

## Modeling the Effect of Chronic Schistosomiasis on Childhood Development and the Potential for Catch-Up Growth with Different Drug Treatment Strategies Promoted for Control of Endemic Schistosomiasis

David Gurarie, Xiaoxia Wang, Amaya L. Bustinduy, and Charles H. King\*

Department of Mathematics, Department of Pediatrics, and Center for Global Health and Diseases,  
Case Western Reserve University, Cleveland, Ohio

**Abstract.** In areas endemic for schistosomiasis having limited healthcare, targeted drug treatment of school-age children is recommended for control of *Schistosoma*-associated morbidity. However, optimal timing, number, and frequency of treatments are not established. Because longitudinal studies of long-term impact of treatment are few, for current policy considerations we performed quantitative simulation (based on calibrated modeling of *Schistosoma*-associated disease formation) to project the impact of different school-age treatment regimens. Using published efficacy data from targeted programs, combined with age-specific risk for growth retardation and reinfection, we examined the likely impact of different strategies for morbidity prevention. Results suggest the need for early, repeated treatment through primary school years to optimally prevent the disabling sequelae of stunting and undernutrition. Dynamics of infection/reinfection during childhood and adolescence, combined with early treatment effects against reversible infection-associated morbidities, create a need for aggressive retreatment of preadolescents to achieve optimal suppression of morbidity where drug-based control is used.

### INTRODUCTION

Schistosomiasis remains one of the most serious and prevalent diseases worldwide. In 2003, there were an estimated 207 million people infected, with 89% of these people living in the less-developed areas of sub-Saharan Africa and South America.<sup>1,2</sup> Although highly effective anti-schistosomal drugs have been marketed for over 25 years,<sup>3</sup> there remain significant challenges to providing treatment (or preventive therapy) to those who are at highest risk for disease.<sup>4,5</sup> Because, until recently, implementation of a large-scale of anti-schistosomal treatment has been very limited, there remain significant gaps in our knowledge about the expected benefits of repeated treatment in areas that continue to have high risk for *Schistosoma* reinfection after therapy.<sup>6</sup> These communities, which often have the highest prevalence and intensity of infection, pose a particular challenge to program development for schistosomiasis morbidity control.<sup>7,8</sup> Clinical and epidemiologic studies indicate that 10–15 year old children typically carry the highest rates of schistosome infection and the highest risk of inflammation-related disease associated with infection.<sup>9,10</sup> The more lethal, late outcomes of infection are more common among adult age groups, and result from progressive infection-associated fibrosis of vital organs.<sup>11,12</sup> However, of recent note, researchers and policy-makers have come to appreciate that schistosomiasis can also be a significant risk factor for chronic anemia, childhood growth stunting, protein calorie malnutrition, cognitive disability, and poor school performance.<sup>13–19</sup> These sub-clinical morbidities are physiologically important but more subtle than the easily recognized, advanced forms of schistosomiasis.<sup>12</sup> Nevertheless, these “subtle morbidities” can have serious day-to-day consequences in the setting of rural poverty,<sup>17,20</sup> and may, in fact, given the substantial numbers of persons who are affected by these pathologies, represent the bulk of schistosomiasis-

associated disability and health burden among endemic populations.<sup>21</sup>

How can available resources be best allocated to prevent both the prevalent sub-clinical morbidity associated with schistosomiasis and the more severe forms of advanced disease (including developmental stunting)? In this analysis, we use a calibrated computer simulation to estimate the relative benefits of different treatment strategies for school-age schistosomiasis control programs. The World Health Organization (WHO) presently advocates schistosomiasis control by a strategy of periodic drug treatment of affected populations, focusing on school-age children as the highest risk group for infection and consequent disease formation.<sup>22</sup> Large-scale control programs have already begun in many countries,<sup>4</sup> but important operational questions regarding the optimal timing and distribution of treatment efforts still remain. To address these questions in greater detail, our present modeling approach builds partly on earlier modeling efforts of Medley and Bundy,<sup>23</sup> Chan and others,<sup>24</sup> and Gurarie and others.<sup>25,26</sup> Those articles focused on late-term *Schistosoma*-related morbidity outcomes and the analysis of the optimal timing for targeted or population-based therapy for control or prevention of “classical” forms of schistosomiasis. The current article takes a different approach, focusing instead on predicting the best means to use available therapy for prevention of the detrimental impact of schistosomiasis on childhood growth and development.<sup>15,16,27–29</sup> Because available field data are presently quite limited, we calibrated a growth-development model for ages 0–20 yr using the Centers for Disease Control and Prevention (CDC) National Center for Health Statistics (NCHS) database (see Figure 1),<sup>30</sup> and evaluated the age-dependent impact of “schistosomiasis-like” chronic infection that causes growth retardation. The model was benchmarked using detailed anthropometric and infection data collected for Kenyan villagers in a *Schistosoma haematobium* endemic area.<sup>31</sup> In addition, the approach was nuanced to include innate age- and gender-related differences in individual risk for growth-related disease formation,<sup>32,33</sup> and the projected impact of preventing reversible nutritional morbidities of childhood.<sup>13,15,34,35</sup>

