Targeted Parasite Elimination for Malaria Elimination in Namibia

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Malaria Elimination Initiative

UCSF

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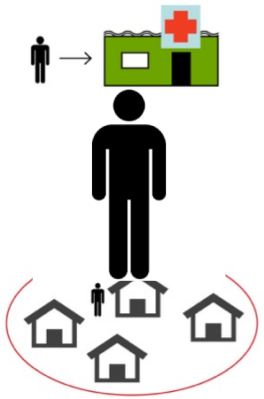
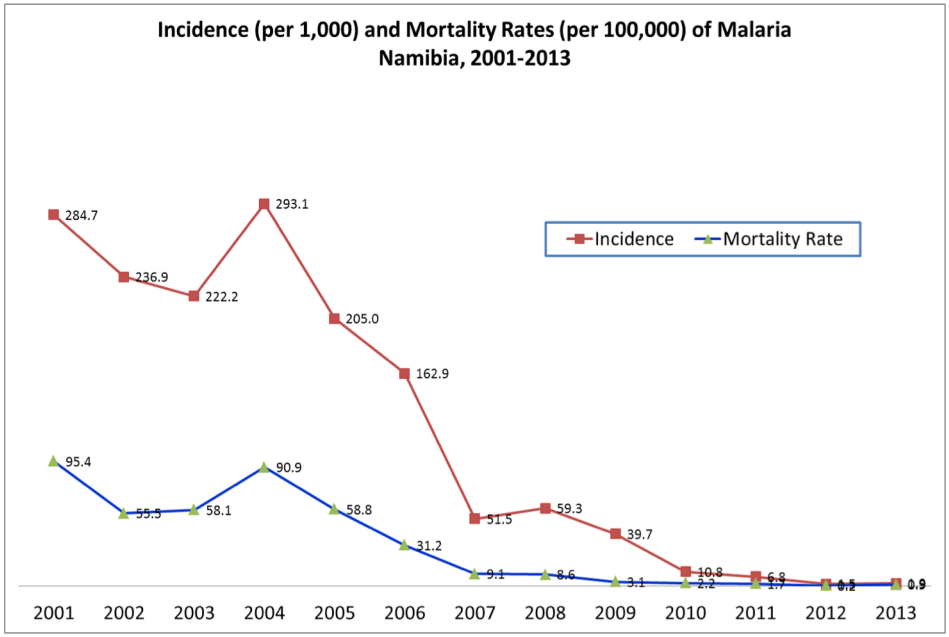
Namibia

- Progress toward malaria elimination has plateaued
- New approaches are likely needed
- Currently used ‘malaria elimination’ interventions:

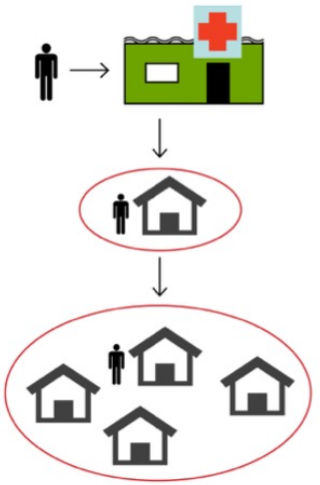
Human reservoir
Reactive case detection (RACD)

Mosquito reservoir
Pre-transmission season, blanket indoor residual spraying





Study Design



Objective: To evaluate the *effectiveness* and *feasibility* of reactive focal interventions for transmission reduction in the low transmission setting of Zambezi Region, Namibia

For human reservoir
***Control*: Reactive Case Detection (RACD)**
Test with a rapid diagnostic and treat positives

***Intervention*: Reactive focal MDA (rfMDA)**
Presumptive treatment or
mass drug administration (Coartem)

For mosquito reservoir
***Control*: No intervention**

***Intervention*: Reactive Vector Control (RAVC)**
Indoor Residual Spraying with Actellic CS

Open label, cluster randomized controlled trial, 2x2 factorial design

		Human reservoir	
		RACD (reactive case detection)	rfMDA (reactive focal mass drug administration)
Mosquito reservoir	No RAVC (no reactive vector control)	RACD only (n)	rfMDA only (n)
	RAVC (reactive vector control)	RACD + RAVC (n)	rfMDA + RAVC (n)

Medzihradsky, BMJ Open, 2018

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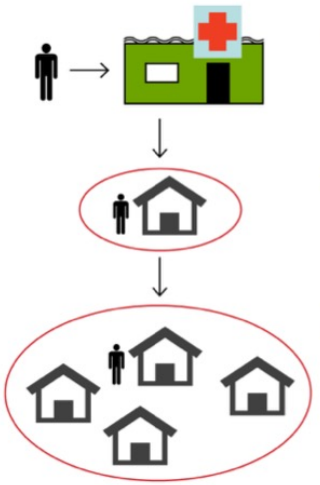

