Outdoor Malaria Transmission Work Stream

Approaches to raise the proof of principle, research evidence based control interventions to tackle outdoor transmission.

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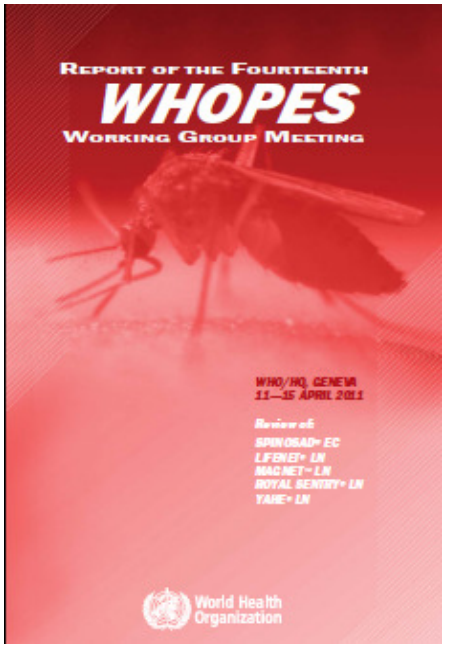
Preamble



Novel PHPs may include new active ingredients as well as new application technologies.

These may include approaches that may fit within existing WHOPES guidelines for evaluation.

However, some of these new approaches (e.g. spatial or even topical repellents for transmission control) will require as proof of principle, epidemiological studies to demonstrate efficacy in reducing malaria transmission and/or disease,

and the development of new evaluation guidelines and criteria.

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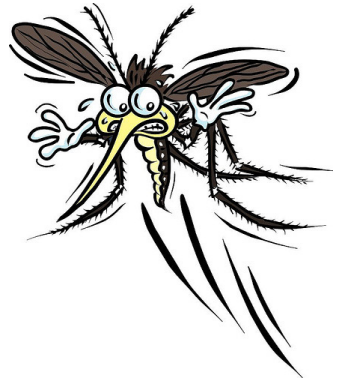
Individual, household, community designs



Individual randomized trials (without placebo)

- high risk individuals: mobile, forest workers, etc
- Less homogenous exposure
- Recruitment?
- Follow up? Adherence?

House hold randomized trials (with placebo):

- aversion effect of mosquitoes from repellent users to non users
- Important spill over effect (exchange of products between the HH)
- Placebo: feeling of being left out.

Community randomized trial (without placebo):

- Advantage: more uniform impact
- less aversion effect, less exchange of product with the control villages
- possible mass effect
- No Placebo:

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Comparison of different epidemiological study designs.

Advantages are highlighted in green, disadvantages are highlighted in red

	Community-based trial (cluster randomized)	Individually randomized trial in Plantations	Individually randomized trial on *P. falciparum* cases
What?	Randomization of intervention based on 'clusters'	Randomization of intervention based on individuals working or living in plantations	Randomization of intervention based on high risk individuals (forest workers and migrants) who already had malaria
Level at which outcome is measured	Cluster level	Individual Level	Individual level
Risk group, expected prevalence & homogeneity of exposure	Normal PCR prevalence of 5% expected More homogeneous exposure to malaria within clusters	Higher PCR prevalence of 5-10% expected More homogeneous exposure to malaria because of controlled and homogeneous environment (plantation)	Highest PCR prevalence of 10-20% expected Less homogeneous exposure to malaria because of high individual variation
Sample size	Large sample size needed: at least 6,200 people in 100 clusters for detecting a 40% decrease in prevalence	Smaller sample size: 2,000 or 4,000 people for detecting a 40% decrease in a prevalence of 10% and 5% respectively	Smallest sample size: 900 or 2,000 people for detecting a 40% decrease in a prevalence of 20% and 10% respectively
Recruitment	In village compounds Recruitment can be done at one time point in different hamlet compounds	In plantations: use of lists of temporary personnel Recruitment can be done at one time point in different plantations	In health centres or free clinics, active case detection Recruitment will be spread over time. To recruit 900 people will take too much time to ensure the follow up during the same transmission season.

