Serological Markers as Efficient Endpoints for Vector Control Trials: A Mechanistic Modeling Framework for Comparative Evaluation with Clinical and Entomological Endpoints

Peiyu Liu, Matt Hitchings, Libin Rong, Derek Cummings

Abstract

The evaluation of vector control interventions through randomized trials is often constrained by large sample sizes necessitated by low and heterogeneous incidence of infection-based or clinical endpoints. Antibodies to mosquito salivary proteins (MSPs) have emerged as a promising marker of exposure to mosquito bites, but their properties as a trial endpoint are not fully understood. To address this gap, we develop a mechanistic modeling framework to describe the dynamics of MSPs in response to biting, and directly compare the power of serological, clinical, and entomological trial endpoints. We construct a novel stochastic process model for anti-MSP antibody dynamics—the Antibody Non-Homogeneous Poisson Process (ANPP) model—that explicitly incorporates seasonal exposure and inter-individual heterogeneity. This model is then coupled with a temperature-driven SEIR–SEI transmission model to create a unified simulation environment. Within this framework, we conduct a systematic comparison of the sample sizes required for each endpoint under various simulated vector control strategies. The results demonstrate a pronounced efficiency hierarchy, with the serological endpoint reducing sample size requirements by up to several orders of magnitude compared to the clinical endpoint, particularly when disease incidence is low. These findings establish a quantitative foundation for the design of vector control trials using serological markers and suggest that their adoption could accelerate the evaluation pipeline for novel public health interventions.

Keywords: mosquito salivary proteins; mosquito bites; vector-borne diseases; clinical trials design and analysis; statistical and mathematical mechanistic modeling;

1 Introduction

Arboviral diseases such as dengue, Zika, and chikungunya pose a growing threat to global public health, driven largely by the widespread distribution and urban adaptation of *Aedes aegypti* mosquitoes [1–6]. Historically, due to the lack of available vaccines for these pathogens, vector control has remained the cornerstone of prevention efforts [7–13]. However, rigorously evaluating the efficacy of vector control interventions is methodologically challenging. Randomized controlled trials (RCTs)—the gold standard for evidence-based public health—have traditionally relied on clinical endpoints such as symptomatic infection; yet, because clinical cases are relatively rare events, with large inapparent fractions and strong seasonal forcing, such trials are often large, lengthy, and costly [14, 15].

Alternative trial endpoints have been explored to address these challenges. Entomological measures (e.g., adult density and biting/feeding frequency) provide an assessment of vector population suppression but do not directly measure human biting rates that are more relevant to public health burden[16, 17]. More recently, serological biomarkers of vector exposure—particularly antibodies against mosquito salivary proteins (MSPs)—have emerged as promising candidates [18, 19]. Immunoglobulin G (IgG) responses to MSPs have been shown to correlate with entomological indices and reflect seasonal variation in mosquito abundance across diverse epidemiological settings [20–29] . Because mosquito bites are far more frequent than clinical infections, MSP antibody responses offer a potentially sensitive and timely measure of intervention impact[30–35].

Despite this promise, the statistical efficiency of MSP-based endpoints in randomized trials has not been rigorously quantified. Immunological research underscores the mechanistic complexity of salivary exposure and host responses, revealing non-linear kinetics and substantial heterogeneity that demand principled, process-based analytical models [36–38]. Yet, existing quantitative studies have largely relied on correlational approaches that cannot capture this underlying stochasticity and dynamism [19, 39, 40]. As a result, the potential gains in trial efficiency afforded by serological endpoints remain undefined, hindering their adoption in pivotal field trials and regulatory decision-making.