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

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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

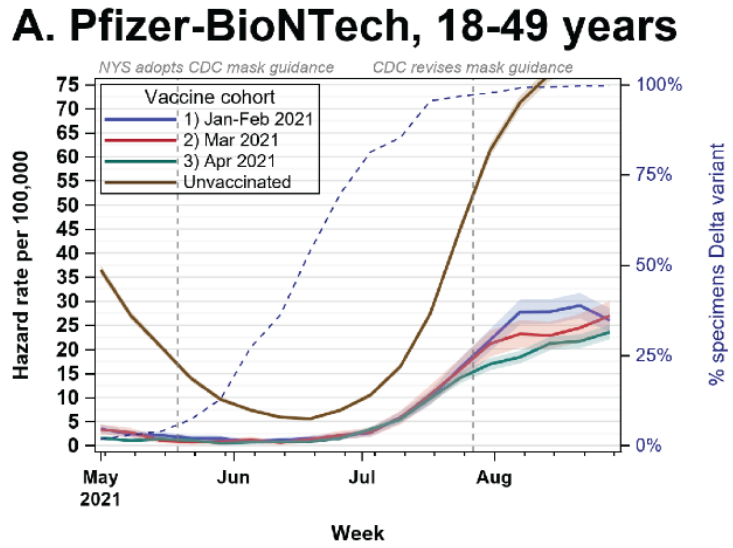
Monkeypox & JYNNEOS in New York State

- 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%

	Monkeypox cases	Control
Vaccinated	10	50
Not Vaccinated	190	150

  - Challenges abound however, particularly for this outbreak!

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…

Vaccine prevalence among controls	OR	VE	Vaccine prevalence among cases	Power: Matched McNemar's test 1:1 ratio, phi = 0.5				
				100	200	300	400	500
5.0%	0.5	50%	2.5%	9%	15%	20%	26%	32%
5.0%	0.25	75%	1.3%	17%	36%	54%	69%	80%
5.0%	0.1	90%	0.5%	26%	69%	91%	98%	100%
10.0%	0.5	50%	5.0%	14%	25%	37%	47%	56%
10.0%	0.25	75%	2.5%	35%	68%	87%	95%	98%
10.0%	0.1	90%	1.0%	67%	98%	100%	100%	100%
15.0%	0.5	50%	7.5%	19%	35%	50%	63%	73%
15.0%	0.25	75%	3.8%	51%	86%	97%	99%	100%
15.0%	0.1	90%	1.5%	89%	100%	100%	100%	100%

Wrap up

- 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!

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