# Impact of the spatial repellents, metofluthrin on malaria incidence rates at two villages in Sumba, Indonesia by cluster-randomized, double-blind placebo-controlled trial

*Clinical trial: ACTRN12611001050943*

**Din Syafruddin *et al***

EIJKMAN INSTITUTE
for molecular biology

SC Johnson
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# Spatial Repellent (SR)

Spatial Repellent is one of the potential tools to explore.

Different from IRS/LLIN, SR does not require a tarsal contact of the vector to chemically-treated surface/space.

The core mechanism of action of an SR is inhibition of vector entry into a treated space by a chemical vapor.

# Aim

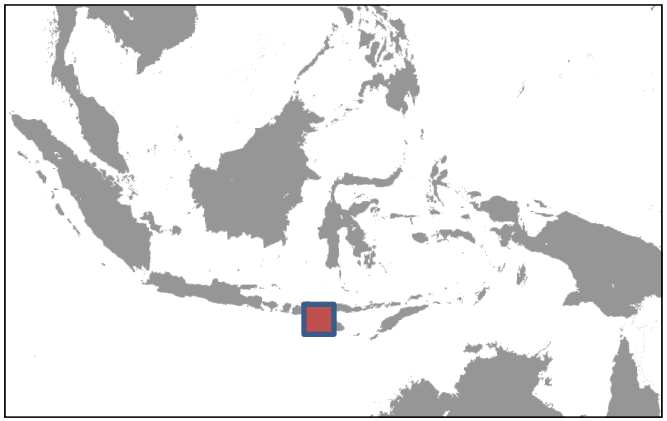
To demonstrate that the spatial repellent (SR) could reduce the malaria attack rates in human population and to prove that the reduction associated with entomological correlates (proof-of-concept)

# Trial end points

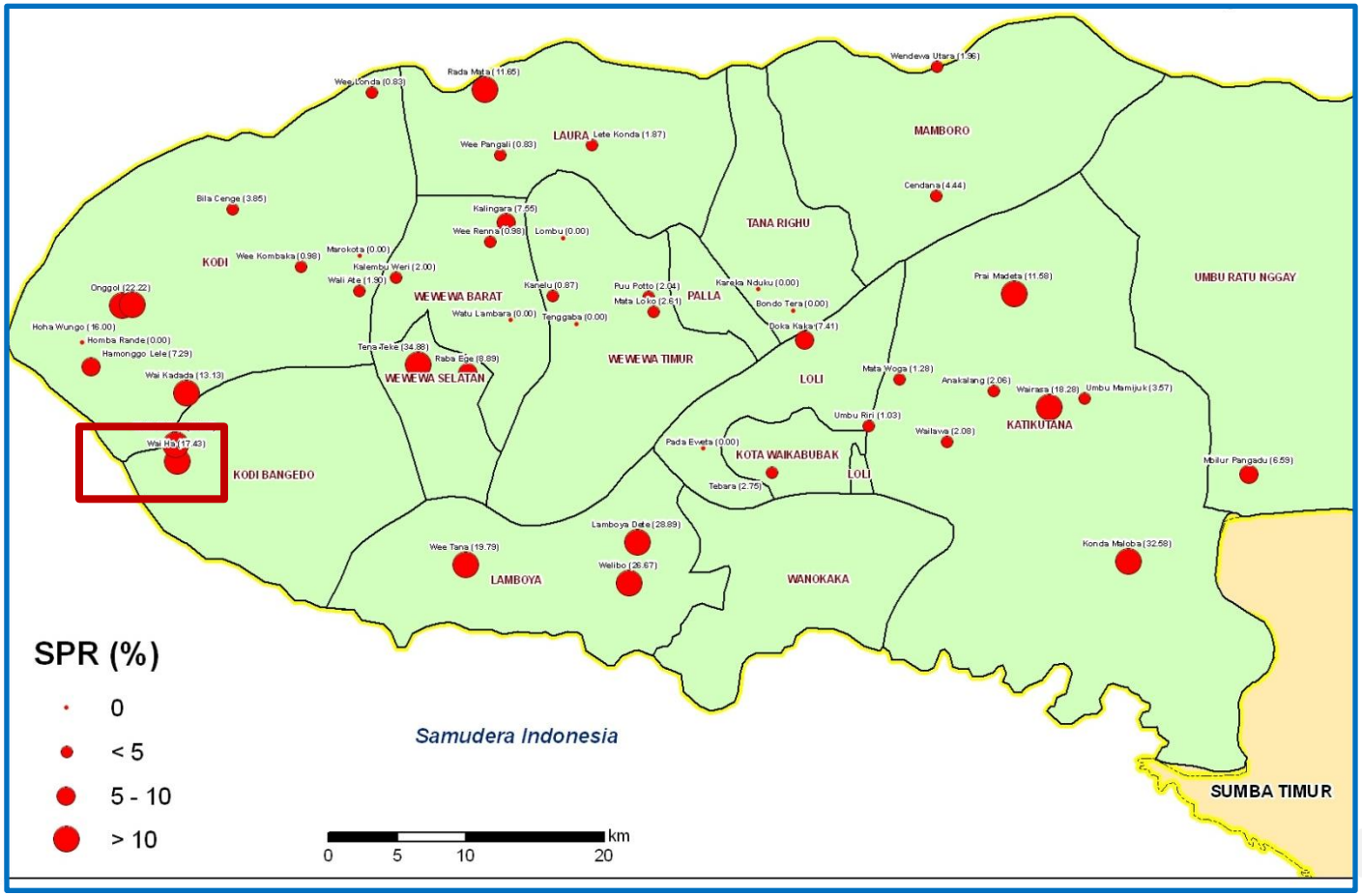
Primary : Protective efficacy of SR intervention on malaria incidence

