Design of Vaccine Effectiveness of Studies Using Large Administrative Databases: How was Bias Addressed?

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Presentation at World Health Organization (WHO) R&D Blueprint's Virtual Global Consultation on Improving Vaccine Effectiveness Studies: A Vital Step before the Next Pandemic

Outline

- Objective plus nuts & bolts
- Administrative Databases
- Examples of recent NYSDOH VE studies
  - COVID-19 **cases and hospitalization**
    - Open cohorts (1)
    - Closed cohorts (2)
  - Mpox –case-control study

Objective + Nuts & Bolts

- Objective: VE design examples (balancing comparison groups) that leverage administrative databases

- Compare the observed experience of 2 groups to make a “fair comparison” that simulates experience of 1 group (effect, in this case the vaccine) to an “identical” group (comparison group)
  - Gold standard RCT
- Next best options used:
  - **Design & Analysis**
    - **Restrictions**
    - **Stratification**
    - **Matching**
  - **Analysis**
    - **Standardization**
    - **Statistical modeling/adjustment**

Design & Analysis
• Restrictions
• Stratification
• Matching
Analysis
• Standardization
• Statistical adjustment

New York State Administrative Databases Utilized

- New York State: Population 20 million; 15 million age 18+
- Rest of State (other than NYC): Population 11 million; 8.8 million age 18+

- Leverage existing administrative databases: **population based, no sample size limitations**

- List of Databases
  - Electronic Clinical Laboratory System (ECLRS): Positive results of all reportable communicable diseases.
  - New York State Immunization Information System (NYSIIS): COVID-19 and JYNNEOS Vaccines given outside of NYC
  - Citywide Immunization Information System (CIR): COVID-19 and JYNNEOS Vaccines given in NYC
  - Communicable Disease Electronic Surveillance System (CDESS): C management system for communicable diseases outside of NYC

- Deterministic name, dob matches between databases

Open Cohort: COVID-19

Morbidity and Mortality Weekly Report

MMWR / September 17, 2021 / Vol. 70 / No. 37

New COVID-19 Cases and Hospitalizations Among Adults, by Vaccination Status — New York, May 3–July 25, 2021

Eli S. Rosenberg, PhD[1,2]; David R. Holtgrave, PhD[2]; Vajeera Dorabawila, PhD[1]; MaryBeth Conroy, MPH[1]; Danielle Greene, DrPH[1]; Emily Lutterloh, MD[1,2]; Bryon Backenson, MS[1,2]; Dina Hoefer, PhD[1]; Johanne Morne, MS[1]; Ursula Bauer, PhD[1]; Howard A. Zucker, MD, JD[1]

- Compare fully-vaccinated **(>=14 days)** vs. unvaccinated adults: cases and hospitalizations
  - **Time period (starting week of May 3rd)**
  - **Restricted to 18+**
  - Age-specific (18-49, 50-64, 64+)
  - Estimated weekly
  - **Age standardization (18+)**
  - **Rates for vaccinated and unvaccinated (outcome/weekly person time)**
  - **Incidence Rate Ratio (IRR)=Rate_Vaccinated/Rate_Unvaccianted**
  - Vaccine Effectiveness (VE) = 1 – IRR
- Maximally uses the population and transparent

Design & Analysis
- Restrictions
- Stratification
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Analysis
- Standardization
- Statistical adjustment

