# DESIGNS TO EVALUATE CANDIDATE VACCINES

## Cluster randomized clinical trials

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## Cluster randomized clinical trials in vaccine trials

- It is increasing being recognized that individually randomized, double-masked, controlled trials although the gold standard for Phase III primary efficacy and safety studies of vaccines, are not possible or do not tell whole story in some situations
- One such alternative is a cluster randomized design.
- Cluster randomized trials may be preferred in settings where individual randomization is not accepted by the trial population or where estimation of indirect and overall vaccine effects is prioritized
- A cluster can be a community, village, household, worksite, school, or medical centre/hospital or group of people who fit a certain definition

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# Indirect vaccine effectiveness:

- **Measures protection** conferred to individuals via the vaccination of others in the same population.
- They are also known as **spillover effects** and directly link to the concept of herd immunity.
- Indirect effects are not directly estimable from individually randomized controlled trials, but they can **generally be inferred in cluster randomized controlled trials** by comparing unvaccinated individuals in vaccinated populations with unvaccinated individuals in vaccinated populations.
- Indirect vaccine effectiveness is **a function both of the vaccination coverage level in the population** and of the ability of the vaccine to reduce disease incidence

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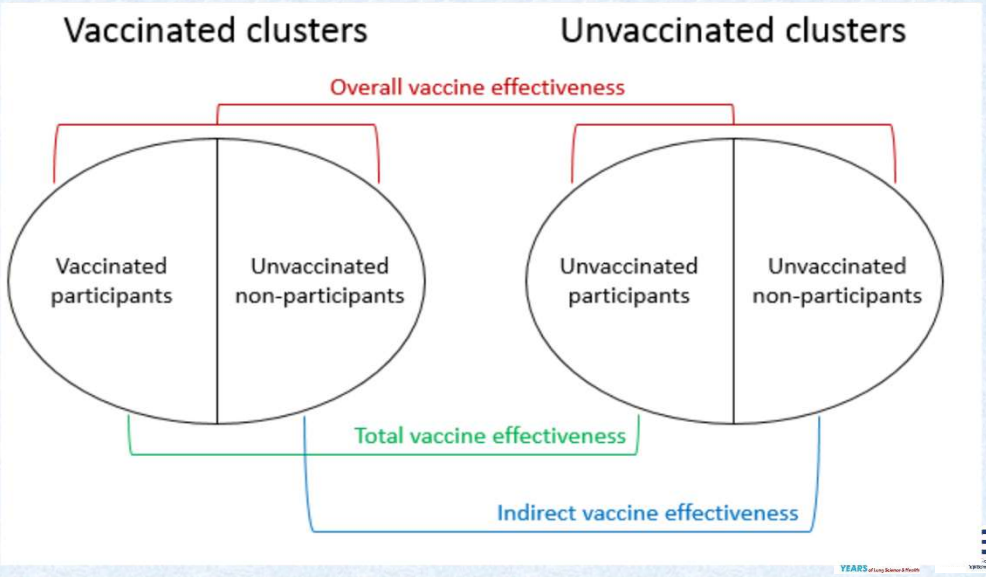
## TYPES OF VACCINE EFFECTIVENESS MEASURED IN A CLUSTER RANDOMIZED CONTROLLED TRIAL.

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## Design descriptions

**Cluster randomized clinical trials (cRCTs) can be of 2 types:**

1. Parallel cRCT
2. Step wedged cRCT

**Parallel cRCT**

- In parallel cluster randomized controlled trials (cRCTs), clusters of individuals are randomized as a unit to the experimental vaccine group or some comparator

**Stepped wedge cRCTs**

- In stepped wedge cRCTs, all clusters commence the trial in the control arm. The intervention is then introduced gradually at regular intervals during the trial, either one cluster at a time or in small groups of clusters, until by the end of the trial it is in place in all clusters
- Not commonly used in epidemics vaccine trials

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## Advantages and disadvantages of cRCTs

- **Advantages**
  - logistically easier to implement than individually randomized cluster trials (iRCTs)
  - Could be cheaper
  - May facilitate informed consent at the community-level
  - Preferred in settings where participants are unwilling to consent to individual randomization within a cluster

- **Disadvantages**
  - With a limited number of available clusters randomisation may fail to balance important covariates between arms, increasing confounding risk
  - Spillover and indirect effects make it difficult to separate direct vaccine protection from indirect (herd immunity) effects

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# Statistical considerations

