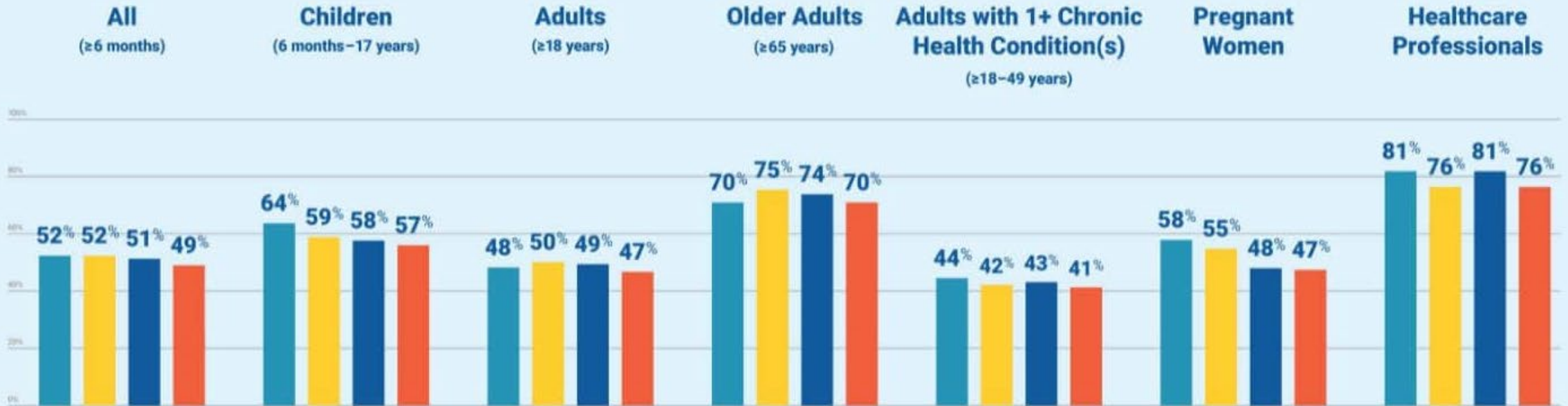
Receipt of ≥1 dose of influenza vaccine during the season

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)

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Randomized Control Trial (RCT)
Cohort Design (Observational)

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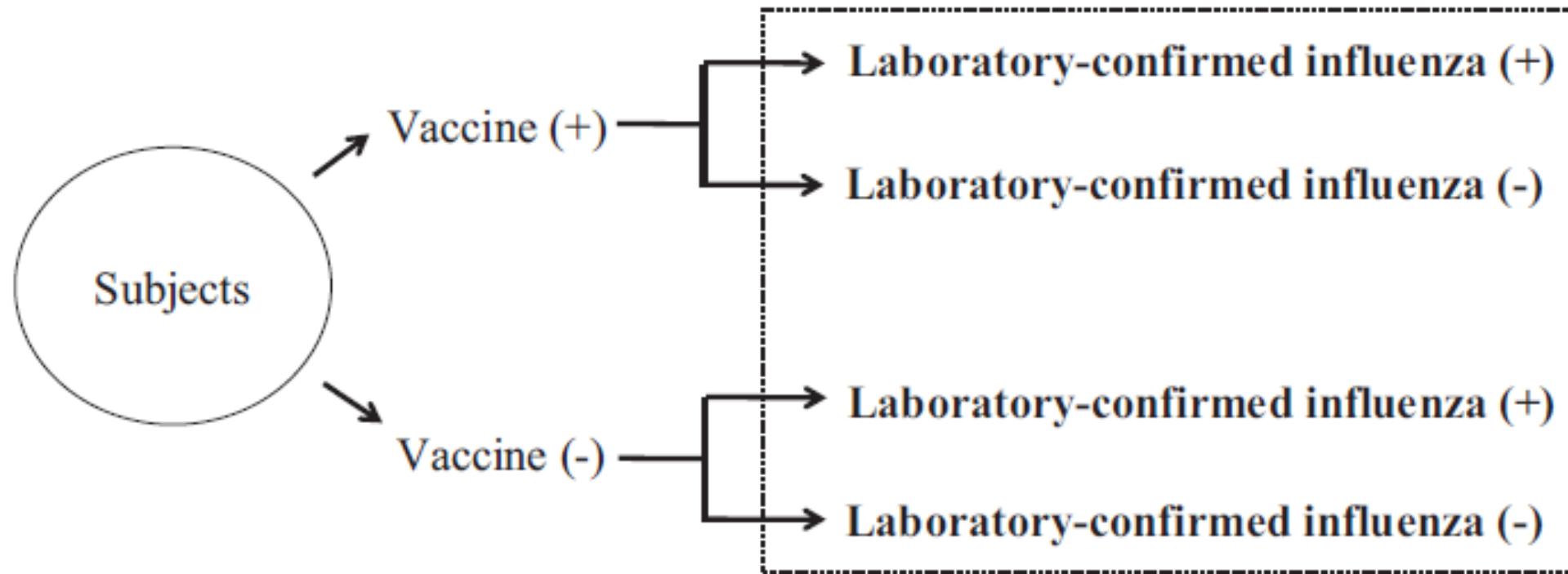
Case Control Design (Observational)

Study Population	Outcome Ascertainment	Exposure Status

People with a laboratory test reported to public health

→ Cases: Test Positive
- Vaccine (+)
- Vaccine (-)

→ Controls: Test Negative
- Vaccine (+)
- Vaccine (-)

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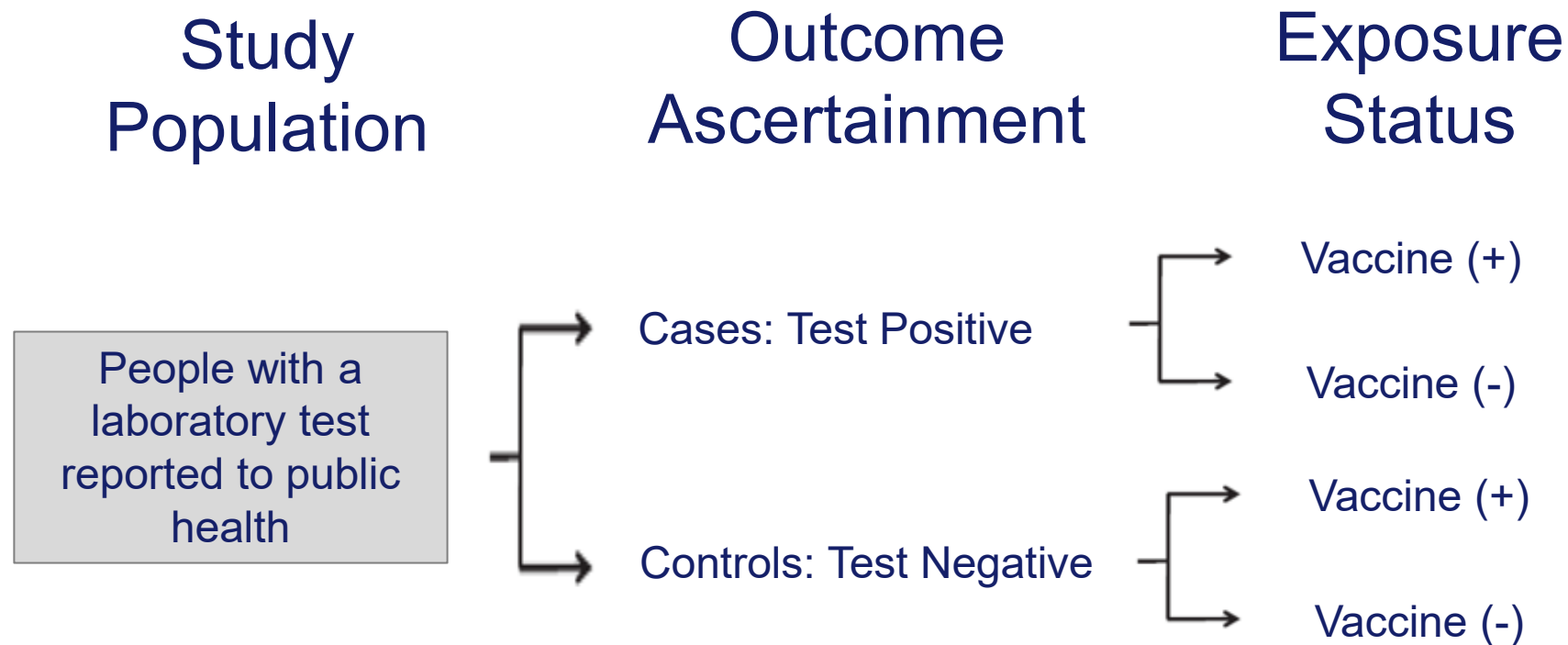
Target Parameter