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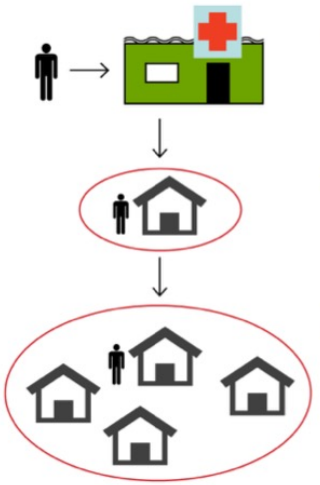

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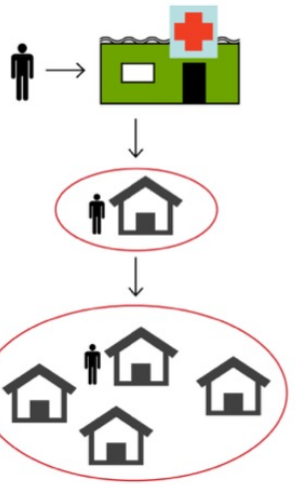

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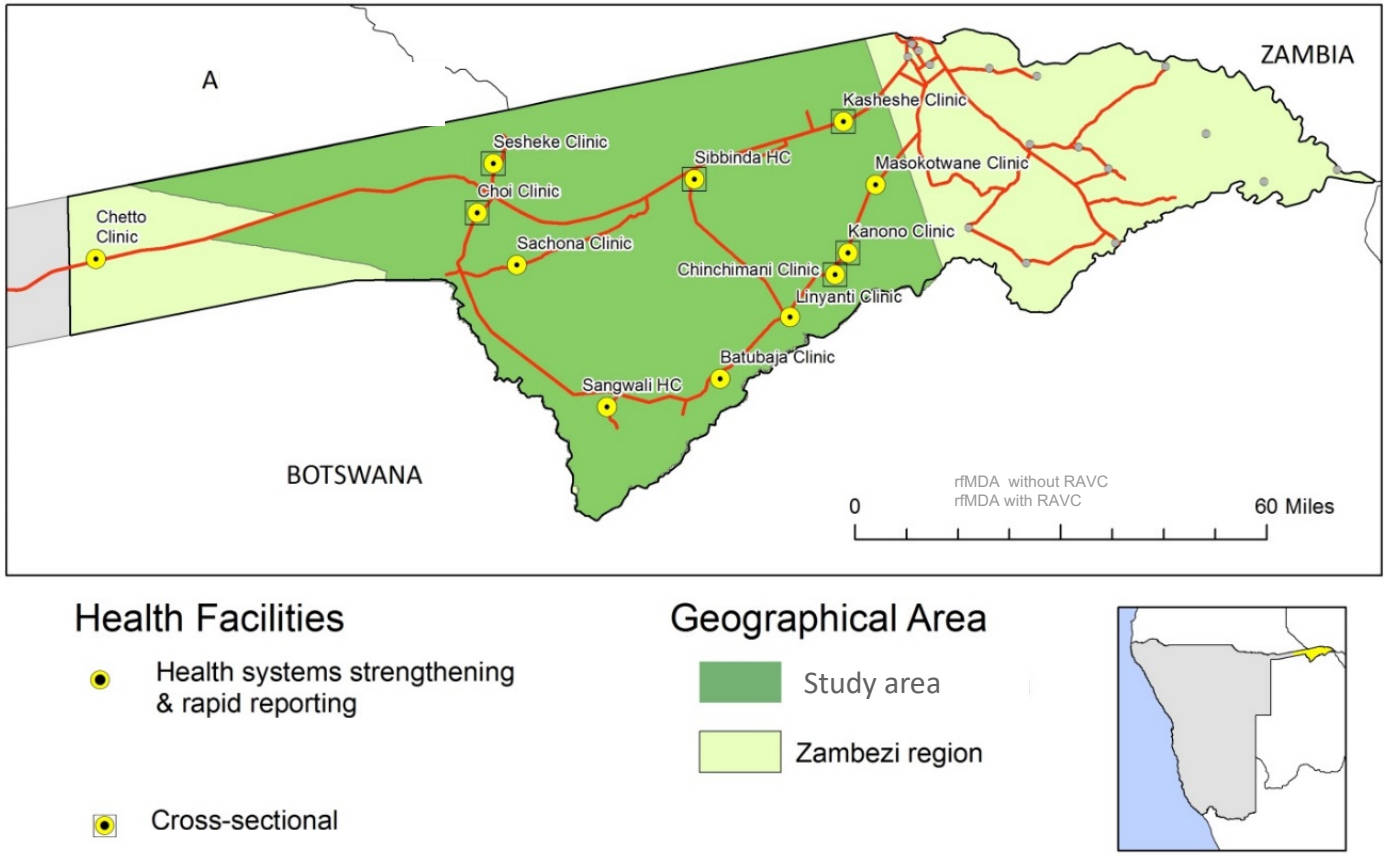
Study site, western Zambezi region



