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# Evaluating the effectiveness and feasibility of reactive focal mass drug administration vs. reactive case detection, with and without reactive vector control, as a community level intervention in response to confirmed, passively identified malaria cases


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## Background

Reactive case detection (RACD), testing and treating individuals around passively detected cases is a strategy commonly used to reduce or interrupt malaria transmission though its effectiveness may be limited by low sensitivity of RDT for low density infections and logistical challenges. Other interventions such as reactive-focal mass drug administration (rfMDA), or reactive vector control (RAVC) may be feasible and more effective. Pre season blanket IRS is the standard of care but there are challenges in achieving adequate coverage; RAVC with a different insecticide may provide additional effect.

## Methods

- Cluster randomized controlled trial with 2x2 factorial design to compare rfMDA *vs.* RACD, and RAVC *vs.* no RAVC in the surrounding 500m of index cases
- 56 enumeration areas (EA) randomized to receive either rfMDA or RACD, with and without RAVC
- rfMDA with Artemether Lumefantrine (AL) and RAVC with Actellic CS
- The primary outcome is passively detected cumulative malaria incidence
- Secondary outcomes include seroprevalence and infection prevalence both measured in a post-intervention cross-sectional survey, intervention coverage, safety, acceptability, adherence, and cost-effectiveness

**Figure 1. 2x2 factorial study design**

| | | rfMDA vs RACD arms | |
|---|---|---|---|
| | | **RACD (28 clusters) :** | **rfMDA (28 clusters):** |
| **RAVC vs No RAVC arms** | **No RAVC ( 28 clusters):** | RACD only (14) | rfMDA only (14) |
| | **RAVC (28 clusters):** | RACD + RAVC (14) | rfMDA + RAVC (14) |

**Figure 2. Reactive approach**

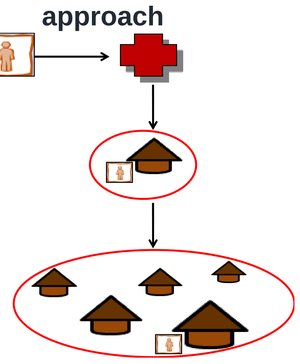
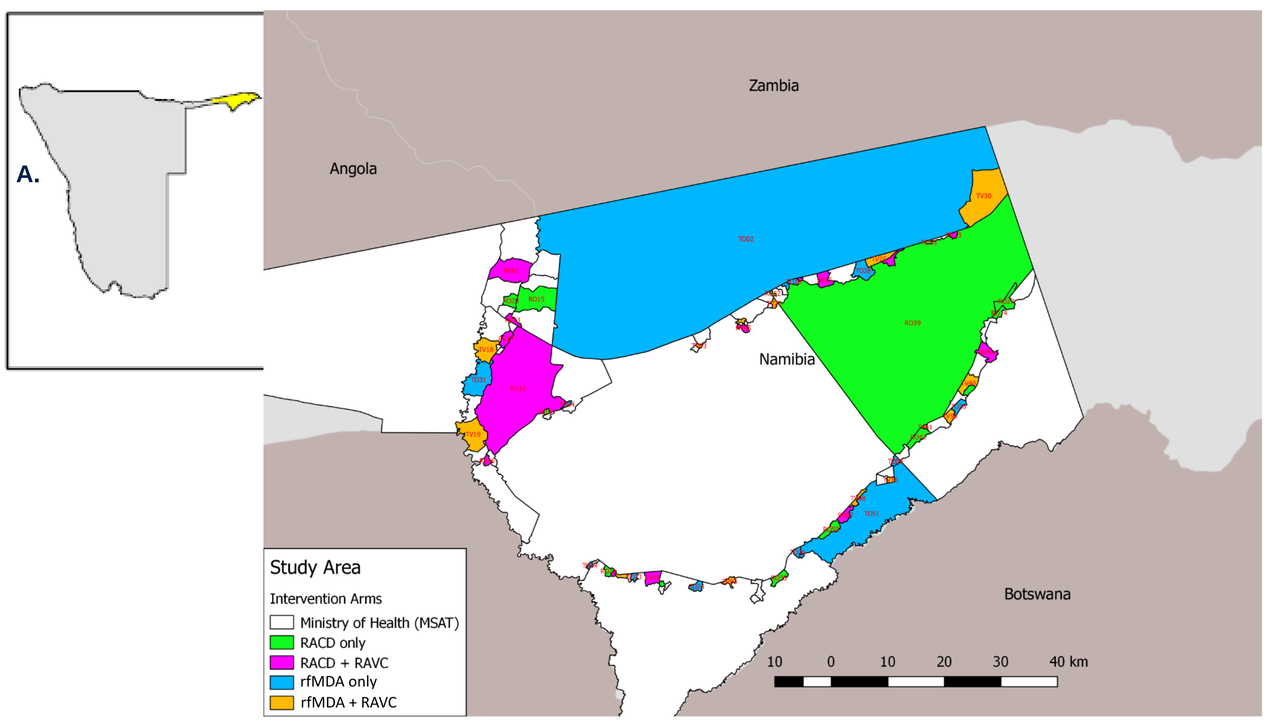