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

Covariates (Confounders)

$\beta_1' =$ **statistical association** between vaccine and disease *(effectiveness)*
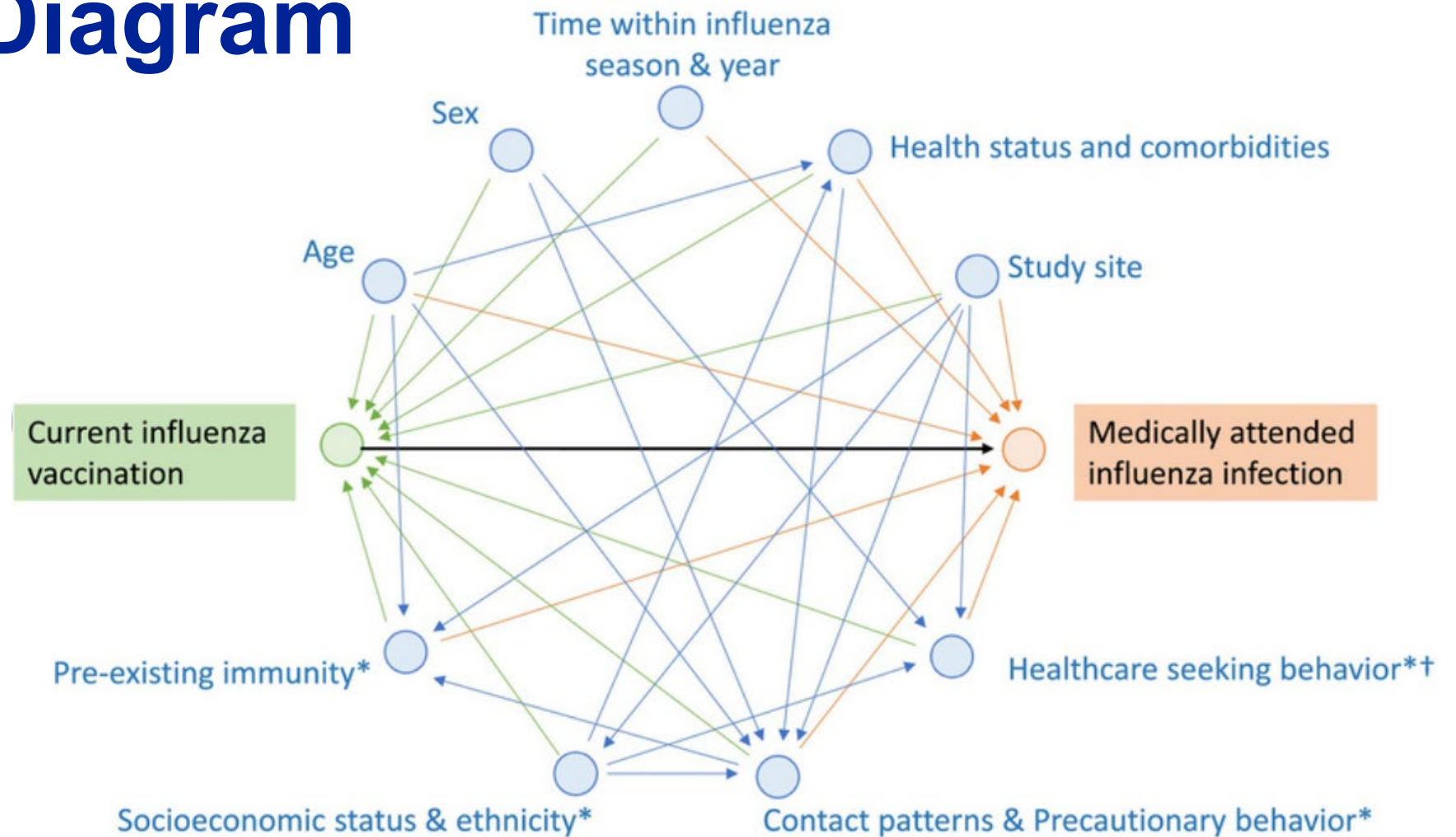
β_1

Exposure
Vaccination (V)

Outcome
Disease (D)

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

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Causal Diagram

Considerations
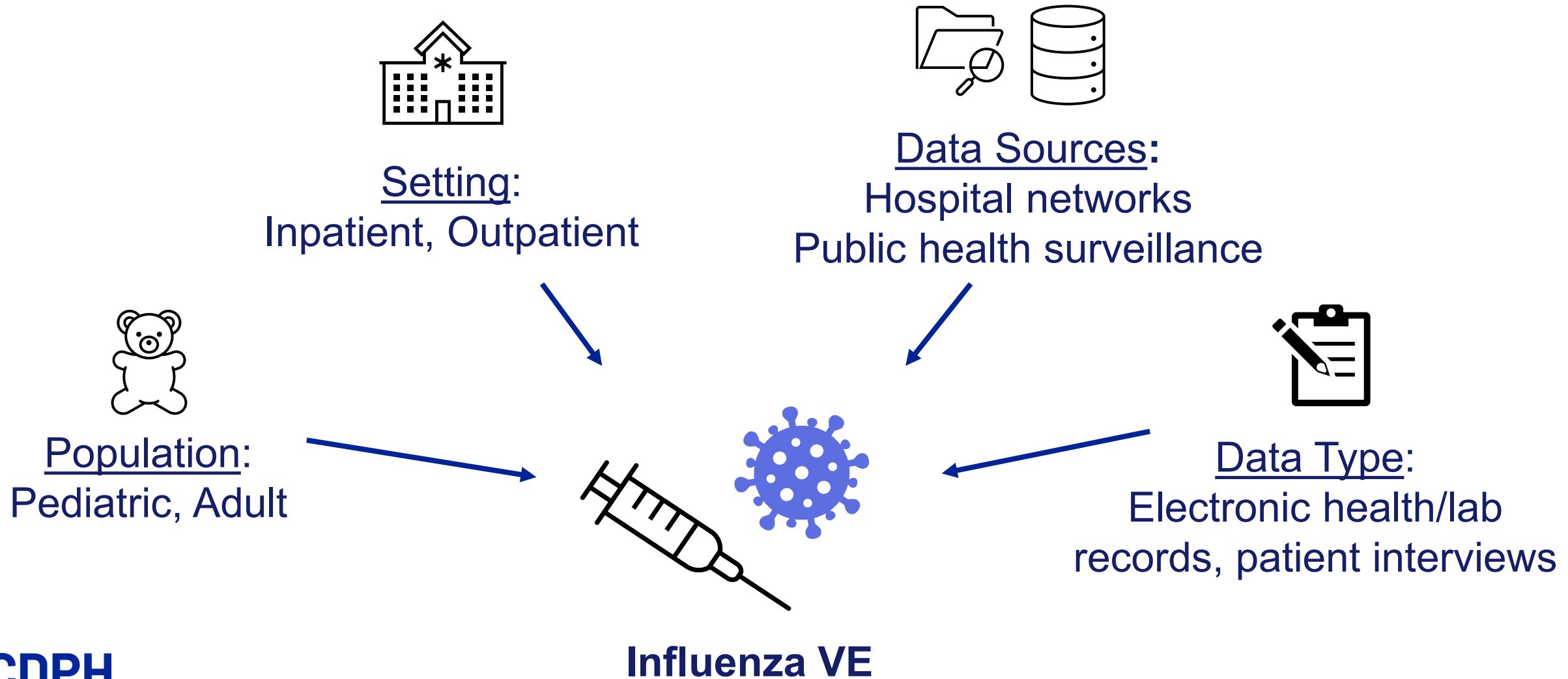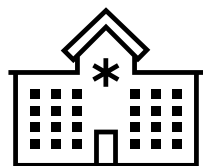
Setting:
Inpatient, Outpatient

