Why do helminth infections rebound? Sources of resilience to elimination by mass drug administration and implications for control strategies with applications to schistosomiasis

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# Introduction

Mathematical models have been used for more than five decades to investigate the complex transmission dynamics of schistosomiasis. Schistosome parasites transition between human and snail hosts via two free-living, host-seeking larval forms: miracidia (shed by humans, infect snails) and cercariae (shed by snails, infect humans). Special attention has been paid to the investigation of control efforts such as mass drug administration (MDA) to treat the human population on schistosomiasis infection dynamics. This focus is at least in part driven by an early finding of Macdonald [CITE] that there exists a transmission breakpoint (also known as a strong Allee effect in ecology) due to the dioecious nature of adult schistosome worms. This implies that elimination could be achieved if schistosome worm burdens were suppressed below the breakpoint, e.g. via widespread treatment of infected individuals with MDA. However, subsequent analyses [CITE] determined that the breakpoint occurrs at such small worm burdens as to be irrelevant to control efforts.

Another key finding of Macdonald’s is that, in the absence of a breakpoint, elimination is only achieved via permanent alterations that suppress the basic reproduction number, , below the critical threshold of 1. This, combined with the finding of extremely small breakpoint population sizes, suggests that efforts to eliminate schistosomiasis should include interventions that suppress . Indeed, a recent analysis of control and elimination efforts over the past century shows that snail control–in addition to or in the context of developmental improvements such as sanitation, water access, and mechanization of agriculture–is most likely to result in successful elimination. But current control strategies rely on preventive chemotherapy by MDA to treat high-risk populations. School-aged children (SAC; ages 5-14) are frequently targeted for MDA as they are both at high risk for infection and are easily reached. Community-based MDA strategies that seek to treat adults and pre-school aged children in addition to SAC are also pursued, but are logistically challenging. [CITE]

In many areas, these MDA-based strategies have reduced schistosomiasis infection levels as measured by overall prevalence, prevalence of heavy infections, and individual parasite burdens. [CITE] National control programs across sub-Saharan Africa, large philanthropic donations from national, international, and private organizations, and donations of the anthelminthic drug Praziquantel from Merck have contributed to this success. [CITE WHO](https://www.who.int/neglected_diseases/resources/9789241503174/en/) [1] [2] However, more than **X** people still require treatment, and **Y** people remain at risk in areas with active schistosomiasis transmission. Furthermore, there is ever increasing understanding of the wide array of disability caused by schistosomiasis infection [CITE] suggesting even more disability-adjusted life-years (DALYs) lost due to schistosomiasis infection than the **Z** estimated by the most recent global burden of disease study.

In addition to shortcomings caused by drug shortages and implementation challenges, schistosomiasis prevalence in many communities remains stable even after multiple years of MDA. [3], [4], [5] In these communities, schistosomiasis prevalence quickly rebounds back to pre-MDA levels, often within a year of treatment. For instance in a large group of studies conducted by the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE; <https://score.uga.edu/>), multiple community- and school-based MDA strategies with different frequencies and “drug holiday years” were tested. Across these strategies, most communities experienced substantial reductions in prevalence between baseline surveys and reassessment at five years. Still other communities, termed “persistent hot-spots”, experienced minor changes or even increases in prevalence. [6] Finescale variation between so-called “responder” communities and persistent hot spots also suggests that highly local factors determine the success or failure of MDA-based control.

Together, this evidence suggests a mismatch between the theoretical underpinnings of schistosomiasis control and elimination and current strategies to achieve these goals. Here, we attempt to elaborate on this discrepancy by documenting sources of resilience to schistosomiasis control and elimination by MDA that may explain rapid rebound and persistent hot-spot phenomena. These sources of resilience are incorporated into a dynamic model of schistosomiasis transmission and their effects on transmission during regular MDA quantified via their influence on the effective reproduction number . From this model, we derive an analytic expression of the transmission breakpoint, , and identify its main determinants. We conclude with simulations of a stochastic version of the schistosomiasis model to determine the probability of elimination across a range of transmission and intervention scenarios.