Secondary : Anopheline mosquitoes attack rates in the house

Time frame : 31 Oct 2011 – 26 April 2012 (26 weeks)



# Study site

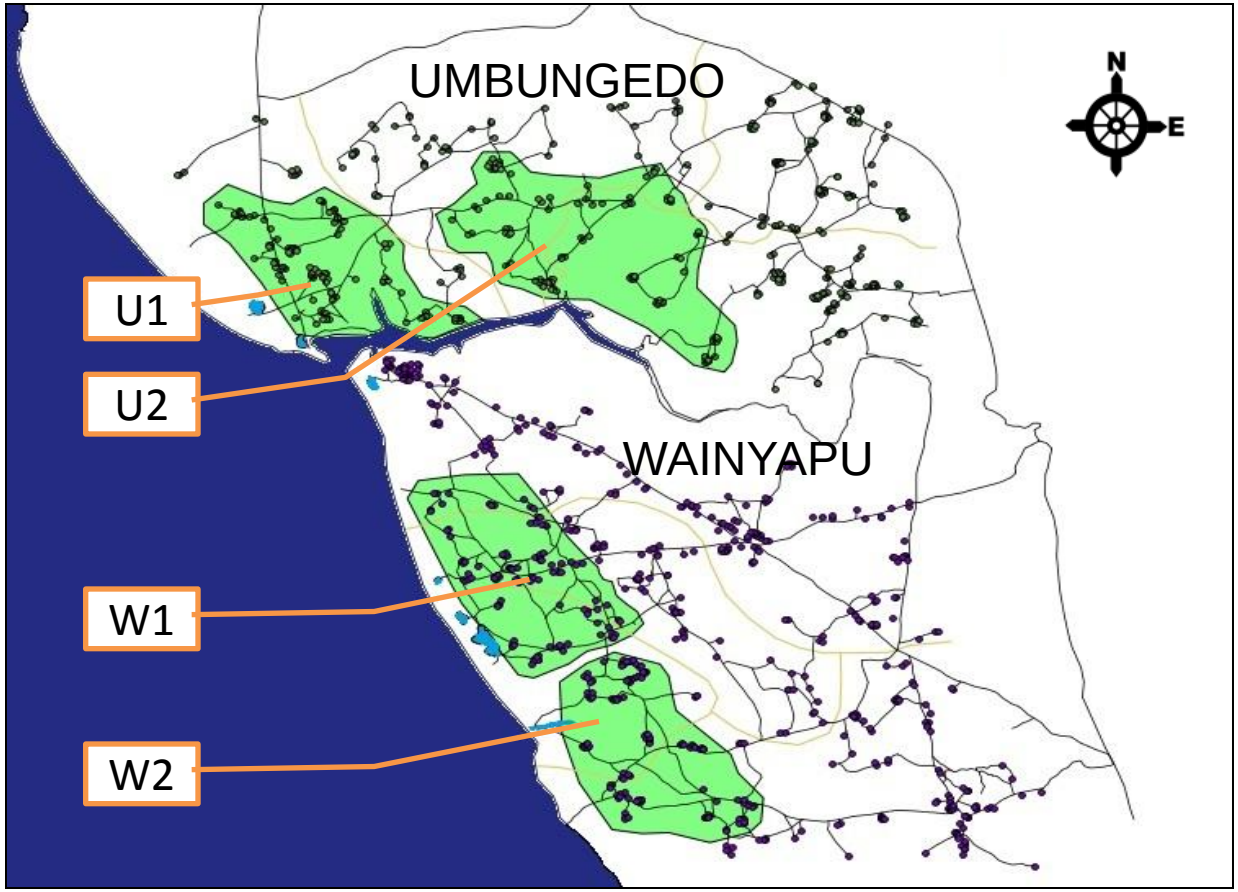



Syafruddin *et al*, Malaria J, 8:8 2009

# Village Snapshot

# Study design (1)

- A randomized, double-blind, placebo-controlled trial
- 4 study clusters in 2 villages
- A total of 400 households were enrolled for mosquito coil placement- total population per cluster, ca 500 people