Data Sources:
Hospital networks
Public health surveillance

Population:
Pediatric, Adult

Data Type:
Electronic health/lab
records, patient interviews

Influenza VE

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Considerations

Setting:
Inpatient, **Outpatient**

Data Sources:
Hospital networks
Public health surveillance

Population:
Pediatric, Adult

Influenza VE

Data Type:
Electronic health/**lab records,**
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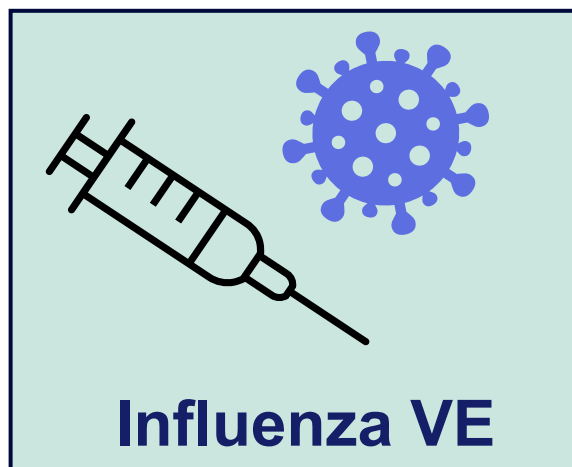
New California Data Reporting Requirements

- 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

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		

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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		

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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

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Vaccine Effectiveness Formula

Simulated Cohort

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

Vaccine efficacy (VE)

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

$$\text{VE} = \left(1 - \frac{0.05}{0.50}\right) x 100$$

$$= (1 - 0.10) x 100$$

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

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Covariates

- Age

- Race

- Ethnicity

- Week of Test

- County of Test

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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

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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**

Statewide disease surveillance system

Statewide immunization registry

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") → `blockfld = "DOB"`

Probabilistic ("fuzzy") → `strcmp = c("LastName", "FirstName", "County")`

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

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Matching

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```

Deterministic ("exact")

Probabilistic ("fuzzy")

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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%

Bar chart of positive influenza detections by Week of Test:
290, 383, 428, 561, 666, 938, 1,588, 2,342, 3,329, 5,139, 7,737, 13,213, 16,805, 16,662, 16,695, 17,066, 16,544, 16,417

X-axis: 01-Oct-2024, 01-Nov-2024, 01-Dec-2024, 01-Jan-2025, 01-Feb-2025
Week of Test

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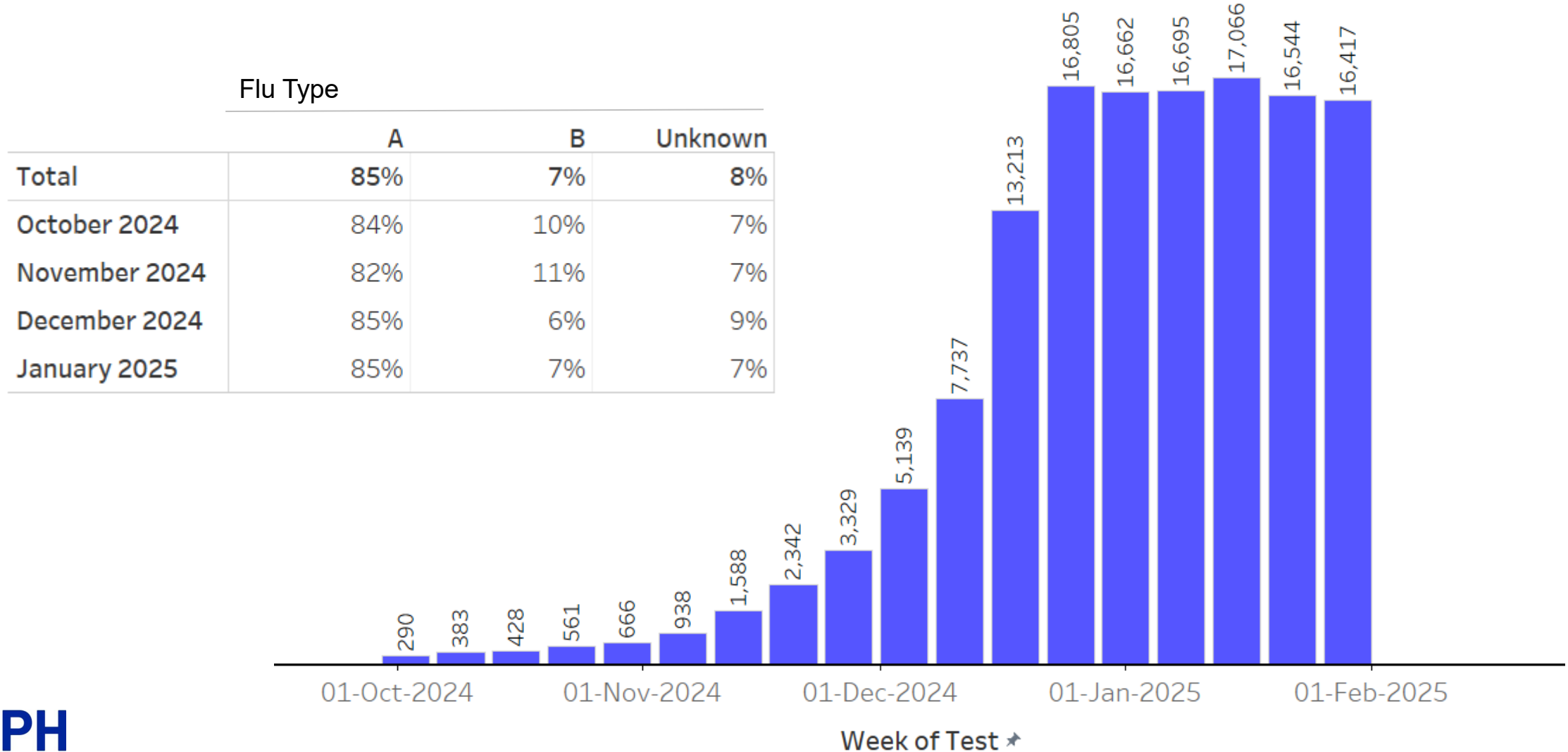
Study Population – Positivity and Vaccination
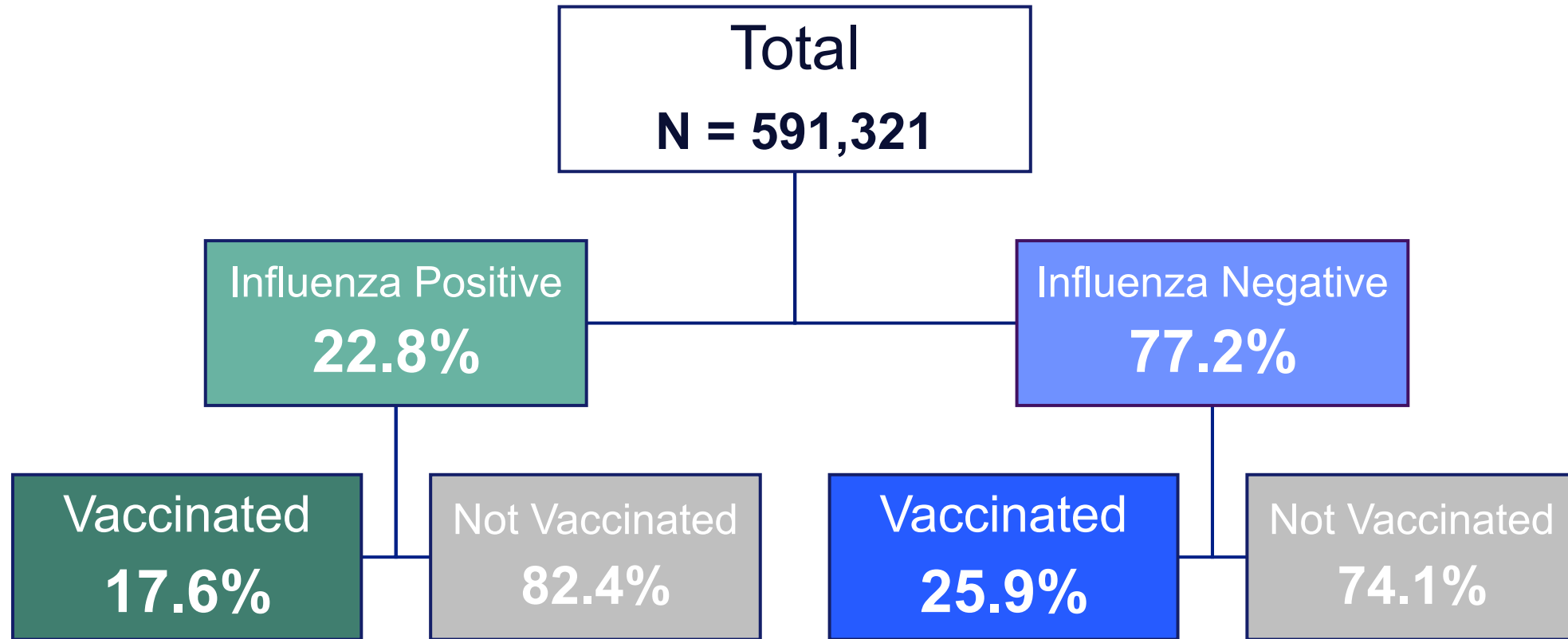
Study Population - Demographics