Study enrollment (Jan-Nov 2017)

1365 Index Cases
in 55 of 56 study clusters

178 RACD events in
4701 individuals (26.4/event)

164 rfMDA events in
4247 individuals (26.9/event)

RAVC in
529 households

No RAVC

RAVC in
392 households

No RAVC

Primary outcome: Cumulative incidence of local cases after 8 week lead-in

Secondary outcome: Prevalence of malaria infection in endline survey

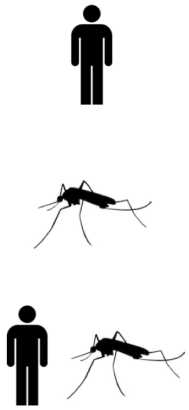
Secondary outcomes of feasibility:
Safety, adherence, acceptability, costs, cost-effectiveness

Photos by Nana Kofi Acquah and Michelle Hsiang

Malaria Outcomes

1. Incident cases
   a. Incidence rate ratio (IRR)
   b. Hazards ratio (HR) of malaria-free survival
2. Prevalence

1a. Incidence rate ratios (IRR) by study arm



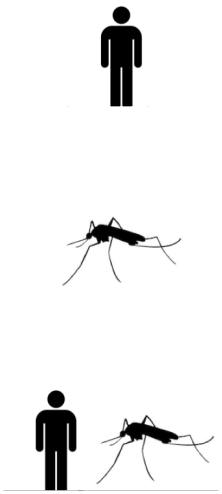
	Mean incidence* (95% CI)	IRR (95% CI)[1]	p-value	aIRR (95% CI)[2]	p-value
RACD (n=27)	28.6 (17.3–39.9)	Ref	0.52	Ref	0.37
rfMDA (n=28)	21.1 (8.78–33.5)	0.81 (0.42–1.54)		0.72 (0.36–1.47)	
No RAVC (n=27)	28.1 (14.8–41.5)	Ref	0.41	Ref	0.28
RAVC (n=28)	21.6 (11.2–32.0)	0.77 (0.41–1.44)		0.71 (0.38–1.32)	
RACD only (n=13)	30.2(14.0–46.5)	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, response time, coverage, co-interventions

1b. Hazards ratios (HR) by study arm

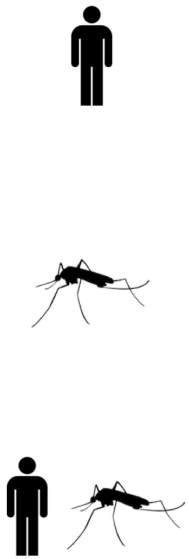


	HR (95% CI)*	p-value	aHR (95% CI)**	p-value
RACD (n=9875)	Ref	0.79	Ref	0.51
rfMDA (n=8929)	0.94 (0.61–1.46)		0.82 (0.45–1.49)	
No RAVC (n=9198)	Ref	0.65	Ref	0.19
RAVC (n=9516)	0.90 (0.59–1.39)		0.82 (0.56 – 1.19)	
RACD only (n=4581)	Ref	0.56	Ref	0.01
rfMDA + RAVC (n=4312)	0.84 (0.46–1.53)		0.69 (0.39–1.20)	

* Cox proportional hazard model, time from first incident case in EA to locally acquired infection, adjusted for clustering by EA – robust standard errors

**additionally adjusted for incidence in 2016, response time, coverage, co-interventions

3. qPCR Prevalence by study arm



	Prevalence	PR (95% CI)*	P-value	aPR (95% CI)**	P-value
RACD (n=2304)	4.01 (2.97-5.39)	Ref	0.15	Ref	0.01
rfMDA (n=2015)	3.15 (2.13-4.63)	0.78 (0.57-1.09)		0.63 (0.44–0.89)	
No RAVC (n=2181)	4.30 (3.05-6.01)	Ref	0.02	Ref	0.001
RAVC (n=2138)	2.91 (2.12-4.00)	0.68 (0.49-0.94)		0.53 (0.36–0.78)	
RACD only (n=1120)	4.16 (2.60-6.62)	Ref	0.002	Ref	0.002
rfMDA + RAVC (n=953)	1.71 (0.97-3.00)	0.41 (0.23-0.72)		0.35 (0.18–0.67)	

- Poisson regression adjusted for clustering at the EA level
- **additionally adjusted for incidence in 2016, response time, coverage, co-interventions

Safety

- 18 mild or moderate adverse Events (AEs)

