Comparison of community-wide, integrated mass drug administration strategies for schistosomiasis and soil-transmitted helminthiasis: a cost-effectiveness modelling study

Nathan C Lo, Isaac I Bogoch, Brian G Blackburn, Giovanna Raso, Eliézer K N'Goran, Jean T Coulibaly, Sören L Becker, Howard B Abrams, Jürg Utzinger, Jason R Andrews

Summary

Background More than 1·5 billion people are affected by schistosomiasis or soil-transmitted helminthiasis. WHO's recommendations for mass drug administration (MDA) against these parasitic infections emphasise treatment of school-aged children, using separate treatment guidelines for these two helminthiases groups. We aimed to evaluate the cost-effectiveness of expanding integrated MDA to the entire community in four settings in Côte d'Ivoire.

Methods We extended previously published, dynamic, age-structured models of helminthiases transmission to simulate costs and disability averted with integrated MDA (of praziquantel and albendazole) for schistosomiasis and soil-transmitted helminthiasis. We calibrated the model to data for prevalence and intensity of species-specific helminth infection from surveys undertaken in four communities in Côte d'Ivoire between March, 1997, and September, 2010. We simulated a 15-year treatment programme with 75% coverage in only school-aged children; school-aged children and preschool-aged children; adults; and the entire community. Treatment costs were estimated at US$0·74 for school-aged children and $1·74 for preschool-aged children and adults. The incremental cost-effectiveness ratio (ICER) was calculated in 2014 US dollars per disability-adjusted life-year (DALY) averted.

Findings Expanded community-wide treatment was highly cost effective compared with treatment of only school-aged children (ICER $167 per DALY averted) and WHO guidelines (ICER $127 per DALY averted), and remained highly cost effective even if treatment costs for preschool-aged children and adults were ten times greater than those for school-aged children. Community-wide treatment remained highly cost effective even when elimination of helminth infections was not achieved. These findings were robust across the four diverse communities in Côte d'Ivoire, only one of which would have received annual MDA for both schistosomiasis and soil-transmitted helminthiasis under the latest WHO guidelines. Treatment every 6 months was also highly cost effective in three out of four communities.

Interpretation Integrated, community-wide MDA programmes for schistosomiasis and soil-transmitted helminthiasis can be highly cost effective, even in communities with low disease burden in any helminth group. These results support an urgent need to re-evaluate current global guidelines for helminthiases control programmes to include community-wide treatment, increased treatment frequency, and consideration for lowered prevalence thresholds for integrated treatment.

Funding Stanford University Medical Scholars Programme, Mount Sinai Hospital-University Health Network AMO Innovation Fund.

Lancet Glob Health 2015; 3: e629–38

See Comment page e583

Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine, Stanford, CA, USA (N C Lo BS, Prof B G Blackburn MD, J R Andrews MD); **Department of Medicine, University of Toronto, Toronto, ON, Canada** (I I Bogoch MD, Prof H B Abrams MD); **Division of General Internal Medicine** (I I Bogoch, Prof H B Abrams), **and Division of Infectious Diseases, Toronto General Hospital, University Health Network, Toronto, ON, Canada** (I I Bogoch); **Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute, Basel, Switzerland** (G Raso PhD, J T Coulibaly PhD, S L Becker MD, Prof J Utzinger PhD); **University of Basel, Basel, Switzerland** (G Raso, J T Coulibaly, S L Becker, Prof J Utzinger); **Unité de Formation et de Recherche Biosciences, Université Félix Houphouët-Boigny, Abidjan, Côte d'Ivoire** (Prof E K N'Goran PhD, J T Coulibaly); **Centre Suisse de Recherches Scientifiques en Côte d'Ivoire, Abidjan, Côte d'Ivoire** (Prof E K N'Goran, J T Coulibaly); **and Institute of Medical Microbiology and Hygiene, Saarland University, Homburg/Saar, Germany** (S L Becker)

Correspondence to:
Mr Nathan C Lo, Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine, Stanford, CA 94305, USA
nathan.lo@stanford.edu

Introduction

Elimination of schistosomiasis and soil-transmitted helminthiasis poses a great challenge, but is an even greater opportunity to alleviate the suffering of the more than 1·5 billion people who are infected with the parasitic worms that give rise to these diseases.[1,2] Discussions surrounding helminth infections, a subset of the neglected tropical diseases, have shifted from control to elimination in the past few years.[3,4] This change has been shown in the increased international funding for mass treatment campaigns from foreign aid programmes, non-governmental organisations, and philanthropy, in addition to expanded drug donation programmes by pharmaceutical companies.[3,5] To achieve these ambitious aims, WHO issued a roadmap[3] for the control and elimination of neglected tropical diseases, which advocates for expansion of mass drug administration (MDA) to address the large disease burden of helminthiases, including schistosomiasis and soil-transmitted helminthiasis (caused by infection with *Ascaris lumbricoides*, the two hookworm species *Ancylostoma duodenale* and *Necator americanus*, and *Trichuris trichiura*).

Consistent with published guidelines by WHO,[6] MDA programmes provide large-scale empirical drug

Research in context

Evidence before this study

We searched PubMed for relevant articles published in English before Aug 22, 2015, using the search terms "helminth" or "schistosomiasis" together with "cost-effectiveness" and "treatment" restricted to the title and abstract fields. This search identified 34 articles. Of these, ten studies reported about the cost-effectiveness of mass drug administration (MDA) against schistosomiasis or soil-transmitted helminthiasis alone and three studies discussed integrated treatment of schistosomiasis, soil-transmitted helminthiasis, or other diseases. However, none of these studies evaluated the cost-effectiveness of integrated community-wide MDA against schistosomiasis and soil-transmitted helminthiasis using the disability-adjusted life-year.

Added value of this study

Our findings suggest that integrated community-wide MDA with high coverage (>75%) and sustained administration (>5 years) against schistosomiasis and soil-transmitted helminthiasis could be crucial in decreasing community disease burden and lowering reinfection. Expanded community-wide MDA was highly cost effective in four Côte d'Ivoire communities across a range of conditions, including when elimination could not be achieved. Increasing treatment intervals to every 6 months was also reported to be highly cost effective. This study goes beyond previous work to provide a rigorous multisetting cost-effectiveness analysis to optimise MDA against two major groups of helminthiases.

Implications of all evidence available

Recent models and our findings support the need to revise global guidelines to address expansion of MDA to the entire community where these diseases are endemic, and improve guidance for integration of treatment programmes for schistosomiasis and soil-transmitted helminthiasis. Alternative or complementary interventions might also be needed to achieve elimination of these infections.

distribution irrespective of individual infection status and have previously targeted school-aged children (aged 5–14 years) through school-based delivery schemes (appendix). This approach has been universally viewed as cost effective and practical, since children are believed to harbour a higher disease burden and greater disability than adults do. Additionally, schools provide an effective distribution platform and drugs are often donated by pharmaceutical companies for these purposes.[6–8] However, despite the efforts of regular MDA campaigns, the disease burden of schistosomiasis and soil-transmitted helminthiasis has remained high.[9,10] The latest WHO recommendations[6,11] are used to guide MDA strategies, but were developed without a goal of elimination, are not based on a cost-effectiveness framework, and provide separate treatment recommendations for schistosomiasis and soil-transmitted helminthiasis with little guidance for the role of integrated treatment programmes. Recent work in the past two years has suggested the importance of expansion of MDA to additional age groups to overcome high reinfection rates and potentially enable elimination of these diseases.[5,12,13] However, the cost-effectiveness of expanding treatment to additional age groups is unknown.

