WHO Core Protocol for monkeypox vaccines efficacy trials

(also for control and containment)

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Ring vaccine trial for monkeypox (also containment)

- The similarity to smallpox points to ring vaccination as the best strategy for both a vaccine trial and for containing spread.
  - Ring vaccination was used to eradicate smallpox
- Index case is located and vaccinated with vaccine or comparator (also isolated if possible)
- The contacts and contacts of those contacts (or other contact tracing structure) of the index case are located, and randomized to either vaccine or comparator (also quarantined if possible)
- Any isolation or quarantined procedures are not part of the vaccine trial
- In addition, it is important to vaccine front-line health care workers who may come into contact with monkeypox cases with vaccine or comparator

Inspiration for trial design (lessons learned)

- WHO Ebola **ring VSV vaccine trial** in Guinea, 2015
  - Successful and rapid determination of the VE during and epidemic
  - rVSV-ZEBOV vaccine is now licensed and is used against Ebola Zaire (Ervebo)
  - Ring vaccination is used to contain Ebola outbreaks
- WHO Solidarity Trial Vaccines (STV) for COVID-19
  - An international, **multi center, multi vaccine, adaptive, shared placebo**, event driven, individually randomized controlled clinical trial that aims to evaluate the efficacy and safety of promising new COVID-19 vaccines
  - Currently in the field in 3 countries, with more to be soon added

Basic trial design

- International, randomized clinical trial platform designed to rapidly evaluate the efficacy and safety of promising new candidate vaccines selected by an independent vaccine prioritization advisory group composed of leading scientists and experts
- Rapidly identify vaccines with worth-while efficacy using an adaptive design
- Vaccines and comparators will be individually randomized whenever possible
  - Populations at risk
  - Transmission clusters (rings, households, sexual contact networks)

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Comparator

- Placebo (preferred)
- Delayed vaccination
- Other monkeypox vaccine (unlikely); noninferiority
- Other intervention such as antiviral agent (unlikely)

Primary Efficacy Endpoint

- To evaluate the effect of selected vaccines on the **rate of virologically confirmed monkeypox disease**, regardless of severity.
- Vaccine safety

Secondary Endpoints (partial list)

- **Protection against transmission to others**
- **Post-exposure prophylaxis against disease progression**
- **Protection against fatal disease**
- **Protection against infection**
- **Duration of efficacy**
  - Assessed by continuing blinded follow-up until some effective vaccine is actually deployed
- **Immune correlates of protection**

Monkeypox vaccines trial

An international randomized trial of several candidate vaccines

1.a: Individually randomized in high-risk populations

Individual randomization to vaccine or comparator in areas of high exposure to monkeypox virus such as health care workers

The vaccine and comparator will be delivered according to a vaccination schedule

All vaccines selected for trial are eligible for testing at all sites

1.b.: Individually randomized within transmission clusters

Individual randomization to vaccine or comparator within clusters of infection transmission

Clusters are ring vaccination

Transmission units such as households, compounds, or other types of contact units

A single vaccine is tested in each ring or cluster, but multiple vaccines tested across rings or clusters

2: Cluster randomized

Clusters themselves are randomized to receive vaccine or comparator

Clusters are ring vaccination

Transmission units such as households, compounds, or other types of contact structures

A single vaccine is tested in each ring or cluster, but multiple vaccines tested across rings or clusters

Long-term accumulation of data where transmission may occur

Rapid accumulation of data during outbreaks

Statistical analysis for monkeypox virus vaccine trial

- Primary endpoint: Laboratory confirmed MPXV disease
- Primary hypothesis test:

$$H_0: VE \leqslant 30\% \quad \text{vs} \quad H_1: VE > 30\%,$$

where VE is defined as $VE = 1 - \lambda_1/\lambda_0$.

  - λ_1 is the hazard rate for MPXD for vaccine recipients
  - λ_0 is the hazard rate for MPXD for comparator recipients

- One sided α = 0.025, power = 0.90, 1% cumulative AR in comparator arm

Sample size summary

- For individual randomization
  - **150** cases of MPXD across these two arms (vaccine and comparator), maximum of about **20,000** participants per arm.
  - Two interim analyses at **50** and **100** cases using Obrien-Fleming boundaries for early termination
- For mixture of individual and cluster randomization
  - Variance inflation factor increases sample size
  - e.g., 25% cluster randomized, total sample size 263 cases, when ICC = 0.05

Expected study duration (in months)

Accrual Rate (/month)	Expected Study Duration (months of outbreak time)	Analysis Times Months of Outbreak Time			Cumulative Total Number of Participants (both arms)		
		1st Interim	2nd Interim	Final	1st Interim	2nd Interim	Final
1,000	14.4	9.4	13.3	16.7	9,370	13,350	13,721
5,000	6.6	4.2	6.0	7.8	20,771	24,248	24,248
10,000	4.9	2.9	4.4	5.9	29,292	29,292	29,292
20,000	3.8	2.1	3.4	4.7	33,873	33,873	33,873
30,000	3.4	1.8	3.0	4.2	36,124	36,124	36,124

Assuming 1% cumulative attack rate in the comparator arm over a 12-month period with an annual drop rate of 10%, and a minimum follow-up period of 6 months after the last accrual.

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Monitoring efficacy

- Each candidate vaccine will be monitored for early evidence of benefit or lack of benefit using prespecified monitoring guidelines and boundaries that may lead to halting further randomization of participants into a vaccine arm.
- Early monitoring for benefit is critical for obtaining and reporting data that could support rapid deployment of efficacious vaccines.
- Reject vaccines with VE ≤ 30% and find vaccines with VE > 50%

Trial governance

- Trial oversight will be provided by a **single Steering Committee** (SC) and a **single data monitoring committee** (DMC).
- Adaptive aspects of the study, to the extent not predefined in the protocol, will be governed by the SC, which will not have access to unblinded study data.
- The role of the DMC will be to apply pre- (and SC-) defined benefit and lack of benefit criteria to the vaccines, and to address potential safety issues as well as data integrity issues.
- Once one or more vaccines meet specified success criteria, new efficacy/lack of benefit criteria will be introduced.

WHO R&D Blueprint: Vaccine Trial Statistical Working Group

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Thank you

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Epidemiological characteristics of past monkeypox relevant to vaccine trial design and use

- Incubation period: 7-14 days
- Infectious period: prodromal syndrome → macular→ papular → vesicular → pustular → scabs: 14 - 21 days
- Serial interval: maybe about 21 days
- Household secondary attack rate: 10 - 15%
- $R_0 < 1$ in the past, but current strain might have $R_0 > 1$ (for current route of spread) or $R_0 < 1$ with superspreading events
- Human-to-human transmission in clusters in close contact networks
  - Sexual contact (seems to predominate in current outbreak)
  - Nosocomial in hospital and clinics treating patients
  - Other close contact, e.g., family members

Characteristics of vaccines relevant to a vaccine trial or vaccine use

- Most of the human information of VE and action is from smallpox
- Vaccine efficacy should be high, i.e., ≈ 85% against clinical disease, with waning
- Vaccine should have some protective effect during the prodromal period into the early stages of rash
- Vaccine should reduce transmission to others

Blending of analysis across designs

- For the primary outcome, results will be combined across individually randomized designs and across cluster randomize designs using a marginal proportional hazards model.
  - Compared to the mixed-effects modelling approaches, the marginal model offers a simple marginal interpretation of intervention effects and avoids the need to specify the correlation structure among the observations.
  - Stratified marginal models will be considered to allow differential baseline hazard functions across studies.

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