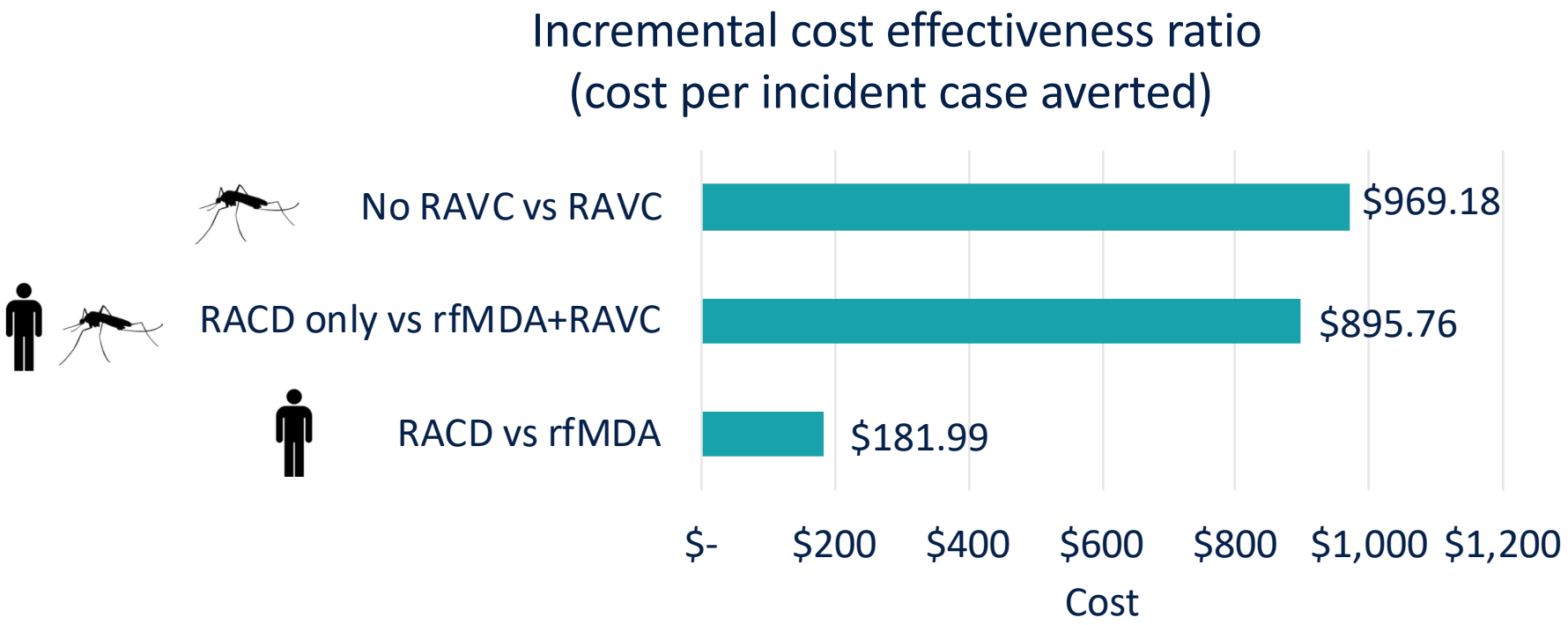
rfMDA: **0.4%** vs. RACD: **0.7%**

RAVC: **0.2%** vs. no RAVC: **0.6%**

Adherence and Acceptability

- Adherence
  - 100% per pill count (n=339/339)
  - 99.7% by self-report (n=314/315)
- Acceptability
  - Refusals <1% for all arms

Cost-effectiveness



- **All cost effective**
- **Drug-based strategy cheapest (leverages existing RACD)**

Summary of results

- **Consistent trends seen with all interventions**
- **All interventions reduce prevalence** of infection, with additive effect with combined intervention

- **May reduce incidence** in the same year, additive effect with combination suggests individual interventions work
- All interventions safe, with high adherence and acceptability
- All interventions cost-effective, especially drug-based approach, though insecticide-based approach could be more cost-effective if Actellic costs lower

Implications

- First trial to evaluate reactive focal interventions in any transmission setting
- High magnitude reductions in prevalence
- Assessment of impact on incidence limited by lack of follow-up in subsequent transmission season
- Intervention safe, acceptable, cost-effective and can leverage existing infrastructure
- **Reactive focal drug and vector control interventions should be considered for malaria elimination**

Infrastructure and capacity building established for malaria activities in Namibia

- Namibia Malaria Elimination Research Partnership (NAMEP)
- UCSF Global Programmes Malaria Office
- Zambezi research office and insectary
- Local and regional partnerships
  - Ministry of Health and Social Services
  - University of Namibia
  - Elimination 8