	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%*

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

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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**

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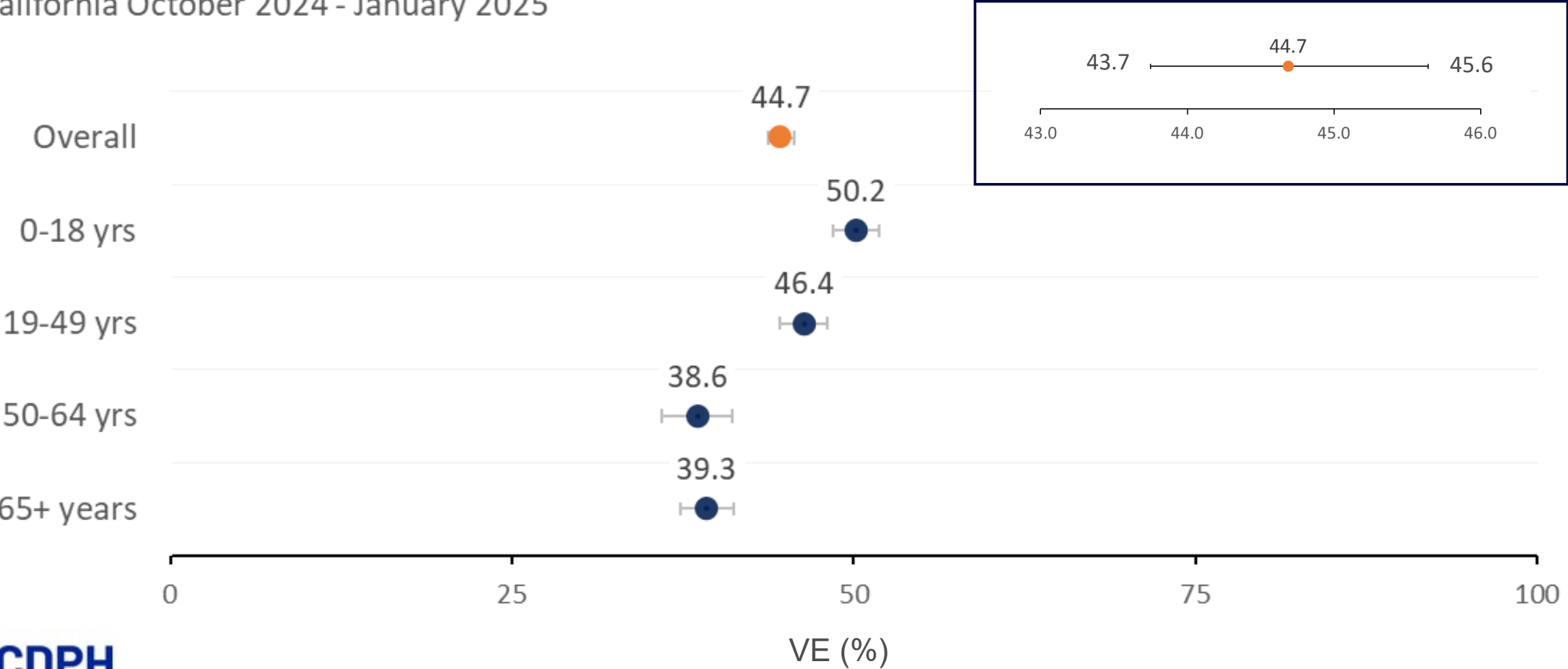
Influenza VE Estimate (Cumulative)
California 2024-2025
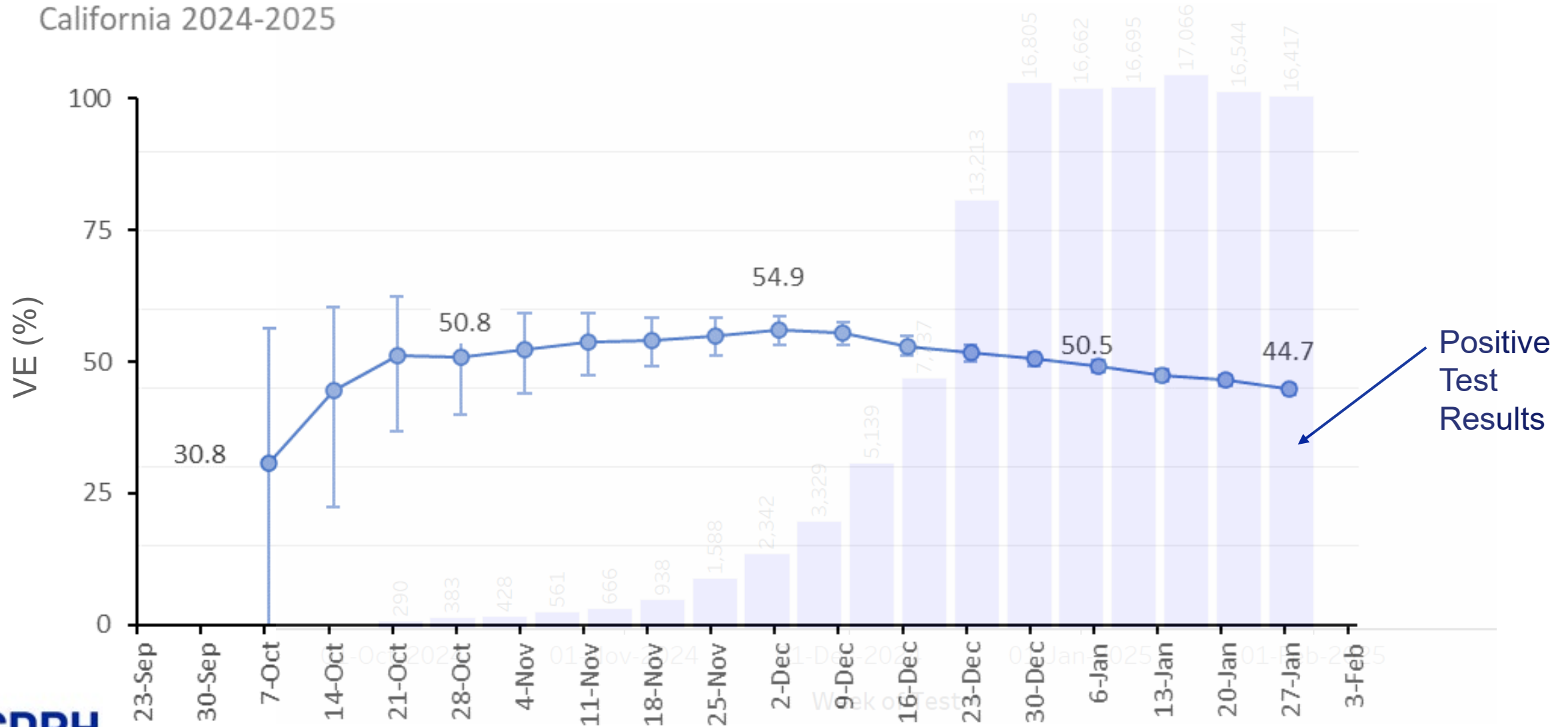
Vaccine Effectiveness by Month