Crucial, policy-relevant questions remain about the cost-effectiveness of integrated MDA programmes that might vary substantially in different contexts and settings—eg, when treatment is provided to the entire community (rather than school-aged children only), whether elimination of diseases is met or not, administration of different frequencies and treatment coverage, and the varying prevalence and intensities of infection in communities. To address these policy-relevant scenarios, we modelled the cost-effectiveness of MDA strategies for schistosomiasis and soil-transmitted helminthiasis using data from four communities in Côte d'Ivoire and compared integrated, community-wide MDA with treatment of only school-aged children, current WHO guidelines, and other MDA scenarios.[6]

See Online for appendix

Methods

Model overview

We extended the work of existing transmission models for helminth infections[13–15] to include multiple helminth infections, disability estimates, costs, and simulation of integrated treatment targeted with praziquantel for schistosomiasis and albendazole for soil-transmitted helminthiasis. By use of empirical data from four communities in Côte d'Ivoire, we simulated communities of 5000 people and projected age-specific prevalence and intensity of infections (ie, mean worm burden, often measured in eggs per g of faeces) over 15 years.[16–20]

We compared annual MDA for school-aged children alone; school-aged children and preschool-aged children (aged 2–4 years); adults alone (aged ≥15 years); and the entire community, using no treatment as a base case. Each treatment strategy was applied for 15 years. Strategies were compared with treatment intervals of 3 months, 4 months, 6 months, 1 year, 2 years, 3 years, and 4 years.[6] We modelled the total disability averted and direct costs of MDA treatment programmes in four simulated communities of 5000 people in Côte d'Ivoire (A–D) to model medium-sized communities.

We defined direct costs in 2014 US dollars (US$) and measured total disability averted in the disability-adjusted life-year (DALY) after published sequelae and weights.[1,8,21–23] Cost-effectiveness was measured with the incremental cost-effectiveness ratio (ICER), defined as the incremental cost divided by the incremental disability averted ($ per DALY averted). We deemed treatment strategies to be highly cost effective if the ICER was below the per-capita

	Infection intensity*	Disability weights
Schistosoma mansoni		
Infection[21]	All	0·005–0·02
Schistosoma haematobium		
Infection[21]	All	0·005–0·02
Ascaris lumbricoides		
Mild abdominopelvic problems	Moderate	0·0108
Symptomatic infection	Heavy	0·0296
Wasting†	Heavy	0·1245
Trichuris trichiura		
Mild abdominopelvic problems	Moderate	0·0108
Symptomatic infection	Heavy	0·0296
Wasting†	Heavy	0·1245
Hookworm		
Mild abdominopelvic problems	Moderate to heavy	0·0108
Wasting†	Heavy	0·1245
Anaemia		
Mild anaemia‡	All	0·0041
Moderate anaemia‡	All	0·0056
Severe anaemia‡	All	0·1615

All infection intensities include light, moderate, and heavy infections. Table adapted from Pullan and colleagues,[1] with permission. *Based on eggs per g in faeces (appendix). †Wasting was applied to only a subset of children harbouring a heavy infection. ‡Anaemia averted through treatment was calculated independent of intensity of infection, and modelled separately as a result of either hookworm infection or schistosomiasis.

Table 1: **Disability weights for infections with *Schistosoma* and soil-transmitted helminths**

	Base-case value
Baseline cohort characteristics	
Mean age (SD), years[16–20]	27·3 (19·6)
Age groups[38]	
Preschool children	10%
School-aged children	25%
Adults	65%
Women	50%
Community population, n	5000
Mean Hb (SD), g/L[33]	
Men	134 (19)
Women	111 (16)
Children	112 (15)
National child wasting[34]	7·0%
Cost (2014 US$) and treatment parameters per person	
Drugs	
Albendazole, 400 mg[6,7,39]	$0·03
Praziquantel, 40 mg/kg[6–8,39]	$0·21
Method of delivery	
School-based delivery[6–8,40–48]	$0·50
Community-based delivery*[8,45,48]	$1·50
Drugs plus school-based delivery	$0·74
Drugs plus community-based delivery	$1·74
Treatment coverage in all communities[3]	75%
Praziquantel and albendazole EPG reduction[27–29]	
Schistosoma spp	85%
Hookworm	89·5%
Ascaris lumbricoides	97·5%
Trichuris trichiura	64%
Life expectancy (years)[15]	
Schistosoma spp	4
Hookworm	2·5
A lumbricoides	1·5
T trichiura	1·5

Hb=haemoglobin. EPG=eggs per g of faeces (except for *Schistosoma haematobium* that is measured in eggs per 10 mL of urine). *Community-based delivery was assumed to be three times the cost of school-based delivery.

Table 2: **Baseline cohort characteristics and selected cost, treatment, and epidemiological parameters**

gross domestic product of Côte d'Ivoire ($1521 in 2013).[24] Future costs and disability averted were discounted at 3% per year, and undiscounted results are also presented.[25]

Transmission model and assumptions

We adapted a dynamic, age-structured, and deterministic transmission model to project population-level burden of helminth infections during the 15-year simulation period. We simultaneously modelled the transmission dynamics of five helminths: *Schistosoma haematobium, Schistosoma mansoni, A lumbricoides, T trichiura,* and hookworm. Every helminth type's lifecycle was modelled by tracking the mean worm burden in every age group. This process is driven by the production of eggs and excretion of this infectious material into the environment, uptake of infectious material through either ingestion of eggs or contact with larvae, and mortality of the worm within the host (appendix). Individuals were modelled as susceptible to reinfection immediately after treatment. On the basis of previous models and empirical observation of helminthiases distribution, prevalence of helminth infection was assumed to follow a negative binomial distribution with respect to burden of infection (worm burden or eggs per g [*S haematobium* is measured in eggs per 10 mL urine]).[12–15] This distribution was recalculated at every time step of the model (1 month). A heterogeneous mixing model was derived to allow various extents of interaction between age groups and the environment. Reproduction number and exposure rate were calculated from primary epidemiological data specific to each Côte d'Ivoire community and age group, using the assumption that preschool-aged children and school-aged children contributed twice the relative amount of eggs to the environment than did adults (appendix).[13]

Treatment and disability model and assumptions

We modelled the treatment effect of MDA with praziquantel (for schistosomiasis) and albendazole (for soil-transmitted helminthiasis) on prevalence of helminth infections and DALYs. Treatment was modelled

