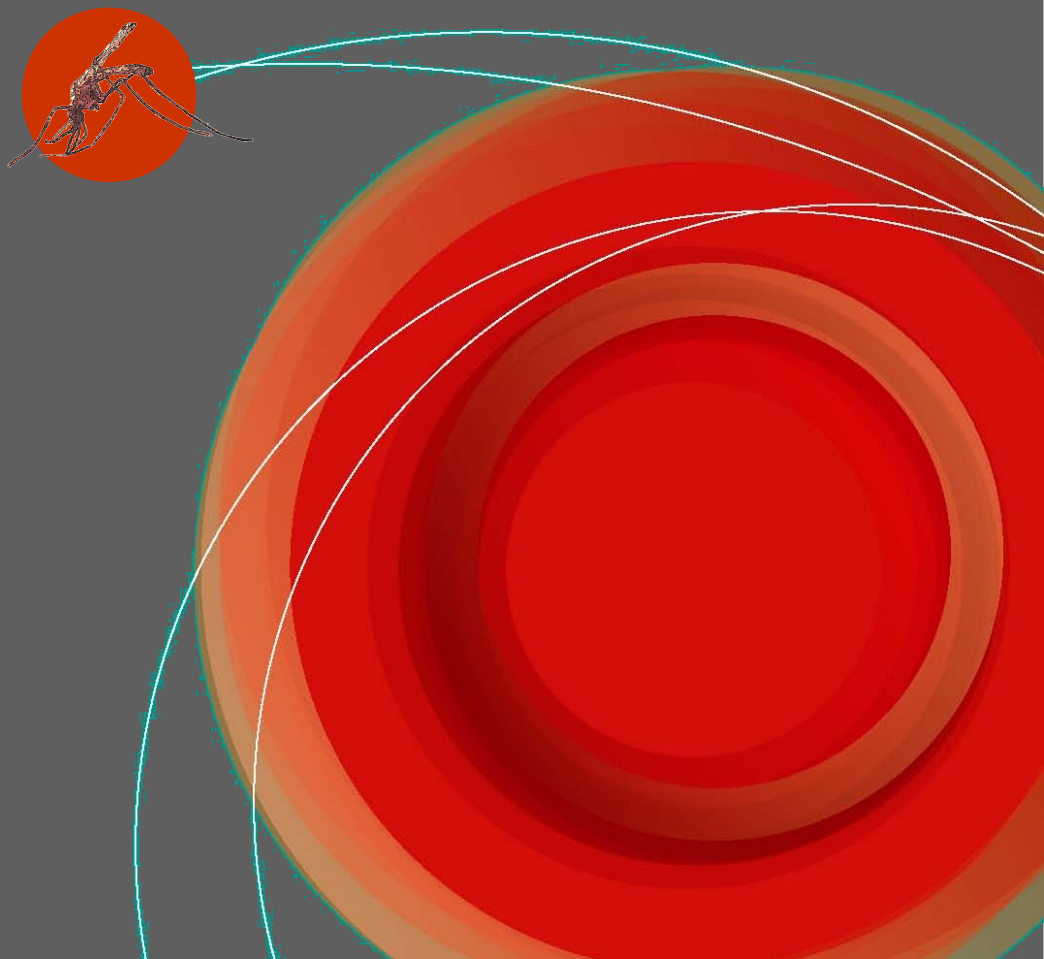
Development of a Global Strategy against Insecticide Resistance in malaria vectors

