Appendix A

This model of physiological growth and development over young ages (0-20 yr old) accounts for different growth strata (“developmental quantiles”) with a population, and the possible growth retardation due to chronic infection (such as schistosomiasis). It is meant to represent a dynamic process, i.e., the life history of an individual or of a given population growth stratum, driven by natural (physiological) growth-factors and growth-inhibitors (e.g., chronic infections). The distributions of heights or weights for the untreated communities are close to normal distributions (shown in supplemental Figure A, below). Therefore, we can reflect the long-term effect of a drug treatment strategy through the shift in population mean and standard deviation of height and weight at age 20 yr.

Model assumptions:

1. For the purposes of this analysis, human populations and transmission environment are stationary, i.e., unchanging.

2. The normal childhood growth and development patterns are based on CDC-WHO standard curves (see http://www.cdc.gov/growthcharts/percentile_data_files.htm, and reference30) reflecting the expected pattern of growth, where growth rates (velocity, Figure 1) can be modified downward (decelerated) or upward (accelerated) to model, respectively, growth inhibition by infection, and its potential remediation by catch-up growth44 after anti-parasite treatment.

3. Persisting parasite burden due to lack of treatment and/or reinfection after treatment, with consequent inflammation73 can impair growth-related developmental processes over the first 20 years of life. However, we assume that the retardation process is partly reversible by remedial growth once the sources of infection and chronic inflammation are removed.
4. The basic biological growth parameters and behavioral patterns (e.g., water contact rates and reinfection risk) are age- and gender-specific, which results in different patterns of worm burden and morbidity between girls and boys.

The basic dynamic variables of the model are: (i) $w(a)$ - worm burden of a host (or mean worm burden (MWB) of a homogeneous population stratum); (ii) development index (height/weight) $h(a)$ of a host (or stratum); both of these being functions of age $0 < a < L$ (L, life span). In general, both infection and developmental variables should be considered functions of ‘age’ and ‘time’ $\{w(a,t); h(a,t)\}$, but here we ignore temporal changes, assuming population structure and transmission remain stationary in time.

Our analysis of drug intervention is based on age-patterned strategies and their (cohort/community) outcomes:

A. Infection dynamics

Age dynamics of burden $w(a)$ is described by differential equation with source term $S = S(a)$ (force of infection that accounts for transmission and parasite establishment), and resolution rate $\gamma = .2/\text{year}$ (assuming worm life-span = 5 years),

$$\frac{dw(a)}{da} = S(a) - \gamma w(a)$$

(1)

We assume source $S(a) = S_0 \eta(a)$ to be a product of environmental ‘risk factor’ $S_0$ (maximal ‘worm accumulation rate’ per ‘unit transmission’), and relative age-dependent transmission pattern $0 \leq \eta(a) \leq 1$. The latter $\eta(a)$ should account for age-dependent behavioral (risk) changes and changing ‘probability of worm establishment’ due to acquired immunity. As proposed by Chan et al., we take

$$\eta(a) = \eta_p(a/a_0); \text{ with } \eta_p(z) = z^p e^{-p(z^2-1)/2}$$
This approach highlights peak-transmission age \( a_0 (\eta(a_0) = 1) \), and the exponent \( p > 0 \) that measures steepness of ‘low to high’ transitions in early or late ages (away from \( a_0 \)) and the follow-up 'high to low' drop. The parameters \( \{a_0, p, S_0\} \) were calibrated using mean worm burden (reflected by egg count) data from community-based field studies of \( S. haematobium \) infection and reinfection in Kenya.\(^{6,31}\) The Kenyan data represents a cross-sectional community survey, and in our calibration scheme (below) we apply it to align the model to outcomes in the respective age cohorts.

**B. Accumulated morbidity**

Chronic worm infection results in morbidity caused by persisting inflammatory immune response to parasite eggs deposited into host tissues.\(^{10}\) Quantitatively, we describe this process by the following differential equation:

\[
\frac{dz(a)}{da} = \rho w(a) - v(a)z(a)
\]  

(2)

Here, variable \( z(a) \) serves as a cumulative proxy for the damage caused by chronic infection that is relevant to impaired host development.\(^{46}\) Variable \( z(a) \), is acquired a rate proportional to worm burden, and is resolved at an age-dependant rate \( v(a) \), given by a sigmoid function,

\[
v(a) = v_0 \frac{\alpha + (a / a_i)^q}{1 + (a / a_i)^q}
\]

with maximum - \( v_0 \), minimum - \( \alpha v_0 (0 < \alpha < 1) \), threshold age \( a_i \) and hill-exponent \( q_i \).

Such form of burden resolution differs from models used in earlier works.