Next steps

- **Additional and secondary analyses**
  - Measure incidence in subsequent transmission season
  - Measure direct and indirect (spillover) effects
  - Explore novel outcome measures (serology)
  - Mathematical modeling to estimate effectiveness and cost-effectiveness in different settings, and identify optimal intervention parameters
  - Compare with similar studies in Eswatini and Zambia
- **Disseminate findings in-country, regionally, and globally to influence policy**
- **Leverage local/regional partnerships and infrastructure for:**
  - **Continued evaluations of novel and practical malaria elimination tools and strategies**
  - **Continued support of more effective and efficient implementation of interventions**

Namibia Partnership

UNAM
UNIVERSITY OF NAMIBIA

Republic of Namibia
Ministry of Health and Social Services

Davis Mumbengegwi
Nelango Indongo
Kenneth Matengu
Munyaradzi Tambo
Mukosa Chisenga
Lucille Dausab
Simataa Nyati
Flavian Libita
Chaze
Ronnie Bock

Petrina Uusiku
Stark Katokele
Hans Angula
Agnes Mwilima
Griffith Siloka
Mwalenga
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Henry Ntuku
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Oliver Medzihradsky
Brighton Mangena
Jennifer Smith
Adam Bennett
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Hugh Sturrock
Bryan Greenhouse
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Maxwell Murphy
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Erika Erlank

NOVARTIS FOUNDATION

Zaahira Gani
Fareed Mirza
Ann Aerts

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Co-funders: BMGF, Horchow Fund

Thank you

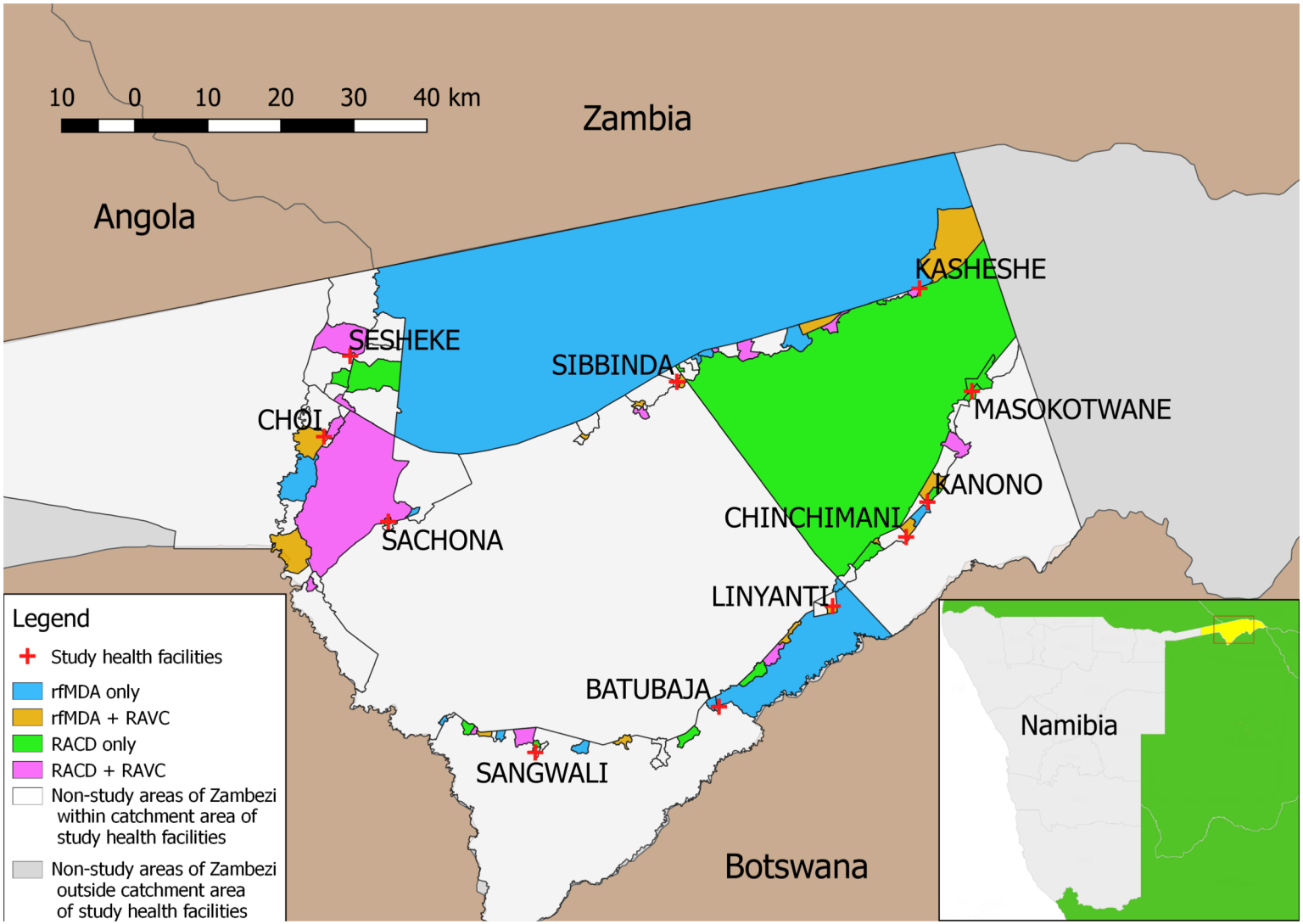
The UCSF Global Health Group's Malaria Elimination Initiative (MEI) accelerates progress towards malaria elimination in countries and regions that are paving the way for global malaria eradication.

