Parasite aggregation increases under intense control efforts, complicating helminthiases elimination

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## Abstract

# Background

Decades of mass drug administration (MDA) have drastically reduced the prevalence and burden of neglected tropical diseases, particularly helminthiases including schistosomiasis, onchocerciasis, lymphatic filariasis (LF), and soil transmitted helminths (STHs). National control programs supported by organizations such as the Gates Foundation and World Health Organization and drug companies which donate necessary drugs for treatment, have made substantial progress reducing the burden of helminthiases. [1] More recently, the global conversation has shifted towards elimination. China, for instance, has made substantial progress towards elimination of schistosomiasis with an integrated control approach that utilizes MDA in addition to environmental and behavioral controls. [2–4] Globally, progress towards elimination is mixed and many areas of sub-Saharan Africa where the vast majority of schistosomiasis and other helminthiases occur have struggled to achieve transmission control and progress towards elimination.

Under sufficient coverage and frequency, elimination using MDA alone is believed to be possible in low and moderate transmission settings. [5] From a practical standpoint, achieving these necessary treatment conditions is challenging due to the programmatic limitations of many control campaigns. School-based interventions, for instance, are often the primary method of drug delivery in communities since they are straightforward to implement and reach school-aged children, who are widely considered the most vulnerable and most heavily infected segment of the population. However, school-based strategies, and even those that seek to reach all members of the broader community, often miss infected individuals that contribute to transmission. [6,7]

Because of this, control efforts are likely to have profound implications for parasite aggregation: the distribution of parasites among the human host population. While the dynamics of parasite burden following MDA and other interventions have been studied extensively, the corresponding dynamics of aggregation are largely unexplored. Aggregation is measured by the aggregation parameter, (also frequently referred to as “dispersion parameter”) of a negative binomial distribution. While is often considered constant in models and other forward-looking analyses of control efforts, there is reason to believe that it is itself a dynamic variable that is positively correlated with transmission intensity. More transmission leads to less-skewed distributions of infection, while reductions in transmission from interventions such as MDA lead to more skewed distributions in which fewer individuals host larger proportions of the total parasite population. Individuals that remain infected in these scenarios may be those who miss treatment, are heavily exposed, are particularly susceptible to infection, or have parasite strains that are resistant to treatment. [8–12]

Aggregation dynamics approaching elimination are important from a number of practical and theoretical vantages. As parasite burden is reduced, so too is the number of individuals contributing to and sustaining transmission—a realization of the “20/80 rule” in which 20% of individuals contribute 80% of the transmission potential. [8] Identifying and treating these individuals is complicated by systematic non-adherence to treatment, treatment failures, and insensitive diagnostics, but will be essential to achieving elimination. [8,13–15] A better understanding of aggregation dynamics could aid the planning and implementation of surveillance and control efforts in low transmission and elimination settings. [13]

From a theoretical standpoint, the conditions under which MDA alone can achieve elimination is dependent on reducing the parasite population below its breakpoint. Breakpoints in helminth transmission are expected to arise from mate limitation in low transmission settings whereby the probability of individuals being infected with fecund worms decreases as parasite burden and transmission decrease. Mate limitation in helminth populations is generally quantified in terms of the probability that a given female parasite in a population is successfully mated, , which is estimated as a function of the mean parasite burden, , and aggregation parameter, . [16,17] In endemic settings, parasite distributions among a population of definitive human hosts are well-represented by a negative binomial distribution with below 1. This implies a heavily right-skewed distribution in which most parasites are aggregated in a few human hosts.

For constant aggregation parameter, , in the range as has been widely observed previously, as , giving rise to the hypothesized breakpoint below which worm mating becomes insufficient to sustain transmission. [18] As transmission decreases, the response of the aggregation parameter could have profound implications for the breakpoint. For instance, if as , implying increasingly skewed distributions that can be realistically interpreted as all parasites being harbored by one individual, remains large and the breakpoint is vanishingly small. [17] However, derivations of the mating probability based on the negative binomial distribution of adult parasites are derived from endemic settings, and stochasticity in worm acquisition at low transmission intensities is likely to play an increasingly important role on the distribution of adult parasites as elimination is approached. [16,17] This raises doubt as to whether analytic estimates of the mating probability and breakpoint, which rely on an assumption of negative binomially distributed parasites, are reliable in elimination settings.