As a basis for discussion in current program planning, we addressed the unanswered questions about long-term

\*Address correspondence to Charles H. King, Center for Global Health and Diseases, Wolstein Research Building 4126, 2103 Cornell Road, Cleveland, OH 44106-7286. E-mail: chk@cwru.edu

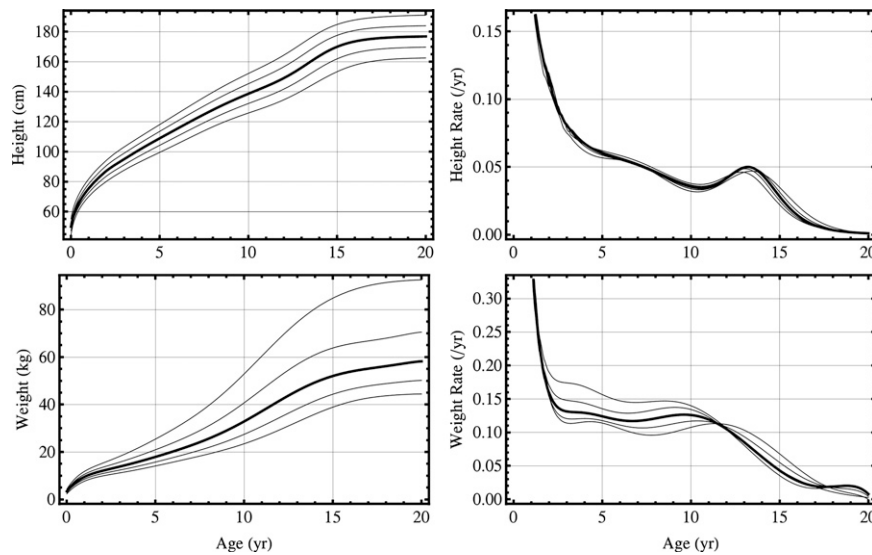


FIGURE 1. Examples of normal growth patterns for children: Left panels indicate Centers for Disease Control and Prevention (CDC) curves for normal weight and height values at different ages during childhood, indicating growth-related gains up to 20 years of age. Right panels indicate their corresponding normal age-specific rates of change (“growth velocity”), based on National Center for Health Statistics (NCHS) data available at: [http://www.cdc.gov/growthcharts/percentile\\_data\\_files.htm](http://www.cdc.gov/growthcharts/percentile_data_files.htm).<sup>30</sup> Representative data for boys’ height and linear growth velocity are shown in the upper panels. Data for girls’ weight and weight gain at different ages are shown in the lower panels. Graphed lines, from bottom to top, represent the observed 3rd, 10th, 50th, 90th, and 97th percentiles of normal childhood growth, respectively.

treatment impacts by developing outcome predictions based on a bounded modeling system that accounted for 1) age-related parasite exposure<sup>36–38</sup>; 2) the kinetics for development of inflammation-related disease<sup>39–42</sup>; 3) the impact of infection on early and mid-childhood growth retardation<sup>17,43</sup>; and 4) a child’s potential for catch-up growth at different stages of childhood and adolescence.<sup>44</sup> Our analysis indicates that optimal drug-based control strategies have the potential to substantially reduce developmental morbidities found among schistosomiasis-affected populations.

## MATERIALS AND METHODS

**Modeling approach.** Given the limited amount of data on long-term clinical outcomes of schistosomiasis control programs, and to estimate and compare the potential long-term benefits of different operational approaches to drug-based control of schistosomiasis, we sought to simulate the deleterious effect of chronic infection on early-life development (0 to 20 yr) by a dynamic model that coupled parasite worm acquisition during childhood to observed deviations from normal human growth patterns among children with schistosomiasis<sup>27,29,45,46</sup> (see Figure 2 and the Supplemental Appendix for details). This linked system allowed us to explore the relative quantitative impacts of different age-targeted control strategies on cumulative schistosomiasis-associated nutritional morbidity at 20 years of age, although in a stationary population with a stable environmental transmission pattern.<sup>6,8</sup>

