Improving the monitoring and evaluation of schistosomiasis by determining appropriate targets and utilizing new technologies

Inauguraldissertation

zur

Erlangung der Würde eines Doktors der Philosophie

vorgelegt der

Philosophisch-Naturwissenschaftlichen Fakultät

der Universität Basel

von

Ryan Earl Wiegand

2022

Genehmigt von der Philosophisch-Naturwissenschaftlichen Fakultät

auf Antrag von

Prof. Dr. Penelope Vounatsou, Prof. Dr. Jürg Utzinger, and Dr. David Rollinson.

Basel, den 25 Mai, 2021

Prof. Dr. Marcel Mayor
Dekan der
Philosophisch-Naturwissenschaftlichen Fakultät

Acknowledgements i
Summary iv
List of figures viii
List of supplemental figures x
List of tables xiii
List of supplemental tables xiv
List of abbreviations xvi
1 Introduction 1
1.1 History 1
1.2 Aetiology 6
1.3 Geographic Range 9
1.4 Burden 10
1.5 Pathology and Morbidity 11
1.5.1 Pathology and morbidity due to urogenital schistosomiasis 13
1.5.2 Pathology and morbidity due to intestinal schistosomiasis 15
1.5.3 Decreasing severe pathology 17
1.5.4 Measurement of pathology 18
1.6 Diagnosis of schistosomiasis 20
1.6.1 Parasitological 20
1.6.2 Circulating antigen 21
1.6.3 Antibody 22
1.7 Treatment 23
1.8 Interventions 25
1.8.1 Ecologic Interventions 25
1.8.2 Pharmaceutical Interventions 26
1.8.3 Educational 28
1.8.4 Water, Sanitation, and Hygiene (WASH) 28
1.9 Monitoring and evaluation goals and framework 29
1.9.1 Programme goals 29
1.9.2 Framework 30
1.9.3 Intensity categories 30
1.9.4 Control and elimination as a public health problem categories 31
1.9.5 Monitoring and evaluation shortcomings 31

2 Goals and objectives 33
2.1 Rationale 33
2.2 Goals 33
2.3 Specific objectives 34
3 Five-Year Impact of Different Multi-Year Mass Drug Administration Strategies on Childhood *Schistosoma mansoni*–Associated Morbidity: A Combined Analysis from the Schistosomiasis Consortium for Operational Research and Evaluation Cohort Studies in the Lake Victoria Regions 35
3.1 Abstract 37
3.2 Introduction 37
3.3 Materials and Methods 39
3.3.1 Ethics statement on subject recruitment 39
3.3.2 Study area and population 40
3.3.3 Data on parasitology and morbidity 41
3.3.4 Statistical analysis 44
3.4 Results 46
3.4.1 Combined cohort characteristics 46
3.4.2 Comparison of infection and morbidity markers between Year 1 and Year 5 49
3.4.3 Age-, and sex-adjusted comparisons between study arms, accounting for village-level intra-class correlation 52
3.4.4 Sensitivity analysis for effects of missing data using multiple imputation 53
3.5 Discussion 53
3.6 Acknowledgements 57
3.7 Financial Support 58
3.8 Disclaimer: 58
3.9 Disclosures: 58
3.10 Supporting information 59
4 SCORE Studies on the Impact of Drug Treatment on Morbidity due to *Schistosoma mansoni* and *Schistosoma haematobium* Infection 60
4.1 Abstract 62
4.2 Overview 62
4.3 Schistosomiasis Consortium for Operational Research Longitudinal Cohort Studies 65
4.4 School Behavioral Assessment Study 68
4.5 Meta-analysis of Cognition and School Performance Outcomes 69
4.6 Meta-analysis of Drug-mediated Reduction in *Schistosoma* Infection Intensity and its Effects on Infection-associated Morbidity 70

4.7 Summary and Next Steps 71
4.8 Funding 73
4.9 Disclosures 73
4.10 Disclaimer 73
4.11 Supporting information 73
4.11.1 SCORE Rapid Answers Project (RAP): Cognitive Deficits and Educational Loss in Children with Schistosome Infections 73
4.11.2 SCORE Rapid Answers Project (RAP): The Decline in Infection-Related Morbidities Following Drug-Mediated Reduction in the Intensity of Schistosoma Infection 77
5 Associations between infection intensity categories and morbidity prevalence in school-age children are much stronger for *Schistosoma haematobium* than for *S. mansoni* 83
5.1 Abstract 85
5.2 Author Summary 86
5.3 Introduction 86
5.4 Methods 88
5.4.1 Ethics statement 88
5.4.2 Study design and data collection 88
5.4.3 *Schistosoma* infection data 90
5.4.4 Morbidity data 91
5.4.5 Data analysis methods 92
5.5 Results 93
5.5.1 *S. haematobium* 93
5.5.2 *S. mansoni* 97
5.6 Discussion 101
5.7 Conclusion 106
5.8 Declaration of interests 106
5.9 Acknowledgments 106
5.10 Supplemental Materials 107
5.10.1 Statistical Methods 107
5.10.2 Implementation 109
5.10.3 JAGS model code for *S. haematobium* logistic model 109
5.10.4 JAGS model code for *S. mansoni* logistic model 111
5.10.5 Supplemental Figures 113
5.10.6 Supplemental Tables 121

6 Control and elimination of schistosomiasis as a public health problem: thresholds fail to differentiate schistosomiasis morbidity prevalence in children 127
6.1 Abstract 128
6.2 Background 128
6.3 Methods 130
6.3.1 Study design and data collection 130
6.3.2 Infection data 131
6.3.3 Morbidity data 131
6.3.4 Data analysis 133
6.3.5 Patient consent statement 133
6.3.6 Role of the funding sources 134
6.4 Results 134
6.4.1 *Schistosoma haematobium* 134
6.4.2 *S. mansoni* 137
6.5 Discussion 140
6.6 Conclusion 143
6.7 Declaration of interests 143
6.8 Acknowledgments 144
6.9 Supplemental Materials 144
6.9.1 Statistical Methods 144
6.9.2 Implementation 146
6.9.3 JAGS model code for logistic model 146
6.9.4 JAGS model code for binomial model 147
6.9.5 Supplemental Figures 150
6.9.6 Supplemental Tables 156
7 Urogenital schistosomiasis infection prevalence targets to determine elimination as a public health problem based on microhematuria prevalence in school-age children 162
7.1 Abstract 163
7.2 Author Summary 164
7.3 Introduction 164
7.4 Methods 166
7.4.1 Ethics statement 166
7.4.2 Study design and data collection 166
7.4.3 Infection and microhematuria data 167

7.4.4 Data analysis methods 168
7.5 Results 169
7.6 Discussion 172
7.7 Conclusion 177
7.8 Declaration of interests 177
7.9 Acknowledgments 177
7.10 Supplemental Materials 177
7.10.1 Model Details 178
7.10.2 Model Implementation 180
7.10.3 JAGS model code for cubic function 180
7.10.4 JAGS model code for van der Werf and colleagues' function 181
7.10.5 Supplemental Tables 182
7.10.6 Supplemental Figures 184
8 Use of a tablet-based system to perform abdominal ultrasounds in a field investigation of schistosomiasis-related morbidity in western Kenya 189
8.1 Abstract 190
8.2 Short Report 190
9 Discussion 196
9.1 Implications for monitoring & evaluation programmes 198
9.1.1 Heavy-intensity prevalence targets are inadequate for control and elimination as a public health problem 198
9.1.2 Targets based on morbidity 202
9.1.3 Changes are needed for *S. mansoni* assessment 203
9.1.4 Lack of incentives to collect heavy-intensity infection data 204
9.1.5 Use of technology to improve programme goals 204
9.2 Limitations 205
9.3 Future directions 206
9.3.1 Correlations between prevalence in 9-12 year olds and adults post-treatment 206
9.3.2 Longitudinal correlations between macrohaematuria and microhaematuria 207
9.3.3 Microhaematuria targets by age 207
9.3.4 Individual intensity level that reduces microhaematuria to a background level 208
9.3.5 Ultrasound scoring utility and longitudinal changes 208
10 Conclusions 209
11 References 210

12 Brief Curriculum Vitae 246

Acknowledgements

When I was working at the Medical University of South Carolina, I had a conversation with my supervisor, Elizabeth Slate, about career progressions and, for academicians, the goal of obtaining tenure. In the context of a regression model, where the Greek parameter ε (epsilon) is used to denote the (hopefully) small, random predicted errors, she made the comment, which I paraphrase, that careers are 'like gathering up a bunch of epsilons and hoping they add up to something larger'.

This applies to my career as a great number of people have contributed epsilons, both large and small, to my development and nudged me to achieve something larger. I'd like to take the opportunity to recognize a subset of the large number of people that have helped me over my approximately 20-year professional career.

I've been privileged to learn from and work with some exceptional statisticians that have helped me hone a variety of skills over the years, including my applied, theoretical, and communication expertise. I'd like to thank David Annis, Dipankar Bandyopadhyay, Craig Borkowf, Bruce Craig, Rebecca Doerge, Timothy Green, Allen Hightower, Elizabeth Hill, John Karon, Lillian Lin, George McCabe, Sherri Pals, Charles Rose, Elizabeth Slate, Jodi Vanden Eng, and Robert Woolson.

Obtaining a PhD while working is a challenge and would not have been possible without help from my CDC colleagues. My interest in schistosomiasis has been cultivated by my CDC colleagues, Sue Montgomery and Evan Secor. Thank you for bringing me into the SCORE project, for initiating and including me in projects, and for the great collaborations. I'd like to especially thank Evan, as your enthusiasm for all things "schisto" is infectious and I am forever indebted to you for having the confidence and trust in me to connect me with the schistosomiasis world. Thanks for being such a huge help in this process; it's highly unlikely this dissertation happens with your assistance. I think we make a

great team. Others at CDC who helped in a variety of ways are Stephanie Bialek, Sibongile Lynch, Barbara Marston, Aaron Samuels, Kimberly Won, and Caitlin Worrell.

I am also grateful for my time spent on the project that got me started with schistosomiasis, the Schistosomiasis Consortium for Operations Research (SCORE). Thanks to Sue and Evan for introducing me to the project and to the SCORE secretariat, especially Tammy Andros, Sue Binder, Carl Campbell, Jennifer Castleman, Dan Colley, Charles King, and Nupur Kittur for all the collaborations and for creating an environment that fostered my growth. The annual meetings were invaluable sources of information for me.

It was through SCORE that I met people from the Swiss Tropical and Public Health Institute (Swiss TPH). Thanks to Penelope Vounatsou and Jürg Utzinger for all that you have taught me and to Christine Mensch and Anja Schreier for always being so helpful and to Pascal Mäser for chairing my dissertation defense. Ultimately, what I will remember most are your compassion and understanding. Your support meant a lot. I am indebted to the professors at the University of Basel and Swiss TPH who were willing to adapt their courses to a virtual platform, especially Max and Zinette Bergman, Günther Fink, Giusi Moffa, and Penelope Vounatsou.

I am especially grateful for the Schistosomiasis Control Initiative (now SCI Foundation), especially Fiona Fleming and Neerav Dhanani, for allowing me to have access to the datasets that became a large portion of this dissertation. Having access to these data made this endeavor go much quicker than it might have otherwise.

I was blessed to have such a supportive and gifted group of collaborators on the manuscripts included in this dissertation. Special thanks to Dan Colley, Arminder Deol, Darin Evans, Fiona Fleming, Michael French, Charlie King, Sue Montgomery, Evan Secor, Ye Shen, Anne Straily, Jürg Utzinger, Sake de Vlas, and Penelope Vounatsou for filling me with ideas and providing constructive and helpful

comments. I'd especially like to thank Sake de Vlas for all his assistance and for providing a true modeler's perspective. I hope to assimilate these lessons into future endeavors.

With most of the chapters of this thesis utilizing data from early Schistosomiasis Control Initiative-supported efforts and SCORE, it was an honor that David Rollinson, who was involved with both projects, agreed to serve as the external reviewer. Thank you for bringing your perspective and experience.

When I was searching for a doctoral program, I wanted to be able to expand my quantitative skills and complete applied work that could be impactful for neglected tropical diseases. I am delighted that my advisor, Penelope Vounatsou, allowed me to achieve these goals. I am now a better Bayesian statistician, though still with much to learn! There are very few statisticians working solely on neglected tropical diseases and I am thankful that we could work together. I hope this is the beginning of many collaborations.

The most special thanks, though, are reserved for my family. Mom, thanks for all your support over the years and for setting a template for working towards a PhD later in life. Kathy, this doesn't happen without you and your gracious encouragement while I vacillated on going back to school over the years. Since starting on the path towards this degree, there's been lots of ups and down. Thanks for helping me climb out of the low spots and for celebrating the high points with me. Thanks to my children, Andy and Julie, for allowing me to miss multiple movie nights in order to write or analyze data. Unfortunately, life's challenges have meant that we had to curtail for now our plans for an international adventure. Hopefully our time will come.

Summary

Background: Schistosomiasis is a human disease caused by blood borne trematode flukes. Three species, *Schistosoma haematobium*, *S. mansoni*, and *S. japonicum* cause most of disease. Morbidity is primarily a result of a human's immune response to eggs that are not shed from the body. The estimated disability-adjusted life years (DALYs) attributed to schistosomiasis have decreased since 2006 largely due to increased mass distribution of preventive chemotherapy. These reductions have accelerated discussions on controlling schistosomiasis morbidity, eliminating schistosomiasis as a public health problem, and even eliminating transmission of schistosomiasis. The World Health Organization's (WHO's) framework for assessing morbidity control utilizes categorizations of an individual's infection intensity and targets for homogenous ecological zones based on heavy-intensity infections. The foundational research for these categorizations is at least 30 years old. Research since then has illuminated the relationship between *Schistosoma* infection and all morbidity. In addition, the decreasing burden of schistosomiasis means that severe, chronic morbidity is less common. Portions of this framework have been evaluated and there are calls for improvements, especially relating to the measurement of schistosomiasis morbidity.

Goals and objectives: The focus of this thesis is to improve the schistosomiasis monitoring and evaluation framework by: (i) adding to the evidence base of studies looking at the associations between morbidity and infection; (ii) evaluating aspects of the current framework and whether those aspects are linked to schistosomiasis morbidity; (iii) suggesting programmatic targets linked to morbidity; and (iv) promoting novel technologies in monitoring and evaluation programmes. The specific objectives for these goals were to: (i) evaluate changes in morbidity in preventive chemotherapy cohorts; (ii) summarize morbidity-related research from the Schistosomiasis Consortium for Operational Research (SCORE); (iii) evaluate the linkage between schistosomiasis intensity categories and related morbidity; (iv) evaluate associations between heavy-intensity infection targets and morbidity levels; (v) derive

empirically-based targets that are linked to morbidity; and (vi) demonstrate the utility of a tablet-based ultrasound system for measuring schistosomiasis morbidity.

Methods: Longitudinal cohorts were used in most analyses. The first analyses utilized cohorts of 9-12-year-old children from SCORE projects in Kenya and Tanzania. These cohorts were observed for five years where the first measurement was taken pre-treatment and the fifth year was either after four years of preventive chemotherapy with praziquantel disseminated via the community or two years of preventive chemotherapy distributed via schools. The second set of analyses involved the pooling of two cohorts of school-aged children from chemoprophylaxis campaigns in Burkina Faso, Mali, Niger, Uganda, Tanzania, and Zambia, all of which were supported by the Schistosomiasis Control Initiative (SCI). The first of these cohorts were consenting children, aged 6-12, enrolled in primary education and followed up two or more years (excluding Zambia, which has only one year of follow up). The second was a community cohort which utilized a random sample of all ages at each year, for which we included the school-aged children in analyses. In both cohorts, this was the first known preventive chemotherapy administration in the area. Each of the cohorts were evaluated for infection (*S. mansoni* only in the SCORE cohorts; *S. haematobium* and *S. mansoni* in the SCI cohorts) as well as morbidity indicators from ultrasound evaluations, lab-based examinations, and questionnaires. The last study used data collected as part of the Morbidity Operational Research for Bilharziasis Implementation Decisions (MORBID) project. Regression-type methods were used in many of these methods, with both frequentist and Bayesian applications.

Results: Reductions in prevalence and heavy-intensity prevalence were noted in the SCORE *S. mansoni* cohorts and these reductions were associated with drops in wasting and elevated portal vein diameter and increases in PedsQL overall and all domain scores over the five years. Though, these changes were associated with increases in stunting and decreases in VO_2 max scores. In SCORE studies, a pilot of the Behavioral Assessment System for Children (BASC-2) instrument provided initial evidence that treatment

can improve school behavior and a meta-analysis showed poorer school attendance and performance are related to *Schistosoma* infection. Another meta-analysis found that preventive chemoprophylaxis is associated with reductions in morbidity for both *S. haematobium* and *S. mansoni*. In studies with data from SCI-supported countries, infection intensity categories were associated with morbidity levels for *S. haematobium* but not for *S. mansoni*. Targets for morbidity control and elimination of schistosomiasis as a public health problem were robustly associated with microhaematuria levels. Schools binned by their morbidity control or elimination as a public health problem status were associated with other *S. haematobium*-associated morbidity levels but not distinguish between participants in <1% prevalence of heavy intensity (PHI) schools and those in 1-5% PHI schools. For *S. mansoni*-related morbidities, participants in <1% PHI schools had less morbidity than those in ≥5% PHI schools. Due to the strong association between the PHI-based control categories for *S. haematobium* and microhaematuria, targets were calculated based on potential background microhaematuria prevalence values of 10%, 13%, and 15%. A school with an infection prevalence of 5% had at least a 90% chance across all three surveys of possessing a microhaematuria prevalence at or below 10%. Schools with infection prevalences of 8% and 11% had at least a 90% chance to possess microhaematuria levels less than 13 and 15%, respectively. School-level PHI was unable to achieve a similar level of certainty as infection prevalence. Only in the baseline survey were schools with a given infection prevalence able to achieve at least a 90% chance of realizing a microhaematuria prevalence less than 10%, 13%, or 15%. In addition, small changes in PHI result in large changes in the chance of having a microhaematuria prevalence at or lower than the threshold, suggesting measurement error can have a large impact on PHI-based targets. Finally, the point-of-care, tablet-based ultrasound system was successful at identifying morbidities, suggesting this technology could be utilized by control programmes in the future to more accurately progress towards eliminating schistosomiasis as a public health problem.

Conclusions: *Schistosoma* infection prevalence and the prevalence of heavy-intensity *Schistosoma* infections decreased in the SCORE and SCI cohorts after treatment. Morbidity indicators also decreased in both cohorts after treatment, though in the SCI cohorts the association between infection and morbidity was stronger with *S. haematobium* as compared to *S. mansoni*. Robust targets based on microhaematuria prevalence were calculated for *S. haematobium* prevalence and further research should incorporate other morbidity indicators into these computations. Given the correlations between infection and most morbidity indicators, arriving at an elimination as a public health problem target based on a suite of morbidity indicators seems feasible. For *S. mansoni*, associations between infection and morbidity were much weaker and it appears unlikely that a reliable target can be found unless further research finds stronger associations. This suggests that *S. mansoni* morbidity control needs major changes in order accurately measure a person's *S. mansoni* morbidity burden. One potential change could be to incorporate technology, especially tablet-based ultrasound systems, to collect more comprehensive morbidity data to measure programme impact, though widespread use will depend on testing in multiple settings, creating training materials, and developing ethical guidelines.

List of figures

Figure 1.1. Life cycle of schistosomiasis. 8

Figure 3.1. Flow diagram of the cohort study. In the upper arm, children lived in communities randomized to receive annual community-wide mass drug administration treatment (CWT). The children in the lower study arm lived in communities randomized to receive only biennial (every other year) school-based treatment (SBT), with drug "holidays" in Year 2 and in Year 4. Final assessment for both groups was performed in Year 5 of the study. 39

Figure 3.2. Comparison of Year 1 and Year 5 *Schistosoma mansoni* prevalence for participating children in each of the combined cohort study arms (annual community-wide treatment (CWT) vs. biennial school-based treatment [SBT]). Dark circles indicate baseline and Year 5 prevalence values for the annual CWT arm. Open squares indicate corresponding prevalence values for the children in the biennial SBT arm. Error bars indicate 95% CI. 47

Figure 3.3. Comparison of Year 1 and Year 5 *Schistosoma mansoni* infection intensities by cohort study arm. Shown are Year 1 baseline intensity values (dark bars) and 95% CI for participating children in the two study arms receiving either annual community-wide treatment (CWT) or biennial school-based treatment (SBT), calculated either as arithmetic mean intensity for egg-positive children (individual-level intensity, left side), or as mean intensity for all children, including those with zero egg counts (cohort-level intensity, right side). Corresponding values for participating children in Year 5, after MDA, are shown by the light bars. 48

Figure 5.1. Line graphs of the percentage of 6-15 year-old children who were *Schistosoma* infection and heavy-intensity positive (row A), *S. haematobium* morbidity positive (row B), and *S. mansoni* morbidity positive (row C) at each survey year (baseline, BL; follow-up 1, FU1; follow-up2, FU2). *S. haematobium* estimates are from Mali, Niger, and Tanzania and are assessed by urine filtration. *S. mansoni* estimates are from Mali, Niger, Tanzania, and Uganda and are assessed by the Kato-Katz technique. 94

Figure 5.2. Line graphs of *Schistosoma haematobium*-related morbidity percentages, broken down by intensity category, across three surveys (baseline, BL; follow-up 1, FU1; follow-up2, FU2). Participants were enrolled between 2003 and 2008 in Mali, Niger, and Tanzania. Clustering by school accounted for in 95% confidence bands. Infections were assessed by urine filtration. 95

Figure 5.3. Line graphs of *Schistosoma mansoni*-related morbidity percentages, broken down by intensity category, across three surveys (baseline, BL; follow-up 1, FU1; follow-up2, FU2). Participants were enrolled between 2003 and 2008 in Mali, Niger, Tanzania, and Uganda. Clustering by school accounted for in 95% confidence bands. Infections were assessed by Kato-Katz stool examination. 99

Figure 5.4. Modification of Figure 5.3 where participants' *Schistosoma mansoni* intensity is split into three categories: 0 EPG, 1-199 EPG, and ≥200 EPG. See Figure 5.3 description for more details. Data are from three surveys (baseline, BL; follow-up 1, FU1; follow-up2, FU2). 101

Figure 6.1. Line graphs of the prevalence of 6-15 year-old school children who were *Schistosoma* infection and heavy-intensity positive (row A), *S. haematobium* morbidity positive (row B), and *S. mansoni* morbidity positive (row C) at each survey year (BL=baseline, FU1=follow up 1, FU2=follow up 2). *S. haematobium* infections were assessed by urine filtration and *S. mansoni* infections by Kato-Katz. Plots of individual ultrasound indicators for *S. haematobium* and additional morbidity indicators for both species are included in Supplementary Figures 6.1 and 6.2. 135

Figure 6.2. Line graphs of *Schistosoma haematobium*-related morbidity positive prevalence. Heavy-intensity prevalence category determined at the school-level. Participants were enrolled between 2003-2008 at each survey year (BL=baseline, FU1=follow up 1, FU2=follow up 2). Clustering by school accounted for in 95% confidence bands. Infections were assessed by urine filtration. Model-based tests comparisons are included in Table 6.1. Plots of individual indicators and model-based comparisons are included in Supplemental Figure 6.3 and Table 6.2, respectively. 136

Figure 6.3. Line graphs of *Schistosoma mansoni*-related morbidity percentages. Heavy-intensity prevalence category determined at the school-level. Participants were enrolled between 2003 and 2008 at each survey year (BL=baseline, FU1=follow up 1, FU2=follow up 2). Clustering by school accounted for in 95% confidence bands. Infections were assessed by Kato-Katz thick smears. Model-based tests comparisons are included in Table 6.2. Plots of additional indicators and model-based comparisons are included in Supplemental Figure 6.4 and Supplemental Table 6.4, respectively. 138

Figure 7.1. Scatter plots of Schistosoma haematobium infection prevalence and microhematuria prevalence of children aged 6-15 years from Burkina Faso, Mali, Niger, Tanzania, and Zambia participating in schistosomiasis control program activities between 2003 and 2008. Points are scaled based on the number of school-age children with *S. haematobium* infection data. Black line indicates model fits and gray shading indicates 95% Bayesian credible intervals (BCIs) from errors in variables model. The dashed line denotes 10% microhematuria prevalence. 170

Figure 7.2. Line plots by survey of the percent chance a school with a given *Schistosoma haematobium* infection prevalence is below the microhematuria threshold. Panel A is for a 10% microhematuria threshold ; panel B for 13%; and panel C for 15%. Estimates utilized children aged 6-15 years from Burkina Faso, Mali, Niger, Tanzania, and Zambia participating in schistosomiasis control program activities between 2003 and 2008. Full description of the methods is in the supplementary materials. The dashed line indicates a 90% chance of being below the threshold. 171

Figure 7.3. Scatter plots of Schistosoma haematobium prevalence of heavy intensity infections (PHI) and microhematuria prevalence of children aged 6-15 years from Burkina Faso, Mali, Niger, Tanzania, and Zambia participating in schistosomiasis control program activities between 2003 and 2008. Points are scaled based on the number of school-age children with *S. haematobium* infection data. Black line indicates model fits and gray shading indicates 95% Bayesian credible intervals (BCIs) from errors in variables model. The dashed line denotes 10% microhematuria prevalence. 173

Figure 7.4. Line plots by survey of the percent chance a school with a given *Schistosoma haematobium* prevalence of heavy intensity infections is below the microhematuria threshold. Panel A is for a 10% microhematuria threshold, panel B for 13%, and panel C for 15%. Estimates utilized children aged 6-15 years from Burkina Faso, Mali, Niger, Tanzania, and Zambia participating in schistosomiasis control program activities between 2003 and 2008. Full description of the methods is in the supplementary materials. The dashed line indicates a 90% chance of being below the threshold. 174

Figure 8.1. Examples of schistosomiasis-related ultrasound liver texture patterns, as defined by WHO's Niamey protocol (Richter et al. 2000), observed during the Morbidity Operational Research for Bilharziasis Implementation Decisions study. (**A**) normal liver parenchyma; (**B**) "starry sky"; (**C**) "rings" (seen here) and "pipe stems", which correspond to the "rings" seen in a scan perpendicular to the one where pipe stems are seen; (**D**) highly echogenic "ruff" seen around the portal bifurcation and main stem; (**E**) highly echogenic "patches" extending from main portal vein and branches into parenchyma. 194

List of supplemental figures

Supplemental Figure 4.1. Examples of significant impact of *Schistosoma* infection - the gray boxes show estimates of SMDs and their 95% confidence intervals for individual studies that assessed learning and memory. Based on our meta-analysis, the blue diamonds indicate the overall summary estimates of the respective impacts of Schistosoma infection on measured learning and memory scores among affected children. 75

Supplemental Figure 4.2. Relative reduction in odds of diseases after treatment of *Schistosoma* infection. 79

Supplemental Figure 4.3. Examples of Meta-Regressions Showing Relations Between ERRs and Odds of Diseases Post-Treatment 80

Supplemental Figure 4.4. relative odds of disease post-treatment against ERRs. 81

Supplemental Figure 5.1. Line graphs of the percentage of 6-15 year-old school children who were *Schistosoma haematobium*-related morbidity positive at each survey year (baseline, BL; follow-up 1, FU1; follow-up2, FU2). Estimates are from Mali, Niger, and Tanzania for all indicators. Data from Burkina Faso are included in laboratory and self-report indicators. Clustering by school accounted for in 95% confidence bands. 113

Supplemental Figure 5.2. Line graphs of *Schistosoma haematobium*-related morbidity percentages including those for individual morbidity sub-scores not included in Figure 2 across three surveys (baseline, BL; follow-up 1, FU1; follow-up2, FU2). Participants were enrolled between 2003 and 2008 in Mali, Niger, and Tanzania. Clustering by school accounted for in 95% confidence bands. Infections were assessed by urine filtration. 114

Supplemental Figure 5.3. Line graphs of the percentage of 6-15 year-old school children who were *Schistosoma mansoni*-related morbidity positive at each survey year (baseline, BL; follow-up 1, FU1; follow-up2, FU2). Estimates are from Mali, Niger, Tanzania, and Uganda. Clustering by school accounted for in 95% confidence bands. 115

Supplemental Figure 5.4. Line graphs of *Schistosoma mansoni*-related morbidity percentages including morbidity scores that were not included in Figure 5.3, across three surveys (baseline, BL; follow-up 1, FU1; follow-up2, FU2). Participants were enrolled between 2003 and 2008 in Mali, Niger, Tanzania, Uganda, and Zambia. Clustering by school accounted for in 95% confidence bands. Infections were assessed by Kato-Katz. 116

Supplemental Figure 5.5. Line graphs of enlarged portal vein percentage by intensity category by country across three surveys (baseline, BL; follow-up 1, FU1; follow-up2, FU2). Participants were enrolled between 2003 and 2008. Clustering by school accounted for in 95% confidence bands. Infections were assessed by Kato-Katz thick smears. 117

Supplemental Figure 5.6. Modification of Figure 5.4 where participants' *Schistosoma mansoni* intensity at each survey is split into three categories: 0 EPG, 1-99 EPG, and ≥100 EPG. See Figure 5 description for more details. Data are from three surveys (baseline, BL; follow-up 1, FU1; follow-up2, FU2). 118

Supplemental Figure 5.7. Modification of Figure 5.4 where participants' *Schistosoma mansoni* intensity at each survey is split into three categories: 0 EPG, 1-299 EPG, and ≥300 EPG. See Figure 5 description for more details. Data are from three surveys (baseline, BL; follow-up 1, FU1; follow-up2, FU2). 119

Supplemental Figure 5.8. Modification of Figure 5.4 where participants' *Schistosoma mansoni* intensity at each survey is split into three categories: 0 EPG, 1-399 EPG, and ≥400 EPG. See Figure 5 description for more details. Data are from three surveys (baseline, BL; follow-up 1, FU1; follow-up2, FU2)..... 120

Supplemental Figure 6.1. Line graphs of the percentage of 6-15 year-old school children who were *Schistosoma haematobium*-related morbidity positive at each survey year (BL=baseline, FU1=follow up 1, FU2=follow up 2) not included in Figure 6.1, row B. Clustering by school accounted for in 95% confidence bands. 150

Supplemental Figure 6.2. Line graphs of *Schistosoma haematobium*-related morbidity percentages not included in Figure 6.1. Heavy-intensity prevalence category determined at the school-level. Participants were enrolled between 2003 and 2008 at each survey year (BL=baseline, FU1=follow up 1, FU2=follow up 2). Clustering by school accounted for in 95% confidence bands. Infections were assessed by urine filtration. Model-based tests comparisons are included in Supplemental Table 6.2. Plots of aggregated indicators, microhematuria, and self-reported pain while urinating are included in Figure 6.2. 151

Supplemental Figure 6.3. Line graphs of any urinary bladder lesion percentage by heavy intensity prevalence category by country across three surveys (baseline, BL; follow-up 1, FU1; follow-up2, FU2). Participants were enrolled between 2003 and 2008. Clustering by school accounted for in 95% confidence bands. Infections were assessed by urine filtration. 152

Supplemental Figure 6.4. Line graphs of the percentage of 6-15 year-old school children who were *Schistosoma mansoni*-related morbidity positive at each survey year (BL=baseline, FU1=follow up 1, FU2=follow up 2). Clustering by school accounted for in 95% confidence bands. Selected indicators here are included in Figure 6.1, row C. 153

Supplemental Figure 6.5. Line graphs of Schistosoma mansoni-related morbidity percentages. Heavy-intensity prevalence category determined at the school-level. Participants were enrolled between 2003 and 2008 at each survey year (BL=baseline, FU1=follow up 1, FU2=follow up 2). Clustering by school accounted for in 95% confidence bands. Infections were assessed by Kato-Katz thick smears. Model-based tests comparisons are included in Supplemental Table 6.4. Plots of other indicators are included in Figure 6.3. 154

Supplemental Figure 6.6. Line graphs of enlarged portal vein percentage by heavy intensity prevalence category by country across three surveys (baseline, BL; follow-up 1, FU1; follow-up2, FU2). Participants were enrolled between 2003 and 2008. Clustering by school accounted for in 95% confidence bands. Infections were assessed by Kato-Katz thick smears. 155

Supplemental Figure 7.1. Posterior distributions of each infection prevalence at the baseline survey as determined by a cubic model with shading for the proportion of the distribution which falls above and below the microhematuria threshold of 10%. Blue indicates the proportion that is above the threshold. The medians correspond to the curve in panel C of Supplemental Figure 7.2. 184

Supplemental Figure 7.2. Focused version of Figure 7.2 with only model fits confined to the range 0-20% infection intensity prevalence. Best fitting models (see Supplemental Table 7.1 for DIC values which were used to determine best fitting) are represented by thicker line and shaded bands representing 95% credible intervals. 185

Supplemental Figure 7.3. Line plots of the percentage chance a school with a given *Schistosoma haematobium* infection prevalence will fall below a microhematuria threshold for all models considered. Thresholds of 10%, 13%, and 15% were considered. Estimates utilized children age 6-15

years from Burkina Faso, Mali, Niger, Tanzania, and Zambia participating in schistosomiasis control program activities between 2003 and 2008. Predictions were based on errors in variable Bayesian models. Models were fit separately for each survey..... 186

Supplemental Figure 7.4. Focused version of Figure 7.4 with only model fits confined to the range 0-5% prevalence of heavy intensity infections. Best fitting models are represented by thicker line and shaded bands representing 95% credible intervals..... 187

Supplemental Figure 7.5. Line plots of the percentage chance a school with a given Schistosoma haematobium prevalence of heavy intensity infections will fall below a microhematuria threshold for all models considered. Thresholds of 10%, 13%, and 15% were considered. Estimates utilized children aged 6-15 years from Burkina Faso, Mali, Niger, Tanzania, and Zambia participating in schistosomiasis control program activities between 2003-2008. Predictions were based on errors in variable Bayesian models. Models were fit separately for each survey..... 188

List of tables

Table 3.1. Baseline and Year 5 characteristics of cohort participants (children with data both in Year 1 and Year 5), and baseline characteristics of those lost to follow-up, by arm[a] 46

Table 3.2. Summary results for morbidity markers, by arm, by year[a] 50

Table 3.3. Outcomes with significant changes from Year 1 to Year 5, for both study arms combined[a] 51

Table 3.4. Age- and sex-adjusted CWT-arm participant odds for study morbidity at Year 5, using the SBT-arm participants as reference[a] 52

Table 3.5. Sex-adjusted comparison of arm-specific changes in infection and morbidity outcomes from Year 1 to Year 5, including interaction term added to account for differences in starting values between groups[a] 54

Table 5.1. Summary of Schistosoma infection data collection procedures by country, Schistosomiasis Control Initiative (SCI) supported monitoring and evaluation data, 2003-2008. 90

Table 5.2. Odds ratios (ORs) and 95% credible intervals from Bayesian logistic regression models comparing morbidity positive proportions between intensity categories within surveys for *S. haematobium*-related morbidities. Bold font indicates the 95% Bayesian credible interval (BCI) does not contain one. Participants are school-age children (6-15 years) enrolled between 2003 and 2008 in Mali, Niger, and Tanzania. 96

Table 5.3. Odds ratios (ORs) and 95% credible intervals from Bayesian logistic regression models comparing morbidity positive proportions between intensity categories within surveys for *S. haematobium*-related morbidities without controlling for age and sex. Bold font indicates the 95% Bayesian credible interval (BCI) does not contain one. Participants are school-age children (6-15 years) enrolled between 2003 and 2008 in Mali, Niger, and Tanzania. 97

Table 5.4. Odds ratios (ORs) and 95% credible intervals from Bayesian logistic regression models comparing morbidity positive proportions between heavy-intensity prevalence categories within surveys for *S. mansoni*-related morbidities. Bold font indicates the 95% Bayesian credible interval (BCI) does not contain one. Participants are school-age children (6-15 years) enrolled between 2003 and 2008 in Mali, Niger, Tanzania, and Uganda. 100

Table 6.1. Odds ratios and 95% credible intervals from Bayesian logistic regression models comparing morbidity positive proportions between heavy-intensity prevalence categories within surveys for *S. haematobium*-related morbidities. 137

Table 6.2. Odds ratios and 95% credible intervals from Bayesian logistic regression models comparing morbidity positive proportions between heavy-intensity prevalence categories within surveys for *S. mansoni*-related morbidities. 139

Table 9.1. Contributions based on the Swiss Tropical and Public Health Institute principles. 199

List of supplemental tables

Supplemental Table 3.1. Non-significant differences in arm-specific changes from Year 1 to Year 5 when the interaction of study arm by survey year is considered[a] 59

Supplemental Table 4.1. Pooled standardized mean difference (SMD) estimates of *Schistosoma* infection/non-treatment effects on educational/cognitive loss – with evaluation of study heterogeneity and publication bias 74

Supplemental Table 5.1. Dates of participant ascertainment in monitoring and evaluation cohorts. Shading indicates surveys that were included in analyses. Treatment was usually immediately following survey times, but occasionally lagged by a few months. 121

Supplemental Table 5.2. Participants included in analyses of *Schistosoma haematobium* infection intensity categories. Numbers in parentheses indicate the number of schools from which participants were sampled. 122

Supplemental Table 5.3. Odds ratios and 95% confidence intervals from Bayesian logistic regression models comparing morbidity positive proportions between *S. haematobium* intensity categories that were not included in Table 2. Bold font indicates the 95% credible interval does not contain one. Participants are school-aged children, aged 6-15 years, enrolled between 2003 and 2008 in Mali, Niger, and Tanzania for all indicators and Burkina Faso, Mali, Niger, and Tanzania for laboratory and self-report indicators. *S. haematobium* assessed by urine filtration. 124

Supplemental Table 5.4. Participants included in cross-sectional analyses of *Schistosoma mansoni* infection intensity categories. Numbers in parentheses indicate the number of schools from which participants were sampled. 125

Supplemental Table 5.5. Odds ratios and 95% confidence intervals from Bayesian logistic regression models comparing morbidity positive proportions between intensity categories within surveys for *S. mansoni*-related morbidities that were not included in Table 5.3. Bold font indicates the 95% credible interval does not contain one. Participants are school-aged children, aged 6-15 years, enrolled between 2003 and 2008 in Mali, Niger, Tanzania, and Uganda 126

Supplemental Table 6.1. Sample sizes of schools and participants in *S. haematobium* analyses. Frequencies are broken down by morbidity and heavy-intensity prevalence category. Cells contain the number of schools with the number of participants in parentheses. Participants are school-age children, with morbidity and infection data, 6-15 years, and enrolled between 2003 and 2008. 156

Supplemental Table 6.2. Odds ratios and 95% credible intervals from Bayesian logistic regression models comparing morbidity positive proportions between heavy-intensity prevalence categories within surveys for *S. haematobium*-related morbidities not presented in Table 6.1. Bold font indicates the 95% credible interval does not contain one. Participants are school-age children (6-15 years) enrolled between 2003 and 2008. Corresponding plots of unmodeled morbidity prevalence are in Figure 6.2 and Supplemental Figure 6.3. 158

Supplemental Table 6.3. Sample sizes of schools and participants in *S. mansoni* analyses. Frequencies are broken down by morbidity and heavy-intensity prevalence category. Cells contain the number of schools with the number of participants in parentheses. Participants are school-age children, with morbidity and infection data, aged 6-15 years, and enrolled between 2003 and 2008. 160

Supplemental Table 6.4. Odds ratios and 95% credible intervals from Bayesian logistic regression models comparing morbidity positive proportions between heavy-intensity prevalence categories within

surveys for *S. mansoni*-related morbidities not presented in Table 6.2. Bold font indicates the 95% credible interval does not contain one. Participants are school-age children (6-15 years) enrolled between 2003 and 2008. Corresponding plots of unmodeled morbidity prevalence are in Figure 6.3 and Supplemental Figure 6.4. 161

Supplemental Table 7.1. Deviance information criterion (DIC) values for all models fit. Bold font indicates lowest DIC value for a dataset and infection prevalence measure (any infection or heavy-intensity infection). 182

Supplemental Table 7.2. Estimated percent chance of falling below 10%, 13% and 15% microhematuria thresholds for infection prevalence targets between 0 and 25% percent. Values in this table are plotted in Figure 7.1. 183

Supplemental Table 7.3. Estimated percent chance of falling below 10%, 13% and 15% microhematuria thresholds for heavy intensity infection prevalence (PHI) targets between 0 and 5% percent. Values in this table are plotted in Figure 7.2. 184

List of abbreviations

BASC-2	Behavioral Assessment System for Children
CAA	Circulating anodic antigen
CCA	Circulating cathodic antigen
CDC	Centers for Disease Control and Prevention
CHW	Community health worker
CI	Confidence interval
$CI_{95\%}$	95% confidence interval
CWT	Community wide treatment
EPG	Eggs per gram
epg	Eggs per gram
ERR	Egg reduction ratio
DALY	Disability-adjusted life-years
ELISA	Enzyme linked immunosorbent assay
GBD	Global Burden of Disease Programme
Hb	Hemoglobin
ICER	Incremental cost effectiveness ratio
ISRCT	International Standard Randomized Controlled Trial
IPB	Irregular image pattern B
IPC	Irregular image pattern C
MDA	Mass drug administration
MORBID	Morbidity Operational Research for Bilharziasis Implementation Decisions
NS	Non-significant
NTD	Neglected Tropical Disease
PedsQL	Pediatric Quality of Life Inventory instrument
PHI	Prevalence of heavy-intensity infections
POC	Point of Care
POC-CCA	Point of care circulating cathodic antigen
PT	Periportal thickening

PVD	Portal vein diameter
RAP	Rapid Answers Project
SBT	School-based treatment
SCI	Schistosomiasis Control Initiative
SCORE	Schistosomiasis Consortium for Operational Research and Evaluation
SD	Standard deviation
SEA	Soluble egg antigen
SMD	Standardized mean difference
spp	Multiple species
SSA	Sub-Saharan Africa
Swiss TPH	Swiss Tropical and Public Health Institute
UCAA2000	Urine circulating anodic antigen 2000 test
UCP-LF CAA	Upconverting particle-lateral flow circulating anodic antigen
USD	United States dollar
VO_2max	Maximal oxygen uptake as estimated by fitness testing
WASH	Water, sanitation, and hygiene
WHA	World Health Assembly
WHO	World Health Organization
YLD	Years lived with disability

1 Introduction

Schistosomiasis, or bilharzia, is the infectious disease caused by worms of the genus *Schistosoma* (Colley et al. 2014a). There are 21 recognized schistosome species, of which eight have been reported in humans: *Schistosoma guineensis*, *Schistosoma haematobium*, *Schistosoma intercalatum*, *Schistosoma japonicum*, *Schistosoma mansoni*, *Schistosoma malayensis*, *Schistosoma mattheei*, and *Schistosoma mekongi* (Standley et al. 2012). Human disease is primarily caused by *S. haematobium*, *S. mansoni*, and *S. japonicum*. *S. haematobium* is the only species to affect the urogenital system; all other species affect the intestinal system.

