Design options for the evaluation of efficacy: advantages and disadvantages

Phil Krause, M.D.
Adviser to WHO

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Vaccines: key data

WT Vaccinia-based vaccine (not approved for monkeypox, but believed to be ~85% effective, and ACIP-recommended)

MVA (replication deficient)

- 2-dose regimen, US and EU approval includes monkeypox
- Possibly less protective in animals compared with WT vaccinia
- Data on efficacy of single dose is lacking
- No data on post-exposure prophylaxis

Lc16m8 (Attenuated vaccinia, produces a “take”)

- 50,000 children received in 1974-75

While there are good reasons to think these vaccines will be effective against monkeypox, we don’t have clinical data to support use in specific situations.
**Vaccinia and MVA vaccines**

### Table 2: Distinctions between ACAM2000 and JYNNEOS that might facilitate decision-making among vaccinees at risk for orthopoxvirus infections — United States, 2022

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ACAM2000*</th>
<th>JYNNEOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine virus</td>
<td>Replication-competent vaccinia virus</td>
<td>Replication-deficient modified vaccinia Ankara</td>
</tr>
<tr>
<td>“Take” following vaccination†</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Risk for inadvertent inoculation and autoinoculation</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Risk for serious adverse event</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Risk for cardiac adverse events</td>
<td>Myopericarditis in 5.7 per 1,000 primary vaccinees</td>
<td>Clinical trial data limited in evaluating this outcome; however, no significant events in data abstracted from single study arms§</td>
</tr>
<tr>
<td>Assessment of effectiveness</td>
<td>FDA assessed by comparing immunologic response and take rates to Dryvax*</td>
<td>FDA assessed by comparing immunologic response to ACAM2000 and animal studies</td>
</tr>
<tr>
<td>Administration</td>
<td>Percutanously using a bifurcated needle by multiple puncture (scarification) technique,¶ single dose</td>
<td>Subcutaneously, 2 doses 28 days apart</td>
</tr>
</tbody>
</table>

Abbreviation: FDA = Food and Drug Administration.

* Both ACAM2000 and Dryvax are derived from the New York City Board of Health strain of vaccinia; ACAM2000 is a second generation smallpox vaccine derived from a clone of Dryvax, purified, and produced using modern cell culture technology.

† A “take” is postvaccination lesion often used as a marker of successful vaccination after ACAM2000.

§ Because JYNNEOS is a replication-deficient virus vaccine, serious adverse events are believed to be fewer. However, the mechanism of myopericarditis in persons who receive ACAM2000 is poorly understood; for this reason, it is unknown whether persons who receive JYNNEOS might experience myopericarditis.

¶ https://www.fda.gov/media/75792/download
Vaccines: additional considerations that could influence trial design

Time to develop protective immune response relative to likely time of exposure and incubation period of virus

Period of shedding/infectivity

Attack rates in people with different exposure histories and risk factors
Antibody titers after 1 vs 2 doses of MVA

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Group 1 (N=185) GMT (95% CI) [n]</th>
<th>Group 2 (N=186) GMT (95% CI) [n]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>10.1 (9.9, 10.2) [185]</td>
<td>10.0 (10.0, 10.0) [186]</td>
</tr>
<tr>
<td>Wks after the 1st Vaccination Two</td>
<td>23.4 (20.5, 26.7) [184]</td>
<td>23.7 (20.9, 26.8) [184]</td>
</tr>
<tr>
<td>Four</td>
<td>23.5 (20.6, 26.9) [185]</td>
<td>84.4 (73.4, 97.0) [186]</td>
</tr>
<tr>
<td>Eight</td>
<td>NA</td>
<td>72.3 (63.7, 82.1) [183]</td>
</tr>
<tr>
<td>Wks after the 2nd Vaccination Two</td>
<td>152.8 (133.3, 175.0) [185]</td>
<td>NA</td>
</tr>
<tr>
<td>Four</td>
<td>118.6 (103.5, 135.9) [179]</td>
<td>NA</td>
</tr>
<tr>
<td>Eight</td>
<td>100.5 (84.9, 118.9) [172]</td>
<td>NA</td>
</tr>
</tbody>
</table>

Source: Adapted from Table 1 of POX-MVA-006 CSR (page 5), STN125878/0.50, Module 1.11.3, Responses to IR32.

Notes: N=number of subjects in the specific group; n=number of subjects with data available; GMT=geometric mean titer; NA=not applicable; Wks=weeks.

PRNT GMT values below LLOQ were imputed as 1/2 LLOQ.
Clinical trial considerations: Study Endpoints

More severe disease is clinically most important, but may be too rare to study practically.

If goal is to interrupt transmission, study should assess vaccine impact on infection, shedding, or secondary infections.

- Even if these are not primary study endpoints, it may be useful to study them.

Need case definition for primary clinical endpoint, ideally corresponding to goal of vaccination.
Clinical trial considerations: Vaccinated populations

The higher the attack rates among trial participants, the lower the sample size and the greater the chance of achieving a statistically meaningful result.

Ring vaccination (i.e., vaccinate contacts [household plus sexual?] +/- contacts of contacts)

- Mimics successful smallpox vaccine deployment and WHO Ebola vaccine trial
- For example, it may be important to define efficacy of single dose MVA in ring vaccination setting

Health care workers (or others at potential high risk)

- Attack rates are much lower than in ring vaccination setting
- Could receive 2-dose regimen before likely exposure
- Randomization to early vs. late deployment could be considered, given likely impracticality of immunizing many people at the same time
Clinical trial considerations: Locations

Multi-center trial could achieve results more rapidly

Multi-center studies can be more difficult to coordinate and perform

Given different underlying risk factors across locations, randomization will be particularly important
Clinical study considerations: Comparators

None?

- Would there be any utility in a vaccine outcomes registry, which collected exposure information and outcomes?

Placebo

- With availability of antivirals to “rescue” people who become infected and meaningful uncertainty about how vaccine should be used, use of placebo is not obviously unethical

Unvaccinated people who were randomized to delayed vaccination

- May be feasible only in individuals at lower risk of exposure to monkeypox

Could there be a comparative study of two vaccines, e.g., MVA vs. Vaccinia, or a comparative trial of MVA vs. an antiviral for post exposure prophylaxis?

- This strategy is most successful when the interventions are likely to have substantially different levels of efficacy

Could observational studies be contemplated?

- Seems difficult because likelihood of vaccination would be inextricably linked to assessment of risks
- Substantial variability in attack rates, depending on degree of exposure, could also confound results
Conclusion

The most reliable data would come from a placebo-controlled study.

If there are concerns about ethics, they may be mitigated by:

- Genuine uncertainty about the intervention under study
- Reliable antivirals
- Providing vaccine to people who would not otherwise be candidates