Considerations for design of case-control studies of JYNNEOS (MVA) vaccine effectiveness: the New York State example

Eli Rosenberg, PhD
Deputy Director for Science, Office of Public Health, New York State Department of Health
Associate Professor, Department of Epidemiology and Biostatistics, University at Albany School of Public Health

AUGUST 2, 2022
Outline for today

- Monkeypox & JYNNEOS in New York State

- Why a case-control design?

- 4 challenges of the case-control design in this context

- Wrap-up
Monkeypox & JYNNEOS in New York State

- New York State (NYS) cases, as of August 1: 1,573
  - New York City: 1,472
  - New York State, outside of NYC: 101

- JYNNEOS (MVA) rollout underway, part of phased national campaign
  - FDA-approved as 2-dose regimen, but not based on human incidence data
  - Real-world effectiveness unclear in context of:
    - Current outbreak and transmission pattern via male-male intimate contact
    - 1-dose strategy
    - Diverse uses:
      - PEP for known contacts
      - PEP++: having recent qualifying behaviors, but not known exposure to contact
      - PrEP: pre-exposure prophylaxis for persons at risk of future exposure

- NYS received 62,000 in Phase 1-2b. Current phases limited to PEP, PEP++
  - Imperative to study rollout. NYS DOH is conducting a case-control study
Why a case-control design?

- Cohort approach most straightforward, feels like RCT
  - Compare incidence between vaccinated and unvaccinated cohorts.
  - VE calculated from gap in incidence rates (1 - IRR)
  - Challenge: inefficient for rare diseases. We’d like a fast answer!

- Case-control study offers efficiency
  - Compare vaccination history between monkeypox cases vs. controls that reflect underlying population.
    - Lower vaccination in cases supports VE: OR = 0.16, VE = 94%
  - Challenges abound however, particularly for this outbreak!

<table>
<thead>
<tr>
<th></th>
<th>Monkeypox cases</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccinated</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>Not Vaccinated</td>
<td>190</td>
<td>150</td>
</tr>
</tbody>
</table>
Challenge 1: Who are the ideal controls?

• In the ideal...
  ▫ Controls would come from the same underlying at-risk population as cases
  ▫ Vaccine distribution establishes “background” for comparisons to cases

• How do we define persons at risk for monkeypox?
  ▫ Epi patterns, transmission modes still being clarified
  ▫ Exposure may be hard to assess, non-specific, and recruit on (e.g. hx of sex-party attendance)

• Some ideas… none feel perfect
  ▫ Monkeypox negative testers → often not reportable, TND bias concerns
  ▫ Persons on HIV PrEP → may be behaviorally similar, can be hard to sample
  ▫ Persons with new STI diagnoses → may be behaviorally similar, can be sampled

• New York State’s case-control study is based on linked monkeypox, STI, immunization surveillance data systems, for ease and efficiency.
Challenge 2: Key sources of bias to consider

- Time matching controls to case: essential due to rapid vaccine ramp-up
- Geography within large jurisdictions with heterogenous outbreak
- Behavioral data collected
  - Can be incomplete, misaligned definitions between cases & controls in surveillance
- Post-vaccine behavioral change?
  - Surveillance and survey instrument for case-control ill-suited to understand history of behaviors pre vs. post vaccine. Cohorts best suited.
Challenge 3: Key sources of effect modification to consider

- **Reason** for dose receipt (PEP, PEP++, PrEP)
  - VE likely to differ by these, particularly for PEP
  - Clever way to limit study only to PEP++? Likely to effectively be.
  - May be difficult to assess at time of sampling. Ideal = time of vaccination.

- Number of doses: 1 vs. 2

- Time since dose receipt
Challenge 4: Vaccine coverage as a limiting factor

• Observational designs have opposite inefficiencies
  ▫ Cohort: rare disease
  ▫ Case-control: rare exposure (low vaccine coverage)

• US still in early stages of rollout, where supply < demand, and coverage of target population unclear

• Power/precision markedly increases as vaccine coverage of target (control) population increases…
Challenge 4: Vaccine coverage as a limiting factor

- Power/precision markedly increases as vaccine coverage of target (control) population increases…

<table>
<thead>
<tr>
<th>Vaccine prevalence among controls</th>
<th>OR</th>
<th>VE</th>
<th>Vaccine prevalence among cases</th>
<th>Power: Matched McNemar's test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1:1 ratio, phi = 0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>5.0%</td>
<td>0.5</td>
<td>50%</td>
<td>2.5%</td>
<td>9%</td>
</tr>
<tr>
<td>5.0%</td>
<td>0.25</td>
<td>75%</td>
<td>1.3%</td>
<td>17%</td>
</tr>
<tr>
<td>5.0%</td>
<td>0.1</td>
<td>90%</td>
<td>0.5%</td>
<td>26%</td>
</tr>
<tr>
<td>10.0%</td>
<td>0.5</td>
<td>50%</td>
<td>5.0%</td>
<td>14%</td>
</tr>
<tr>
<td>10.0%</td>
<td>0.25</td>
<td>75%</td>
<td>2.5%</td>
<td>35%</td>
</tr>
<tr>
<td>10.0%</td>
<td>0.1</td>
<td>90%</td>
<td>1.0%</td>
<td>67%</td>
</tr>
<tr>
<td>15.0%</td>
<td>0.5</td>
<td>50%</td>
<td>7.5%</td>
<td>19%</td>
</tr>
<tr>
<td>15.0%</td>
<td>0.25</td>
<td>75%</td>
<td>3.8%</td>
<td>51%</td>
</tr>
<tr>
<td>15.0%</td>
<td>0.1</td>
<td>90%</td>
<td>1.5%</td>
<td>89%</td>
</tr>
</tbody>
</table>
Case control designs offer efficient approach to studying JYNNEOS VE. With coverage at 15% and moderate VE, may only need few hundred cases.

Numerous opportunities for bias. Some can be anticipated and controlled.

Multiple studies and studies of pooled data will be needed to understand this question… and case-control data very amenable to pooling.
  ▫ Join us?
Thank you!

Eli Rosenberg, PhD
New York State Department of Health
eli.rosenberg@health.ny.gov