Age plays an important role in the schistosome transmission, as it is strongly correlated with behavioral factors linked to risk for transmission (water contact rate, snail contamination, and new infection),<sup>36–38</sup> and to the phenomenon of gradual acquisition of age- or experience-dependent partial resistance to new infection.<sup>39–42</sup> The modeling system used for this analysis can be viewed as the average state of growth, infection, and

disease (mean worm burden, accumulated damage, and resulting developmental impairment) of an age cohort for whom infection and disease state are then “perturbed” by various treatment intervention strategies.<sup>23,24</sup>

Because morbidity and developmental stunting in schistosomiasis are linked to infection intensity and its cumulative duration,<sup>10</sup> chemotherapy-based disease control can take its cues from two different perspectives: 1) a global reduction of community intensity of infection (average worm burden) at a given time  $t$ , to be effected in the short term through broad-based drug treatment intervention; or 2) a targeted, age-based reduction of infection, based on a person’s year of life (as a surrogate of his or her current infection intensity and projected exposure to infection over the near future).<sup>25</sup> In this work, we focused on the latter, i.e., age-targeted treatment and its effects on age-dependent patterns of development.

Details of the mathematical modeling approach, and its programming and calibration are presented in the Supplemental Appendix. The related Mathematica programming used for this analysis is available from authors DG and XW.

## RESULTS

On the basis of modeling of schistosomiasis-associated growth retardation observed among untreated children (shown in Figure 2), Figure 3 shows potential remediation of growth deficits by a hypothetical, three-session praziquantel (PZQ) treatment regimen (given at 6, 9, and 12 years of age) for a typical resident of a schistosomiasis-endemic area. The analysis indicates that, despite continuing transmission and risk of reinfection, improvements can occur gradually by the end of childhood (age 20 yr) in terms of height and weight among treated as compared with untreated children (Table 2). Results of the modeling analysis, which quantified potential recovery from infection-associated weight deficits for both

