WHO Core Protocol for filovirus vaccine clinical trials

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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)
- 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 placebos will be individually randomized whenever possible
  - Populations at risk
  - Transmission clusters

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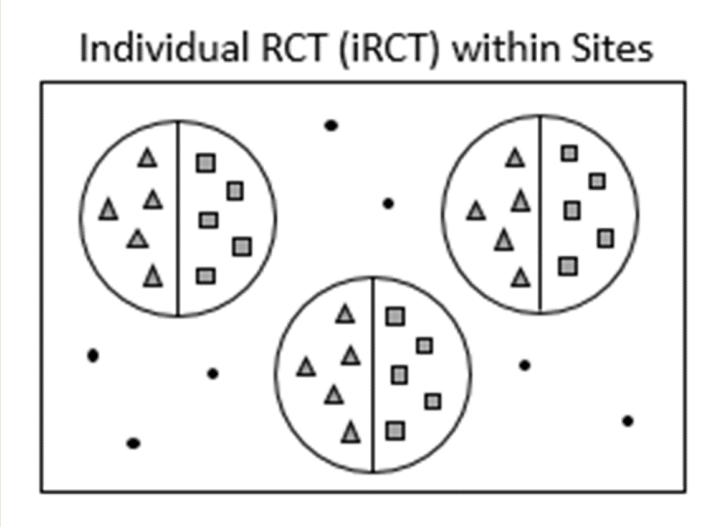
Primary Efficacy Endpoint

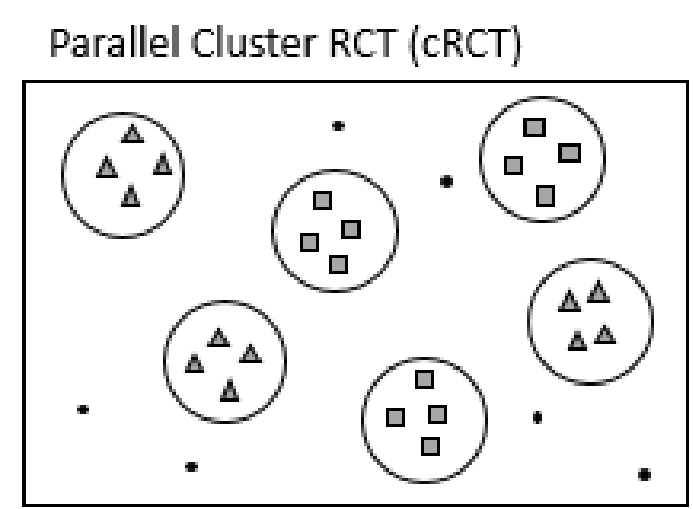
- To evaluate the effect of selected vaccines on the **rate of virologically confirmed filovirus disease**, regardless of severity.
- Vaccine safety

Secondary Endpoints (partial list)

- **Protection against infection based on serology and PCR**
- **Protection against fatal disease**
- **Duration of efficacy**
  - Assessed by continuing blinded follow-up until some effective vaccine is actually deployed