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Comparison of different epidemiological study designs.

Advantages are highlighted in green, disadvantages are highlighted in red

	Community-based trial (cluster randomized)	Individually randomized trial in Plantations	Individually randomized trial on *P. falciparum* cases
Homogeneity of intervention & possible bias in results	Intervention is homogeneous: - no bias introduced by 'switching' of treatment (repellent) bottles - no aversion effect of mosquitoes	Intervention is heterogeneous - Possible bias because of 'switching of treatments' - Certain bias because of aversion effect of mosquitoes from repellent users to non-users	Intervention is heterogeneous - Possible bias because of 'switching of treatments' - Possible bias because of aversion effect of mosquitoes from repellent users to non-users
Follow up	- Although the number of persons to follow up will be high, it will be easy to locate the selected households for epidemiological follow up - When people are clustered together it will be more easy to control the adherence	- The epidemiological follow up will be easier because of a lower sample size, but limited to one harvest season - The environment of the plantation makes it easy to control the adherence	- The epidemiological follow up will be extremely difficult given the movements of this risk groups and taking into account difficulties of access (bad road conditions) and communication (no cell phone coverage in some areas) - Because of the same reasons it will be extremely difficult to control the adherence
Outcome for policy makers	The knowledge on the impact of the intervention on malaria incidence and prevalence at community level provides crucial information for policy makers in future malaria elimination strategies.	This design will only provide knowledge on protection of workers in plantations.	This design will only provide knowledge on protection of mobile populations.

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To study the added value of repellents to ITNs for the control/elimination of malaria in Cambodia

Epidemiology study

1. Assess impact of additional use of repellent on the prevalence of malaria carriers and malaria incidence
2. Assess other parameters important for elimination of malaria and arboviroses

Entomology study

1. Perform an entomological evaluation of the mass effect of repellents on residual malaria transmission in the communities
2. Estimate the individual protective efficacy of the used repellent on wild mosquito populations in controlled studies

Social science study

Assess the acceptability, adherence and adequacy of topical repellents

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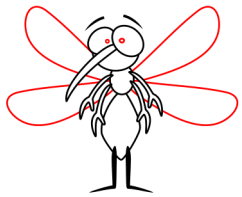
Epidemiology Study: Randomized community based trial



Control arm

- 50 villages
- Large coverage of LLINs
- No placebo repellent

Treatment arm

- 50 villages
- Large coverage of LLINs
- Massive use of topical repellent KBR3023

- Census and Pre-trial survey for randomization (stratification?? based on PCR prevalence of malaria infection)
- Baseline survey (65 members per village)
- Follow up
  - Of treatment compliance (measure LLIN use and repellent use)
  - Of prevalence of malaria (and incidence): 6 monthly surveys in 65 members per village
  - **Important: limited number of surveys to avoid a survey effect!**

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Epidemiology Study: Sample size calculation

- **Principal indicator of PCR prevalence**
  - Estimated to be 5% in this region (based on previous data)

- **Detection of a <u>minimum of 40% decrease</u> in PCR prevalence by the additional use of repellent.**

- **Power of 80%, coefficient of variation between clusters k = 0.5**

$\Rightarrow$

According to Hayes and Bennett (1999): 50 villages needed per arm with 50 persons per village for follow-up.

Taking into account 30% loss in follow-up $\rightarrow$ 3,100 persons per arm needed