1.1 History

Evidence of schistosomiasis dates back at least 6,000 years based on identification of schistosomes in skeletal remains in present-day Syria (Anastasiou et al. 2014). The disease was likely mentioned in Egyptian medical papyri as early as 1500 BCE (Di Bella et al. 2018) and evidence of calcified eggs was found in mummified kidneys of Egyptians from the twentieth dynasty (Ruffer 1910). A high incidence of haematuria, a common symptom of *S. haematobium* infection, was noted in Egypt in the 16th century (Alpino 1591). In the late 18th century, a French physician recorded an outbreak of haematuria that was likely caused by *S. haematobium* during Napoléon's campaign in Egypt and Syria (Renoult 1808). He also noted that Egyptian men appeared to menstruate (Sarant 2017).

Schistosomiasis is potentially referred to in the Bible in relation to a curse. When Joshua invaded Palestine, he captured Jericho along his way to Judea and cursed Jericho (*Joshua*, 6:26, R.S.V.). The language Joshua used in his curse, the defeatist attitude of Jericho when invaded (*Joshua*, 2:1, R.S.V.), and the comments of "bad water" and "unfruitful land" that were used when the city is cleansed (II *Kings*, 2:19, R.S.V.) are consistent with citizens of Jericho suffering from urogenital schistosomiasis (Hulse 1971). Although no known evidence of *S. haematobium* in Jericho exists, excavations of the area

found a juvenile example of *Bulinus truncatus*, the intermediate host for *S. haematobium*, preserved in mud bricks from the same era (Biggs et al. 1960) suggesting a circumstantial link.

Two German parasitologists, Theodor Maximilian Bilharz and Carl Theodor Ernst, first described schistosomiasis during an autopsy in 1851 in Cairo (Bilharz 1852). Initially called *Distomum haematobium* (Bilharz 1853), the disease process of schistosomiasis, including fibrosis and ulcer formation, was described not long after (Griesinger 1854; Bilharz 1856). Only a few years later, schistosomes were identified in a primate, *Cercopithecus fuliginosus* (Cobbold 1859).

Around the same time as Bilharz was working in Cairo, Yoshinao Fujii first described acute schistosomiasis (Katayama syndrome) in the medical literature in 1847 (Fujinami 1909), though mentions appeared in other literature early in the 19th century (Ishii et al. 2003). About forty years later, Tokuho Majima reported schistosome eggs in patients with acute schistosomiasis and made the connection between the two (Majima 1888). Research in Japan in the last quarter of the 19th century led to concurrent discoveries by Akira Fujinami of a *S. japonicum* female worm in the hepatic system during an autopsy (Fujinami 1904) and a series of findings by Fijiro Katsurada on the discovery of worms in the portal vein a cat, which he referred to as *Schistosomum japonicum* (Katsurada 1904b; 1904c; 1904a).

Research on *S. japonicum* continued and many milestones were established by Japanese scientists (Fairley 1919; Tanaka et al. 1997). The two lead researchers who first recognized *S. japonicum*, Fujinami and Katsurada, also worked simultaneously on describing transmission. In 1909, one group immersed a dog and cat in water suspected to be infectious and found flukes in the cat's portal vein after it had died (Katsurada et al. 1909). The second team immersed calves to demonstrate transmission by water (Fujinami et al. 1909). This was quickly followed by the description of human transmission by the dermatologist Matsuura who walked through water considered to be infectious and eventually shed eggs (Matsuura 1909). These groups succeeded after early efforts to establish transmission of Egyptian

strains of *S. haematobium* to humans failed (Cobbold 1872; Sonsino 1884; Fairley 1919). Through a series of experiments on animals in 1912 and 1913, Miyagawa found that, after penetrating the skin, worms migrated through the heart to get to the portal system (Miyagawa 1912a; 1912b; 1913a; 1913b). Although it had been hypothesized that the lifecycle included snails, Japanese researchers were finally able to establish that mollusks serve as the intermediate host for *S. japonicum* shortly thereafter (Miyairi et al. 1913).

Confirming the existence of *S. mansoni* was more complicated. In 1902, Patrick Manson suggested the possibility of another species beyond *S. haematobium* that was causing schistosomiasis (Manson 1902). Five years later, *S. mansoni* was identified from a single worm in Brazil (Sambon 1907a; 1907b) although there were arguments in the literature (Looss 1908; Sambon 1909) regarding whether this was a new schistosome species or *S. haematobium* (Katz 2008).

A key piece to this puzzle was the morphology of the eggs. Bilharz established that *S. haematobium* eggs have a terminal spine, though eggs with lateral spines were found in 1884 in a bladder infection (Sonsino 1884) and then again two years later in a purely *S. mansoni* bladder infection (Belleli 1886), which is now known to be a rare occurrence (Depaquit et al. 2019). In Brazil, the eggs had a lateral spine (Sambon 1907a; 1907b) and extensive work was done by Manoel Augusto Pirajá da Silva to demonstrate that all eggs identified from Brazil had lateral spines (Pirajá da Silva 1908b; 1908a; 1908d; 1908c; 1909). Robert Leiper, with help from Pirajá da Silva, articulated the complete lifecycle of schistosomiasis in 1915 and definitively distinguished between *S. haematobium* and *S. mansoni*, thus putting an end to the argument that they were the same species (Leiper 1915c; 1915a; 1915b; Leiper et al. 1916; Leiper 1918).

In the interwar period, *S. intercalatum* was described as a separate species (Fisher 1934) and attention turned to establishing control efforts. Many surveys had been performed to understand the

prevalence and distribution of schistosomiasis in the Nile Delta region of Egypt (Scott 1937). The only national programme against schistosomiasis was in Egypt until Venezuela started a control programme in 1942 (Sandbach 1976). A request was made by the Egyptian Ministry of Health to the League of Nations to begin control work at an international level (Bey 1938). Despite a report from the commission that called for more research (League of Nations Health Organization 1938) nothing was done. This was due to a variety of reasons including poor representation from affected areas, poor organization, a lack of data and understanding of disease burden, and the prospect of another major war (Shousha 1949; Sandbach 1976).

World War II brought more exposure to schistosomiasis as many allied soldiers acquired the disease while serving in tropical regions (Sandbach 1976). After World War II, the first assessment of the global distribution of schistosomiasis was included in Norman Stoll's summary of parasites around the world (Stoll 1947). There was a growing recognition that schistosomiasis is an international problem (Shousha 1949) and the newly formed World Health Organization convened their first study group on schistosomiasis in Africa (WHO 1950). Many surveys and other reports of the distribution and extent of schistosomiasis around the world were performed during this era (Dewhurst 1949; Meira 1949; Cowper 1953; Ayad 1956; Blair 1956; White et al. 1957; Mao 1958).

An extremely productive period followed that was marked by many advances in the understanding, evaluation, and control of schistosomiasis. A great deal of knowledge was gained about how *Schistosoma* worms oviposit, such as how many eggs are produced by a worm pair per day (Moore et al. 1956) and the distribution of trapped eggs throughout the human body (Gelfand et al. 1953; von Lichtenberg et al. 1973; Cheever et al. 1977). Extensive headway was made in the understanding of disease progression and pathology (Cheever et al. 1967; Edington et al. 1970; Sadun et al. 1970; Andrade et al. 1971; Cook et al. 1974; Smith et al. 1974; Cheever et al. 1978; Kamel et al. 1978; Miller et al. 1978; 1980). Parasitological tests that remain the standard for determining the presence and

intensity of infection were developed and refined (Katz et al. 1972; Peters et al. 1976a; Peters et al. 1976b). In addition, antigens that form the basis of tests which may soon supplant parasitological tests were identified (Deelder et al. 1980). Initial reports of the utility of ultrasonic evaluation were published (Abdel-Wahab et al. 1978). This period is bookended by two important findings related to disease control. At the beginning was widespread use of molluscicides, including niclosamide, which were evaluated for snail control (Foster et al. 1960). At the end was the discovery and demonstration of the effectiveness of praziquantel for the treatment of adult worms of all major schistosome species that predominantly affect humans (Pearson et al. 1983).

These findings helped spur an expansion in schistosomiasis research and control efforts. Ultrasonic evaluation was utilized to evaluate severe pathology (Cerri et al. 1984; Hussain et al. 1984; Burki et al. 1986; Hatz et al. 1990; Doehring-Schwerdtfeger et al. 1992a) and a WHO working group was formed to standardize ultrasound methodology (The Cairo Working Group 1992; Richter et al. 2000). Investigation of disease pathogenesis progressed, leading to a deeper understanding of schistosomiasis immunology (Colley et al. 1986; Boros 1989). The control of schistosomiasis became a focus of the World Health Organization (WHO 1980; WHO Expert Committee on the Control of Schistosomiasis 1985; WHO 1993) and schistosomiasis morbidity was brought into focus (Mott et al. 1983; Warren et al. 1983; WHO 1987; 1988; 1989). Highs and lows of disease control were experienced with successes, e.g., the eradication of schistosomiasis from Japan (Tanaka et al. 1997), and failures, such as the devastating outbreak of schistosomiasis in the Senegal River Basin after the construction of two dams (Talla et al. 1990; Stelma et al. 1994; Southgate 1997).

The introduction of preventive chemotherapy using mass drug administration led to a decreasing burden of schistosomiasis from 2006 onward (Global Burden of Disease Collaborative Network 2020), resulting in large part from donations of praziquantel from Merck KGaA (Hotez et al. 2010; Fenwick et al. 2016) and the success of nascent schistosomiasis control programmes, such as those supported by the

Schistosomiasis Control Initiative (Fenwick et al. 2009; Deol et al. 2019). This spurred discussions about eliminating schistosomiasis transmission (London Declaration on Neglected Tropical Diseases 2012; WHO 2012; World Health Assembly 2012) even though those discussions were likely premature (Ross et al. 2015b; Toor et al. 2018a). Nevertheless, control programme targets were developed (WHO 2011c; 2013) and the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) implemented a wide array of projects to improve control and elimination initiatives (Colley et al. 2020a; Colley et al. 2020b).

Recently, efforts to better evaluate disease burden (Steinmann et al. 2006) and morbidity, both subtle (King et al. 2005) and underreported, such as female genital schistosomiasis (Christinet et al. 2016), have heighted our understanding of the global impact of schistosomiasis. Further development is needed to improve diagnostics, such as CAA (Corstjens et al. 2008) and CCA (van Dam et al. 2004) and advanced analytics, such as spatial statistics (Clennon et al. 2004; Raso et al. 2005; Clements et al. 2006; Brooker 2007; Simoonga et al. 2009; Magalhães et al. 2011; Schur et al. 2011; Scholte et al. 2012; Schur et al. 2012; Schur et al. 2013; Chammartin et al. 2014; Scholte et al. 2014; Lai et al. 2015; Wiegand et al. 2017; Fornace et al. 2020; Kokaliaris et al. 2021) and mathematical modelling (Lo et al. 2015; Lo et al. 2018; Toor et al. 2018a; Toor et al. 2018b; NTD Modelling Consortium Schistosomiasis Group 2019; Toor et al. 2019; Coffeng et al. 2020; Kura et al. 2020; Toor et al. 2020) are being utilized to better describe and predict the disease burden and distribution and the effects of interventions. Further technology, such as the use of light unmanned aerial vehicles (Chamberlin et al. 2021) and smartphone based diagnostic tests (Diehl et al. 2020), could provide more low-cost options for facilitating schistosomiasis control.

1.2 Aetiology

Humans infected with *S. haematobium* shed *Schistosoma* eggs in urine while eggs of all other species are shed through stool. Eggs hatch in freshwater and release miracidia. These free-swimming

larvae then penetrate the tissue of specific snail species. The snail acts as an intermediate host where asexual reproduction happens. Over the course of 4-6 weeks, mother and daughter sporocysts are produced, develop, and eventually cercariae are released into the water (Pan 1965). The cercariae swim and look to penetrate the skin of a mammalian host. Cercariae that enter a human host lose their forked tails and become schistosomulae. The migration through the human body is largely unknown, but has been studied using murine experimental models, especially with *S. mansoni* (Wilson 2009). Given mice and humans have the same beginning and end to the process, the process in mice is assumed to be the same as humans (Colley et al. 2014b). Through the bloodstream, the schistosomulae feed on blood and travel to the lungs, through the heart, and eventually migrate to the liver. The larvae mature into male and female adults, mate, and produce eggs. *S. haematobium* worms generally reside in the venous plexus of the bladder and shed eggs through urine. *S. mansoni*, *S. intercalatum*, and S*. guineensis* are mostly found in the inferior mesenteric veins of the large intestine, but at different places. *S. japonicum* most often resides in the superior mesenteric veins of the small intestine. The complete lifecycle for both intestinal and urogenital species is included in Figure 1.1.

The longevity of schistosome infection has been a challenge to estimate empirically since the date of infection is left censored (before the observation date but the exact date is unknown) and the time a schistosome would naturally die is right censored (after the observation date but the exact date is unknown) since it's unethical to deny someone treatment to clear an infection. Two subpopulations have been useful for guessing the maximum age of a *Schistosoma* worm: permanent emigres from endemic areas (Wallerstein 1949; Berberian et al. 1953; Hall et al. 1970; Joyce et al. 1972; Harris et al. 1984; Hornstein et al. 1990; Payet et al. 2006) and soldiers returning from conflicts in endemic areas

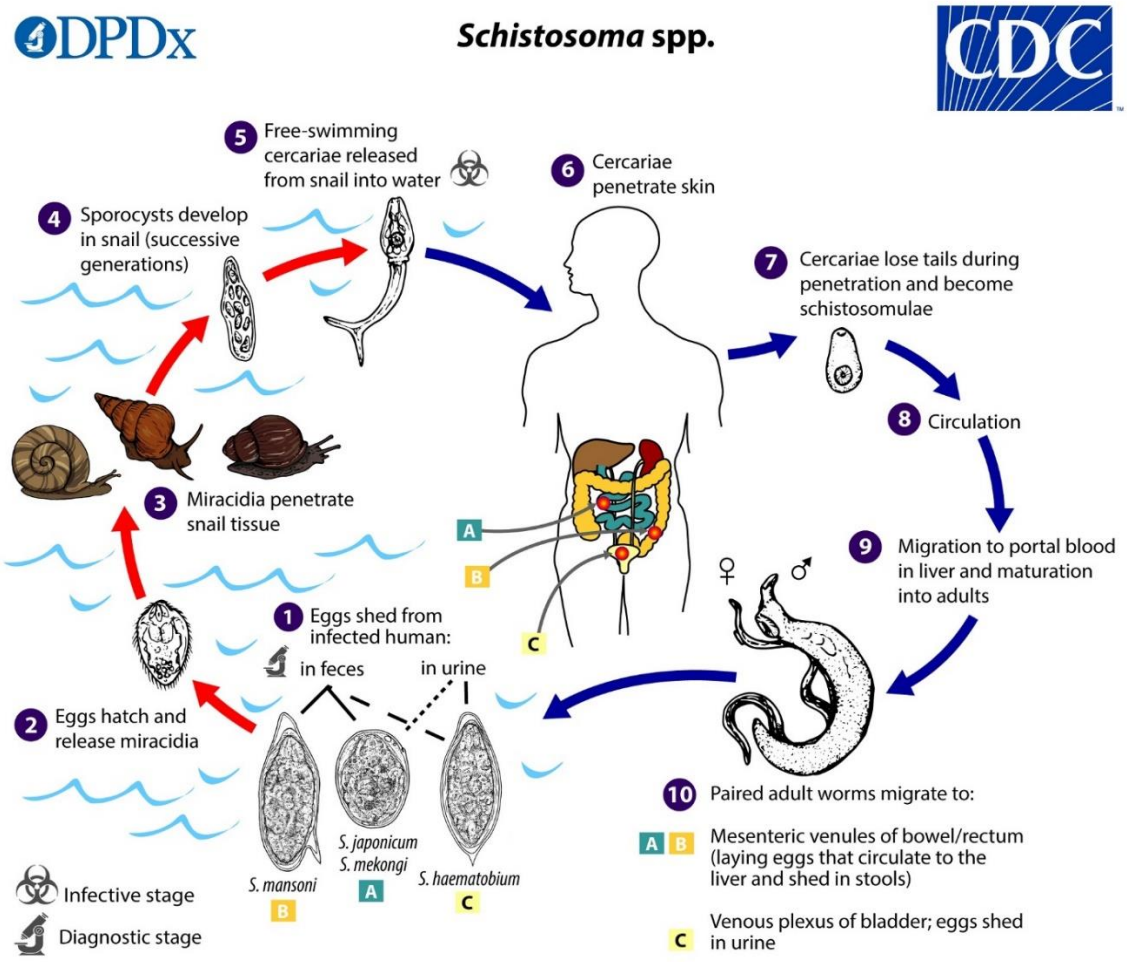


Figure 1.1. Life cycle of schistosomiasis.

(Markel et al. 1978; Chabasse et al. 1985; Vieira et al. 2007). The maximum lifespan from those reports appears to be 47 years (Hall et al. 1970). Studies have combined data from people who have been removed from infection risk and, with some modelling assumptions, estimated the average lifespan of *Schistosoma* worms (Hairston 1965; Bradley et al. 1973; Warren et al. 1974; Holford et al. 1976; Hiatt et al. 1980; Vermund et al. 1983; Wilkins et al. 1984; Fulford et al. 1995). Estimates range from 3-10 years, with the most thorough estimate possessing a confidence interval of 5.7-10.5 years (Fulford et al. 1995).

During most of this time, females produce eggs and males fertilize them. Due to the challenges of using rodents with *S. haematobium* infections (Colley et al. 2014b), data on egg output has only been reported for intestinal species. Studies using hamsters (Moore et al. 1956) and mice (Cheever et al. 1994) found *S. mansoni* females produced 300 and 350 eggs per day, respectively, while *S. japonicum* females produced 3,500 and 2,200 eggs per day, respectively.

Quantification of *Schistosoma* worm burdens in humans is not possible to measure (Gryseels et al. 1996). Utilizing a model designed to describe observed egg counts, de Vlas and colleagues (de Vlas et al. 1992b; de Vlas et al. 1992c) estimated that people infected with over 100 *S. mansoni* worms would be plentiful in communities of all endemicities (Gryseels et al. 1996). In addition, 3% of people in low endemicity communities and 17% of people in moderate endemicity communities would have over 1,000 *S. mansoni* worms.

1.3 Geographic Range

Schistosomiasis is primarily a disease of sub-Saharan African (SSA). Approximately 93% of the estimated global burden of schistosomiasis is in SSA (Steinmann et al. 2006), with 25% of the population being infected (Hotez et al. 2009b). The range spans most of the subcontinent, with variability by species (Lai et al. 2015). Schistosomiasis is also found in parts of Asia, South America, and the Caribbean. *Schistosoma* species are associated with certain snail species and the geographic range of each species is largely driven by the habitats of those snail hosts.

S. haematobium infection is found in Africa and the Middle East where *Bulinus* snails live (Rollinson et al. 2001). In SSA, the range spans the entire subcontinent, with especially high prevalence in many countries along or near the African meningitis belt (the Gambia, Senegal, Guinea-Bissau, Guinea, Sierra Leone, Mali, Burkina Faso, Ghana, Togo, Benin, Niger, Nigeria, Cameroon, Chad, Central African Republic, Sudan, South Sudan, Kenya, and Somalia), northern Mozambique, and northeastern

South Africa (Lai et al. 2015). Other more focal areas of high prevalence include parts of Somalia, eastern Kenya, northern and central Tanzania, northern Angola, and northern Zimbabwe.

The geographic range of *S. mansoni* infections in SSA is more limited than that of *S. haematobium* (Lai et al. 2015). Focal areas can be found in the African meningitis belt, especially in Guinea, Sierra Leone, and Liberia, northeastern and east-central parts of the Democratic Republic of the Congo, the Great African Lakes, and focal areas of Madagascar, Mozambique, and eastern South Africa. *S. mansoni* is also endemic in the Americas, where Brazil has the most infection hotspots with multiple other countries in the Americas needing further data on their epidemiologic status as transmission has potentially been interrupted (Zoni et al. 2016), e.g., in St. Lucia (Gaspard et al. 2020). The spread to the Americas was through the slave trade (Lammie et al. 2007) and made possible by the presence of *Biomphalaria* snails, the intermediate hosts for *S. mansoni*.

S. japonicum is only found in Asia where *Oncomelania* snails live. *O. hupensis* is found in and around the Yangtze River (Wilke et al. 2000) and in lake and marshland regions of China (Jia-Gang et al. 2005; Yang et al. 2006). Infections in Indonesia are confined to Sulawesi island, especially the Lindu, Napu, and Bada valleys where *O. hupensis lindoensis* lives (Satrija et al. 2015). *O. nosophora* was the intermediate host in Japan before schistosomiasis was eradicated there (Tanaka et al. 1997).

S. mekongi is found in Lao People's Democratic Republic and Cambodia where *Neotricula aperta* snails live (Khieu et al. 2019). *S. guineensis* and *S. intercalatum* were recognized as distinct species in 2003 (Kane et al. 2003) in west and central Africa. *Bulinus* spp. snails serve as the intermediate host.

1.4 Burden

Estimates of the disease burden of schistosomiasis have varied (King 2010). Schistosomiasis, like many neglected tropical diseases (NTDs), rarely causes mortality, meaning schistosomiasis burden is largely due to years lived with disability; succinctly, schistosomiasis is a disabler and not a killer (Hotez et

al. 2014). Unfortunately, this makes the public health impact of schistosomiasis and other NTDs hard to quantify. A simplified version of the function used by Global Burden of Disease (GBD) Programme to calculate the years lived with disability (YLDs) (King et al. 2008a) is

YLDs = (duration of disease) x (prevalence) x (disability weight) x (age weight) x (future discount).

Components of this function illustrate the reasons for the low estimate. First, the prevalence component of the equation has been underestimated by flawed estimates (Brooker et al. 2000; van der Werf et al. 2003b; Steinmann et al. 2006). A portion of this is driven by diagnostic tests with poor sensitivity that lead to misclassification bias (de Vlas et al. 1992a; Lamberton et al. 2014; Knopp et al. 2015) where light infections are treated as negative (King 2015). In addition, the geographic overlap with other parasitic infections, especially soil transmitted helminths (Handzel et al. 2003; Kabatereine et al. 2006), has potentially driven prevalence estimates downward. The overlap with other disabling NTDs could also affect the second aspect (the disability weight) by attributing disability to other NTDs. This misappropriation of morbidity to other causes is likely due to a lack of recognition of schistosomiasis-linked morbidity (King et al. 2005), especially the effects of chronic schistosomiasis (King et al. 2008b).

All of these factors have resulted in an underestimation of the morbidity caused by schistosomiasis (King 2010). Debate continues regarding these calculations pertaining to schistosomiasis (Goldberg et al. 2018; King et al. 2018) as well as about the ethics of these estimates (Arnesen et al. 1999; Murray et al. 2020). Global Burden of Disease (GBD) estimates of the disability-adjusted life-years (DALYs) attributed to schistosomiasis ranges between 1.6 and 2.1 million DALYs (Global Burden of Disease Collaborative Network 2020).

1.5 Pathology and Morbidity

Acute pathologies account for a trivial part of the overall morbidity burden. Early pathology of schistosomiasis infections includes cercarial dermatitis, or swimmer's itch (Cort 1928), due to cercarial

penetration of the skin, resulting in pruritus that can last for approximately a week (Horák et al. 2015). Acute schistosomiasis (or Katayama syndrome), a hypersensitivity reaction that generally occurs after initial infection, is the most observed early pathology of schistosomiasis (Ross et al. 2007; Jauréguiberry et al. 2010), especially in travelers to endemic areas. Typically, symptoms arise suddenly and include fever, fatigue, myalgia, malaise, cough, and eosinophilia and recovery is often rapid (Boros 1989; Ross et al. 2007; Montgomery 2020). Other pathologies during the initial infection stage are rare, though some may have more severe outcomes, such as neuroschistosomiasis (Ferrari et al. 2011). Acute pathologies are typically described in travelers (Zuidema 1981; Colebunders et al. 1995; Visser et al. 1995; Lambertucci et al. 2013; Meltzer et al. 2013), but acute manifestations may also occur in endemic areas and are likely overlooked (Lambertucci 2010).

Pathology and morbidity associated with schistosomiasis are largely driven by the host's long-term immune responses to parasite eggs. As infections become chronic, urogenital and intestinal species begin to diverge in their pathology and morbidity, primarily as a function of different oviposition locations. The immune responses that lead to pathology are similar (Wynn et al. 2004) with clinical manifestations and morbidity resulting from eggs lodged in tissues instead of exiting the body via urine or faeces. Experimental studies of egg shedding in hamsters found that only 22% of *S. mansoni* eggs and 16% of *S. japonicum* eggs were shed in faeces (Moore et al. 1956). In mice, approximately a third of *S. mansoni* eggs and a half of *S. japonicum* eggs were shed in faeces (Cheever et al. 1994). These findings suggest a large proportion of eggs do not leave the body. The association between parasite eggs and pathology has been recognized from the earliest studies of schistosomiasis as Bilharz postulated that the inflammation he observed in his initial autopsy was due to ova caught in the submucosa (Bilharz 1856). The trapped eggs release soluble egg antigens (von Lichtenberg 1964) that elicit a granulomatous immune response of lymphocytes, eosinophils, and macrophages (Pearce et al. 2002).

The extent of a person's schistosomiasis-related morbidity is dependent on a few factors. The first factor is the species causing the infection since egg laying patterns differ between species (von Lichtenberg et al. 1973; Cheever et al. 1980; Cheever et al. 1982; Colley et al. 2014a). Second, is the infection intensity, which is crude approximation of the number of worms pairs present in the body (Gryseels et al. 1996), since people who tend to shed more eggs tend to have more severe symptoms (Kloetzel 1962; Forsyth et al. 1964; Forsyth et al. 1965; Forsyth et al. 1966; Cheever 1968; Cook et al. 1974; Cheever et al. 1975; Arap Siongok et al. 1976; Lehman et al. 1976; Omer et al. 1976; Cheever et al. 1977; Pugh et al. 1979; Warren et al. 1979; Gryseels et al. 1987; Kardorff et al. 1997). Third, repeated infections have an effect on parasite burdens (Crombie et al. 1985). Finally, some people's immune systems are better able to regulate their response to trapped ova which reduces the disease severity (Colley et al. 2014b).

1.5.1 Pathology and morbidity due to urogenital schistosomiasis

Many studies from the first half of the 20th century commented on the distribution of ova in infected humans (Ferguson 1913; Begg 1920; Fairley 1920; Des Ligneris 1921; Dew 1923; Ibrahim 1923; Gibson 1925; Hutchison 1928; Blackie 1932; Gelfand et al. 1940; Gilbert 1943). These studies, largely from autopsies, found patterns of egg distribution are uneven, with ova lodged throughout the genital and urinary tracts. Usually the egg accumulation is focal (Gelfand et al. 1953; Christie et al. 1986a; Christie et al. 1986b), resulting in a greater inflammatory response and greater likelihood of symptoms (Gelfand et al. 1953). The clustering of eggs generally results in a continuum of appearance and consistency, ranging from polypoid patch, to a fibrous patch, to a sandy patch (Sadun et al. 1970), and results in heterogeneity of fibrosis within and between individuals (Smith et al. 1986).

The most characteristic symptom of *S. haematobium* infection is haematuria (van der Werf et al. 2003b; Barsoum et al. 2013; Colley et al. 2014a) which is also usually the first sign of infection in children (WHO 1987). This is generally caused by granulomatous lesions of the bladder resulting in ulceration

(Farid et al. 1968), but could be caused by the parasites themselves since adult worms lay eggs as near as possible to the bladder (Barsoum et al. 2013). Dysuria and increased micturition are also common clinical presentations that are associated with haematuria (King et al. 1988; Barsoum 2013).

Deposition of *S. haematobium* eggs in the submucosa of the urinary bladder leads to inflammation, ulceration, and fibrosis in the inner surface of the bladder wall (Pollack et al. 1981) and thickening of the bladder wall (Degremont et al. 1985; Abdel-Wahab et al. 1992a; Abdel-Wahab et al. 1992b; Medhat et al. 1997). Bladder polyps, a more pronounced pathology caused by large, localized egg burdens, have been associated with *S. haematobium* infection (Edington et al. 1970; Sadun et al. 1970; von Lichtenberg et al. 1971; Lehman et al. 1973; Smith et al. 1974; Smith et al. 1975; Smith et al. 1977b) during chronic infection (Sadun et al. 1970) or infections with rapidly accumulating egg burdens (Smith et al. 1975). Early radiography studies found a direct association between the prevalence of these pathologies and intensity of infection (Forsyth et al. 1964; Forsyth et al. 1965; Forsyth et al. 1966; Cheever et al. 1975; Pugh et al. 1979; Warren et al. 1979).

Ureters are also a focal point for *S. haematobium* morbidity (Edington et al. 1970; Lehman et al. 1973; Smith et al. 1974; Cheever et al. 1978; Elem 1984). Egg accumulation in the ureters is asymmetric and generally highest where the ureter meets the bladder (Smith et al. 1974; Smith et al. 1977a; Christie et al. 1986a; Christie et al. 1986b). Problems occur when stenoses form as a result of fibrosis and scarring of the ureters (Lehman et al. 1973; Smith et al. 1974; Smith et al. 1977a; Cheever et al. 1978) and the resulting strictures can result in hydroureter and, with continued progression, to hydronephrosis (Edington et al. 1970; Smith et al. 1974; Cheever et al. 1977). Pain can occur due to the back of up of urine in the ureter as well as chronic bacterial infections (Carter et al. 1970). Renal failure is possible (Kardorff et al. 1994).

Genital schistosomiasis, which affects females (Christinet et al. 2016) and males (Kayuni et al. 2019), is caused when ova become lodged in the reproductive organs. *S. haematobium* causes the majority of genital schistosomiasis, though disease can be obtained from all species (WHO 2020a). Genital schistosomiasis was characterized over a century ago for both sexes (Madden 1899; 1911). Every female reproductive organ (Christinet et al. 2016) and most male genital organs (Kayuni et al. 2019) can be affected by schistosomiasis. Uterine pathology (Attia 1962) and cervical schistosomiasis (Kjetland et al. 2005; Kjetland et al. 2012; Kjetland et al. 2014; Randrianasolo et al. 2015) are the most common pathologies in female genital schistosomiasis (FGS) though pathology is likely underreported (Christinet et al. 2016). Pathology for male genital schistosomiasis (MGS) is less well-established.

Chronic urogenital schistosomiasis has been associated with bladder cancer (Mostafa et al. 1999; Gouda et al. 2007) which is hypothesized to be a result of chronic inflammation that promotes the development of bladder cancer (Rosin et al. 1994; Nesi et al. 2015). Novel studies in mice suggest pre-cancerous conditions may develop (Fu et al. 2012) and potential molecular markers have been identified (Koonrungsesomboon et al. 2015). It appears as though schistosomiasis is not a sole cause of bladder cancer but probably contributes to carcinogenesis (Ishida et al. 2018).

1.5.2 Pathology and morbidity due to intestinal schistosomiasis

After pairing in the liver, *S. mansoni* male and female worms travel to the hepatic portal system (Miller et al. 1980) about one month after infection and oviposition begins. *S. mansoni* worms seem to favour laying eggs in the colon (Cheever et al. 1977), but tend to move around the mesenteric veins and lay eggs throughout the entire system (Pellegrino et al. 1978), resulting in widespread dissemination of lesions. Eggs deposited in the intestinal tract results in thickening of the intestinal wall as a normal reaction of the intestine to inflammation (Dittrich et al. 1994). Colonic polyps can form, which can present as blood in stool (Nash et al. 1982) and patients with severe cases may lose significant blood, fluid, and protein (Lehman et al. 1970).

Because blood in the hepatic system flows toward the liver, eggs can become lodged in the presinusoidal capillary venules where they form granulomas. After egg deposition in the hepatic portal system, gradual enlargement of the liver may occur (Prata et al. 1968) along with non-specific symptoms such as abdominal pain, diarrhoea, blood in stools, and fatigue (Lambertucci et al. 2000). The immune system's repeated granulomatous response to trapped eggs causes the accumulation of collagen (Warren 1984) which advances to fibrosis (Phillips et al. 1986; Dunne et al. 1999; Cheever et al. 2000; Pearce et al. 2002; Colley et al. 2014b) and eventually to extensive destruction to the hepatic blood vessels (Andrade et al. 1971). Periportal fibrosis, also referred to as Symmers' clay pipestem fibrosis (Symmers 1904; Cheever et al. 1967), can extend throughout the portal veins (Nash et al. 1982) and impede blood flow, leading to portal hypertension and hepatosplenic disease (Cheever et al. 1967; Coutinho 1968; Andrade et al. 1971).

Persons with hepatosplenic disease can develop esophageal varices, potentially resulting in ischemic necrosis from repeated bleeding (Andrade et al. 1962). Variceal ruptures can cause esophageal and gastrointestinal bleeding and, potentially fatal exsanguination (Rodriguez et al. 1955; Cheever et al. 1967; De Cock 1986; Richter et al. 1998).

In later stages of hepatic disease, portal hypertension combined with low albumin levels can cause ascites, the accumulation of fluid in the peritoneal cavity (Dunn et al. 1981). Ascites can also occur after intestinal bleeding (El-Rooby 1985). The prevalence of ascites can vary substantially, especially geographically (WHO 1988). Patients with heavy worm burdens may form portosystemic collaterals in the intestines causing eggs to circulate and become lodged and induce granulomas in the lungs and heart, causing cardiopulmonary schistosomiasis (Clark et al. 1935; Cheever 1968; Andrade et al. 1970). Hepatosplenic patients can suffer from portal vein thrombosis (Cheever et al. 1967; Andrade et al. 1971) and glomerulonephritis (Andrade et al. 1979).

Severe manifestations of chronic intestinal schistosomiasis usually do not occur until many years of infection and accumulated inflammatory response to eggs (Cook et al. 1974; Arap Siongok et al. 1976; Lehman et al. 1976; Andrade et al. 1979; Homeida et al. 1988a; Gonçalves et al. 1995; Lambertucci et al. 2000; Caldas et al. 2008) although periportal fibrosis has been observed in children as young as six (Doehring-Schwerdtfeger et al. 1992a). Severe morbidity only presents in a small proportion of chronically infected people and correlates with infection intensity (Arap Siongok et al. 1976; Omer et al. 1976; Gryseels et al. 1987; Kardorff et al. 1997), meaning people with lower intensity infections are less likely experience these symptoms.

The course of infection and morbidity from other intestinal *Schistosoma* species is similar, though some differences exist. Egg-laying patterns differ for *S. japonicum* (von Lichtenberg et al. 1973). *S. japonicum* worms also tend to lay eggs throughout the mesenteries, but oviposition tends to be more focal and worms cluster together resulting in more focal lesions of greater severity (Cheever et al. 1980; Cheever et al. 1982) and more disease severity (von Lichtenberg et al. 1973). Although *Schistosoma* infections of the brain are rare, *S. japonicum* infections are more likely to involve the brain compared to *S. mansoni* (Kane et al. 1948). Pathology for *S. mekongi* has largely resembled *S. japonicum* (Muth et al. 2010), with portal hypertension, hepatosplenomegaly, and ascites all noted (Biays et al. 1999). *S. intercalatum* pathology is less severe than *S. japonicum* or *S. mansoni* while infections with other species are too rare to fully understand their pathology (King 2001).

1.5.3 Decreasing severe pathology

Reversibility of pathology has been noted both in the short term (Pugh et al. 1979; Doehring et al. 1986; Hatz et al. 1998) and long term (Subramanian et al. 1999; Richter 2003; King et al. 2005; Ouma et al. 2005; Kjetland et al. 2008; Mduluza et al. 2017; Miller-Fellows et al. 2017). The expansion of mass treatment leads to fewer people with severe pathology and more with light infections (Richter 2003; Mutapi et al. 2017; Wilson 2020), meaning less severe schistosomiasis manifestations have become

more common. These less clinically severe manifestations, which can occur with light infections and are common in children, have a greater impact on DALYs lost compared to the most severe pathologies (King et al. 2005). Evidence and recognition that any *Schistosoma* infection can lead to unfavourable health outcomes is growing (King et al. 2008b; King 2009; 2015; King et al. 2020b). Paediatric and maternal populations (Bustinduy et al. 2017a; Freer et al. 2018) and school-aged children (Musuva et al. 2017; Ezeamama et al. 2018) are especially vulnerable.