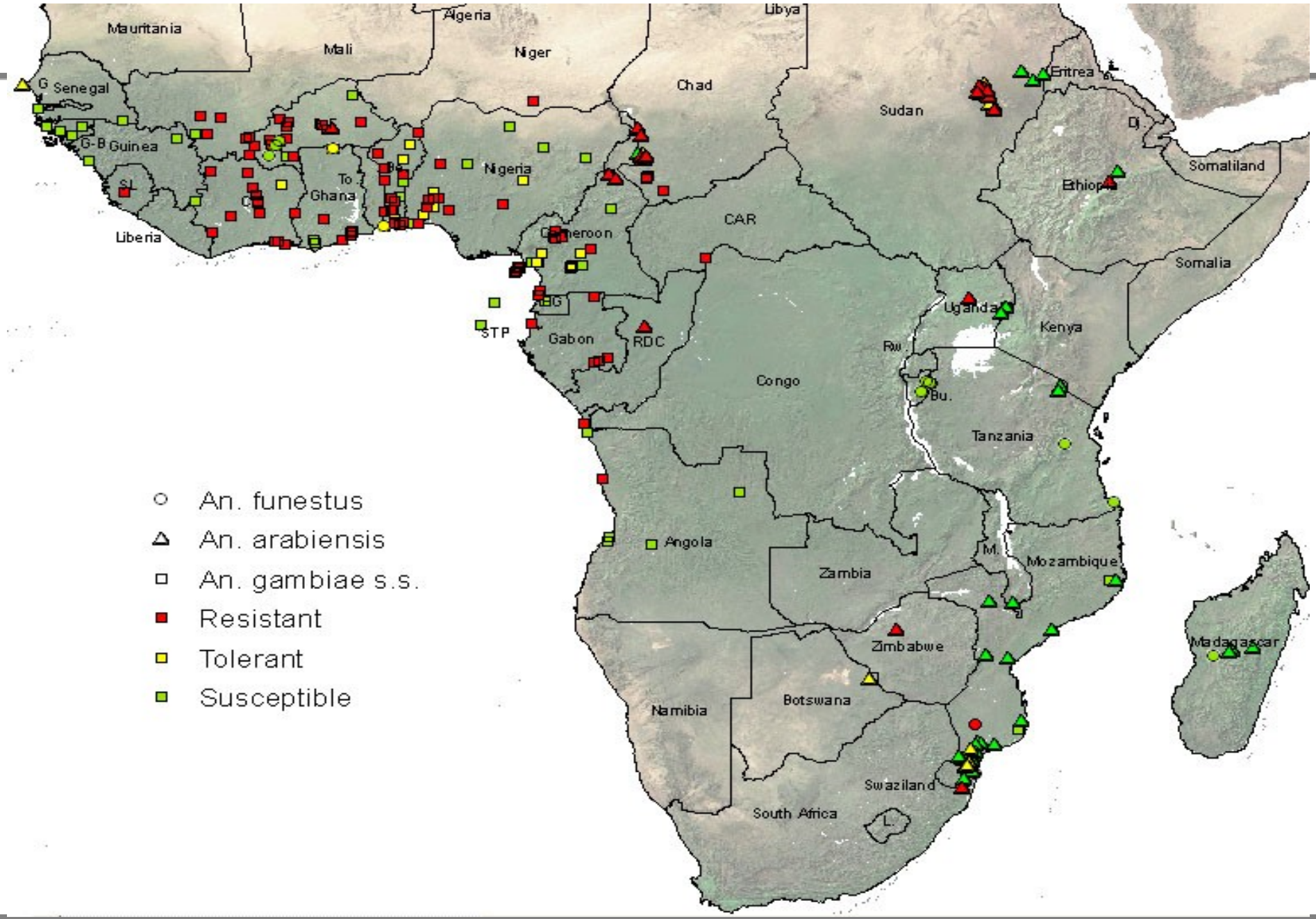


Vector Control & Prevention
Global Malaria Programme
World Health Organisation

World Health Organization

Outline

- The current situation – the threat of pyrethroid resistance for malaria control
- Strategies to find new molecules for nets and walls
- Strategies to slow down the spread of resistance
- The policy process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Mozambique
Zimbabwe
Madagascar
Namibia
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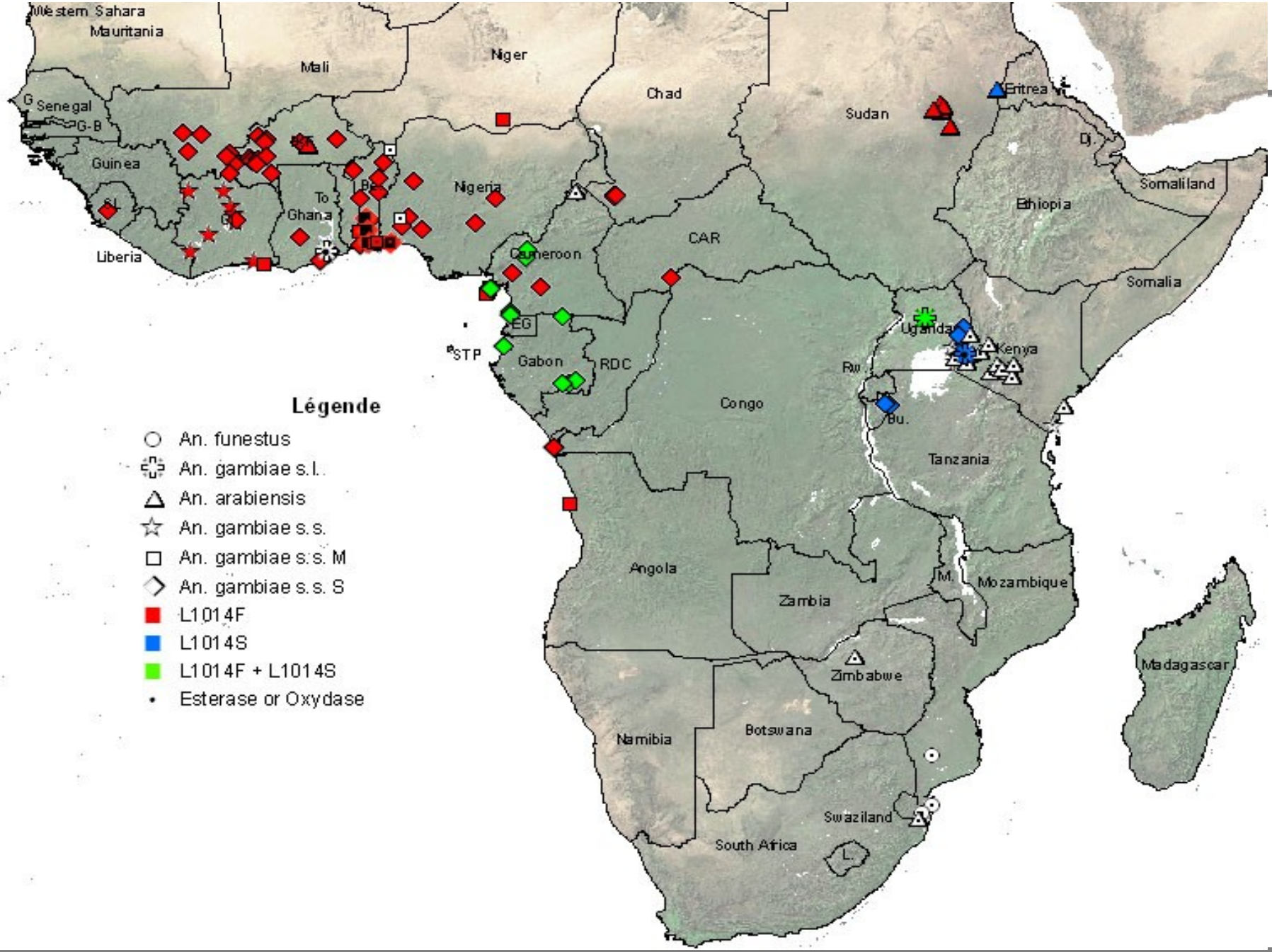
Swaziland
South Africa
An. funestus
An. arabiensis
An. gambiae s.s.
Resistant
Tolerant
Susceptible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Madagascar
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Swaziland
South Africa
Légende
An. funestus
An. gambiae s.l.
An. arabiensis
An. gambiae s.s.
An. gambiae s.s. M
An. gambiae s.s. S
L1014F
L1014S
L1014F + L1014S
Esterase or Oxydase

Insecticide Resistance - 1

1. Already a major issue in Africa – some reports from India

1. *kdr* genes are already widespread – but other metabolic mechanisms are spreading rapidly – oxidases & esterases
   - too little data about distribution or importance of these mechanisms
   - may be more powerful as causes of control failure

2. Big gaps in the data – but consolidated regional databases do exist.

1. Disconnection between data and insecticide choice decisions: e,g:
   - Zanzibar, Kagera

Impact of insecticide resistance

- Very little data on impact of insecticide resistance on malaria control
- Most studies have used experimental huts and impact on entomological parameters
- Mozambique/KZN case (*An. funestus*) showed potential impact on malaria cases (although there are confounding factors as always)
- Urgent need for well conducted studies on epidemiological impact of resistance (multi-country study about to be launched, funded by BGMF & coordinated by GMP)

Summary points

- Pyrethroid resistance is widespread in *An gambiae* (and perhaps even more so in *An funestus*).
- Resistance to DDT also common.
- Carbamate and OP resistance so far restricted to W. Africa.
- *kdr* alone has not yet been shown to be a cause of control failure.
- But combination of *kdr* and other mechanisms is potentially much more serious – focus on *kdr* may have led to a false sense of security?

Insecticide Resistance - Response

1. Recommend that in GF (and other donor) proposals, resistance data should be quoted (for large-scale IRS or ITNs) and used to justify insecticide choice (for IRS) - as a condition for funding.

1. Expert consultation planned for March to review the current situation and recommend global policies – roll out via WIN / VCWG
   - Acceptance by the 3 or 4 main donors is necessary…. and probably sufficient !