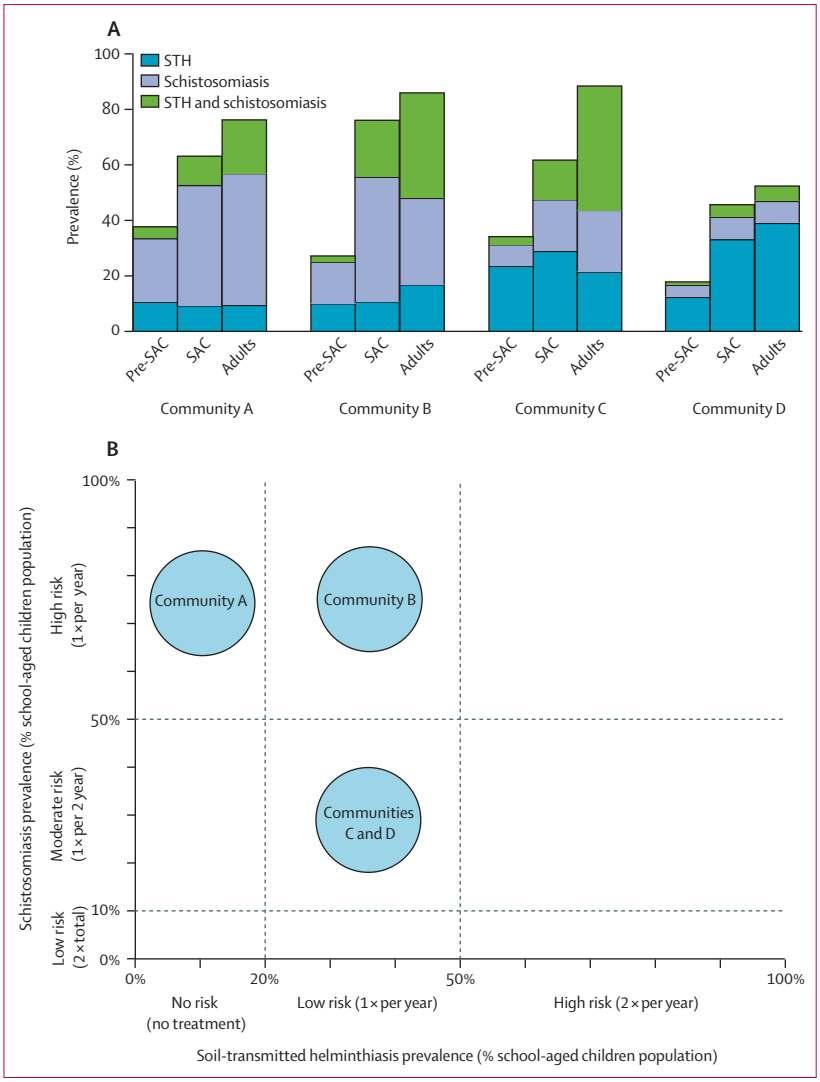

Figure 1: **Baseline epidemiology of four communities in Côte d'Ivoire and associated WHO-recommended control programmes**
(A) Initial observed helminth prevalence and (B) WHO guidelines[6,11] for helminthiases control programmes with associated prevalence values that categorise the risk for schistosomiasis and soil-transmitted helminthiasis of communities A–D.[16–20] STH=soil-transmitted helminthiasis. Pre-SAC=preschool-aged children. SAC=school-aged children.

as an instant reduction in mean worm burden,[5,8,12–14,26] estimated from extent of reduction of eggs per g of faeces reported in clinical trials.[27–29] We used a treatment coverage of 75% to adhere with the WHO goal for helminthiases MDA by 2020.[3]

Disability was calculated on the basis of the infection intensity of individuals within the population and updated disability weights (DALYs; table 1).[1,8,21–23] For soil-transmitted helminthiasis, the population was divided into four categories—no infection, light intensity, moderate intensity, and heavy intensity infection—with associated sequelae based on eggs per g of faeces, which was used as an indicator for severity of infection. Schistosomiasis was treated as binary, whereby individuals were either regarded as uninfected or infected according to reported disability weights.[21,23]

Anaemia was modelled by a calculation of the proportion of mild, moderate, and severe anaemia that resolved through treatment of hookworm infection and schistosomiasis. This calculation consisted of a mixture model methodology and documented downward shifts in haemoglobin for any individual with hookworm infection or schistosomiasis (appendix).[30–33] Wasting was estimated by determining the proportion of national child wasting in Côte d'Ivoire attributable to heavy helminth infections on the basis of reported *Z*-score estimates of the reduction in weight for height due to heavy helminth infection.[34,35]

Polyparasitism is common in Côte d'Ivoire[36] and was modelled under the assumptions that acquisition of each infection was independent from one another, which was supported by an absence of strong or consistent correlation between infections detected from cross-sectional surveys completed in Côte d'Ivoire (appendix). Disability for individuals with polyparasitism and multiple sequelae were treated as multiplicative following convention.[37]

Input epidemiological and cost data

For epidemiological parameters specific to every community and age group, we used primary age-structured data on prevalence and intensity of infection of *Schistosoma* and soil-transmitted helminths from cross-sectional surveys done in four separate untreated communities with diverse geography and climate within Côte d'Ivoire.[16–20] Prevalence and intensity of infection were adjusted for imperfect diagnostics (appendix).

Treatment costs included both drug and delivery costs, and were calculated from the perspective of financial costs of a neglected tropical diseases treatment programme under the framework of a national campaign (table 2). School-based delivery costs were applied to school-aged children, and community-based delivery costs were used for preschool-aged children and adults. These costs were estimated from the scientific literature and the International Drug Price Indicator Guide, and reflected the cost of praziquantel, albendazole, and delivery costs, adjusted through the US Consumer Price Index to 2014 US dollars. We conservatively assumed that praziquantel and albendazole were not donated, and priced at \$0·21 and \$0·03, respectively.[6–8,39] School-based delivery costs were estimated at \$0·50, which represent the higher end of price estimations from the literature.[7,8,40–48] Estimated delivery costs from the literature included drug shipment, vehicle use, staff salaries, planning costs, technical support, and daily compensation, among other included costs. Indirect delivery costs associated with volunteer time for school-based delivery (eg, teachers) were not explicitly included in many of these estimations. Community treatment was assumed to have delivery costs that were three times

that of school-based programmes because of the increased logistical costs of community delivery and remuneration to community health workers.[8,45,48] Although we did not scale delivery costs with the size of the treated population, we used cost estimations that were conservative and did not assume advantages from economies of scale. The composite cost for treatment was estimated to be $0·74 for school-aged children and $1·74 for community treatment to preschool-aged children and adults.[7,8,29]

Statistical analysis

We did a series of one-way sensitivity analyses and a probabilistic sensitivity analysis by varying key parameters of our model across a range of feasible values. We used these data to determine the robustness of our results and the effect of specific assumptions. Our one-way sensitivity analyses assessed the effect of varying one parameter on the ICER value of integrated community-wide treatment compared with targeting only school-aged children. We examined the most influential parameters, including the school-based and community-based delivery cost, disability weight for schistosomiasis, frequency of treatment, coverage, and association between the relative contribution of infectious material into the environment between preschool-aged children, school-aged children, and adults (appendix). The authors fully support the importance of data sharing and transparency in research; full model code and data are available on request to the authors.

Role of the funding source

The funder of this study had no role in the design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Four communities in Côte d'Ivoire were surveyed between March, 1997, and September, 2010, for helminth infections.[16–20] The prevalence of helminth infections investigated was highly variable between age groups and the four communities (figure 1A, appendix). All four communities had a higher prevalence of helminth infections in adults than in school-aged children. Of the four communities, communities A and B had high burdens (>50% prevalence in school-aged children) for schistosomiasis, whereas communities C and D had a moderate burden (10–50%). Communities B, C, and D had a low burden (20–50% prevalence among school-aged children) for soil-transmitted helminthiasis, whereas community A was deemed no risk (<20%). Following WHO guidelines for helminthiases control programmes, the four communities would have been classified under three unique recommendations for MDA (figure 1B).