Case Results

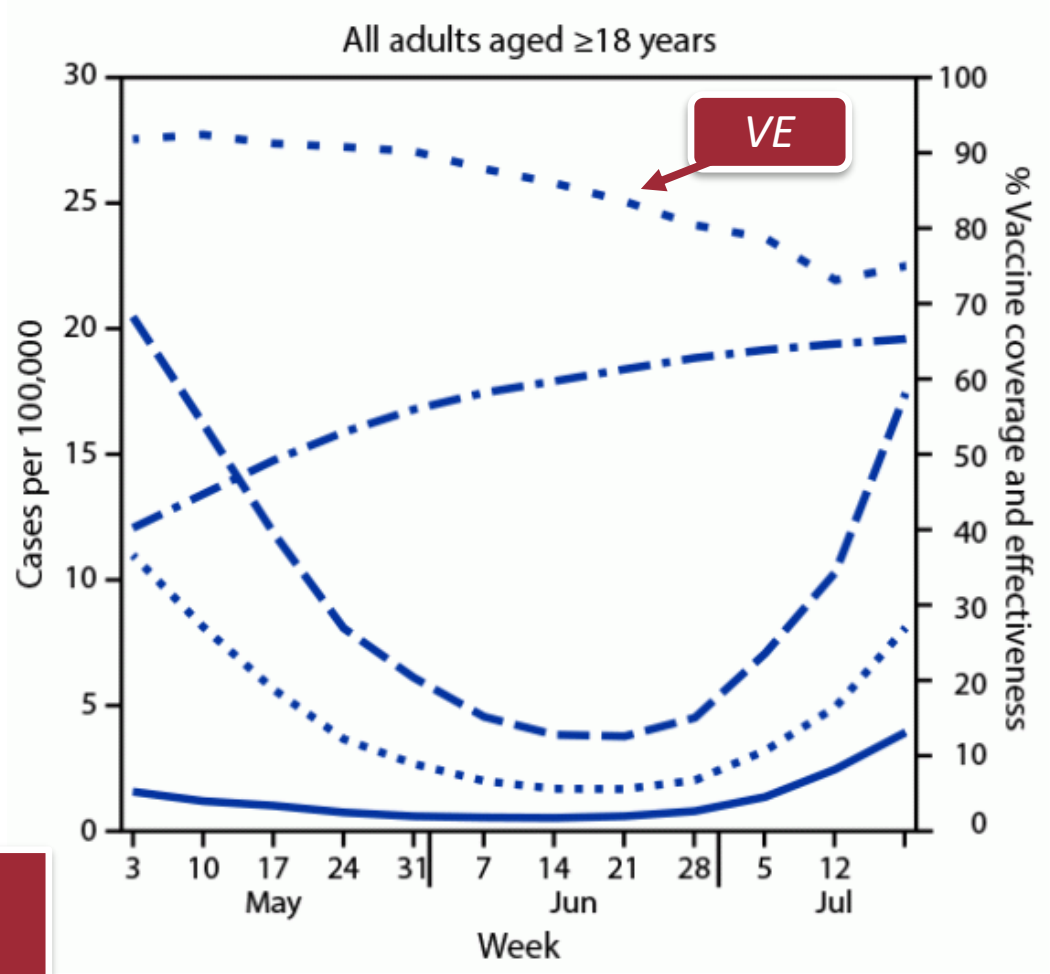
Age standardized, weekly, from week of May 3rd to week of July 19th

Laboratory-confirmed cases (PT range ; cases=52,169; May 3-July 19, 2021)

- May 3 week: VE = 91.8%
- Decline coincides with Delta variant increase to >99%
- Mid-July minimum, small rebound thereafter

Hospitalization (n=8,573)

- Consistent, higher VE, between 89.5% and 95.2%



Limitations

- **Unvaccinated can become vaccinated and contribute to person time and outcome in both groups**
- **Individuals not followed across time steps**
- **Challenging to understand sources of VE changes**
  - Products, time since vaccination, time period when variants and behaviors changed …

Design & Analysis
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1. Closed Cohorts

Covid-19 Vaccine Effectiveness in New York State

Eli S. Rosenberg, Ph.D., Vajeera Dorabawila, Ph.D., Delia Easton, Ph.D., Ursula E. Bauer, Ph.D., Jessica Kumar, D.O., Rebecca Hoen, Dr.P.H., Dina Hoefer, Ph.D., Meng Wu, Ph.D., Emily Lutterloh, M.D., Mary Beth Conroy, M.P.H., Danielle Greene, Dr.P.H., and Howard A. Zucker, M.D., J.D.