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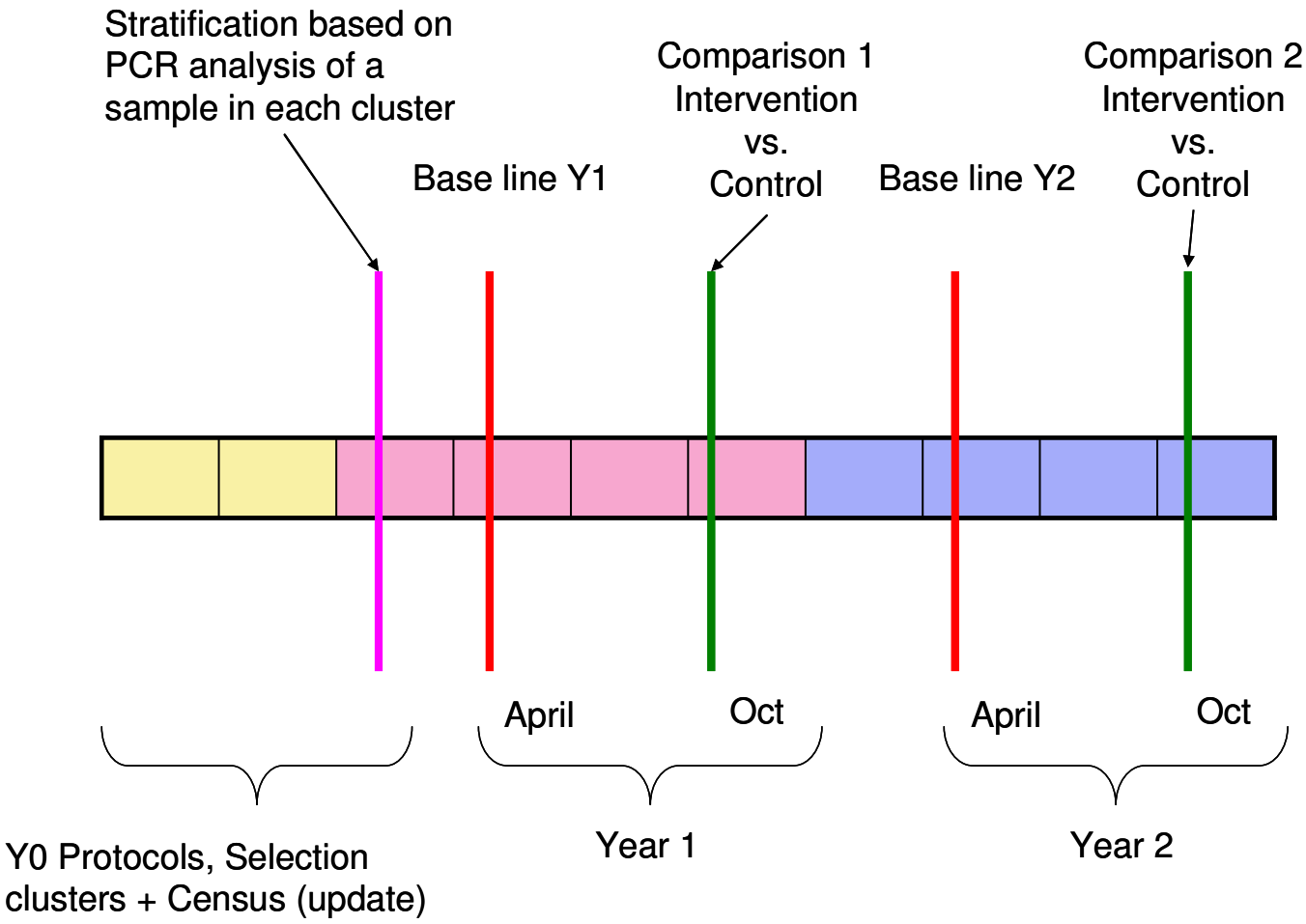
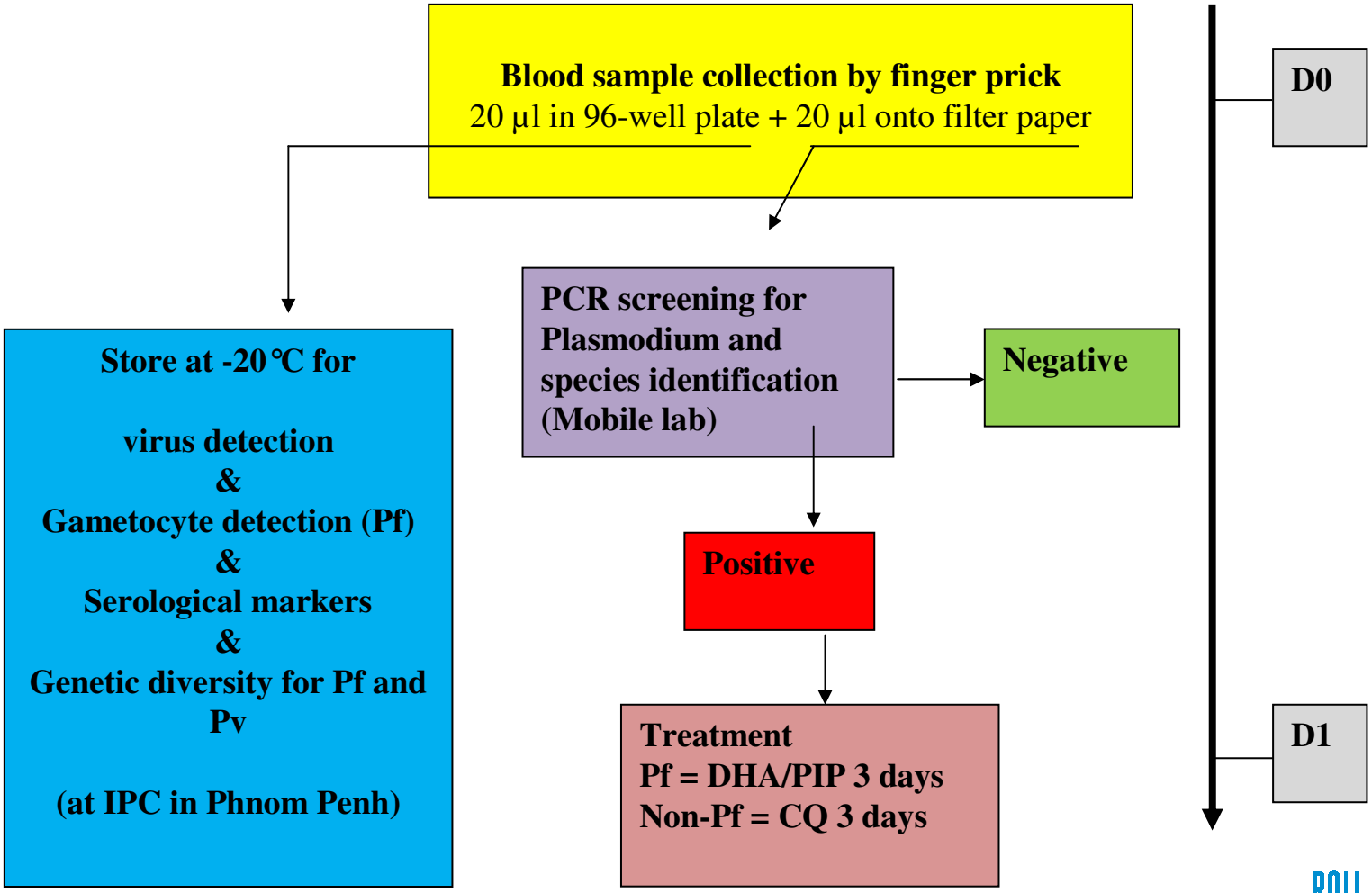
Timeline Epidemiology Study



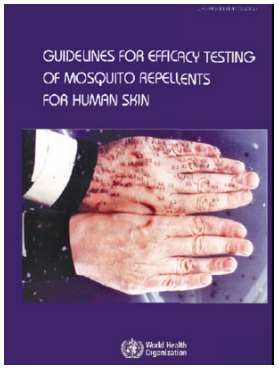
Epidemiology Study: algorithm for diagnostic testing and treatment



Entomological studies

1. DURING THE TRIAL: perform an entomological evaluation of the **mass effect of repellents** on residual/outdoor malaria transmission in the communities.

2. Estimate the **individual protective efficacy** of the used repellent on wild mosquito populations in controlled studies (outside the trial region).



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Social Science Study: Methods

Objective: To assess the acceptability, adherence and adequacy of topical repellents

Mixed methods social science study, including:

- Qualitative **data from ethnographic field research**
- Quantitative **survey data using a pre-coded questionnaire designed to allow for further quantification and testing of hypotheses.**

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Mosquito repellents