	Total costs (2014 US$)		Total disability (DALYs)		ICER (US$ per DALY averted)
	Discounted	Undiscounted	Discounted	Undiscounted	
No treatment	$0	$0	3252·1	4090·7	NA
SAC only	$34 122	$41 625	2964·1	3718·6	118
SAC and pre-SAC	$66 214	$80 775	2899·9	3636·3	Dominated*
Adults only	$208 603	$254 475	2429·3	3033·4	Dominated*
Community-wide	$274 817	$335 250	1521·6	1836·5	167

Costs and disability are discounted at 3% annually. DALY=disability-adjusted life-year. ICER=incremental cost-effectiveness ratio. NA=not applicable. SAC=school-aged children (5–14 years). Pre-SAC=preschool-aged children (2–4 years). *Dominated strategy defined as intervention with higher ICER than more effective strategy.

Table 3: **Costs, disability, and incremental cost-effectiveness of strategies for integrated mass drug administration to treat schistosomiasis and soil-transmitted helminthiasis in Côte d'Ivoire**

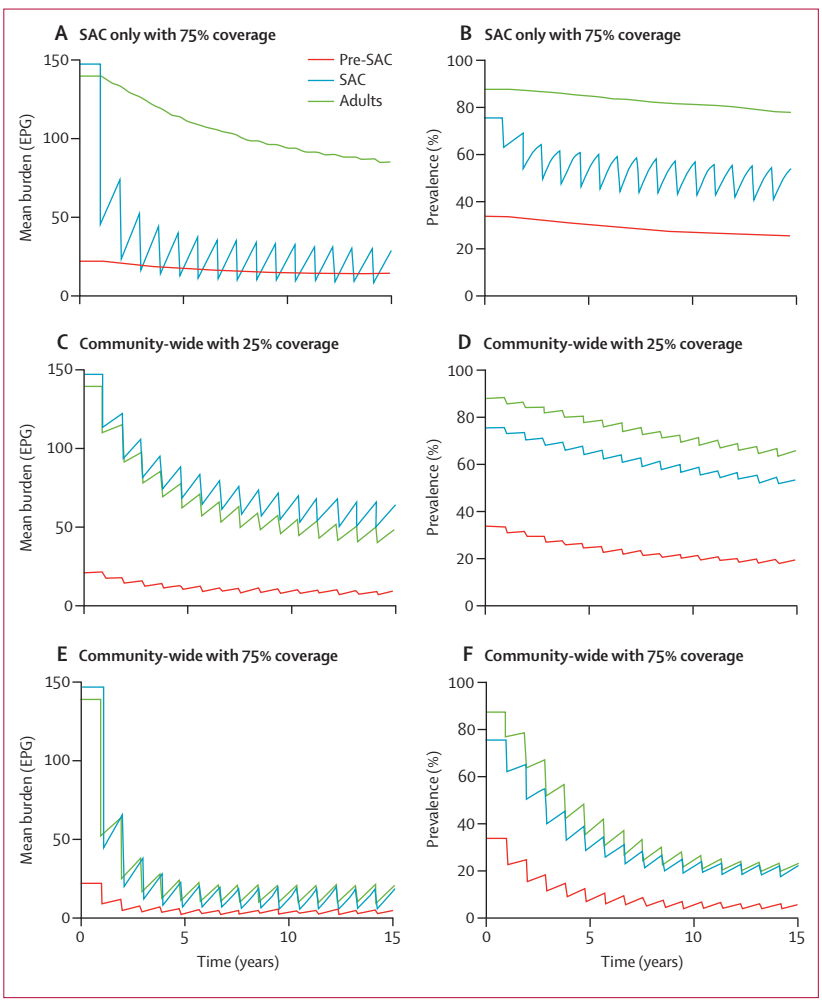

Figure 2: **Effect of expanding treatment to broader age groups and increasing coverage on combined helminth burden and mean prevalence**

A heterogeneous population of preschool-aged children (pre-SAC), school-aged children (SAC), and adults in Côte d'Ivoire who received annual treatment; SAC only with 75% coverage (A and B), annual community-wide treatment with 25% coverage (C and D), and annual community-wide treatment with 75% coverage (E and F) which approached elimination. Reproduction number and beta ratios were fitted to initial epidemiological data from Côte d'Ivoire. Mean prevalence represents the independent combination of all five helminth species. Pre-SAC and SAC were assumed to have twice the reproduction number of adults. EPG=eggs per g of faeces.

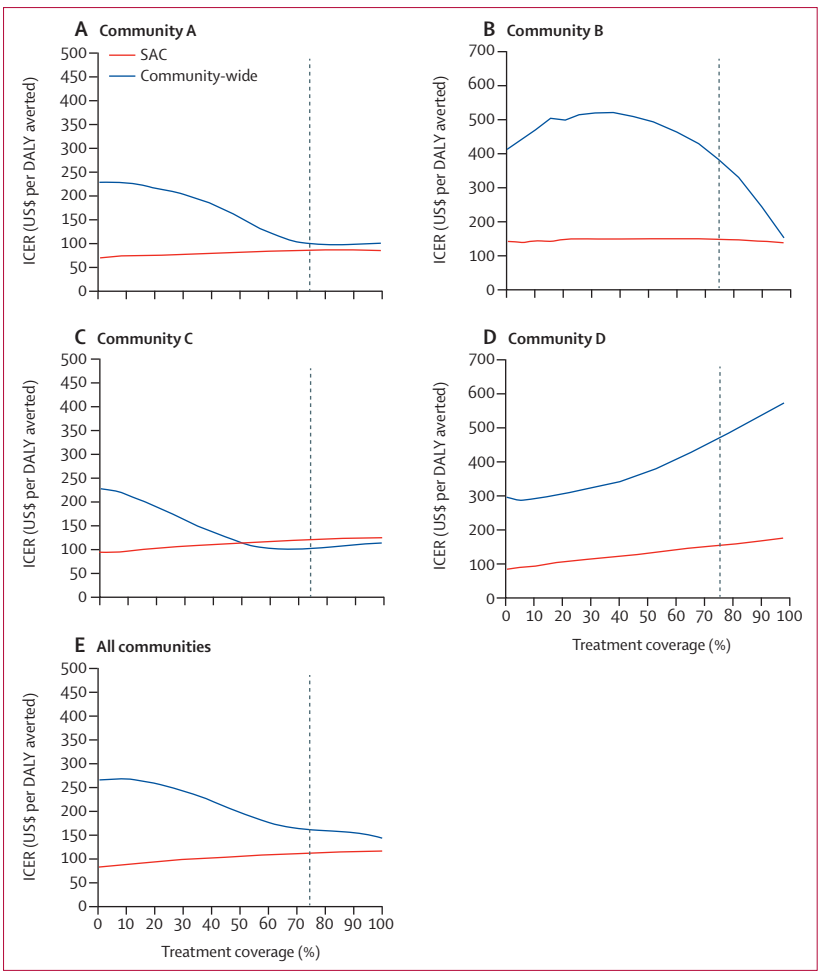

Figure 3: **Effect of treatment coverage on cost-effectiveness of mass drug administration against schistosomiasis and soil-transmitted helminthiasis in Côte d'Ivoire**
The incremental cost-effectiveness ratio (ICER) of community-wide treatment compared with treatment of school-aged children (SAC) alone was assessed across all coverage rates for communities A–D (A–D), and aggregated (E). The vertical line at 75% coverage was the base-case assumption in the analysis, and represents WHO's 2020 goal for global coverage.[3] DALY=disability-adjusted life-year.