**C. Drug treatment**

Anti-schistosomal drugs such as praziquantel remove about 90% of each child’s mature worm burden for each treatment, as estimated by reductions in egg output.\(^3\) For the purposes of our analysis, we assumed that this happens very quickly once treatment is implemented. To do this, chemotherapy was modeled in equation (1) by augmenting natural worm death rate \( \gamma \) with an
additional clearing term, made of step-function of short duration $T$ (or its Dirac delta approximation) whose strength $r = -\log(1 - e)$ depends on the efficacy of drug ($e =$ fraction of worms killed per session). Thus a sequence of several sessions administered at ages $\{a_j\}$, gives the combined clearing term

$$\gamma + \frac{r}{T} \sum \delta(a - a_j).$$

**Modeling normal and impaired growth and development.**

For the present analysis, we examine the cumulative impact of infection at age 20 yr (adulthood), when normal development typically would terminate.

**Normal growth** was assumed to be driven by an age-dependent *natural growth rate* (NGR) $g(a)$ (per unit weight or height, etc.). We estimated $g(a)$ using CDC (NCHS) data on juvenile development in the USA (Figure 1). Specifically, NCHS data gives quantile development curves (indices) $\{H(a) = H_q(a)\}$ from which we compute NGR function

$$g(a) = g_q(a) = H_q'(a)/H_q(a)$$

for each quantile $0 < q < 1$. Here, $H'(a) = \frac{dH(a)}{da}$ denotes the derivative of $H(a)$. We further assumed that NCHS growth patterns are inborn characteristics, so that an individual born into any $q$-quantile would, with some oscillation, tend to maintain it through later normal development.  

**Chronic infection** (along with malnutrition) interferes with normal development at younger ages, and can ultimately result in lifelong developmental retardation.\[^{44,74}\] To model the dynamics of disease-related impairment, we chose a suitable physiological characteristic (e.g., one’s weight or height), $h(a)$, and related it to the normal *developmental index* $H(a)$, for each
quantile. Furthermore, we included the effect of remediation via ‘catch-up’ growth potential at different ages.

The *catch-up growth* is believed to reflect a feedback response to an impaired developmental state that deviates from an expected set-point. This departure then stimulates an additional component of growth.\textsuperscript{44,71,74} For children with developmental deficiencies, we estimated a *remedial growth rate* (RGR) that, like normal growth, was assumed to depend on age \( \{a\} \), but also on some form of ‘departure from the norm’ i.e., deficit, either an ‘absolute’,

\[ d(a) = H(a) - h(a) \]  \hspace{1cm} (4)

or a ‘relative’ one,

\[ d(a) = 1 - h(a) / H(a) \]  \hspace{1cm} (5)

such that \( \text{RGR} = R(a, d) \). One can think of ‘catch-up' growth as a built-in ability by the body to ‘read’ its current state \( h(a) \), to ‘compare’ it with the ‘programmed' normal value \( H(a) \), and provide an additional growth term in the \( h \)-equation (through enhanced metabolic-hormone regulation).

The *deleterious effect* of a chronic infection such as schistosomiasis on growth-development could be linked either to accumulated worm burden \( w(a) \), or a suitable morbidity variable \( z(a) \) (e.g., inflammation) derived from \( w \). Using \( z \) as a the main source of inhibition, we represented its diminishing effect on both growth rates, \( \text{NGR} \) and \( \text{RGR} \) by factor \( 0 < \phi(z) < 1 \), its value decreasing with greater \( z \). The combined *inhibited growth* equation for index \( h(a) \)

\[
\frac{h'(a)}{h(a)} = \phi(z) g(a) + \phi(z) R(a, d).
\]  \hspace{1cm} (6)
Let us note that in the absence of infection \((\phi = 1, \text{or } d = 0)\), equation (4) should turn into the normal growth equation (3) for \(h = H(a)\). So we expect \(R(a, d) = 0\), if \(d = 0\). The simplest such choice should be linear function in \(d = H - h\), or \(1 - h/H\). So we assumed

\[
R(a, 1 - h/H) = r(a)(1 - h/H)
\]

(7)

Here, \(r(a)\) is the (hypothetical) maximal catch-up rate (under 'extreme deficit' conditions). We made three additional assumptions:

(i) Growth inhibition factor \(\phi\) is a sigmoid function between 2 levels: \(\phi_0 < \phi(z) < \phi_1\), with a 50% threshold - \(z_0\) and a Hill exponent \(m\)

\[
\phi(z) = \phi_0 + \frac{\phi_1 - \phi_0}{1 + (z/z_0)^m}
\]

(8)

Its maximal value \(\phi_1 < 1\) (at \(z = 0\)), rather difference \(1 - \phi_1\), should account for other (non-schistosomiasis) inhibiting factors (e.g., co-infections or malnutrition). Here, the schistosomiasis-specific contribution corresponds to the gradual transition from high value \(\phi_1\) (at low \(z\)) to low \(\phi_0\) (at large \(z\)).

(ii) The observed height/weight retardation for a single human host or a homogeneous growth stratum results from the same accumulated damage (morbidity) of this group.

(iii) In the absence of more detailed information on ‘natural’ and ‘remedial’ growth mechanisms we assumed a simple linear relation between two rates

\[
r(a) = Kg(a)
\]

(9)

with parameter \(K\) equal to ‘relative efficiency’ of remediation.