California 2024-2025

October | November | December | January

VE (%)

100
75
50
25
0

October: 51.4
November: 55.5
December: 49.3
January: 39.9

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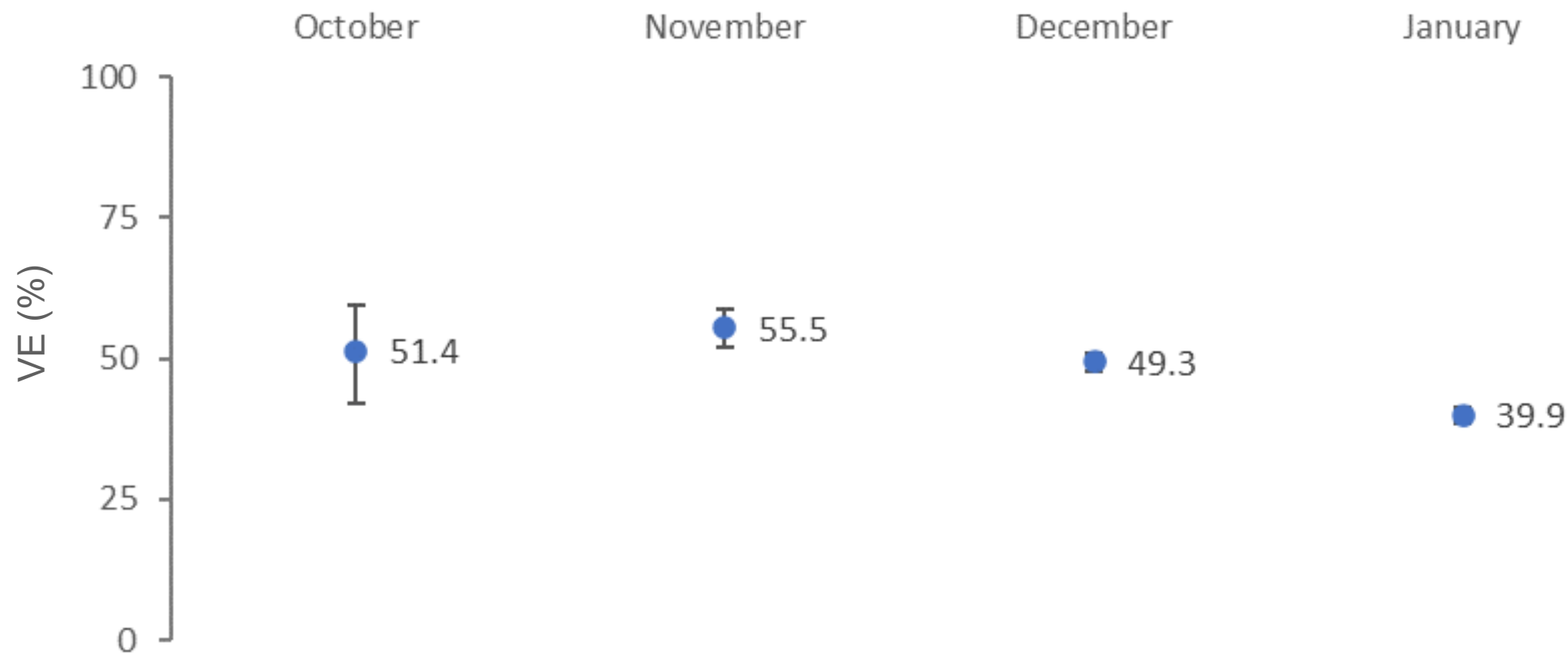
Vaccine Effectiveness by Month and Type
California 2024-2025
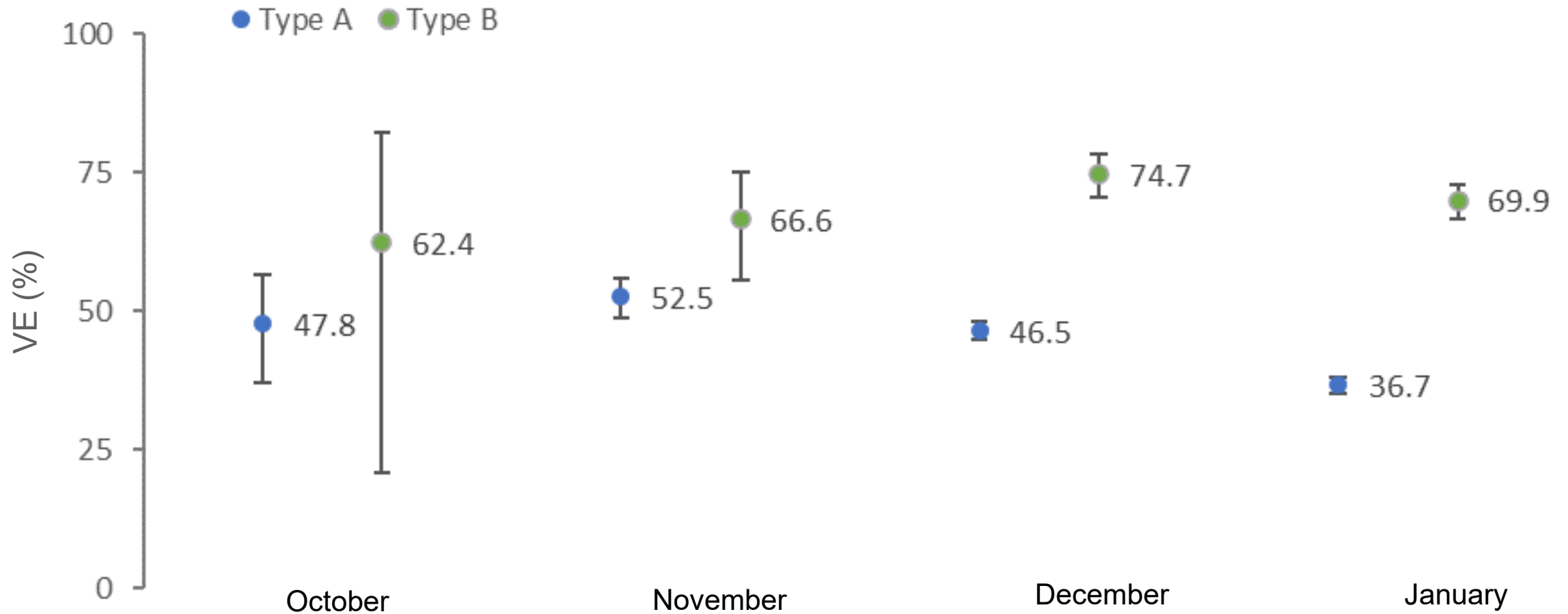
Limitations

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)

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How did we do?