In the four simulated communities of 5000 people in Côte d'Ivoire (A–D), the total disability attributable to helminth infections, in the absence of treatment, was projected to be 3252·1 DALYs (undiscounted 4090·7 DALYs) during 15 years (table 3). Schistosomiasis was the leading cause of disability in all four communities. Most disability resulted from *Schistosoma* infections (92%) and combined anaemia from hookworm and schistosomiasis (6%; appendix). Notably, *T trichiura* and *A lumbricoides* infections together accounted for only 1% of total disability.

We modelled the effect of changing coverage of treatment and inclusion of broader age groups (preschool-aged children and adults) on mean burden and prevalence. For most helminth species and communities, approaching elimination required substantial treatment coverage (>75% of the population), sustained administration (>5 years), and broad inclusion of age groups (community-wide treatment). By comparison, the latest WHO guidelines[6,11] that propose annual treatment of only school-aged children with 75% coverage resulted in a minimum decrease in prevalence and mean burden of helminths (figure 2). Notably, the school-aged children and adult populations in community B who had high-intensity schistosomiasis and the preschool-aged children in community C with high-intensity *T trichiura* needed treatment every 6 months to approach elimination of these infections (data shown in appendix).

Implementation of an integrated MDA programme with 75% coverage in school-aged children was a highly cost-effective intervention compared with giving no treatment. We projected that treatment of only school-aged children would avert 288 DALYs over 15 years at a cost of $34 122 (ICER $118 per DALY averted [table 3], varying among the communities from $87 to $141 per DALY averted). Our model suggests that coverage of the entire community would result in an additional 1443 DALYs averted at an incremental cost of $240 695 (ICER $167 per DALY averted, varying among the communities from $101 to $463 per DALY averted). Community-wide MDA was therefore highly cost effective by comparison with treatment of only school-aged children (table 3; appendix). Treatment of preschool-aged children and school-aged children together or adults alone was dominated by community-wide treatment, in that these alternative strategies had a higher ICER and lower overall effectiveness than community-wide treatment (appendix).

We also did a cost-effectiveness analysis independently for all of the four communities (appendix). These communities ranged from low to high disease-burden regions, and varied in *Schistosoma* prevalence from 11% to 63%. In all settings, community-wide treatment was highly cost effective compared with treatment of school-aged children alone (appendix).

The cost-effectiveness of all treatment strategies was quite robust across the full range of treatment coverage ($149–277 per DALY averted from 100% to 5% coverage), suggesting that both control and elimination strategies were highly cost effective (figure 3). For three (A–C) of the four communities, community-wide administration showed improving cost-effectiveness as the coverage rate increased above 50%. This occurrence was only reported in the community-wide treatment strategy, and was presumably a result of approaching elimination through broad inclusion of age groups and high coverage. More frequent treatments resulted in higher incremental cost-effectiveness of all strategies due to decreasing incremental gains (table 4). Nevertheless, more frequent treatment was highly cost effective, including biannual treatment of school-aged children (ICER $347 per DALY averted) and community-wide treatment (ICER $335 per DALY averted) compared with annual treatment (see appendix for community analysis).

The proposed strategy of integrated community-wide treatment was highly cost effective compared with

treatment following WHO guidelines (ie, treatment of school-aged children for schistosomiasis and soil-transmitted helminthiasis, with additional treatment of preschool-aged children and women of childbearing age for soil-transmitted helminthiasis alone) with an ICER of $127 per DALY averted (appendix). Community-based treatment averted an additional 1364 DALYs compared with WHO guidelines during the 15-year simulation.

A series of one-way sensitivity analyses showed that expansion of treatment from school-aged children to community-wide treatment with 75% coverage would be highly cost effective across a range of tested parameters (figure 4). The base delivery cost and community delivery cost multiplier were the most important parameters, and were assessed by use of an upper end of $1·50 delivery cost per school-aged child and using a community delivery multiplier of up to ten times the cost of school-based delivery. The ICER was highly robust when varying the schistosomiasis disability weight, treatment frequency, coverage, and relative environmental contribution between preschool-aged children, school-aged children, and adults. The probabilistic sensitivity analysis, which varied many uncertain parameters simultaneously, was also used to assess the effect of uncertainty in the model on our main result: community-wide treatment is highly cost effective compared with school-aged children alone. This analysis showed study findings were robust with a mean ICER of $219 (95% CI 63–524) per DALY averted (appendix).

	School-aged children*			Community-wide		
	Total costs in 2014 (US$)	Total disability (DALYs)	ICER (US$ per DALY)	Total costs in 2014 (US$)	Total disability (DALYs)	ICER (US$ per DALY)
No treatment	0	3252·1	NA	0	3252·1	NA
48 months	9377	3095·5	60	75 527	2652·6	126
36 months	11 712	3071·2	96	94 326	2522·2	144
24 months	18 217	3035·4	182	146 718	2250·5	Dominated†
12 months	34 122	2964·1	223	274 817	1521·6	180
6 months	68 243	2865·7	347	549 634	700·9	335
4 months	102 365	2809·7	609	824 451	366·0	821
3 months	136 486	2769·4	845	1 099 269	266·4	2758

DALY=disability-adjusted life-year. ICER=incremental cost-effectiveness ratio. NA=not applicable. *Aged 5–14 years. †Dominated strategy defined as intervention with higher ICER than more effective strategy.

Table 4: **Costs, disability, and incremental cost-effectiveness of varying frequency of mass drug administration**

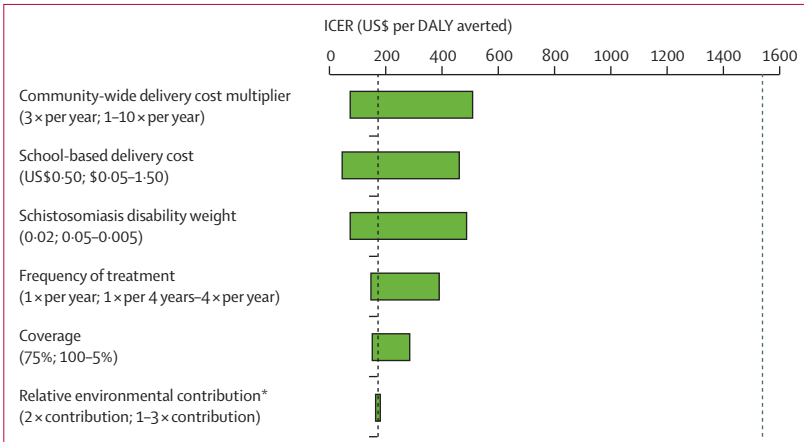

Figure 4: **One-way sensitivity analysis of key model parameters**
This analysis tested the effect of varying key model parameters on the incremental cost-effectiveness ratio (ICER) of expanding mass drug administration to entire communities compared with only treatment of school-aged children. The horizontal bar represents the range of ICER values for the specified range of the tested parameter. All strategies left of the dashed vertical line at US$1521 per disability-adjusted life-year (DALY) averted (2013 gross domestic product per capita in Côte d'Ivoire) are regarded as highly cost effective. *Relative environmental contribution refers to the relative rate of excretion of eggs into the environment among preschool-aged children and school-aged children when compared with adults.