#### Other potential intro anecdotes

Mothers with small children may be a particularly relevant class that is both vulnerable to schistosomiasis (re)infection and may play a key role in sustaining it following MDA campaigns in which they are not routinely targeted [7]

Metrics of success that incorporate environmental surveillance of intermediate host snails as well as detection of free-swimming miracidia and cercariae using eDNA techniques have been suggested [7].

Integrated strategies targeting the intermediate host snail population through both mollusciciding and habitat reduction, zoonotic reservoirs, improved sanitation and water access (e.g. WASH interventions), and education on exposure and transmission prevention have been extremely successful in reducing transmission in Chengdu Province, China. [8] Fuerthermore, recent analyses have shown that adding routine mollusciciding to MDA efforts is highly cost-effective in terms of DALYs-averted per dollar invested. [9]

## Sources of resilience

* History of modeling schistosomiasis dynamics in the context of control
* Density dependence and presence of a transmission breakpoint
* Importance and implications of the breakpoint
* Sources of resilience and brief explanations:
* Non-linear man-to-snail transmission dynamics
* Density-dependent fecundity
* Acquired immunity
* Changes in worm burden distribution among infected individuals

### Density-dependencies

#### Dispersion parameter responsive to worm burden in each population

We model the dispersion parameter, , of the negative binomially distributed mean worm burden in separate age, , and treatment groups, , as a function of the mean worm burden in each group:

Previous analyses of the distribution of estimated worm counts within definitive human host populations have shown that the dispersion parameter varies predictably as a function of the overall mean worm burden and can change quite dramatically following MDA. [10], [11] In particular, decreases, implying more skewed distributions in which fewer individuals harbor more worms, as decreases. This leads to an increase in the mating probability, , even as worm populations decrease due to MDA or other interventions.

#### Density dependent fecundity

#### Acquired immunity

#### Snail logistic population growth

Snail reproduction is modeled assuming logistic population growth such that the fecundity rate, , is a function of the intrinsic reproduction rate, , the environmental carrying capacity, , and the total snail population, :

As , . This implies resilience to interventions such as mollusciciding as the fecundity rate increases as the sail population decreases, leading to quicker rebound of the snail population following perturbation than would be expected given a constant fecundity rate.

And also “Civitello effect”?

#### Non linear snail FOI (can be framed as a density dependence?)

Compared to a linear snail FOI of the form , this formulation leads to higher FOIs at lower values of , implying that less infectious material from the human population is required to reach higher rates of infection in the intermediate host snail population. A small number of infected individuals could therefore be sufficient to maintain man-to-snail transmission, even as the majority of a community is treated via MDA.

### Reservoirs of infection

Miracidial density, , is estimated as the sum of infectious input across all definitive human host populations:

with mean worm burden, , modeled separately for each age and treatment group; is the number of individuals in the group; is the mating probability of adult worms in each population with the dispersion parameter of the negative binomially distributed worm population, , estimated as a function of the mean worm burden, (see below); is the density-dependent fecundity ; and is a contamination coefficient related to the relative difference in sanitation and other behaviors between SAC and adults.

MDA in the affected population is modeled as a reduction in the mean worm burden by , the efficacy of the drug intervention, in the following timestep of the model: . Mean worm burden in the other populations remain unaffected except via reductions in the man-to-snail FOI as a result of treating the affected population.

## Framing of the problem

* Systematic investigation of sources of resilience and their implications for control
* Quantifying the influence of sources of resilience
* Identifying (optimal?) control strategies when accounting for sources of resilience

# Methods

## Basic schistosomiasis model

We expand on classic “MacDonald-type” models [CITE] and our more recently published models [CITE] to explore the role of X, Y, and Z on \_\_\_\_. The basic schistosomiasis model represents susceptible-exposed-infected (state variables , , and respectively) infection dynamics among the intermediate host snail population, , in order to account for the delay (pre-patent period) between infection () and active shedding of cercariae (patency, ()). Human infection across age groups, , and treatment groups, is modeled via state variables representing the mean worm burden in each segment of the human population, assumed to be negative binomially distributed with independent clumping parameters :

We assume infected snails, , do not reproduce and the snail population growth rate, , is logistic with max reproduction rate, , and carrying capacity, , giving . The snail and mean worm burden compartments of the model are linked by snail-to-man force of infection (FOI), , and man-to-snail FOI, , each of which is described further below.