# Study design (2)

*Spirit Sumba*

- A cluster-block randomized sample of 45 men in each cluster (totally 180 men) were enrolled for malaria radical cure
- Subjects completed a supervised malaria radical cure (regardless of blood film status at enrolment) consisting of DHA/PP+PQ prior to the coil intervention
- Weekly monitoring of malaria infection during intervention

## Inclusion Criteria:

Male >17 years of age, weight ≥40 kg, G6PD normal. No severe anaemia, No chronic illness, Sleeps in village >90% of nights during any given month. No plans for extended travel during study, Willingness to sign informed consent

## Exclusion Criteria:

Men <17 years of age or female, Weight <40 kg, G6PD deficient and Haemoglobin of <8 mg/dL

# Study design (3)

- Five sentinel houses selected per cluster and randomized as either 2 ‘active’, 2 ‘blank’ and 1 ‘no coil’

- Two identical appearing coils, either 4 active (metofluthrin 0.00975% AI) or 4 blank (inert ingredients only) placed inside each house, using a 90:10 distribution ratio of each treatment within a single study cluster (W1, W2, U1 and U2) each night beginning at 1800hr.

- Weekly monitoring of sentinel houses in each sub-cluster (5 houses each) by Human Landing Collection (HLC).

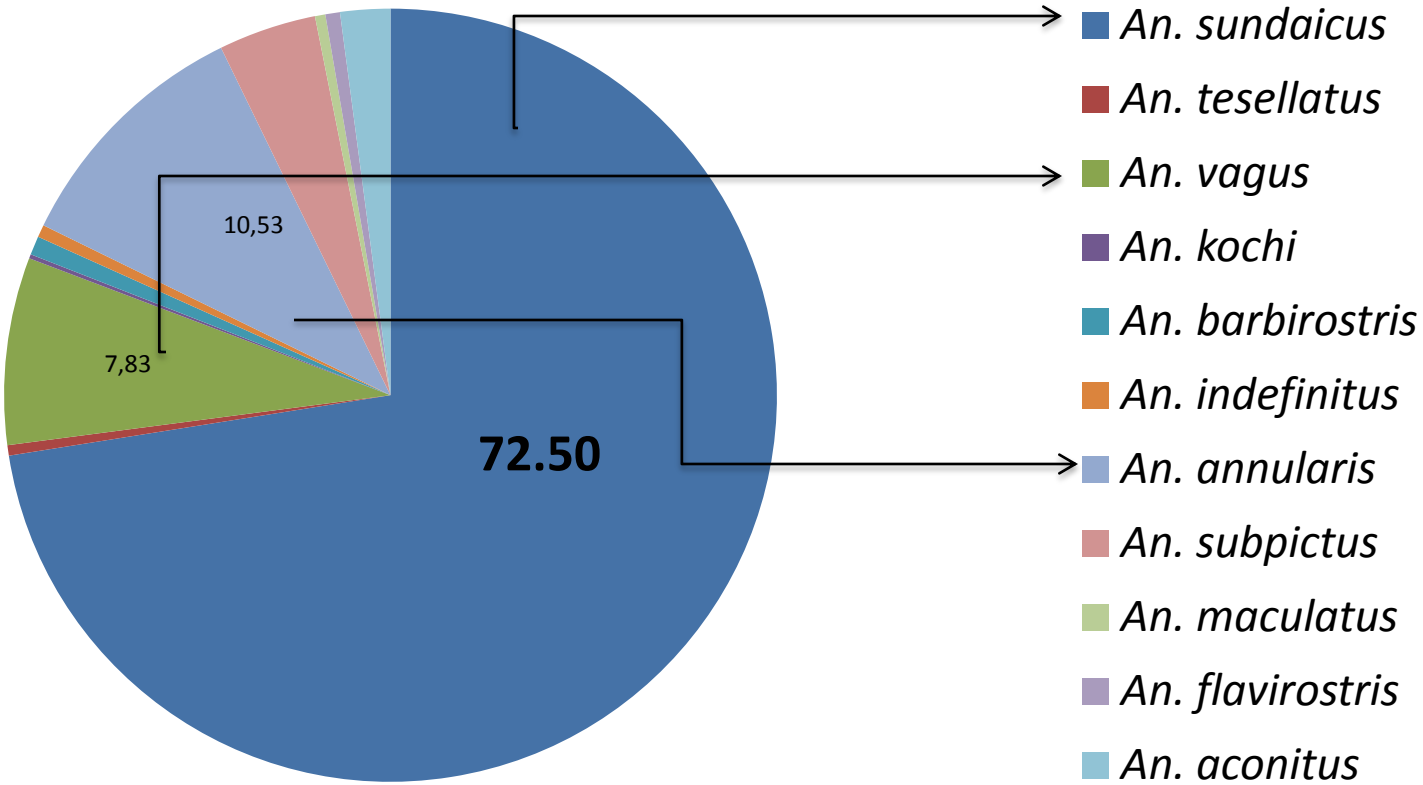
# Study design (4)