Discussion

Our modelling study has shown that integrated community-wide MDA targeting two major helminthiases is a highly cost-effective strategy. Great progress has been made in decreasing the burden of helminthiases with use of MDA programmes, but even communities with repeated treatment of school-aged children have been unable to achieve elimination of schistosomiasis and soil-transmitted helminthiasis.[5,10,12,49] Recent models in the past two years have reported the potential benefits for expansion of drug coverage to the entire community.[5,12,13] The results of our study support these findings and suggest that expanded, community-wide treatment alongside high coverage (>75%) and sustained administration (>5 years) could be crucial in sufficiently decreasing the community worm load to prevent high reinfection rates and make elimination a possibility in many communities. Importantly, we noted that community-wide treatment would be highly cost effective even if elimination could not be achieved, due to substantial disability averted in preschool-aged children, school-aged children, and adults. As a result, MDA will avert much disability and be highly cost effective even when prevalence is not substantially reduced. These findings held true across all four communities in Côte d'Ivoire with differing prevalence of *Schistosoma* and soil-transmitted helminth infections. Crucially, treatment of both sets of helminths was highly cost effective even in communities with a low prevalence of one of these helminth types, because most costs were spent on treatment delivery and not on the drugs themselves. We also determined that integrated treatment every 6 months could be highly cost effective. These findings lend support to the movement towards integrated treatment programmes for schistosomiasis and soil-transmitted helminthiasis, and underscore the need to develop guidelines that address the importance of expanding treatment to include more than only school-aged children and are based on the local burden of many helminth infections rather than each individually.

If the latest WHO guidelines[6] had been followed (which are specific to either schistosomiasis or soil-transmitted helminthiasis), individuals in only one of the four

communities in our study would have received integrated annual MDA. Individuals in the other communities would have received either albendazole for soil-transmitted helminthiasis or praziquantel for schistosomiasis at different frequencies, and often would have omitted one of the anthelmintic drugs completely. However, because the costs of drugs themselves are low, the infrastructure to deliver MDA—particularly at the community level—accounts for the bulk of total costs. Addition of a second drug to MDA programmes therefore benefits from reduced incremental costs, making their use cost effective at lower prevalence values than those recommended in non-integrated programmes.

The cost-effectiveness of integrated community-wide treatment was robust to local epidemiology and assumptions on cost of treatment, coverage, frequency of treatment, disability measurement, and prevalence of infection. Although the quantitative result (ICER) will vary in other settings as a function of local costs and disease burden, we believe our sensitivity analyses suggest that our main finding—that integrated community-wide MDA is highly cost effective—will be applicable in many low-resource settings where schistosomiasis and soil-transmitted helminthiasis coexist. The price of community-based delivery was calculated by applying a three-times multiplier to the school-based delivery cost, to account for the increased cost to administer treatment throughout a community. Conservatively high estimates for school-based delivery costs ($0·50) could make the absolute incremental cost between school-based and community-based delivery larger than the three-times multiplier might suggest. Community-wide treatment remained highly cost effective across a large range of the community-wide multipliers (1–10 times) and base delivery costs ($0·05–1·50). The 75% coverage used in the main analysis, which is representative of WHO's goal, provided a similar result when compared with present global coverage (15–30%), as shown in the sensitivity analysis.

The latest WHO guidelines suggest treatment of high-risk adults in endemic regions and consideration of community-wide treatment for schistosomiasis in highly endemic communities (>50% prevalence), but this is not usually done in practice.[50] MDA in school-aged children (ICER $118 per DALY averted) and community-wide treatment (ICER $167 per DALY averted) were both highly cost effective with similar ICERs, particularly at coverage that exceeded 75%. Treatment of school-aged children and preschool-aged children or adults alone were dominated strategies, meaning that community-wide treatment averted more disability at a lower incremental cost-effectiveness. Following an existing treatment framework that focuses on treatment of school-aged children and school-based delivery, one efficient strategy would be first scaling up to adequate coverage of school-based treatment followed by implementation of community-wide treatment.

Even though the specific prevalence threshold that is cost effective for inclusion of each age group was not examined explicitly, both school-aged children only and community-wide treatment were deemed highly cost effective in all communities ranging from low to highly endemic settings. This result suggests the possibility of lowering prevalence thresholds used in treatment guidelines and the need for cost-effectiveness work to inform the specific thresholds. In line with previous studies, the use of mean burden (usually estimated by mean eggs per g of faeces) rather than prevalence of infection should also be thought about in creation of these thresholds based on the distribution of disease.[13]

The results of this study should be interpreted within the context of the limitations of model parameters and a number of simplifying assumptions. We modelled treatment as an instantaneous reduction in mean burden and increase in haemoglobin; annual treatment was applied simultaneously throughout all communities; perfect mixing was assumed in the subpopulation mean burden; coverage assumed random rather than repeated treatment of individuals within the population; heterogeneity was assumed to be constant throughout the population despite treatment pressure that might concentrate disease burden in a smaller number of hosts; and contributions of animal reservoirs, migration, and so-called superspreaders (highly infectious individuals who transmit their infection to several other people) were not included and could represent important barriers to helminth elimination. We modelled a 15-year period, and assumed constant treatment coverage throughout this period; in reality, treatment acceptance could change over time. Treatment decisions were made on the basis of initial prevalence and were not re-evaluated during the simulation. However, the results show that WHO-recommended treatment (focused on school-aged children only) had little effect on prevalence (figure 2B) and would be less likely to reduce prevalence substantially enough to change the recommended treatment strategy from WHO.

Treatment costs were not separated into the fixed component of setting up a programme, and a variable component of increasing treatment frequency or coverage. Helminth disease distribution was modelled with a negative binomial distribution after analysis with primary data and previous models. We did not model disability because of toxic effects of therapy, as single dose administration is associated with a very low risk of substantial toxic effects in comparison with the extent of disability due to disease.[51] Of the most uncertain parameters is the relative contribution of eggs to the environment from each age group; we assumed that preschool-aged children and school-aged children contributed twice as much in the base case as did adults, and the results were ultimately minimally affected across a broad range of assumptions for this parameter.

The disability weight given to schistosomiasis and soil-transmitted helminthiasis has been much debated, and

varies greatly depending on the published source used (ie, WHO [Global Burden of Disease 2004],[52] and King and colleagues' meta-analysis[53]). The disability weight for schistosomiasis varies from 0·005 to 0·15 on a scale from 0 (perfect health) to 1 (death).[21] We ultimately chose a binary disability weight of 0·02, which represents the lowest value of a meta-analysis that examined this disability weight, and assessed the effect of this disability weight in sensitivity analyses.[21] The disability structure for soil-transmitted helminthiasis was updated in 2014, and we used these weights.[1] In view of recent controversy about treatment of soil-transmitted helminth infections in the past months,[54,55] of note is that updated weights for these helminths did not assign any disability for light infections, and did not include any cognitive or educational benefit from treatment. By contrast, individuals with schistosomiasis received the same disability weight irrespective of infection intensity. Generally, disability weights for these diseases might not truly account for long-term cognitive impairment, which would increase treatment cost-effectiveness and could favour treatment of preschool-aged children and school-aged children rather than adults. Although many studies have reported greater prevalence of helminths in school-aged children than in adults, growing scientific literature supports our finding that adults can often have equivalent or greater disease burden than children, especially for hookworm infections and schistosomiasis.[56,57] To the best of our knowledge, the empirical data used in our study came from communities that had not received MDA, but there is still a potential undocumented exposure to anthelmintics.