Individual and cluster randomized trials





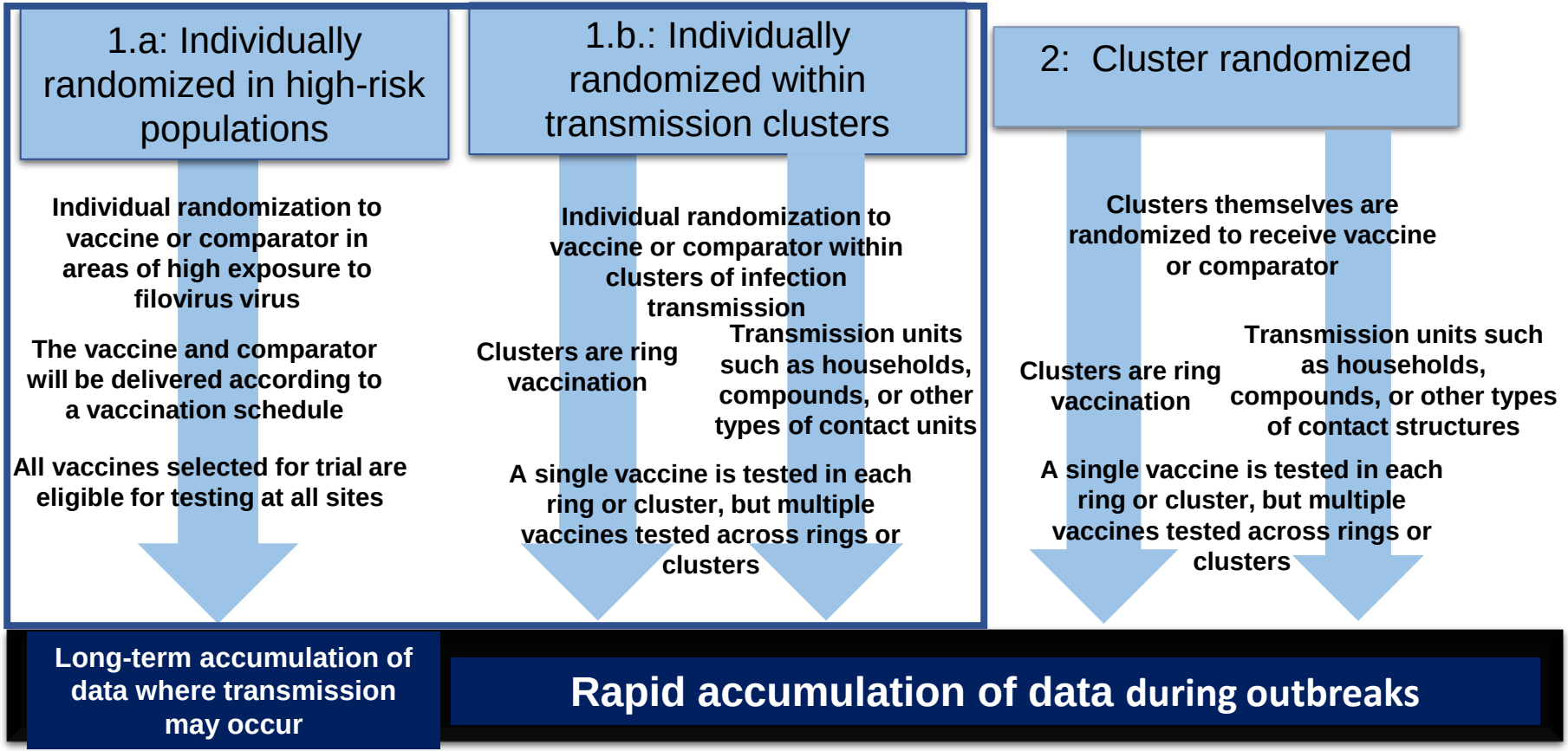
△ vaccinated participant

□ comparator participant

• non-participant

Filovirus vaccines trial

An international randomized trial of several candidate vaccines



Statistical analysis for filovirus virus vaccine trial

- Primary endpoint: Laboratory confirmed COVID-19 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 MVD for vaccine recipients
  - λ_0 is the hazard rate for MVD for comparator recipients

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

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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A note on design 1.a using infection as the primary outcome

- Simple individual randomization to vaccine or placebo/control in areas of high risk of exposure to filovirus virus, including populations living near the proposed reservoirs (e.g., miners exposed to bat caves)
- Follow the population serologically with periodic blood samples
- Identify infections as significant titer rises between serial blood samples
- Statistical analysis on interval censored data with survival model for VE against infection, CI's and hypothesis testing.

Sample size summary

- For individual randomization
  - **150** cases of MVD 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.

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.

Vaccine Trial Statistical Working Group

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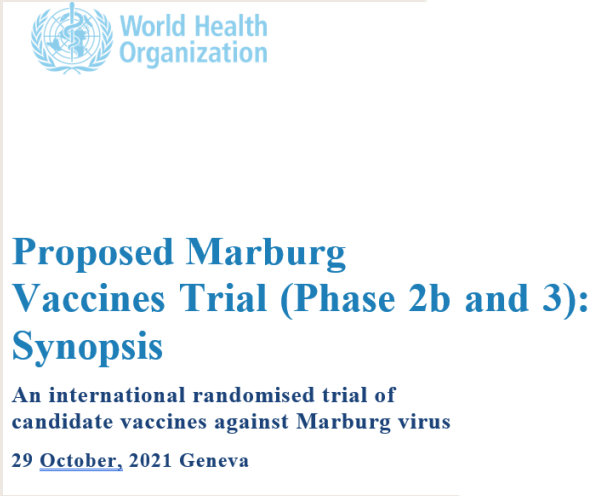

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Thank you

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Supportive endpoints at some sites

Blood samples at baseline, post last vaccination and at longer times after vaccination

- To assess the effects on antibody levels and on the secondary endpoint of rate of infection with filovirus (This requires a serological assay that can distinguish responses to infection from those to vaccination)
- To assess Immune responses induced by the vaccine, and evaluate immunological markers as correlates of protection
- Sequencing of a sample of breakthrough viruses
    - Sieve analysis

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%