www.shrinkingthemalariamap.org

Sample Size

- 56 EA or clusters (14 or 28 per arm)
- Hypothesized baseline incidence of 32.5/1000 (per 2016 figures)
- Powered to detect a 50% difference in cumulative incidence for
  - rfMDA compared to RACD
  - RAVC compared to no RAVC
- Powered to detect 75% difference
  - combination rfMDA+RAVC compared RACD only

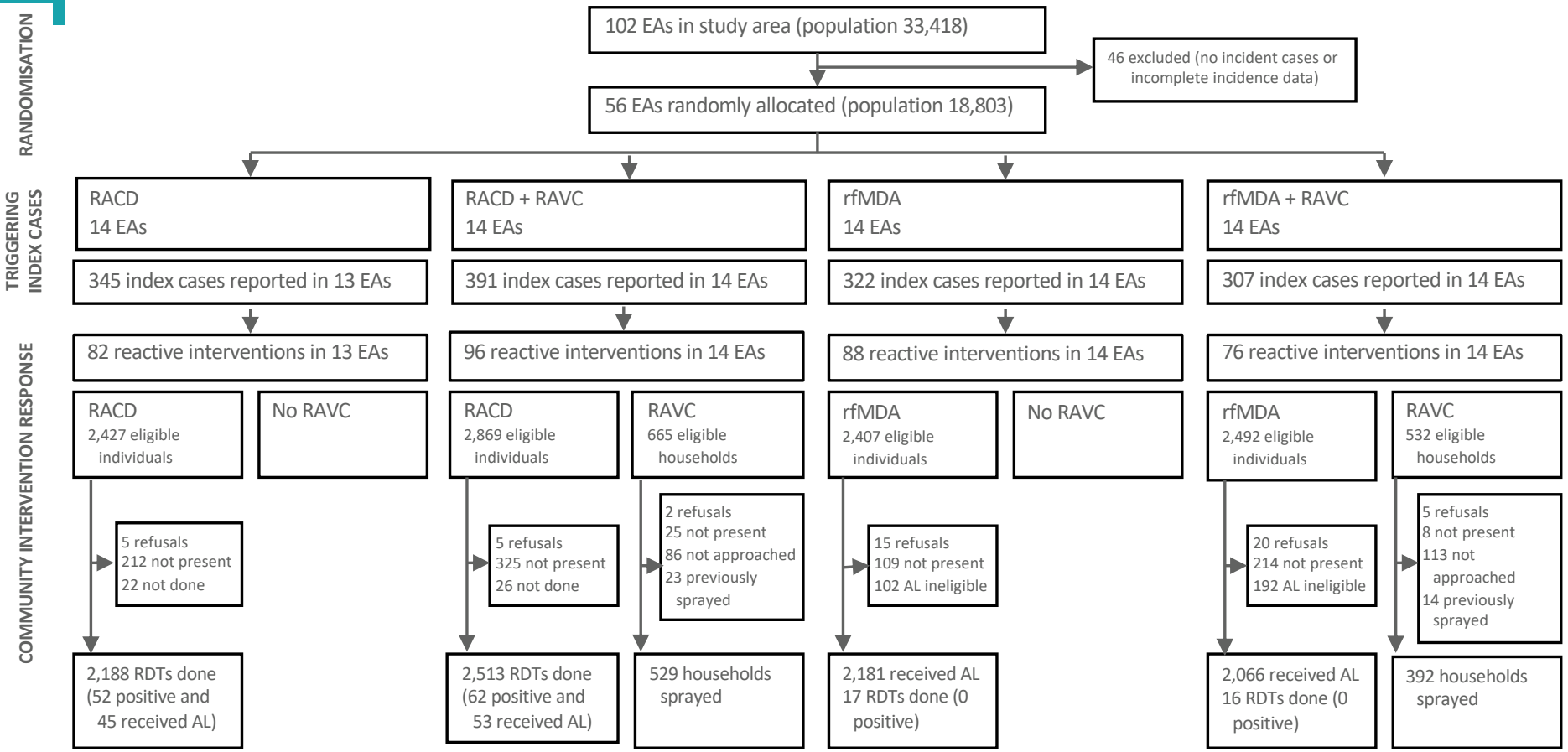
- Expected recruitment:
  - 206 intervention events over one transmission seasons in 56 EAs or clusters
  - 5150 individual encounters in all arms of the study (4635 unique individuals)