We did not assess treatment of malaria, filarial infections, strongyloidiasis, or other helminth infections that are often co-endemic in many communities and can be treated concomitantly. Additionally, thought should be given to the role of different helminthiasis control methods—these include water, sanitation, and hygiene, community education, vaccine development, and other measures[58,59]—which are likely to be important in future elimination efforts but were not included in this model. Importantly, not every cost-effective programme will be affordable in all settings and might be subjected to changing funding priorities; however, our findings suggest that expanded community-wide MDA would be cost effective while being undertaken, even if the programme was not subsequently maintained. Thus, the goal of this study is to assist in prioritising among the many needed health interventions in low-income settings.

With renewed enthusiasm for control and elimination efforts targeting helminth infections, questions remain about how to effectively deploy resources. Present WHO guidelines, which are based on the individual prevalence of helminth infections and focus on school-aged children alone, are inadequate for informing treatment programmes. Revised guidance is urgently needed to inform the scale-up of treatment programmes worldwide to avert the substantial disability created from soil-transmitted helminthiasis, schistosomiasis, and other neglected tropical diseases.

Contributors

NCL, IIB, BGB, JU, and JRA designed the study and did the scientific literature review. Data collection was done by GR, EKN, JTC, and SLB. NCL did the data analysis. NCL, IIB, BGB, HBA, JU, and JRA interpreted the data. NCL, IIB, BGB, SLB, JU, and JRA wrote the Article.

Declaration of interests

IIB, HBA, and JRA report grants from Ontario Alternative Funding Plan, during the study. EKN and JU report grants from Schistosomiasis Consortium for Operational Research and Evaluation and Schistosomiasis Control Initiative, during the study. EKN is on an expert committee for WHO. JU reports non-financial support from WHO and Children Without Worms, outside the submitted work. NCL, BGB, GR, JTC, and SLB declare no competing interests.

Acknowledgments

We thank the health, education, and village authorities, study participants, and laboratory technicians who assisted with the original epidemiological studies in Côte d'Ivoire.

References

1 Pullan RL, Smith JL, Jasrasaria R, Brooker SJ. Global numbers of infection and disease burden of soil transmitted helminth infections in 2010. *Parasit Vectors* 2014; **7:** 37.
2 Colley DG, Bustinduy AL, Secor WE, King CH. Human schistosomiasis. *Lancet* 2014; **383:** 2253–64.
3 WHO. Accelerating work to overcome the global impact of neglected tropical diseases: a roadmap for implementation. Geneva: World Health Organization, 2012.
4 Rollinson D, Knopp S, Levitz S, et al. Time to set the agenda for schistosomiasis elimination. *Acta Trop* 2013; **128:** 423–40.
5 Truscott JE, Hollingsworth TD, Brooker SJ, Anderson RM. Can chemotherapy alone eliminate the transmission of soil transmitted helminths? *Parasit Vectors* 2014; **7:** 266.
6 WHO. Preventive chemotherapy in human helminthiasis. Coordinated use of anthelminthic drugs in control interventions: a manual for health professionals and programme managers. Geneva: World Health Organization, 2006.
7 Guyatt H. The cost of delivering and sustaining a control programme for schistosomiasis and soil-transmitted helminthiasis. *Acta Trop* 2003; **86:** 267–74.
8 King CH, Olbrych SK, Soon M, Singer ME, Carter J, Colley DG. Utility of repeated praziquantel dosing in the treatment of schistosomiasis in high-risk communities in Africa: a systematic review. *PLoS Negl Trop Dis* 2011; **5:** e1321.
9 Hotez PJ, Kamath A. Neglected tropical diseases in sub-Saharan Africa: review of their prevalence, distribution, and disease burden. *PLoS Negl Trop Dis* 2009; **3:** e412.
10 Karagiannis-Voules D-A, Biedermann P, Ekpo UF, et al. Spatial and temporal distribution of soil-transmitted helminth infection in sub-Saharan Africa: a systematic review and geostatistical meta-analysis. *Lancet Infect Dis* 2015; **15:** 74–84.
11 WHO. Helminth control in school-age children: a guide for managers of control programmes, 2nd edn. Geneva: World Health Organization, 2011.
12 Anderson R, Truscott J, Hollingsworth TD. The coverage and frequency of mass drug administration required to eliminate persistent transmission of soil-transmitted helminths. *Philos Trans R Soc Lond B Biol Sci* 2014; **369:** 20130435.
13 Anderson RM, Truscott JE, Pullan RL, Brooker SJ, Hollingsworth TD. How effective is school-based deworming for the community-wide control of soil-transmitted helminths? *PLoS Negl Trop Dis* 2013; **7:** e2027.
14 Chan MS, Guyatt HL, Bundy DAP, Medley GF. The development and validation of an age-structured model for the evaluation of disease control strategies for intestinal helminths. *Parasitology* 1994; **109:** 389–96.
15 Anderson RM, May RM. Infectious diseases of humans: dynamics and control. Oxford: Oxford University Press, 1991.
16 Coulibaly JT, Fürst T, Silué KD, et al. Intestinal parasitic infections in schoolchildren in different settings of Côte d'Ivoire: effect of diagnostic approach and implications for control. *Parasit Vectors* 2012; **5:** 135.

17 Becker SL, Sieto B, Silué KD, et al. Diagnosis, clinical features, and self-reported morbidity of *Strongyloides stercoralis* and hookworm infection in a co-endemic setting. *PLoS Negl Trop Dis* 2011; **5:** e1292.

18 Raso G, Luginbühl A, Adjoua CA, et al. Multiple parasite infections and their relationship to self-reported morbidity in a community of rural Côte d'Ivoire. *Int J Epidemiol* 2004; **33:** 1092–102.

19 Keiser J, N'Goran EK, Traoré M, et al. Polyparasitism with *Schistosoma mansoni*, geohelminths, and intestinal protozoa in rural Côte d'Ivoire. *J Parasitol* 2002; **88:** 461–66.

20 Utzinger J, N'Goran EK, Esse Aya CM, et al. *Schistosoma mansoni*, intestinal parasites and perceived morbidity indicators in schoolchildren in a rural endemic area of western Côte d'Ivoire. *Trop Med Int Health* 1998; **3:** 711–20.

21 King CH, Dickman K, Tisch DJ. Reassessment of the cost of chronic helmintic infection: a meta-analysis of disability-related outcomes in endemic schistosomiasis. *Lancet* 2005; **365:** 1561–69.

22 Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380:** 2095–128.

23 Salomon JA, Vos T, Hogan DR, et al. Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. *Lancet* 2012; **380:** 2129–43.

24 The World Bank. World development indicators. Washington, DC: The World Bank, 2013.

25 Tan-Torres Edejer T, Baltussen R, Adam T, et al. WHO guide to cost-effectiveness analysis. Geneva: World Health Organization, 2003.

26 Anderson RM, May RM. Population dynamics of human helminth infections: control by chemotherapy. *Nature* 1982; **297:** 557–63.