1.5.4 Measurement of pathology

Ultrasonographic evaluation of schistosomiasis is the standard for measuring pathology. First proposed in the late 1970's (Abdel-Wahab et al. 1978), the value of ultrasound grew as it was shown to be as good as or better than a radiograph or bladder scope for detecting *S. haematobium* urinary tract lesions. Ultrasonography detects bladder fibrosis and urinary tract lesions associated with *S. haematobium* (Degremont et al. 1985; Burki et al. 1986) as well as periportal fibrosis (Hussain et al. 1984) and portal hypertension associated with *S. mansoni* and *S. japonicum* infections (Abdel-Latif et al. 1981). The WHO Special Programme for Research and Training in Tropical Diseases and the Swiss Tropical Institute organized a workshop in 1990 to develop standardized ultrasonography approaches. The meeting resulted in the Cairo protocol (WHO 1991; The Cairo Working Group 1992) which contained a set of standardized examinations and reporting practices. The protocol contained annexes for *S. mansoni*, *S. haematobium*, and *S. japonicum*. Each annex contained modules for placing the scanner to obtain the various views of the abdomen, descriptions and scoring for each abnormality, and a recording sheet. A second workshop was convened in Niamey, Niger in 1996 and a third in Belo Horizonte, Brazil in 1997 to review field tests of the Cairo protocol and revise the standards. A White Paper Report was then written to summarize the discussions and conclusions from both workshops, which has come to be known as the Niamey or Niamey-Belo Horizonte protocol (Richter et al. 2000). Both Cairo and Niamey protocols worked from the criteria that the evaluation be suitable for field use, short (5-10 minutes),

consist of abnormalities which specifically indicate schistosomiasis, have unambiguous template images, and collect data in a quantitative form (Richter et al. 2000). In addition, indicators collected should be ones which are indicative of chronic infection, suggest development into severe condition, and should change with treatment. Revisions to the protocol primarily centered around grading and scoring, quality control measures, and some additional data collection standardization for the *S. mansoni* exam. The *S. japonicum* annex was dropped due the proposal to have a meeting specifically on Asian schistosomiasis; unfortunately, that meeting does not appear to have happened.

The Niamey protocol has been the standard since its publication. Training clinicians is reasonably quick; after five sessions, most reach proficiency (Bonnard et al. 2011). The urogenital schistosomiasis exam consists of two intermediate scores which are then summed together to create a global score. The urinary bladder intermediate score comprises measurements of irregular bladder shape, irregularities in the bladder wall, thickening of the bladder wall, localized bladder masses, and the number of pseudopolyps. Second is the urinary bladder intermediate score which consists of measurements of whether the left and right ureters are dilatated and whether the kidneys have moderate or severe dilatation. Additional investigations include evaluating whether there is calcification of the bladder wall or residual urine in the bladder.

Evaluations of *S. mansoni* pathology aggregate three scores: hepatic image pattern, periportal thickening, and portal hypertension. The image pattern score is concerned with measuring abnormalities in the liver parenchyma, i.e., if periportal fibrosis is present. Pattern A denotes no abnormalities, B is an indeterminate pattern, and C through F are abnormal patterns in the liver due to observable fibrosis. Image pattern B (IPB) has been considered to be an intermediate stage of hepatic fibrosis due to schistosomiasis, but IPB has been associated with malaria infection suggesting IPB is not exclusively caused by schistosomiasis (Samuels et al. 2012; Davis et al. 2015). Periportal thickening (PT) is measured via a two-step process where, first, the technician decides if PT is suspected. If so, the liver

wall thickness is measured at multiple places and the mean is compared to a reference table based on body height to determine if it is in normal range or at increased thickness. For portal hypertension, the diameter between the inner walls of the portal vein is compared against a height-based standard to determine whether dilatation is present. These scores are them summed to create an aggregate score and the protocol includes guidance on interpretation. Apart from the scoring section, there are instructions on investigating splenomegaly and gall-bladder wall thickening.

1.6 Diagnosis of schistosomiasis

1.6.1 Parasitological

The primary method for schistosomiasis diagnosis has been microscopic examination of urine or stool for the presence of ova. For *S. haematobium*, the primary technique is the filtration of urine through a nucleopore filter (Peters et al. 1976b). Typically, 10 ml of urine is pressed through a filter that captures *S. haematobium* ova that were expelled in the urine sample. The filter is then dried and stored until it can be transported back to the laboratory for examination. Microscopic examination of stained filters for the presence of eggs is WHO's recommended method.

The thick smear technique for evaluating intestinal species was first proposed by Kato and Miura in 1954 (Kato et al. 1954). The Kato technique underwent modifications (Komiya et al. 1966; Martin et al. 1968) until Katz and colleagues in the early 1970s proposed a version which has remained in usage (Katz et al. 1972). The Kato-Katz thick smear technique involves sieving 41.7 mg of faeces onto paper and wet mounting them to a cellophane strip. The stool is then pressed against a microscope slide to evenly spread out the fecal material. The slide is then examined under a microscope and the eggs counted.

The main shortcoming of both approaches is a lack of sensitivity. Urine filtration has day-to-day variability (Vinkeles Melchers et al. 2014) that can have a large effect in low prevalence settings (Kosinski et al. 2011). Other diagnostic tests are likely to estimate a higher prevalence. For example, in a

low prevalence setting, an antigen test had two to three times higher prevalence than urine filtration (Knopp et al. 2015). The same is true for Kato-Katz thick smear tests for intestinal infections where a single Kato-Katz thick smear underestimated prevalence in a modelling study by 50% (de Vlas et al. 1992a) while an empirical study found a similar upper bound of around 40% (Lamberton et al. 2014). As with urine filtration, the Kato-Katz thick smear also has significant day-to-day variability (Engels et al. 1996; Yu et al. 1998), though the intra-specimen variation of egg counts was shown to be 4.3 times higher than the day-to-day variability (Utzinger et al. 2001). This may partially be due to heterogeneity in the spatial distribution of eggs in a fecal sample, but this has only been shown for *S. japonicum* (Yu et al. 1998) and not for *S. mansoni* (Krauth et al. 2012). The sensitivity of detecting an infection increases with multiple evaluations and the infection intensity (Lamberton et al. 2014; Bärenbold et al. 2017).

1.6.2 Circulating antigen

Experiments looking for circulating antigens in animals for *S. mansoni* date back to the 1960s (Berggren et al. 1967). Glycosaminoglycan-like carbohydrates circulating cathodic antigen (CCA) and circulating anodic antigen (CCA) produced in the vomitus of adult schistosome worms could be detected in mice, hamsters, and humans with *S. mansoni* infections (Deelder et al. 1980). Like egg excretion, the advantage of antigen detection with CCA and CAA as compared to antibody tests is they can delineate individuals with active infections from those who have been cured but continue to have antibodies circulating.

Commercially available, point-of-care (POC) CCA-based tests have been evaluated in multiple field trials and shown to be at least as accurate as Kato-Katz thick smear performed in triplicate (Coulibaly et al. 2011; Shane et al. 2011; Tchuem Tchuenté et al. 2012), though there is some debate about the accuracy in low prevalence settings (Foo et al. 2015). POC-CCA may also be able to diagnose Asian schistosome species but more research is needed (van Dam et al. 2015). This gave rise to the hope that the POC-CCA test may be able to supplant Kato-Katz thick smear testing in control programmes for

S. mansoni (Bärenbold et al. 2018). A more complete, multi-country assessment found the test was sufficiently sensitive and specific compared to Kato-Katz thick smear for disease mapping but the test was not accurate enough to support elimination (Colley et al. 2013). Sadly, recent batches of the POC-CCA test have given conflicting results (Colley et al. 2020c). This could be due to changes in the test (Colley et al. 2020c), different batches of components (Cavalcanti et al. 2019), or different levels of quality control in different locations (Viana et al. 2019). Regardless of the reason, this suggests the test may not be reliable enough yet.

Unfortunately, POC-CCA has not been able to consistently detect *S. haematobium* infections (Stothard et al. 2009b; Ashton et al. 2011; Sanneh et al. 2017; Rubaba et al. 2018). Other point-of-care tests for *S. haematobium* have been proposed but appear to be at a proof-of-concept stage (Nausch et al. 2014; Holmström et al. 2017; Panic et al. 2019).

CAA is measured in an upconverting particle-lateral flow circulating anodic antigen (UCP-LF CAA) assay that can detect a single worm pair in experimental non-human primate infections (Corstjens et al. 2020). Recent advancements include making the UCP-LF CAA test more user friendly (van Dam et al. 2013). Field tests of the urine circulating anodic antigen 2000 (UCAA2000) test have been performed in an *S. haematobium* elimination setting (Knopp et al. 2015) and in multiple *S. mansoni* locations (Clements et al. 2018; Gaspard et al. 2020; Ruberanziza et al. 2020). For any of the CAA-based tests to be programmatically useful, a POC version is needed and the assay will need to be commercialized.

1.6.3 Antibody

Measuring host antibody production to schistosome antigens is highly sensitive. Most tests detect antibodies reactive with preparations of soluble egg antigen (SEA). However, programmatic use of antibody detection is challenging for two primary reasons. First, the antibody response to SEA lasts long after active infection has cleared, making it ineffective for monitoring and evaluation of control programmes as it is challenging to know whether a positive response to an antibody test is due to

current or past infection. Second, the process of isolating eggs to produce SEA has remained largely unchanged since being introduced (Coker et al. 1956). This process cannot be standardized meaning variability is highly likely between laboratories and potentially between batches from the same laboratory. Therefore, detection of antibodies against SEA has largely been used to measure the impact of control programmes at an aggregate level. Such studies have shown promise by demonstrating reductions in SEA for pre-school-aged children in areas where interventions have been implemented (Won et al. 2017; Arnold et al. 2020).

1.7 Treatment

Treatment against all *Schistosoma* species is predominantly done with praziquantel. Prior to praziquantel, metrifonate for *S. haematobium* and oxamniquine for *S. mansoni* were used as chemotherapy. While both were well-tolerated and effective, they were only effective against a single species and had shown potential mutagenic activity (Batzinger et al. 1977). Early phase results of praziquantel demonstrated it was well tolerated by animals (Murmann et al. 1976) and effective against all schistosome species (Gönnert et al. 1977; Thomas et al. 1977; Webbe et al. 1977) with no known mutagenic activity (Obermeier et al. 1977; Bartsch et al. 1978; Machemer et al. 1978). Multicenter randomized controlled clinical trials demonstrated the therapeutic efficacy of praziquantel (Davis et al. 1979a; Davis et al. 1979b; Ishizaki et al. 1979; Katz et al. 1979; Santos et al. 1979; Davis et al. 1981; El-Alamy et al. 1981; Omer 1981).

The mechanism of how praziquantel works is unknown and many potential theories exist (Thomas et al. 2018). Regardless of the exact mechanism, praziquantel paralyzes adult worms making them susceptible to destruction by the immune system or some other process (Harnett 1988). The efficacy of praziquantel is dependent on the maturity of the worm. In experimental mice, the relationship between mortality and week of infection appears to be U- or V-shaped (Sabah et al. 1986). Initially, larval worms have some susceptibility to praziquantel, but this drops to a nadir at

approximately week 3 or 4 and increases after that. The median effective dose of praziquantel for 4-week old worms is 30 times that of 7-week old worms (Pica-Mattoccia et al. 2004).

Praziquantel is a useful drug for multiple reasons. First, a single dose is effective. A meta-analysis of praziquantel cure rates based on egg excretion found that a single dose of praziquantel 40 mg/kg achieved high cure rates for multiple species (Zwang et al. 2014), though cure rates for *S. mansoni* when using the POC-CCA antigen test were only 41.6% (31.1-52.9) 10 weeks after a single treatment in a randomized controlled trial (Hoekstra et al. 2020). Treatment usually consists of a single dose of 40 mg/kg for *S. haematobium* and *S. mansoni* and 60 mg/kg for *S. japonicum* and *S. mekongi*. For children, the dose is determined by height as a proxy for weight (Montresor et al. 2001; Sousa-Figueiredo et al. 2012b). No paediatric formulation exists (Bustinduy et al. 2016), meaning pills need to be crushed, which is not feasible in mass treatment programmes. Treatment has had lower effectiveness in pre-school-aged children, possibly due to dosing difficulty or biologic reasons (Sousa-Figueiredo et al. 2012a; Coulibaly et al. 2017). Second, the drug has low toxicity (Montero et al. 1997; Dayan 2003) and is well tolerated (Cioli et al. 2003; Utzinger et al. 2004; Caffrey 2007; Doenhoff et al. 2008) with only minor side effects (Zwang et al. 2014) that may be associated with intensity of infection (Cioli et al. 2003) or not (Midzi et al. 2008). In addition, praziquantel has been shown to be safe in pre-school aged children (Coulibaly et al. 2017; Olliaro et al. 2020) and pregnant women (Olveda et al. 2016b). Finally, the cost of praziquantel has decreased significantly. Initial excitement regarding praziquantel effectiveness was tempered by the high cost (Anonymous 1980), but by the late 1980s, a tablet cost approximately USD 1 per 600 mg tablet (Stothard et al. 2009a) or between USD 2-5 for a treatment (King et al. 1989). Drug costs are now approximately USD 0.56 per treatment with an total of all costs per person averaging USD 1.37 (standard deviation=USD 1.14) (Salari et al. 2020).

1.8 Interventions

Broadly, interventions for schistosomiasis can be categorized into four groups which try to break the life cycle at three different places. Ecologic interventions primary attempt to stop transmission in the environment. Pharmaceutical interventions try to stop transmission by reducing the number of worms in humans and, in turn, reduce the number of ova that reach freshwater bodies. Two groups of other interventions, educational interventions and water, sanitation, and hygiene (WASH) interventions attempt to stop transmission by keeping humans out of infected water sources.

1.8.1 Ecologic Interventions

The predominant ecological intervention for schistosomiasis is snail control through the application of molluscicides. Molluscicide has the advantages of directly interrupting transmission and reasonably simple implementation while the disadvantages are the need for repeat application, increased effort compared to chemotherapy interventions, costly labor, delayed impact, difficulty achieving wide coverage, and collateral damage to other wildlife (King et al. 2015a).

Early control activities focused on molluscicides before the development of chemotherapy interventions. Up until the early 1960s many compounds were utilized (WHO 1965). By 1980, the compounds in use effectively shrunk to only one, niclosamide (Foster et al. 1960), as it was the only one produced commercially without the need of a large order (McCullough et al. 1980). The shift to niclosamide, sold as Bayluscide, Fenasal, Nicloside, and others (National Center for Biotechnology Information 2020) were due to its low toxicity and ability to kill snails, snail eggs, and cercariae at low concentrations (McCullough et al. 1980; King et al. 2015a).

Despite niclosamine application proving to be a component of successful control programmes, such as in St. Lucia (Ivy et al. 2018), new pharmaceutical treatment options decreased the interest in snail control strategies. Recently, there has been a resurgence in the recognition that snail control is an important component of schistosomiasis control, especially in efforts to interrupt transmission (King et

al. 2015a; Shiff 2017; French et al. 2018; Sokolow et al. 2018). A recent meta-analysis demonstrated that application of niclosamide significantly reduced the odds of infection alone and when used in conjunction with chemotherapy (King et al. 2015b). This approach has been estimated to be cost effective (Lo et al. 2018) despite the high cost of mollusiciciding.

Other snail control approaches include the introduction of snail predators into the environment (Slootweg et al. 1994; Gashaw et al. 2008; Duval et al. 2015; Sokolow et al. 2015; Younes et al. 2017) and introduction of competitor snails (Pointier et al. 2000; Gashaw et al. 2008).

1.8.2 Pharmaceutical Interventions

Since the development of praziquantel, preventive chemotherapy has become the favoured intervention of WHO and control programmes given the high cure rates, effectiveness in a single dose, low toxicity and high tolerability, and low cost. In addition, large donations of praziquantel from Merck KGaA have made treatments available to control programmes. Initial grants from The Bill and Melinda Gates Foundation allowed the Schistosomiasis Control Initiative (SCI) to purchase generic praziquantel for use in six country control programmes (Fenwick et al. 2009). Merck KGaA initially committed to donating 20 million tablets annually between 2007 and 2010. Calls to increase this donation (Hotez et al. 2010) were heeded and in 2010 Merck KGaA committed to ramp up donations to 250 million tables by 2016 (Fenwick et al. 2016). The drug was given to 98.7 million people in 2017, nearly a 10-fold increase over of the number of people treated in from 2006 (WHO 2018).

In large part, these donations have been distributed to people via preventive chemotherapy campaigns, also known as mass drug administrations (MDAs). For most of sub-Saharan Africa, the only active control intervention after Merck KGaA began donating treatments has been preventive chemotherapy (French et al. 2018). Control programmes have demonstrated effectiveness of the expanded use of praziquantel by noting decreases in infections and morbidity levels with annual treatments (Fenwick et al. 2009; Deol et al. 2019; Mduluza et al. 2020).

Currently, guidelines recommend that praziquantel be distributed in schools to school-aged children (Montresor et al. 2002; WHO 2002; 2011b). Debate is ongoing regarding whether preventive chemotherapy should be expanded to include the entire community. The burden to pre-school aged children is high (Kalinda et al. 2021) and modeling suggests this expansion would be cost effective (Lo et al. 2015). In trials of treatment delivery schedules, community delivery reduced infection levels in adults and pre-school aged children while school-based delivery to school-aged children did not (King et al. 2020c) except for one study were reductions were found regardless of delivery (Secor et al. 2020). Reviews have also come to different conclusions with one suggesting that combining the two approaches would be beneficial because it would improve coverage (Burnim et al. 2017) while another found that school- and community-based dissemination have similar effectiveness at reducing infections (Cribb et al. 2019).

Disappointingly, when community treatment has been implemented, coverage has generally been lower than hoped. Lack of understanding of MDAs and general health education as well as drug stock outs have contributed to the lack of coverage (Tuhebwe et al. 2015). Popular reasons for failing to participate have included being away from home when volunteers visited (Knopp et al. 2016) and failure to be offered treatment (Adriko et al. 2018). Receipt of treatment has been shown to vary by ethnicity (Dabo et al. 2013; Chami et al. 2016), sex (Inobaya et al. 2018), poverty status (Chami et al. 2016), and type of employment (Coulibaly et al. 2018). Similar uptake has been noted in school-aged children in both school and community distribution (Binder et al. 2020).

Preventive chemotherapy has demonstrated short term effectiveness, but sustainability and the impact over the long term is mixed since usually transmission does not get interrupted (Olveda et al. 2016a). Initial evaluations suggested that annual administration of praziquantel through ministries of health could achieve morbidity control (Fenwick et al. 2009). Many have noted that annual preventive chemotherapy without other interventions is unlikely to interrupt schistosomiasis transmission (Knopp

et al. 2013; Njenga et al. 2014; Ross et al. 2015a; Ross et al. 2015b; Secor 2015; King et al. 2020c) and there is a need to supplement pharmaceutical interventions. In addition, there is the potential of reduced effectiveness of praziquantel after repeated applications (Crellen et al. 2016).

1.8.3 Educational

Health education has long been incorporated into schistosomiasis control programmes (Kloos 1995). The motivation behind educational interventions is to increase people's knowledge of the causes, transmission, symptoms, and morbidity of schistosomiasis (Mwanga et al. 2013) and reduce misconceptions of the disease (Musuva et al. 2014; Person et al. 2016a), which in turn help reduce disease transmission and prevalence. These interventions can have other goals which may also reduce disease indirectly, such as increasing treatment compliance (Omedo et al. 2014). Health education programmes may increase people's attitudes and practices (Sacolo et al. 2018) and have been associated with decreases in *S. japonicum* prevalence (Zhou et al. 2013). For educational programmes to make sizable gains, it is recognized that they must be accompanied by infrastructure changes such as improved water and sanitation opportunities (Kabatereine et al. 2014; Dawaki et al. 2015). For instance, Senegalese survey participants knew schistosomiasis was transmitted in fresh water but continued to engage in risky behaviours because no clean water options existed (Lund et al. 2019). Finally, inadequate consideration of the sociological context in which an intervention is applied can lead to failure (Hubley 1986; Kloos 1995; Secor 2014; Grimes et al. 2015; Mwanga et al. 2020).

1.8.4 Water, Sanitation, and Hygiene (WASH)

Living or working in close proximity to infectious water increases one's risk of schistosomiasis (Karanja et al. 2002; Steinmann et al. 2006; Kapito-Tembo et al. 2009; Woodhall et al. 2013; Won et al. 2017) since transmission is entangled into the environmental, sociological, and physical structure of a community (Grimes et al. 2015). WASH-based programmes are generally designed to reduce people's contact with infectious water (Secor 2014). This can be done via behavioral interventions or by

improving people's access to clean water and improved sanitation. Access to clean water and adequate sanitation have both been associated with lower odds of schistosomiasis (Grimes et al. 2014). As a result, it is argued that WASH is an important and potentially necessary component of control programmes (Campbell et al. 2014; Grimes et al. 2015; Campbell et al. 2018).

The most common activities associated with increased exposure to infectious water are laundry, bathing, and swimming (Grimes et al. 2015). Facilities such as sinks, showers, and swimming pools can address each one of these exposure points and provide people with clean water access. Specific needs depend on the social context. Comprehensive plans which address all exposures simultaneously have the greatest chance of success (Person et al. 2016b).

There is debate on the beneficial effect of latrines for interrupting schistosomiasis transmission. Adequate latrines may be able to prevent contamination of fresh water with eggs, but this does not guarantee they always will be used and eggs may still enter water bodies during bathing, from soiled clothing, from animal reservoir hosts, or via flooding (Grimes et al. 2015).

1.9 Monitoring and evaluation goals and framework

1.9.1 Programme goals

The successes of praziquantel distribution, steady increases in the number of people treated with preventive chemotherapy, and achievement of 21 country programmes with over 75% national coverage in school-aged children (WHO 2018) fueled discussion of interrupting transmission of schistosomiasis (King 2009; Gray et al. 2010; Fenwick et al. 2011; Hotez 2011; Zhang et al. 2011). This led to the 2012 London Declaration (London Declaration on Neglected Tropical Diseases 2012) and the 2012 World Health Assembly (WHA) calling for countries to initiate elimination campaigns, "where appropriate" (World Health Assembly 2012) and excitement about preparing for elimination (Rollinson et al. 2013).

While this enthusiasm is important, there is a recognition of the large challenges facing schistosomiasis elimination (Rollinson et al. 2013; Ross et al. 2013; Ross et al. 2015a; Fenwick et al. 2016; Tchuem Tchuenté et al. 2017). The WHO has stated since the early 2000s that the primary goal of schistosomiasis control programmes is morbidity reduction (WHO 2002; 2011b). Those goals remain in place today and the latest NTD Roadmap (WHO 2020b) includes the target of reducing morbidity to a locally-acceptable level.

1.9.2 Framework

The current monitoring and evaluation framework for schistosomiasis involves setting up a network of sentinel sites (usually schools since data are typically collected from 9-12 year old children) across homogeneous ecological zones, where a zone will typically cover several districts (WHO 2011b). A stratified random sample of schools, where ecologic zones serve as strata, is administered. A school is picked for every 200,000 to 300,000 targeted children and a random selection of 50 children are examined in each school. Those children then provide a sample of urine (for *S. haematobium*) or stool (for *S. mansoni* and *S. japonicum*) which is saved and transported back to a laboratory to examine under a microscope. Alternatively, for *S. haematobium*, a dipstick or reagent strip can be used to detect the presence of microhaematuria due to the long history of correlation between haematuria and urogenital infection (Savioli et al. 1990; Krauth et al. 2015) and good test characteristics when compared to egg detection across different locations and subgroups (King et al. 2013). The results from each participant's test are recorded, aggregated, and analyzed to determine whether a target population is deemed to have controlled schistosomiasis or eliminated schistosomiasis as a public health problem.

1.9.3 Intensity categories

Programme evaluation of schistosomiasis after preventive chemotherapy has been based on two categorizations. First, are categories for the intensity of a schistosome infection. *S. haematobium* infection intensity has consistently been characterized by the number of schistosome eggs per 10 ml of

urine with 1-49 eggs per 10 ml of urine defining a light infection and ≥ 50 eggs per 10 mL of urine indicating a heavy infection (WHO Expert Committee on the Control of Schistosomiasis 1985; WHO 2002).

For *S. mansoni*, infection intensity is measured as the number of schistosome eggs per gram (EPG) of stool. Different categorizations have appeared in WHO documents (WHO Expert Committee on the Control of Schistosomiasis 1985; Dixon 1987), but infection intensity is now commonly split into three categories: 1-99 EPG for a light infection; 100-399 EPG signifying a moderate infection; and ≥ 400 EPG for a heavy infection (Montresor et al. 1998; WHO 2002).

1.9.4 Control and elimination as a public health problem categories

The second categorization utilized for programme evaluation are the targets for determining whether a geographic area has controlled schistosomiasis morbidity or eliminated schistosomiasis as a public health problem (WHO 2013). These categories utilize the prevalence of heavy-intensity infections (PHI) and state that a country or smaller geographic area with a PHI less than 5% across communities has controlled schistosomiasis morbidity, with the caveat that a single community can be treated as a separate implementation unit if this allows the remaining implementation units to achieve control. A country is considered to have eliminated schistosomiasis as a public health problem when all communities have less than 1% PHI. These categories are based on multiple studies prior to the mid-1980s that demonstrated an association between severe schistosomiasis morbidities and the infection intensity (WHO 1973; 1987; 1988) and the belief that only heavy-intensity infections cause disease (Mott 2004). Plus, the high cost and limited availability of praziquantel at that time meant policymakers focused on the most severe morbidities caused by schistosomiasis.

1.9.5 Monitoring and evaluation shortcomings

The foundational research for the monitoring and evaluation framework was performed in the 1970s and 1980s (WHO 1987; 1988) and the framework was developed after the turn of the century

(WHO 2002; 2011b; 2013). There is a growing recognition that the framework needs to be changed. For instance, there have been calls to focus control on morbidity (Lo et al. 2017; French et al. 2018) and to include people other than school-aged children in assessments (Stothard et al. 2011; Lo et al. 2017; Toor et al. 2018b). Early programme review and targeted interventions could help achieve goals quicker (Li et al. 2019). Incorporating geostatistical analysis into study planning could result in more efficient preventive chemotherapy distribution (Fornace et al. 2020) and integration with other programmes could be beneficial (Lammie et al. 2006; Baker et al. 2010) potentially utilizing serologic data (Lammie et al. 2012; Arnold et al. 2018; Arnold et al. 2020; Njenga et al. 2020).

Though, no evaluations exist of WHO's intensity categories and PHI targets. These targets for control of morbidity and elimination as a public health problem are utilized by control programmes to determine success (Deol et al. 2019) and in predictive modelling studies (Toor et al. 2018a; Toor et al. 2018b; Kura et al. 2019; Li et al. 2019; Coffeng et al. 2020; Kura et al. 2020; Toor et al. 2020). There is no evidence that these targets were developed based on specific morbidity levels, only general trends observed in systematic reviews (WHO 1987; 1988).

2 Goals and objectives

2.1 Rationale

No thorough assessment of the relationship between morbidity and the current targets for elimination as a public health problem (1% PHI) and morbidity control (5% PHI) has been performed. If these targets do not appear to associate with morbidity levels, then these targets should be changed to establish, evidence-based targets that are grounded in morbidity control. This would bring the targets in line with WHO's goal for schistosomiasis control programmes, specifically to reduce morbidity to a locally acceptable level (WHO 2020b). Since elimination is not currently a realistic target for schistosomiasis, it is important to refocus schistosomiasis control programmes on morbidity reduction (French et al. 2018). A target that identifies the point at which schistosomiasis is eliminated as a public health problem would be useful immediately since there is an expectation to rapidly validate countries as having eliminated schistosomiasis as a public health problem (WHO 2020b).

One modeling study explored the best criteria for predicting the elimination of *S. mansoni* after stopping MDA and found that using a threshold of 1% Kato-Katz thick smear prevalence would provide slightly over 90% power that, two years after stopping MDA, elimination will occur (Toor et al. 2019). Using 2% and 5% thresholds drop that certainly to around 85% and 75%, respectively. Though, the prevalence threshold was based on elimination of transmission and not on morbidity levels.

2.2 Goals

The overall goal of the PhD thesis is to improve the monitoring and evaluation framework for schistosomiasis with the following objectives:

- To further the evidence of the association between morbidity and infection;
- To determine whether the current monitoring and evaluation demonstrates that schistosomiasis morbidity is eliminated as a public health problem;

- To suggest programmatic targets that are linked to morbidity indicators and are measurable by schistosomiasis control programmes; and
- To promote the use of novel technologies in monitoring and evaluation.

2.3 Specific objectives

The specific aims are:

- To assess changes in morbidity levels in cohorts of participants receiving preventive chemotherapy;
- To summarize the morbidity research from the SCORE project;
- To evaluate the association between current intensity categories for schistosomiasis and morbidity levels;
- To evaluate the association between control of morbidity and elimination as a public health problem targets and morbidity levels;
- To develop an empirically based elimination of a public health problem target for morbidity indicators that possess a strong association with infection levels; and
- To demonstrate the utility of a tablet-based ultrasound system for evaluating schistosomiasis morbidity.

3 Five-Year Impact of Different Multi-Year Mass Drug Administration Strategies on Childhood *Schistosoma mansoni*–Associated Morbidity: A Combined Analysis from the Schistosomiasis Consortium for Operational Research and Evaluation Cohort Studies in the Lake Victoria Regions

Ye Shen[1], Ryan E. Wiegand[2,3,4], Annette Olsen[5], Charles H. King[6,7]*, Nupur Kittur[7], Sue Binder[7], Feng Zhang[1], Christopher C. Whalen[1], William Evan Secor[2], Susan P. Montgomery[2], Pauline N. M. Mwinzi[8], Pascal Magnussen[9], Safari Kinung'hi[10], Carl H. Campbell Jr.[7], Daniel G. Colley[7,11]

[1] *Department of Epidemiology & Biostatistics, University of Georgia, Athens, Georgia*

[2] *Parasitic Diseases Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, Georgia*

[3] *Swiss Tropical and Public Health Institute, Basel, Switzerland*

[4] *University of Basel, Basel, Switzerland*

[5] *Section for Parasitology and Aquatic Pathobiology, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark*

[6] *Center for Global Health and Diseases, Case Western Reserve University, Cleveland, Ohio*

[7] *Schistosomiasis Consortium for Operational Research and Evaluation, Center for Tropical and Emerging Global Diseases, University of Georgia, Athens, Georgia*

[8] *Centre for Global Health Research, Kenya Medical Research Institute, Kisumu, Kenya*

[9] *Centre for Medical Parasitology, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark*

[10] *National Institute for Medical Research, Mwanza Research Centre, Mwanza, Tanzania*

[11] *Department of Microbiology, University of Georgia, Athens, Georgia*

* Corresponding author

E-mail: chk@cwru.edu

[This manuscript has been published in *The American Journal of Tropical Medicine and Hygiene* (2019) 101(6):1336-1344; https://doi.org/10.4269/ajtmh.19-0273]

3.1 Abstract

The WHO recommends mass treatment with praziquantel as the primary approach for *Schistosoma mansoni*-related morbidity control in endemic populations. The Schistosomiasis Consortium for Operational Research implemented multi-country, cluster-randomized trials to compare effectiveness of community-wide and school-based treatment regimens on prevalence and intensity of schistosomiasis. To assess the impact of two different treatment schedules on *S. mansoni*-associated morbidity in children, cohort studies were nested within the randomized trials conducted in villages in Kenya and Tanzania having baseline prevalence ≥25%. Children ages 7-8 years were enrolled at baseline and followed to ages 11-12. Infection intensity and odds of infection were reduced both in villages receiving four years of annual community-wide treatment (CWT) and those that received biennial school-based treatment (SBT) over four years. These regimens were also associated with reduced odds of undernutrition and reduced odds of portal vein dilation at follow-up. However, neither hemoglobin levels nor the prevalence of the rare abnormal pattern C liver scores on ultrasound improved. For the combined cohorts, growth stunting worsened in the areas receiving biennial SBT, and maximal oxygen uptake as estimated by fitness testing scores declined under both regimens. After adjusting for imbalance in starting prevalence between study arms, children in villages receiving annual CWT had significantly greater decreases in infection prevalence and intensity than those villages receiving biennial SBT. Although health-related quality-of-life scores improved in both study arms, children in the CWT villages gained significantly more. We conclude that programs utilizing annual CWT are likely to achieve better overall *S. mansoni* morbidity control than those implementing only biennial SBT.

3.2 Introduction

Schistosomiasis remains a major public health problem in much of Africa. The clinical consequences of *S. mansoni* infections result from tissue damage and blood loss caused by schistosome eggs trapped in host tissues (Colley et al. 2014a). Chronic immunologic reactions to the eggs cause granuloma formation in intestines, liver, and spleen, and can progress to cause hepatic and splenic

enlargement, periportal fibrosis, portal hypertension, and esophageal varices (Bustinduy et al. 2014). Other impacts of infection, particularly in children, include anemia, malnutrition, impaired growth, impaired cognitive development, and generalized body weakness (Colley et al. 2014a; Ezeamama et al. 2018).

Current World Health Organization (WHO) guidelines call for mass treatment with praziquantel in endemic communities to achieve morbidity control (WHO 2002; 2006; 2013). However, questions remain about optimal programmatic implementation of mass drug administration (MDA).

The overall goal of the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) project (https://score.uga.edu/) is to provide an evidence base for programmatic decision-making related to control and elimination of schistosomiasis (Ezeamama et al. 2016). Among the studies in the SCORE portfolio were multi-arm, multi-year, randomized intervention trials that assessed changes in prevalence and intensity of schistosomiasis in children aged 9-12 years in villages receiving MDA using different strategies over a four-year intervention period (Ezeamama et al. 2016). The results from the randomized trials in Kenya and Tanzania have been reported elsewhere (Wiegand et al. 2017; Olsen et al. 2018).

These longitudinal studies also provided an opportunity to explore the impact of MDA on schistosomiasis-associated morbidity in children (Shen et al. 2017). Therefore, SCORE nested cohort studies of morbidity within intervention trials in Kenya and Tanzania that were occurring in villages that had prevalence of $\geq$ 25% *S. mansoni* infection during village eligibility testing (Shen et al. 2017). The treatment regimens in the two study arms that included cohorts were either: i) four years of annual community-wide treatment (CWT); or ii) every-other-year school-based treatment (SBT) (Figure 3.1). In the present analysis, we combined the data from the *S. mansoni* cohorts in Kenya and Tanzania to assess

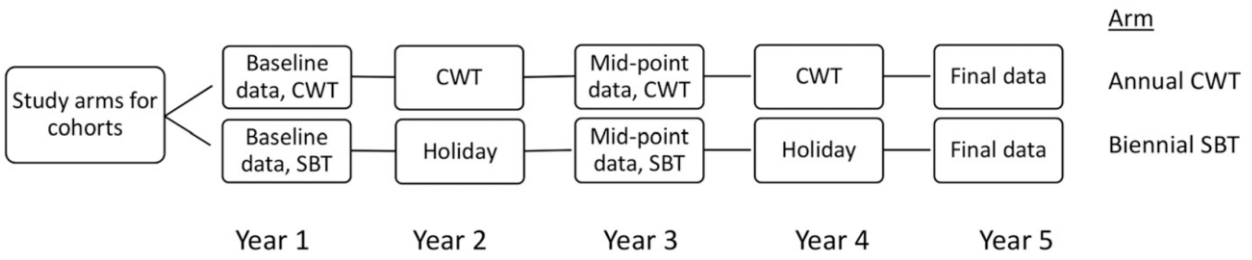


Figure 3.1. Flow diagram of the cohort study. In the upper arm, children lived in communities randomized to receive annual community-wide mass drug administration treatment (CWT). The children in the lower study arm lived in communities randomized to receive only biennial (every other year) school-based treatment (SBT), with drug "holidays" in Year 2 and in Year 4. Final assessment for both groups was performed in Year 5 of the study.

and compare the impact of the two regimens on a range of infection-associated morbidity markers. While results of analysis of the Kenya cohort (Sircar et al. 2018) and the baseline data from the Tanzania cohort (Kinung'hi et al. 2016) have been previously published, the present secondary analysis, combining the Kenya and Tanzania data, increases the statistical power to detect significant differences between CWT and SBT treatment regimens. The current paper describes changes in anthropometric growth indices, hemoglobin (Hb) levels, measures of physical fitness, and quality of life, as well as the liver abnormalities and portal vein findings among study cohort children (aged 7-8 years at baseline) at the end of their four-year study participation (Shen et al. 2017). Our hypothesis was that annual CWT with praziquantel could provide incremental health benefits in terms of reductions in observed morbidity when compared with the effects of every-other-year treatment administered in a school-based program (Shen et al. 2017).

3.3 Materials and Methods

3.3.1 Ethics statement on subject recruitment

Approval for the SCORE in Kenya and Tanzania intervention studies (the "gaining control" studies) and their related cohort studies was obtained from Institutional Review Boards at the Kenya Medical Research Institute (Nairobi, Kenya), the Centers for Disease Control and Prevention (Georgia),

and the Medical Research Coordination Committee of the National Institute for Medical Research (Tanzania). Trials Registration numbers are ISRCT 16755535 (Kenya) and ISRCT 95819193 (Tanzania) (Ezeamama et al. 2016). Only children who assented to participate and had written informed consent from parents or their legally authorized representatives were eligible for inclusion. Before examination and sample collection, the reason for the survey and the procedures for sample collection were explained to the children and the adult population in the communities, as well as local leaders, school administrators, teachers, and health and education personnel.

3.3.2 Study area and population

The results reported here are a secondary analysis of data combined from parallel cohort studies that took place in the Nyanza region (Siaya, Kisumu, and Homa Bay Counties) of Kenya (Onkanga et al. 2016) and the Mwanza region (Misungwi and Sengerema Districts) of Tanzania (Olsen et al. 2018), both of which have high prevalence of *S. mansoni*. All study villages were located on or near the Lake Victoria shoreline.

The cohort study design is described in detail in earlier articles (Samuels et al. 2012; Kinung'hi et al. 2016; Shen et al. 2017). Briefly, the cohort studies were nested in larger intervention trials on gaining control of schistosomiasis mansoni in moderate- to high-risk communities. In these parent SCORE intervention trials, 150 villages per country were randomized to one of six treatment arms and given MDA using different approaches (CWT versus SBT) at different frequencies (either two or four treatments) over a four-year period (Ezeamama et al. 2016). Villages for inclusion in the nested cohort studies reported came from the 25 villages in the treatment arm with annual CWT (the most intense treatment arm) and the 25 villages with every-other-year SBT (a less intense treatment arm) (see Figure 3.1 for flow diagram) (Shen et al. 2017). To achieve the target of enrolling 800 seven-to-eight-year-old children in each country, Tanzania included three of the 25 villages in the annual CWT arm and four of the 25 in the biennial SBT arm, whereas Kenya included six villages from each arm (Shen et al. 2017).

Parasitologic and morbidity parameters were measured at baseline and in Year 5, and although some measures were made in Year 3, these were not uniform between sites and are not included in the present analysis. In years when villages were scheduled to receive treatment, the protocol called for efforts to treat all village school-age children, whether in school or not, and irrespective of their egg-positive or egg-negative status. In CWT villages, schools were used as a supplemental venue to locate children not found at home. In SBT villages, community mobilization teams were used to encourage parents to have their children who were not attending school come to receive treatment at the school on a subsequent day. During praziquantel drug holiday years, children having symptoms could seek evaluation and treatment at health facilities, which sometimes were able to provide individual praziquantel treatment. However, few, if any children received treatment during drug holiday years. There was no untreated comparison group. Only those children who participated in both Year 1 and Year 5 are included in the analyses presented in this article.