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2023-2024 VE Platform Estimates
Pediatric: 0-18 yrs

CDC Vision VE Estimates

	Vaccine Effectiveness (%)
NVSN (outpatient)	59 (48, 67)
US Flu VE (outpatient)	67 (48, 80)
VISION (outpatient)	60 (57, 64)
NVSN (inpatient)	61 (40, 75)
VISION (inpatient)	52 (16, 72)
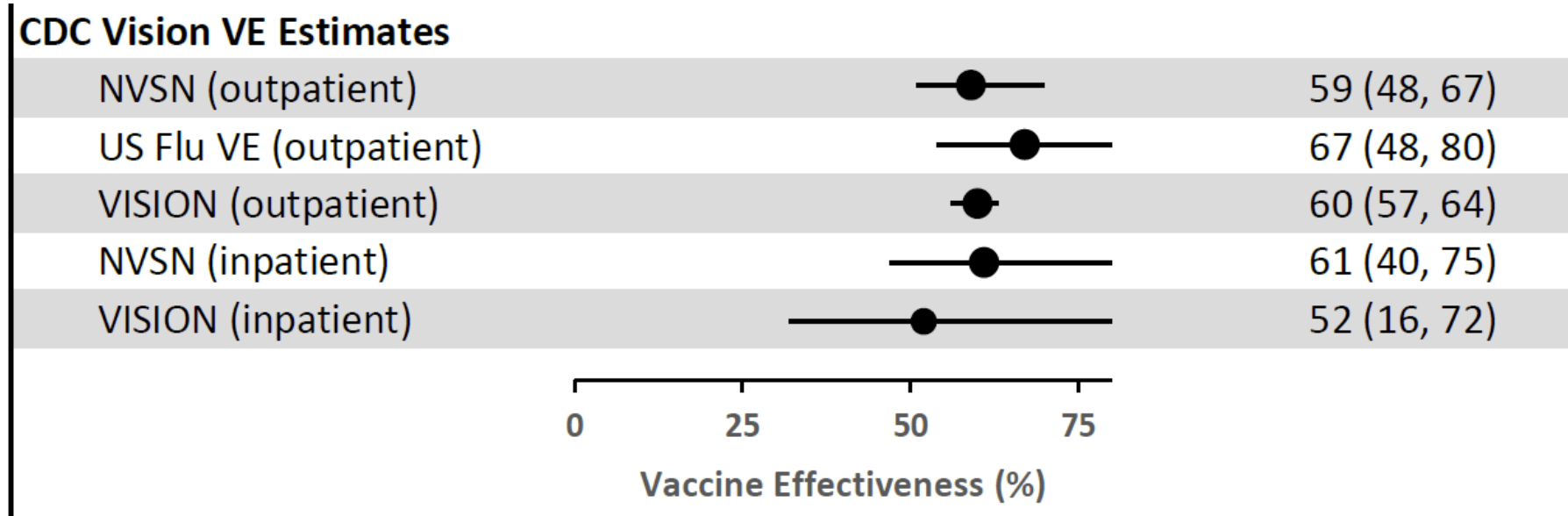
CA estimates similar to CDC VE platforms

Pediatric: 0-18 yrs

	Adjusted† VE % (95% CI)
California VE Estimates	
Influenza A and B	56 (54, 57)
CDC Vision VE Estimates	
NVSN (outpatient)	59 (48, 67)
US Flu VE (outpatient)	67 (48, 80)
VISION (outpatient)	60 (57, 64)
NVSN (inpatient)	61 (40, 75)
VISION (inpatient)	52 (16, 72)

Vaccine Effectiveness (%)

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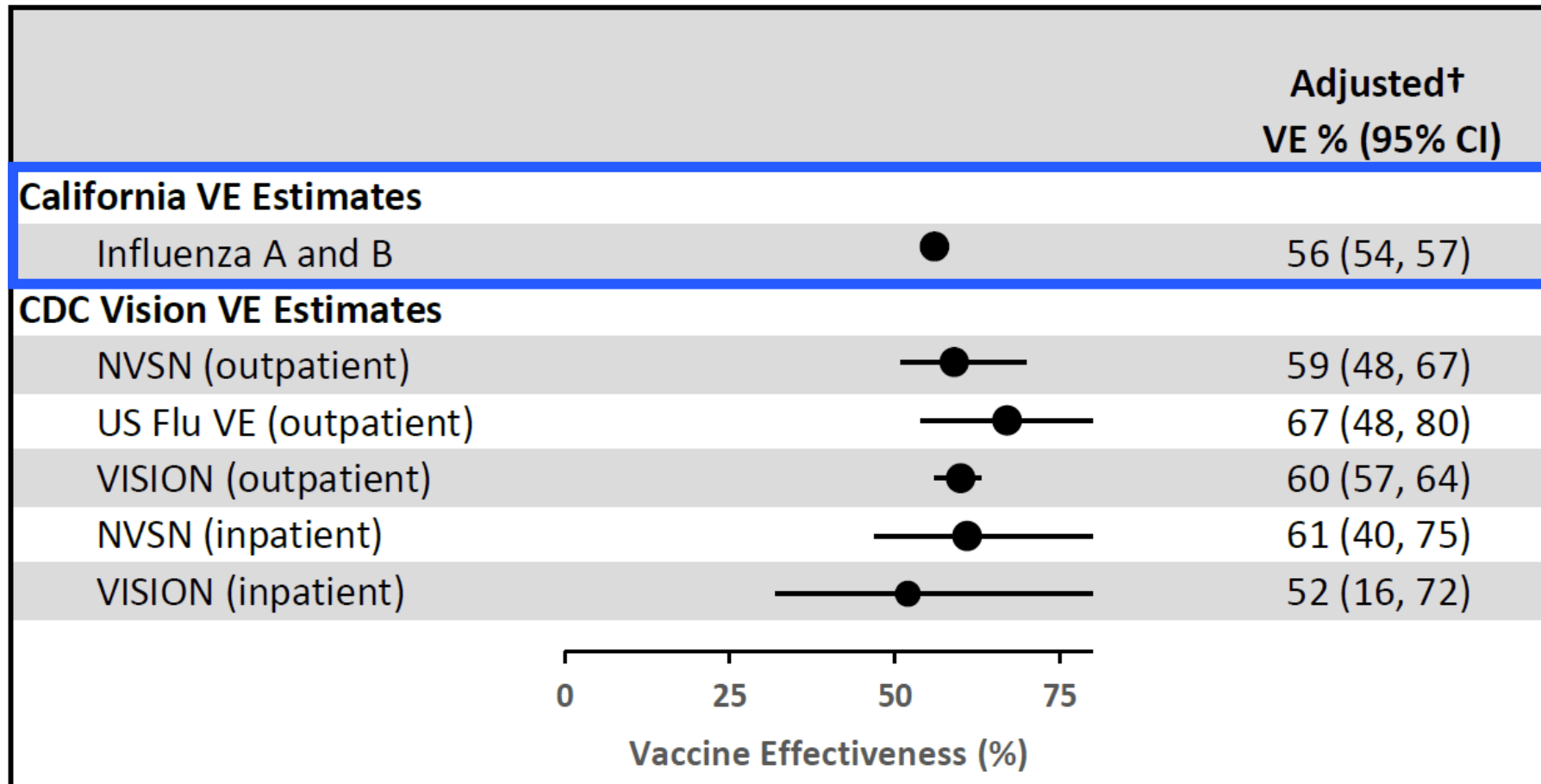
What about timing?
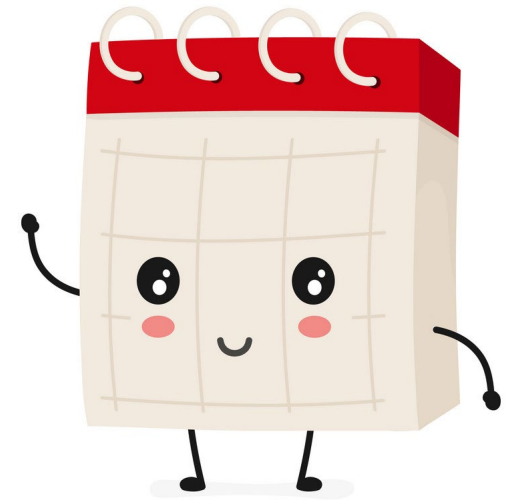
2023-2024 VE estimates stabilized by early January