January 13, 2022
N Engl J Med 2022; 386:116-127
DOI: 10.1056/NEJMoa2116063

Address role of products and timing

- **Closed cohorts**
  - **Fully vaccinated Jan-April, split by age at vaccination and product received**
  - **Unvaccinated never vaccinated by Sept 23 (data freeze)**
  - **Adjust unvaccinated denominator to account for deaths**
- **Follow-up**: **May 1** to **September 3** (cases), **August 31** (hospitalization)
- **Stratified analysis**
  - **Age** **(18-49, 50-64, ≥65 years)**
  - **Product** **(Pfizer-BioNTech, Moderna, Janssen)**
  - **Time of full-vaccination** **(January/February, March, April)**
  - **Weekly**

- Laboratory-confirmed COVID-19 cases *(1 per person) (8,690,825 persons; 150,865 cases)*
  - **Time-to-diagnosis, life-table method (7 day intervals)**
    - **Hazard rates, with 95% CI**
    - VE = 1 – HR, with 95% CI

- Laboratory-confirmed COVID-19 hospitalizations *(repeats possible within person, ~9% of admissions) (14,477 hospitalizations)*
  - **Aggregate "$events/PT$" rates (1 month intervals)**
    - **Incidence rates, with exact 95% CI**
    - **VE = 1 – IRR, with exact 95% CI**

- Sensitivity Analysis: impact of bias
  - **Population size**
  - **Matching bias**
  - **Hospitalization with COVID vs for COVID**
  - **Stratification by urbanicity**
  - **Impact of unmeasured confounding (simulations)**

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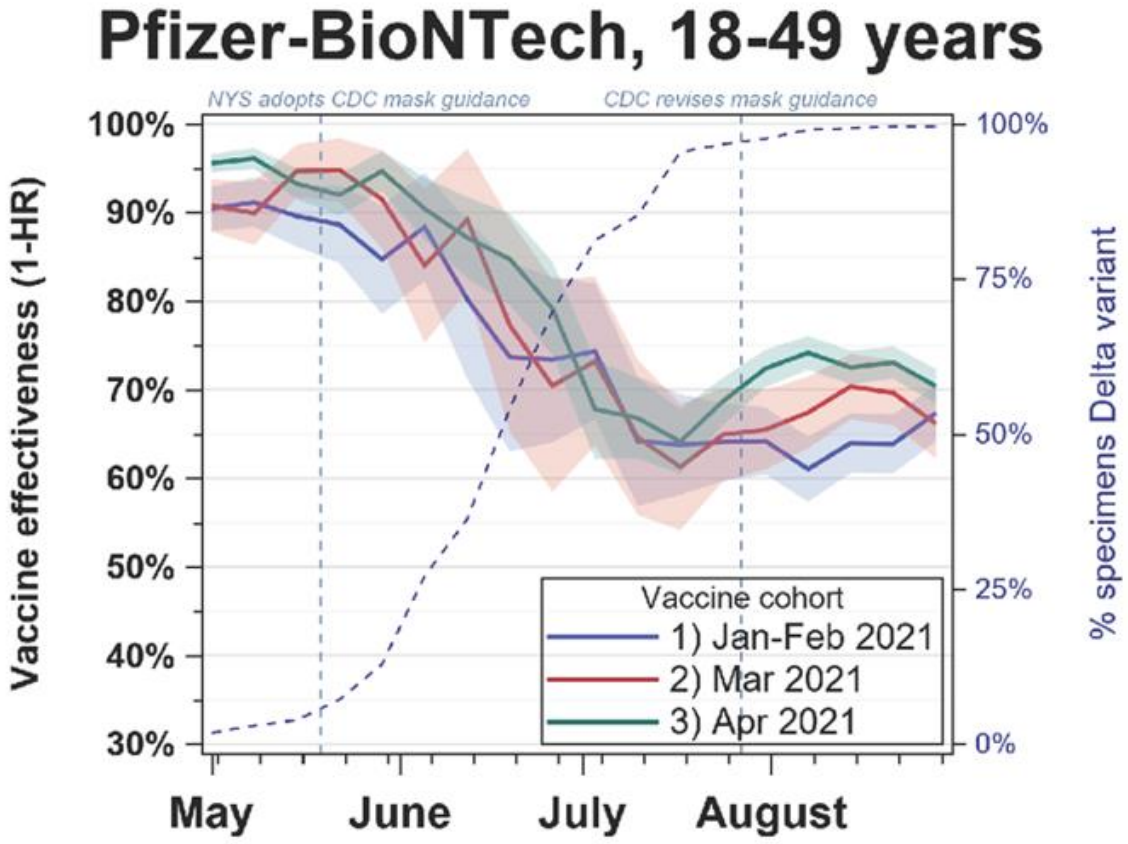
Case Results: One Age Group, One Product