3.3.3 Data on parasitology and morbidity

The methods for the collection of cohort data are described in detail elsewhere (Samuels et al. 2012; Kinung'hi et al. 2016), but are briefly presented in the following paragraphs.

Stool sample collection and examination. Participants provided stool specimens on each of three consecutive days. Duplicate Kato-Katz thick smears were made with a 41.7 mg template (Katz et al. 1972) from each specimen and examined for *S. mansoni* eggs by trained microscopists.

Blood collection and Hb assessment. A 5 mL tube was used to collect a 2-3 mL sample of venous blood sample (Kenya) or a finger-prick blood sample (Tanzania) was collected from each individual, and Hb was measured using a portable HemoCue photometer (HemoCue, Inc., Ängelholm, Sweden). The Hb level was reported in gm/dL and final values used in analysis were adjusted for altitude (ca. 1,000 m) by subtracting 2 gm/dL from the raw values for both study sites (WHO 2011a). Anemia was defined as Hb

values < 11.5 gm/dL for children aged below 12 years and Hb < 12.0 gm/dL for children of 12 years and above but below 15 years, according to World Health Organization guidelines (Sullivan et al. 2008).

Anthropometric measurements. Height was measured for barefoot children using a wooden stadiometer. The child looked straight ahead while standing on the base of the stadiometer with their heels, buttocks, shoulder blades, and back of the head touching the vertical backboard. Once the child was correctly positioned, the stadiometer head plate was lowered and the height measured in centimeters to one decimal place. Weight was measured on a digital scale in kilograms to one decimal place on barefoot children after excess clothing was removed. Height and weight were measured twice by the same examiner and the mean value recorded. Z-scores were calculated using the WHO AnthroPlus software (available at https://www.who.int/growthref/tools/en/) based on the WHO growth reference data tables for 5-19 year old children (WHO Multicentre Growth Reference Study Group et al. 2006). In Tanzania, the exact birthdays of some children (and hence, their exact age in days) were not known. For such cases, the midpoint of the Z-score limits was used, for example, for children reported to be 7 years old, the Z-score for children aged 7 years and 6 months was used. Wasting was defined as a body mass index-for-age Z-score of ≤ -2 and stunting as a height-for-age Z-score ≤ -2.

Physical fitness. Physical fitness was assessed using the 20 m shuttle run fitness test (20mSRT) as described by Bustinduy et al. (Bustinduy et al. 2011) In brief, during the test, children run continuously between two lines that are 20 m apart (Léger et al. 1984; Léger et al. 1988). A run from one line to the other is considered a shuttle. There are 21 levels in the test, and the higher the level, the greater the number of shuttles and faster the pace required to complete it. The running field was prepared in the school compound and runners were laterally separated by at least 1 m. Recorders were placed at each end of the field, and every recorder was responsible for monitoring three to five children. The recorder noted the level at which the test subject stopped and how many shuttles the child had completed within that level. These numbers were converted to a maximal oxygen uptake, the VO_2max (maximal oxygen

uptake as estimated by fitness testing), in mL/kg/minute, as previously described (Léger et al. 1982; Müller et al. 2011).

Quality of life. Quality of life was assessed using the previously validated Pediatric Quality of Life Inventory instrument (PedsQL) for children (Varni et al. 1999; Varni et al. 2006; Samuels et al. 2012; Terer et al. 2013; Kinung'hi et al. 2016). Kenya used a 23-question version of the PedsQL survey (Samuels et al. 2012), and Tanzania used a 16-question version, but discarded the last question due to irrelevance to the local setting (Kinung'hi et al. 2016; Shen et al. 2017). The PedsQL questionnaire is divided into four parts, with three to six questions in each section. The four parts describe four dimensions of functioning: 1) problems with physical activity (physical), 2) problems with feelings (emotional), 3) problems with getting along with others (social), and 4) problems with keeping up in school (school). The answers are scored on a Likert-like scale from 0 to 4, where 0 is never, 1 is almost never, 2 is sometimes, 3 is often, and 4 is almost always. Responses are transformed to scores that range from 0 to 100, with higher scores indicating a better perceived quality of life.

Abdominal ultrasonography. Abdominal ultrasound was performed using portable ultrasound machines (Aloka Sonocamera SSD-500 with a 3.5 MHz curvilinear probe, Hitachi Aloka Medical America, Wallingford, CT) in both Kenya and Tanzania. The examinations were performed according to the WHO's Niamey protocol for imaging of schistosomiasis (Richter et al. 2000) by senior sonographers with extensive experience in the field of ultrasonography of *S. mansoni*-infected individuals. Children were examined while lying on their backs on an examination table with their legs extended. Measurements included: length of the left liver lobe (mm), spleen length (mm), portal branch thickness, and portal-vein diameter. The liver image was scored as one of six patterns, A-F, as described in the WHO protocol (Richter et al. 2000). Image patterns A and B are considered normal or non-specific. Image patterns C and D are considered characteristic of mild and moderate *S. mansoni* infection-related fibrosis, respectively, while liver patterns E and F indicate advanced infection-related liver fibrosis. Increased

portal vein diameter was defined as 2 SD above standard reference measurements developed from healthy, uninfected children of corresponding height in other endemic countries (Richter et al. 2000; Vennervald et al. 2004).

3.3.4 Statistical analysis

Subjects were considered positive for infection if at least one egg was found on any of the Kato-Katz slides prepared from their stool specimens. The mean egg count for the six slides was calculated and multiplied by 24 to estimate the child's infection intensity in eggs per gram of stool (epg). In Kenya, egg counts were truncated at 42 eggs per slide, indicating a heavy infection having > 1,000 epg. In cases where specimens were missing, the calculation was performed using data from the available slides for each affected child. Consistent with WHO guidelines (WHO 2002), infected individuals with <100 epg were considered to have light infections, those with 100–399 epg to have moderate intensity infections, and individuals with ≥400 epg to have severe infections. For the present analysis, group-wise infection intensity is reported in two different ways: 1) as the arithmetic mean of epg for all tested persons, including those with epg = zero (mean intensity for the entire cohort), and 2) as the mean of epg only for those children found to be egg positive (mean intensity among those infected). Absolute change in prevalence from Year 1 to Year 5 was calculated as (prevalence in Year 5 minus prevalence in Year 1). For example, a 20% decrease in prevalence in a location having a starting prevalence of 40% means a decline to 20% prevalence, whereas in a location with a starting prevalence of 80%, 20% prevalence reduction would result in a prevalence of 60%. Relative percent change in prevalence from Year 1 to Year 5 was calculated as ([prevalence in Year 5 minus prevalence in Year 1/prevalence Year 1] × 100). This would determine the relative percent change in prevalence, regardless of starting prevalence. Using this method, the starting prevalence would influence the level of decline, such that going from 80% to 60% would be a 25% drop in prevalence, whereas going from 40% to 20% would be classified as a 50% decline in prevalence.

Summary statistics were calculated to compare the characteristics of the combined cohort in terms of demography, infection status, and morbidity markers, and to compare those who had only Year 1 data (i.e., those lost to follow up) to those who remained in the cohort at Year 5. Following the SCORE project's a priori statistical analysis plan, linear or generalized linear mixed effect models adjusting for village-level clustering effects, and, where appropriate, age and sex were used to obtain odds ratios (for binary outcomes) and group-wise differences (for continuous outcomes) for comparisons between study arms. The ability to detect differences by treatment arm at Year 5 was diminished as a consequence of the parent SCORE studies' village-level cluster randomization design and resultant imbalances in baseline infection factors between study arms. Even though all villages in the Kenyan and Tanzanian locations were selected based on having a baseline school age prevalence of infection of ≥25%, because of the village-level cluster randomization design, there were resultant imbalances in baseline infection factors (average prevalence and intensity) between study arms. As a result, our ability to detect differences by treatment arm at Year 5 was diminished. To compensate for these starting imbalances and to better detect differences between the two arms from Year 1 to Year 5, we also studied the interaction effects of survey year with study arm on relative changes in results for infection, infection intensity, and morbidity markers, although adjusting for gender. For outcome variables missing in 10% or more children from the entire cohort, analyses initially conducted for complete cases were later repeated with missing data imputed using multiple imputation procedures (Rubin 2004; Shen et al. 2017). Results obtained from the multiply-imputed datasets were compared with those generated from the original dataset. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). An $\alpha = 0.05$ level was used for significance of all statistical tests and for the confidence interval calculations.

3.4 Results

3.4.1 Combined cohort characteristics

Table 3.1 describes the characteristics of participants in Year 1 at baseline, and in Year 5 after four years of intervention. Of 1,374 individuals who were enrolled at baseline in the combined cohort, 891 (64.5%) participated in Year 5 data collection. In aggregate, females comprised 55% of participants in the annual CWT arm and 50% of participants in the biennial SBT arm at both baseline and Year 5 (difference not

Table 3.1. Baseline and Year 5 characteristics of cohort participants (children with data both in Year 1 and Year 5), and baseline characteristics of those lost to follow-up, by arm[a]

	Year 1, cohort children		**Year 5, cohort children**		**Year 1 data for children lost to follow-up in Year 5**	
	Annual CWT arm[b]	**Biennial SBT arm[b]**	**Annual CWT arm**	**Biennial SBT arm**	**Annual CWT arm**	**Biennial SBT arm**
Number of children	450	441	450	441	220	263
Percent female	54.9%	49.7%	54.9%	49.7%	54.1%	50.2%
Age in years (SD)	7.4 (0.5)	7.6 (0.5)	11.5 (0.5)	11.6 (0.5)	7.5 (0.5)	7.6 (0.5)
No. tested for schistosomiasis	446	438	406	413	217	252
No. infected	320	248	175	199	154	122
Prevalence	72.1%	56.6%	43.1%	48.2%	71.0%	48.4%
Full cohort arithmetic mean infection intensity (epg)	148.4	109.7	41.0	59.9	144.9	113.8
Egg-positive children's mean infection intensity (epg)	206.0	193.7	95.1	124.2	204.1	235.0

[a]*Abbreviations*: CWT, community-wide treatment; SBT, school-based treatment; SD, standard deviation; epg, *S. mansoni* eggs per gram feces

[b]After the baseline (Year 1) survey, communities in the annual CWT arm received community-wide praziquantel treatment every year for four years; communities in the biennial SBT arm received school-based treatment every other year.

significant (NS), P = 0.118). At baseline (Year 1), 72% of participants in the annual CWT arm and 57% in the biennial SBT arm were infected (Figure 3.2), and this difference was statistically significant (P < 0.0001). Mean intensities for the entire cohort at baseline were 148 epg for children in the annual CWT arm, significantly higher than the 110 epg for those in the biennial SBT arm (Figure 3.3). Baseline individual-level intensity, including only those children who were egg-positive, was 206 epg in the annual CWT arm and 194 epg in the biennial SBT arm (difference NS).

By Year 5, prevalence had declined to 43% in the annual CWT arm and 48% in the biennial SBT arm (difference NS, Figure 3.2). Both cohort-level and individual-level infection intensities declined in both arms, with relatively higher egg-reduction rates in the annual CWT arm (Figure 3.3). Baseline

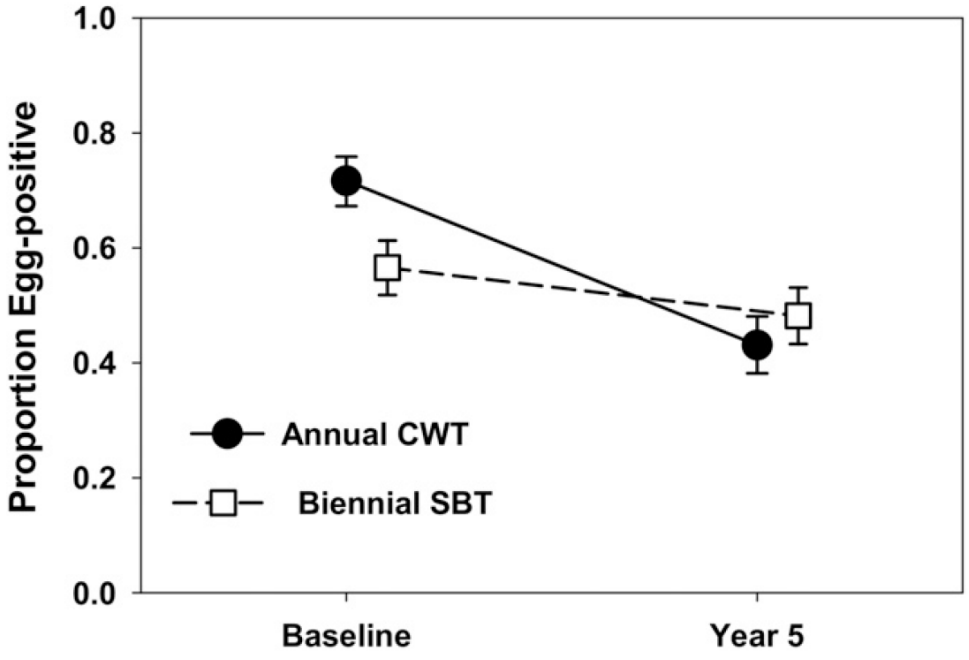


Figure 3.2. Comparison of Year 1 and Year 5 *Schistosoma mansoni* prevalence for participating children in each of the combined cohort study arms (annual community-wide treatment (CWT) vs. biennial school-based treatment [SBT]). Dark circles indicate baseline and Year 5 prevalence values for the annual CWT arm. Open squares indicate corresponding prevalence values for the children in the biennial SBT arm. Error bars indicate 95% CI.

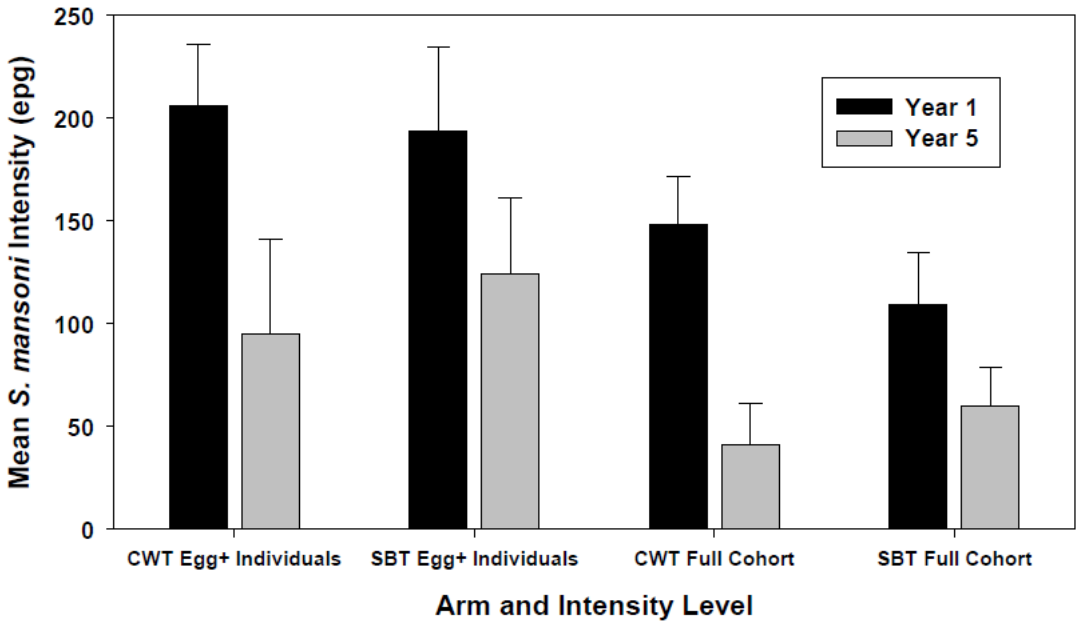


Figure 3.3. Comparison of Year 1 and Year 5 *Schistosoma mansoni* infection intensities by cohort study arm. Shown are Year 1 baseline intensity values (dark bars) and 95% CI for participating children in the two study arms receiving either annual community-wide treatment (CWT) or biennial school-based treatment (SBT), calculated either as arithmetic mean intensity for egg-positive children (individual-level intensity, left side), or as mean intensity for all children, including those with zero egg counts (cohort-level intensity, right side). Corresponding values for participating children in Year 5, after MDA, are shown by the light bars.

characteristics of lost-to-follow-up subjects were similar to those of children who had remained in the study through Year 5 (Table 3.1).

The absolute differences in prevalence between Year 5 and Year 1 in the annual CWT arm and in the biennial SBT arm were 29.0 ($CI_{95\%}$ = 22.6-35.3) and 8.4 ($CI_{95\%}$ = 1.8-15.1) percentage points, and the relative changes in prevalence for the two arms were 40.2% and 14.8% reductions, respectively. Absolute differences for full cohort mean intensity for treatment subgroups were 107.4 ($CI_{95\%}$ = 76.2-138.6) epg in the annual CWT arm, and 49.8 ($CI_{95\%}$ = 18.4-81.3) epg in the biennial SBT arm, with corresponding relative reductions of 72.4% and 45.4%. Absolute changes in individual-level intensity of

egg-positive children in the two arms were 110.8 ($CI_{95\%}$ = 57.7-163.9) epg and 69.5 ($CI_{95\%}$ = 13.0-126.0) epg, and their relative changes were 53.8% and 35.9%, respectively. In each category, the annual CWT arm subjects had greater declines in these measures. Between Year 1 and Year 5, prevalence of heavy infections declined from 11.1% to 1.7% in the annual CWT arm, and from 8.9% to 2.6% in the biennial SBT arm. After adjustment for village-level clustering effects, these between arm differences in heavy intensity prevalence were not significant (Rao-Scott $\chi^2 = 0.116$, $P = 0.73$ for between-arm difference in Year 1; $\chi^2 = 1.07$, $P = 0.30$ for between arm difference in Year 5).

We observed a significant increase in stunting among children in the biennial SBT arm, and significant decreases in wasting prevalence in both arms over the course of the study (Table 3.2). Hemoglobin levels did not change significantly during the study period. The prevalence of anemia remained roughly stable between Year 1 and Year 5 in the annual CWT arm and declined slightly, but not significantly, in the biennial SBT arm. Maximal oxygen uptake as estimated by fitness testing scores dropped in both arms from Year 1 to Year 5. Among PedsQL outcomes, the total score, as well as scores on the physical, emotional, and school sub-domains, increased over time in both study arms. There were significant Year 1 to Year 5 declines in the percentage of children with elevated portal vein diameter in both study arms. Abnormal liver pattern (Pattern C or higher) was rare, and no significant changes were noted for this finding in either arm between Year 1 and Year 5.

3.4.2 Comparison of infection and morbidity markers between Year 1 and Year 5

Table 3.3 presents prevalence, intensity, and the morbidity markers with statistically significant changes between Year 1 to Year 5 for all children in the combined cohorts, regardless of arm assignment (N = 891). All comparisons use Year 1 as the reference group. For the combined groups, overall prevalence declined significantly from Year 1 to Year 5, as did the prevalence of heavy infections and infection intensity. Wasting was significantly less common, but stunting was significantly more common in Year 5

Table 3.2. Summary results for morbidity markers, by arm, by year[a]

	Annual CWT arm		**Biennial SBT arm**	
	Year 1	**Year 5**	**Year 1**	**Year 5**
BMI: average Z score (SD)	-1.3 (1.1)	-0.9 (1.1)	-1.0 (1.0)	-0.3 (1.0)
Prevalence of stunting ($CI_{95\%}$)	9.9% (7.1, 12.7%)	11.5% (8.4, 14.6%)	5.1% (3.0, 7.1%)	10.8% (7.9, 13.8%)
Prevalence of wasting ($CI_{95\%}$)	24.9% (20.9, 29.0%)	12.7% (9.5, 15.9%)	13.2% (10.0, 16.4%)	3.9% (2.0, 5.7%)
Mean hemoglobin gm/dL (SD)	12.0 (2.3)	11.7 (1.8)	11.9 (2.1)	12.1 (1.8)
Prevalence of anemia ($CI_{95\%}$)	42.6% (37.9, 47.2%)	45.8% (40.8, 50.7%)	42.9% (38.2, 47.6%)	37.9% (33.3, 42.6%)
Mean VO_2 max score (SD)	49.2 (3.3)	43.5 (6.2)	49.2 (3.4)	44.4 (5.8)
Mean PedsQL scores				
Total score (SD)	83.6 (12.4)	91.9 (11.6)	85.0 (14.3)	90.7 (11.8)
Physical (SD)	88.9 (14.9)	94.5 (11.2)	88.2 (19.7)	93.2 (15.1)
Emotional (SD)	71.9 (15.1)	89.8 (16.1)	77.1 (16.8)	87.1 (18.2)
Social (SD)	90.4 (16.4)	91.9 (16.4)	91.3 (18.6)	93.1 (14.1)
School (SD)	80.0 (16.3)	90.7 (13.7)	81.6 (18.6)	89.2 (14.0)
Prevalence of increased portal vein diameter ($CI_{95\%}$)	10.8% (7.9, 13.7%)	1.7% (0.4, 2.9%)	9.0% (6.3, 11.7%)	1.2% (0.2, 2.2%)
Ultrasound Pattern Prevalence				
Pattern B ($CI_{95\%}$)	16.6% (13.0, 20.1%)	11.4% (7.5, 13.4%)	8.9% (6.2, 11.6%)	11.7% (7.8, 13.7%)
Pattern C or higher ($CI_{95\%}$)	0.7% (0.1, 2.0%)	0.5% (0.0, 1.7%)	0.9% (0.3, 2.4%)	0.7% (0.1, 2.0%)

[a]*Abbreviations*: BMI, body mass index; CI, confidence interval, CWT, community-wide treatment; dL, deciliter; SBT, school-based treatment; SD, standard deviation; VO_2max, maximal oxygen uptake as estimated by fitness testing.

relative to Year 1. In addition, the percentage of children with elevated portal vein diameter values declined significantly from Year 1 to Year 5. Maximal oxygen uptake as estimated by fitness testing max

decreased significantly from Year 1 to Year 5. By contrast, all the PedsQL measures increased significantly from Year 1 to Year 5.

Table 3.3. Outcomes with significant changes from Year 1 to Year 5, for both study arms combined[a]

	Odds Ratio (Reference = Year 1)	**$CI_{95\%}$**	**P-value**
Infection prevalence	0.36	0.28, 0.47	<0.0001
Prevalence of heavy infections	0.22	0.14, 0.36	<0.0001
Wasting	0.37	0.27, 0.50	<0.0001
Stunting	1.56	1.10, 2.21	0.02
Elevated portal vein diameter	0.13	0.07, 0.25	<0.0001
	Average Change	**$CI_{95\%}$**	**P-value**
VO_2 (mL/kg/min)	-5.5	-5.9, -5.2	<0.0001
PedsQL			
Total score	8.0	7.0, 9.1	<0.0001
Physical	6.2	4.8, 7.6	<0.0001
Emotional	14.8	13.3, 16.3	<0.0001
Social	2.9	1.5, 4.3	<0.0001
School	10.1	8.7,11.5	<0.0001
	Coefficient	**$CI_{95\%}$**	**P-value**
Mean cohort-level infection intensity (epg)	-0.92	-0.93, -0.91	<0.0001

[a]*Abbreviations*: CI, confidence interval; epg, *S. mansoni* eggs per gram feces; VO_2max, maximal oxygen uptake as estimated by fitness testing.

3.4.3 Age-, and sex-adjusted comparisons between study arms, accounting for village-level intra-class correlation

In this first-stage modeling analysis of the SCORE project's a priori statistical analysis plan, no significant differences were observed between the two study arms across the range of measured infection and morbidity markers (Table 3.4).

Table 3.4. Age- and sex-adjusted CWT-arm participant odds for study morbidity at Year 5, using the SBT-arm participants as reference[a]

	Odds Ratio (Reference = the biennial SBT arm)	**$CI_{95\%}$**	**P-value**
Infection prevalence	0.77	0.19, 3.06	0.70
Wasting	2.73	0.94, 7.90	0.06
Stunting	1.19	0.57, 2.47	0.65
Anemia	1.26	0.51, 3.12	0.62
Increased PVD	1.40	0.25, 7.72	0.70
	Arm Difference	**$CI_{95\%}$**	**P-value**
VO_2 (mL/kg/min)	-0.5	-4.8, 3.7	0.80
PedsQL			
Total score	0.7	-7.1, 8.5	0.86
Physical	0.7	-5.6, 7.0	0.82
Emotional	1.8	-9.6, 13.2	0.76
Social	-1.4	-9.3, 6.6	0.73
School	1.4	-6.2, 8.9	0.73
	Coefficient	**$CI_{95\%}$**	**P-value**
Mean cohort-level intensity (epg)	-0.1	-1.9, 1.7	0.92

[a]*Abbreviations*: CI, confidence intervals; CWT, community-wide treatment; epg, *S. mansoni* eggs per gram feces; SBT, school-based treatment; PVD, portal vein diameter; VO_2max, maximal oxygen uptake as estimated by fitness testing.

To account for the imbalances in baseline disease status, we next studied the interaction effects of survey year (Year 5 vs. Year 1) and study arm (CWT vs. SBT) on relative changes in results for the cohort indicators of infection and morbidity, adjusting for sex, village-level clustering effects, and individual year 1 starting values (Table 3.5). By this analysis, prevalence and intensity dropped significantly more by Year 5 in the annual CWT arm, as compared to the SBT arm. Maximal oxygen uptake as estimated by fitness testing max levels declined in both arms, but decreased significantly more in the annual CWT arm than in the biennial SBT arm. By contrast, changes of total PedsQL score and its emotional and school subdomains were all significantly positive from Year 1 to Year 5 for both arms, but children in the annual CWT arm gained more. Not shown, changes in prevalence of anemia, wasting, stunting, or increased PVD were not statistically different between arms (see Supplemental Table 3.1).

3.4.4 Sensitivity analysis for effects of missing data using multiple imputation

The potential impact of missing data was investigated and the result from the imputed datasets did not differ significantly.

3.5 Discussion

This combined cohort analysis of morbidity outcomes in Kenya and Tanzania (Samuels et al. 2012; Kinung'hi et al. 2016; Shen et al. 2017) demonstrates that regular treatment of schoolchildren is associated with reductions in both *S. mansoni* infection and infection intensity. For schoolchildren who were followed to 11-12 years of age, participation in either annual CWT or biennial SBT programs was also associated with reductions in the prevalence of wasting and portal vein dilation. Health-related quality-of-life scores improved in both treatment groups. These findings suggest cumulative benefits from regular preventive treatment (whether CWT or SBT) for *S. mansoni*-endemic communities that are similar to those included in this study. Reduction in portal vein dilation, the study pathology most closely tied to adverse outcomes from intestinal schistosomiasis, is of particular importance. In the absence of an untreated concurrent control group, we cannot definitively ascribe these benefits to treatment

Table 3.5. Sex-adjusted comparison of arm-specific changes in infection and morbidity outcomes from Year 1 to Year 5, including interaction term added to account for differences in starting values between groups[a]

Outcomes	**Predictors**	**Coefficient**	**$CI_{95\%}$**	**P-value**
Infection Prevalence	Year 5	-0.4	-0.8, -0.1	0.01
	Annual CWT	0.6	-0.7, 1.9	0.35
	Annual CWT x Year 5	-1.1	-1.5, -0.6	<.0001
Intensity (epg)	Year 5	-0.59	-0.61, -0.58	<.0001
	Annual CWT	0.7	-1.1, 2.6	0.41
	Annual CWT x Year 5	-0.68	-0.70, -0.65	<.0001
VO_2 max	Year 5	-5.0	-5.5, -4.5	<.0001
	Annual CWT	0.4	-2.6, 3.4	0.81
	Annual CWT x Year 5	-1.0	-1.7, -0.3	0.004
PedsQL Total	Year 5	6.1	4.6, 7.6	<.0001
	Annual CWT	-2.6	-8.9, 3.6	0.40
	Annual CWT x Year 5	3.9	1.8, 6.0	0.0003
PedsQL Emotional	Year 5	10.2	8.1, 12.3	<.0001
	Annual CWT	-6.6	-13.2, -0.1	0.05
	Annual CWT x Year 5	9.4	6.4, 12.4	<.0001
PedsQL School	Year 5	7.7	5.8, 9.7	<.0001
	Annual CWT	-2.7	-9.3, 3.9	0.43
	Annual CWT x Year 5	4.9	2.1, 7.7	0.0007

[a]*Abbreviations*: CWT, community-wide treatment; epg, *S. mansoni* eggs per gram feces; VO_2max, maximal oxygen uptake as estimated by fitness testing;

intervention. However, prolonged nontreatment was considered to be an unethical choice at the time of study design (Ezeamama et al. 2016). It is thus possible that unmeasured confounding factors such as food insecurity and intercurrent infections or reinfections may have influenced the observed study outcomes.

Because the overall research trial used cluster-based random assignment of villages to treatment regimens, there were differences in baseline *S. mansoni* prevalence and infection intensity between the two arms in our analysis and this initially obscured the significance of between-arm differences in outcomes, that is between children in villages receiving annual CWT and those receiving biennial SBT. After adjusting for the higher starting prevalence and intensity, it was noted that annual CWT led to significantly greater decreases in infection prevalence and intensity than did biennial SBT. In addition, children in annual CWT villages gained significantly more in emotional well-being and school satisfaction.

The reasons for persistent morbidity despite MDA are likely to be multifactorial. Location-related variations in reinfection risk, in growth indices, in anemia, and in fitness have been previously demonstrated between the Kenyan and Tanzania areas included in this study. There were also significant differences in sanitation knowledge and practices, and in intake of high-quality protein foods (Mohamed et al. 2018). Unfortunately, as children grow up in resource-limited areas, cumulative growth deficits are a common finding (LaBeaud et al. 2015; Nayakwadi Singer et al. 2017) and our combined studies' outcomes are in accord with that frequent observation.

Twenty-meter SRT–based VO_2 scores have been shown to decline as children age into adolescence, with girls more affected than boys (Léger et al. 1988; Bustinduy et al. 2011). The higher prevalence of stunting and wasting in the annual CWT arm, both at baseline and in Year 5, may have contributed to the observed between-arm difference in VO_2 max results, which are affected both by

stature and muscle mass. Although socioeconomic status can affect PedsQL scores (Varni et al. 2006), the average scoring does not appear to change as a function of age, either for healthy or chronically ill children and adolescents (Varni et al. 2006). The improvements reported in our cohort analysis are thus unlikely to reflect an age effect and may more likely reflect the impact of continued participation in preventive treatment of chronic schistosomiasis (WHO 2006).

There are several limitations to our study. Our study populations live in areas highly endemic for malaria and soil-transmitted helminths, which likely had an impact on anemia outcomes through blood loss, anemia of chronic inflammation (Righetti et al. 2013), and intermittent episodes of symptomatic malaria associated with hemolysis (Samuels et al. 2012; Mohamed et al. 2018). Although both the Kenyan and Tanzanian sites tested for the presence of co-infection with malaria, the sensitivity of the techniques they used (blood smear vs. rapid diagnostic tests) and timing of their testing (Y5 versus Y3) were sufficiently different so that we were unable to estimate the impact of malarial infection across the combined cohort. Perhaps the most critical study limitation was the parent studies' village-level cluster randomization design, which provided only a limited number of evaluation units (i.e., villages) available for analysis (Shen et al. 2017). Village-to-village variation in response to MDA schedules proved to be much higher than anticipated in the initial design of the SCORE studies (Kittur et al. 2017; Sircar et al. 2018), which likely obscured the differences in MDA impact by study arm (Olsen et al. 2018; Sircar et al. 2018). Therefore, a relative strength of our analysis is the inclusion of a somewhat larger number of study locations, with extended analysis to adjust for differing baseline prevalence between the two study arms. Measurement of infection status only in Year 1 and in Year 5 may not have adequately captured cumulative parasite exposure. A child who tested negative at baseline and in Year 5 could still have spent several years repeatedly infected with *S. mansoni* between the beginning and end of the study, despite periodic MDA treatments, and could have accrued significant residual morbidity without evidence of active infection in Year 5.

The current WHO strategy for reduction of schistosomiasis morbidity is based on achieving reductions in the community-level prevalence of heavy infections among school-age children (WHO 2013). Few children in our cohorts had heavy infections by the WHO definition (≥ 400 epg in feces), so we could not assess whether reduction of intensity changed individual morbidity risk. Nevertheless, even though most of the combined cohort children were not heavily infected, in aggregate, they were found to benefit significantly from their community's participation in MDA. It is not clear, however, whether these improvements will remain in effect if MDA is stopped and exposure to infection continues.

Larger studies are currently being designed to better define the community-level infection prevalence and intensity levels below which morbidity associated with schistosomiasis cannot be detected. These studies will more fully measure the spectrum of schistosomiasis-related morbidities, and control for cofactors that contribute to their occurrence. Such additional data should be extremely helpful as WHO refines its global programmatic guidelines for control of *Schistosoma* infection-related morbidity.

3.6 Acknowledgements

This paper is published with the permission of the Director of the Kenya Medical Research Institute and the Tanzania Medical Research Coordination Committee of the National Institute for Medical Research. We thank the local administration; the Assistant Chiefs and village heads, and community health workers (CHWs) and school health teachers for help with community mobilization at all study sites. The authors also wish to thank Jennifer D. Castleman for invaluable assistance with data management and Steve Rathbun for participation in the early development of this project.

3.7 Financial Support

These studies received financial support from University of Georgia Research Foundation, Inc., which was funded by the Bill & Melinda Gates Foundation for the SCORE project. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

3.8 Disclaimer:

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the CDC.

3.9 Disclosures:

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

3.10 Supporting information

Supplemental Table 3.1. Non-significant differences in arm-specific changes from Year 1 to Year 5 when the interaction of study arm by survey year is considered[a]

Outcomes	Predictors	Coefficient	$CI_{95\%}$	P-value
Stunting	Year 5	0.8	0.3, 1.4	0.002
	Annual CWT	0.6	-0.2, 1.5	0.14
	Annual CWT x Year 5	-0.6	-1.3, 0.1	0.08
Wasting	Year 5	-1.4	-2.0, -0.8	<.0001
	Annual CWT	0.7	0, 1.4	0.05
	Annual CWT x Year 5	0.5	-0.1, 1.2	0.12
Anemia	Year 5	-0.2	-0.5, 0.1	0.17
	Annual CWT	0	-0.6, 0.5	0.87
	Annual CWT x Year 5	0.3	-0.1, 0.7	0.12
Increased PVD	Year 5	-2.1	-3.1, -1.2	<.0001
	Annual CWT	0.1	-0.5, 0.8	0.67
	Annual CWT x Year 5	0.1	-1.1, 1.4	0.83
PedsQL Physical	Year 5	5.4	3.4, 7.3	<.0001
	Annual CWT	-0.6	-6.6, 5.4	0.85
	Annual CWT x Year 5	1.7	-1.1, 4.5	0.23
PedsQL Social	Year 5	2.5	0.5, 4.4	0.01
	Annual CWT	-2.1	-10.1, 5.8	0.60
	Annual CWT x Year 5	0.9	-1.9, 3.6	0.54

[a]*Abbreviations*: CI, confidence interval; CWT, community-wide treatment; SBT, school-based treatment; PVD, portal vein diameter; VO_2max, maximal oxygen uptake as estimated by fitness testing; epg, *S. mansoni* eggs per gram feces

4 SCORE Studies on the Impact of Drug Treatment on Morbidity due to ***Schistosoma mansoni*** and ***Schistosoma haematobium*** Infection

Charles H. King[1,2]*, Sue Binder[2], Ye Shen[3], Christopher C. Whalen[3], Carl H. Campbell Jr.[2], Ryan E. Wiegand[4,5,6], Annette Olsen[7], W. Evan Secor[4], Susan P. Montgomery[4], Rosemary Musuva,[8] Pauline N. M. Mwinzi[8], Pascal Magnussen[9], Safari Kinung'hi[10], Gisele N. Andrade[11], Amara E. Ezeamama[3,12], and Daniel G. Colley[2,13]

[1] *Center for Global Health and Diseases, Case Western Reserve University, Cleveland, Ohio*

[2] *Schistosomiasis Consortium for Operational Research and Evaluation, Center for Tropical and Emerging Global Diseases, University of Georgia, Athens, Georgia*

[3] *Department of Epidemiology & Biostatistics, University of Georgia, Athens, Georgia*

[4] *Parasitic Diseases Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, Georgia*

[5] *Swiss Tropical and Public Health Institute, Basel, Switzerland*

[6] *University of Basel, Basel, Switzerland*

[7] *Section for Parasitology and Aquatic Pathobiology, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark*

[8] *Centre for Global Health Research, Kenya Medical Research Institute, Kisumu, Kenya*

[9] *Centre for Medical Parasitology, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark*

[10] *National Institute for Medical Research, Mwanza Research Centre, Mwanza, Tanzania*

[11] *Escola de Enfermagem, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil*

[12] *Department of Psychiatry, College of Osteopathic Medicine, Michigan State University, East Lansing, Michigan*

[13] *Department of Microbiology, University of Georgia, Athens, Georgia*

*Corresponding author

E-mail: chk@cwru.edu

[This manuscript has been published in *The American Journal of Tropical Medicine and Hygiene* (2020) 103(1_Suppl):30-35; https://doi.org/10.4269/ajtmh.19-0830]

4.1 Abstract

The Schistosomiasis Consortium for Operational Research (SCORE) was funded in 2008 to improve the evidence base for control and elimination of schistosomiasis—better understanding of the systemic functional morbidities experienced by children in schistosomiasis-endemic areas, and the response of these morbidities to treatment, being essential for updating WHO guidelines for mass drug administration (MDA) in endemic areas. This article summarizes the SCORE studies that aimed to gauge the impact of MDA-based treatment on schistosomiasis-related morbidities. Morbidity cohort studies were embedded in the SCORE's large field studies of gaining control of schistosomiasis in Kenya and Tanzania. Following MDA, cohort children had less undernutrition, less portal vein dilation, and increased quality of life in Year 5 compared with baseline. We also conducted a pilot study of the Behavioral Assessment System for Children (BASC-2) in conjunction with the Kenya Gaining Control Study, which demonstrated beneficial effects of treatment on classroom behavior. In addition, the SCORE's Rapid Answers Project (RAP) performed systematic reviews and meta-analysis of previously available data, providing two meta-analyses related to morbidity. The first documented children's infection-related deficits in school attendance and achievement and in formal tests of learning and memory. The second showed that greater reductions in egg output following drug treatment correlates significantly with reduced odds of most morbidities. Overall, these SCORE morbidity studies provided convincing evidence to support the use of MDA to improve the health of school-age children in endemic areas. However, study findings also support the need to use enhanced metrics to fully assess and better control schistosomiasis-associated morbidity.

4.2 Overview

The Schistosomiasis Consortium for Operational Research (SCORE) was funded in 2008 to improve the evidence base for control and elimination of schistosomiasis (Colley et al. 2020b). As part of its mission, the SCORE sought to develop a better understanding of the anatomic and systemic functional morbidities experienced by people at risk in schistosomiasis-endemic areas and their

response to antischistosomal praziquantel treatment. Such data are essential for updating WHO guidelines for schistosomiasis control and making the case for mass drug administration (MDA) in endemic areas. This article reviews and summarizes the results of SCORE-supported projects that detailed specific human health impacts of *Schistosoma* infection and their response to treatment.