Here, we examine evidence for dynamic aggregation from the Zanzibar Elimination of Schistosomiasis Transmission (ZEST) study, a randomized control trial with the aim of eliminating schistosomiasis as a public health problem and halting schistosomiasis transmission on the two main islands of the Zanzibar archipelago off the coast of Tanzania. [19,20] We revisit classic assumptions of how adult schistosomes are distributed among human hosts and propose a novel, mechanistic data-generating process for worm acquisition and resulting mating dynamics. We then explore how these assumptions and underlying data-generating processes affect estimation of the mating probability and discuss implications for ongoing control and elimination efforts for schistosomiasis and other helminthiases.

# Methods

## Data

The ZEST project enrolled 45 administrative regions called shehias on the island of Pemba with the goal of eliminating urogenital schistosomiasis as a public health problem (defined as reducing the prevalence of heavy infections below ) and 45 Shehias on the island of Unguja with the goal of interrupting *S. haematobium* transmission (defined as reducing the number of incident cases to zero). [19,20] On each island, shehias were randomly assigned to receive biannual MDA, biannual MDA plus snail control, or biannual MDA plus a behavioral intervention. [20–22] Cross-sectional parasitological surveys were conducted annually from 2012-2017 in each shehia. Data used here were acquired via a formal data request to the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) and are comprised of 27,626 observations of parasite burden among adults and 75,039 observations of parasite burden among school-aged children, each measured as *S. haematobium* eggs per 10mL urine.

## Aggregation dynamics from observed egg burdens

The likelihood of the inverse negative binomial aggregation parameter, , and mean community egg burden, , can be estimated for each shehia, , and year, , from individual, , egg counts, , as:

While aggregation is most frequently reported and discussed in terms of , its inverse, has more desirable properties for statistical estimation and inference (see e.g. [23]). Therefore results are presented in terms of following trivial transformation from estimates derived using .

The maximum likelihood estimate of is simply the empirical mean of individual egg counts, and maximum likelihood estimates of were estimated using the Brent method within the optim function in R. [24] Uncertainty in estimates of were derived from the Hessian matrix. Both and were estimated among the adult (A), child (C), and total (T) populations in each shehia-year.

Weighted generalized estimating equations (GEE) with unstructured correlation matrices of the form:

were used to estimate the relationship between aggregation and parasite burden. Weights were assigned as the inverse of the standard error of . Models stratifying by population (child, adult, or total), by intervention type (MDA only, behavioral, or snail control), and by island (Pemba or Unguja) were also estimated. Results are reported for each stratum as the change in associated with an interquartile range increase in mean egg burden, . Clustered nonparametric bootstrapping was used to estimate uncertainty in estimates of with bootstrapped samples at the shehia level.

## Estimating parasite burden and aggregation

Because egg counts are an indirect estimate of parasite burden, are prone to undercounts at low burdens, and may change non-linearly with parasite burden [25], we next seek to determine if changes in aggregation as measured by egg counts are indicative of changes in aggregation of the adult parasite population. We use approximate Bayesian computation (ABC) to estimate mean community parasite burden and aggregation, denoted and , respectively, under four proposed data-generating mechanisms, (described below). Briefly, ABC proceeds by: 1) sampling parameter sets from a prior distribution, ; 2) simulating datasets, , from the priors under the given data generating mechanism; 3) deriving summary statistics, , from the generated data to compare to the observed data, ; 4) generating distance metrics, , to assess the fit of the generated data to the observed data; and 5) accepting parameter sets that fall within a provided distance tolerance. [25] The accepted parameter sets thus represent an approximation of the posterior distribution of , but the estimation procedure does not require exact calculation of the likelihood of every proposed prior. Here, ABC was preferred to MCMC methods due to the number of estimates needed combined with the complexity of the likelihood function of the parasite population estimated from observed egg counts (see e.g. [26,27]).

The four data-generating mechanisms considered correspond to the “distributed together” and “distributed separately” assumptions (Cases 1 and 2) from Robert May’s seminal work on schistosome mating dynamics [16]; a mechanistic model (termed Case 3) that considers susceptibility and exposure as independent parameters; and a hybrid of Case 1 and 2 (termed Case 4) in which a proportion of parasites are distributed together while the remaining parasites are distributed separately.

Prior parameter distributions and data generating processes that connect simulated worm burdens to egg counts are delineated in Table 1. Briefly, Case 1 assumes worms are distributed among human hosts according to a single negative binomial distribution with 1:1 sex ratio. Case 2 assumes male, , and female, , worms are distributed according to separate negative binomial distributions, each with mean . Case 4 relies on a partitioning parameter, , drawn from a standard uniform prior which determines the proportion of total worm burden that follows a Case 1 “together” distribution with the remaining () portion of the total worm burden following a Case 2 “separate” distribution.

