I. RESEARCH PROJECT SUMMARY

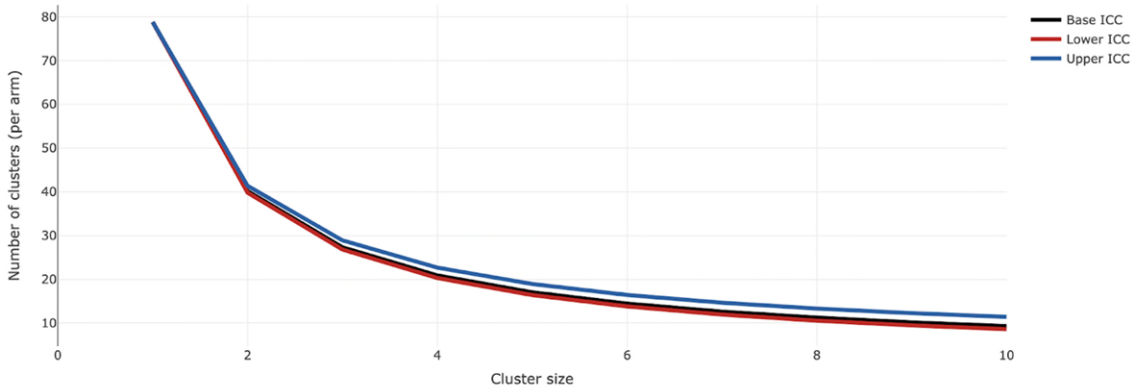
IMPLEMENTATION OF A CULTURALLY TAILORED DECENTRALIZATION PROGRAMME FOR TREATMENT OF SNAKEBITES IN INDIGENOUS COMMUNITIES IN THE BRAZILIAN AMAZON

Principal investigator: Wuelton Monteiro, PhD
Institution: Fundação de Medicina Tropical Dr. Heitor Vieira Dourado, Manaus
Type of research award: Research Grant
Country: Brazil
Duration in months: 48 months

REPRODUCIBILITY AND STATISTICAL DESIGN

Aim 2 is a cluster randomized trial. The clusters are the community health centers (CHCs) and the sampling unit within a cluster is snakebite envenoming (SBE) patients at their encounter with the health care system. Our sample size estimation assumes 90% power and 5% significance to identify a difference in the proportion of cases with delayed presentation to care (>6 hours). Preliminary data suggests more than 30% of indigenous SBE patients in the state of Amazonas arrive late to care. We anticipate a 20% difference, with 10% of delayed cases only in the intervention arm. A total of ten clusters per arm will be randomized. An average cluster size of eight participants per cluster, assuming a plausible intra-cluster correlation of 0.03 (CI 95% 0.01;0.05) reported elsewhere in public health bases cluster trials. We expect to enroll 80 participants per arm, with additional 20% inflation for loss to follow-up, totaling 96 participants per arm (n=192). This sample size is calculated to test the primary implementation hypothesis that randomization to the intervention arm will result in lower time from SBE to antivenom care upon health system encounter relative to those in the control arm. This sample is also sufficient to identify a difference in patient functionality of 1.5 points (SD 3.4) on the patient functionality scale used in SBE clinical trials in the United States. A minimal clinical important difference of one point in the patient functionality scale is considered a conservative, significant result. Given the cRCT design, over-sampling of clusters is vital as the loss of a single cluster due to unforeseen reasons would compromise the rigor. As a real-world, pragmatic trial, we erred on the conservative

side.



We calculated our sample size based on the methodology proposed by Hooper et al. (2016), using the open access shiny web application proposed by Hemming et al. 2020. Our parameters were: seven clusters per arm, an ICC of 0.03 (0.01;0.05), a coefficient of variation of 0.05, a cluster auto-correlation of 0.8, and an individual auto-correlation of 0.8. We powered our study to (a) estimate the difference in the time to uptake of antivenom of 20% for the intervention arm, compared to the control arm (with a 30% prevalence of delayed care for the control arm). We also evaluated the power to estimate a reduction in the patient reported functionality of 1.5 (SD 3.4) points in the Patient Specific Functionality Scale (PSFS). Figure 1 and 2 describe the power for the study for each cluster size. Our proposed sample size of eight participants per cluster would yield, for seven clusters per arm, a power of 0.87 (0.81;0.93) for our binary outcomes and a power of 0.92 (0.88;0.95) for the continuous outcomes. We also anticipate enrolling 10 clusters per arm to ensure we will not be underpowered in case a cluster needs to drop out during the study.