Persons living in schistosomiasis-endemic areas may spend one-third to a half of their lives carrying *Schistosoma* parasitic worms because their continuing environmental exposure leads to overlapping schistosome infections (King et al. 2011). Morbidity associated with schistosomiasis is caused by parasite eggs that are deposited daily into the human host's organs, creating thousands of foci of granulomatous inflammation, particularly in the bowel and liver (*Schistosoma mansoni, Schistosoma mekongi,* and *Schistosoma japonicum*) or urogenital organs (*Schistosoma haematobium*). Although these granulomas can cause critical dysfunction of the affected organs, more frequently, the granuloma's chronic inflammation contributes to multiple systemic deficits, including chronic pain (King et al. 2005; Galappaththi-Arachchige et al. 2018), diarrhoea (King et al. 2005), fatigue (Kvalsvig 1986; Whitty et al. 2000), reduced quality-of-life (Terer et al. 2013; Kinung'hi et al. 2016), anemia of chronic inflammation (Leenstra et al. 2006), impaired childhood growth and development (Stephenson et al. 1989; Assis et al. 1998), blunted response to childhood vaccines (Malhotra et al. 2018; Ondigo et al. 2018), and impaired school performance (Musuva et al. 2017; Ezeamama et al. 2018). The disease impact can become permanent, persisting even after the active infection has resolved (Giboda et al. 1999). Often overlooked as part of *S. haematobium*-associated morbidity, genital schistosomiasis with pain, bleeding (Leutscher et al. 2008), and subfertility (Miller-Fellows et al. 2017) can result in increased rates of HIV transmission (Wall et al. 2018).

Current WHO strategies for schistosomiasis morbidity control focus on regular delivery of antischistosomal drugs to at-risk populations as a form of "preventive chemotherapy" to limit (or even reverse) the impact of active infection and to prevent new disease sequelae from developing (WHO

2006; 2013). Prioritization for control of neglected tropical diseases such as schistosomiasis is often done using disability-adjusted life-years (DALYs) within international governmental and non-governmental programs (Murray et al. 1996; Hotez et al. 2014). The DALY construct is based on the perceived disability and persistence of a condition and is used to rank the relative contribution of different disabling conditions to the overall global burden of disease (WHO 2013; GBD 2017 Collaborators 2017). The DALY rankings are sometimes assumed to reflect the importance of a given disease to world health (Jamison et al. 2006). The DALYs attributed to schistosomiasis are derived primarily on the prevalence of classic organ-specific chronic anatomic pathologies of schistosomiasis (hepatosplenic disease, bladder fibrosis) observed in the most severe chronic infections, and not on the systemic functional conditions that are also related to *Schistosoma* infection. In response, SCORE researchers decided to use an expanded set of metrics for morbidity appraisals during the course of their MDA trials. These included nutrition and growth assessments, anemia testing, exercise capacity, and formal measurement of school behavior and of health-related quality of life before and after treatment (Shen et al. 2017). The impact of disease-associated stigma and depression (Hofstraat et al. 2016), especially related to female and male genital schistosomiasis is undoubtedly part of the disabling impact of schistosomiasis. Unfortunately, SCORE resources did not allow for study of these latter effects nor was there a sufficient timeline to evaluate the link between *Schistosoma* infection and long-term focal and systemic pathologies that persist beyond the period of active infection (Bustinduy et al. 2009).

Underlying all SCORE projects was the goal of providing data that would provide evidence to help program managers make decisions related to controlling and eliminating schistosomiasis. A related issue was providing evidence that would convince ministers in endemic countries to prioritize schistosomiasis treatment and prevention. Given the underestimation of DALYs related to schistosomiasis, in part related to the lack of high-quality data on the impact of lower-intensity infections and the lifetime consequences, the SCORE saw the need to revisit and contribute data to help

redefine schistosomiasis “morbidity” based on newer developments in the field. Its specific aim was to reevaluate how regular MDA could improve the health of school-age children in schistosomiasis endemic areas (Shen et al. 2017). As a result, the SCORE portfolio related to morbidity and its control included separate longitudinal cohort studies, a school behavioral assessment study, and two systematic reviews and meta-analyses of infection-related morbidity outcomes.

4.3 Schistosomiasis Consortium for Operational Research Longitudinal Cohort Studies

Because there were few clinical research studies evaluating the long-term benefits of praziquantel in terms of prevention of new disease or amelioration of existing disease, SCORE partners incorporated nested comparison studies of the impact of MDA on *Schistosoma* infection-associated morbidity in school age children in each of the SCORE prospective randomized gaining control studies (Shen et al. 2017).

The gaining control studies were large, cluster-randomized studies, with communities randomized to receive either two or four MDAs during the four-year intervention period, with a follow up assessment in Year 5 (King et al. 2020c). The morbidity cohort studies discussed here were conducted in the gaining control studies in Kenya and Tanzania and included four to six communities from the study arm receiving the most intensive treatment (four years of MDA through community-wide treatment [CWT]) compared to four communities from an arm receiving standard every-other-year MDA through school-based treatment (SBT) (Shen et al. 2017). Morbidity studies were also initiated in the gaining control studies in Niger and Mozambique, but these were discontinued after baseline data were collected because of a failure to appropriately randomize communities in Niger (resulting in dramatically different starting prevalences among study arms) and to extremely high loss to follow-up rates in Mozambique related to very low school attendance there.

One hundred 7- to 8-year-old children per community were targeted for enrollment at baseline (Year 1) for the cohort studies, with a goal of having 800 children prospectively monitored in each

country (Shen et al. 2017). The decision to focus on this age-group was based on their greater likelihood of availability for follow up throughout the five-year study period.

After considering 17 different types of morbidity-related markers, the outcomes chosen for measurement in the planned five-year longitudinal cohort studies were as follows (Shen et al. 2017):

1. anthropometric measures: age-standardized height, weight, body mass index (BMI), mid-upper arm circumference (MUAC) (Stephenson et al. 1989; Parraga et al. 1996; Bustinduy et al. 2013),
2. blood hemoglobin (King et al. 2005; Leenstra et al. 2006; Ezeamama et al. 2008; Righetti et al. 2013),
3. exercise tolerance measured by the 20-m shuttle run (beep) test (Léger et al. 1982; Léger et al. 1984; Léger et al. 1988),
4. health-related quality-of-life, measured by the standardized Pediatric Quality of Life (PedsQL) survey instrument (Varni et al. 2003; Terer et al. 2013),
5. ultrasonography of the abdomen and liver (for *S. mansoni*) or of the kidneys and bladder (for *S. haematobium*), using standardized WHO protocols (Richter et al. 2000; Andrade et al. 2017).

At baseline, 62% of children in the selected *S. mansoni* communities in Kenya and Tanzania had detectable eggs in their stool, and 10% had heavy infections (≥400 eggs/g feces). Heavy *S. mansoni* infections were associated with increased baseline prevalence of anemia, although children with moderate or heavy intensity infections had lower odds of having physical wasting.

Prevalence of egg-positive infection in the combined *S. haematobium* communities in Mozambique and Niger was 27%, with 5% of individuals having heavy infection (≥50 eggs/10 mL urine). In contrast to the findings at the *S. mansoni* study sites, at baseline, it was light intensity *S.*

haematobium infections that were significantly associated with anemia. They were also associated with lower scores in the social domain of the standardized PedsQL inventory survey. Individual country-level baseline findings for Kenya and Tanzania have been published elsewhere (Samuels et al. 2012; Kinung'hi et al. 2016), and the baseline results from the four countries that initiated subtle morbidity studies have been summarized by country in tabular form by Shen and colleagues (Shen et al. 2017).

The Kenya and Tanzania gaining control studies were able to successfully complete their Year 3 and Year 5 cohort re-examinations (Mohamed et al. 2018; Sircar et al. 2018; Olsen et al. 2020). In a secondary analysis of their pooled *S. mansoni* longitudinal data, overall infection intensity and odds of infection were significantly reduced in both treatment arms of the study (Shen et al. 2019). Furthermore, both annual CWT and every-other-year SBT were associated with reduced odds of undernutrition in Year 5 (at the time the children were 12-13 years old). They also had reduced odds of portal vein dilation on ultrasound, as compared to their baseline when they were 7 or 8 years old. Although the prevalence of anemia did not improve significantly, this may have been confounded by increased malaria prevalence in the years following baseline examination in Kenya; malaria was not assessed in Tanzania. For the combined Kenya and Tanzania cohorts, growth stunting worsened in the areas receiving biennial SBT, and VO_{2max} scores declined under both CWT and SBT regimens.

After adjusting for imbalance in starting prevalence between the two study arms (Shen et al. 2019; King et al. 2020d), children in communities receiving annual CWT were found to have had significantly greater reductions in infection prevalence and intensity than those in communities receiving only biennial SBT. Although health-related quality-of-life scores improved in both study arms, children in the CWT communities gained significantly more. In aggregate, these SCORE findings suggested that programs implementing annual CWT are likely to achieve better overall *S. mansoni* morbidity control than those implementing biennial SBT alone (Shen et al. 2019).

4.4 School Behavioral Assessment Study

There has been ongoing controversy about the public health benefits of "deworming" via MDA and whether regular treatments of school-aged children can improve their school performance and contribute to greater educational achievement (Majid et al. 2019). The SCORE investigators in Kenya attempted to rigorously investigate this issue by using a validated multidimensional survey instrument, the Behavioral Assessment System for Children (BASC-2), to assess emotional and behavioral problems among children in grades two through six (Musuva et al. 2017). Thirty-six children in six schools within *S. mansoni*-endemic communities near Lake Victoria were assessed both parasitologically and with the BASC-2 Teacher Rating Scale, both before and three weeks after MDA delivery. Teachers were blinded to the infection status of these participating children. Following this initial assessment of behavior using the BASC-2, study children were given praziquantel by MDA using a standard SBT approach, along with all other children in their schools. Then the BASC-2 was repeated for the same children who had completed the pre-MDA BASC-2 assessment.

Participating children's BASC-2 scores improved significantly after treatment in each of the "problem" behavioral categories, with fewer externalizing problems (hyperactivity, aggression, and conduct problems that are disruptive in nature), internalizing problems (anxiety, depression, somatization, atypicality, and withdrawal), and school problems (academic difficulties, attention problems and learning problems) (Musuva et al. 2017). Changes in BASC scores were seen in both egg-positive and egg-negative children.

A high level of heterogeneity in behavior score changes was observed among children who were egg-negative, with posttreatment scores not changing much for some egg-negative children but changing dramatically for others. This could reflect the fact that because of its limited diagnostic sensitivity, a negative Kato-Katz stool examination in an *S. mansoni*-endemic zone does not exclude the presence of symptomatic low-level chronic infection (Verani et al. 2011; Mwinzi et al. 2015a; Bustinduy

et al. 2016; Kittur et al. 2016). Because such low intensity infections often go undetected by stool testing, our posttreatment behavioral findings among egg-negative children suggests that their praziquantel MDA likely had a treatment-specific impact on their performance. It supports the concept that MDA can improve school performance and have a greater effect in endemic areas than that measured by only focusing on treatment impacts for *S. mansoni* egg-positive children.

4.5 Meta-analysis of Cognition and School Performance Outcomes

The SCORE's Rapid Answers Project initiative (King et al. 2020a) used systematic reviews and meta-analysis of available data to answer other policy-relevant questions about schistosomiasis morbidity control. Two of these projects involved assessment of the impact of active infection and its drug therapy on risk of morbidity due to *Schistosoma* infections (Andrade et al. 2017; Ezeamama et al. 2018). Brief graphical summaries of their findings are provided in the supplementary figures.

First, in developing a meta-analysis of the effects of infection and treatment on children's cognition and school performance, we performed a systematic review of the available published data prior to 2016 (Ezeamama et al. 2018). Although there was a relatively large body of published reports and studies on childhood cognitive development and school performance, the variability in study quality necessitated a critical synthesis of their aggregate findings. A SCORE-affiliated team headed by Dr. Amara E. Ezeamama performed a systematic review of over 2900 articles and produced a meta-analysis of 30 relevant studies (Ezeamama et al. 2018).

Our findings from the meta-analysis indicated that, compared with uninfected children or with children who received praziquantel treatment, children who had active *Schistosoma* infection or who had not been treated had significant deficits in school attendance and scholastic achievement and deficits in formal tests of learning and memory (Ezeamama et al. 2018). By contrast, there were no significant differences between the two groups in tests of reaction time or of innate intelligence.

Schistosoma infection-related deficits in learning and memory tests, but not scholastic achievement, were invariant across the range of observational and interventional studies included in the meta-analysis.

4.6 Meta-analysis of Drug-mediated Reduction in *Schistosoma* Infection Intensity and its Effects on Infection-associated Morbidity

Praziquantel treatment is not completely curative for *Schistosoma* infections, particularly when heavy infection is present (Picquet et al. 1998). Furthermore, praziquantel does not protect against rapid reinfection of those who live in high-risk environments (Gryseels et al. 2001; Satayathum et al. 2006). However, most individuals do experience a considerable reduction in the intensity of their *Schistosoma* infections after treatment, which has often been assumed to be a proxy for decreased overall morbidity.

Our second morbidity-related meta-analysis evaluated the actual scale of morbidity reduction when treatment reduces intensity of infection, even in the absence of cure (Andrade et al. 2017). The SCORE also wished to determine whether there is a way to translate commonly reported “egg reduction ratios (ERRs)” into a quantifiable morbidity reduction benefit. The aim was to provide a conversion factor to capture “morbidity control” for later cost-effectiveness studies that would compare different schistosomiasis control strategies (Lo et al. 2018).

The SCORE partners, led by Dr. Gisele N. Andrade, conducted a systematic review of 309 studies that recorded morbidity levels in affected individuals or populations before and after drug treatment interventions (Andrade et al. 2017). A technique called meta-regression was performed to correlate the observed reductions in parasite egg outputs with the posttreatment reductions in measured morbidity prevalence.

The study found that larger reductions in measured egg output following treatment were indeed correlated with lower odds of continuing to have most kinds of infection-associated morbidity. Specifically, for *S. mansoni* and *S. japonicum*, more profound reductions in egg output were linked with

less liver morbidity, and for *S. haematobium*, better treatment response in terms of egg output was linked to reduced odds of urinary tract bleeding and deformity (Andrade et al. 2017). Thus, despite posttreatment persistence of active infections, the meta-analysis results suggested that even if total elimination of egg output is not achievable in all patients within endemic areas, MDA can still result in significant reductions in *Schistosoma*-associated morbidity prevalence if average reductions of egg output ≥90% are achieved.

4.7 Summary and Next Steps

There is a need to better define the impact of *Schistosoma* infection in early childhood and its effects on concurrent and cumulative scholastic achievement (Bustinduy et al. 2017b). Such loss of human capital may actually represent the bulk of schistosomiasis-related disability within endemic areas (Baird et al. 2016).

The SCORE morbidity studies, by adding new markers for physical and psychological functioning, provided better focus on the impact of Schistosoma infection on human performance. However, the studies' scope was still limited by available resources, and in some cases, the effects of treatment in reducing morbidity were smaller than expected. Now, in follow-up to our assessments of functional morbidities, we think that larger cohort studies, involving different age-groups, additional testing, and tracking of coinfections, diet, and other effect modifiers are clearly needed (Colley et al. 2020a). In follow up to the SCORE BASC-2 behavior study (Musuva et al. 2017), more extensive and more detailed psychological and behavioral studies will help to triangulate and refine estimates of the overall impact of *Schistosoma* infection on childhood scholastic performance.

The analyses presented here reinforce the need for a complete reassessment of DALYs related to schistosomiasis. The number of morbidities included in DALY disability weighting needs to be

expanded, and the often subcurative effect of praziquantel needs to be considered in case count estimation. One of the approaches buttressing the calculation of DALYs in the Global Burden of Disease program is the “counterfactual,”, that is what global burden would be like if the disease came under control or were eliminated (Murray 1996)? Current DALY estimates based on *Schistosoma*-infection intensity assume that the prevalence of high-intensity infections are declining in the face of MDA implementation. This is not always true (Walker et al. 2016), and we suggest that newer estimates of persistent posttreatment infection be included in DALY calculations for schistosomiasis. These changes would provide a more realistic valuation of the schistosomiasis-associated DALYs that can be averted through MDA intervention.

Current WHO targets for control are primarily focused on reducing infection intensity (WHO 2013). There is a clear need to redefine the required community-level prevalence targets for effective “morbidity control”. Large-scale initiatives such as the Morbidity Operational Research for Bilharziasis Implementation Decisions (MORBID) study (Neglected Tropical Diseases Support Center 2019) are being planned to more clearly demonstrate the level of post-MDA community infection prevalence and intensity that are associated with persistent disease, in terms of both anatomical and functional pathology. The use of newer more sensitive point-of-care rapid diagnostics (Corstjens et al. 2020) for both infection and morbidity will facilitate this assessment. Moving beyond the use of egg-counting diagnostics, which underestimate the prevalence of low intensity infections (Savioli et al. 1990; de Vlas et al. 1992a; de Vlas et al. 1997; Mwinzi et al. 2015a; Clements et al. 2018), should enhance our ability to determine the attributable role of *Schistosoma* infections in widely prevalent multicausal pathologies such as anemia, growth stunting, cognitive dysfunction, depression, and infertility. This expanded knowledge will be critical for accurate estimation of the actual worldwide disease burden of *Schistosoma* infections and for optimal decision-making regarding health policy investment and development (Colley et al. 2020a).

4.8 Funding

These studies received financial support from University of Georgia Research Foundation, Inc., which was funded by the Bill & Melinda Gates Foundation for the SCORE project. The funders had no role in the study design, data collection and analysis, decision to publish or preparation of the manuscript.

4.9 Disclosures

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

4.10 Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the CDC.

4.11 Supporting information

4.11.1 SCORE Rapid Answers Project (RAP): Cognitive Deficits and Educational Loss in Children with Schistosome Infections

Summary: Empirical evidence for cognitive or education benefits of treating *Schistosoma* infection in children is limited. In a study completed in 2016, we addressed this knowledge gap by synthesizing information from 30 relevant epidemiologic studies reporting on 38,992 children between 5-19 years of age from 14 countries. In those studies, children with *Schistosoma* infection, or those who had not received treatment, were compared to uninfected children or to children dewormed with praziquantel. Children with *Schistosoma* infection or who had not been de-wormed performed worse on psychometric tests of learning and memory. However, they performed similarly to the uninfected or dewormed children in tests of innate intelligence or reaction time. Infected or non-dewormed children had less school attendance and poorer scholastic achievement. Overall, the presence of *Schistosoma* infection or non-dewormed status was associated with educational, learning, and memory deficits in school-aged children. The combined evidence suggests that early treatment of children in *Schistosoma*-endemic regions could mitigate these deficits (Ezeamama et al. 2018).

Questions:

1. Among school-aged children examined in the context of cross sectional or case-control studies, is *Schistosoma* infection associated with worse performance in neurocognitive tests, or with educational loss?
2. Among school-aged children enrolled in prospective studies with specific treatment for *Schistosoma* infection, is lack of treatment with praziquantel associated with worse performance in neurocognitive tests, or with educational loss?

Supplemental Table 4.1. Pooled standardized mean difference (SMD) estimates of *Schistosoma* infection/non-treatment effects on educational/cognitive loss – with evaluation of study heterogeneity and publication bias

	# Studies	SMD (95% CI)[‡]	Heterogeneity[Ψ] I^2	Publication bias P-value[α]
Cognitive Domain				
Memory	8	**-0.28 (-0.52, -0.04)**	78.6	0.786
Learning	6	**-0.39 (-0.70, -0.09)**	79.4	0.793
Intelligence Quotient Based Assessments	4	-0.25 (-0.57, 0.06)	74.8	0.450
Reaction Time	6	-0.06 (-0.42, 0.30)	88.5	0.142
Educational Loss Assessments				
Achievement	16	**-0.58 (-0.96, -0.20)**	97.9	0.595
School Attendance	16	**-0.36 (-0.60, -0.12)**	98.7	0.991

[‡]Standardized Mean Difference (SMD)<0 suggests a negative effect of infection/non-treatment on the indicated outcome; SMD>0 indicates a positive effect of infection on respective outcomes. Bold font indicates statistically significant differences.

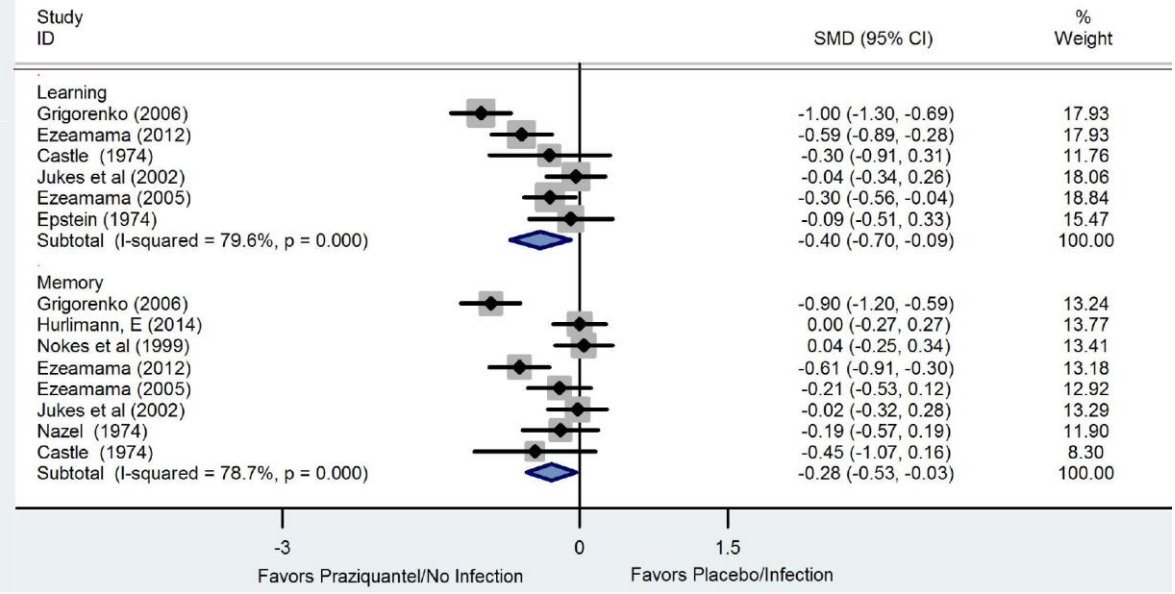
[Ψ]: measures the extent to which there is heterogeneity across studies in terms of underlying results.

[α]: evaluates the tendency for increased publication of studies that show a statistically robust finding; a $P < 0.05$ suggests presence of publication bias.

Key Finding: *Schistosoma* infection/non-treatment was significantly associated with educational, learning, and memory deficits in school-aged children.

The findings of infection-related cognitive deficits and educational loss reported here are clinically relevant and should become an essential pillar in the design of schistosomiasis-related health policy. They reinforce the need to treat children with schistosomiasis early in life, so as to reduce their cumulative cognitive and functional morbidities.

Supplemental Figure 4.1. Examples of significant impact of *Schistosoma* infection - the gray boxes show estimates of SMDs and their 95% confidence intervals for individual studies that assessed learning and memory. Based on our meta-analysis, the blue diamonds indicate the overall summary estimates of the respective impacts of Schistosoma infection on measured learning and memory scores among affected children.



An estimated 800 million persons in tropical and subtropical countries are at risk of infection by one of three main human Schistosoma parasites - *S. mansoni*, *S. haematobium*, and *S. japonicum*.

Findings

- *Schistosoma* infection was associated with small-to-moderate deficits in psychometric tests of learning and memory.
- Infection was also associated with lower school attendance and scholastic achievement. Average effects on scholastic achievement were substantially larger for infection with *S. haematobium* than with *S. mansoni* infection.
- Deficits in learning and memory were clear both in analysis of observational studies and in longitudinal studies. Deficits related to educational achievement appeared robust among observational studies. They were less robust in the longitudinal studies, and risk of study bias was of potential concern.

Implications for school-aged children

Schistosoma infection often occurs in the context of malnutrition, coincident parasitic infections, and extreme poverty. Given the impacts of *Schistosoma* infection, increasing efforts to prevent or eliminate this disease are critical. If that is not yet possible, ensuring infected children receive treatment is important for their health and well-being. We hope that future studies of early childhood interventions, including treatment of schistosomiasis, will clarify to what extent the deficits we observed are reversible.

Implications for pre-school-aged children

Children from endemic areas are often infected by two years of age and remain chronically infected throughout their school-age years. These children may therefore suffer cumulative damage to their health and functioning that is currently not reflected in most short-term study outcomes. At present, there is no specific guidance for anti-Schistosoma drug treatment of pre-school children, partly because of the lack of a child-friendly pediatric formulation.

Given that we observed an adverse impact of *Schistosoma* infection on cognitive and educational domains in school-aged children, it is likely that the impact on younger children is at least as large or larger. Future longer-term studies should evaluate the impact of infection on pre-school children. These would provide important information for guiding decisions about preventive chemotherapy for and ensuring regular treatment of infected pre-school children.

The small-to-moderate deficits we observed at the individual level may amount to large and important differences in population achievement at the community level. It is not currently possible to estimate what the lifetime impact might be for individuals, as relatively small decrements in cognition or educational attainment in childhood may have larger impact on personal performance in later adult life.

4.11.2 SCORE Rapid Answers Project (RAP): The Decline in Infection-Related Morbidities Following Drug-Mediated Reduction in the Intensity of Schistosoma Infection

Background: Since 1984, WHO has endorsed drug treatment to reduce Schistosoma infection and its consequent morbidity. Cross-sectional studies suggest pre-treatment infection intensity correlates with risk for Schistosoma-related pathology. However, other evidence suggests that even if drug treatment reduces intensity, morbidity may not be reversed because some morbidities occur at all levels of infection, and some reflect permanent tissue damage. The aim of this project was to systematically review evidence on the impact of drug-based control on schistosomiasis-related morbidities, and to develop a quantitative estimate of this impact (Andrade et al. 2017).

Question: Does treatment of Schistosoma infection translate into reduced odds of infection-related morbidity? If so, by how much?

The Problem: Schistosomiasis is the disease caused by infection with Schistosoma parasitic flukes. Infection can cause anemia, diarrhea, abdominal pain, difficulties with learning, and decreased physical

fitness. Depending on the infecting species, chronic Schistosoma infection can cause a variety of pathologies. *S. mansoni* and *S. japonicum* can cause liver and spleen enlargement, fibrosis and hypertension of the portal vein of the liver, and in some cases, death due to gastrointestinal bleeding. S. haematobium can cause bladder ulceration and kidney blockage, bladder cancer, and genital lesions that lead to fertility problems in both women and men. Approach: In our study, we quantified the reductions in prevalence of infection-related morbidities among populations with Schistosoma infection, as achieved by giving one or more drug treatments. We systematically reviewed 71 available reports of *Schistosoma*-related morbidity reduction and conducted a meta-analysis of the available data to quantify the odds of persisting morbidity after treatment in relation to the egg reduction rate, ERR, a measure of how much egg counts change from pre- to post-treatment. A higher ERR indicates a greater impact on infection intensity with drug treatment.

Worldwide, schistosomiasis control is a constant challenge for public health services in endemic regions, mainly due to difficulties in preventing frequent reinfection during childhood and early adulthood. Chronic or recurrent infections lead to progressive inflammatory damage from parasite eggs that remain trapped in human tissues.

Morbidities that Could be Evaluated by Meta-analysis

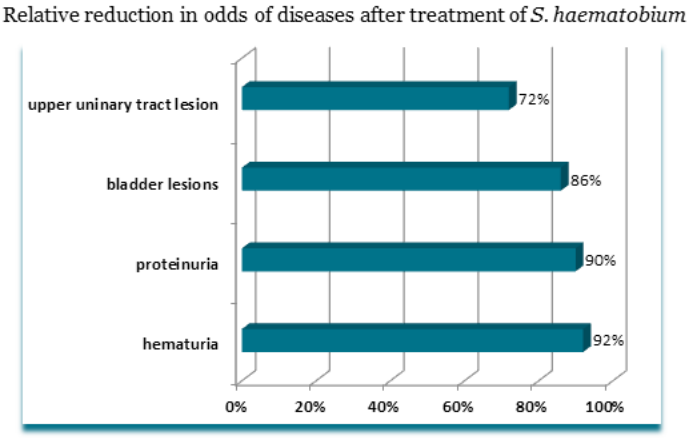
For intestinal schistosomiasis caused by *S. mansoni* or *S. japonicum*: blood in stool, diarrhea, periportal fibrosis, portal vein dilation, splenomegaly, right-sided hepatomegaly, left-sided hepatomegaly, anemia

For urogenital schistosomiasis caused by *S. haematobium*: upper urinary tract lesions, bladder lesions, proteinuria, hematuria, anemia

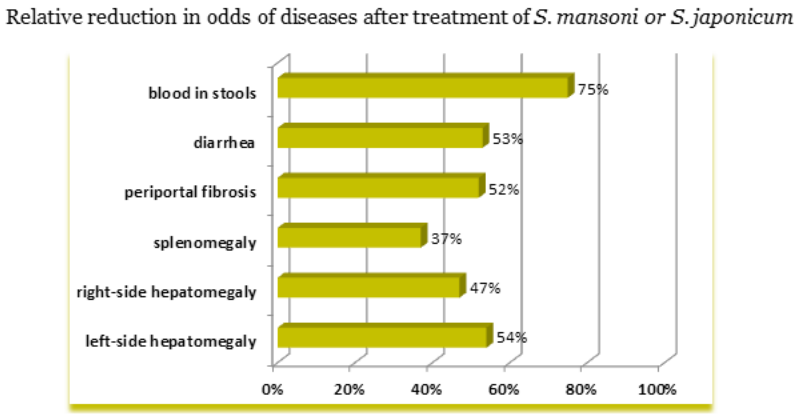
Key Findings

Our meta-regression indicates that post-treatment reductions in egg burden are significantly correlated with decreased morbidity. In particular, larger ERRs, which indicate acute reductions in worm burden, are associated with reversal of most acute pathology. More advanced chronic pathologies appear less responsive to single rounds of treatment, even with adequate ERRs, multiple rounds of treatment may be necessary to improve those outcomes. Factors affecting the magnitude of morbidity reductions include *Schistosoma* species, population studied, age and infection status of study participants, and how long after treatment follow-up occurred.

Supplemental Figure 4.2. Relative reduction in odds of diseases after treatment of *Schistosoma* infection.

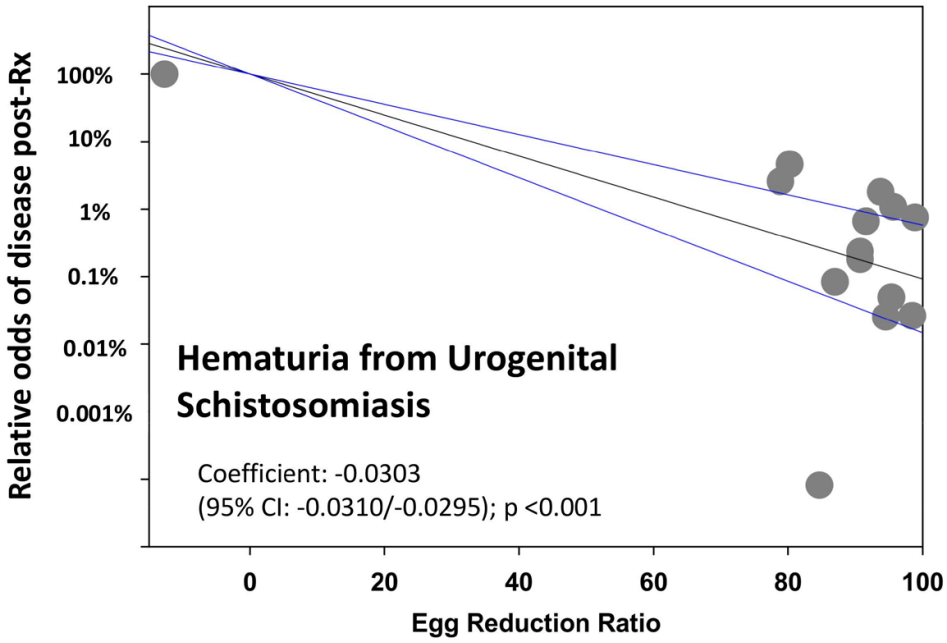


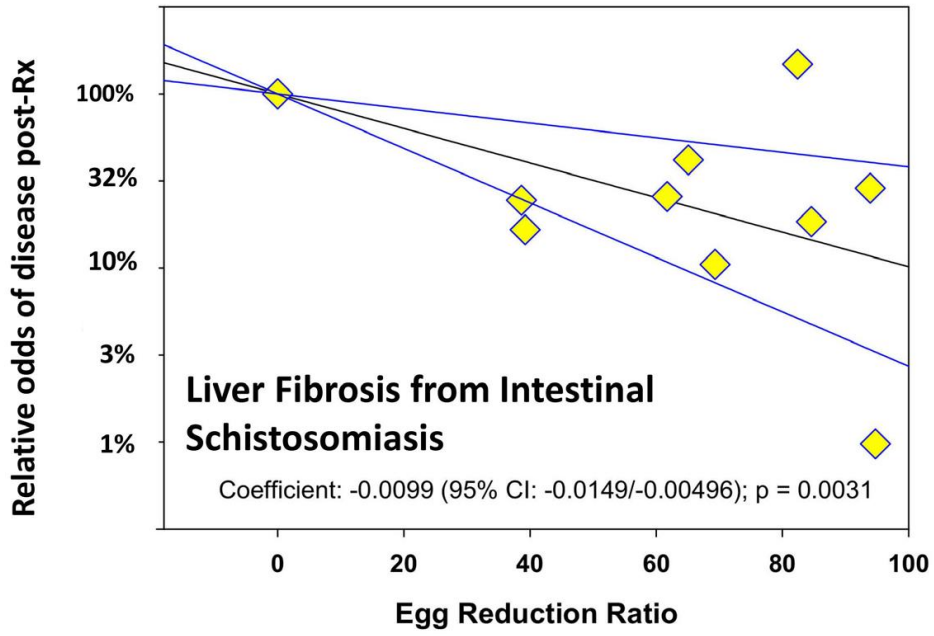
Supplemental Figure 4.3. Examples of Meta-Regressions Showing Relations Between ERRs and Odds of Diseases Post-Treatment



The graphs below plot the relative odds of disease post-treatment against ERRs (Supplemental Figure 4.4). The higher the ERR, the greater the impact of treatment on infection intensity. These plots show that higher ERRs are associated with lower odds for post-treatment disease. Meta-regression lines (center black lines) and their 95% confidence limits (upper and lower blue lines) are shown for urinary tract bleeding when subjects had *S. haematobium* infections (top panel), and for periportal fibrosis of the liver when subjects had *S. mansoni* or *S. japonicum* infections (bottom panel).

Supplemental Figure 4.4. relative odds of disease post-treatment against ERRs.





Implications

Our study shows that oral drug treatment reduces disease burden and supports continued efforts to reach populations at risk. Reducing all morbidity may require providing repeated treatment for people at risk for chronic and more intense infection. Because the reduction in egg output is significantly correlated with decreased morbidity, our estimates of the post-treatment odds of morbidity can be used to predict diminution in disease burden after successful program implementation. Nevertheless, our study was limited by gaps in the literature; additional well-designed and well-reported cohort studies are needed to strengthen the evidence base related to treatment impact on *Schistosoma* morbidity control.

5 Associations between infection intensity categories and morbidity prevalence in school-age children are much stronger for *Schistosoma haematobium* than for *S. mansoni*

Ryan E. Wiegand[1,2,3*], W. Evan Secor[1], Fiona M. Fleming[4], Michael D. French[5], Charles H. King[6], Arminder K. Deol[7], Susan P. Montgomery[1], Darin Evans[8], Jürg Utzinger[2,3], Penelope Vounatsou[2,3], Sake J. de Vlas[9]

[1] *Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America*

[2] *Swiss Tropical and Public Health Institute, Basel, Switzerland*

[3] *University of Basel, Basel, Switzerland*

[4] *SCI Foundation, London, United Kingdom*

[5] RTI International, Washington DC, United States of America

[6] *Center for Global Health and Diseases, Case Western Reserve University, Cleveland, Ohio, United States of America*

[7] *Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom*

[8] *United States Agency for International Development, Washington, DC, United States of America*

[9] *Department of Public Health, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands*

*Corresponding author

Email: rwiegand@cdc.gov

[This manuscript has published in *PLOS Neglected Tropical Diseases* (2021) 15(5): e0009444;

https://doi.org/10.1371/journal.pntd.0009444.]

5.1 Abstract

Background: World Health Organization (WHO) guidelines for measuring global progress in schistosomiasis control classify individuals with *Schistosoma* spp. infections based on the concentration of excreted eggs. We assessed the associations between WHO infection intensity categories and morbidity prevalence for selected *S. haematobium* and *S. mansoni* morbidities in school-age children.

Methodology: A total of 22,488 children aged 6-15 years from monitoring and evaluation cohorts in Burkina Faso, Mali, Niger, Tanzania, Uganda, and Zambia from 2003-2008 were analyzed using Bayesian logistic regression. Models were utilized to evaluate associations between intensity categories and the prevalence of any urinary bladder lesion, any upper urinary tract lesion, microhematuria, and pain while urinating (for *S. haematobium*) and irregular hepatic ultrasound image pattern (C-F), enlarged portal vein, laboratory-confirmed diarrhea, and self-reported diarrhea (for *S. mansoni*) across participants with infection and morbidity data.

Principal findings: *S. haematobium* infection intensity categories possessed consistent morbidity prevalence across surveys for multiple morbidities and participants with light infections had elevated morbidity levels compared to negative participants. Conversely, *S. mansoni* infection intensity categories lacked association with prevalence of the morbidity measures assessed.

Conclusions/significance: Current status infection intensity categories for *S. haematobium* were associated with morbidity levels in school-age children, suggesting urogenital schistosomiasis morbidity can be predicted by an individual's intensity category. Conversely, *S. mansoni* infection intensity categories were not consistently indicative of childhood morbidity at baseline or during the first two years of a preventive chemotherapy control program.

Financial support: The Schistosomiasis Control Initiative (now the SCI Foundation) was supported by the Bill and Melinda Gates Foundation (grant 13122).

5.2 Author Summary

Infections with *Schistosoma* parasites are commonly classified by the presence and concentration of excreted *Schistosoma* eggs. Guidelines put forward by the World Health Organization (WHO) include classifications of *S. haematobium* infections assessed by urine filtration into light and heavy infections and *S. mansoni* infections assessed by Kato-Katz thick smears into light, moderate, and heavy infections. Past evidence has demonstrated an association between intensity of infection with morbidity for severe morbidities, but this was before recognition of the effect of light-intensity infections on morbidity and was done in treatment naïve populations. In these analyses, we assessed the associations between the WHO classifications for infection intensity and a wide array of *S. haematobium* and *S. mansoni* morbidity indicators in school-age children ascertained in monitoring and evaluation cohorts before and after initiation of deworming. Our analyses found a high correlation with *S. haematobium* intensity categories and morbidity indicators, especially microhematuria, but weaker correlation between *S. mansoni* intensity categories and morbidity indicators. The results indicate that, on the aggregate, the intensity categories represent a person's *S. haematobium*-related morbidity but are poor at representing a person's *S. mansoni*-related morbidity.

5.3 Introduction

Schistosomiasis is the disease caused infection with the blood fluke *Schistosoma* spp. Morbidity is caused by the host's response to parasite eggs. As part of the life cycle, eggs are excreted via urine (for *Schistosoma haematobium*) or stool (for *S. mansoni* and other species), but some eggs become lodged in host tissue and stimulate inflammation and granulomatous reactions, which are responsible for the pathology associated with the infection (Colley et al. 2014a). Chronic disease can manifest due to the accumulation of tissue damage by repeated infections or because schistosomes can survive in the human body and produce eggs for many years. Morbidity varies by species (King et al. 2005; Colley et al. 2014a). *S. haematobium* infections affect the urogenital system and most often clinically present as hematuria (van der Werf et al. 2003b). Chronic infections can result in urinary tract fibrosis (Khalaf et al.

