

Elimination of a Primary Filariasis Vector Population at an Endemic Field Site

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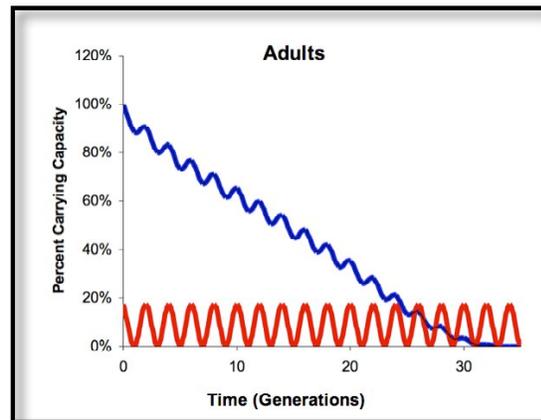
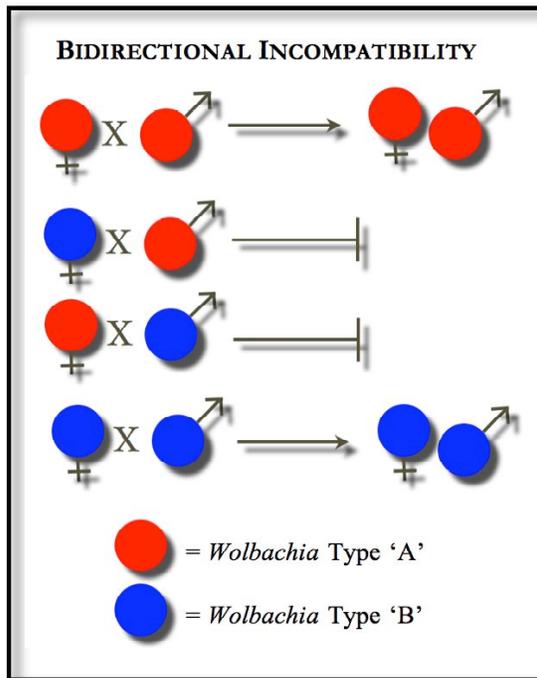
Lymphatic filariasis (Elephantiasis) affects over 120 million people in 80 countries, with 1.2 billion people at risk worldwide. Over 90% of infections are caused by *Wuchereria bancrofti*, for which humans are the exclusive host. The absence of a nonhuman reservoir has prompted an elimination strategy premised upon the hypothesis that transmission can be interrupted by elimination of the microfilariae reservoir via community-wide treatment (Mass Drug Administration, MDA), which is the current focus of the Global Programme for the Elimination of Lymphatic Filariasis. While MDA strategies can be effective, history suggests that elimination of lymphatic filariasis in Polynesia is unachievable without vector control. An example is provided by Maupiti in French Polynesia, where filariasis persists despite decades of constant MDA. The biology of the primary mosquito vector, *Aedes polynesiensis*, has been hypothesized as a primary cause for the lack of MDA success. Since mosquitoes are obligate vectors of *W. bancrofti*, this suggests an additional approach for filariasis elimination: removal of the mosquito vectors will break the disease transmission cycle. Unfortunately *Ae. polynesiensis* currently cannot be controlled, much less eliminated.

A novel strategy will be described in which releases of male *Ae. polynesiensis* mosquitoes infected with Wolbachia bacteria result in the sterilization of female mosquitoes at a site endemic for filariasis transmission. Wolbachia are maternally inherited, obligate, intracellular bacteria that naturally infect *Ae. polynesiensis*, other mosquito species, and an estimated >20% of insects. Through a mechanism known as 'cytoplasmic incompatibility' (CI), Wolbachia bacteria promote infection spread into mosquito populations by sterilizing female mosquitoes that lack the infection. In natural populations, CI-induced sterility is a transient event, since CI does not occur following Wolbachia invasion and once the population is uniformly infected. In the proposed strategy however, the occurrence of CI-induced sterility will be artificially prolonged by releasing males only. Since Wolbachia is only transmitted through females, the infection does not establish in the field, and the CI-induced sterility persists. By repeating a constant level of male releases, an increasing impact (i.e., Wolbachia-induced sterility) on the *Ae. polynesiensis* population is predicted, resulting in the elimination of the targeted mosquito population. It is emphasized that male mosquitoes do NOT blood feed and therefore are not disease vectors. Furthermore, the proposed strategy employs a naturally occurring bacteria infection and does NOT include genetically modified organisms. The geography of Polynesia will simplify an elimination approach by reducing problems of vector reinfestation via immigration.

Existing data will be presented, describing the generation of the Wolbachia-infected *Ae. polynesiensis* strain and lab assays demonstrating male competitiveness and an ability to sterilize female *Ae. polynesiensis* mosquitoes. A research plan will also be presented,

describing laboratory and field cage tests of the elimination strategy, followed by field trials in which an *Ae. polynesiensis* population is eliminated from an endemic focus of filariasis. Additional planned experiments include the characterization of the targeted field site prior to, during, and following the field trial. Prior to the field trial, experiments will compare the release strain and field population in their fitness, population dynamics and genetic structure, mating competitiveness, and vector competency. An economic model for transitioning from field trials to a vector elimination campaign will also be discussed, emphasizing the economic feasibility of an elimination campaign relative to ongoing vector control in Polynesia. This research is funded through a grant [R01AI067434] from NIH/NIAID.

Relevant to the Workshop, the proposed field trials will provide important risk- and cost-assessment information relevant for future bio-control and transgenic strategies, including: determining appropriate release ratios, estimating the migration and competitiveness of released mosquitoes, monitoring for an unexpected negative ecological impact and assessing the hypothesized beneficial epidemiological impact (i.e., elimination of lymphatic filariasis transmission) resulting from vector population modification. Successful elimination will provide rationale for extending the strategy to a broader geographic range and additional insect species that act as pests and disease vectors.



Predicted elimination of natural mosquito population (blue line, above) resulting from the repeated release of bidirectionally incompatible males (red line, above). Cross pattern of bidirectional cytoplasmic incompatibility is shown in the figure to the left.