Case 3 is mechanistic in that it considers susceptibility and exposure as distinct processes with independent distributions. It assumes susceptibility, , interpreted as the probability a given cercarial exposure will result in an adult worm, follows a gamma distribution, and cercarial exposures follow a negative binomial distribution independent of susceptibility. Worm pairing in individual hosts is then determined from a hypergeometric distribution that incorporates individual susceptibility, cercarial exposure, and 1:1 sex ratio among cercarial exposures (Table 1). The susceptibility distribution parameters are fixed, with parameters derived from previous work on *S. japonicum* [11,12], such that Case 3 estimation is based on the same number of parameters as Case 1 and 2, and estimates of the mean worm burden and aggregation parameter can be estimated from the expectation and combined variances of the Case 3 susceptibility and exposure parameters.

The number of eggs shed per mated worm pair per day is assumed to follow a negative binomial distribution with mean and dispersion for all four cases (Table 1). Additionally, egg output from mated pairs is affected by density dependent fecundity (DDF) as described previously [CITEs]. The DDF parameter , and the egg shedding parameters and are fixed across all data-generating mechanisms (Table 1).

Summary statistics used in ABC to compare the observed and simulated datasets consist of the mean community egg burden, ; standard error of individual egg counts, ; and an adjusted egg-prevalence measure—the number of egg positive individuals squared over the number of individuals—for every shehia-year in which at least one individual had an egg count . The distribution of this adjusted prevalence measure—as opposed to the prevalence (bounded between 0 and 1) or raw number of individuals infected (an integer)—leads to more stable ABC estimates. We used the default standardized distance metric in the R package ABC [28] to compare the observed summary statistics, , to simulation summary statistics,, derived from simulated datasets for each data-generating Case in each eligible shehia-year. The parameter sets with the smallest estimated distance for each simulation (e.g. tolerance of ) were accepted. These accepted parameter sets were weighted based on their distance from the observed data to derive estimates of the posterior distributions of .

## Parasite aggregation dynamics and implications for mating probability

Posterior predictive checks were performed to assess the ability of posterior parameter sets of each data-generating Case to emulate observed data from ZEST. For each data-generating Case and each eligible shehia-year, weighted draws from the posterior distribution, , were used to simulate community-wide egg burdens as delineated in Table 1. These egg burdens were then summarized using the same summary statistics as used in ABC estimation and compared to the observed summary statistics values visually and via the mean squared error between the distribution median and the observed summary statistics.

Posterior distributions of and were extracted as part of the posterior data generation and input into GEE models of the same form used for egg burdens to estimate the change in parasite aggregation per unit change in parasite burden. Weights for shehia-year observations were derived as the inverse of the sum of the mean squared errors between the observed and median generated summary statistics.

Finally, analytic and simulated estimates of the mating probability were compared to evaluate the influence of dynamic aggregation and assumptions on the underlying data-generating mechanisms. Analytic formulas derived previously [16] for Case 1 together and Case 2 separate assumptions with constant aggregation were used to estimate the mating probability associated with worm burdens in the range . Next, analytic estimates of the mating probability allowing for dynamic aggregation were derived by incorporating as a function of from the marginal estimates of the egg burden GEE, and from the marginal estimates of the worm burden GEEs fitted for each data-generating Case. Simulated estimates of the mating probability for every shehia-year were recorded from posterior as the number of mated worms per worm () in the simulated data.

**Table 1**: Priors and data-generating processes for approximate Bayesian computation estimation of community parasite burden and aggregation. Data generation proceeds by first drawing from the multivariate prior, , containing shehia-year level summaries of parasite burden and aggregation (for Cases 1, 2, and 4) or of individual susceptibility and exposure (for Case 3), then generating individual worm burdens, worm pairs, and finally egg burdens. Summaries of individual egg burdens for each shehia-year are then compared to observed data summaries from ZEST to derive a posterior estimate of model parameters.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Case 1 (Males and females distributed together) | Case 2 (Males and females distributed separately) | | Case 4 (Explicit susceptibility and exposure) | Case 3 (Hybrid together and separate) |
| Priors |  |  | |  |  |
| Fixed Parameters |  |  | | ; |  |
| Worms |  |  | |  |  |
| Pairs |  | | | | |
| Eggs |  | | | | |
| : multivariate prior for data-generating case,  : mean worm burden in shehia, , and year,  : individual, , worm burden in shehia, , and year, , with sex (*m*ale or *f*emale) and distribution assumption (*t*ogether or *s*eparate),  : aggregation parameter in shehia, , and year,  : mean cercarial exposure in shehia, , and year, | | | : shape parameter of gamma-distributed susceptibility,  : rate parameter of gamma-distributed susceptibility,  : mean eggs produced per mated worm pair  : aggregation parameter of negative binomially distributed daily egg release  : density dependent fecundity parameter | | |

