The Design of a Phase 2 Malaria Vaccine Trial
Based on a Cohort Study

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Abstract

INTRODUCTION: With multiple vaccines targeting blood stage antigens of malaria under development, we needed efficient methods for Phase 2 trials aimed at demonstrating a biological impact of the vaccine. There are two important factors: 1. packing endpoints that will predict final efficacy in reducing death and severe disease in children 2. trial design that minimizes the number of volunteers required. Using longitudinal data from an endemic population in Mali, we studied several possible clinical, parasitologic and combination endpoints.

METHODS: We assume that the differences in endpoints between 4 year old control subjects and 4 year old vaccinated subjects are similar to the observed differences between non-vaccinated 4 year olds and 4 year olds from a longitudinal study in Donégouébugou, Mali. Children had weekly visits with monthly blood samples, with additional unscheduled visits when malaria symptoms were present. Children with malaria symptoms had axillary temperatures measured immediately and if positive, were treated. Sample size calculations were done by: 1) only using data from children close to the target ages and using the associated means and variances in standard sample size formulas, or 2) fitting the whole data set to a mathematical model of age related responses. We calculated bootstrap confidence intervals on the sample size estimates using the calculated means at each age group.

RESULTS: The data come from a longitudinal study in Donégouébugou, Mali, which is a rural village 30 km northeast of Bamako with approximately 1200 inhabitants. Preliminary Cohort Study Design: Children were treated with either sulfadoxine-pyrimethamine (uncomplicated malaria) or parenteral quinine (severe malaria) if smear-positive. Children were followed after treatment to ensure an adequate response, and thick films were performed at some but not all follow-up visits. Each time that capillary blood was obtained for a malaria film, the axillary temperature was taken. Malaria thick blood films were stained with Giemsa and parasitemia was determined.

Example Data: The above graphs represent sample data from 4 individuals. Solid dots by the x-axis are parasitemia levels, open circles by the right axis are hemoglobin levels. T-treated, B-control, H-hemoglobin.