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
• 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
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): Case management system for communicable diseases outside of NYC

- Deterministic name, dob matches between databases
Open Cohort: COVID-19

• 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_Unvaccinated
  ▫ Vaccine Effectiveness (VE) = 1 – IRR

• Maximally uses the population and transparent
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...
1. Closed Cohorts

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)
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
2. Closed Cohorts

- 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!

<table>
<thead>
<tr>
<th>Follow-up week</th>
<th>Jan 3 – 9</th>
<th>Jan 10-16</th>
<th>Jan 17-23</th>
<th>Jan 24-30</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 – 11 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dec 13-19</td>
<td>1,808</td>
<td>1,234</td>
<td>781</td>
<td>472</td>
</tr>
<tr>
<td>Dec 20-26</td>
<td>1,536</td>
<td>1,054</td>
<td>635</td>
<td>403</td>
</tr>
<tr>
<td>Dec 27-Jan 2</td>
<td>712</td>
<td>522</td>
<td>320</td>
<td>204</td>
</tr>
<tr>
<td>12-17 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dec 13-19</td>
<td>132</td>
<td>82</td>
<td>42</td>
<td>22</td>
</tr>
<tr>
<td>Dec 20-26</td>
<td>126</td>
<td>65</td>
<td>33</td>
<td>23</td>
</tr>
<tr>
<td>Dec 27-Jan 2</td>
<td>84</td>
<td>55</td>
<td>41</td>
<td>15</td>
</tr>
</tbody>
</table>

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

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.
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)
### 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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mpox case-patients (n = 252)</th>
<th>STI control patients* (n = 255)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age group, yrs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–29</td>
<td>94 (37.3)</td>
<td>111 (43.5)</td>
<td>0.34</td>
</tr>
<tr>
<td>30–39</td>
<td>90 (35.7)</td>
<td>75 (29.4)</td>
<td></td>
</tr>
<tr>
<td>40–49</td>
<td>37 (14.7)</td>
<td>33 (12.9)</td>
<td></td>
</tr>
<tr>
<td>≥50</td>
<td>31 (12.3)</td>
<td>36 (14.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Race and ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black or African American, NH</td>
<td>48 (19.8)</td>
<td>68 (32.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White, NH</td>
<td>69 (28.4)</td>
<td>90 (42.5)</td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>106 (43.6)</td>
<td>40 (18.9)</td>
<td></td>
</tr>
<tr>
<td>Other, NH</td>
<td>20 (8.2)</td>
<td>14 (6.6)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>9 (3.6)</td>
<td>43 (16.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metropolitan region outside NYC</td>
<td>173 (68.7)</td>
<td>91 (35.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rest of New York outside NYC</td>
<td>79 (31.3)</td>
<td>164 (64.3)</td>
<td></td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th>Vaccination status</th>
<th>Mpox case-patients (n = 252)</th>
<th>All STI controls (n = 255)</th>
<th>VE (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unvaccinated</td>
<td>230 (91.3)</td>
<td>204 (80.0)</td>
<td>Ref</td>
</tr>
<tr>
<td>0–13 days after first dose</td>
<td>10 (4.0)</td>
<td>9 (3.5)</td>
<td>-36.2 (&lt;-100 to 56.3)</td>
</tr>
<tr>
<td>≥14 days after first dose</td>
<td>10 (4.0)</td>
<td>23 (9.0)</td>
<td>68.1 (24.9 to 86.5)</td>
</tr>
<tr>
<td>≥0 days after second dose</td>
<td>2 (0.8)</td>
<td>19 (7.5)</td>
<td>88.5 (44.1 to 97.6)</td>
</tr>
<tr>
<td>≥14 days after first dose or ≥0 days after second dose</td>
<td>12 (4.8)</td>
<td>42 (16.5)</td>
<td>75.7 (48.5 to 88.5)</td>
</tr>
</tbody>
</table>

**Abbreviations:** Mpox = monkeypox; Ref = referent group; STI = sexually transmitted infection; VE = vaccine effectiveness.

* Outside of New York City.

- Age comparable, differences in race/ethnicity and region
- Model adjustment to address bias; confidence intervals
- Vaccine categories

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

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](http://dx.doi.org/10.15585/mmwr.mm7225a3)
Thank you!

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