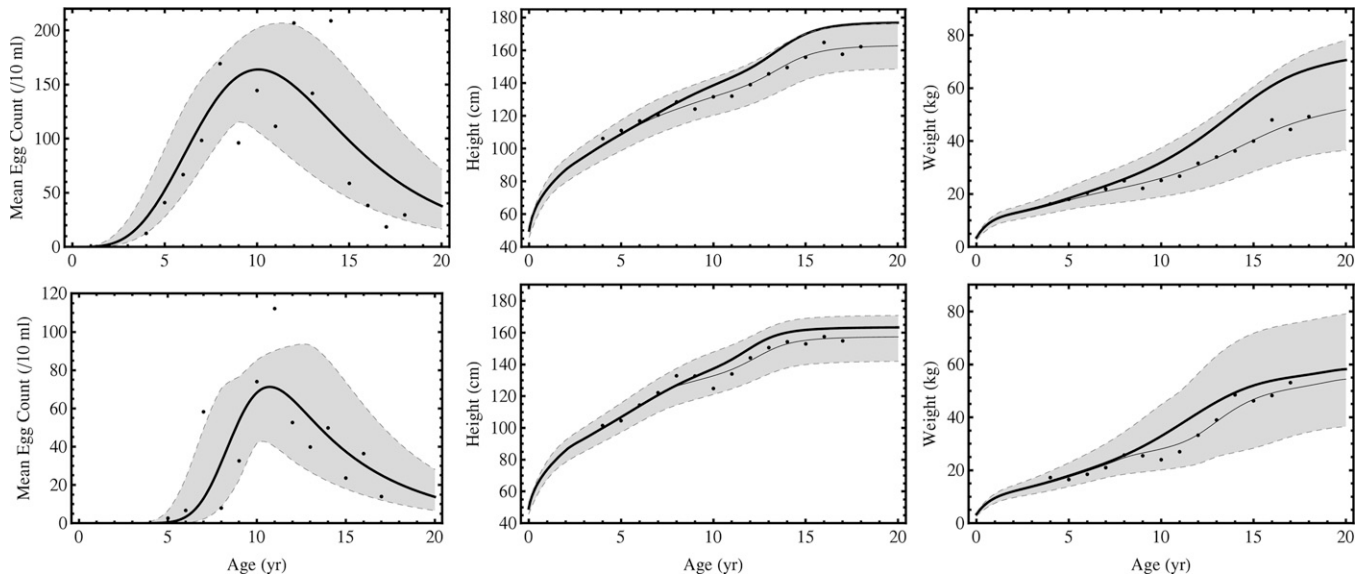


FIGURE 2. Envelopes of *Schistosoma* infection intensity (worm burden, approximated by counts of excreted eggs)<sup>47</sup> and related effects on growth patterns (in terms of height and weight) for the modeled heterogeneous endemic population. Boys are indicated in the upper panels and girls are indicated in the lower panels. Each hypothetical gender cohort was assembled from five quantile groups, reflecting the range of their initial potential for healthy growth, i.e., normally capable of reaching the 5th, 25th, 50th, 75th, or 95th percentiles, respectively. Left panels indicate the range of likely egg counts for each age group. Middle panels indicate the range of likely heights, and right panels indicate the likely range of weights at different ages among the affected childhood populations. In each height and weight plot, the thick solid curve represents the desired United States median growth, dashed lines from bottom to top represent, respectively, the community minimum and maximum values as affected by recurrent *Schistosoma* infection; small dots represent calibration data from field studies,<sup>31</sup> and the thin solid line is the best-fit curve with the parameters shown in Table 1.

girls and boys, indicate that treatment campaigns with greater adherence (i.e., 80% as compared with 20% yearly coverage) would result in the greatest improvement in growth outcomes (Figure 4).

We next explored the relative impact of three different regimens currently recommended by WHO for school-age treatment of schistosomiasis in high, medium, and low prevalence areas.<sup>48</sup> These regimens were 1) treat children every year from age 5 to 15 yr (recommended in high [ $\geq 50\%$ ] prevalence areas); 2) treat children every 2 years from age 5 to 15 yr (recommended in medium [10–30%] prevalence areas); and 3) treat children on school entry and at primary school completion (recommended in low [ $< 10\%$ ] prevalence areas). We also examined differences in outcomes among programs that commenced treatment either at age 4 or 6 yr. As compared with United States median values, Table 2 shows the mean relative heights and weights obtained at 20 years of age by boys

and girls living in communities following these different strategies, and compares results obtained for different levels of community participation (adherence). Figure 4 shows the same results from a different point of view, i.e., the resulting deficits (as a percentage of normal growth) in height and weight for boys and girls either after no therapy, or after participation in differently timed treatment programs during the childhood years from 5 to 15 yr. From Table 2 we see that for the benchmark population, starting treatment at age 4 yr instead of age 6 yr appears to make little difference in ultimate outcomes, both for the every-1 year and every-2 year strategies. The model also suggests that treatment at 6, 9, and 12 years of age has comparable benefits to those of an every-2 year treatment program. In contrast, the 2-session regimen (i.e., at only ages 5 and 15 yr) appears not to be very effective in improving net growth outcomes, no matter how high the adherence with this regimen. Overall, boys, who are often more wasted or

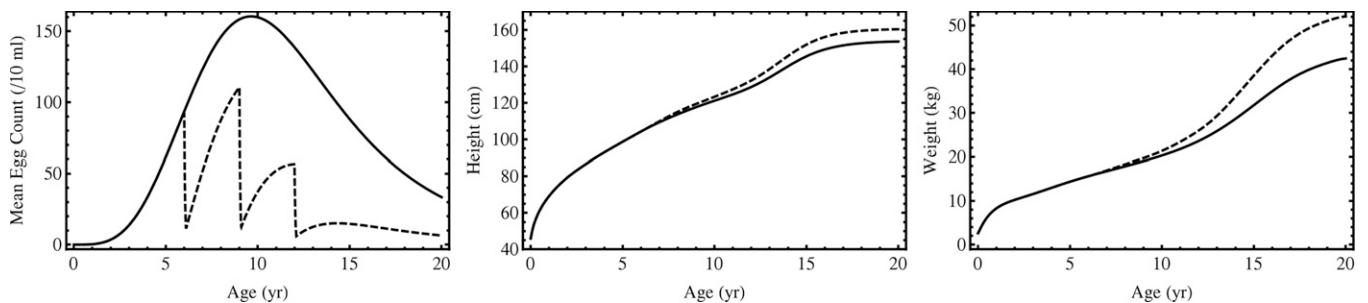


FIGURE 3. Projected effects of treatment at 6, 9, and 12 years of age (with the fraction of worms killed in each session being 90%) on worm burden and developmental growth of an individual randomly selected from the modeled community. Solid curves are for baseline state (untreated infection) and dashed lines show the expected impact of the three treatment schedule.