All analyses were performed in R version 4.0.2 utilizing the geepack [29], tidyverse [30], and ABC [28] packages. All code and derived data files necessary to reproduce the analysis can be found at <https://github.com/cmhoove14/SchistoDynAgg>.

# Results

There were 93 shehia-years in which no individuals had positive egg counts and 16 shehia-years in which the maximum individual egg count was 1 and therefore variance estimates for could not be derived. This left 447 observations of and , shown in Figure 1A along with the marginal estimate of from the fitted GEE. We estimate a median 0.012 (Bootstrapped IQR: 0.011-0.013) increase in associated with an IQR increase in , implying a negative relationship between mean egg burden and aggregation. This relationship appears to be driven by dynamics in children, as there was weak evidence for a relationship between and among adults (Fig 1B). Egg burden in adults ( 1.36) was substantially lower than in children ( 4.65), however. Shehias receiving the MDA+snail control and MDA+behavior change interventions appeared to have a stronger burden-aggregation relationship (larger , Fig 1B). An additional GEE model including main effects of intervention arm and island showed that reductions in were significantly larger in shehias receiving the MDA+snail control and MDA+behavioral change interventions ( 0.01 and 0.016, respectively).

Chart

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Figure 1: Relationship between community egg burden and aggregation. Panel A shows the scatterplot of all estimates of and where each point is sized according to its weight, derived as the inveerse of the standard error of . Points are also symbolized according to their assigned intervention group—MDA only (▲), MDA+snail control (♦), or MDA+behavioral intervention (■)—and the island of the shehia. The solid black line in panel A represents the marginal estimate of from the fitted GEE. Panel B shows estimates of , the change in aggregation for an interquartile range increase in community egg burden stratified by population, treatment group, and island. The black point and error bars correspond to the unstratified marginal estimate of as in panel A. Error bars correspond to the interquartile range of estimates derived from B=10,000 bootstrapped samples.

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Figure 2: Comparison of observed summary statistics to the median summary statistics generated from 1,000 simulated datasets derived from the ABC posterior distributions for every shehia-year. Colors and right-hand facet labels indicate the data generating Case and the 1:1 line implying perfect agreement between observed and generated data is shown. Posterior predictions from the mechanistic Case 3 data-generating mechanism (row 3, purple) were found to better reproduce the observed data, particularly the adjusted prevalence measure (see annotated means of mean-squared errors across all shehia-years).

Examination of the Bayes factors comparing the posterior probabilities of each Case shows that the mechanistic Case 3 performs better than the canonical Case 1 (mean Bayes factor = 1.97, range 0-12.78), while Case 2 (mean Bayes factor = 0.89, range 0.07-5.98), and the hybrid Case 4 (mean Bayes factor = 0.97, range 0-6.9) generally performed worse than Case 1. Superior performance of Case 3 was further confirmed by examination of the mean squared errors between the generated and observed data, with Case 3 generated data resulting in the lowest MSE across all three summary statistics (Fig 2).

Case 1 and 3 estimates of and exhibited a similar pattern to and , namely increasing aggregation (indicated by decreasing ) with decreasing measures of burden (Fig 1 and Fig 3a and 3c). However, Case 2 and Case 4 estimates showed the opposite effect of decreasing aggregation with decreasing worm burden (Fig 3b and 3d), though it should be noted that these two data-generating cases performed poorly both in terms of the MSE of the summary statistics and the Bayes factor.

This poor performance of Case 2 and 4 prompted further comparisons of Cases 1 and 3. Figure 4 shows that Case 3 estimates of the aggregation parameter were nearly identical to those from Case 1 estimation at high community egg burdens, but diverged at lower burdens. In particular, Case 3 estimates of the aggregation parameter were much lower than those of Case 1.

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Figure 3: Summary of approximate Bayesian computation estimates of community worm burden () and aggregation () for Case 1 (Together, A), Case 2 (Separate, B), Case 3 (Mechanistic, C), and Case 4 (Hybrid, D). Dashed lines depict the marginal estimates of the fitted GEE for each Case: . Axes are log transformed to aid visualization.

