Platform trial design for preventive vaccines against Marburg virus

Ira Longini
University of Florida
Consultant to WHO R&D Blueprint

World Health Organization

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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

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 (or delayed comparator) will be individually and/or cluster randomized depending on trial operation conditions
  - Populations at risk
  - Transmission clusters

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A platform trial design for preventive vaccines against Marburg virus and other emerging infectious disease threats

Ira M Longini[1], Yang Yang[1], Thomas R Fleming[2], César Muñoz-Fontela[3,4], Rui Wang[5,6], Susan S Ellenberg[7], George Qian[8], M Elizabeth Halloran[2,9], Martha Nason[10], Victor De Gruttola[6], Sabue Mulangu[11], Yunda Huang[8], Christl A Donnelly[12,13] and Ana-Maria Henao Restrepo[14]

Abstract

Background: The threat of a possible Marburg virus disease outbreak in Central and Western Africa is growing. While no Marburg virus vaccines are currently available for use, several candidates are in the pipeline. Building on knowledge and experiences in the designs of vaccine efficacy trials against other pathogens, including SARS-CoV-2, we develop designs of randomized Phase 3 vaccine efficacy trials for Marburg virus vaccines.

Marburg Vaccine Trial Core Protocol Working Group
Met about 10 times, July – September, 2022

Nancy Sullivan (NIH) Chair
Abdourahamane Diallo (WHO/Africa)
Alhassane Toure (WHO/Africa)
Sabue Mulangu (U Kinshasa, DRC)
Martha Nason (NIH)
Amy Finan (Sabin)
Ian Crozier (NIH)
John Beigel (NIH)
Galina Yamshchikov (NIH)
Winnie Janssens
Ira Longini (U Florida)
Yunda Huang (Fred Hutch)
Ana Maria Heano Restrepo (WHO)
William Fischer (U North Carolina)

Draft pro

World Health Organization

Solidarity Trial Vaccines

An international randomised trial of candidate vaccines against Marburg

10 August 2022

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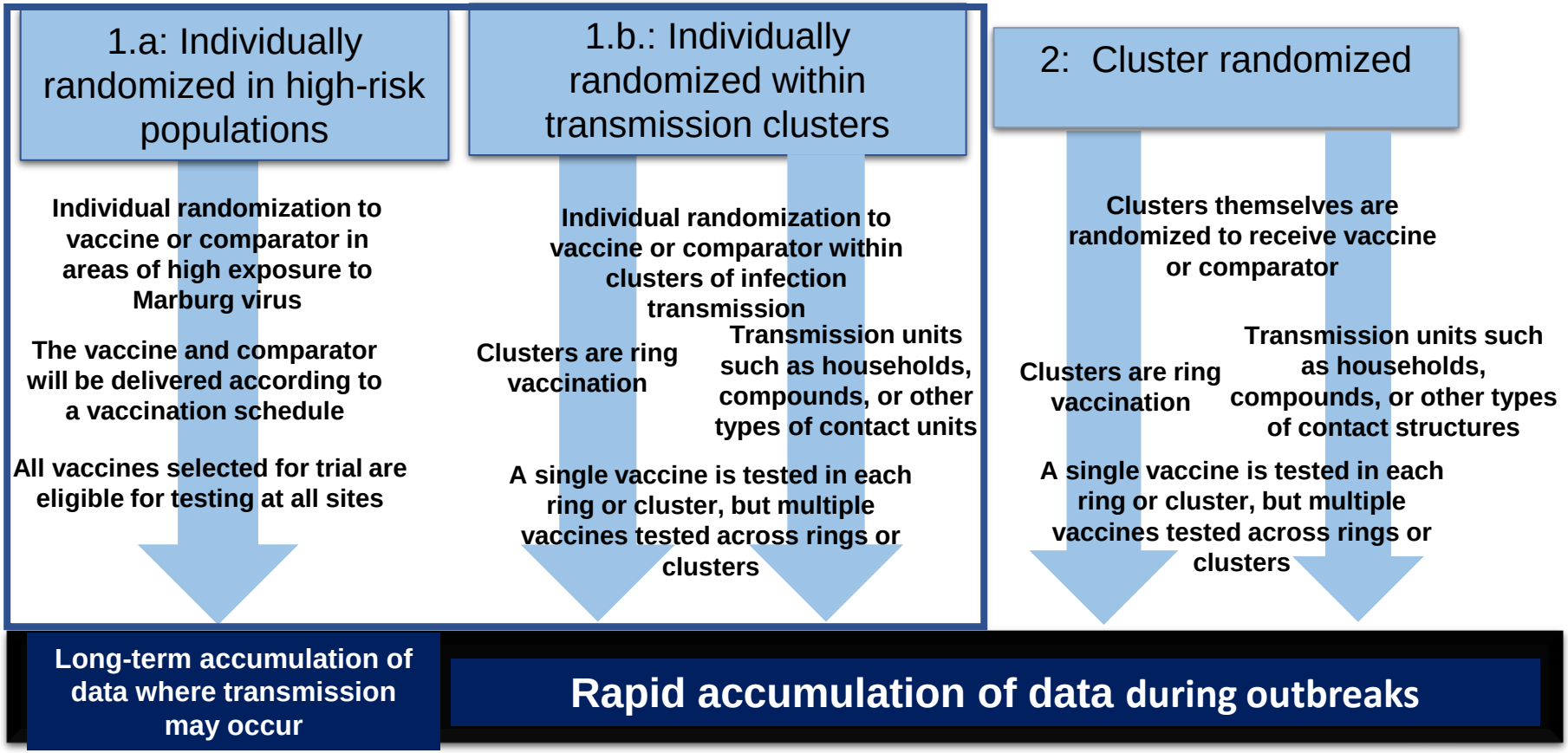
Primary Efficacy Endpoint

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

Secondary Endpoints (partial list)

- Protection against infection based on serology and PCR
- Immune correlates of risk and protection
- Protection against fatal disease

Marburg vaccines trial (blending across designs)



Statistical analysis for Marburg virus vaccine trial

- Primary endpoint: Laboratory confirmed Marburg virus 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

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Rough 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 (or **200** clusters per arm).
  - Two interim analyses at **50 (67 clusters per arm)** and **100** (**133 clusters per arm**) cases using Obrien-Fleming boundaries for early termination.

Way Forward

- Goal is to initiate trial rapidly (within days) once first vaccines are selected
- Select the feasible trial design options and extract from the overall protocol
  - Such designs could be sequentially implemented across time and outbreaks if necessary
- For an emergency outbreak situation, probably cluster randomization (option 2) comparing immediate to delayed vaccination of rings is the most implementable design

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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.

Thank you

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