TABLE 1

Simulation parameter descriptions (see the Supplemental Appendix) and their best-fit values based on infection and anthropometric data from Kajiwi village, Kenya<sup>31</sup>

Type	Symbol	Description	Girls	Boys
			Height/weight	Height/weight
Worm burden	$S_0$	Maximum force of infection among ages	31.2	52.6
	$a_0$	Age (in years) when the rate of new infections begins to decline	8.7	7.1
	$p$	Exponential in contact pattern	15.13	2.96
Morbidity	$v_0$	Maximum morbidity resolution rate	10.18	0.75
	$\alpha$	Rate of min/max of resolution rate	0.2	0.07
	$a_1$	Threshold age for resolution jump	11.3	8.3
	$q_1$	Hill exponent for morbidity resolution	5.47	1.0
Remedial growth	$z_0/\rho$	Threshold of stunting factor $\phi$ /morbidity accretion rate	7.67/9.85	122.96/103.61
	$\phi_0$	Maximum stunting (growth reduction) rates caused by morbidity	0.5/0.13	0.52/0.18
	$\phi_1$	Baseline stunting rates (norm = 1), caused by factors other than schisto infection)	0.99/0.82	0.96/0.8
	$m$	Hill exponent in $\phi$	7.1/5.15	4.93/1.7
	$K$	Ratio of age-specific remedial growth rate to normal growth rate	11.13/8.0	9.37/7.84

stunted than girls when untreated,<sup>29,49</sup> were predicted to experience greater benefits after treatment than girls, for whatever strategy used.

As shown in the lower panels of Figure 4, in communities with 80% or higher adherence to repeated annual treatment, cumulative deficits (estimated for 20-year-old individuals in the face of continuing risk for reinfection with *S. haematobium*) were reduced in magnitude for height outcomes by 70% in boys and by about 76% in girls. Corresponding weight deficits at 20 years of age were reduced by 72% for boys and by 70% in girls. Where treatment was less frequent (only 2–3 treatments in childhood) or where adherence was less good (e.g., 20%; see Figure 4, upper panels) the impact of drug-

based treatment campaigns on the childhood population’s growth and development profile was projected to be much more modest, on the order of only 3–60% reductions in the cumulative height and weight deficits overall.

DISCUSSION

The nonlinear dynamics of *Schistosoma* transmission and the complexity of age- and time-related factors influencing infection-related disease formation have made it difficult for experts to gauge the potential lifetime benefits of repeated anti-schistosomal treatments in endemic communities.<sup>50</sup> Risk of infection-associated morbidity increases with both

TABLE 2

Predicted community height and weight values (relative to United States median at age 20 yr), ensuing from different school-age treatment regimens\*

Strategy	Female		Male	
	Height	Weight	Height	Weight
A. Untreated	0.962 (0.036)	0.939 (0.138)	0.924 (0.033)	0.757 (0.115)
B. Treat at school entry and completion (ages 5 and 15 yr) with:				
20% adherence	0.962 (0.036)	0.939 (0.138)	0.926 (0.033)	0.771 (0.122)
50% adherence	0.962 (0.036)	0.940 (0.138)	0.930 (0.033)	0.792 (0.121)
80% adherence	0.963 (0.036)	0.941 (0.138)	0.933 (0.033)	0.812 (0.122)
C. Treat at ages 6, 9, and 12 yr, with:				
20% adherence	0.968 (0.037)	0.948 (0.142)	0.934 (0.040)	0.793 (0.135)
50% adherence	0.976 (0.038)	0.963 (0.146)	0.950 (0.043)	0.846 (0.146)
80% adherence	0.985 (0.034)	0.978 (0.144)	0.967 (0.041)	0.896 (0.145)
D. Treat every other year beginning age 6 yr, with:				
20% adherence	0.968 (0.038)	0.949 (0.143)	0.935 (0.042)	0.799 (0.142)
50% adherence	0.979 (0.039)	0.965 (0.147)	0.954 (0.046)	0.861 (0.154)
80% adherence	0.989 (0.035)	0.980 (0.145)	0.973 (0.043)	0.919 (0.150)
E. Treat every other year beginning age 4 yr, with:				
20% adherence	0.968 (0.038)	0.949 (0.143)	0.935 (0.042)	0.799 (0.142)
50% adherence	0.979 (0.035)	0.965 (0.147)	0.955 (0.046)	0.861 (0.155)
80% adherence	0.989 (0.035)	0.980 (0.145)	0.974 (0.043)	0.920 (0.151)
F. Treat every year beginning age 6 yr, with:				
20% adherence	0.969 (0.039)	0.949 (0.143)	0.936 (0.043)	0.802 (0.146)
50% adherence	0.980 (0.040)	0.965 (0.148)	0.956 (0.048)	0.868 (0.160)
80% adherence	0.991 (0.035)	0.982 (0.145)	0.976 (0.044)	0.930 (0.155)
G. Treat every year beginning age 4 yr, with:				
20% adherence	0.969 (0.039)	0.949 (0.143)	0.936 (0.043)	0.802 (0.146)
50% adherence	0.980 (0.040)	0.965 (0.148)	0.957 (0.048)	0.869 (0.160)
80% adherence	0.991 (0.035)	0.982 (0.145)	0.977 (0.044)	0.931 (0.155)