- Entomological Measures
  - **Indoor/outdoor HLC (biting densities)**
  - Vector identification/incrimination (sporozoite infection)
  - Parity (age structure)
  - Resting collections (host preference)
  - Blood meal analysis
  - Larval habitat monitoring (population structure)
  - Climate (rainfall, temperature, RH, wind speed)

# Study Implementation

- HLC Methodology
  - Two collectors per house
  - 1 positioned Indoor & 1 outdoor (~1m from house)
  - Collections for 50 min/hr, 1800-0600.
  - Rotate positions (in/out) each hour.
  - *Anopheles* morphologically ID; proportion parity dissections and sporozoite detection (ELISA/PCR)

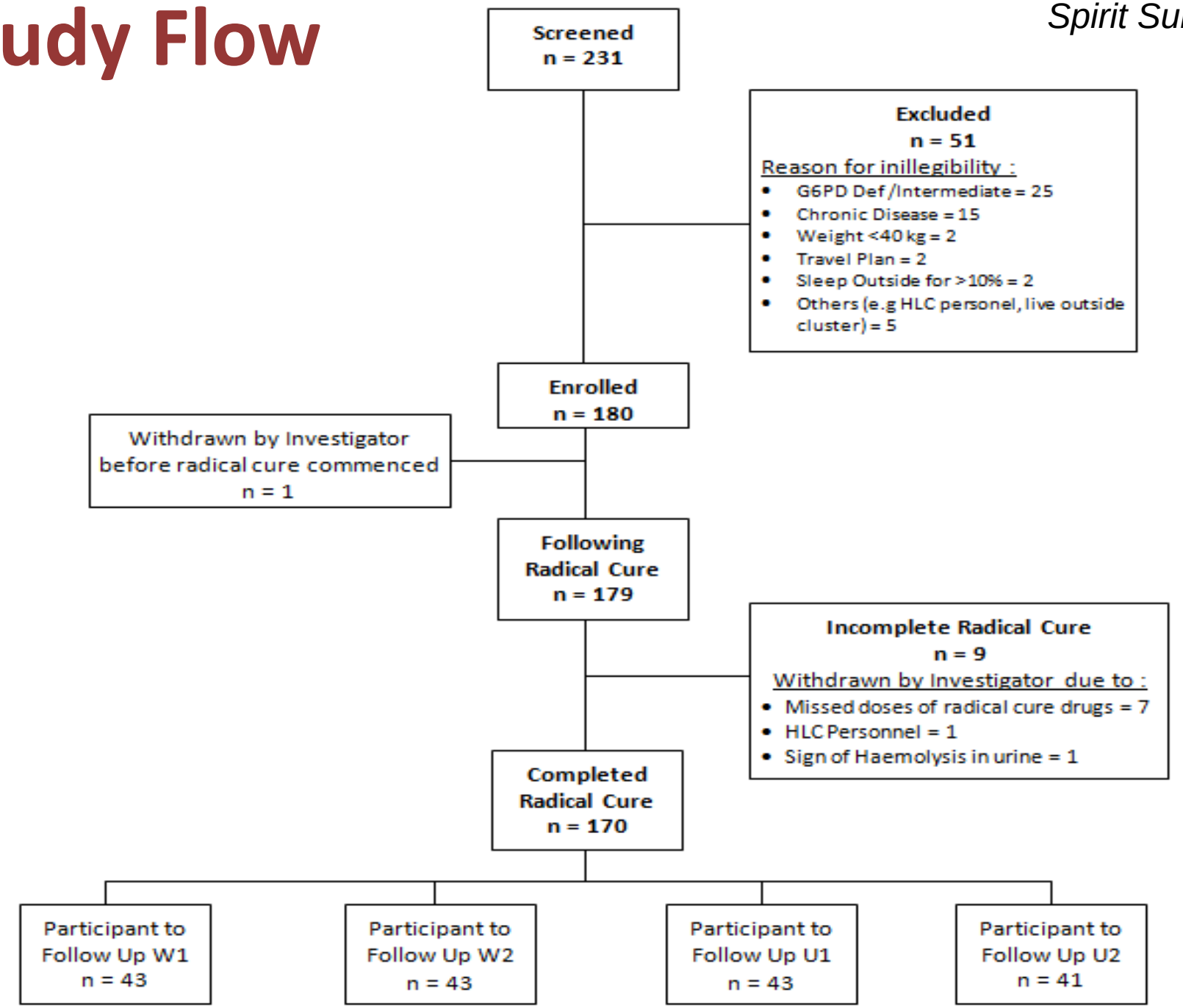
# Indoor Proportion of Anopheles Species