Time period	Adjusted† VE % (95% CI)
October 31, 2023	46 (35, 56)
November 30, 2023	51 (49, 54)
December 31, 2023	44 (43, 46)
January 31, 2024	42 (41, 43)
February 29, 2024	42 (41, 43)
March 31, 2024	42 (41, 43)
April 30, 2024	42 (41, 43)
May 31, 2024	41 (40, 42)
June 30, 2024	41 (40, 42)

Vaccine Effectiveness (%)

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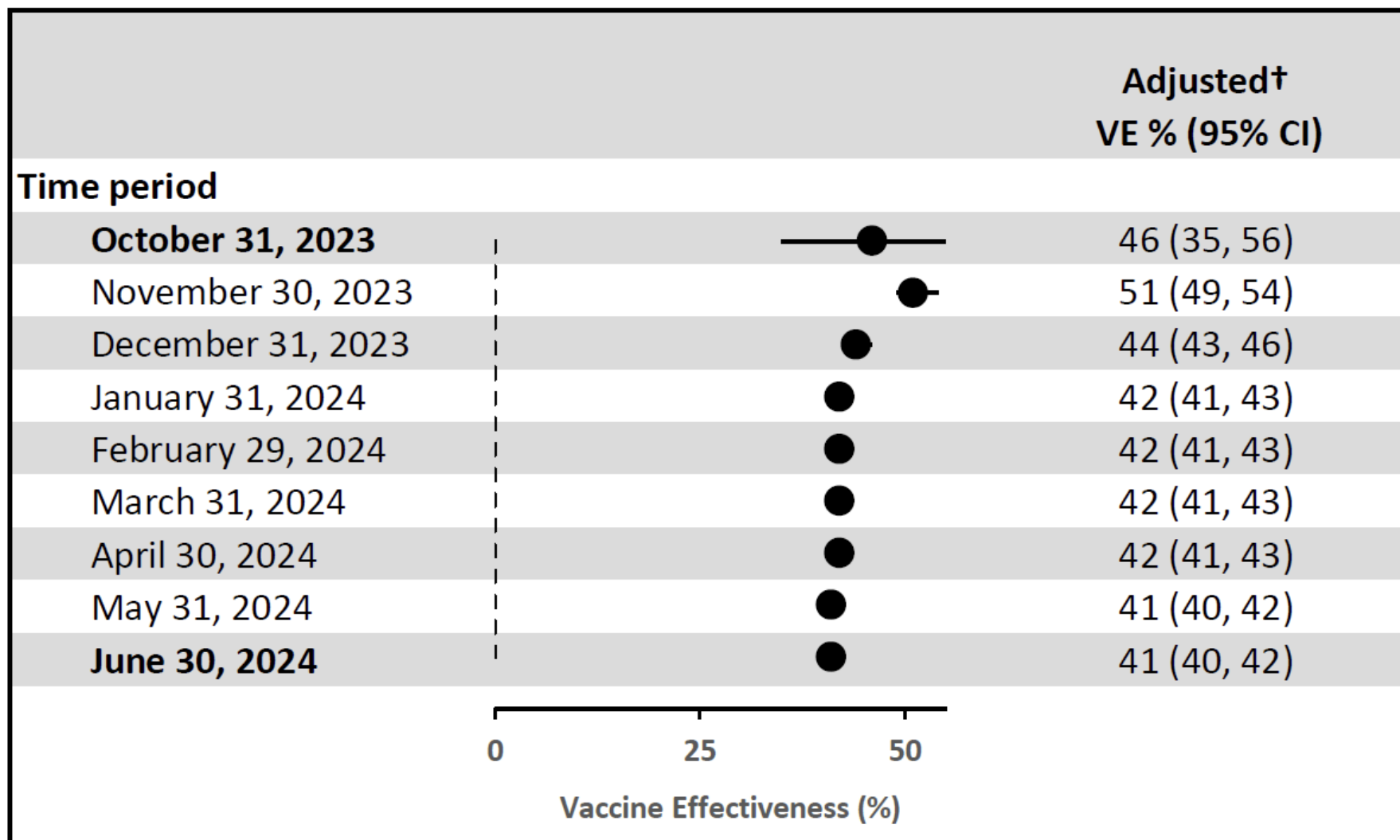
Conclusion

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

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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

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What to watch for…

- **Selection bias**
  - Missing data from certain kinds of labs or vaccine providers

- **Confounding**
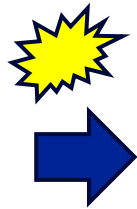 - Missing data on important covariates
  - Model misspecification

- **Information bias**
  - Poor data quality (inaccurate values for exposure, outcome, or covariates)

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Generalizability/Selection Bias

Source Population		Study Population		Outcome Ascertainment		Exposure Status

People experiencing influenza-like illness who visit a medical institution

→ People with a laboratory test reported to public health

Cases: Test Positive
- Vaccine (+)
- Vaccine (-)

Controls: Test Negative
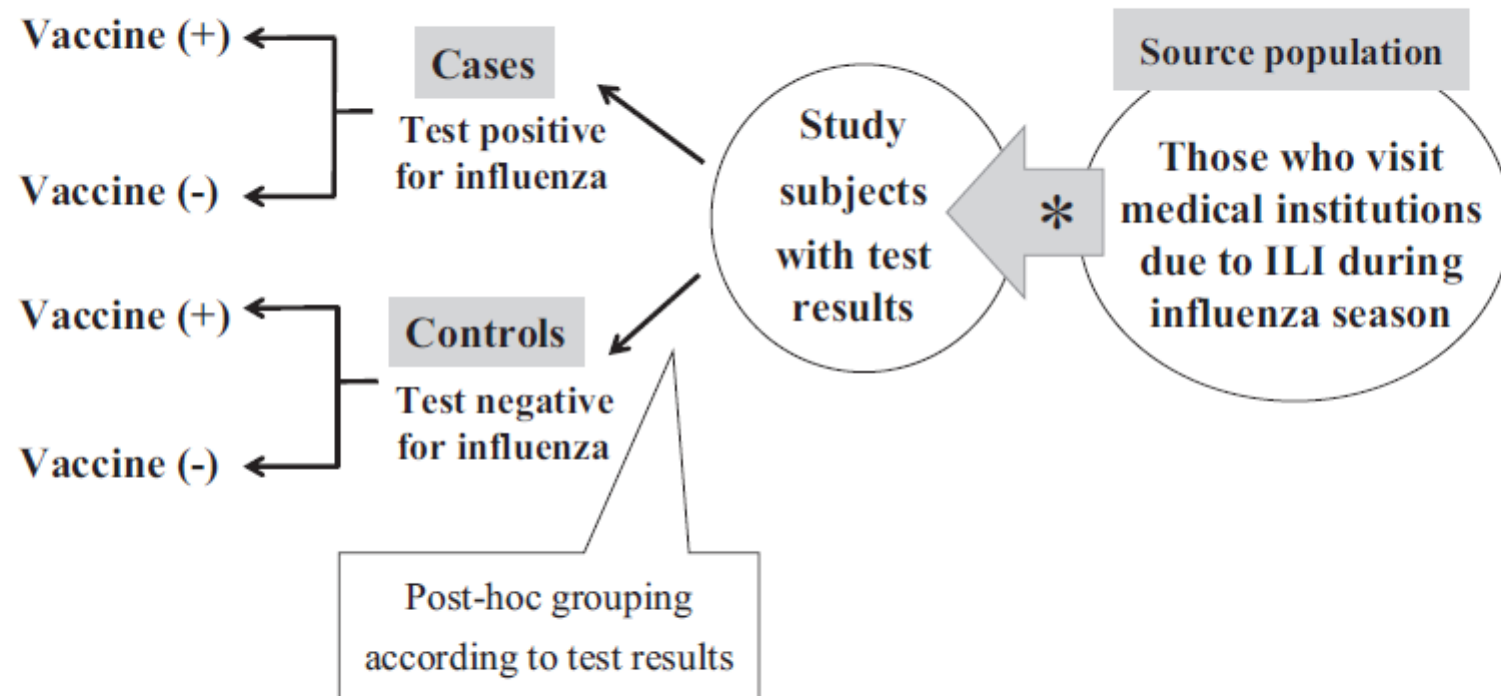- Vaccine (+)
- Vaccine (-)

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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.

