

Current strategies for vaccine deployment and their implications for the design of observational studies

Phil Krause and Ira Longini

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Deployment of monkeypox vaccines

There is currently a significant shortfall of monkeypox vaccine doses, relative to current and anticipated needs. This gap is being filled, but in the short term, there will be many people who desire vaccine and cannot get it. This will naturally lead to vaccinated and unvaccinated groups.

In many (but not all) places, vaccines are being prioritized for people perceived to be at highest risk

In many places, the (normally 2-dose) MVA vaccine is being administered as a single dose

Monkeypox vaccines

Vaccines have been approved for monkeypox indications

- With greatest confidence that vaccines will ameliorate severe monkeypox, with less confidence that vaccines will prevent monkeypox disease or transmission
- As a two-dose schedule (for MVA) or a one-dose schedule (for LC16m8)
- Supported by animal challenge studies via a different route of infection
- With expectation for greatest effect among immunocompetent people

There remains significant uncertainty regarding how well these vaccines will work in the current outbreak in the context of current plans for their use, and thus a need to collect reliable data as soon as possible

Risk-based plans for vaccine distribution

Risks associated with an individual case of monkeypox can be influenced by behaviors and underlying conditions:

- Risk of exposure to monkeypox

- Risk of getting infected if exposed

- Risk of getting more severe disease if exposed

- Risk of further transmitting if infected

There is a desire to deliver limited quantities of vaccine to people at the greatest risk

People who perceive themselves at greater risk will make more efforts to get vaccine

Physicians who consider certain patients at higher risk will help those people get vaccine

A simple comparison of outcomes among people who get vaccine vs. those who don't will not reliably estimate vaccine effectiveness. **If increased risk is always associated with increased likelihood of vaccination, this leads to underestimation of VE.**

Case-control studies

Determine vaccination rate in the group at risk, and compare with vaccination rate among those who got monkeypox. If the vaccine is effective, the rate among those who got monkeypox should be lower.

The major difficulty is making sure that the group at risk truly has the same risk as those who ultimately got monkeypox.

Health-seeking behaviors can reduce the likelihood that underlying risk is similar among people who get diagnosed with monkeypox vs. those who don't (e.g., those who seek medical care for and receive a diagnosis of monkeypox might either be more or less likely to also have sought vaccine). Test negative designs, in which vaccination rates are compared only among people who seek care for possible monkeypox, can help to control for health-seeking bias.

Unknown differences between the groups can sometimes be controlled for in the analysis by adjusting for possible influencers of risk.

These strategies don't address other types of possible risk differences between the groups, such as participation in specific events where transmission occurs.

Cohort studies

Vaccinated vs. unvaccinated people are followed over time and rates of monkeypox are compared

The major difficulty is making sure that the group who got vaccine truly has the same risk as those who didn't

To reduce risk of bias, cohorts can be selected based on known risk factors, including nested matching

Study results can be adjusted based on demographics or known risk factors

These strategies don't address other types of possible risk differences between the groups, such as participation in specific events where transmission occurs

Example:

If participation in high-exposure events drives most transmission, ideally, it would be possible to perform case-control or cohort analyses among people who participate in these events.

Even then, individuals who participate in these events may have different levels of risk, which might be associated with vaccination

If it isn't known who will participate in these events, other markers may be used to “guess” at underlying risk— evidence of frequent other STDs, use of HIV Pre-exposure prophylaxis, etc.— but these will be imperfect predictors

While these other markers can be accounted for in the analysis to improve assessment of vaccine effectiveness, this type of analysis may provide false confidence in the result

Are some outcomes less sensitive to underlying likelihood of being vaccinated?

Severity of disease

- If likelihood of vaccination depends mostly on perceived risk of getting monkeypox in the first place, and less on perceived risk of getting severe disease, one might expect **less biased estimates** in observational studies of effectiveness against severe disease, but the numbers would be smaller resulting in **reduced power**
- People with severe disease are more likely to seek care, which reduces the potential for health-seeking or missed diagnoses to influence results
- In general, vaccine effectiveness against severe disease is higher than against mild disease

Number of doses

- Likelihood of receiving 1 vs 2 doses may be less dependent on perceived risk of monkeypox than likelihood of getting vaccinated in the first place. This could enable less biased estimates of relative effectiveness of 1 vs. 2 doses

High effectiveness in observational studies

Where estimates of vaccine effectiveness in observational studies are high, possible sources of bias are less likely to be responsible for the entire observed effect

Where vaccine deployment is likely greatly influenced by underlying risks, observational studies will underestimate true vaccine effectiveness

Vaccine effectiveness against severe disease generally is more accurately estimated and exceeds that against milder disease, although the numbers are generally smaller

If observational studies report high vaccine effectiveness, this likely is correct— especially for severe disease. If observational studies report low to moderate vaccine effectiveness, it is more difficult to interpret the results