The net result is a coupled system of equations (1)-(4) for variables \(\{w(a), z(a), h(a)\}\) that described the life progression of a chronic infection and its deleterious effect on growth/development. In what follows we shall use an alternative variable for
growth/development, namely relative index \( D(a) = h(a) / H(a) \) and change equation (4) to an appropriate D-equation.

**Heterogeneous communities.** We apply the above 'infection-morbidity-development' system to heterogeneous communities both in terms of worm acquisition (contact patterns) and the resulting growth and development. The latter requires to stratify such community into developmental quantiles (labeled by index \( q \)), each stratum having a specific NGR and RGR \( \{ g_q(a); r_q(a) \} \) (eqn (6) and (7)), as well as the programmed normal growth \( H_q(a) \). We assume that all hosts have statistically similar levels of exposure described by 3 parameters \( \{ S_0, a_0, p \} \) of contact pattern \( \eta(a) \) in equation (1), and similar infection-induced growth impairment patterns described by another 4 morbidity and 5 growth (height/weight) parameters (Table 1). This assumption provides us a feasible way to calibrate the model and predict the effect of drug treatment to the most reliable level. Under this assumption, the egg count data (geometric mean) and the anthropometric data (median) from the Kenyan village can be taken as the representative of the infection and resulting retarded growth status of this community. Using the US median anthropometric as the normal index for this representative, we then estimated the unknown parameters in the system. We then mimicked the heterogeneous community population by considering its 5 quantile groups, each containing of a proper fraction of population. Each individual in one group has the group-specific standard normal growth index \( \{ H_q(a), g_q(a) \} \), and was described by a set of parameters randomly perturbed up to 20% from the estimated base-case values.

**Input data for calibration**

Normal growth data for weight and height of boys and girls aged up to 20 years were obtained from CDC tables available at http://www.cdc.gov/growthcharts/percentile_data_files.htm. Figure 1 shows the appropriate range
of height and weight values and their typical deceleration (rate of change in growth rate) as a function of age. While these CDC standards were developed from USA residents,\textsuperscript{30} following recent WHO guidance we took several quantile-specific weight-for-age and height-for-age as the normal growth-development curves (designated by $H(a)$) and applied them for children in schistosomiasis-endemic areas. Estimation of age-specific, schistosomiasis-related impairment of childhood development ($h(a)$) was taken from anthropometric data from community surveys performed in Coast Province, Kenya, as part of a treatment study.\textsuperscript{31} The infection data included age-specific mean egg counts typical for $S. \text{haematobium}$-endemic areas. In this cross-sectional community study of 356 children, co-infection with hookworm was 93\%, $Trichuris trichiura$ 84\%, and $Ascaris lumbricoides$ 36\%. Details of nutritional intake were not studied.

**Model calibration**

As mentioned above, the typical values of the unknown parameters were estimated based on the age-specific geometric mean egg count and the observed retardation of growth (in terms of median heights and weights) for the Kenyan village population. Note that worm equation (1) is independent of the morbidity and growth equations, so we may proceed in two steps. First we calibrated the transmission part of the system (worm burden accumulation), then extended it to calibrate its ‘accumulated inflammation + growth impairment’ part.

**Step 1.** We computed the solution of function $w(a)$ of equation (1) (which depends on the unknowns $\{S_0, a_0, p\}$) by fitting observed infection data to get the ‘best-fit’ (least squares) estimates for the equation parameters.

**Step 2.** Taking the infection history as the worm input for morbidity equation (2), coupled with the growth equation (7) (with (8)), we estimated the 4 chronic morbidity parameters $\nu_0, \alpha, a_1, q_1$ and two sets of developmental parameters $\frac{z_0}{\rho}, \phi_0, \phi_1, q, K$ (morbidity $z(a)$ is rescaled by dividing $\rho$ in (2)). Parameters for height and weight for a typical individual are estimated.
together because they are resulted from the same infection-induced morbidity. To this end we created a random ensemble of 10,000 parameter choices (within appropriate ranges), and numerically simulated solutions of differential system (2), (7) for each choice (based on US median as the putative norm), compared it to the Kenyan median anthropometrics (height/weight). The one with the least error (Euclidean distance) was chosen as the best-fit values of the 17 parameters.

With the best-fit values of the 20 parameters (3 for worm and 17 for morbidity and growth), we were ready to build the virtual heterogeneous community. The 5 quantiles were chosen to be .05, .25, .5, .75 and .95, respectively. Each individual had his or her own infection, morbidity, and growth profile described by a system of equations (1), (2), and (6), with each parameter being a random choice within the interval (.8, 1.2) multiplied by the best-fit value.

**Calibration results**

In Table 1, we list the best-fit values for the parameters for each gender group. The community range of the infection and growth profiles based on these values is shown in Figure 2.

**Supplemental Figure A:** Simulated distribution of population heights and weights for untreated boys (upper panels) and girls (lower panels), based on expected range of growth potential as described above.