



Combination nets – draft testing guidelines

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Definition

- **Combination nets (next generation nets, 2 in 1 nets, resistance breaking nets etc) defined as:**

Nets that contain pyrethroids plus a second active ingredient

- 2 manufacturers have produced combination nets that have interim WHO approval as LLIN:
 - Sumitomo – Olyset Plus
 - Vestergaard – Permanet 3.0
- How can claims of superiority be verified?

Claims for Combination Nets



- **PermaNet® 3.0 has a significantly improved efficacy** when compared with mono-treated long lasting nets (i.e. pyrethroid only nets) and conventionally treated nets **in terms of both mortality and/or personal protection.**



**The Next-Generation Net
with Added Protection**



How should combination nets be evaluated?

- Claim 1: Nets are more effective against pyrethroid resistant mosquitoes
- Claim 2: Nets are effective in reducing selection for resistance in the population.

Nets are more effective against pyrethroid resistant mosquitoes

- **Phase I:** Demonstrate that the combination net is significantly better at killing pyrethroid resistant mosquitoes than a conventional LLIN.

Standard methodology appropriate (with modifications depending on second AI)

But

How to define resistant strain to be tested?

- Resistance needs to be at a level that conventional nets are compromised
- 2 or more *Anopheles* strains must be tested and at least one of these must be significantly synergised by PBO
- RR of strain for AI being tested must be determined and reported



Nets are more effective against pyrethroid resistant mosquitoes

- **Phase II – Experimental hut studies**
- Experimental hut studies need to be conducted in areas where the mosquito population is known to be resistant to the **specific pyrethroid** used in the combination net.
- Standard methodology (washed holed nets, blood feeding & mortality recorded) but vector population must be clearly defined
- At least three sites, with differing vector populations, tested



Site selection for Expt Hut Trials

- Cone bioassays on washed conventional LLINs and local vectors must be performed prior to the study – study should only proceed if evidence that resistance is compromising conventional LLINs.
- WHO, or CDC, diagnostic dose assays for all actives being tested where available.
- If a synergist is being tested, effect of pre-exposure to the synergist on insecticide mortality needs to be recorded.
- If second insecticide, the efficacy of this alone must be determined prior to the trial
- The species composition of malaria vectors collected in control experimental huts must be compared to those in huts with nets

Nets are more effective against pyrethroid resistant mosquitoes



- **Phase III**
- Demonstrate that, under operational conditions, the combination net significantly reduces the number of blood fed mosquitoes collected resting and exiting houses, compared to a conventional LLIN, and this effect is sustained for the lifespan of the net.
- **Potential sites need to be characterized prior to trial to ascertain:**
 - Species distribution
 - Resistance profiles (by bioassay, including establishment of LT or LC50)
 - Synergist bioassays (if nets utilize synergists)
 - Efficacy of conventional LLINs by cone/petri dish assay

Evaluation of claim that nets are 'effective at reducing selection for resistance'

Claim = Use of nets causes reduction in the frequency of resistant alleles in a population and this results in a reduction in the resistance level

- Studies must determine LC50 before and after net use.

Initial studies could be done in biosphere with continuous culture for multiple generations (> 20?)

But ultimately, large scale community trials needed.



Summary

- An additional set of standards needs to be agreed upon to evaluate combination nets
- Defining resistance level (and agreeing a meaningful threshold) is key to this process
- Standard guidelines for reporting characteristics of mosquito population being tested are needed.
- Guidelines need to be flexible enough to cover multiple MOA but rigid enough to allow comparisons between products.