**Figure 3. A. Map of Namibia** with the Zambezi region shown in yellow**. B. Map of the study area** showing colored coded EA by intervention arms




## Preliminary results

**Table1. Intervention coverage and implementation** (* interventions included multiple index cases)

| | rfMDA | rfMDA +RAVC | RACD | RACD +RAVC | Total |
|---|---|---|---|---|---|
| Number of incident cases | 257 | 291 | 339 | 227 | 1114 |
| Number of interventions* | 85 | 75 | 81 | 93 | 334 |
| rfMDA/RACD coverage (index case level) | 208 (80.8%) | 243 (83.6%) | 261 (77.0%) | 181 (80.0%) | 893 (80.3%) |
| rfMDA/RACD coverage (Individual level) | 1770/2124 (83.3%) | 1761/2219 (79.4%) | 1940/2101 (92.3%) | 2327/2501 (93%) | 7798/8945 (87%) |
| RAVC coverage (n=households) | N/A | 367/416 (88.2%) | N/A | 495/532 (93.0%) | 862/948 (91%) |
| Median time to intervention (days) | 10.9 (1.09 – 13.3) | 9.9 (1.02 – 12.06) | 12.7 (1.12 – 15.16) | 11.9 (1.12 – 14.3) | 11.3 (0.55 – 10.2) |

**Table2. Malaria incidence per 1000 person years(excluding first 8 weeks run in period)**

| | | | Unadjusted | | Adjusted | |
|---|---|---|---|---|---|---|
| | Mean incidence* (95% CI) | p-value | Incidence rate ratio (95% CI)[1] | p-value | Incidence rate ratio (95% CI)[2] | p-value |
| RACD (n=27) | 28.6 (17.3 – 39.9) | 0.37 | Ref | 0.52 | Ref | 0.37 |
| rfMDA (n=28) | 21.1 (8.78 – 33.5) | | 0.81 (0.42 – 1.54) | | 0.72 (0.36 – 1.47) | |
| No RAVC (n=27) | 28.1 (14.8 – 41.5) | 0.43 | Ref | 0.41 | Ref | 0.28 |
| RAVC (n=28) | 21.6 (11.2 – 32.0) | | 0.77 (0.41 – 1.44) | | 0.71 (0.38 – 1.32) | |
| RACD only (n=13) | 30.2(14.0 – 46.5)) | 0.14 | Ref | 0.22 | Ref | 0.23 |
| rfMDA + RAVC (n=14) | 16.1 (3.8 – 28.4) | | 0.58 (0.25 – 1.38) | | 0.52 (0.18 – 1.52) | |

*t-test [1]Poisson regression [2] Poisson regression adjusted for incidence in 2016, median time to intervention, and proportion of cases covered

- **Adherence**: performed on a subsample of 654 participants (611 rfMDA and 43 RACD)
  - Blister pack was available in 339 (51.8%) participants (51.1% rfMDA and 62.7% RACD)
  - 100% adherence when blister pack available and 99.7% when self reported
- **Safety**
  - rfMDA: 17 (0.4%, n=3870) vs. RACD: 1 (0.7%, n=148); RAVC: 4 (0.2%, n=1828) vs. no RAVC: 14 (0.6%, n=2203)
  - No SAEs and all subjects with AEs completed the AL dose
- **Personnel time**
  - Median personnel-minutes per participant enrolled was 29.4(24.6-37.8) for rfMDA and 37.8(34.8-43.8) for RACD
  - Median personnel-minutes per structure sprayed was 33.6(25.8-39.6)

## Summary of preliminary results

- Primary outcome measure of incidence is not significant but trends suggest effectiveness
  - rfMDA vs RACD – 28% risk reduction
  - RAVC vs no RAVC – 29% risk reduction
  - rfMDA + RAVC vs RACD shows additive effect and highest risk reduction ( 48%)
- rfMDA, RACD, and RAVC were safe and acceptable to community
- rfMDA is time-saving compared to RACD
- Reactive interventions likely to have larger impact in lower transmission settings
- Infection prevalence and seroprevalence as secondary outcome measures of effectiveness from the post-intervention cross-sectional survey are pending
- Costing analysis and qualitative analysis on acceptability are pending

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