27 Danso-Appiah A, Olliaro PL, Donegan S, Sinclair D, Utzinger J. Drugs for treating *Schistosoma mansoni* infection. *Cochrane Database Syst Rev* 2013; **2:** CD000528.

28 Keiser J, Utzinger J. Efficacy of current drugs against soil-transmitted helminth infections: systematic review and meta-analysis. *JAMA* 2008; **299:** 1937–48.

29 Zwang J, Olliaro PL. Clinical efficacy and tolerability of praziquantel for intestinal and urinary schistosomiasis-a meta-analysis of comparative and non-comparative clinical trials. *PLoS Negl Trop Dis* 2014; **8:** e3286.

30 Kassebaum NJ, Jasrasaria R, Naghavi M, et al. A systematic analysis of global anemia burden from 1990 to 2010. *Blood* 2014; **123:** 615–24.

31 Smith JL, Brooker S. Impact of hookworm infection and deworming on anaemia in non-pregnant populations: a systematic review. *Trop Med Int Health* 2010; **15:** 776–95.

32 WHO. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Geneva: World Health Organization, 2011.

33 Staubli-Asobayire F, Adou P, Davidsson L, Cook JD, Hurrell RF. Prevalence of iron deficiency with and without concurrent anemia in population groups with high prevalences of malaria and other infections: a study in Côte d'Ivoire. *Am J Clin Nutr* 2001; **74:** 776–82.

34 Department of Maternal, Newborn, Child and Adolescent Health, WHO. Côte d'Ivoire: Neonatal and child health profile, 2013. http://http://www.who.int/maternal_child_adolescent/epidemiology/profiles/neonatal_child/civ.pdf (accessed Aug 25, 2015).

35 Hall A, Hewitt G, Tuffrey V, de Silva N. A review and meta-analysis of the impact of intestinal worms on child growth and nutrition. *Matern Child Nutr* 2008; **4** (suppl 1)**:** 118–236.

36 Hürlimann E, Yapi RB, Houngbedji CA, et al. The epidemiology of polyparasitism and implications for morbidity in two rural communities of Côte d'Ivoire. *Parasit Vectors* 2014; **7:** 81.

37 van Baal PH, Hoeymans N, Hoogenveen RT, de Wit GA, Westert GP. Disability weights for comorbidity and their influence on health-adjusted life expectancy. *Popul Health Metr* 2006; **4:** 1.

38 US Central Intelligence Agency. The world factbook, 2014. https://www.cia.gov/library/publications/the-world-factbook/ (accessed April 15, 2015).

39 Management Sciences for Health, WHO. International drug price indicator guide, 2013 edition. http://erc.msh.org/dmpguide/pdf/DrugPriceGuide_2013_en.pdf (accessed April 15, 2015).

40 Goldman AS, Guisinger VH, Aikins M, et al. National mass drug administration costs for lymphatic filariasis elimination. *PLoS Negl Trop Dis* 2007; **1:** e67.

41 WHO. Deworming for health and development: report of the third global meeting of the partners for parasite control. Geneva: World Health Organization, 2005. http://whqlibdoc.who.int/hq/2005/WHO_CDS_CPE_PVC_2005.14.pdf (accessed April 15, 2015).

42 Brooker S, Kabatereine NB, Fleming F, Devlin N. Cost and cost-effectiveness of nationwide school-based helminth control in Uganda: intra-country variation and effects of scaling-up. *Health Policy Plan* 2008; **23:** 24–35.

43 Evans D, McFarland D, Adamani W, et al. Cost-effectiveness of triple drug administration (TDA) with praziquantel, ivermectin and albendazole for the prevention of neglected tropical diseases in Nigeria. *Ann Trop Med Parasitol* 2011; **105:** 537–47.

44 Fitzpatrick C, Asiedu K, Jannin J. Where the road ends, yaws begins? The cost-effectiveness of eradication versus more roads. *PLoS Negl Trop Dis* 2014; **8:** e3165.

45 Gabrielli AF, Touré S, Sellin B, et al. A combined school- and community-based campaign targeting all school-age children of Burkina Faso against schistosomiasis and soil-transmitted helminthiasis: performance, financial costs and implications for sustainability. *Acta Trop* 2006; **99:** 234–42.

46 Kabatereine NB, Tukahebwa EM, Kazibwe F, et al. Soil-transmitted helminthiasis in Uganda: epidemiology and cost of control. *Trop Med Int Health* 2005; **10:** 1187–89.

47 Leslie J, Garba A, Boubacar K, et al. Neglected tropical diseases: comparison of the costs of integrated and vertical preventive chemotherapy treatment in Niger. *Int Health* 2013; **5:** 78–84.

48 Leslie J, Garba A, Oliva EB, et al. Schistosomiasis and soil-transmitted helminth control in Niger: cost effectiveness of school based and community distributed mass drug administration [corrected]. *PLoS Negl Trop Dis* 2011; **5:** e1326.

49 Gray DJ, McManus DP, Li Y, Williams GM, Bergquist R, Ross AG. Schistosomiasis elimination: lessons from the past guide the future. *Lancet Infect Dis* 2010; **10:** 733–36.

50 WHO. Schistosomiasis: number of people treated worldwide in 2013. *Wkly Epidemiol Rec* 2015; **90:** 25–32.

51 Sousa-Figueiredo JC, Betson M, Atuhaire A, et al. Performance and safety of praziquantel for treatment of intestinal schistosomiasis in infants and preschool children. *PLoS Negl Trop Dis* 2012; **6:** e1864.

52 WHO. Health statistics and information systems. The global burden of disease: 2004 update. Geneva: World Health Organization, 2004.

53 King CH, Dickman K, Tisch DJ. Reassessment of the cost of chronic helmintic infection: a meta-analysis of disability-related outcomes in endemic schistosomiasis. *Lancet* 2005; **365:** 1561–69.

54 Aiken AM, Davey C, Hargreaves JR, Hayes RJ. Re-analysis of health and educational impacts of a school-based deworming programme in western Kenya: a pure replication. *Int J Epidemiol* 2015; published online July 22. DOI: 10.1093/ije/dyv127.

55 Davey C, Aiken AM, Hayes RJ, Hargreaves JR. Re-analysis of health and educational impacts of a school-based deworming programme in western Kenya: a statistical replication of a cluster quasi-randomized stepped-wedge trial. *Int J Epidemiol* 2015; published online July 22. DOI: 10.1093/ije/dyv128.

56 Evans DS, King JD, Eigege A, et al. Assessing the WHO 50% prevalence threshold in school-aged children as indication for treatment of urogenital schistosomiasis in adults in central Nigeria. *Am J Trop Med Hyg* 2013; **88:** 441–45.

57 Njenga SM, Mwandawiro CS, Muniu E, Mwanje MT, Haji FM, Bockarie MJ. Adult population as potential reservoir of NTD infections in rural villages of Kwale district, Coastal Kenya: implications for preventive chemotherapy interventions policy. *Parasit Vectors* 2011; **4:** 175.

58 Bieri FA, Gray DJ, Williams GM, et al. Health-education package to prevent worm infections in Chinese schoolchildren. *N Engl J Med* 2013; **368:** 1603–12.

59 Grimes JET, Croll D, Harrison WE, Utzinger J, Freeman MC, Templeton MR. The relationship between water, sanitation and schistosomiasis: a systematic review and meta-analysis. *PLoS Negl Trop Dis* 2014; **8:** e3296.