\* Shown are projected mean values, with standard deviations in parentheses, for the fraction of normal growth obtained by boys and girls under each regimen.

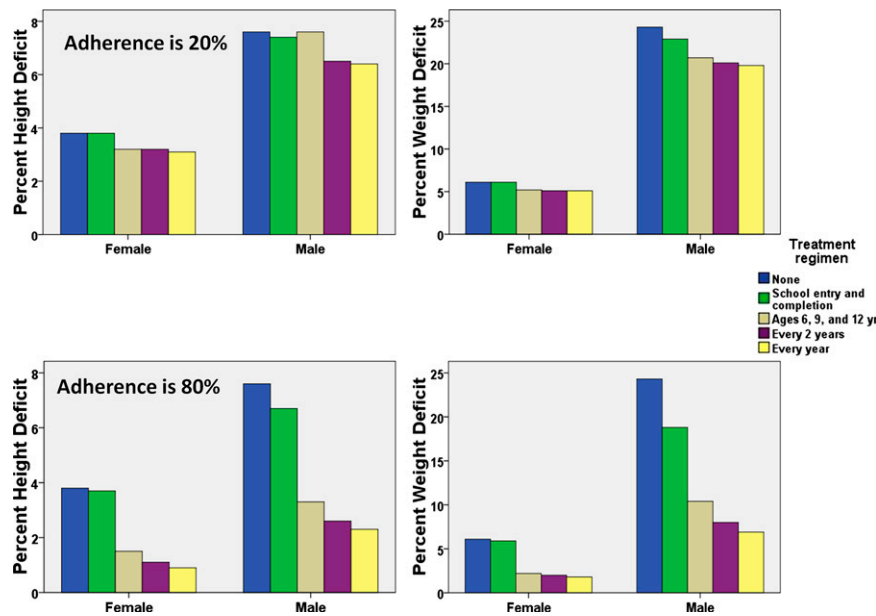


FIGURE 4. Projected impact of different schistosomiasis treatment regimens on accrued growth (relative to normal) at 20 years of age for infected girls and boys exposed to possible reinfection in endemic areas, based on model simulations of growth, reinfection, and potential for catch-up growth after treatment. In each panel, clustered bars for girls and boys compare the projected outcomes of five proposed strategies: 1) no treatment; 2) treatment at the time of school entry and completion (ages 5 and 15 yr); 3) treatment at 6, 9, and 12 years of age; 4) treatment every 2 years; and 5) treatment every year during school ages from 4 up to 15 years of age. Upper panels show substantially reduced impact when community participation is low (20%), as compared with where projected uptake and adherence are high (80%, lower panels).

the duration and the intensity of infection, reflecting an aggregate effect of local tissue injury from granulomatous inflammation to parasite eggs deposited in host tissues, and the systemic effects of chronic inflammation.<sup>15,21,51</sup> In particular, chronic anemia and growth stunting during childhood are believed to be the result of chronic anti-parasite inflammation that persists throughout childhood and adolescence.<sup>16</sup> Although school-based treatment has long been recommended as a means to suppress the heaviest burden of *Schistosoma* infection that occurs during childhood,<sup>52</sup> field studies indicate that such programs may fail to suppress transmission in high- and medium-risk communities, such that reinfection remains highly likely despite repeated treatments given during school age.<sup>6</sup> Although inflammation may subside after successful elimination of infection (with substantial benefits in terms of improved hemoglobin levels and rebound growth)<sup>8,13,27,45,53</sup> early reinfection appears to reactivate these inflammation-associated morbidities, resulting in only limited benefits from any single round of therapy.<sup>34,54</sup>