- Pfizer, 18-49 years
- Weekly
- Vaccine cohorts (Jan-Feb, March, April)
- VE (ratio of standardized rates)
- Confidence intervals



- **Simultaneous drop-off in VE against cases for all cohorts**
  - When Delta increased & mask guidance changed
  - Waning
- Drop-off ceased when Delta reached >90%, followed by revised mask guidance
- Gradient by time-cohort in August, supportive of waning, but lesser magnitude than earlier drop

Design
- Restrictions
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2. Closed Cohorts

Risk of Infection and Hospitalization Among Vaccinated and Unvaccinated Children and Adolescents in New York After the Emergence of the Omicron Variant

JAMA 2022;327(22):2242-2244. doi:10.1001/jama.2022.7319

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Emily Lutterloh, MD
Eli S. Rosenberg, PhD

- Capture when FDA authorized the vaccine for all 5-17
- **Open cohorts (cases and hospitalization as the 1st study)**
- **Restrictive closed cohorts: Only *include* those newly fully-vaccinated in 3 weeks of December, 2021, and follow them up in January (Omicron >90%)**
  - **Weekly groups for both 5-11 years and 12-17 years**
  - Obviously, no one boosted then!

Follow-up week

	Cohort	Jan 3 – 9	Jan 10-16	Jan 17-23	Jan 24-30
5 – 11 years	Dec 13-19	1,808	1,234	781	472
	Dec 20-26	1,536	1,054	635	403
	Dec 27-Jan 2	712	522	320	204
12-17 years	Dec 13-19	132	82	42	22
	Dec 20-26	126	65	33	23
	Dec 27-Jan 2	84	55	41	15

Weeks since fully-vaccinated

3	4	5	6
2	3	4	5
1	2	3	4

- **Combined groups of weeks since fully-vaccinated**
- **IRR unvaccinated vs vaccinated**
- Compared average rates during all of January

Design & Analysis
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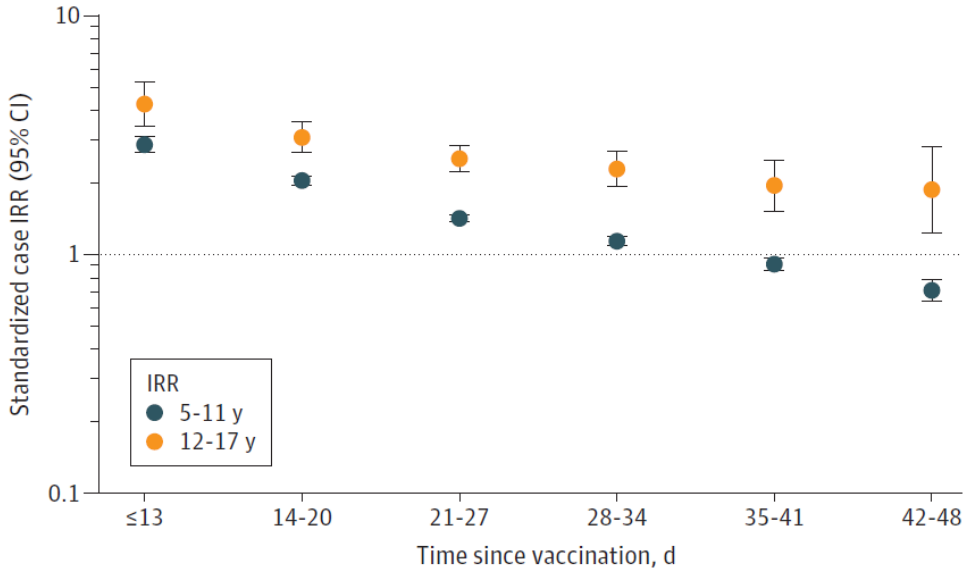
Case Results: Time Since Vaccination

