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Dear Editors: April 24, 2021

I am pleased to submit the enclosed original research manuscript, “*Aggregation of* Schistosoma haematobium *increases under intense control efforts, potentially complicating schistosomiasis elimination*,” for your consideration for *PLoS Neglected Tropical Diseases*. The research represents, to our knowledge, the first attempt to characterize the aggregation of a human parasite of international global health importance in an elimination setting. As elimination of schistosomiasis and other helminthiases becomes more feasible, understanding the distribution of parasites among human hosts will be essential to maintaining progress towards elimination of schistosomiasis and other helminthiases. We use data from the Zanzibar Elimination of Schistosomiasis Transmission (ZEST) community randomized trial to make three main contributions:

1. We use nearly 30,000 individual measurements of human urinary schistosomiasis egg burden to derive estimates of community mean egg burden and aggregation. Using generalized estimating equations, we use these community-level measures to estimate changes in egg aggregation as a function of egg burden. We find a significant increase in aggregation associated with decreasing egg burden.
2. We derive a novel data-generating mechanism relating parasite acquisition to measured egg burdens. Previous models assume individual male and female parasites are acquired from the same negative binomial distribution, giving rise to observed negative binomially distributed egg burdens, but this assumption is found to be inaccurate approaching elimination. By incorporating prior estimates of the distribution of individual susceptibility to schistosome infection, we propose a model that explicitly accounts for individual heterogeneity in susceptibility and exposure. Using approximate Bayesian computation to estimate the best fitting model that reproduces observed egg burdens from the ZEST data, we find that this mechanistic model performs best.
3. As part of the approximate Bayesian computation procedure, we estimate the mating probability, a key determinant of schistosomiasis transmission breakpoints and thus elimination feasibility, for every community. We find that analytic estimates of the mating probability, even allowing for increasing aggregation approaching elimination, sometimes underestimate the mating probability. Because higher mating probabilities will lead to higher breakpoints, this finding could have profound implications for achieving schistosomiasis elimination.

Given the importance of schistosomiasis as the second most debilitating human parasitic infection globally, this research will be of mutual interest to policymakers, epidemiologists, and disease ecologists engaged in public health research. This manuscript has not been and will not be submitted elsewhere pending your publication decision. We know of no relationships or funding sources that might be perceived as a conflict of interest on the part of any of the co-authors.

Sincerely yours,

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