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Figure 4: Difference between Case 3 and Case 1 aggregation estimates across mean community egg burdens. At low infection intensities, canonical Case 1 estimates tend to predict higher values of , implying lower aggregation and higher mating probability, than mechanistic Case 3 estimates.

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Figure 5: Comparison of mating probabilities derived analytically and from ABC posterior distributions. Points depict the median mating probability across the median community worm burden from data generated for every shehia-year and Case from ABC posterior distributions. Solid lines depict analytical estimates of the mating probability assuming constant aggregation parameter, , equal to the median across all shehia-year observations. Dotted lines depict analytical estimates of the mating probability assuming aggregation changes as a function of burden according to the fitted egg burden GEE, and dashed lines depict analytical estimates of the mating probability assuming aggregation changes as a function of worm burden according the fitted worm burden GEE for each case (shown in Figure 3). Note that Case 2 analytical mating probability estimates are derived according to the Case 2 (distributed separately) mating probability function from [CITE Anderson], while all others are derived for the canonical Case (distributed together) mating probability function.

Figure 5 shows the mating probability produced from the posterior distributions of all four data-generating cases. These estimates are also compared to analytic predictions of the mating probability for both static aggregation (Fig 5 solid lines) and dynamic aggregation (, , Fig 4 dashed and dotted lines, respectively). These analytic predictions generally align well with Case 1 and Case 3 estimates, but do frequently underestimate the mating probability at low worm burdens.

# Discussion

Here we use data from the ZEST study to explore how parasite aggregation dynamics change as elimination is approached due to intense control efforts. We find that parasite aggregation as measured directly by community egg distributions and through estimation of adult parasite distributions likely increases as elimination is approached. In addition, the classic (Case 1) assumption that male and female parasites are distributed together appears to hold at large mean community worm burdens. However, as proposed previously, this assumption appears to break down at smaller worm burdens as elimination is approached. [16]

The distribution of individual egg counts from ZEST was highly aggregated, with in the range 0.001-0.067. Community egg aggregation was found to significantly decrease as the community worm burden decreased, and this effect was driven by children. As children frequently have the highest exposure and may be most susceptible to infection due to lack of acquired immunity, [28] this is not surprising. We also found that the relationship between the aggregation parameter and mean community egg burden was significantly greater in shehias from the ZEST study that received snail control or behavioral interventions in addition to biannual MDA. This could be driven by higher starting prevalence and burden among these intervention arms, [20] though could also have theoretical underpinnings that will be the topic of future analyses.

We propose a novel, mechanistic data-generating process (Case 3) that explicitly models the interaction of individual susceptibility and exposure to allow the data to determine the most likely distribution of male and female parasites. Using approximate Bayesian computation to estimate mean parasite burdens and parasite aggregation, we find that this Case 3 data-generating process generally provides a better fit to the observed ZEST data. Due to the flexibility and superior fit of the proposed Case 3 mechanism, we believe it represents a compelling theoretical basis for analyzing and modelling the dynamics of parasite aggregation and mating.

Case 3 estimation suggest that male and female parasites are distributed together (Case 1) at high transmission intensities that result in high worm burdens. Case 3 estimates of worm burden and aggregation were more similar to estimates recovered from Case 1 estimation at higher worm burdens. However, as infection intensities decrease, Case 3 estimates diverge from Case 1. This, together with the superior posterior fits of Case 3, suggest that Case 1 dynamics may fail to capture the aggregation dynamics and resulting distribution of mated pairs of schistosomes in very low transmission intensity environments such as those found in elimination settings.

One explanation for this is the hypothesis of Robert May that the distribution of male and female parasites is not strictly “together” (Case 1) or “separate” (Case 2), but is rather a blend of both that is dependent on the worm burden itself. [16] We tested this hypothesis explicitly with the Case 4 data-generating distribution, but found that Case 4 generally provided a poor fit to the observed data. The fact that Case 3 provides the best fit suggests that capturing variability in both exposure and susceptibility is important to capture aggregation dynamics at very low transmission intensities.

This suggests that identifying individuals who are particularly susceptible to infection could be extremely valuable for control efforts, since these individuals are both most susceptible to pathology associated with infection and are most likely contributing to sustaining transmission. These individuals could be identified through a sufficiently accurate biomarker or simply by taking note of individuals who are most heavily infected. This information could then be used in targeted drug administration campaigns that prioritize treatment of such high-risk individuals, rather than prioritizing broad coverage of the population regardless of individuals’ susceptibility or exposure. Such strategies will be the topic of subsequent modeling analyses that build on the results presented here.