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

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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?

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Causal Diagram

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/
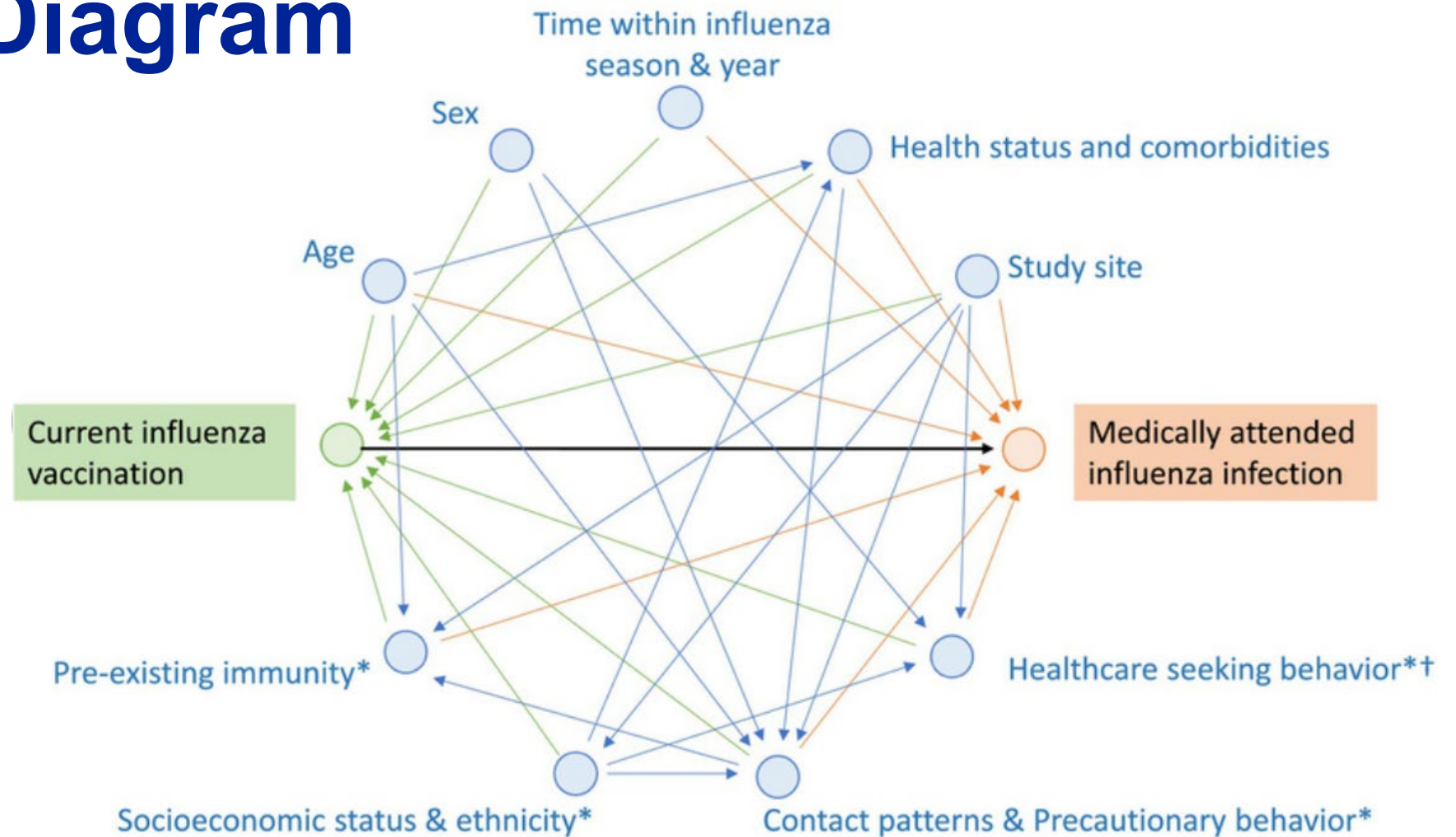
Missing Covariates

★ = factors not currently in the model (missing data)

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/
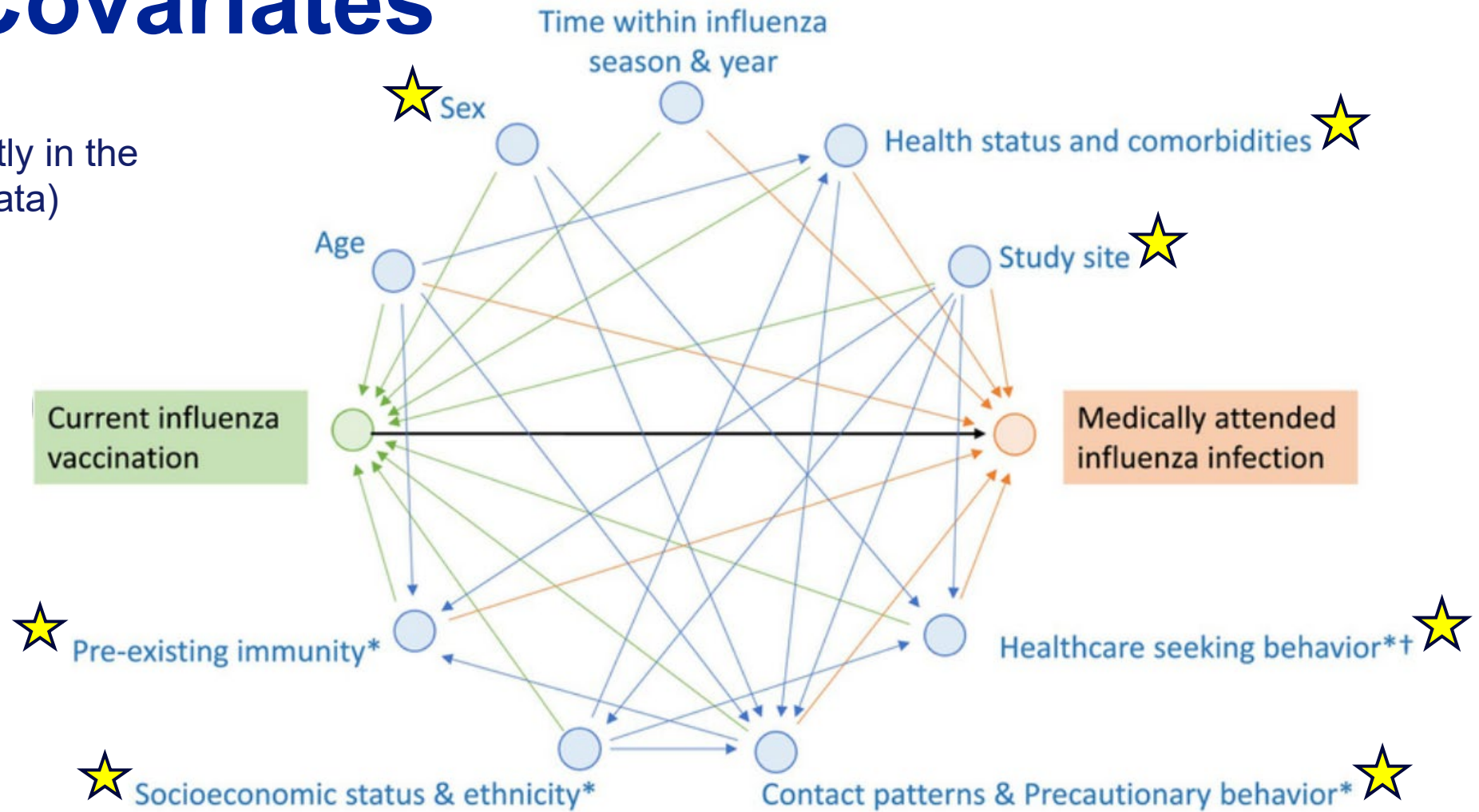
References and Resources

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

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Thank you to our presenters, and thanks to all of you for joining us!

Please complete a brief evaluation survey.

The next Discovery Session
will be on **March 24, 2025**