Modeling transmission of infection in a distributed heterogeneous environment: Schistosomiasis control

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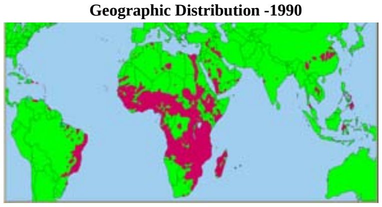
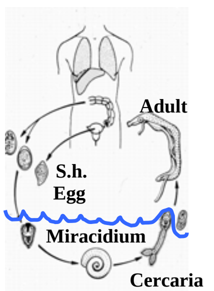
Schistosomiasis

- •Chronic parasitic trematode infection
- •200-300 million people worldwide
- •Significant morbidity (esp. anemia)
- •Premature mortality
- •Life-cycle is complex, requiring species-specific intermediate snail host
- •Optimal control strategies have not been established.

Geographic Distribution -1990





Life Cycle of Schistosomiasis involves definitive human host, intermediate snail host and two larvae stages. Adult worms mature and reproduce in human body, but the eggs must be released in water (Miracidium), invade snails, reproduce and be released as another larva stage (Cercaria), which reenters human host to complete the cycle.

Transmission
at water sites shared by humans and snails

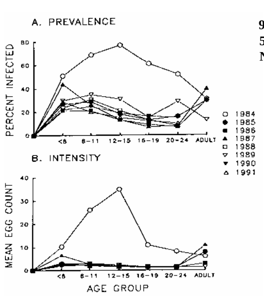
Control Strategies
- •Chemotherapy
- •Vector (snail) control
- •Vaccination
- •Environmental modification; Development

Epidemiology

- •Transmission is highly focal
- •Prevalence and intensity vary with age
- •Morbidity varies with age
- •Infection intensity not randomly dispersed
- •Signs of early chronic disease correlated with greater intensity of infection

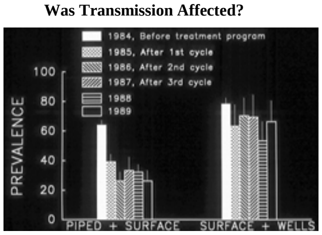
Results of some field studies

Impact of age-targeted therapy on prevalence and intensity of *S. haematobium* infection

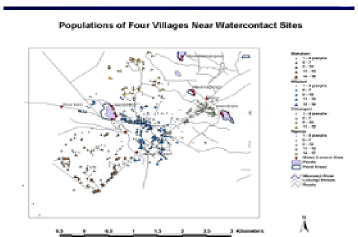


9 villages
5 schools
N = 7700

Was Transmission Affected?



Partial success, depending on location



Typical environment

Mathematical model

Simplest model: 1 human and 1 snail population (2 variables):

$w(t)$ - mean worm burden in humans

$y(t)$ - infected snail prevalence

(1) $$\frac{dw}{dt} = A\,y - \gamma\,w \qquad \frac{dy}{dt} = B\,w(1-y) - \mu\,y$$

γ - worm mortality in human hosts; μ - snail mortality

A, B - transmission coefficients (Snail-to-Human, and Human-to-Snail)

Endemic equilibria ($w^* > 0,\ y^* > 0$) exist, iff the Basic Reproduction Number: $R_0 = \frac{AB}{\gamma\mu} > 1$.

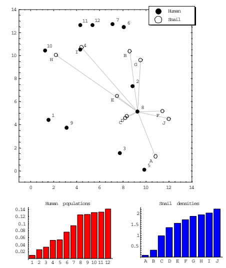


Figure 1: Model environment made of 12 human clusters and 10 snail sites with selected marked distances (top), along with population fractions and snail densities (bottom).

General system accounts for (i) age structure and aging, (ii) age dependent contact/ contamination rates, (iii) age targeted chemotherapy

$$\frac{d}{dt} w_{ia} = \alpha \sum_{j=1}^{L} \eta_{ia,j}(N_j y_j) - \left(\gamma + \frac{1}{\Delta a} + \tau_a\right) w_{ia} + \frac{h_{ia-1}}{h_{ia}} w_{ia-1} \qquad \frac{d}{dt} y_j = \sum_{i,a} \beta_a \eta_{j;ia}(H_{ia} w_{ia})(1-y_j) - \mu y_j \quad (2)$$

Parameters: h_{ia} - populations fractions, $\eta_{ia,j}$ - contact rate of i,a strata at j site, α -probability of worm establishment per contact; β_a - age dependent contamination rate, Δa -age bin (time step). The effect of chemotherpy is increased worm mortality: $\gamma \to \gamma + \tau_a$ (age dependent).

Matrix formulation:

$\hat{w} = (w_{ia})$ - burden vector; $\hat{y} = (y_j)$ - prevalence vector

$$\frac{d\hat{w}}{dt} = A \cdot \hat{y} - (\Gamma + G + \Theta) \cdot w \qquad \frac{dy}{dt} = B \cdot \hat{w}(1-\hat{y}) - \mu\,\hat{y}$$

A, B - transmission matrices; Γ, G, Θ - worm attrition, aging, therapy control matrix. The role of R_0 is played by the Basic Reproduction Matrix

$$R = \frac{1}{\mu} B \cdot (\Gamma + G + \Theta)^{-1} \cdot A$$

It determines endemic equilibria, the community mean burden (affected by "treatment parameters" - frequencies τ_a): $w^*(\tau_1, \dots \tau_P)$, and allows to formulate and solve (numerically) the optimal control problem:

Minimize $w^*(\tau_1, \dots \tau_P)$, subject to cost constaint $C(\tau_1, \dots \tau_P) = C_0$

Cost constaints are important in many developing countries.

Basic hypothsis:

Environmental variables are independent of age/bahavioral ones, i.e.