- **cRCTS can be analysed at:**
  - **cluster-level analysis** *-treats each cluster as the unit of analysis*
  - **individual level analysis**, *by treating each individual as the unit of analysis.* , must account for clustering of individuals outcomes-mixed effects models or GEE
- **Sample size and power** calculations but should take into account the degree of clustering of outcomes in the population, as measured by the intracluster (or intraclass) correlation coefficient (ICC).
- The ICC measures the proportion of total variability in individual outcomes explained by the correlation between individuals in the same cluster.
- The ICC is used to calculate the trial design effect, which is a multiplicative factor that reflects how much larger a trial needs to be to achieve the same statistical efficiency as an iRCT

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# The Ring Vaccine Trials

- Ring Vaccine trials are the best example of cluster randomized trials used in public health emergencies
- In ring vaccination vaccines are administered to contacts & contacts-of-contacts of identified disease cases (cluster), creating a protective "ring" of immunity around infected individuals
- This approach breaks transmission chains by immunizing those at highest risk of exposure, rather than vaccinating entire populations
- This strategy was instrumental in smallpox eradication (1967-1980) & has been adapted for modern vaccine efficacy trials
- *By defining eligibility around a confirmed cases ring vaccine trials borrow principles from case-ascertained study designs*

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## Preliquisites for success of a ring vaccination strategy

- **Fast-acting vaccines**
  - The vaccine must provide protection quickly, ideally within days of a single dose.
- **Robust surveillance**
  - Requires the ability to find & test cases rapidly to trigger the "ring" before the virus spreads further
- **Effective contact tracing**
  - Must have the logistics & community trust to identify all contacts
- **Containable pathogen**
  - Works best for diseases that spread relatively slowly through close contact (e.g., Smallpox, Ebola) rather than highly airborne or vector-borne diseases

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## Advantages of ring trials

- **Efficient resource utilization**
  - Targets high-risk populations who have the highest probability of exposure hence maximizing the impact of each vaccine dose
- **Natural phased rollout**
  - New rings are identified over time as the epidemic progresses hence creating a naturally stepped implementation that enables adaptive trial design
- **Enhanced statistical power**
  - Higher **attack rates** in exposed populations reduce the required sample size compared to population-based trials with lower background incidence

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## Advantages 2

- **Operational Flexibility**
  - Mobile teams can follow epidemic progression—moving into new hotspots as they emerge and scaling down where incidence wanes
- **Cost-Effectiveness**
  - Lower per-dose delivery costs through targeted administration & reduced logistics burden compared to population-wide campaigns
- **Operational Flexibility**
  - Mobile teams can follow epidemic progression—moving into new hotspots as they emerge & scaling down where incidence wanes

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## Field experiences with Ring Vaccine trials in Public Health Emergencies

- The best example of modern day ring vaccine trial is the **Ebola ça Suffit Ring Vaccination Trial** in Guinea (Henao-Restrepo et al. 2015, 2017).
- This cRCT was used to rapidly evaluate one of the most effective EVD vaccines ever

***Design***

- *Open-label, cluster-randomised ring vaccination trial (Ebola ça Suffit!) in the communities of Conakry and eight surrounding prefectures in the Basse-Guinée region of Guinea, and in Tomkolili and Bombali in Sierra Leone*

***Intervention***

- *rVSV-ZEBOV; a recombinant, replication competent vesicular stomatitis virus-based candidate vaccine expressing a surface glycoprotein of Zaire Ebolavirus*
- *Single intramuscular dose of rVSV-ZEBOV ($2\times10^7$ plaque-forming units administered in the deltoid muscle*