2012), female (Christinet et al. 2016) and male (Kayuni et al. 2019) genital schistosomiasis, and, in rare cases, bladder cancer (Ishida et al. 2018). *S. mansoni* infections affect the gastrointestinal tract and frequently are associated with abdominal pain and bleeding into the stool (van der Werf et al. 2003b). Longer term infections put patients at greater risk for periportal fibrosis (Colley et al. 2014a), which can lead to portal vein hypertension, hepatosplenic disease, and esophageal varices that can result in exsanguination into the digestive tract.

Prior to the introduction of mass distribution of praziquantel as preventive chemotherapy, multiple studies in the 1970's and early 1980's found an association between the intensity of a schistosome infection and morbidity (WHO 1973; 1987; 1988). These studies became the basis for two important components of schistosomiasis morbidity control. First, they established the concept of infection intensity categorizations, now commonly used by the World Health Organization (WHO). *S. haematobium* infection intensity has consistently been characterized by the number of schistosome eggs per 10 ml of urine with 1-49 eggs per 10 ml of urine defining a light infection and ≥ 50 eggs per 10 ml of urine indicating a heavy infection (WHO Expert Committee on the Control of Schistosomiasis 1985; WHO 2002). For *S. mansoni*, infection intensity is measured as the number of schistosome eggs per gram (EPG) of stool. Different categorizations have appeared in WHO documents (WHO Expert Committee on the Control of Schistosomiasis 1985; Dixon 1987), but infection intensity is now commonly split into three categories: 1-99 EPG for a light infection; 100-399 EPG signifying a moderate infection; and ≥400 EPG for a heavy infection (Montresor et al. 1998; WHO 2002). Second, they led to current WHO guidelines that use community-level prevalence of heavy-intensity infections as the basis for morbidity control (WHO 2013), even though it is recognized that light and moderate infections can cause considerable morbidity (King et al. 2005; King 2015).

The primary objective of this study was to determine whether the intensity categories, i.e., a measure of someone's current infection status, can differentiate between participants' morbidity

prevalence for multiple, schistosomiasis-related morbidity indicators. For *S. haematobium*, we analyzed two aggregated ultrasound indicators, as well as microhematuria, and pain while urinating. For *S. mansoni*, we analyzed irregular liver image pattern, enlarged portal vein, laboratory-confirmed diarrhea, and self-reported diarrhea. We used data from preventive chemotherapy control programs in Burkina Faso (Koukounari et al. 2007; Touré et al. 2008; Garba et al. 2009), Mali (Koukounari et al. 2006; Garba et al. 2009), Niger (Garba et al. 2009), Uganda (Kabatereine et al. 2007), Tanzania (Kabatereine et al. 2006), and Zambia (Kabatereine et al. 2006) between 2003 and 2008 supported by the Schistosomiasis Control Initiative (SCI) (Fenwick et al. 2009). To our knowledge, no thorough evaluation of the association between infection intensity categories and morbidity before and after the mass distribution of praziquantel has been performed.

5.4 Methods

5.4.1 Ethics statement

The Imperial College Research Ethics Committee (ICREC_8_2_2, EC No. 03.36, R&D No. 03/SB/003E) and the ethical review boards of the Ministries of Health of the six countries included here provided ethical approval for use of these data. The Centers for Disease Control and Prevention (CDC) was determined to be a non-engaged research partner.

5.4.2 Study design and data collection

Data collection was performed as part of national control programs for schistosomiasis and soil-transmitted helminthiasis. Details on country programs and development of SCI are presented elsewhere (Kabatereine et al. 2006; Koukounari et al. 2006; Kabatereine et al. 2007; Koukounari et al. 2007; Touré et al. 2008; Fenwick et al. 2009; Garba et al. 2009). Briefly, all countries created a multifaceted, national program scale-up and initiated distribution of praziquantel and albendazole to target populations based on WHO guidance (Montresor et al. 2002). Schools were randomly selected from areas with various endemicity levels that were purposively selected. Countries created two monitoring and evaluation cohorts: a randomly selected group of children, aged 6-12 years in primary

education, were followed for two or more years; and a second cohort of communities were tracked with a random sample of participants ascertained each year. The first survey (baseline) was the first known year of preventive chemotherapy in the area. The subsequent years of follow-up are referred to as follow up 1 and follow up 2. Data were collected from communities which had been treated annually and measured approximately one year after treatment. Treatment was usually immediately following survey times, but occasionally lagged by a few months. Details on surveys included in the analyses and reasons for exclusions are included in the supplementary materials (Supplemental Table 5.1). Participants were required to be above 94 cm in height and not currently ill. Consent was obtained from parents or guardians and assent was obtained from children. Participants were surveyed and evaluated before receiving praziquantel (for schistosomiasis) and albendazole (for soil-transmitted helminthiasis). We pooled the monitoring and evaluation cohorts and limited the participants to 6-15 year-old children to include the largest number of participants possible and to align with the current monitoring and evaluation guidelines of sampling school-aged children (WHO 2011c). Datasets were created for each morbidity where participants were required to possess both infection and morbidity data.

5.4.3 *Schistosoma* infection data

Each control program chose independently how to evaluate *S. haematobium* and *S. mansoni* infections (Table 5.1). Urine filtration was used to determine *S. haematobium* infection intensity. A single urine sample was used in Burkina Faso, Niger, Tanzania, and Zambia. All countries performed a single filtration except Niger which prepared two filtrations from one urine sample. In Mali, program officials took two urine samples from consecutive days and filtered each. A stained filter was microscopically examined for *S. haematobium* eggs after passing approximately 10 ml of urine through it. An individual's infection intensity was calculated as the arithmetic mean of the number of eggs per 10 ml of urine across all available samples. Participants were then grouped into three intensity infection categories: negative (0 eggs per 10 ml urine), light (1-49 eggs per 10 ml of urine), and heavy (≥ 50 eggs per 10 ml of urine) (WHO 2002).

S. mansoni infection intensity was determined by the Kato-Katz technique. Mali, Niger, and the baseline Ugandan survey used a single stool with counting of two separately prepared Kato-Katz thick smears. Two stools from consecutive days with two slides each were used in Tanzania and all follow-up surveys in Uganda. Slides were microscopically examined for *S. mansoni* eggs. Individual intensity of infection was determined by calculating the arithmetic mean of the number of eggs on all available

Table 5.1. Summary of Schistosoma infection data collection procedures by country, Schistosomiasis Control Initiative (SCI) supported monitoring and evaluation data, 2003-2008.

Country	*S. haematobium* 10 ml urine filtrations	*S. mansoni* 41.7mg Kato-Katz (KK) slides
Burkina Faso	One	One stool sample with two slides
Mali	Two from different samples taken on consecutive days	One stool sample with two slides
Niger	Two from the same urine sample	One stool sample with two slides
Tanzania	One	Two stool samples with two slides
Uganda	No evaluation	Baseline: one stool sample with two slides Follow-up: two stool samples with two slides
Zambia	One	Two stool samples with two slides

slides multiplied by a factor of 24 to scale the measurement to eggs per 1 g of stool. Participants were classified into four intensity infection categories: negative (0 EPG), light (1-99 EPG), moderate (100-399 EPG), and heavy (≥400 EPG) (WHO 2002).

5.4.4 Morbidity data

Morbidity data were collected from the same participants as the infection data. *S. haematobium* ultrasound variables utilized in these analyses included all elements of an *S. haematobium* ultrasound evaluation (Richter 2003) performed in accordance to the standardized Niamey protocol (Richter et al. 2000). These included a distorted bladder shape, the presence of irregularities in the bladder wall, detection of any bladder wall masses >10 mm in size, presence of pseudopolyps, a focal or diffuse thickening of the bladder wall, any dilation of the left or right pelvis, and any visualization of the left or right ureter. The first five indicators were aggregated into an outcome denoting whether a participant was positive for any urinary bladder lesion while the pelvic dilation and ureter visualization indicators were aggregated into an outcome denoting whether a participant was positive for any upper urinary tract lesion. Participants missing any of the *S. haematobium* ultrasound indicators were excluded from these analyses. Additionally, as a sensitivity analysis, a second approach utilized the number of positive indicators and the total number of indicators measured and are referred to as the urinary bladder rate and upper urinary tract rate. All participants with at least one indicator measured were included in the second analysis. Two additional morbidity indicators were also analyzed: microhematuria assessed with Hemastix dipsticks (French et al. 2007) and self-reported pain while urinating (Danso-Appiah et al. 2010). The analyses of individual morbidity indicators are included in the supplementary material.

Four main morbidity variables were analyzed for *S. mansoni.* Two ultrasound indicators of *S. mansoni* infection, collected according to the Niamey protocol (Richter et al. 2000), were included in analyses: the presence of a hepatic image pattern of C or worse to measure where a participant has any echogenic fibrosis; and an enlarged portal vein, defined as a portal vein diameter with a score of > 2

standard deviations from the Senegalese population data used in the Niamey protocol. Unfortunately, other indicators were not consistently measured in all countries. The final two morbidity variables for *S. mansoni* were laboratory-confirmed and self-reported diarrhea (Polderman et al. 1984; Stelma et al. 1994). Laboratory-confirmed diarrhea was indicated by the technician, while self-reported diarrhea was based on participants' responses when asked if they had experienced diarrhea in the last 2 weeks. Analyses of hepatic irregular image pattern B or worse, blood in stool, and abdominal pain for *S. mansoni* are included in the supplementary materials.

5.4.5 Data analysis methods

R version 4.0.3 (R Development Core Team 2018) and the tidyverse package (Wickham 2017) were used to prepare data for analyses. All analyses that required a level of significance used the 5% level. Analyses included in this report's figures treated the data as a stratified (country level) and clustered (school level) sample via the survey package (Lumley 2019). Logistic regression was used to compare the relative odds of possessing a morbidity between categories within a survey. These models have the goal of comparing participants' current infection status within the same survey and do not make comparisons between surveys or identify the best infection categories.

The regression model contained fixed effects for countries to control for differences between control programs, age and sex of participants, survey year, intensity infection category, and the interaction between survey year and intensity category. A random intercept for each school was included to account for any correlation between children sampled from the same school. Participants who contributed data at multiple surveys had individual random intercepts, while those participants who contributed for a single year did not. All comparisons were estimated via contrast statements and reported as odds ratios (ORs) with 95% Bayesian credible intervals (BCIs) from the posterior distributions. Regression models were chosen via Markov chain Monte Carlo (MCMC) methods in JAGS (Plummer 2003) using the rjags package (Plummer 2019). Three chains were chosen with an adaptive

phase of 10,000 iterations and a total of 80,000 iterations per chain. The first 10,000 iterations were discarded. All fixed effect coefficients used have Cauchy prior distributions with a center of zero and a scale of 2.5 (Gelman et al. 2008). For *S. haematobium*-related morbidities, additional models were run without controlling for participants' age and sex for comparison.

In addition, we explored whether using three categories of *S. mansoni* infection intensity (rather than four levels) might show a stronger association with morbidity indicator prevalence. Multiple categorizations were used to define the new *S. mansoni* infection intensity categories, each with zero EPG of stool treated as negative and the remaining two categories were split at a new threshold. We chose thresholds of 100 EPG, 200 EPG, 300 EPG, and 400 EPG to split infected participants. Thus, for example, the threshold of 200 EPG, produced a categorization of 0 EPG, 1-199 EPG, and ≥200 EPG.

5.5 Results

5.5.1 *S. haematobium*

A range of 8,615 to 11,948 school-age children were included at baseline depending on each morbidity's missing data (Supplemental Table 5.2). This dropped to a range of 5,107 to 6,941 for follow-up 1 and 3,599 to 3,672 for follow-up 2. The prevalence of any infection and heavy-intensity infection prevalence were demonstrably higher for participants sampled at baseline compared to those sampled at follow-up 1 as the confidence intervals did not overlap; however, infection levels did not differ between follow-up 1 and follow-up 2 (Figure 5.1, row A). Similarly, most morbidities were more prevalent among participants sampled at baseline compared to participants sampled at follow-up 1 or at follow-up 2 (Figure 5.1, row B; Supplemental Figure 5.1).

With a few exceptions, infection intensity category prevalence estimates for *S. haematobium*-related morbidity indicators were consistent across surveys (Figure 5.2). Microhematuria prevalence was almost identical in each intensity category across surveys. Participants in the heavy intensity category at follow up 2 had a much higher prevalence of any urinary bladder lesion and the prevalence

Figure 5.1. Line graphs of the percentage of 6-15 year-old children who were *Schistosoma* infection and heavy-intensity positive (row A), *S. haematobium* morbidity positive (row B), and *S. mansoni* morbidity positive (row C) at each survey year (baseline, BL; follow-up 1, FU1; follow-up2, FU2). *S. haematobium* estimates are from Mali, Niger, and Tanzania and are assessed by urine filtration. *S. mansoni* estimates are from Mali, Niger, Tanzania, and Uganda and are assessed by the Kato-Katz technique.

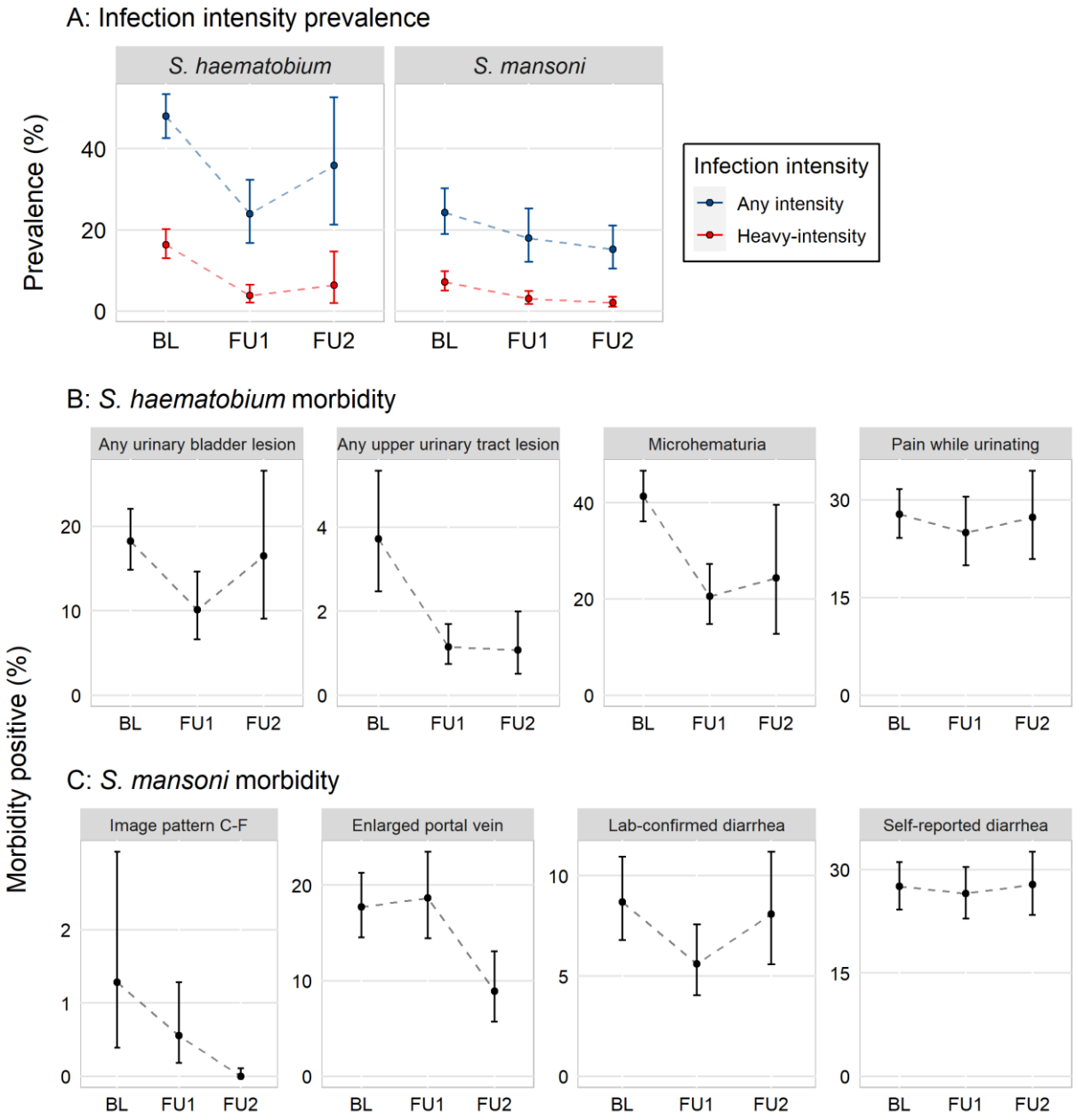
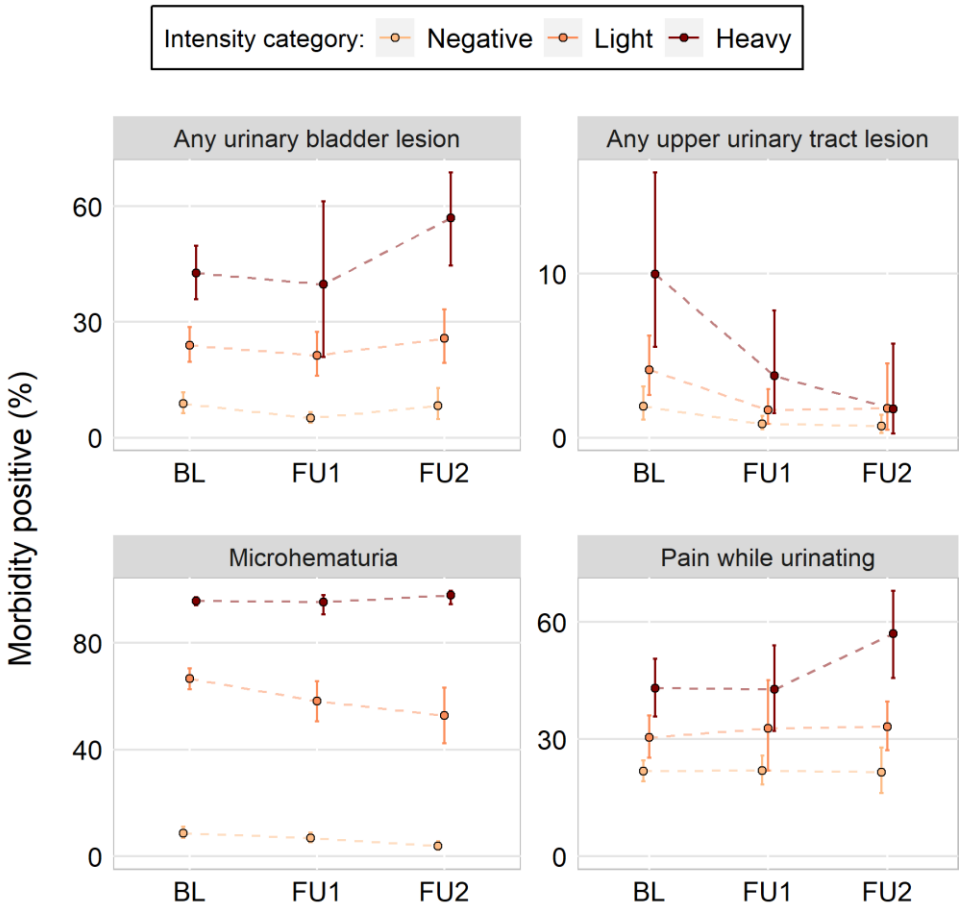


Figure 5.2. Line graphs of *Schistosoma haematobium*-related morbidity percentages, broken down by intensity category, across three surveys (baseline, BL; follow-up 1, FU1; follow-up2, FU2). Participants were enrolled between 2003 and 2008 in Mali, Niger, and Tanzania. Clustering by school accounted for in 95% confidence bands. Infections were assessed by urine filtration.



of pain while urinating; those morbidity indicators were consistent across surveys for the other intensity categories. The prevalence of any upper urinary tract lesion trended downward for participants in the heavy intensity infection category in each successive survey. Individual ultrasound indicators followed similar patterns but tended to have more variability (Supplemental Figure 5.2).

ORs comparing participants in different intensity categories at each survey were roughly consistent for any urinary bladder lesions, any upper urinary tract lesions, microhematuria, and pain

while urinating (Table 5.2). Compared to negative participants, participants with light infections were at increased odds for all morbidity indicators. The same was also true for participants with heavy infections, with the exception of the follow-up 2 survey for any upper urinary tract lesions. There was a lack of consistency between participants with heavy versus light infections for any upper urinary tract lesion, but differences were consistent at all timepoints for other morbidities. Similar results were found for binomial outcomes (Supplemental Table 5.3).

Table 5.2. Odds ratios (ORs) and 95% credible intervals from Bayesian logistic regression models comparing morbidity positive proportions between intensity categories within surveys for *S. haematobium*-related morbidities. Bold font indicates the 95% Bayesian credible interval (BCI) does not contain one. Participants are school-age children (6-15 years) enrolled between 2003 and 2008 in Mali, Niger, and Tanzania.

Morbidity	Survey	Light versus negative	Heavy versus negative	Heavy versus light
Any urinary bladder lesions	Baseline	**1.42 (1.22, 1.64)**	**1.76 (1.46, 2.11)**	**1.24 (1.04, 1.48)**
	Follow up 1	**1.58 (1.33, 1.87)**	1.39 (0.99, 1.94)	0.88 (0.62, 1.23)
	Follow up 2	**2.32 (1.85, 2.90)**	**2.73 (1.93, 3.85)**	1.18 (0.84, 1.65)
Any upper urinary tract lesions	Baseline	**1.39 (1.02, 1.89)**	**1.74 (1.22, 2.48)**	1.26 (0.92, 1.72)
	Follow up 1	1.19 (0.81, 1.74)	1.67 (0.86, 3.02)	1.41 (0.72, 2.58)
	Follow up 2	1.96 (0.96, 4.02)	1.88 (0.54, 5.29)	0.96 (0.28, 2.67)
Microhematuria	Baseline	**2.11 (1.92, 2.33)**	**3.25 (2.88, 3.68)**	**1.54 (1.36, 1.73)**
	Follow up 1	**2.19 (1.91, 2.53)**	**2.84 (2.17, 3.74)**	1.29 (0.97, 1.73)
	Follow up 2	**2.00 (1.69, 2.38)**	**4.40 (3.27, 5.93)**	**2.19 (1.62, 2.98)**
Pain while urinating	Baseline	**1.19 (1.07, 1.34)**	**1.58 (1.38, 1.81)**	**1.32 (1.15, 1.52)**
	Follow up 1	1.02 (0.87, 1.20)	0.93 (0.67, 1.27)	0.91 (0.65, 1.27)
	Follow up 2	**1.27 (1.06, 1.54)**	1.26 (0.90, 1.77)	0.99 (0.70, 1.40)

The differences in the odds of possessing a morbidity between intensity categories was dramatically different when age and sex were not controlled for in regression models (Table 5.3). When age and sex are not included, the OR estimates are more closely aligned with those found the raw data (Figure 5.2) than those in models with age and sex included (Table 5.2).

Table 5.3. Odds ratios (ORs) and 95% credible intervals from Bayesian logistic regression models comparing morbidity positive proportions between intensity categories within surveys for *S. haematobium*-related morbidities without controlling for age and sex. Bold font indicates the 95% Bayesian credible interval (BCI) does not contain one. Participants are school-age children (6-15 years) enrolled between 2003 and 2008 in Mali, Niger, and Tanzania.

Morbidity	Survey	Light versus negative	Heavy versus negative	Heavy versus light
Any urinary bladder lesions	Baseline	**3.49 (2.98, 4.10)**	**10.15 (8.37, 12.34)**	**2.91 (2.46, 3.44)**
	Follow up 1	**3.89 (3.15, 4.80)**	**13.10 (9.36, 18.36)**	**3.37 (2.42, 4.70)**
	Follow up 2	**3.08 (2.47, 3.86)**	**10.07 (7.17, 14.23)**	**3.26 (2.34, 4.58)**
Any upper urinary tract lesions	Baseline	**1.75 (1.30, 2.35)**	**3.35 (2.43, 4.63)**	**1.92 (1.46, 2.51)**
	Follow up 1	1.15 (0.66, 1.94)	**2.77 (1.29, 5.46)**	**2.41 (1.08, 5.03)**
	Follow up 2	1.93 (0.99, 3.80)	1.63 (0.47, 4.43)	0.84 (0.25, 2.27)
Microhematuria	Baseline	**23.75 (20.67, 27.35)**	**296.27 (229.36, 388.21)**	**12.47 (9.90, 15.95)**
	Follow up 1	**14.45 (12.10, 17.29)**	**249.79 (143.44, 470.70)**	**17.28 (10.02, 32.37)**
	Follow up 2	**29.17 (22.56, 38.24)**	**1165.70 (506.17, 3363.16)**	**39.82 (17.86, 112.05)**
Pain while urinating	Baseline	**1.41 (1.26, 1.58)**	**2.40 (2.10, 2.75)**	**1.70 (1.48, 1.94)**
	Follow up 1	**1.59 (1.35, 1.86)**	**2.37 (1.77, 3.16)**	**1.49 (1.09, 2.03)**
	Follow up 2	**1.58 (1.31, 1.91)**	**4.58 (3.31, 6.38)**	**2.89 (2.07, 4.06)**

5.5.2 *S. mansoni*

The sample sizes for *S. mansoni* analyses ranged from 5,158 to 13,483 school-age children at baseline, 4,881 to 11,484 for follow-up 1, and 3,901 to 6,216 for follow-up 2 (Supplementary Table 5.4). Although the prevalence of any infection and heavy-intensity infection prevalence was higher for participants sampled at baseline as compared to those sampled at follow-up 1, the declines were modest and confidence intervals overlap (Figure 5.1, row A; Supplemental Figure 5.3). *S. mansoni*-related morbidities collected via ultrasound or in the laboratory and validated by a technician, also experienced decreases when participants at each follow-up survey were compared to baseline participants (Figure 5.1, row C; Supplementary Figure 5.4), though the confidence intervals often overlap. The prevalence of enlarged portal vein slightly increased for participants in follow up 1 compared to baseline. Self-reported morbidities remained similar across the surveys.

In contrast to *S. haematobium*, *S. mansoni*-related morbidities demonstrated no clear pattern and fewer associations with intensity categories (Figure 5.3; Table 5.4 and Supplementary Table 5.4). For instance, while baseline participants with heavy and moderate intensity infections were more likely to have an enlarged portal vein than their negative counterparts (moderate versus negative: OR=1.53, 95% BCI=1.09-2.13; heavy versus negative: OR=2.48, 95% BCI=1.86-3.30), these associations were much weaker at follow-up 1 (moderate versus negative: OR=1.31, 95% BCI=0.86-1.97; heavy versus negative: OR=1.25, 95% BCI=0.70-2.12), but then were much stronger at follow up 2 (moderate versus negative: OR=3.29, 95% BCI=1.91-5.47; heavy versus negative: OR=4.68, 95% BCI=2.24-9.18). Percentages of enlarged portal vein broken down by country (Supplementary Figure 5.5) showed very high estimates of enlarged portal vein for Nigerian and Zambian participants with no infection. This resulted in negative participants having a higher estimate of enlarged portal vein than other intensities at both follow up surveys (Figure 5.3). Though, since the modeled results took into account differences between countries and the age and sex of the participant, the ORs represent a more accurate comparison between the intensity categories (Table 5.4). Results for all *S. mansoni* morbidity indicators are included in the supplementary material (Supplementary Table 5.5).

Under the consideration that the different patterns observed between *S. haematobium* and *S. mansoni* could be a statistical artifact of the number of intensity categories between species, we explored using three *S. mansoni* intensity categories instead of four. Using 200 EPG as the breakpoint between the light- and heavy-intensity categories, patterns similar to the four-category definition were seen (Figure 5.4). This was also true when 100 EPG, 300 EPG, and 400 EPG were utilized as the breakpoint between a light and heavy infection (Supplemental Figures 5.6-5.8).

Figure 5.3. Line graphs of *Schistosoma mansoni*-related morbidity percentages, broken down by intensity category, across three surveys (baseline, BL; follow-up 1, FU1; follow-up2, FU2). Participants were enrolled between 2003 and 2008 in Mali, Niger, Tanzania, and Uganda. Clustering by school accounted for in 95% confidence bands. Infections were assessed by Kato-Katz stool examination.

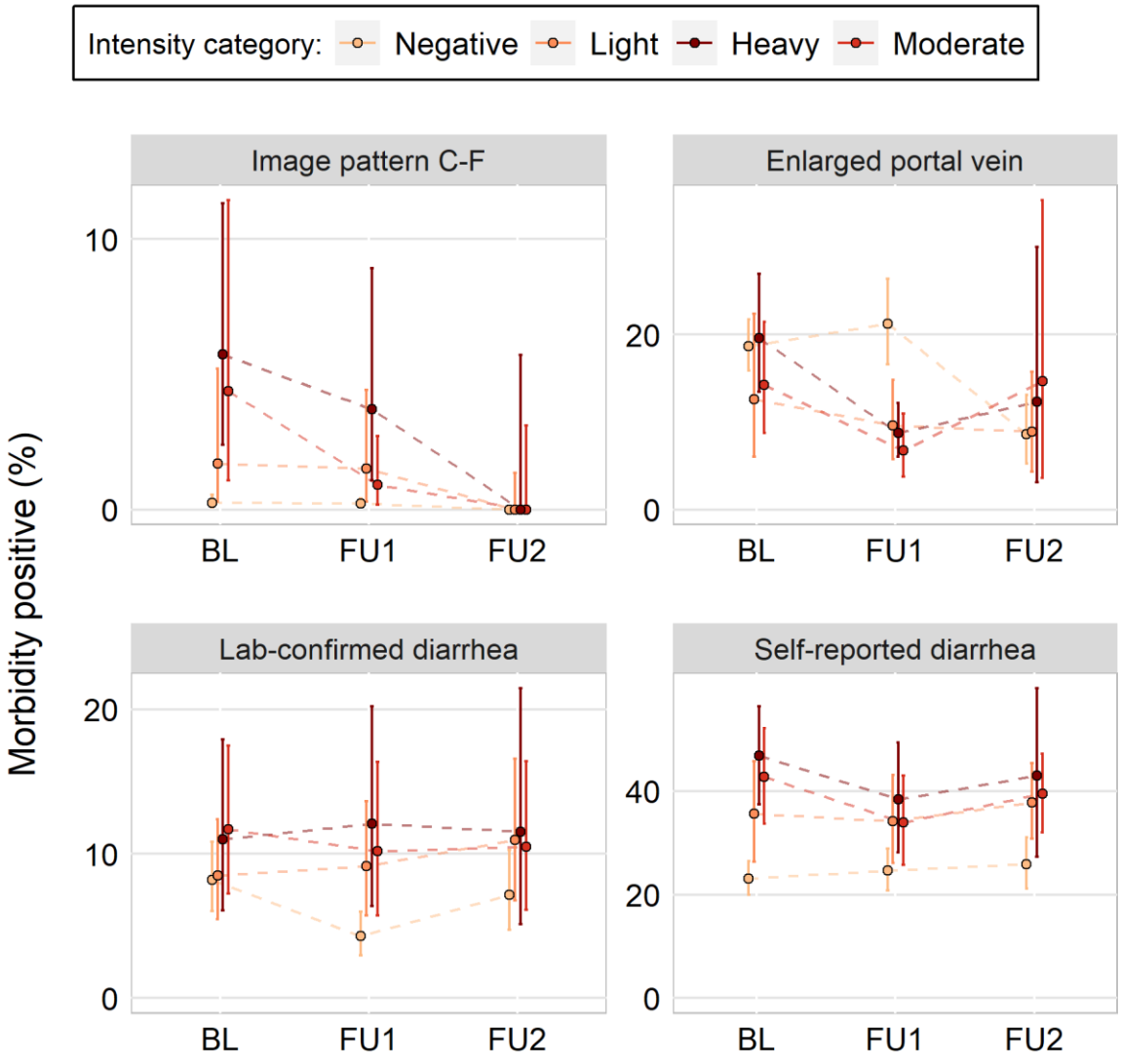
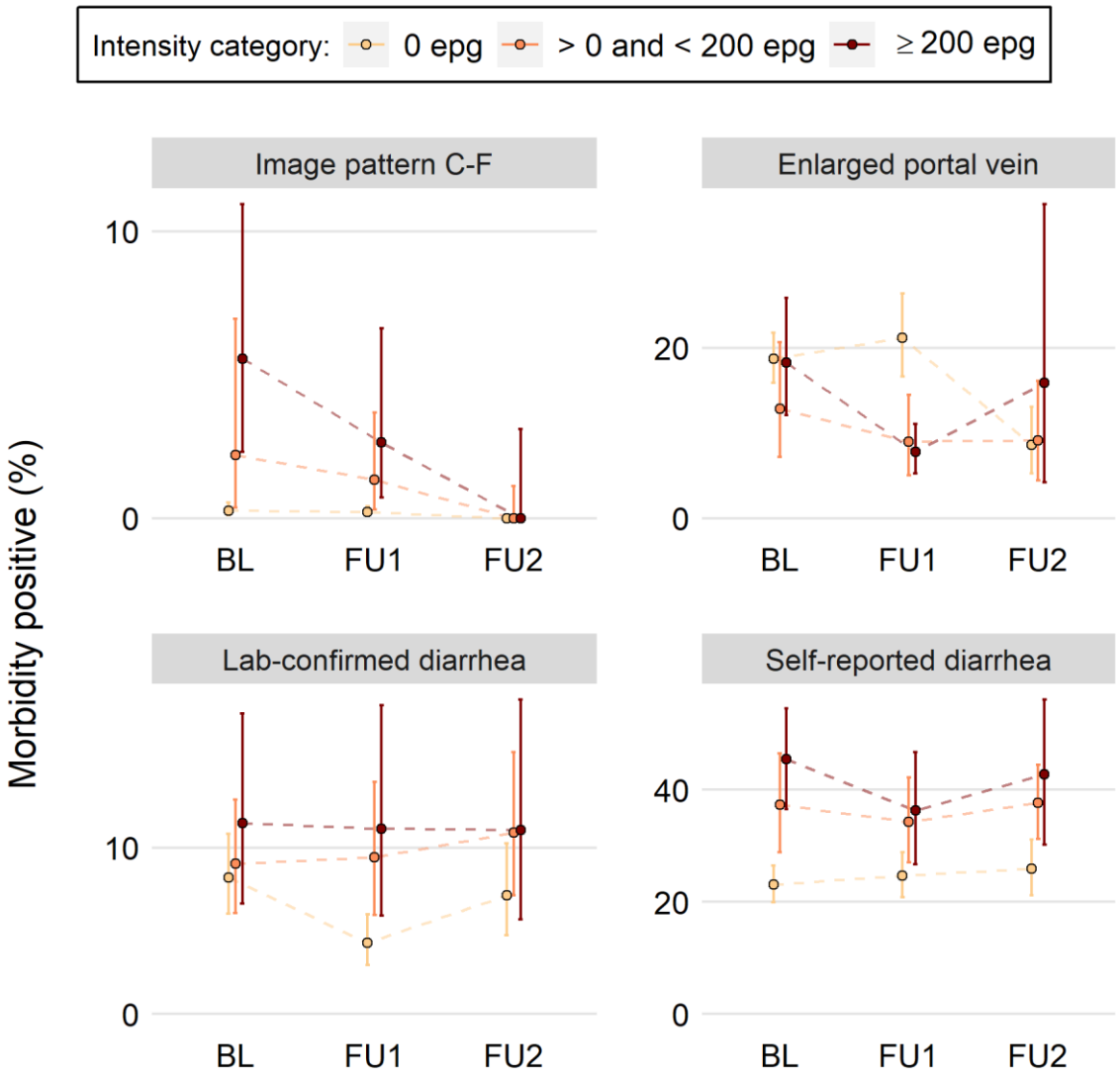


Table 5.4. Odds ratios (ORs) and 95% credible intervals from Bayesian logistic regression models comparing morbidity positive proportions between heavy-intensity prevalence categories within surveys for *S. mansoni*-related morbidities. Bold font indicates the 95% Bayesian credible interval (BCI) does not contain one. Participants are school-age children (6-15 years) enrolled between 2003 and 2008 in Mali, Niger, Tanzania, and Uganda.

Morbidity	Survey	Light v. Negative	Moderate v. Negative	Heavy v. Negative	Moderate v. Light	Heavy v. Light	Heavy v. Moderate
Image pattern C-F	Baseline	1.95 (0.79, 5.05)	2.08 (0.86, 5.39)	**3.97 (1.67, 10.19)**	1.06 (0.50, 2.29)	2.03 (0.97, 4.37)	1.91 (0.96, 3.85)
	Follow up 1	1.13 (0.45, 2.90)	0.70 (0.22, 2.12)	0.43 (0.07, 1.81)	0.62 (0.21, 1.68)	0.38 (0.06, 1.47)	0.62 (0.09, 2.69)
	Follow up 2	*	*	*	*	*	*
Enlarged portal vein	Baseline	0.98 (0.74, 1.27)	**1.53 (1.09, 2.13)**	**2.48 (1.86, 3.30)**	**1.57 (1.06, 2.31)**	**2.55 (1.79, 3.63)**	**1.62 (1.11, 2.39)**
	Follow up 1	1.18 (0.83, 1.65)	1.31 (0.86, 1.97)	1.25 (0.70, 2.12)	1.11 (0.68, 1.79)	1.06 (0.57, 1.91)	0.95 (0.49, 1.79)
	Follow up 2	1.34 (0.81, 2.12)	**3.29 (1.91, 5.47)**	**4.68 (2.24, 9.18)**	**2.46 (1.26, 4.82)**	**3.50 (1.52, 7.82)**	**1.42 (0.61, 3.23)**
Lab-confirmed diarrhea	Baseline	**1.32 (1.05, 1.66)**	**1.58 (1.23, 2.02)**	**1.69 (1.32, 2.15)**	1.20 (0.89, 1.60)	1.28 (0.96, 1.71)	1.07 (0.80, 1.44)
	Follow up 1	**1.77 (1.38, 2.27)**	**1.76 (1.28, 2.40)**	**1.68 (1.14, 2.43)**	0.99 (0.70, 1.40)	0.95 (0.63, 1.42)	0.96 (0.61, 1.48)
	Follow up 2	**1.47 (1.08, 1.97)**	1.32 (0.80, 2.11)	0.86 (0.42, 1.60)	0.90 (0.52, 1.51)	0.59 (0.28, 1.13)	0.65 (0.28, 1.41)
Self-reported diarrhea	Baseline	**1.17 (1.03, 1.33)**	**1.56 (1.34, 1.83)**	**1.43 (1.23, 1.66)**	**1.34 (1.11, 1.61)**	**1.22 (1.02, 1.46)**	0.91 (0.75, 1.11)
	Follow up 1	1.14 (0.98, 1.33)	1.18 (0.96, 1.45)	1.29 (1.00, 1.66)	1.04 (0.82, 1.32)	1.13 (0.86, 1.49)	1.09 (0.80, 1.48)
	Follow up 2	1.16 (0.97, 1.40)	1.29 (0.96, 1.73)	1.09 (0.76, 1.57)	1.11 (0.80, 1.54)	0.94 (0.64, 1.39)	0.85 (0.54, 1.33)

* Due to the low prevalence of image pattern C-F, all comparisons between categories were unstable and possessed a large amount of error uncertainty; and therefore they were omitted from this table.

Figure 5.4. Modification of Figure 5.3 where participants' *Schistosoma mansoni* intensity is split into three categories: 0 EPG, 1-199 EPG, and ≥200 EPG. See Figure 5.3 description for more details. Data are from three surveys (baseline, BL; follow-up 1, FU1; follow-up2, FU2).