(i) population fractions: $H_{ia} = H\,h_i\,h_a^*$, H - total population, $\{h_i,\ h_a^*\}$ - population fractions by site and age.

(ii) contact rates η, factor into age -dependent frequency $\omega_a \times \chi_{ij}$ - geographic "hurdle factor", taken as a function of distance between i human and j snail site).

(iii) Natural worm attrition γ is age independent.

As consequence of (i)-(iii) all basic variables and parameters factor into products of "age dependent"×"environmental" terms.

Results

1) Equilibration

Equilibrium prevalence vector obeys nonlinear system

$$R \cdot Y = \frac{Y}{1-Y} \quad (3)$$

in terms of the basic reproduction matrix R . The latter factors into L×L "environmental (hurdle) matrix" and a Scalar Reproduction scalar

$$\rho = \frac{\alpha H}{\mu} \hat{\beta}\,\hat{\omega}\,\hat{h}^* \cdot (\Gamma + G + \Theta)^{-1} \cdot \hat{\omega} \quad (4)$$

The corresponding community mean burden is

$$w^* = \sigma\, f(\rho) \quad (5)$$

where r and similarly defined s encode all age/behavioral (plus therapy treatment) data, while *f* is environmental infection potential.

Analysis of eradication

Equilibrium $\boldsymbol{Y = 0}$ in (3) requires largest eigenvalue $\lambda_1(R) \le 1$. It sets up a relation between controls $\{\tau_a, N_j\}$and fixed environmental matrix R^0. Under independence hypothesis $\lambda_1(R^0) = \rho\,\lambda_1(R^0)$, and in our case (Fig. 1) $\lambda_1(R^0) = .31$. Fig.2 shows community worm burden $\frac{w^*}{\sigma}$ as a function of ρ

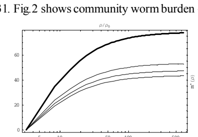


Fig. 2: Community worm burden w^*/σ as function of ρ, w/o treatment (thick), and with uniform (across age) treatment at frequencies τ=.5,1,2/year (shows substantial reduction).

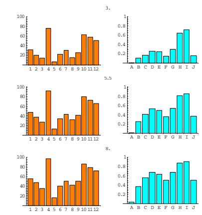


Fig. 3: Equilibrium burden (left) and prevalence (right) at selected values ρ

Age targeted control

We take typical age structure and contamination rates and implement the cost constrained optimization of w*. The constraint is a fraction ξ of "allocated cost" over "requisite cost" of treatment. We show two results of optimal treatment: Fig.4 compares treated vs. untreated worm distribution by age; Fig.5 shows the community burden reduction and the corresponding treatments frequencies τ_a for different age groups.

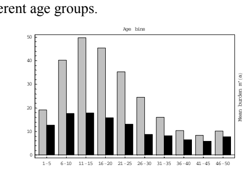


Figure 4: Comparison of age distributed equilibrium worm burdens $\{w_a\}$ without treatment (gray), and with optimal treatment (black) at ratio (allocated/required treatment cost) C0/c0 = .2.

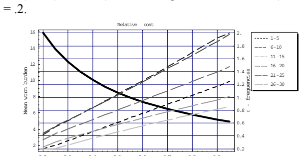


Figure 5: Worm mean burden (solid black) and optimal therapy frequencies for 6 youngest groups (dashed curves), as functions of available funding, in terms of the ratio (allocated cost) ξ= C_0/c_0, shown on the ordinate. In the setting where only 50% or fewer can be covered, then annual or biennial treatment of younger age groups (t = 1 or 0.5) , combined with treatment every 4-10 years for older age groups (t = 0.25 to 0.1), provides the maximal possible reduction in community worm burdens.

Site specific control

High risk sites, raise the question of site-specific control strategy (targeting high risk site rather than age groups). Example is site #4 on Fig.1, close to snail site I attains high endemic levels (Fig.3). Mathematically, site - specific control is more involved. The full implementation of the optimal control will require further work. Here we give two preliminary results: Fig.6 shows the difference between community worm burden "w/o treatment" vs. "extreme treatment" of site 4 (as functions of the basic reproduction scalar ρ); Fig. 7 gives the worm-burden distribution by site in two cases ("untreated" vs. "treated #4") at two select values of ρ.

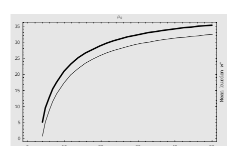


Figure 6: Community mean burden as function of the basic reproduction scalar ρ_0 in two cases: untreated population (thick curve), and site 4 removed through eradication (thin curve). The difference between two curves shows the best possible gain (about 10%) attained through the targeted treatment of site 4.

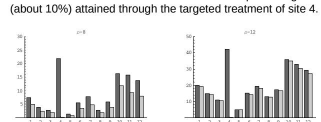


Figure 7: Site distribution of worm burden for untreated population (dark), and the effect of extremely treated site 4 on the remaining sites (light).

Conclusions

- **Schistosome infection** in highly endemic areas can be mathematically modeled via a distributed "burden-prevalence" (Macdonald-type) system.
- We place it in a **heterogeneous environment** made of human and snail clusters with **age-stratified** populations and behavioral patterns.
- We study **endemic equilibria** in such systems and their dependence on the essential control parameters: snail densities and worm attrition rates. The latter, in particular allows an optimal control strategy of the community "mean worm burden" via repeated (cyclic) chemotherapy.
- For **age targeted chemotherapy** (high risk groups) the computed optimal solutions show significant reduction of the mean worm burden at a relatively low cost.
- On the contrary **site specific control** (of high risk sites) proves largely inefficient, which can be explained by an overall connectivity pattern of the human-snail.