2. Options for management:
   - Likely to recommend rotations - but mixtures are probably much more effective
   - Need more mixture (combination) products esp for nets
   - Reserve pyrethroids for ITNs? (NOT for IRS? Agriculture?)

Strategies to find new molecules for walls

- Chemical companies are the key source – they have the experience and knowledge
- IVCC – critical support, stimulus
- IVCC and Chemical companies
  - a few compounds new to public health are coming through
  - in the pipeline and medium-term prospects
  - but as IRS and/or wall-sheeting products
- But IRS needs repeated application once or twice a year
- Wall-sheetings last much longer but need elaborate fitting

Strategies to find new molecules for nets

- RBM needs effective ITNs! Nets have many advantages as a medium for insecticide!
  - between mosquito and the host
  - even untreated nets protect if intact
  - distribution at long intervals, village-scale or through EPI (don't have to visit every house)
  - can't cover 450m people at risk any other way!
- Nothing in the pipeline for nets
  - a molecule discovered tomorrow would take >5y to develop
- Much less incentive for primary chemical companies
  - they take 30% to 60% of expenditure on IRS
  - but only ~ 5% of expenditure on LLINs
  - They stand to gain from a shift to IRS from LLINs !!
- Need to find a solution to this unbalanced incentive !!

Strategies to slow down the spread of resistance

- Rotations - yes
  - but not reliable, not enough?
  - depend on fitness disadvantage of R, so only effective when R is rare ?
- Combined products - yes
  - e.g. roof and walls with different products
  - Encouraging preliminary results
- Mixtures - yes
  - The most robust approach - less dependent on assumptions about resistance
  - industry ready, but little experience so far
  - Issues of tox, regulation, barriers to market entry
- Must act early -
  - Waiting for proof of control failure is no strategy at all !!

Strategies to slow down the spread of resistance

Reserve pyrethroids for use on Nets?

- From IRS ? Would greatly reduce cost of IRS
  - e.g. at current prices would reduce IRS coverage from 29m to 11m population
  - might still be worthwhile, if it helped to slow down resistance enough…
- From agriculture ? Desirable if feasible, at least for some applications (rice)

- The Lesson from Agriculture? Don't do it like they do it in agriculture = 'scramble competition' , i.e. a race to maximise profit !!

- All Resistance-delaying strategies raise short-term costs
  - Co-operation - Everyone must join in – Solid consensus needed
  - But some will lose out !!
  - but strategies not guaranteed!

- Evidence Issues - Current evidence is indirect & argumentative:
  - Problem: Evolutionary events are large-scale – can't do village scale trials with R gene frequency change as the outcome
  - Need better evidence on sources of selection, methods to evaluate management strategies

Two populations: 25% are resistant; sporozoite rate = 1%

	Total population	Negative Sporozoite	Positive Sporozoite	*Sporozoite rate*
Susceptible	800			
Resistant	200			
Total	1000	990	10	*1 %*

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	Total population	Negative Sporozoite	Positive Sporozoite	*Sporozoite rate*
Susceptible	800	792	8	*1 %*
Resistant	200	198	2	*1 %*
Total	1000	990	10	*1 %*

	Total population	Negative Sporozoite	Positive Sporozoite	*Sporozoite rate*
Susceptible	800	796	4	*0.5 %*
Resistant	200	194	6	*3 %*
Total	1000	990	10	*1 %*

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Fisher's exact test P = 0.0006

Two populations: 25% are resistant; sporozoite rate = 1%

	Total population	Negative Sporozoite	Positive Sporozoite	Sporozoite rate
Susceptible	400	396	4	1%
Resistant	100	99	1	1%
Total	500	495	5	1%

	Total population	Negative Sporozoite	Positive Sporozoite	Sporozoite rate
Susceptible	400	398	2	0.5%
Resistant	100	97	3	3%
Total	500	495	5	1%

Fisher's exact test P = 0.057

	Human blood	Animal blood
Susceptible		
Resistant		

	Human Landing Catch **Inside** treated net with holes	Human Landing Catch **Outside** net
Susceptible		
Resistant		

	Nulliparous	Parous
Susceptible		
Resistant		

The policy process

1. Review now being completed
   - Current situation
   - Strategy options
1. Techical Consultation on this issue - 1st qtr
2. Roll-out to RBM constituencies via Vector Control Working Group (VCWG)
   - Need for careful consensus building
   - New Products
   - Choosing insecticide / strategy based on subregional data
   - M & E tools