5.6 Discussion

These analyses indicated that there were consistent associations between infection intensity categories and the prevalence of some morbidity indicators for children aged 6-15 years for *S. haematobium,* as measured prior to the initiation of preventive chemotherapy (the baseline survey) and before each subsequent round of

annual mass drug administration (follow-up 1 and follow-up 2 surveys). However, the same associations were not found for *S. mansoni* for the measures of morbidity that were collected. For the infection categories to effectively discriminate between morbidity directly associated with schistosomiasis, the odds of morbidity should be greater for a higher intensity category. ORs between *S. haematobium* infection intensity categories were largely consistent for most morbidity indicators before and after praziquantel administration. For example, across the three surveys, participants with light infection intensity infections had approximately two (or 15 to 30 without controlling for age and sex) times higher odds of microhematuria compared to participants without *S. haematobium* eggs in their urine. Consistent ORs were also found for heavy versus negative intensity. For *S. mansoni*, there was no morbidity measure where ORs between infection intensity categories were consistent. When raw prevalence and confidence intervals were plotted (Figure 5.3 and Supplemental Figure 5.4), the categories are indistinguishable as confidence intervals overlap for almost all categories. This transpired in the context of effective preventive chemotherapy programs (Deol et al. 2019).

Our analyses had some limitations. Only morbidity indicators that were measured in multiple countries were analyzed, meaning many indicators from the *S. mansoni* ultrasound protocol were omitted. Some of those indicators suffer from high intra-observer variability (Doehring-Schwerdtfeger et al. 1992b; Thomas et al. 1997; Sebastianes et al. 2010), which suggest that those measures may not have been as useful as anticipated. Of note, enlarged portal vein measurements were taken against the Senegalese population utilized in the Niamey protocol, which may not be an appropriate comparison given these data come from other countries. The collection of stools (for Kato-Katz thick smears) and urine (for urine filtrations) varied across countries. Furthermore, additional stool and urine samples would have provided a more accurate assessment of infection and infection intensity. Although similar data systems were used by most countries, there was variability in the data collected, meaning that only subsets of the SCI-supported countries appear in most analyses. While recommendations were made for an appropriate number of schools and participants per school to enroll, data collection was a part of monitoring and evaluation cohorts without specific hypotheses. In addition, control programs had the final say on sample sizes and utilized different approaches which were likely driven by

available financial and human resources in some countries. While we realize these sample size considerations influenced the analyses, we were limited in our ability to power these analyses appropriately given the context in which the data were collected. Finally, there is the potential for systematic selection bias in these analyses as the school-age children sampled from these communities may be consistently different from those who were not sampled. In addition, while some people were measured multiple times, others were not, meaning the loss to follow up is high in these data. Nevertheless, if the intensity categories, which are purported to measure a person's current infection status, have a robust relationship with morbidity, then we should see a similar relationship regardless of whether selection bias, heterogeneous age distributions, and other potential biases are present.

An important finding is that participants with light and moderate *S. haematobium* infections had elevated morbidity levels compared to their non-infected counterparts for ultrasound indicators and microhematuria. This appears to be at odds with the notion that morbidity is only caused by heavy-infections (Mott 2004) which has driven monitoring and evaluation goals for schistosomiasis (WHO 2002; 2011b; 2013). Our results add to the literature that morbidity is present in people with even light and moderate infections (King et al. 2005; King et al. 2008b) and strengthens the evidence-base that morbidity control should be based on any infection instead of heavy infections (King 2015).

We explored some potential reasons for the stronger association between *S. haematobium* infection categories and morbidity as compared to the *S. mansoni* infection categories and morbidity. One consideration was whether the poorer performance could be due to *S. mansoni* possessing a fourth intensity category compared to three for *S. haematobium*. Additional analyses were performed to evaluate whether separating *S. mansoni* intensity into three categories would improve discrimination. None of the multiple thresholds chosen hinted at an improvement to the association between infection intensity categories and morbidity.

Differences between species could be due to the diagnostic tests. Both the urine filtration and Kato-Katz techniques have considerable day-to-day variability (Utzinger et al. 2001; Vinkeles Melchers et al. 2014).

Separate studies of the day-to-day fluctuation in these tests using the intra-person correlation coefficient found reasonably similar estimates for *S. haematobium* in Gabon (0.81, 95% confidence interval (CI): 0.71-0.89) (Van Etten et al. 1997) and *S. mansoni* in Burundi (0.77, 95% CI: 0.66-0.85) (Polman et al. 1998). Though, the latter result differed from a study in Côte d'Ivoire where the intra-specimen variation of egg counts was 4.3 times higher than the day-to-day variability (Utzinger et al. 2001). A comparable analysis could not be found for *S. mansoni* egg counts, but this variation could explain the worse performance of the Kato-Katz technique. Finally, small changes in *S. mansoni* egg counts have a much larger effect on the final intensity measure than for *S. haematobium*. For a 10 ml sample of urine, 50 *S. haematobium* eggs are needed for a heavy-intensity infection. For a single Kato-Katz thick smear only 41.7mg of stool are utilized, and hence, 17 *S. mansoni* eggs on a slide are defined as a heavy-intensity infection. Thus, measuring an additional egg in a positive sample has a considerably larger effect in a Kato-Katz thick smear examination compared to a urine filtration test.

The age at which these morbidity indicators commonly develop was shown to hugely influence the association between infection category and microhematuria and may have an impact with other morbidity indicators. Microhematuria and ultrasound-related morbidity associated with *S. haematobium* has been found to be more prevalent in children, as compared to adults (King et al. 1988; van der Werf et al. 2004). Conversely, multiple studies have shown the risk for *S. mansoni* morbidity indicators of periportal fibrosis to be higher in adults, as compared to children (Boisier et al. 2001; King et al. 2003; Booth et al. 2004). This could be due to *S. haematobium* ultrasound indicators being observable sooner than *S. mansoni* ultrasound indicators and with the availability of more practical ultrasound examination equipment (Straily et al. 2021), potential challenges such as this will need to be addressed if such a tool will be programmatically useful. Regardless, the likelihood of *S. mansoni* morbidity indicators in these school-age participants was much lower than the likelihood of *S. haematobium* indicators and likely contributed to the poorer associations between *S. mansoni*-related morbidity indicators and *S. mansoni* infection prevalence. In addition, the lower prevalence of *S. mansoni* morbidity indicators potentially created a floor effect where *S. mansoni* indicators had less chance to decline as compared to *S. haematobium* indicators. We conjecture that with the large sample size and analyses of ratios, we have

guarded against this. Exploring how age and sex moderate relationships between morbidity and intensity categories will require a thorough evaluation.

Differences could also be due to variation in the effect of preventive chemotherapy. The follow-up time may not have been long enough for reductions in ultrasound to present at an aggregate level, especially for *S. mansoni*. For instance, past research suggested urinary tract pathology appears to reverse more rapidly than hepatic pathology (Richter 2003). More recent studies have suggested that *S. haematobium*-related morbidity improves in less than a year in school-aged children (Bocanegra et al. 2018) and in 1-2 years in adults (Magak et al. 2015), whereas liver pathologies have been shown to reduce in severity a year after initiation of treatment (Mohamed-Ali et al. 1991), but full resolution requires longer, approximately 2 years (Doehring-Schwerdtfeger et al. 1992a; Boisier et al. 1998).

Bias or error in measurement was also possible for morbidity evaluations, though it is unclear how this affected the differences in results by species. Both *S. haematobium* and *S. mansoni* ultrasounds have had reliable inter-observer agreement (el Scheich et al. 2014; Akpata et al. 2015), though there have been some differences in portal branch measurements (el Scheich et al. 2014) and portable ultrasonographic devices may have reduced sensitivity to detect bladder wall abnormalities (Akpata et al. 2015). The reliability of reagent strips is good for detecting infection (Stothard et al. 2014), and a meta-analysis found that sensitivity and specificity were 81% and 89%, respectively, compared to measurement of eggs in urine (King et al. 2013).

In addition, some morbidities presented here are not specific to schistosome infection. For ultrasonic measures, there is the possibility for other causes of morbidity. Indeed, hepatosplenic disease in the absence of periportal fibrosis in children has been observed (Vennervald et al. 2004; Davis et al. 2015) and associated with current or recent malaria infection (Samuels et al. 2012; Davis et al. 2015). This could be due to some organ enlargement being caused by malaria infection (Vennervald et al. 2004). There is potential that hepatitis C virus infection could lead to portal vein dilation (el Scheich et al. 2014), though this hypothesis is based on correlations at an aggregate level and may be due to different populations possessing different susceptibilities

to liver disease (Blanton et al. 2002). Hematuria, painful urination, blood in stool, diarrhea, and abdominal pain are not solely caused by schistosomiasis and may introduce bias into the results. Self-reported morbidity also has moderate diagnostic performance (Utzinger et al. 2000) and many sources of bias are possible from questionnaires (Delgado-Rodríguez et al. 2004). For these morbidities, reductions or lack thereof may not be wholly attributable to the decreases in infection and heavy-intensity infection observed after initiation of preventive chemotherapy.

5.7 Conclusion

Schistosoma infection intensity categories are utilized to evaluate disease burden and associate with other outcomes. The current analyses found that the infection intensity categories correlated reasonably well for *S. haematobium* but not for *S. mansoni*. Control programs and researchers that utilize *Schistosoma* infection intensity categories based on egg count thresholds should be aware that the *S. mansoni* categories do not appear to align with the morbidity indicators used in this study and that, for both schistosome species, low-intensity infections are not morbidity-free. These analyses show that heavy-intensity infections do not capture all morbidity in these school-age children. Control program infection thresholds for *S. mansoni* that utilize these intensity categories based on Kato-Katz thick smear examinations should be reconfigured in order to align with morbidity levels.

5.8 Declaration of interests

In the last five years, the authors have collaborated or are collaborating with preventive chemotherapy programs and have served on WHO advisory committees. Beyond this, the authors declare that they do not have any commercial or other association that might pose a conflict of interest.

5.9 Acknowledgments

The Schistosomiasis Control Initiative (now the SCI Foundation) was supported by the Bill and Melinda Gates Foundation (grant 13122). We thank all the school and community participants in the surveys of the national control programs; the staff of the national Ministries of Health for managing and implementing these programs; the Ministries of Health for granting the authors permission to access and reanalyze these data for the study;

and the past and present staff from the Schistosomiasis Control Initiative team. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

5.10 Supplemental Materials

5.10.1 Statistical Methods

Our outcome in all models was the presence of a morbidity, y_i, where

$$y_i = \begin{cases} 0, \text{if negative} \\ 1, \text{if positive} \end{cases}.$$

We assume

$$y_i \sim \text{Bernoulli}(p_i)$$

where i denotes an observation. p_i is forced to be bounded on $[0,1]$. For the logistic model, we assume a logit transform of the linear predictor, specifically

$$p_i = \frac{e^{\eta_i}}{1 + e^{\eta_i}}$$

where η_i is the linear predictor. The form of η_i depends on whether participant was sampled in multiple waves. We had n observations in the dataset, where $i = 1, \ldots, n_1$ come from children who were only sampled once during these three surveys and $i = n_1 + 1, \ldots, n_2$ come from children who were only sampled more than once. For the *Schistosoma haematobium* model, with $i = 1, \ldots, n_1$, we used the following equations since there are three intensity categories

$$\begin{aligned} \eta_i = {} & \beta_0 + \beta_1 * \text{Light}_i + \beta_2 * \text{Heavy}_i + \beta_3 * \text{FU1}_i + \beta_4 * \text{FU2}_i + \beta_5 * \text{Light}_i * \text{FU1}_i + \beta_6 * \text{Light}_i * \text{FU2}_i + \beta_7 \\ & * \text{Heavy}_i * \text{FU1}_i + \beta_8 * \text{Heavy}_i * \text{FU2}_i + \beta_{9_1} * \text{age}_{1,i} + \cdots + \beta_{9_j} * \text{age}_{j,i} + \beta_{10} * \text{female}_i + \beta_{11_1} \\ & * \text{country}_{1,i} + \cdots + \beta_{11_j} * \text{country}_{j,i} + \gamma_{1,k} \end{aligned}$$

and for $i = n_1 + 1, \ldots, n_2$,

$$\eta_i = \beta_0 + \beta_1 * \text{Light}_i + \beta_2 * \text{Heavy}_i + \beta_3 * \text{FU1}_i + \beta_4 * \text{FU2}_i + \beta_5 * \text{Light}_i * \text{FU1}_i + \beta_6 * \text{Light}_i * \text{FU2}_i + \beta_7 * \text{Heavy}_i * \text{FU1}_i + \beta_8 * \text{Heavy}_i * \text{FU2}_i + \beta_{9_1} * \text{age}_{1,i} + \cdots + \beta_{9_j} * \text{age}_{j,i} + \beta_{10} * \text{female}_i + \beta_{11_1} * \text{country}_{1,i} + \cdots + \beta_{11_j} * \text{country}_{j,i} + \gamma_{1,k} + \gamma_{2,l}$$

For the *S. mansoni* model, there is the additional intensity category, meaning the model becomes

$$\eta_i = \beta_0 + \beta_1 * \text{Light}_i + \beta_2 * \text{Moderate}_i + \beta_3 * \text{Heavy}_i + \beta_4 * \text{FU1}_i + \beta_5 * \text{FU2}_i + \beta_6 * \text{Light}_i * \text{FU1}_i + \beta_7 * \text{Moderate}_i * \text{FU1}_i + \beta_8 * \text{Heavy}_i * \text{FU1}_i + \beta_9 * \text{Light}_i * \text{FU2}_i + \beta_{10} * \text{Moderate}_i * \text{FU2}_i + \beta_{11} * \text{Heavy}_i * \text{FU2}_i + \beta_{12_1} * \text{age}_{1,i} + \cdots + \beta_{12_j} * \text{age}_{j,i} + \beta_{13} * \text{female}_i + \beta_{14_1} * \text{country}_{1,i} + \cdots + \beta_{14_j} * \text{country}_{j,i} + \gamma_{1,k}$$

and for $i = n_1 + 1, \ldots, n_2$,

$$\eta_i = \beta_0 + \beta_1 * \text{Light}_i + \beta_2 * \text{Moderate}_i + \beta_3 * \text{Heavy}_i + \beta_4 * \text{FU1}_i + \beta_5 * \text{FU2}_i + \beta_6 * \text{Light}_i * \text{FU1}_i + \beta_7 * \text{Moderate}_i * \text{FU1}_i + \beta_8 * \text{Heavy}_i * \text{FU1}_i + \beta_9 * \text{Light}_i * \text{FU2}_i + \beta_{10} * \text{Moderate}_i * \text{FU2}_i + \beta_{11} * \text{Heavy}_i * \text{FU2}_i + \beta_{12_1} * \text{age}_{1,i} + \cdots + \beta_{12_j} * \text{age}_{j,i} + \beta_{13} * \text{female}_i + \beta_{14_1} * \text{country}_{1,i} + \cdots + \beta_{14_j} * \text{country}_{j,i} + \gamma_{1,k} + \gamma_{2,l}$$

In these equations,

- β's are the coefficient estimates (on the log odds scale),
- Light_i is an indicator variable denoting whether observation i has a light infection,
- Moderate_i is an indicator variable denoting whether observation i has a moderate infection,
- Heavy_i is an indicator variable denoting whether observation i has a heavy infection,
- FU1_i equals 1 when observation i was ascertained in follow up 1,
- FU2_i equals 1 when observation i was ascertained in follow up 2,
- age_i is an indicator variable for the age of the participant treated as a category with 6 as the reference category to ages 7 to 15,
- female_i is an indicator variable for whether participant is a female with male as the reference category,

- country_i is an indicator variable for the country of the observation with j countries in each model where j depends on the morbidity studied, and
- $\gamma_{1,k}$ and $\gamma_{2,l}$ are random effects for school and person, respectively, where an observation is from school k and person l, with the latter only for $i = n_1 + 1, \ldots, n_2$.

All β's have Cauchy prior distribution with a center of zero and a scale of 2.5.(Gelman et al. 2008) For the random effect for school, $\gamma_{1,k} \sim \text{Normal}(0, \tau_1)$ where $\tau_1 = {\rho_1}^{-2}$ and ρ_1 is given a scaled Gamma prior with 1 degree of freedom and a scale of 25. This is equivalent to the standard deviation being distributed as a half-t distribution.(Gelman 2006) The random effect for person follows similarly.

Binomial models are fit in the same way, except $y_i \sim Bn(t_i, p_i)$ where y_i is the number of morbidity indicators present and t_i is the total number of morbidity indicator tests completed for observation i.

Specific estimates for the intensity categories by survey are then estimated by contrast statements.

5.10.2 Implementation

Models were fit via Markov Chain Monte Carlo using JAGS (Plummer 2003) and CODA (Plummer et al. 2006) in R via the rjags package (Plummer 2019). Three chains were fit with an adaptive phase of 20,000 iterations per chain. For the final model, the iterations from the adaptive phase were discarded and each chain was run for another 100,000 iterations. After completing the 100,000 iterations, graphical displays of the trace and densities functions were used to determine if any chains or a subset of iterations should be discarded. Results were then summarized.

5.10.3 JAGS model code for *S. haematobium* logistic model

```
model {
 for (i in 1:n.1) {
   y.1[i] ~ dbin(p.bound.1[i], 1)
   p.bound.1[i] <- max(0, min(1, p.1[i]))
   logit(p.1[i]) <- y.hat.1[i]

   y.hat.1[i] <- fixed.1[i] + random2.1[i]

   random2.1[i] <- r2.b0[r2.cluster.i[i]]
   fixed.1[i] <- inprod(b[1:P], X.1[i,1:P])
```

```
}

for (i in 1:n.2) {
  y.2[i] ~ dbin(p.bound.2[i], 1)
  p.bound.2[i] <- max(0, min(1, p.2[i]))
  logit(p.2[i]) <- y.hat.2[i]

  y.hat.2[i] <- fixed.2[i] + random1.2[i] + random2.2[i]

  random1.2[i] <- r1.b0[r1.cluster.i[i]]
  random2.2[i] <- r2.b0[r2.cluster.i[i]]
  fixed.2[i] <- inprod(b[1:P], X.2[i,1:P])
}

for (j in 1:r1.cluster.n) {
  r1.b0[j] ~ dnorm(r1.b0.mu, r1.b0.tau)
  r1.b0.hat[j] <- r1.b0.mu
}
r1.b0.mu <- 0
r1.b0.tau <- pow(r1.b0.noise, -2)
r1.b0.noise ~ dscaled.gamma(25, 1)

for (j in 1:r2.cluster.n) {
  r2.b0[j] ~ dnorm(r2.b0.mu, r2.b0.tau)
  r2.b0.hat[j] <- r2.b0.mu
}
r2.b0.mu <- 0
r2.b0.tau <- pow(r2.b0.noise, -2)
r2.b0.noise ~ dscaled.gamma(25, 1)

for (f in 1:P) {
   b[f] ~ dt(0, pow(2.5,-2), 1)
}

c[1] <- b[4]
c[2] <- b[4] + b[6]
c[3] <- b[4] + b[7]
c[4] <- b[5]
c[5] <- b[5] + b[8]
c[6] <- b[5] + b[9]
c[7] <- b[5] - b[4]
c[8] <- b[5] + b[8] - b[4] - b[6]
c[9] <- b[5] + b[9] - b[4] - b[7]
c[10] <- b[2]
c[11] <- b[3]
c[12] <- b[3] - b[2]
c[13] <- b[2] + b[6]
c[14] <- b[3] + b[7]
c[15] <- b[3] + b[7] - b[2] - b[6]
c[16] <- b[2] + b[8]
```

```
  c[17] <- b[3] + b[9]
  c[18] <- b[3] + b[9] - b[2] - b[8]

  for (g in 1:P) {
    pr.b[g] <- step(b[g])
  }
  for (h in 1:18) {
    pr.c[h] <- step(c[h])
  }
}
```

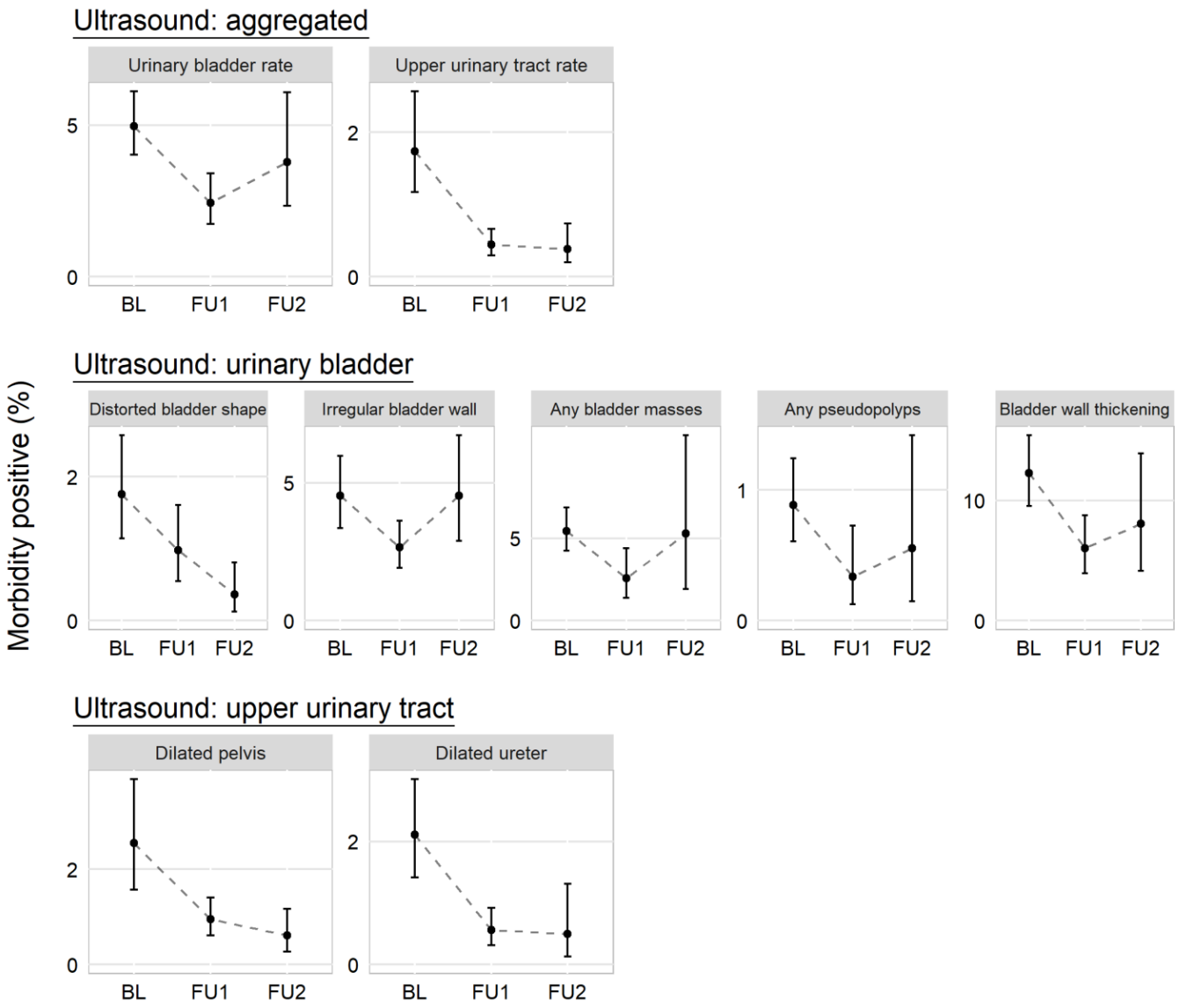
5.10.4 JAGS model code for *S. mansoni* logistic model

```
model {
  for (i in 1:n.1) {
    y.1[i] ~ dbin(p.bound.1[i], 1)
    p.bound.1[i] <- max(0, min(1, p.1[i]))
    logit(p.1[i]) <- y.hat.1[i]

    y.hat.1[i] <- fixed.1[i] + random2.1[i]

    random2.1[i] <- r2.b0[r2.cluster.i[i]]
    fixed.1[i] <- inprod(b[1:P], X.1[i,1:P])
  }

  for (i in 1:n.2) {
    y.2[i] ~ dbin(p.bound.2[i], 1)
    p.bound.2[i] <- max(0, min(1, p.2[i]))
    logit(p.2[i]) <- y.hat.2[i]

    y.hat.2[i] <- fixed.2[i] + random1.2[i] + random2.2[i]

    random1.2[i] <- r1.b0[r1.cluster.i[i]]
    random2.2[i] <- r2.b0[r2.cluster.i[i]]
    fixed.2[i] <- inprod(b[1:P], X.2[i,1:P])
  }

  for (j in 1:r1.cluster.n) {
    r1.b0[j] ~ dnorm(r1.b0.mu, r1.b0.tau)
    r1.b0.hat[j] <- r1.b0.mu
  }
  r1.b0.mu <- 0
  r1.b0.tau <- pow(r1.b0.noise, -2)
  r1.b0.noise ~ dscaled.gamma(25, 1)

  for (j in 1:r2.cluster.n) {
    r2.b0[j] ~ dnorm(r2.b0.mu, r2.b0.tau)
    r2.b0.hat[j] <- r2.b0.mu
  }
  r2.b0.mu <- 0
```

```
  r2.b0.tau <- pow(r2.b0.noise, -2)
  r2.b0.noise ~ dscaled.gamma(25, 1)

  for (f in 1:P) {
    b[f] ~ dt(0, pow(2.5,-2), 1)
  }
  c[1] <- b[5]
  c[2] <- b[5] + b[7]
  c[3] <- b[5] + b[8]
  c[4] <- b[5] + b[9]
  c[5] <- b[6]
  c[6] <- b[6] + b[10]
  c[7] <- b[6] + b[11]
  c[8] <- b[6] + b[12]
  c[9] <- b[6] - b[5]
  c[10] <- b[6] + b[10] - b[5] - b[7]
  c[11] <- b[6] + b[11] - b[5] - b[8]
  c[12] <- b[6] + b[12] - b[5] - b[9]
  c[13] <- b[2]
  c[14] <- b[3]
  c[15] <- b[4]
  c[16] <- b[3] - b[2]
  c[17] <- b[4] - b[2]
  c[18] <- b[4] - b[3]
  c[19] <- b[2] + b[7]
  c[20] <- b[3] + b[8]
  c[21] <- b[4] + b[9]
  c[22] <- b[3] + b[8] - b[2] - b[7]
  c[23] <- b[4] + b[9] - b[2] - b[7]
  c[24] <- b[4] + b[9] - b[3] - b[8]
  c[25] <- b[2] + b[10]
  c[26] <- b[3] + b[11]
  c[27] <- b[4] + b[12]
  c[28] <- b[3] + b[11] - b[2] - b[10]
  c[29] <- b[4] + b[12] - b[2] - b[10]
  c[30] <- b[4] + b[12] - b[3] - b[11]

  for (g in 1:P) {
    pr.b[g] <- step(b[g])
  }
  for (h in 1:30) {
    pr.c[h] <- step(c[h])
  }
}
```

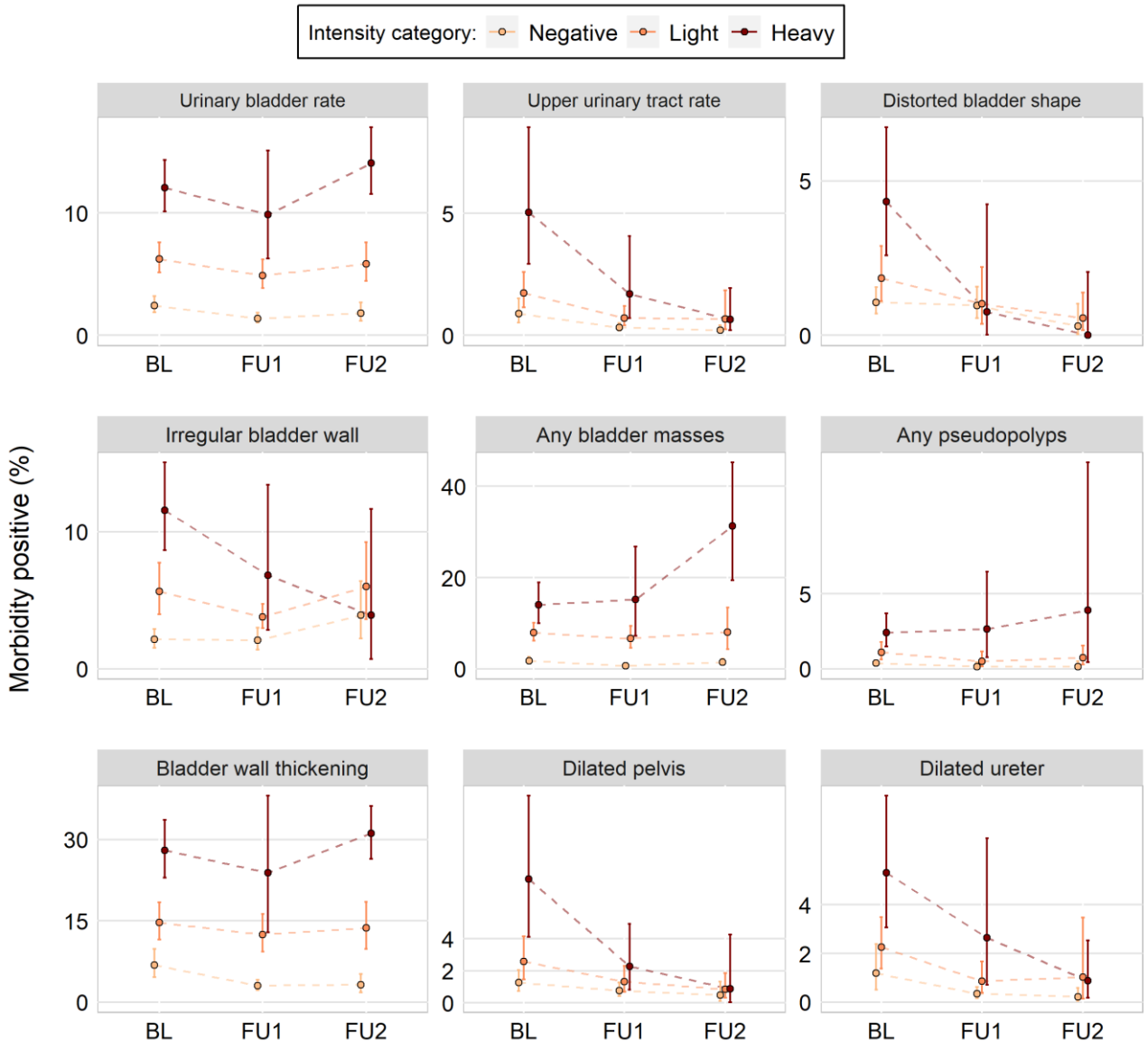
5.10.5 Supplemental Figures

Supplemental Figure 5.1. Line graphs of the percentage of 6-15 year-old school children who were *Schistosoma haematobium*-related morbidity positive at each survey year (baseline, BL; follow-up 1, FU1; follow-up2, FU2). Estimates are from Mali, Niger, and Tanzania for all indicators. Data from Burkina Faso are included in laboratory and self-report indicators. Clustering by school accounted for in 95% confidence bands.



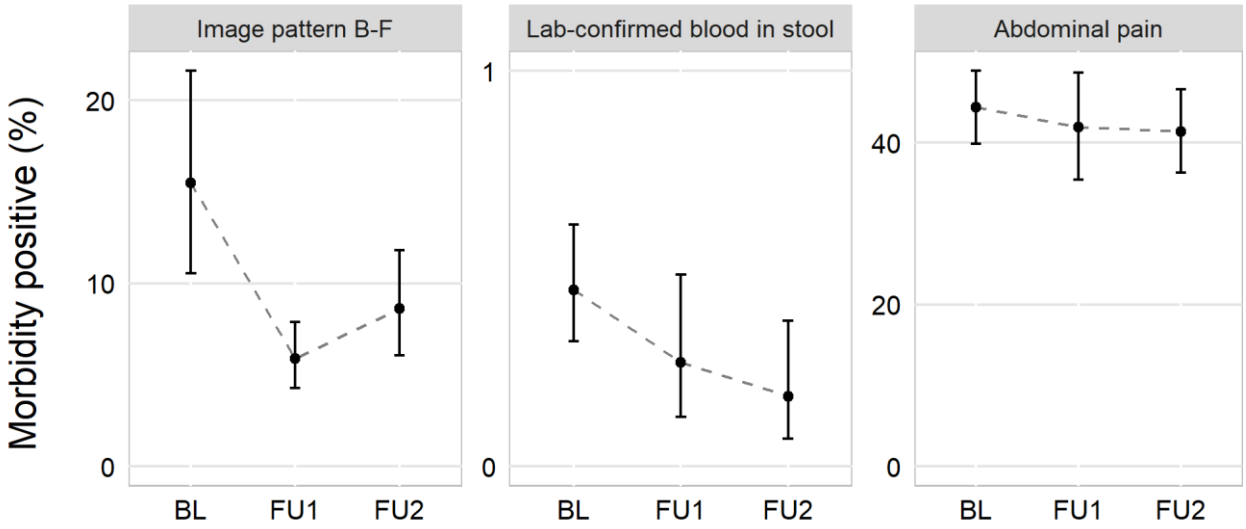
Note: Aggregated ultrasound measures include both dilated left and right pelvis and both visualized left and right ureters, but results shown for dilated pelvis and visualized ureter combine the left and right indicators into a single, binary variable of present in either or not present in either.

Supplemental Figure 5.2. Line graphs of *Schistosoma haematobium*-related morbidity percentages including those for individual morbidity sub-scores not included in Figure 2 across three surveys (baseline, BL; follow-up 1, FU1; follow-up2, FU2). Participants were enrolled between 2003 and 2008 in Mali, Niger, and Tanzania. Clustering by school accounted for in 95% confidence bands. Infections were assessed by urine filtration.

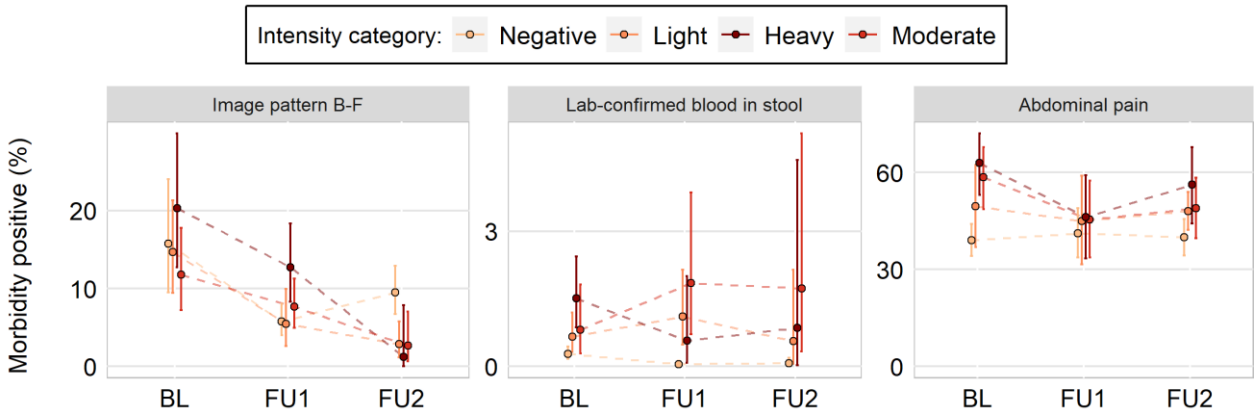


Note: Aggregated ultrasound measures include both dilated left and right pelvis and both visualized left and right ureters, but results shown for dilated pelvis and visualized ureter combine the left and right indicators into a single, binary variable of present in either or not present in either.

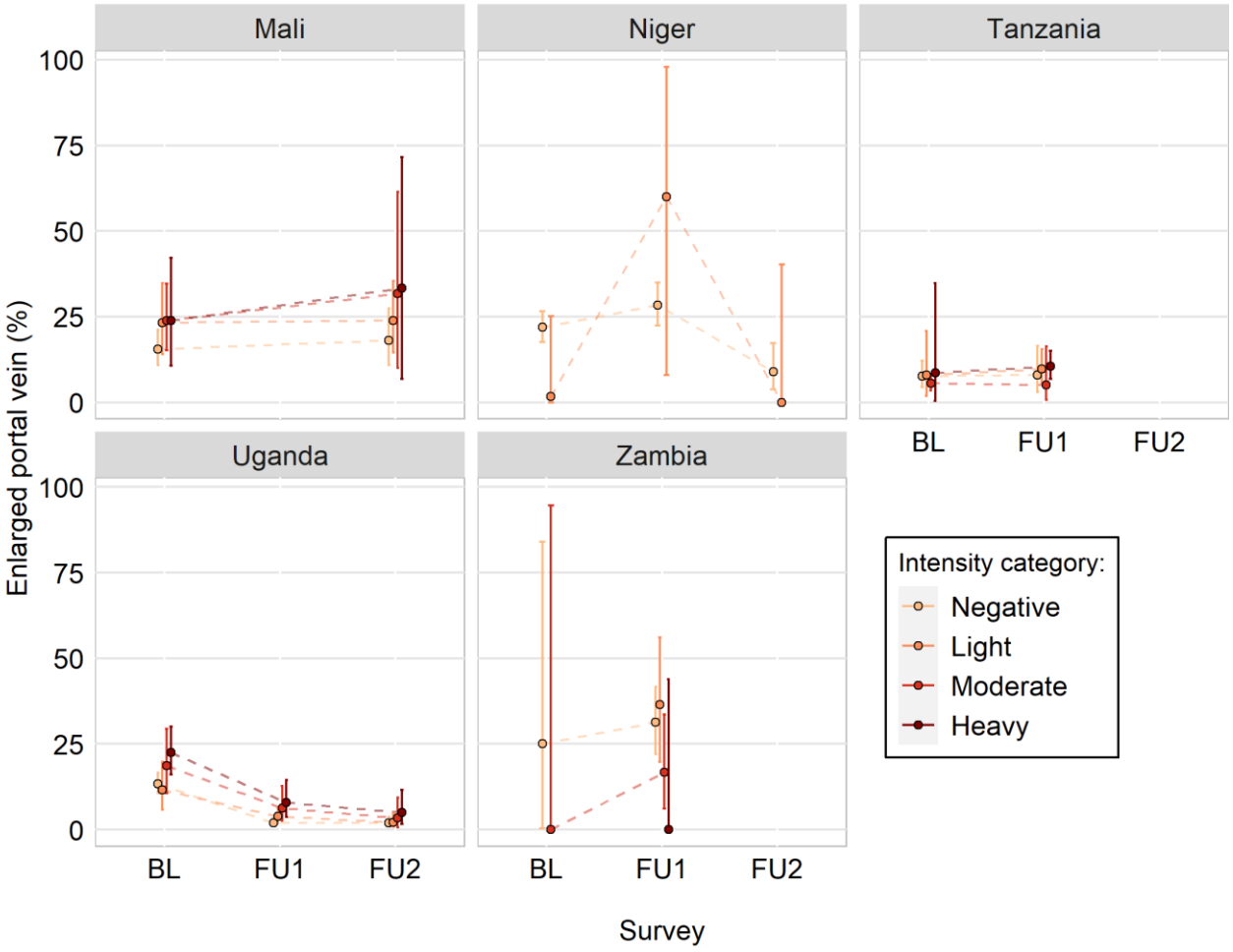
Supplemental Figure 5.3. Line graphs of the percentage of 6-15 year-old school children who were *Schistosoma mansoni*-related morbidity positive at each survey year (baseline, BL; follow-up 1, FU1; follow-up2, FU2). Estimates are from Mali, Niger, Tanzania, and Uganda. Clustering by school accounted for in 95% confidence bands.