# RESULTS

# Study Flow

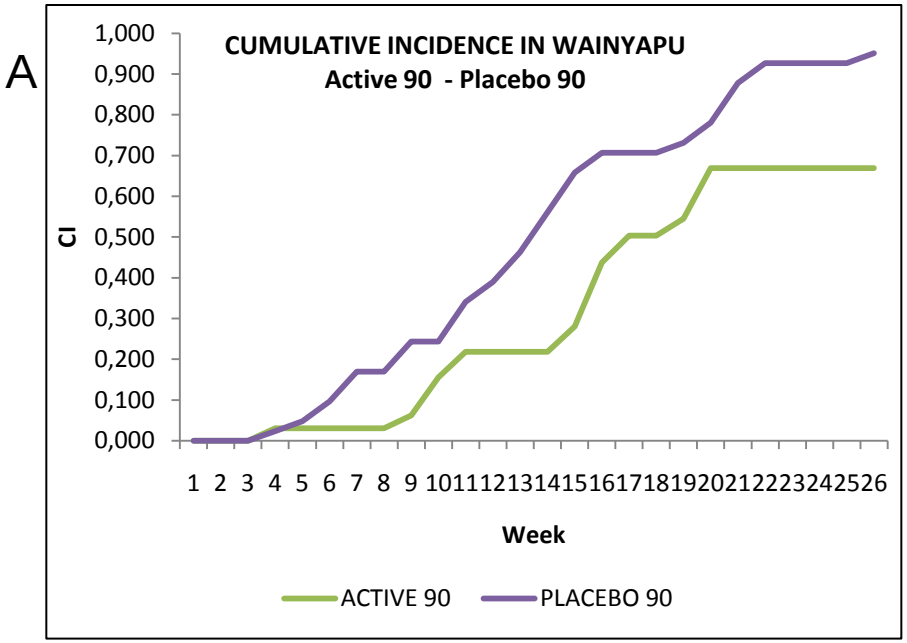
*Spirit Sumba*

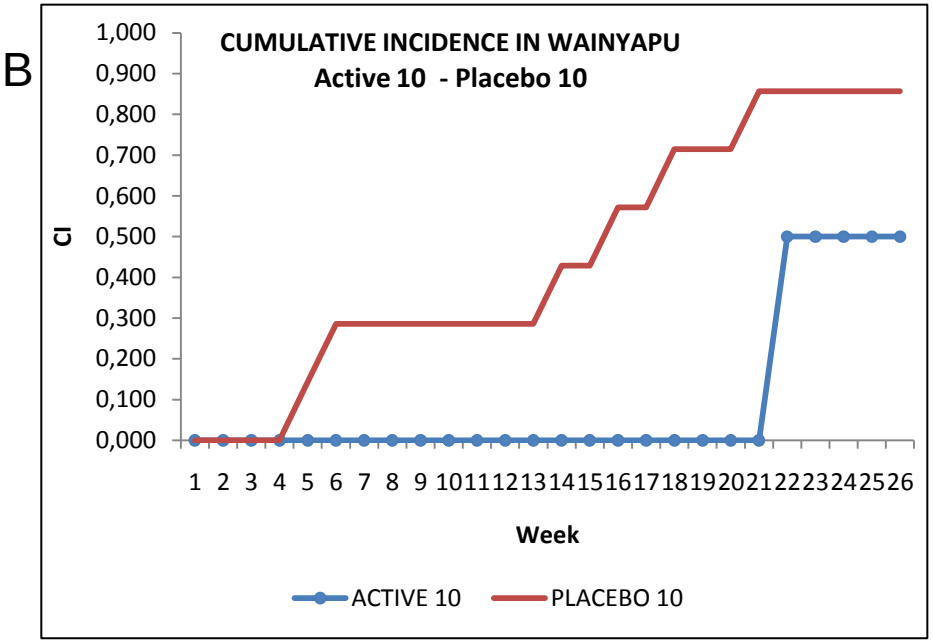


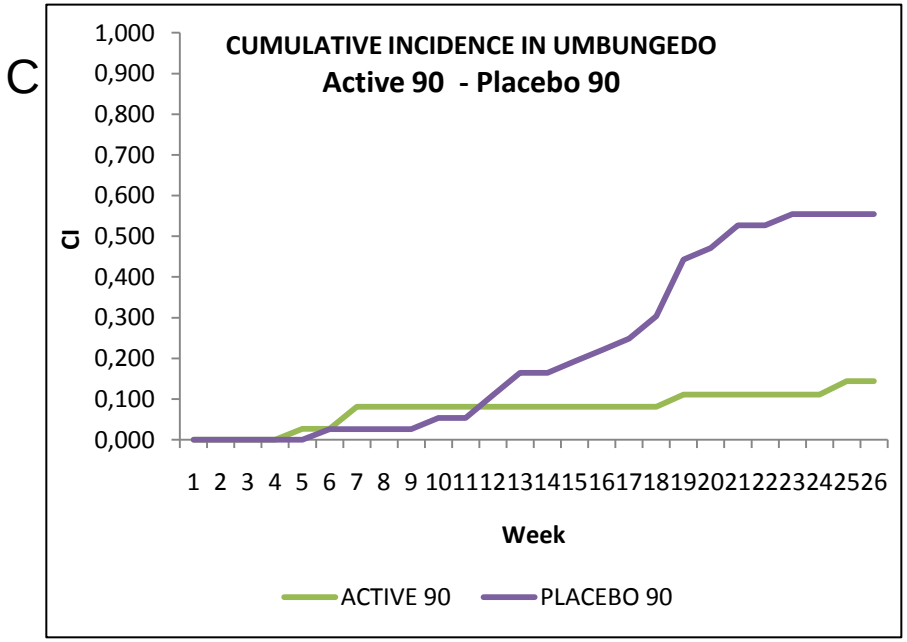
# Malaria status of men lives in active and blank coil clusters along the 6 month coil intervention

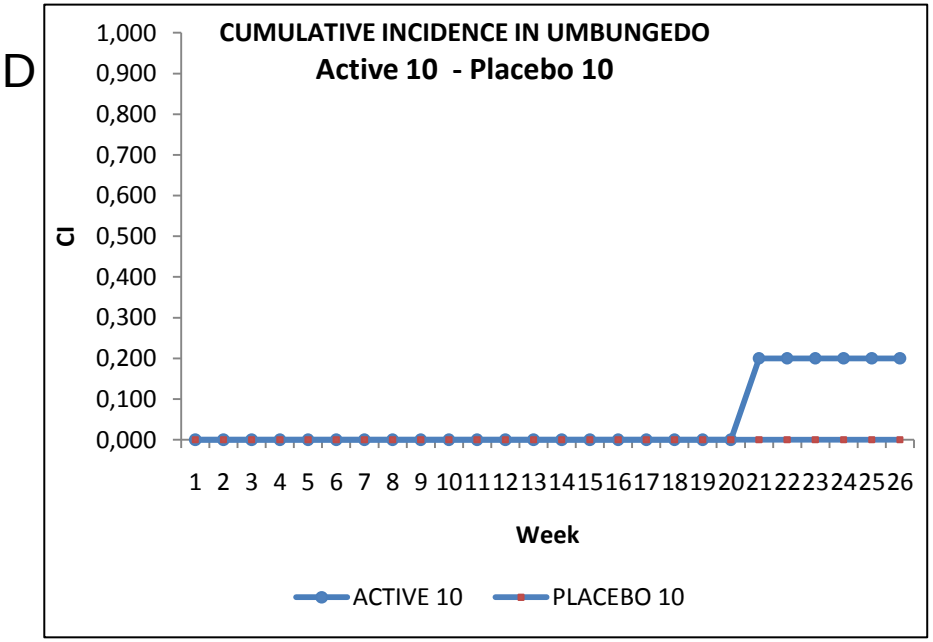
| Village | Cluster (Coil status*) | Develop malaria | Person Week (6 month) | Incidence rates | p value ** | Rate Difference | 95% CI |
|---|---|---|---|---|---|---|---|
| Wainyapu | ACTIVE (W1) | 21 | 594 | 0,0353 | 0,011 | 3,283 | 0,78 – 5,78 |
| | BLANK (W2) | 45 | 660 | 0,0681 | | | |
| Umbungedo | ACTIVE (U2) | 6 | 794 | 0,0062 | 0,006 | 15,600 | 4,73 – 26,47 |
| | BLANK (U1) | 20 | 959 | 0,0218 | | | |
| Total | ACTIVE | 27 | 1454 | 0.904 | 0.00001 | 2.732 | 1.463-4.001 |
| | BLANK | 65 | 1553 | 2.324 | | | |

*) Unblinded after 6 month period
**) *p value* for comparing 2 person-time rates


A
CUMULATIVE INCIDENCE IN WAINYAPU
Active 90 - Placebo 90
CI
1,000
0,900
0,800
0,700
0,600
0,500
0,400
0,300
0,200
0,100
0,000
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26
Week
ACTIVE 90
PLACEBO 90


B
CUMULATIVE INCIDENCE IN WAINYAPU
Active 10 - Placebo 10
CI
1,000
0,900
0,800
0,700
0,600
0,500
0,400
0,300
0,200
0,100
0,000
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26
Week
ACTIVE 10
PLACEBO 10