Such strategies should also be pursued with caution if relying on diagnostics such as haematuria or egg-assays that are known to have low sensitivity for light infections. Indeed, reliance on these diagnostics represents a limitation of this analysis as sensitivity in egg counts is not explicitly considered in analysis of the community egg burdens or in the data-generating Cases considered. However, high variability in daily egg counts produced by even heavily infected individuals [26] is a part of the data-generating processes of the ABC estimation, meaning that generated egg distributions would be expected to match observed ones if diagnostic sensitivity in the real world were perfect. Future analyses using more sensitive diagnostics such as circulating cathodic antigen (CCA) or incorporating additional diagnostics into the data generation procedures could be pursued to confirm these findings.

Heterogeneity in susceptibility and exposure (and their joint distribution) are not the only processes that could explain the dynamics of parasite burden and aggregation identified here, though they most likely play a significant role. Recent analyses have found that mated pairs may survive praziqauntel treatment and resume egg-laying shortly after treatment. [8] This would lead individuals harboring such resistant pairs to maintain their high worm burden following treatment, while others are cleared of adult worms, thus increasing aggregation as is seen in these analyses. Similarly, individuals who miss treatment due to absence, pregnancy, or non-compliance would also maintain their high worm burdens as others are treated and cleared of adult worms, leading to increased aggregation as the mean community burden decreases.

Regardless of the exact mechanism or combination of mechanisms that give rise to increased aggregation, the practical implications are noteworthy. [31] Because some individuals maintain high worm burdens and egg output, they are more likely to maintain transmission among the snail population, which could contribute to infection rebound in the entire community. From a theoretical perspective, this can be expressed in terms of the mating probability. Our results show that increased aggregation may lead to mating probabilities higher than are commonly predicted assuming Case 1 dynamics with constant aggregation.

Deriving an analytic solution for the mating probability as a function of the mean worm burden—or better still the mean egg burden—from the proposed Case 3 data distribution would be valuable to further explore aggregation dynamics arising from heterogeneities in susceptibility and exposure. However, we also believe it is likely that Case 3 simply provides a more flexible framework to capture the high amount of stochasticity inherent in systems approaching elimination, meaning any analytic estimate may prove unreliable.

These results imply that the hypothesized breakpoint in schistosomiasis transmission could be exceedingly small or non-existent. Widespread resilience to elimination [32–36] and the recent outbreak of schistosomiasis in Corsica that appears to have been introduced by a single egg-shedding individual [37] also provide evidence in support of this finding. Breaking schistosomiasis transmission to achieve elimination may therefore be more dependent on reducing environmental transmission through snail control, sanitation improvements, and behavioral interventions and on identifying and successfully treating the few individuals who remain infected and maintain transmission as elimination is approached. [38–40]

A renewed focus on snail control as an important component of schistosomiasis elimination is encouraging. Heterogeneities in susceptibility, exposure, and sex differentiation—and resulting aggregation dynamics—are just as complex in intermediate host snail populations as in human hosts. [41] Additional focus on even more integrated strategies that incorporate snail control, MDA, environmental remediation, sanitation, and behavioral changes could prove even more successful, as they were in bringing about widespread elimination of schistosomiasis transmission in China. [2,42] Emerging evidence that zoonotic components of transmission such as hybrid *S. bovis* and *S. haematobium* [43] strains and infected rodents [44] are capable of sustaining transmission even in the presence of widespread MDA make such integrated strategies even more important. Identifying such integrated intervention strategies that result in the highest probability of successful elimination, particularly in the context of resistance to elimination due to dynamic aggregation as described here, is the subject of an ongoing modeling analyses that will be presented separately.

In conclusion, we have identified dynamic aggregation as an important aspect of schistosomiasis transmission in elimination settings. We propose a novel, generalizable quantitative framework for modeling parasite acquisition and subsequent mating dynamics among the human host population that suggests the canonical Case 1 assumption that male and female parasites are distributed together may not be applicable approaching elimination. This implies that the mating probability of adult worms remains high as elimination is approached, and the feasibility of achieving elimination using MDA alone may be overestimated. We suggest more targeted treatment strategies and a focus on integrated intervention strategies that target other components of the schistosome lifecycle to combat this source of resilience and maintain global progress towards the elimination of schistosomiasis.

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