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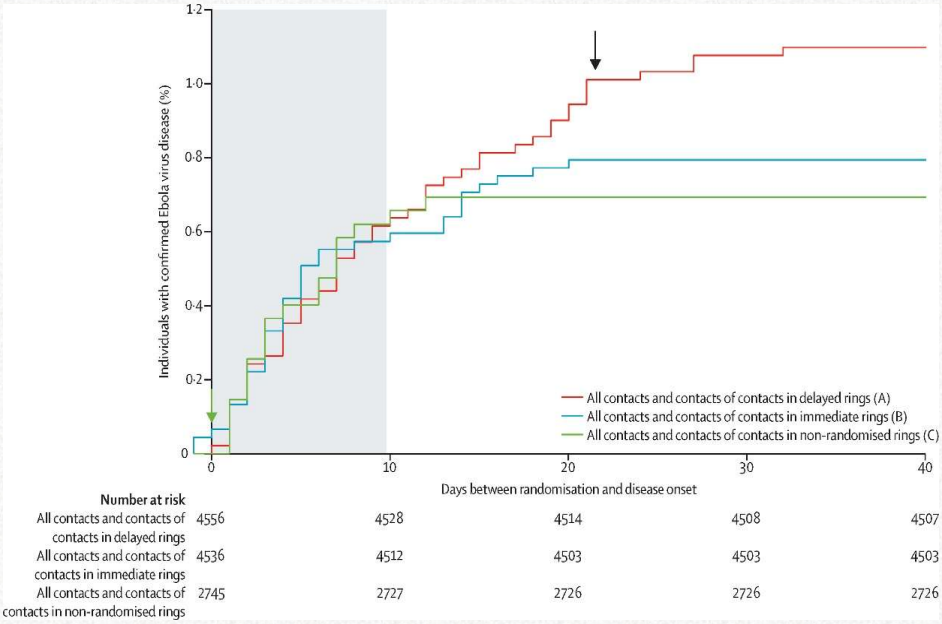
## Findings

- 0 cases of Ebola virus disease occurred 10 days or more after randomization among randomly assigned contacts and contacts of contacts vaccinated in immediate clusters versus 16 cases individuals in delayed clusters.
- Vaccine efficacy was 100% (95% CI 68·9–100·0, p=0·0045)




| Number at risk | | | | | |
|---|---|---|---|---|---|
| All contacts and contacts of contacts in delayed rings | 4556 | 4528 | 4514 | 4508 | 4507 |
| All contacts and contacts of contacts in immediate rings | 4536 | 4512 | 4503 | 4503 | 4503 |
| All contacts and contacts of contacts in non-randomised rings | 2745 | 2727 | 2726 | 2726 | 2726 |

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## Uganda Solidarity trial 2025 (TOKOMEZA EBOLA trial)

- Is a Ring vaccination trial to evaluate the efficacy and safety of a Sudan ebolavirus vaccine in Uganda

**AIM:**
**to assess the effect of candidate vaccines in protecting against laboratory-confirmed SUDV.**

**PRIMARY OBJECTIVE:**
Primary analysis is laboratory-confirmed SUVD (from samples taken either while the person is living, or within 48 hours of their death).

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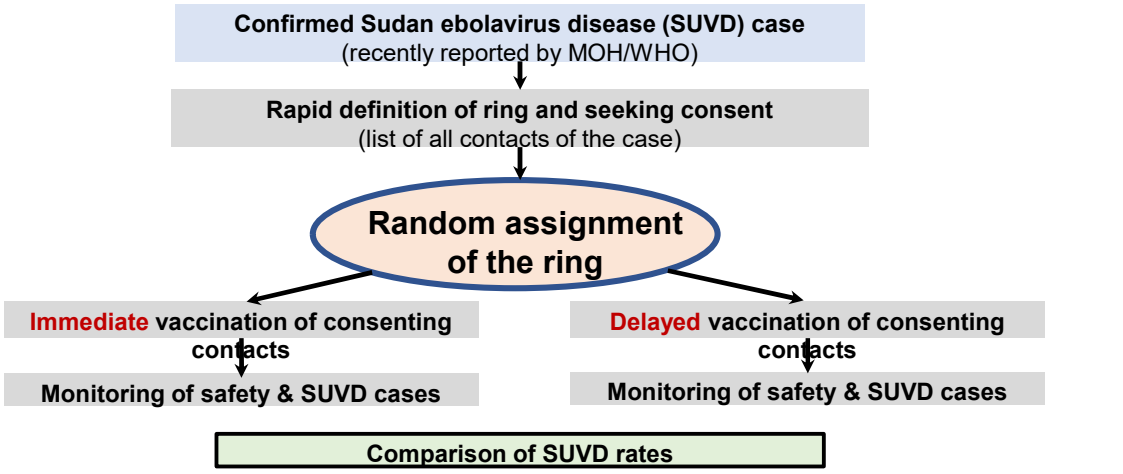
# Trial design




Primary endpoint: Lab-confirmed disease ≥10 days post-randomization (allows for incubation + immune ramp-up)

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# Endpoints

- **Primary end point is confirmed SUDV cases**- alive or deceased
- **Secondary outcomes include**
  - Probable SUDV deaths
  - Suspected SUDV case
- In the TOKOMEZA Ebola trial, protocol was amended to include a sub-study:
- assess the Laboratory Safety & Immunogenicity profiles of a SUDV vaccine among primary contacts of active cases

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# Thank you

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