C
CUMULATIVE INCIDENCE IN UMBUNGEDO
Active 90 - Placebo 90
CI
1,000
0,900
0,800
0,700
0,600
0,500
0,400
0,300
0,200
0,100
0,000
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26
Week
ACTIVE 90
PLACEBO 90


D
CUMULATIVE INCIDENCE IN UMBUNGEDO
Active 10 - Placebo 10
CI
1,000
0,900
0,800
0,700
0,600
0,500
0,400
0,300
0,200
0,100
0,000
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26
Week
ACTIVE 10
PLACEBO 10

# Sub-Cluster Effect Analysis

**Protection Independent of Neighbors**

| | Active | Placebo | Odds Ratio | 95% CI (p value) |
|---|---|---|---|---|
| Malaria | 2 | 6 | 1.69 | 0.73 – 3.9 (0.22) |
| No Malaria | 6 | 4 | | |

Insufficient statistical power to draw definitive conclusions regarding village level effects

# Protective efficacy on malaria Incidence

- Inactive coils
  - 59 infections among 1,296 person-weeks at risk
  - 2.367 infections/person-year

- Active coils
  - 25 infections in 1,381 person-weeks at risk
  - 0.9413 infections/person-year

[(2.324 – 0.904)/2.324] X 100 = **61.1%** protective efficacy
(95%CI =37%-75%)

# Entomological correlates

# Overview: Entomological Findings

- Active breeding sites in Wainyapu cluster more consistent and productive with adult densities
- Larval collection: 11.8% of all females identified as *An. sundaicus* (note one temporary site [W2C] responsible for ~48% of entire collection)
- Distinct differences in anopheline densities between clusters
- Total HLC (26 wks)
  - W1+W2 = 1,603 (3.1 *An. sundaicus*/person/night)
  - U1+U2 = 74 (0.14 *An. sundaicus*/person/night)

# Target species: *Anopheles sundaicus*

- HLC: U1+U2= 82.2%; W1+W2= 86% of all anophelines
- Mean Indoor : Outdoor Ratio
  - W1 1 : 1.8
  - W2 1 : 1.85
  - U1+U2 1 : 1.96
- Parity: predominantly parous
- Resting collections: 73% of all anophelines captured were *An. sundaicus*.
- Sporozoite infection: Only *An. sundaicus* in clusters W1 and W2, all *P. falciparum* [15+/2,030]
- *An. sundaicus* is primary vector based on sporozoite infections and HLC data. *An. subpictus* s.l. regarded as secondary.

# EIR

$$\left(\frac{\text{Positive ELISA Indoor}}{\text{\# } \textit{An. sundiacus} \text{ Indoor}}\right) \times \left(\frac{\text{\# } \textit{An. sundaicus} \text{ Indoor}}{\text{Person-Nights Indoors}}\right)$$

| Treat | # Night | # House | Collector (In+Out) | Person-Night | | | # *An. sundaicus* | | | Positive ELISA | | | EIR | | | Days to 1st Infective Bite |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | IN | OUT | TOTAL | IN | OUT | TOTAL | IN | OUT | TOTAL | IN | OUT | TOTAL | |
| Placebo | 26 | 8 | (8+8) | 208 | 208 | 416 | 247 | 452 | 699 | 2 | 1 | 3 | 0.0156 | 0.0078 | 0.0122 | 82 |
| AI | 26 | 8 | (8+8) | 208 | 208 | 416 | 164 | 359 | 523 | 0 | 2 | 2 | 0.0000 | 0.0156 | 0.0122 | 82 |
| No Coil | 26 | 4 | 8 | 104 | 104 | 208 | 324 | 484 | 808 | 5 | 5 | 10 | 0.0296 | 0.0296 | 0.0296 | 34 |
| | 13 (W3) | 5 | 10 | 65 | 65 | 130 | | | | | | | | | | |