#### Man-to-snail FOI, "

As in [12], is estimated as a non-linear function of miracidial density, , :

where approximately represents the maximum infection rate among susceptible snails and corresponds to the probability of infection given miracidial to snail host density. Miracidial density is estimated as the product of mean egg output in each worm burden group, ; a contamination coefficient related to the relative difference in sanitation and other behaviors between SAC and adults, ; schistosome egg viability, , and the number of people in each group, .

Mean egg output is estimated assuming a sex ratio of 1 and a single negative binomial distribution describing the distribution of adult worms amongst the human population. This leads to an estimate of the mean number of mated adult female worms per host, , with mating probability, estimated as in [13]. Mated female worms lay viable eggs at rate , measured in eggs per 10mL urine, which combined with density dependent fecundity, , and the mean volume of urine per individual, , gives the product as an estimate of the mean miracidia produced per person in each age and treatment group. Summing across all groups gives an estimate of total miracidial density:

#### Snail-to-man FOI,

## Model fit

In previous modeling efforts we have fit mean worm burden outputs from the model to longitudinal reinfection data measured via parasitological surveys of SAC over the course of a multi-year MDA campaign [14], [15], [16]. Because estimates of the contribution to transmission of the adult population are key in the analyses presented here, we instead rely on the data sources and approximate methods presented in [9], [12] to estimate the parameters , , and .

## and

From this model, we derive an analytic expression of two key quantities: the breakpoint worm burden, , and the effective reproduction number, . We next describe different sources of resilience to control and elimination by MDA and the quantitative representation of each in the model. Each source of resilience is incorporated individually into expressions of and to estimate their effect on these key metrics.

## Sources of resilience and their representation in the model

## Stochastic model simulating control strategies and probability of elimination as a metric of potential success

### Transmission scenarios

### Control strategies

* No intervention (baseline)
* School-based MDA (coverage informed by estimates from Senegal? Score?)
* Community-wide MDA (coverage informed by estimates from Senegal? Score?)
* Each MDA strategy with snail control
* Initial \_% reduction in snail habitat followed by \_\_\_ MDA strategy
* Gradual \_% reduction in snail habitat in conjunction with \_\_\_ MDA strategy
* Gradual improvements in sanitation and hygiene in conjunction with MDA

### Metrics from stochastic model

* 100 rounds of 100 stochastic simulations used to estimate:
* **Probability of elimination as a public health problem** – Morbidity control and less than 1% prevalence of heavy (>50 eggs/mL) infections
* **Probability of interruption of transmission** – No incident cases
* **Probability of outright elimination** – No infected vectors or individuals after ten years

# Results

### Potential Figures (in no particular order)

#### - curve pointing out ,

#### - time series

Shows that MDA except at extremely high levels of coverage increases transmission (as measured by ) by reducing influence of negative density dependence, leads to return towards pre-intervention levels of infection

#### - comparisons between models to show influence of sources of resilience on the breakpoint population size. e.g. what is breakpoint with no PDD, with PDD, with PDD+non-linear huma-snail FOI, etc…

#### - across values of parameters that can be changed via control measures

#### - Example stochastic time series from different control strategies, delineate chains that successfully control/eliminate (based on WHO definition) from those that rebound with different colors

### Table (further divided by intervention strategy):

|  |  |  |  |
| --- | --- | --- | --- |
|  | Probability.of.transmission.control | Probability.of.elimination.as.a.public.health.problem | Probability.of.outright.elimination |
| High prevalence setting | NA | NA | NA |
| Medium prevalence setting | NA | NA | NA |
| Low prevalence setting | NA | NA | NA |

# Discussion

Diagnostics that are more sensitive than egg-counts from urine or stool samples are necessary in low-transmission and post-elimination settings. [17]

Additional drugs already approved for other uses may be helpful in the treatment and prevention of schistosomiasis by targeting different parasite development stages. [18]

Positive density dependent sources in other helminth infections: L3 suppression in Lymphatic Filiriasis [19], immunosuppression in onchocerciasis [20]

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