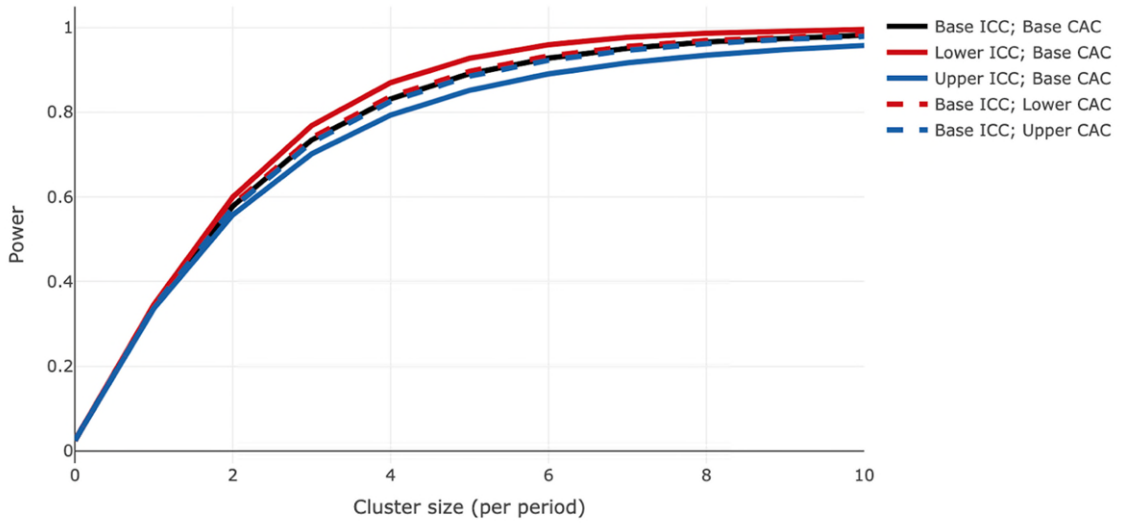


Figure 1. Power calculations by cluster size for the comparison of the binary indicator of delayed uptake of antivenom.

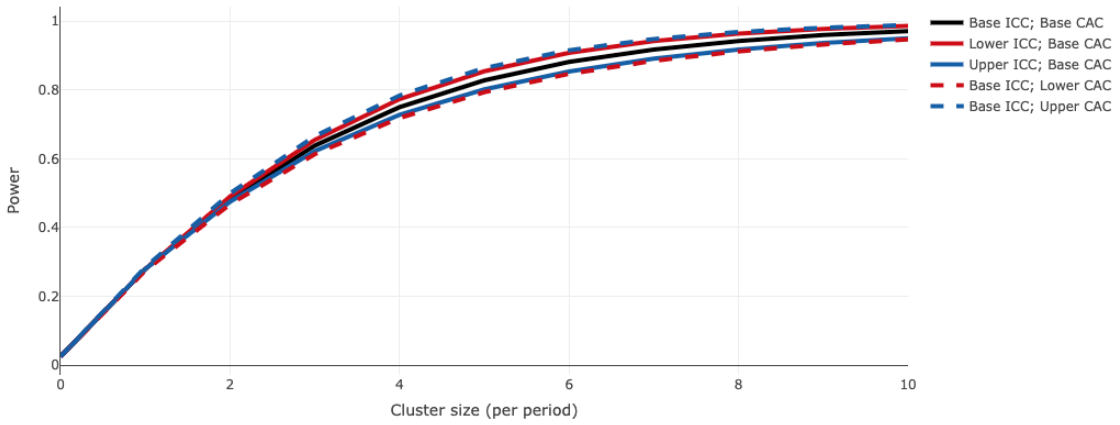


Figure 2. Power calculating by cluster size for the comparison of the continuous outcome of functionality score.

For **Aim 3**, we will collect secondary state-level data to conduct our pre-post comparison analysis. We expect to identify a large volume of data with more than 2000 cases per year. Thus, we will have enough variation to detect significant changes in the time series. We will collect full cycles of 12 months to account for seasonal variability, with at least three time points after the intervention.

Data analysis: ***Quantitative data analysis.*** We will use an intention-to-treat design with a generalized estimating equations (GEE) model to estimate the intervention effect at patient enrollment, when the time from injury to antivenom care will be acquired, and at 14 days when patient functionality will be collected. A linear identity-link will be used with an assumed continuous distribution for the co-primary outcomes and secondary outcomes that fit the distribution. A log-link will be used with an assumed binomial distribution for the secondary outcome that fits the assumption to obtain risk ratios. Models will include an exchangeable correlation structure to account for the correlation of outcomes among SBE patients within the same cluster. We will also use Kauermann-Carroll bias-corrected variances to account for the relatively small number of clusters in our study. To ensure the rigor and validity of the effect estimates, we will include any additional baseline covariates that predict missing outcome data or which are imbalanced across arms at baseline in the statistical model. All variables used in the constrained randomization will be included in the primary statistical models. In

addition, we will perform sensitivity analyses using multiple imputation to assess robustness of our findings to different response patterns, using covariates hypothesized to influence missingness in the imputation model. *Mediation and moderation analysis:* Mediation analysis will be conducted to evaluate the theoretical assumptions that SBE severity, sex (as a biological variable), age, ethnicity, race, and fidelity might individually influence the effect of the intervention on outcomes and the extent to which of these individual variables mediate the effect, conditional on the presence of other mediators in the model. A set of structural equation modeling (SEM) will be fit to evaluate the direct and indirect (mediated) effects. The indirect effect of the intervention on outcomes via each individual mediator will be the product of the path from intervention to mediator and the path from mediator to outcome, with a bootstrapping correction that has shown to improve the rigor of this approach. The impact of all mediators included in the model will be expressed as the total indirect effect of intervention outcome. ***Qualitative data analysis.*** Qualitative data will be analyzed through inductive content analysis, identifying emerging themes for each phase of intervention development. Two investigators, at least one being native to Brazil, will conduct the content analysis independently and cross-validate the results by comparison. In cases where consensus is not reached, an MPI will evaluate the content to reach agreement. Analysis will be conducted via Nvivo software.