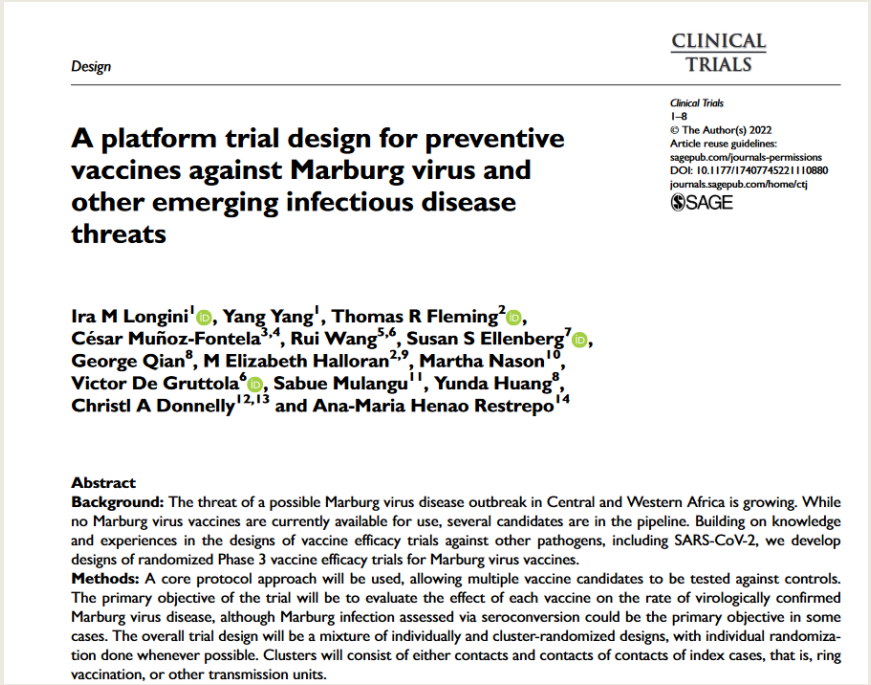
Cluster randomized vaccine trials

Ira Longini
University of Florida

Cluster randomized design with core protocol



Design

CLINICAL TRIALS

Clinical Trials
1–8

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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.

Methods: A core protocol approach will be used, allowing multiple vaccine candidates to be tested against controls. The primary objective of the trial will be to evaluate the effect of each vaccine on the rate of virologically confirmed Marburg virus disease, although Marburg infection assessed via seroconversion could be the primary objective in some cases. The overall trial design will be a mixture of individually and cluster-randomized designs, with individual randomization done whenever possible. Clusters will consist of either contacts and contacts of contacts of index cases, that is, ring vaccination, or other transmission units.

- Randomization unit is a cluster that is a geographic area such as a neighborhood, village, city, or some other geo unit.
- Vaccines or comparator are randomly allocated to clusters.
- The comparator can be a placebo, but more likely will be delayed vaccination.
- More than one vaccine can be tested.
- Randomization scheme can be **pre-determined** or **during deployment**.

https://journals.sagepub.com/doi/pdf/10.1177/17407745221110880

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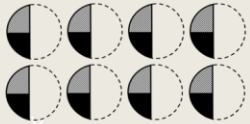
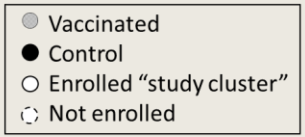
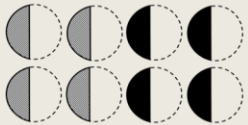
One thing to know about cRCT vs iRCT

Individually randomized controlled trial





Cluster-randomized controlled trial



- Relative to iRCT, sample size is inflated by design effect (m is cluster size)

$$DE = 1 + (m - 1)\rho$$

- Three determinants of necessary sample size:
  - Expected incidence rate among the controls
  - Expected measured effect
  - Clustering

$$\mathrm{n} = \frac{2(z_{1-\frac{\alpha}{2}} + z_{1-\beta})^2 p(1-p)}{\delta^2} DE$$

CHIKV vaccine – product profile

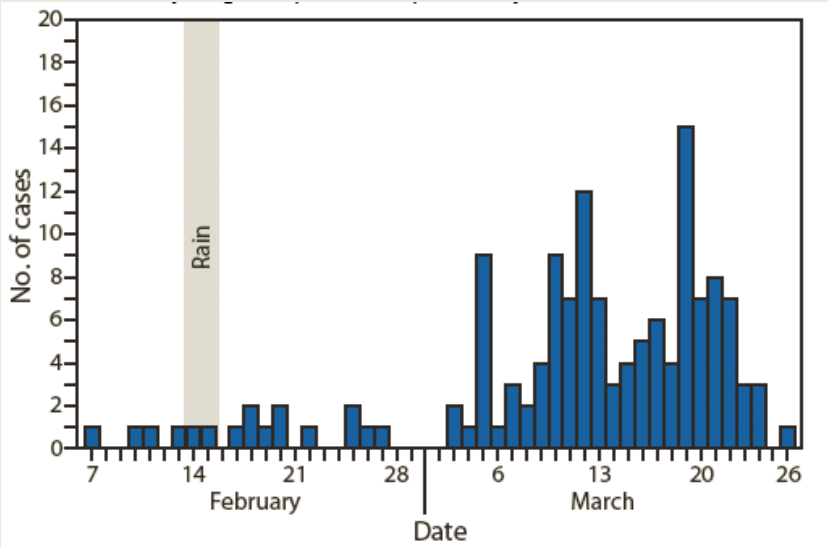
Emergency setting (Reactive/Outbreak use):
Protection of **at-risk people in the area of an ongoing outbreak of chikungunya.**

Non-emergency setting (Preventive Use):
Populations living in **areas where chikungunya is endemic**.