10 0 10 20 30 40 km
Zambia
Angola
KASHESHE
SESHEKE
SIBBINDA
CHOI
MASOKOTWANE
KANONO
CHINCHIMANI
SACHONA
LINYANTI
BATUBAJA
SANGWALI
Botswana
Namibia
Legend
Study health facilities
rfMDA only
rfMDA + RAVC
RACD only
RACD + RAVC
Non-study areas of Zambezi within catchment area of study health facilities
Non-study areas of Zambezi outside catchment area of study health facilities

Baseline characteristics

	EA level characteristic	RACD N=27	rfMDA N=28	No RAVC N=27	RAVC N=28	RACD only N=13	rfMDA + RAVC N=14
Transmission intensity	Mean cumulative incid (/1000, 95% CI) 2013, 2014, and 2016	25.6 (16.3–35.3)	27.9 (13.5–42.2)	26.2 (16.0–36.4)	27.3 (13.2 –41.3)	28.3 (14.4–42.1)	31.4 (5.6–57.1)
	Mean cumulative incid (/1000, 95% CI) 2016 only	30.6 (19.3 – 42.0)	42.2 (14.3 – 70.1)	30.6 (14.9 – 46.3)	42.2 (16.3 – 68.0)	30.1 (11.8 – 48.4)	53.3 (1.1 – 105.5)
Population characteristics	Median Population size, (range)	312 (129–526)	277 (141–432)	287 (141–526)	292 (129–437)	287 (165–526)	272 (144–426)
	Mean Distance between households, meters (95% CI)	45.4 (37.0–53.8)	45.8 (38.2–53.4)	48.9 (38.9–58.9)	42.4 (37.3–47.6)	48.1 (31.9–64.3)	42.0 (34.9–49.0)
	Health care access (mean distance to health facility, km (95% CI))	5.6 (4.0–7.1)	6.2 (4.2–8.2)	4.9 (3.3–6.6)	6.8 (5.0–8.7)	3.9 (2.1–5.8)	6.6 (3.4–9.8)
Ecological factors	Mean monthly EA rainfall for November 2016 - April 2017, mm, median (range)	23.2 (18.4 – 26.7)	23.3 (18.4 – 26.7)	23.5 (18.4 – 26.6)	23.7 (18.4 – 26.7)	23.7 (18.4 – 26.7)	23.4 (18.4 – 26.7)