It is only recently that growth and nutrition-related morbidities have become more widely recognized as significant components of the schistosomiasis-associated disease burden.<sup>17</sup> Notably, only two studies have examined the long-term effects of repeated anti-schistosomal treatments (given during childhood) on later adult health.<sup>55,56</sup> For now, because the data on the late benefits of treatment are limited, and considering the need for informed policy formulation in this area, it is appropriate at this point to use established modeling techniques (calibrated on available data) to estimate the benefits of repeated treatment campaigns on *Schistosoma*-associated growth deficits that may occur during childhood. Our modeling analysis, benchmarked to available individual-level field data, was based on the well-recognized potential of chil-

dren for “catch-up growth” following recovery from chronic diseases.<sup>44</sup> Individuals can acutely increase their post-insult growth velocity up to 4-fold after the growth restriction ceases. This is known as type A catch-up growth. In another form of catch-up growth, known as type B, puberty can be delayed by several years, allowing linear bone growth to continue for an extended compensatory period.<sup>44</sup> However, for schistosomiasis, the net impact of any type B recovery is likely to be complex, in that pubertal hormonal changes per se have been shown to down-modulate anti-parasite inflammation and reduce nutritional deficits associated with *Schistosoma japonicum* infection.<sup>57</sup> We recognize that one of the limitations of our simulation model is that we are not able to distinguish the relative contributions of these two types of growth recovery. Future longitudinal studies, using careful Tanner staging for sexual maturity<sup>57</sup> will be needed to clarify the relative effects of type A and type B recovery following treatment. Other factors, such as diet quality and co-infection with other parasitic worms, including soil-transmitted helminths, may serve to limit actual catch-up growth in treatment campaigns. Our study is limited in that it focused primarily on schistosomiasis and data on the impact of *S. haematobium* infection. Outcomes of mass-treatment may prove different for *Schistosoma mansoni*- or *S. japonicum*-affected areas,<sup>29,45,49</sup> particularly if the risk for reinfection is highly episodic or changes significantly during the treatment campaign.

Like other studies of the growth impact of schistosomiasis,<sup>27,29,45,49</sup> we have used CDC/NCHS growth standards<sup>58</sup> as our norms for affected children. Even though their formulae were developed on the basis of sampling children within the United States population, these 2000 CDC/WHO standards are widely accepted as reference parameters for childhood growth among most other populations.<sup>30,59</sup> New reference

standards based on sampling in six countries are being developed by the WHO,<sup>60</sup> but, at the time of this study, they had not been implemented for children > 5 years of age. Undoubtedly, for future research, the use of these newer international standards should be considered.

We should stress that, as constructed, our model gives a lower bound estimate of growth remediation, and the real benefits could be higher. Indeed, mass drug administration (MDA) may have a double effect in some communities—it can lower human infection levels and may also reduce transmission in some locales, particularly if high-risk adults are included in the treatment campaign. Our present simulation does not account for the coupled process of “human-to-snail transmission” (only its “snail-to-human” part), so that part (1) of the model system could underestimate the effect of drug treatments on the process of contamination and snail infection. However, human-to-snail transmission remains a patchy, nonlinear phenomenon in which a single infected individual (alone) can continue to contaminate one or more snail contact sites and maintain transmission for several months within any given community. This is the likely reason that MDA programs have not reliably reduced transmission in many high-prevalence areas.<sup>8,61</sup> Nevertheless, our projections do suggest an increasing benefit from repeated treatments during childhood, even in the face of continuing reinfection.

Our results suggest that repeated treatment during childhood has the potential to reverse most, but not all, growth impairment associated with schistosomiasis. In particular, early treatment of *S. haematobium* with PZQ beginning at or before 6 years of age, with repeated treatments into the adolescent years, appears likely to be most effective in facilitating catch-up growth among repeatedly infected children. The gender-specific differences in growth observed among our benchmark Kenyan population (Figure 2) were consistent with those found in treatment studies of *S. mansoni* infection in Brazil.<sup>29,49</sup> In those studies, infected males were found to suffer more undernutrition, but they also had more dramatic improvements after anti-schistosome therapy.<sup>49</sup> Among our calibration sample of children, boys had higher average egg burdens than girls (geometric mean = 96 eggs/10 mL urine versus 36 eggs/10 mL urine), which might explain a higher risk of inflammation with corresponding worsening of growth-related morbidity outcomes. Another possible factor contributing to gender difference may be a difference in daily activity patterns, with higher rates of caloric consumption and/or higher rates of reinfection among boys.<sup>62</sup> More research on the question of the relative gender-specific, growth-related disease risk is needed.