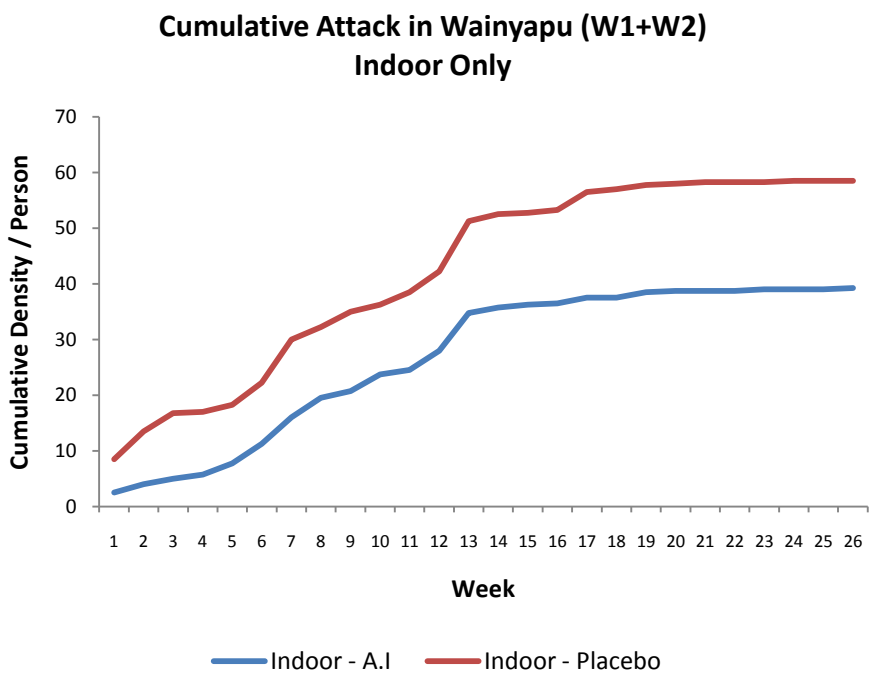
## Indoor – Baseline

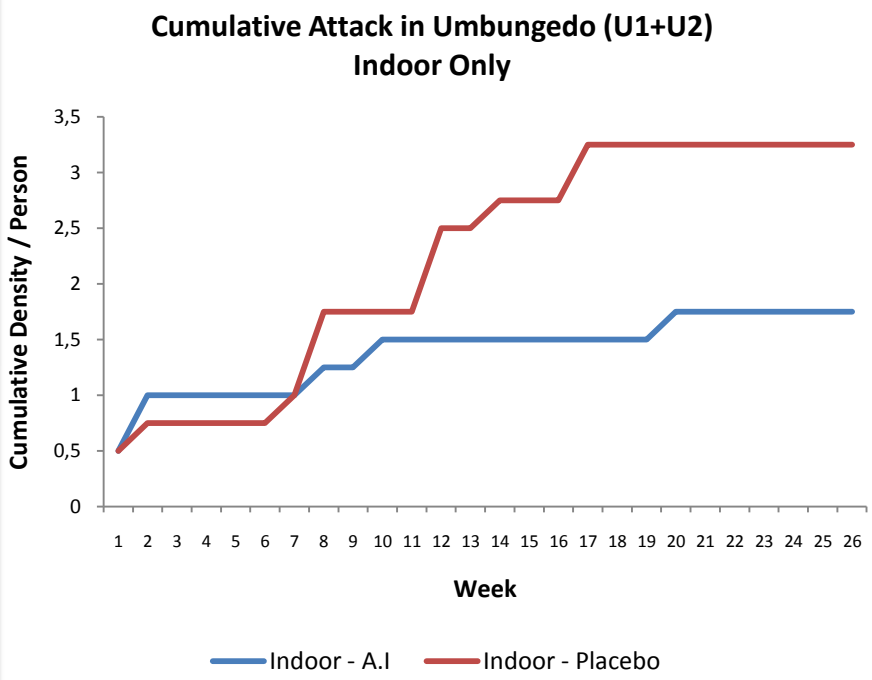
| | EIR | Days to 1st Infective Bite |
|---|---|---|
| Placebo | 0.0110 | 91 |
| AI | 0.0105 | 95 |
| No Coil | 0.0122 | 82 |

## Indoor – Post Intervention

| | EIR | Days to 1st Infective Bite |
|---|---|---|
| Placebo | 0.0156 | 64 |
| AI | 0.0000 | INF |
| No Coil | 0.0296 | 34 |

# Cumulative attack rates of *An. sundaicus* pooled by village (indoor only)




Wilcoxon Paired Test: Statistically different densities between AI vs. Placebo ($p$=0.0342)

CMLE Rate Ratio: 32.9% reduction in attack rate for a person inside an active coil house ($p$=0.04388)

Wilcoxon Paired Test: No Significant difference in densities between AI vs. Placebo ($p$=0.1562)

CMLE Rate Ratio: Not applicable

# Conclusions

1. Active coil in the homes of subjects was associated with a significant protective efficacy (60%) against new infections by plasmodial parasites

2. No evidence of village-level effects, but this requires greater statistical power to ascertain

3. Mosquito attack rate in the homes with SR was significantly reduced

4. Reduction in mosquito attack rate might be associated with reduction in malaria attack rates

# *Acknowledgement*

Residents in the study sites :

1. Dr. Kate Aultman (Bill and Melinda Gates Foundation)

2. Drs. Daniel Lawson and Maude Maier (SC Johnson and Son Corp, USA)

3. Officials of the Southwest Sumba District Health Department

4. Parasitology and Entomology teams, field workers, data entry clerks and local volunteers

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   Dian Sidik

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   Claus Bogh

5. SOS Indonesia
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Thank you