- Weekly time since vaccination
- Separately for 5-11 and 12-17 age groups
- **Standardized IRR** and confidence intervals

Figure. New COVID-19 Cases Among Unvaccinated Children vs Fully Vaccinated Children by Time Since Vaccination and Age Group



IRR (95% CI)

12-17 y	4.3 (3.4-5.3)	3.1 (2.7-3.6)	2.5 (2.2-2.9)	2.3 (1.9-2.7)	1.9 (1.5-2.5)	1.9 (1.2-2.8)
5-11 y	2.9 (2.7-3.1)	2.0 (1.9-2.1)	1.4 (1.4-1.5)	1.1 (1.1-1.2)	0.9 (0.9-1.0)	0.7 (0.6-0.8)

Time since full vaccination was defined as days subsequent to 14 days after completion of the primary 2-dose series. Incidence rate ratio (IRR) values less than 1 observed in later times likely reflect estimator instability, residual confounding, or both as opposed to true relative increased risk for those vaccinated.

- IRR higher for 12-17 years group
- Marked declines in IRR
- For 5-11 years group:
  - IRR near 0% after 1 month against cases
  - May be related to lower dose for 5-11 year vs. 12-17 years group at that point
- Actions in response
  - Changes made to the 5-11 doses
  - Impact on the 0-4 years roll-out

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JYNNEOS VE Study during 2022 mpox Outbreak

- Mpox outbreak
  - May 2022 –tapering in Fall 2022
  - Peak August, 2022
  - Study period: **July 24-October 31**

- **Case-Control Study Design**
  - **Cases: mpox case men**
  - **Control: Men with diagnosed rectal gonorrhea or primary syphilis and a history of male-to-male sexual contact.**

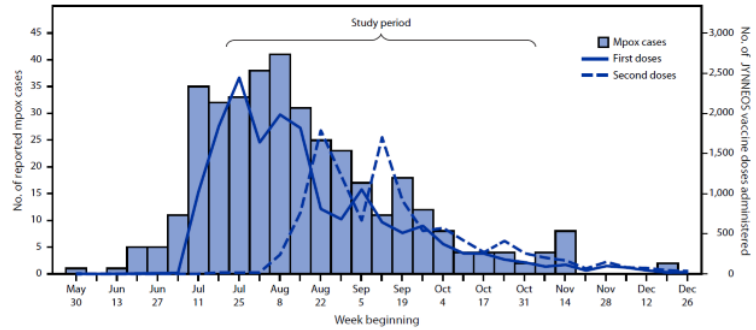
- Statistical approach
  - **Conditional logistic regression**
    - Matched (stratified) on week
    - **Covariate adjustment for age, region (metro-NYC vs. not), race**
    - **1 - adjusted OR → VE**
  - **Vaccine categories**
  - Sensitivity analyses (limit to age 18-49; include secondary syphilis in control group; testing due to symptoms/partner referral for control group)
  - Other matching, control strategies considered (e.g. test negative not feasible; only lab record available)

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Weekly / Vol. 72 / No. 20
May 19, 2023

Effectiveness of JYNNEOS Vaccine Against Diagnosed Mpox Infection — New York, 2022