Reactive vaccination should be possible

- Serial interval is long ≈ 23 days

Trapeang Roka, Cambodia, February and March 2012*



*CDC, Morbidity and Mortality Weekly Report (MMWR), September 21, 2012 / 61(37);737-740

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CHIKV – endpoint considerations

Primary endpoint
Laboratory-confirmed acute clinical illness

Secondary endpoints (possible)
- Subacute clinical illness
- Chronic clinical illness
- Strain-specific illness
- Infection
- Immunological correlates of risk and surrogates of protection, i.e., surrogates for vaccine efficacy

Statistical analysis

The primary analysis will be the estimated vaccine effectiveness against confirmed Chikungunya illness:

$$\widehat{\mathrm{VE}} = 1 - \widehat{\lambda_1}/\widehat{\lambda_0}$$

$\widehat{\lambda_1}$ = estimated hazard of illness for clusters that receive vaccine.

$\widehat{\lambda_0}$ = estimated hazard of illness for clusters that receive placebo.

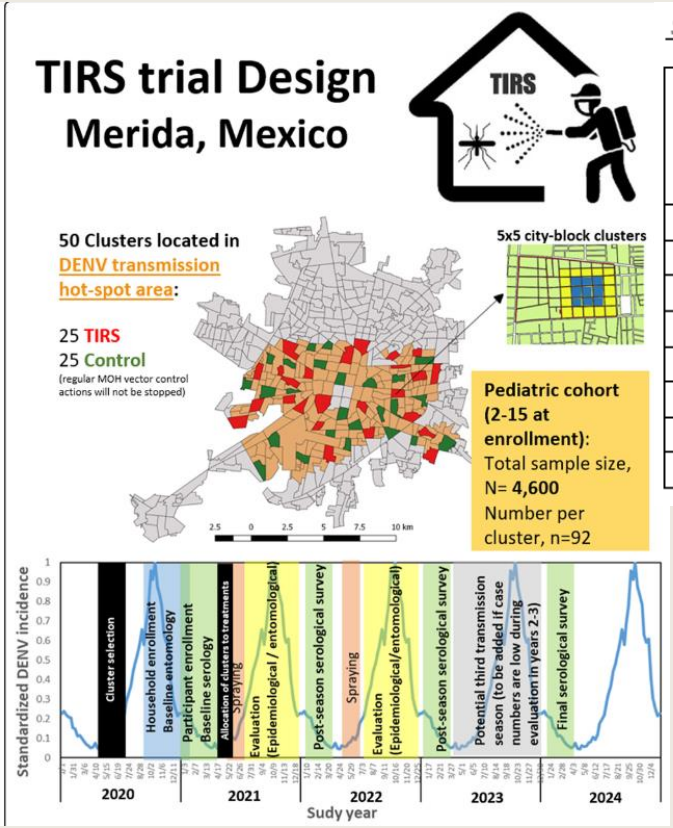
One-sided hypothesis test for the primary outcome:

H_0: $\mathrm{VE} \leq 0.3$ versus H_a: $\mathrm{VE} > 0.3$. In addition, a lower 95% confidence bound will be calculated for $\widehat{VE}$

Secondary analyses using same setup

Statistical method: Cox proportional hazards model with clustering, and with appropriate α – spending for interim analyses

Sample size example TIRS cRCT Merida, Mexico



Sample size calculations

POWER	TIRS Efficacy	Number of events	Total effective sample size	Number per cluster, Unadjusted	Number per cluster, Adjusted for LTFU	Total sample size, Adjusted for LTFU
90%	70%	38	1390	>500		
	75%	30	1164	122	152	7600
	80%	24	984	62	77	3850
	90%	16	714	28	35	1750
80%	70%	28	1038	74	92	4600
	75%	22	870	43	54	2700
	80%	18	734	30	37	1850
	90%	12	534	17	21	1050

- 4% incidence over a 2-year period
- ICC = 0.035, Power = 0.80, α = 0.05 two-sided
- DE = 3.6
- 50 total clusters

Manrique-Saide, et al. The TIRS trial: protocol for a cluster randomized controlled trial assessing the efficacy of preventive targeted indoor residual spraying to reduce Aedes-borne viral illnesses in Merida, Mexico. Trials 21:839 (2020). https://doi.org/10.1186/s13063-020-04780-7 .

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Data monitoring strategy

- Ideal to have a single steering committee and data monitoring committee, or at least some sort of sharing structure if not possible to have one.
- Interim analyses to assess efficacy or futility can be timed to occur at after reaching a targeted # of events, e.g., 50%
- Study data would not be released unless the trial was stopped, for efficacy, futility, or reaching its targeted number of endpoints
    - This could involve combining several outbreaks, locations, years of data.
    - It is possible to combine both individual and cluster randomized vaccine trials in a joint analysis: Wang, *et al.* Methods for the estimation of direct and indirect vaccination effects by combining data from individual- and cluster- randomized trials. *Statistics in Medicine* 1-13. doi: 10.1002/sim.10030 (2024).

Thank You!