World Health Organization

Meeting summary

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R&DBlueprint
Powering research to prevent epidemics

Meeting on Monkeypox Research Priorities
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Conclusions, Day 2

Clinical summary DRC: 72% animal exposure, 38% household contactmean age 14, rash w skin lesions (> in serious cases), lymphadenopathy (cervical>inguinal>submand which may track inoculation sites), malaise, sore throat, 10% abnormal lung sounds. Duration average 18 days. Complications: keratitis, superinfection, dermatitis, edema

Therapeutics: tecovirimat (exceptional circumstances/animal rule including orthopox in EU), oral or IV, targets VP37 with low resistance barrier. Brincidofovir (US animal rule), oral, GI and other side effects. VIG: no data. Possible interference antivirals/vaccine. For low risk, placebo controlled study could be considered. PEP. Combination Rx. Vulnerable groups.

Selection of therapeutics: Safety profile. Likelihood of efficacy: dose, time/efficacy window, route. preclinical efficacy in NHP, availability of surrogate markers. cGMP considerations. Access & deployability.

Randomized trial value and feasibility is supported by Ebola experience. Reliability should not be sacrificed for efficiency. Master protocols can be used across outbreaks to compare therapeutics with SOC, placebo, active control, or in factorial designs.

Observational cohort: 1º endpoint time to lesion resolution. 2º: other clinical and virological outcomes

Placebo/SOC controlled RCT of tecovirimat: 14 days in hospital to collect data. Endpoint: time to lesion resolution. Secondary clinical, virologic, safety endpoints.

Conclusions, Day 2

Key clinical considerations: diagnostics, virology, clinical spectrum including role of route of transmission, innovative study design. Role of host factors, timing and pathogenesis in transmission, potential efficacy. Endpoint should correspond to desired outcomes. Surrogates and CoPs are valuable. For tecovirimat, we need more info on dose and duration, resistance, larger numbers.

Randomized trials strongly encouraged by FDA and EMA. Even for approved products, could be conducted in patients with mild disease. Strong support for evaluating antivirals for treatment of monkeypox.

VIG and tecovirimat developers commit to maintain supply and work with other stakeholders to further evaluate products.

Importance of answering questions about how vaccines can and should be used with reliable clinical studies

TPP considerations: impact of antiviral could be more rapid recovery and reduced transmission. Severe disease. PEP esp. close contact. Combination therapy may be needed esp. in immunocompromise. Stable, oral, safe, high barrier to resistance. Available & deployable. Opinion: Due to toxicity and weak efficacy data, brincidofovir should only be used in RCTs.

Conclusions, Day 2

First & second generation vaccines are less attenuated. 4th generation vaccines are still investigational. ACAM2000 efficacy inferred by take rates vs Dryvax. MVA-BN efficacy from NI of neut response, take attenuation, and monkeypox NHP prevention vs. ACAM. New vaccines could potentially be licensed based on combined human/animal data.

Core protocol: ring vaccination-based, 1º endpoint rate of virologically confirmed disease. Consider blending of individual randomization within high-risk and within transmission clusters. Consider 30% lower bound, which would require 150 cases.

CDC study: DRC background rate 17.4/10K in HCW, lower in others. Study conducted over 2 years after 2 doses of MVA-BN vaccine. 1600 participants but no disease (1 vaccinee had monkeypox >2 yrs later). Immune responses peak d42 then rapidly declined in naives.

Need for reliable data that can be useful in deciding how to practically use vaccines. Perform studies in Africa and Northern hemisphere. Importance of safety data. Use existing and established case definitions. Animal studies suggest potential efficacy of single dose MVA. What is primary goal? Transmission vs. disease? Vaccine hesitancy could affect ability to do trials. Cost, vaccine delivery strategies. Focus on those susceptible to most severe disease. Vaccine efficacy in IC. Duration of vaccine effect. Immunogenicity studies in vaccinated, to support possible CoP. Considier vaccine effect against different clades. Organize clinical trials in higher risk people. Could vaccines be used to generate herd immunity? Could asymptomatic vaccinated people transmit?

General research priorities

Worldwide interdisciplinary collaborations are critical, Importance of documenting and sharing best practices.

Epi: surveillance (including serosurveillance gaps), transmission dynamics, role of possible endemic circulation in Europe, why are case numbers increasing recently?, relative importance of transmission from animals vs humans

Clinical: risk groups (for infection, for severe illness, for transmission, for relapse), disease characterization, modes/routes of transmission (including intimate/sexual maternal/fetal and if pre- or a-symptomatic?), duration of contagion, incubation period in context of intimate contact, exposure outcomes (in relation to previous immunity, other factors), investigation of monkeypox-negative suspected cases (which will require more assays & QA panels, e.g., enteroviruses, VZV, MCV), long-term outcomes

Virology: virus in fluids (including persistence), immunity (to virus & vaccines), sequencing/genomics, serology, role (if any) of mutations in possibly changing pathogenesis, differences between clades

Diagnostics : capacity & availability, validation, need for BSL-3/inactivation

Standardization: case definitions, differential diagnosis, detection/diagnosis methods including positive controls, standards, Q/A

Social (including stigma) and environmental (including quarantines, PPE) dimensions of transmission, containment and response

Animal reservoirs and how to prevent spillover

Optimizing supportive care

Treatment/Vaccination: effectiveness (which will also help to validate animal models)

Lab Research priorities

How to make sure that infrastructure for addressing these needs persists beyond the current monkeypox-related concerns

Development of new diagnostic methods & approaches

- Further development of serological assays– monkeypox-specific serology and IgM assays
- Rapid diagnostics to enable quick response
- Improved definition of what sites to sample
- Biosafety considerations
- Diagnostics to enable other research

Determine best testing strategies to effectively find cases

Lab-based studies

- Modes of transmission (virus in different fluids, environment, some potentially in animal models)
- Immunological response
  - Duration of serological response
  - Correlates of protection
- More data on reservoir and prevalence in it
- Genomics
- Modeling and waste-water studies

How to distribute vaccines and therapeutics

Resources to scientists in endemic areas

Antiviral research priorities

Existing antiviral data come just from animal models, with continued uncertainties about their efficacy, especially against monkeypox

Randomized trials with SOC control can be done and are ethical. Randomized trials strongly encouraged by FDA and EMA. Even for approved products, could be conducted in patients with mild disease. Strong support for evaluating antivirals for treatment of monkeypox.

Importance of defining who should be treated

Possible interference antivirals/vaccine. PEP. Combination Rx. Vulnerable/special groups (e.g., peds, pregnancy, immunocompromised).

Effect of antivirals on virology, including drug resistance

Globally organized studies organized as partnerships enhance equity, speed, generalizability and local capacity.

Trials should consider variable course of disease

Attempt to design well-controlled observational studies as complement to RCTs

Importance of clear and transparent communication

Vaccine research priorities

- Critical importance of continued research on vaccines
- Importance of defining the goal: preventing transmission and/or disease
- Need for reliable data that can be useful in deciding how to practically use vaccines, including PEP
- Global perspective with collaborative effort to obtain data in all regions
- Placebo controlled studies
- Post-approval effectiveness studies- real world evidence where feasible to collect reliable data
- Clinical safety studies
- Characterization of immune responses to identify biomarkers that could predict protection
- More animal studies in parallel with human studies

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

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

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 8: Vaccinia Specific Neutralizing Antibody Titers Determined by Plaque Reduction Neutralization Test (PRNT) at Various Time Points after Vaccination-PPS-IMM

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

Source: Adapted from Table 1 of POX-MVA-006 CSR (page 5), STN125678/0.50, 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 as1/2 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