Historically, policy-makers have tended to underestimate the health impact of non-lethal morbidities associated with schistosomiasis (compare, e.g., the conclusions stated in References 63–66 to the meta-analysis in Reference 15). However, multiple cross-sectional studies have documented growth retardation in children infected with all species of *Schistosoma* parasites.<sup>45,49,67,68</sup> In terms of policy implications, there are likely to be important economic effects of childhood growth retardation that results in permanent stunting of adults. Short stature is associated with a decrease in productivity in many settings: previous studies estimate that a 1% decrease in adult stature is associated with a 1.4% decrease in productivity in less-developed economies.<sup>69–71</sup> Unmeasured confounders, such as differences in food availability, undoubtedly exist,<sup>13</sup> but the

reproducibility of the benefits of specific anti-schistosomal therapy suggest a significant growth effect of chronic schistosomiasis wherever it occurs.<sup>27,28,45,49</sup> Although the durable long-term impact of anti-schistosomal treatment in reversing wasting or stunting has not been as well studied, treatment outcomes studies, including randomized-placebo controlled trials, indicate the potential for growth improvement with specific anti-schistosomal therapy. In the Philippines, in villages endemic for *S. japonicum*, children who were most wasted or stunted at baseline had the best relative outcomes after treatment.<sup>45</sup> In Kenya, marked improvement in growth was observed after a single dose of an anti-schistosomal drug (metrifonate or PZQ) for the treatment of *S. haematobium* at follow-up after 8 months.<sup>27</sup> Of note, an inflammatory response related to growth impairment has been shown when reinfection occurs after successful primary treatment of *S. japonicum*.<sup>54</sup> This association, however, has not been examined in areas endemic for *S. haematobium* or *S. mansoni*, and the potential importance of this link to later growth impairments remains an important area for future study.

Other aspects of schistosomiasis-related morbidity and impairment were not included in our model. However, the age dynamics and reversibility of outcomes such as anemia and learning-related disabilities could easily be incorporated into future modeling efforts to identify the optimal timing and frequency for their prevention. Other modifications may need to be considered as new data emerge. Children’s growth patterns exhibit different rates according to levels of bone maturity and sexual development.<sup>44,57,72,73</sup> Retardation in growth will continue if inflammation persists or quickly recurs,<sup>74</sup> but there is a potential for regaining a normal growth velocity.<sup>75</sup> Changes in environment and nutrient availability are not necessarily sufficient to reverse early growth impairment.<sup>72</sup> However, the effect of a delayed puberty, sometimes seen in low resource settings, can be beneficial for catch-up growth if the causative insult has ceased.<sup>75</sup> Our results suggest that in the typical setting of endemic schistosomiasis, where reinfection can rapidly occur after treatment, mass administration campaigns that include periodic retreatment through adolescence may be needed to obtain a healthy rate of growth.

Data are scarce on the true prevalence of schistosomiasis among preschool-age children.<sup>76</sup> Our analysis was calibrated on detailed information from school-age children (5–20 yr) in one affected village. In the future, to assess the potential benefit of anti-schistosomal treatment during preschool years, it will be important to include these younger subjects in community-based studies, including more sensitive diagnostics for *Schistosoma* infection than the standard, relatively insensitive assays based on egg-detection in stool and urine.<sup>77–81</sup> Quantifying pro-inflammatory markers such as interleukin-6 (IL-6) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) among preschool-age children with serologic evidence of early infection could provide evidence of early effects of infection before egg numbers reach their threshold to be reliably detected in the excreta.<sup>47,80,81</sup> Our simulations indicate that if growth deficits are associated with infection in preschool years, then starting treatment at earlier ages (preschool years) might yield the best results for achieving near-normal growth in high-risk areas. As structured, our model did not indicate a benefit for early age therapy. However, it was based only on data for children 5 years of age and older, and in areas where earlier growth deficits can be tied to schistosomiasis, then initiation of treatment

in preschool years will likely prove beneficial. For now, and for the particular type of village setting studied here, our model clearly suggests that every other year treatments during school age (6–20 yrs) and high community adherence to treatment (> 50%) will provide the best aggregate growth outcomes among at-risk individuals.

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Authors' addresses: David Gurarie and Xiaoxia Wang, Department of Mathematics, Yost Hall, Case Western Reserve University, Cleveland, OH, E-mails: [dxg5@cwru.edu](mailto:dxg5@cwru.edu) and [xxw@cwru.edu](mailto:xxw@cwru.edu). Amaya L. Bustinduy, Division of Infectious Diseases, Department of Pediatrics, Rainbow Babies and Children's Hospital, Cleveland, OH, E-mail: [axb342@case.edu](mailto:axb342@case.edu). Charles H. King, Center for Global Health and Diseases, Wolstein Research Building, Cleveland, OH, E-mail: [chk@cwru.edu](mailto:chk@cwru.edu).

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