Supplementary Material – Simulation and Power Calculation Details

Data were simulated using the simstudy package in R.[1]

Data Generation

Villages

From the mean cluster size plus the minimum and maximum cluster sizes, an estimate for the cluster size coefficient of variation (cv) was generated using the standard deviation approximation from the minimum and maximum, which has been previously described.[2]

Cluster level cv:

$$S_M \approx \frac{M_{(n)} - M_{(1)}}{4}$$

$$S_M \approx \frac{134 - 39}{4} = 23.75$$

$$cv = \frac{S_M}{\bar{M}}$$

$$cv = \frac{23.75}{95} = 0.25$$

Where $M_{(n)} - M_{(1)}$ are the maximum and minimum of cluster sizes (134 and 39), $\bar{M}$ is the average cluster size (95) and cv is the ratio between the standard deviation of cluster sizes S_M and the mean. Simulating 1000 potential sample sizes from a Normal distribution with mean 95 and variance of 23.75^2, a dataset with similar mean, max, min and cv was selected and fixed for all simulations (intervention village sizes: 70, 88, 127, 112, 98, 81, 123; control village sizes: 98, 118, 37, 95, 83, 109, 78). Furthermore, we assumed that there would be no change in sample size between year one and two. We

also assumed that the addition of newborn children would be offset by the exit of children who were too old to be followed. Lastly, the purpose of this work was to inform the approach to the analysis of RIMAMAL II and CRTs that have a small number of clusters in which the number of participants in each cluster is not random (e.g., fixed by the size of the villages in RIMADMAL II). In this situation, the analysis will condition on the actual sample sizes of the villages. Simulations that include random variation in the sample size would not reflect the analysis approach and would not correctly characterize the statistical properties of the analysis methods that we compared; leading to the decision to fix sample sizes across simulations.

Outcome Model

Year 1

$$\log(\lambda_{ijk}) = \alpha + \beta_1 X_i + \beta_2 X_{ijk} + u_{ij}$$

Year 2

$$\log(\lambda_{ijk}) = \alpha_2 + \beta_1 X_i + \beta_2 X_{ijk} + u_{ij}$$

The model is specified as follows for subjects k within village j within treatment i : α is the intercept, indicating the rate for the control group with the sex covariate at zero and α_2 refers to the expected reduction in effect for year two; $\beta_1 X_i$ is the binary treatment effect; $\beta_2 X_{ijk}$ is the binary subject level sex covariate; and u_{ij} refers to the random effect where:

$$u_{ij} \sim Normal(0, {\sigma^2}_b)$$

Outcomes were generated using the statistical models above with a Poisson distribution.

<u>Scenarios</u>

The variance for the village random effect was simulated from a Normal distribution with mean 0 and variance of 0.05. Estimates of the village random effect can be generated using the assumption that the standard deviation is approximately equal to the coefficient of variation for cluster rates.[17] Estimates for cluster rate cv in Burkina Faso have been estimated at 0.258,[3] which was used for the power calculation. We elected to use a random effect variance of 0.05 based on observations from previous studies and results from RIMDAMAL I. An evaluation of the rate cv from the year one simulations yielded an average cv of 0.2415.

Single period outcomes were generated from changes in the random effect variance (σ^2_b = 0.05, 0.10), the addition of a sex covariate, the year of the study, distribution (Poisson), the number of clusters (6, 10, 14, 18) and treatment assignment (parallel and crossover). For the two-year analyses, the year one and year two simulated results were merged to generate one data set with the expected reduction in year two serving as a period effect. The treatment effect was assigned to the same clusters with fixed sample sizes for all simulations; a crossover effect assigned the treatment in year two to the clusters not receiving the treatment in year one. Null models with the treatment effect set to zero were also generated for all scenarios listed previously. The random effect variance was the same for each village across years one and two, regardless of parallel or crossover design but changed for each of the 1000 simulations.

<u>Treatment Effects:</u>

- Expected: Treatment 0.619 cases per child per year; Control 1.088 cases per child per year. Simulated Effect = ln(0.619/1.088) = -0.56399. Rate Ratio = 0.5689

- Rate Ratio 60: Treatment 0.6528 cases per child per year; Control 1.088 cases per child per year. Simulated Effect = ln(0.6528/1.088) = -0.5108. Rate Ratio = 0.60
- Rate Ratio 70: Treatment 0.7616 cases per child per year; Control 1.088 cases per child per year. Simulated Effect = ln(0.7616/1.088) = -0.35667. Rate Ratio = 0.70
- Rate Ratio 80: Treatment 0.8704 cases per child per year; Control 1.088 cases per child per year. Simulated Effect = ln(0.8704/1.088) = -0.2231. Rate Ratio = 0.80
- Rate Ratio 90: Treatment 0.9792 cases per child per year; Control 1.088 cases per child per year. Simulated Effect = ln(0.9792/1.088) = -0.10536. Rate Ratio = 0.9
- Rate Ratio 1: Null Model, no treatment effect. Simulated Effect = ln(1.088/1.088) = 0. Rate Ratio = 1

<u>Sample Sizes</u>

- 6 Clusters – 576 subjects
    - intervention: 70, 88, 127
    - control: 112, 98, 81
- 10 Clusters – 952 subjects
    - intervention: 70, 88, 127, 112, 98
    - control: 81, 123, 98, 118, 37
- 14 Clusters – 1317 subjects
    - intervention: 70, 88, 127, 112, 98, 81, 123
    - control: 98, 118, 37, 95, 83, 109, 78
- 18 Clusters – 1593 subjects
    - intervention: 38, 62, 56, 120, 70, 88, 127, 112, 98
    - control: 81, 123, 98,118, 37, 95, 83,109, 78

Outcomes Reported

- Bias: Average difference between observed treatment effect and simulated effect
- Coverage: Proportion of times the 95% confidence interval for each simulated dataset contains the simulated effect out of 1000 simulated datasets.
- Power: Proportion of times the treatment effect was significant at the 0.05 alpha level out of 1000 simulated datasets
- Type-I Error: Proportion of times the null model yielded a significant treatment effect (two-way).

Power Calculation Details

Calculated from the previously described sample size calculation.[4]

Cluster rate cv: 0.25

Lambda (control): 1.088

Lambda (intervention): 0.619

Number of children in each cluster: 95

One-sided alpha Z score: 1.96

Number of clusters per arm: 7

Results:

Beta Z score: 1.12

Power: 86.9%

References

1. Keith Goldfeld. simstudy: Simulation of Study Data. 2019. https://CRAN.R-project.org/package=simstudy (28 July 2020, date last accessed)

2. Eldridge SM, Ashby D and Kerry S. Sample size for cluster randomized trials: effect of coefficient of variation of cluster size and analysis method. *Int J Epidemiol* 2006; 35: 1292-1300.

3. Tiono AB, Ouedraogo A, Ogutu B, et al. A controlled, parallel, cluster-randomized trial of community-wide screening and treatment of asymptomatic carriers of Plasmodium falciparum in Burkina Faso. *Malar J* 2013; 12: 79.

4. Hayes RJ and Bennett S. Simple sample size calculation for cluster-randomized trials. *Int J Epidemiol* 1999; 28: 319-326.

Previously cited in main text:

17. Bennett S, Parpia T, Hayes R, et al. Methods for the analysis of incidence rates in cluster randomized trials. *Int J Epidemiol* 2002; 31: 839-846.