Eli S. Rosenberg, PhD[1,2,3]; Vajeera Dorabawila, PhD[1]; Rachel Hart-Malloy, PhD[1,2,3]; Bridget J. Anderson, PhD[1]; Wilson Miranda, MPH[1]; Travis O'Donnell[1]; Charles J. Gonzalez, MD[1,3]; Meaghan Abrego, MPH[1]; Charlotte DelBarba, MPH[1]; Cori J. Tice, MPH[1]; Claire McGarry, MPH[1]; Ethan C. Mitchell, MPH[1]; Michele Boulais, MPA[1]; Bryon Backenson, MS[1,2]; Michael Kharfen[1]; James McDonald, MD[1]; Ursula E. Bauer, PhD[1]

FIGURE. Reported mpox cases and first and second JYNNEOS vaccine doses administered, by week — New York,* June 2–December 31, 2022



Abbreviation: Mpox = monkeypox.
* Outside of New York City.

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Results

TABLE 1. Demographic characteristics of case-patients with mpox and control patients with sexually transmitted infections* — New York,† July 24, 2022–October 31, 2022

Characteristic	No. (%) Mpox case-patients (n = 252)	No. (%) STI control patients* (n = 255)	p-value
Age group, yrs			
18–29	94 (37.3)	111 (43.5)	0.34
30–39	90 (35.7)	75 (29.4)	
40–49	37 (14.7)	33 (12.9)	
≥50	31 (12.3)	36 (14.1)	
Race and ethnicity§			
Black or African American, NH	48 (19.8)	68 (32.1)	<0.001
White, NH	69 (28.4)	90 (42.5)	
Hispanic or Latino	106 (43.6)	40 (18.9)	
Other, NH	20 (8.2)	14 (6.6)	
Unknown	9 (3.6)	43 (16.7)	
Region			
Metropolitan region outside NYC¶	173 (68.7)	91 (35.7)	<0.001
Rest of New York outside NYC	79 (31.3)	164 (64.3)	

- Age comparable, differences in race/ethnicity and region

TABLE 2. JYNNEOS vaccination history and estimated vaccine effectiveness among case-patients with mpox and control patients with sexually transmitted infections — New York,* July 24, 2022–October 31, 2022

Vaccination status	Mpox case-patients (n = 252) No. (%)	All STI controls (n = 255) No. (%)	VE (95% CI)
Unvaccinated	230 (91.3)	204 (80.0)	Ref
0–13 days after first dose	10 (4.0)	9 (3.5)	−36.2 (<−100 to 56.3)
≥14 days after first dose	10 (4.0)	23 (9.0)	68.1 (24.9 to 86.5)
≥0 days after second dose	2 (0.8)	19 (7.5)	88.5 (44.1 to 97.6)
≥14 days after first dose or ≥0 days after second dose	12 (4.8)	42 (16.5)	75.7 (48.5 to 88.5)

Abbreviations: Mpox = monkeypox; Ref = referent group; STI = sexually transmitted infection; VE = vaccine effectiveness.
* Outside of New York City.

- Model adjustment to address bias; confidence intervals
- Vaccine categories

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Prior Infection: VE Studies with NYS Data

León TM, Dorabawila V, Nelson L, et al. **COVID-19 Cases and Hospitalizations by COVID-19 Vaccination Status and Previous COVID-19 Diagnosis — California and New York, May–November 2021**. MMWR Morb Mortal Wkly Rep 2022;71:125–131. DOI: http://dx.doi.org/10.15585/mmwr.mm7104e1external icon.

Ma KC, Dorabawila V, León TM, et al. **Trends in Laboratory-Confirmed SARS-CoV-2 Reinfections and Associated Hospitalizations and Deaths Among Adults Aged ≥18 Years — 18 U.S. Jurisdictions, September 2021–December 2022. MMWR** Morb Mortal Wkly Rep 2023;72:683–689. DOI: http://dx.doi.org/10.15585/mmwr.mm7225a3

Thank you!

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