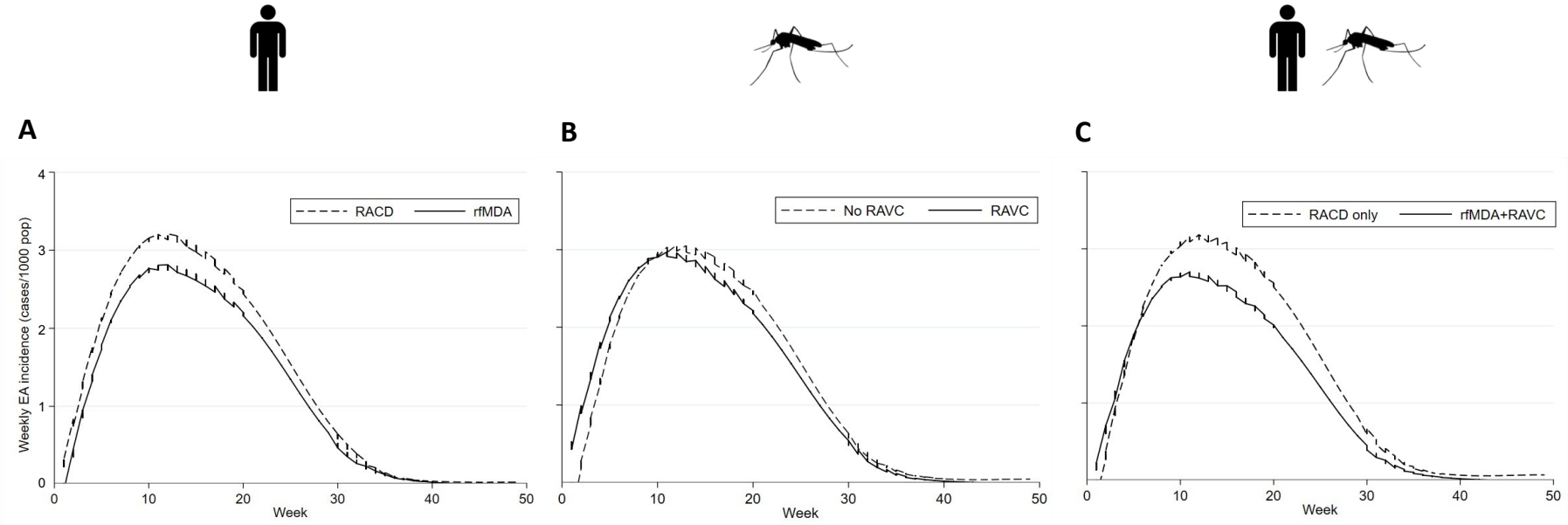
Trial profile



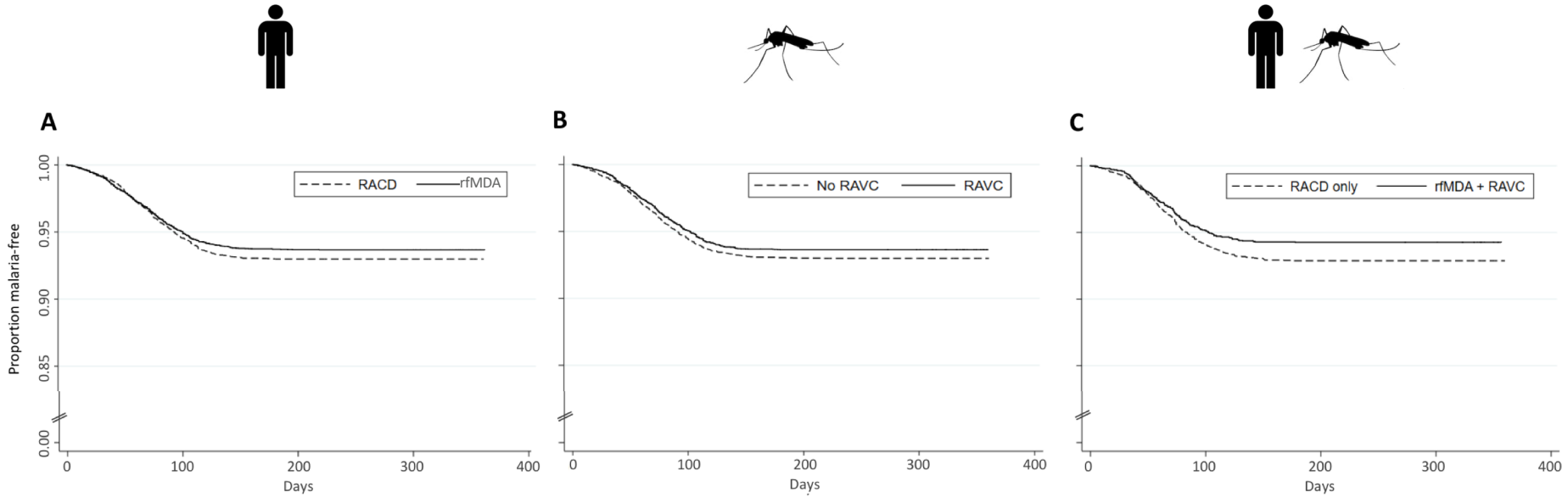
Coverage, response time

EA or cluster-level characteristic	Overall n=55*	Targeting human reservoir		Targeting mosquito reservoir		Targeting human and mosquito reservoir	
		RACD n=27**	rfMDA n=28**	No RAVC n=27	RAVC n=28	RACD only n=13	rfMDA + RAVC n=14
RACD coverage	84.3	84.3		84.6	84.0	84.6	
rfMDA coverage	90.8		90.8	93.2	88.5		88.5
RAVC coverage	79.9	79.8	79.9		79.9		79.9
Response time, median (range)	13 (6-29)	14 (6-25)	13 (7-29)	14 (8-29)	13 (6-18)	14 (8-25)	13 (7-17)

1. Weekly incidence by study arm



Malaria-free survival curves



Entomological surveillance

- Bioassay tests
  - 100% mortality to pirimiphos methyl (N=90) and bendiocarb (N=46)
  - 98% mortality to DDT (N=46)
  - 71% mortality to deltamethrin (N=111)
- Morphological identification of “resistant” mosquitoes
  - all belonged to the *An. gambiae* complex
- Molecular testing
  - *An. arabiensis* (66%) the remainder being *An. quadriannulatus*
  - No alleles with *Vgsc-L104F* and *Vgsc-L1014S* mutations were present in *An. arabiensis* “survivors”

Design/Analytic challenges

- Study designed for a lower transmission setting
- Contamination (clusters contiguous)
- Co-interventions by local Ministry
- Not able to adjust for RAVC coverage
- Did not have a control of no intervention