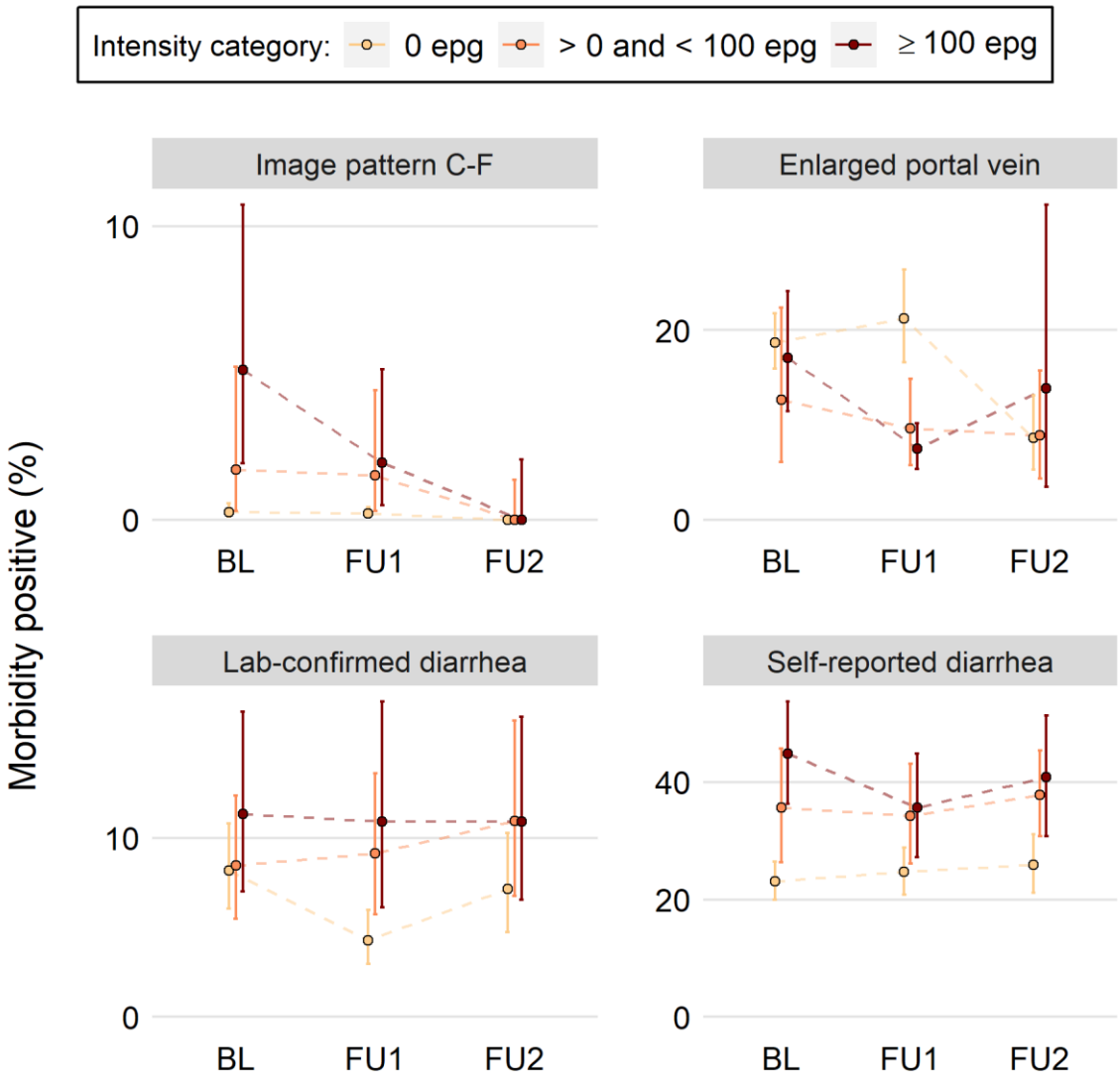
Supplemental Figure 5.4. Line graphs of *Schistosoma mansoni*-related morbidity percentages including morbidity scores that were not included in Figure 5.3, across three surveys (baseline, BL; follow-up 1, FU1; follow-up2, FU2). Participants were enrolled between 2003 and 2008 in Mali, Niger, Tanzania, Uganda, and Zambia. Clustering by school accounted for in 95% confidence bands. Infections were assessed by Kato-Katz.



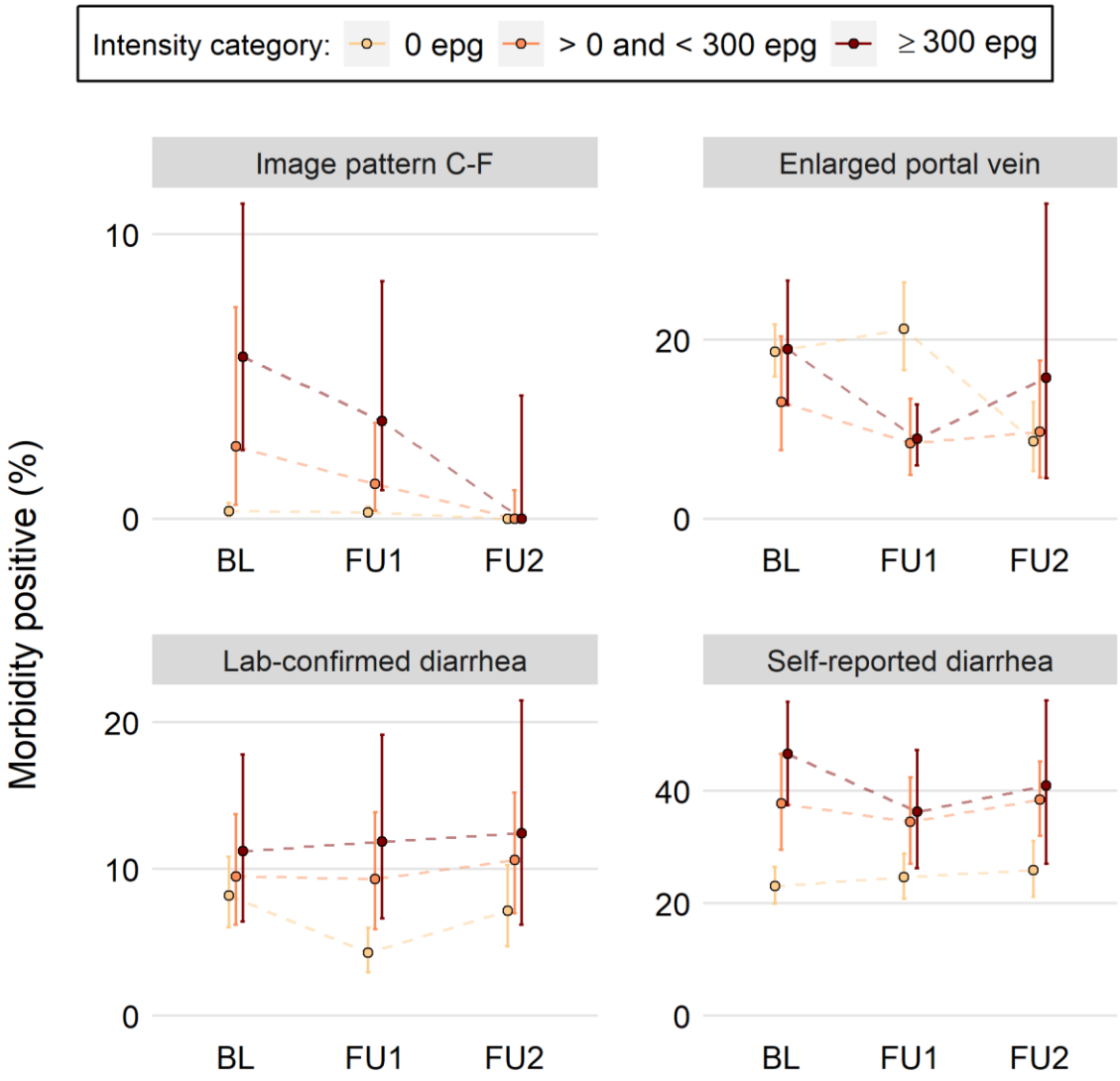
Supplemental Figure 5.5. Line graphs of enlarged portal vein percentage by intensity category by country across three surveys (baseline, BL; follow-up 1, FU1; follow-up2, FU2). Participants were enrolled between 2003 and 2008. Clustering by school accounted for in 95% confidence bands. Infections were assessed by Kato-Katz thick smears.



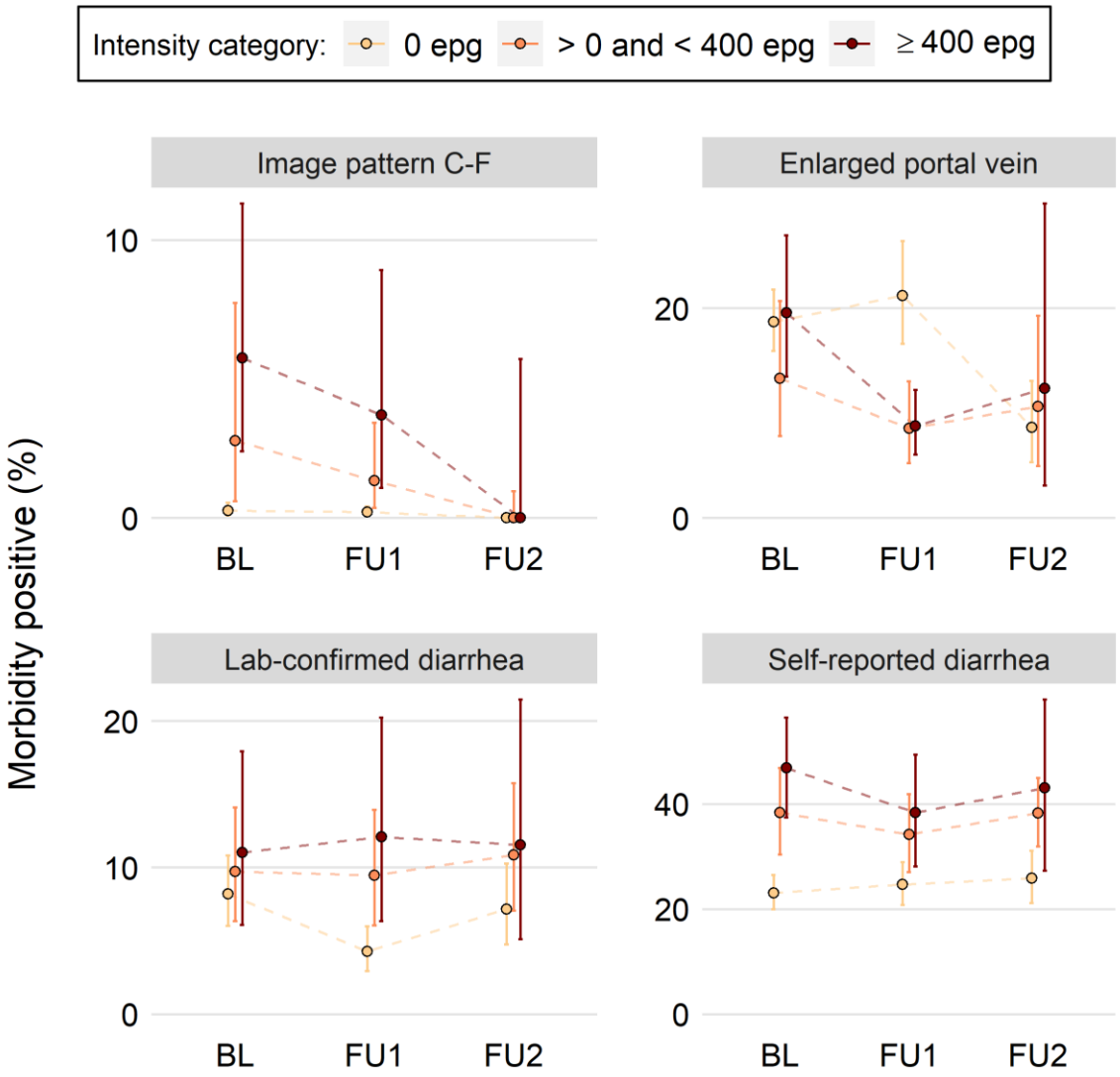
Supplemental Figure 5.6. Modification of Figure 5.4 where participants' *Schistosoma mansoni* intensity at each survey is split into three categories: 0 EPG, 1-99 EPG, and ≥100 EPG. See Figure 5 description for more details. Data are from three surveys (baseline, BL; follow-up 1, FU1; follow-up2, FU2).



Supplemental Figure 5.7. Modification of Figure 5.4 where participants' *Schistosoma mansoni* intensity at each survey is split into three categories: 0 EPG, 1-299 EPG, and ≥300 EPG. See Figure 5 description for more details. Data are from three surveys (baseline, BL; follow-up 1, FU1; follow-up2, FU2).



Supplemental Figure 5.8. Modification of Figure 5.4 where participants' *Schistosoma mansoni* intensity at each survey is split into three categories: 0 EPG, 1-399 EPG, and ≥400 EPG. See Figure 5 description for more details. Data are from three surveys (baseline, BL; follow-up 1, FU1; follow-up2, FU2).



5.10.6 Supplemental Tables

Supplemental Table 5.1. Dates of participant ascertainment in monitoring and evaluation cohorts. Shading indicates surveys that were included in analyses. Treatment was usually immediately following survey times, but occasionally lagged by a few months.

Country	Site selection	Baseline	Follow up 1	Follow up 2
Burkina Faso	Highly endemic areas	2004	No treatment and all schools removed from analyses	All schools removed at prior follow up
Mali	Highly endemic areas	March-April 2004 (Ségou); May-July 2004 (Bamako); June-August 2004 (Koulikoro)	Two treatments during the year were performed in Ségou and those locations were dropped from further analyses; Other schools treated but not evaluated	April-May and October 2006 (Bamako); May 2006 (Koulikoro)
Niger	Endemic areas (5 schools); Integrated control areas with lymphatic filariasis and trachoma (3 schools)	October-November 2004 and March-May 2005 (5 schools); 2008 (3 schools)	October-December 2005 and March-April 2006 (5 schools); 2009 (3 schools)	November-December 2006 and January, March, April, and May 2007 (5 schools); February 2010 (3 schools)
Tanzania	Coastal areas with high prevalence	March-September 2005	March-September 2006	No treatment and no evaluation
Uganda	Eight districts with different transmission settings	February-March, March-April, October November 2003	February-March, March-April, October-November 2004	February-March, March-April, October-November 2005
Zambia	Areas at high risk of infection	July-August 2005 and May-June 2006	September 2006 and May-June 2007	No treatment and no evaluation

Supplemental Table 5.2. Participants included in analyses of *Schistosoma haematobium* infection intensity categories. Numbers in parentheses indicate the number of schools from which participants were sampled.

		Intensity category		
Morbidity	Survey	Negative	Light	Heavy
Ultrasound: aggregated				
Any urinary bladder lesions	Baseline	5333 (70)	3126 (68)	1305 (60)
	Follow up 1	4635 (37)	1374 (34)	264 (29)
	Follow up 2	2313 (22)	1058 (22)	228 (17)
Any upper urinary tract lesions	Baseline	5305 (69)	3118 (68)	1315 (60)
	Follow up 1	4626 (37)	1374 (34)	264 (29)
	Follow up 2	2316 (22)	1070 (22)	229 (18)
Urinary bladder rate	Baseline	5348 (70)	3139 (68)	1330 (60)
	Follow up 1	4643 (37)	1376 (34)	264 (29)
	Follow up 2	2324 (22)	1071 (22)	231 (18)
Upper urinary tract rate	Baseline	5337 (69)	3138 (68)	1329 (60)
	Follow up 1	4642 (37)	1377 (34)	264 (29)
	Follow up 2	2325 (22)	1072 (22)	231 (18)
Ultrasound: urinary bladder				
Distorted bladder shape	Baseline	5338 (70)	3134 (68)	1317 (60)
	Follow up 1	4638 (37)	1374 (34)	264 (29)
	Follow up 2	2317 (22)	1063 (22)	229 (17)
Irregular bladder wall	Baseline	5343 (70)	3138 (68)	1323 (60)
	Follow up 1	4643 (37)	1376 (34)	264 (29)
	Follow up 2	2320 (22)	1069 (22)	231 (18)
Any bladder masses	Baseline	5347 (70)	3138 (68)	1329 (60)
	Follow up 1	4642 (37)	1376 (34)	264 (29)
	Follow up 2	2320 (22)	1069 (22)	230 (18)
Any pseudopolyps	Baseline	5346 (70)	3135 (68)	1325 (60)
	Follow up 1	4641 (37)	1376 (34)	264 (29)
	Follow up 2	2320 (22)	1071 (22)	231 (18)
Bladder wall thickening	Baseline	5345 (70)	3135 (68)	1323 (60)
	Follow up 1	4643 (37)	1376 (34)	264 (29)
	Follow up 2	2320 (22)	1070 (22)	231 (18)
Ultrasound: upper urinary tract				
Dilated left or right pelvis	Baseline	5312 (69)	3122 (68)	1324 (60)
	Follow up 1	4628 (37)	1375 (34)	264 (29)
	Follow up 2	2318 (22)	1071 (22)	231 (18)
Visualized left or right ureter	Baseline	5330 (69)	3134 (68)	1319 (60)
	Follow up 1	4639 (37)	1376 (34)	264 (29)
	Follow up 2	2320 (22)	1071 (22)	229 (18)

Laboratory and self-report				
Microhematuria	Baseline	6221 (91)	3773 (88)	1954 (77)
	Follow up 1	5285 (41)	1386 (36)	270 (31)
	Follow up 2	2354 (22)	1084 (22)	234 (18)
Pain while urinating	Baseline	5973 (83)	3382 (80)	1703 (70)
	Follow up 1	5258 (41)	1385 (36)	271 (31)
	Follow up 2	2328 (22)	1076 (22)	233 (18)

Supplemental Table 5.3. Odds ratios and 95% confidence intervals from Bayesian logistic regression models comparing morbidity positive proportions between *S. haematobium* intensity categories that were not included in Table 2. Bold font indicates the 95% credible interval does not contain one. Participants are school-aged children, aged 6-15 years, enrolled between 2003 and 2008 in Mali, Niger, and Tanzania for all indicators and Burkina Faso, Mali, Niger, and Tanzania for laboratory and self-report indicators. *S. haematobium* assessed by urine filtration.

Morbidity	Survey	Light v. Negative	Heavy v. Negative	Heavy v. Light
Ultrasound: aggregated				
Urinary bladder rate	Baseline	**1.45 (1.29, 1.63)**	**1.65 (1.42, 1.90)**	1.14 (1.00, 1.30)
	Follow up 1	**1.50 (1.31, 1.71)**	**1.42 (1.09, 1.83)**	0.95 (0.73, 1.23)
	Follow up 2	**1.94 (1.59, 2.37)**	**2.59 (1.95, 3.42)**	**1.34 (1.01, 1.75)**
Upper urinary tract rate	Baseline	**1.32 (1.03, 1.69)**	**1.57 (1.18, 2.10)**	1.19 (0.93, 1.52)
	Follow up 1	**1.45 (1.04, 2.00)**	1.31 (0.74, 2.24)	0.91 (0.50, 1.58)
	Follow up 2	**2.09 (1.14, 3.87)**	1.53 (0.50, 3.98)	0.73 (0.24, 1.87)
Ultrasound: urinary bladder				
Distorted bladder shape	Baseline	**1.91 (1.28, 2.83)**	**2.39 (1.43, 3.94)**	1.25 (0.77, 2.01)
	Follow up 1	1.61 (0.78, 3.10)	2.59 (0.97, 5.89)	1.61 (0.54, 4.44)
	Follow up 2	0.28 (0.02, 1.39)	1.43 (0.11, 7.29)	5.08 (0.29, 96.12)
Irregular bladder wall	Baseline	**1.55 (1.21, 1.97)**	**1.93 (1.43, 2.58)**	1.25 (0.95, 1.64)
	Follow up 1	**1.44 (1.04, 1.99)**	1.58 (0.83, 2.80)	1.09 (0.56, 2.00)
	Follow up 2	1.49 (0.99, 2.22)	1.27 (0.55, 2.58)	0.85 (0.36, 1.76)
Any bladder masses	Baseline	**1.44 (1.13, 1.85)**	1.28 (0.93, 1.75)	0.89 (0.66, 1.18)
	Follow up 1	**1.83 (1.42, 2.38)**	**1.96 (1.21, 3.06)**	1.07 (0.66, 1.66)
	Follow up 2	**2.35 (1.60, 3.46)**	**3.04 (1.80, 5.06)**	1.29 (0.79, 2.07)
Any pseudopolyps	Baseline	1.09 (0.61, 1.90)	1.49 (0.74, 2.86)	1.36 (0.68, 2.63)
	Follow up 1	1.69 (0.86, 3.24)	1.03 (0.19, 3.48)	0.61 (0.11, 2.17)
	Follow up 2	2.00 (0.57, 7.19)	**6.38 (1.52, 25.48)**	3.19 (0.74, 12.63)
Bladder wall thickening	Baseline	**1.47 (1.23, 1.76)**	**1.88 (1.52, 2.33)**	**1.28 (1.05, 1.56)**
	Follow up 1	**1.44 (1.19, 1.75)**	1.16 (0.78, 1.69)	0.81 (0.54, 1.18)
	Follow up 2	**2.47 (1.84, 3.32)**	**3.54 (2.36, 5.29)**	1.43 (0.97, 2.09)
Ultrasound: upper urinary tract				
Dilated left or right pelvis	Baseline	1.35 (0.93, 1.95)	**1.92 (1.26, 2.90)**	1.42 (0.98, 2.06)
	Follow up 1	1.39 (0.87, 2.18)	1.85 (0.87, 3.61)	1.34 (0.62, 2.67)
	Follow up 2	1.68 (0.70, 4.07)	0.69 (0.05, 3.34)	0.41 (0.03, 2.05)
Visualized left or right ureter	Baseline	1.36 (0.91, 2.03)	1.49 (0.92, 2.40)	1.10 (0.70, 1.69)
	Follow up 1	1.43 (0.85, 2.38)	1.49 (0.56, 3.37)	1.04 (0.39, 2.40)
	Follow up 2	1.91 (0.77, 4.86)	1.86 (0.43, 6.42)	0.97 (0.22, 3.30)
Laboratory and self-report				
Pain while urinating	Baseline	**1.19 (1.07, 1.34)**	**1.58 (1.38, 1.81)**	**1.32 (1.15, 1.52)**
	Follow up 1	1.02 (0.87, 1.20)	0.93 (0.67, 1.27)	0.91 (0.65, 1.27)

	Follow up 2	**1.27 (1.06, 1.54)**	1.26 (0.90, 1.77)	0.99 (0.70, 1.40)

Supplemental Table 5.4. Participants included in cross-sectional analyses of *Schistosoma mansoni* infection intensity categories. Numbers in parentheses indicate the number of schools from which participants were sampled.

Morbidity	Survey	Negative	Light	Moderate	Heavy
Ultrasound					
Irregular image pattern (B-F or C-F)	Baseline	3590 (54)	648 (39)	433 (25)	487 (23)
	Follow up 1	4229 (51)	730 (37)	325 (27)	189 (24)
	Follow up 2	4009 (43)	348 (29)	150 (18)	80 (17)
Enlarged portal vein	Baseline	3539 (51)	665 (37)	456 (25)	516 (23)
	Follow up 1	3820 (47)	541 (36)	326 (27)	194 (24)
	Follow up 2	4015 (43)	349 (29)	150 (18)	81 (17)
Laboratory					
Lab-confirmed blood in stool	Baseline	10324 (108)	1373 (70)	858 (50)	928 (47)
	Follow up 1	9417 (82)	1178 (52)	541 (38)	348 (37)
	Follow up 2	5390 (40)	536 (34)	173 (21)	117 (20)
Lab-confirmed diarrhea	Baseline	8398 (96)	1358 (67)	857 (50)	926 (47)
	Follow up 1	6778 (74)	1173 (50)	541 (38)	348 (37)
	Follow up 2	2996 (35)	584 (33)	191 (23)	130 (22)
Self-report					
Self-reported diarrhea	Baseline	11242 (121)	1603 (87)	999 (61)	1091 (55)
	Follow up 1	9325 (80)	1157 (50)	524 (36)	339 (35)
	Follow up 2	6137 (57)	700 (46)	251 (29)	151 (25)
Abdominal pain	Baseline	6229 (80)	1125 (62)	648 (48)	918 (43)
	Follow up 1	5532 (46)	858 (37)	326 (27)	232 (27)
	Follow up 2	6131 (57)	699 (46)	251 (29)	151 (25)

Supplemental Table 5.5. Odds ratios and 95% confidence intervals from Bayesian logistic regression models comparing morbidity positive proportions between intensity categories within surveys for *S. mansoni*-related morbidities that were not included in Table 5.3. Bold font indicates the 95% credible interval does not contain one. Participants are school-aged children, aged 6-15 years, enrolled between 2003 and 2008 in Mali, Niger, Tanzania, and Uganda.

Morbidity	Intensity category	Light v. Negative	Moderate v. Negative	Heavy v. Negative	Moderate v. Light	Heavy v. Light	Heavy v. Moderate
Image pattern B-F	**Baseline**	**1.74 (1.30, 2.31)**	**1.59 (1.11, 2.24)**	1.17 (0.84, 1.62)	0.91 (0.62, 1.34)	0.67 (0.46, 0.98)	0.74 (0.49, 1.11)
	Follow up 1	1.19 (0.82, 1.69)	**1.93 (1.23, 2.95)**	**2.16 (1.24, 3.60)**	1.62 (0.97, 2.70)	1.82 (0.99, 3.25)	1.12 (0.59, 2.08)
	Follow up 2	**0.56 (0.31, 0.94)**	**0.38 (0.12, 0.91)**	0.32 (0.06, 1.02)	0.67 (0.19, 1.90)	0.57 (0.10, 2.05)	0.85 (0.13, 4.27)
Lab-confirmed blood in stool	Baseline	**2.46 (1.07, 5.23)**	2.40 (0.88, 5.70)	**3.53 (1.49, 7.83)**	0.98 (0.33, 2.72)	1.44 (0.55, 3.74)	1.48 (0.52, 4.44)
	Follow up 1	**3.50 (1.54, 7.50)**	**3.67 (1.30, 8.92)**	**3.91 (1.14, 10.79)**	1.05 (0.35, 2.82)	1.12 (0.31, 3.44)	1.07 (0.27, 3.82)
	Follow up 2	4.29 (0.91, 17.42)	0.23 (0.00, 7.51)	0.34 (0.00, 11.21)	0.05 (0.00, 2.22)	0.08 (0.00, 3.27)	*
Abdominal pain	Baseline	1.13 (0.98, 1.32)	1.14 (0.95, 1.38)	**1.32 (1.12, 1.55)**	1.01 (0.81, 1.26)	1.16 (0.95, 1.42)	1.15 (0.92, 1.44)
	Follow up 1	1.08 (0.91, 1.29)	1.03 (0.80, 1.33)	0.90 (0.67, 1.21)	0.95 (0.72, 1.27)	0.83 (0.60, 1.15)	0.88 (0.61, 1.26)
	Follow up 2	0.90 (0.75, 1.08)	1.11 (0.83, 1.47)	1.17 (0.82, 1.68)	1.23 (0.89, 1.69)	1.30 (0.89, 1.91)	1.06 (0.68, 1.64)

* The odds ratio for this effect was highly variable due to the prevalence at both surveys being close to zero. We chose to omit this effect due to its instability.

6 Control and elimination of schistosomiasis as a public health problem: thresholds fail to differentiate schistosomiasis morbidity prevalence in children

Ryan E. Wiegand[1,2,3*], W. Evan Secor[1], Fiona M. Fleming[4], Michael D. French[5], Charles H. King[6], Susan P. Montgomery[1], Darin Evans[7], Jürg Utzinger[2,3], Penelope Vounatsou[2,3], Sake J. de Vlas[8]

[1] *Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America*

[2] *Swiss Tropical and Public Health Institute, Basel, Switzerland*

[3] *University of Basel, Basel, Switzerland*

[4] *SCI Foundation, London, United Kingdom*

[5] RTI International, Washington DC, United States of America

[6] *Center for Global Health and Diseases, Case Western Reserve University, Cleveland, Ohio, United States of America*

[7] *United States Agency for International Development, Washington, DC, United States of America*

[8] *Department of Public Health, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands*

*Corresponding author

Email: rwiegand@cdc.gov

[This manuscript has been electronically published in *Open Forum Infectious Diseases* (2021) ofab179, https://doi.org/10.1093/ofid/ofab179.]

6.1 Abstract

Background: Current World Health Organization guidelines utilize prevalence of heavy-intensity infections (PHI), i.e., ≥50 eggs per 10ml of urine for *Schistosoma haematobium* and ≥400 eggs per gram of stool for *S. mansoni*, to determine whether a targeted area has controlled schistosomiasis morbidity or eliminated schistosomiasis as a public health problem. The relationship between these PHI categories and morbidity is not well understood.

Methods: School-age participants enrolled in schistosomiasis monitoring and evaluation cohorts from 2003-2008 in Burkina Faso, Mali, Niger, Tanzania, Uganda, and Zambia were surveyed for infection and morbidity at baseline and after 1 and 2 rounds of preventive chemotherapy. Logistic regression was used to compare morbidity prevalence among participants based on their school's PHI category.

Findings: Microhematuria levels were associated with the *S. haematobium* PHI categories at all three time points. For any other *S. haematobium* or *S. mansoni* morbidity that was measured, PHI categories did not differentiate morbidity prevalence levels consistently.

Interpretation: These analyses suggest that current PHI categorizations do not differentiate the prevalence of standard morbidity markers. A reevaluation of the criteria for schistosomiasis control is warranted.

Funding: The Schistosomiasis Control Initiative (now the SCI Foundation) was supported by the Bill and Melinda Gates Foundation (grant 13122).

6.2 Background

Schistosomiasis was estimated to have caused 1.1 million years lived with disability in 2017, roughly a third of the disability years associated with tuberculosis and about three-quarters that of malaria (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators 2018). The disease is caused by *Schistosoma* spp. trematode worms which can survive in the human body for years to decades. Morbidity mainly occurs due to inflammation and scarring from parasite eggs that become lodged in the capillaries of either the urogenital system as a result of infection with *Schistosoma haematobium* or the liver and intestines from infection with *S. mansoni* and other schistosome species (King et al. 2005; Colley et al. 2014a). Urogenital schistosomiasis causes hematuria in children (van der Werf et al. 2003b). More chronic infections are characterized by fibrosis of the

urinary tract (Khalaf et al. 2012), obstruction of urine flow (Khalaf et al. 2012), female (Christinet et al. 2016), and male (Kayuni et al. 2019) genital schistosomiasis, and rarely, bladder cancer (Ishida et al. 2018). Intestinal species commonly cause abdominal pain, diarrhea, and blood loss in the stool (van der Werf et al. 2003b). Chronic infections can lead to scar tissue in the bowels, hepatosplenic disease, periportal fibrosis, and collateral circulation (Colley et al. 2014a), which can lead to exsanguination.

The World Health Organization (WHO) has stated the primary goal of schistosomiasis control programs is to reduce morbidity (WHO 2002; 2011b; 2020b). Current WHO guidelines (WHO 2013) use heavy intensity infections (≥ 50 *S. haematobium* eggs per 10 mL of urine or ≥ 400 *S. mansoni* eggs per gram of stool (WHO 2002)) to categorize a target population's status. Target populations with a prevalence of heavy intensity infections (PHI) less than 5% are classified as having controlled schistosomiasis morbidity, and when a target population has less than 1% PHI, that population has eliminated schistosomiasis as a public health problem. These PHI thresholds are used despite treatment frequency being determined by the prevalence of any infection (WHO 2013). The selection of the PHI thresholds was based on correlations between infection intensity and severe pathology reported from limited data that were collected prior to 1990 (WHO 1987; 1988). Those studies demonstrated a statistically significant difference between non-infected and heavily infected participants, but not between non-infected and lightly infected participants. These findings, in an era in which treatment was limited and expensive, led to the development of program guidance focused on reducing heavy-intensity infections associated with the types of severe morbidity that are more common in older individuals (Mott 2004). More recent studies have found that less clinically severe manifestations, which can occur even with light infections and are common in school-age children, have a greater impact on population-level disability adjusted life years lost, i.e., an estimate of the years of life lost due to poor health, disability, or early death, compared to the most severe pathologies (King et al. 2005). Furthermore, the earlier guidelines failed to consider the limitations of a single stool or urine sample from study participants. As a result, lighter infections and their association with morbidity were likely underestimated (King 2015).

Our search of the literature did not uncover a formal assessment of the relationship between morbidity and the 1% and 5% PHI thresholds. Therefore, in response to a recent call to update the WHO guidelines for monitoring morbidity control to evidence-based targets (French et al. 2018; Colley et al. 2020a), we evaluated the relationship between aggregate morbidity and the WHO heavy-intensity infection thresholds used to define control and elimination of schistosomiasis as a public health problem. Data from Schistosomiasis Control Initiative (SCI)-supported preventive chemotherapy programs collected between 2003 and 2008 in different African countries (Fenwick et al. 2009) were used to test for differences in morbidity levels in children between PHI categories before and after initiation of the mass drug administration (MDA) of praziquantel (Webster et al. 2009).

6.3 Methods

6.3.1 Study design and data collection

Data were collected as part of national programs for schistosomiasis and soil-transmitted helminthiasis control from 2003-2008 in six African countries (Burkina Faso, Mali, Niger, Tanzania, Uganda, and Zambia) supported by SCI (Koukounari et al. 2006; Kabatereine et al. 2007; Koukounari et al. 2007; Touré et al. 2008; Fenwick et al. 2009). Each country developed a control program for national scale-up, which involved prevalence mapping to determine at-risk populations, MDA of praziquantel (for schistosomiasis) and albendazole (for soil-transmitted helminthiasis) to school-age children and, in some countries, adults in high-risk communities, and a monitoring and evaluation framework. Each country implemented praziquantel distribution to target populations at the frequency recommended by WHO guidance (Montresor et al. 2002). Countries maintained two types of monitoring and evaluation cohorts. The first was a cohort of children aged 6-12 years enrolled in primary school. These children were ascertained for infection and morbidity indicators at baseline and evaluated prior to receiving treatment. They were then followed and treated annually for two more years, with some exceptions: Zambia, where there was only one year of follow up; Mali, where some schools were treated twice between baseline and follow up 1 and others were treated annually but not followed up at follow up 1; and Tanzania, where schools were not treated between follow up 1 and 2. At the point when a school was not treated once annually, it omitted from that survey and subsequent surveys. The second was a community cohort

mostly of adults but included persons 4-88 years old. A random sample of the community was ascertained for infection and morbidity indicators and evaluated prior to treatment at each round. The small sample of children in this cohort were likely absent from school that day. Each community was followed up for the same number of years as the longitudinal cohort. In both cohorts, individuals feeling unwell or below 94 cm in height were ineligible for praziquantel treatment and excluded. Communities were randomly selected via stratified sampling. Strata were based on endemicity levels to provide a wide representation of different areas. For these analyses, we limited our analyses to 6-15 year-olds in either cohort with at least thirty participants in a school possessing infection and morbidity data.

6.3.2 Infection data

A single urine filtration to evaluate *S. haematobium* was used in Burkina Faso, Tanzania, and Zambia. Two filtrations from the same urine sample were used in Niger and two different urine samples from consecutive days were used in Mali. Uganda did not collect *S. haematobium* infection data. Urine filtration was performed by passing approximately 10 ml of urine through a filter that was then stained and microscopically examined for eggs. An individual's intensity was calculated as the arithmetic mean number of eggs per 10 ml of urine across all available samples. Heavy-intensity infection was defined as ≥50 eggs per 10 mL of urine (WHO 2002).

For *S. mansoni*, the Kato-Katz technique with thick fecal smears microscopically examined for eggs was used. A single stool, with two different slides (each 41.7 mg) examined per stool, was used in Burkina Faso, Mali, Niger, and at baseline in Uganda. Tanzania, follow-up surveys in Uganda, and Zambia used two stools from consecutive days with two slides each per stool. Individual intensity was computed by multiplying the number of eggs per slide by 24 to calculate the eggs per gram of stool (EPG), then taking the arithmetic mean of all available samples measured for that child. Participants with ≥400 EPG were defined as having a heavy-intensity infection (WHO 2002).

6.3.3 Morbidity data

Ultrasound exams were performed according to the Niamey protocol, which has standardized examinations and reporting practices *S. haematobium* and *S. mansoni* ultrasonic evaluations (Richter et al.

2000). *S. haematobium* ultrasounds were done in Mali, Niger, Tanzania, and Zambia, though in Zambia results were rare at baseline and are confined to follow up 1. Participants were evaluated by ultrasound for bladder abnormalities, defined as distorted bladder shape, irregular bladder wall, bladder wall masses, pseudopolyps, or thickening of the bladder wall, and for upper urinary tract abnormalities, defined as a dilated renal pelvis (left or right) or dilated ureter (left or right). For analyses, we deviated from the scoring system used in the Niamey protocol and categorized abnormalities in two ways. The first approach looked across indicators and coded a participant positive who had at least one ultrasound abnormality and coded a participant negative if the participant had no ultrasound abnormalities. Only participants with data for all ultrasound indicators were included in those analyses to ensure each participant possessed the same chance of possessing a positive ultrasound indicator. The second approach summed up the number of ultrasound abnormalities per person among participants with any available ultrasound data, which allowed all ultrasound data to be included. *S. mansoni* ultrasounds were performed in Mali, Niger, Tanzania, Uganda, and Zambia, with Zambian results only in follow up 1 as noted above. Participants were evaluated for enlarged portal vein and liver image patterns indicative of schistosomiasis-associated fibrosis. Under the Niamey protocol, image pattern A is considered normal, image pattern B as indeterminate, and image pattern C and above are considered indicative of schistosomiasis-associated fibrosis, where these correspond to small patches of rings and pipe stems throughout the liver parenchyma (pattern C), fibrosis around the main stem of the liver (D), more substantial fibrotic patches around the main stem (E), and extensive fibrosis throughout the parenchyma (F). Since the Niamey protocol scores a person with image pattern B with one point and, at a minimum, does not exclude the possibility of periportal fibrosis, we assessed frequency of both image patterns C-F and B-F as evidence of periportal thickening.

Additional morbidities were collected in all six countries. These included microhematuria assessed with Hemastix dipsticks (French et al. 2007) and self-reported painful urination (Danso-Appiah et al. 2010) for *S. haematobium* and two measures confirmed by laboratorians (diarrhea and blood in stool) and two self-reported

measures from the last two weeks (diarrhea and abdominal pain (Polderman et al. 1984; Stelma et al. 1994)) for *S. mansoni*.

6.3.4 Data analysis

Data from all countries were harmonized and pooled for analyses in R version 4.0.3 (R Development Core Team 2018). The PHI was calculated per school and schools were split into three categories of PHI (PHI < 1%; PHI ≥ 1% and < 5%; and PHI ≥ 5%). Individuals were analyzed based on the school's category.

Prevalence estimates were calculated in the survey package (Lumley 2019) after accounting for clustering at the school level and countries as strata. These analyses used the 5% level of significance. Bayesian logistic regression models were fit via Markov chain Monte Carlo (MCMC) methods in JAGS (Plummer 2003) for each indicator except for the sums of *S. haematobium* ultrasound indicators for which binomial models was used. Survey year, heavy-intensity infection category, and their interaction were included as fixed effects. Indicator variables for countries were added to control for differences between control programs. Random intercepts were included for schools and individuals to account for multiple observations sampled from the same school or individual, respectively. All comparisons are reported as odds ratios (OR) with 95% Bayesian credible intervals (BCI) from the posterior distributions. Full details of the models as well as results from the binomial models, individual ultrasound indicators, and other laboratory and self-reported morbidities are included in the supplementary materials.

6.3.5 Patient consent statement

The Imperial College Research Ethics Committee (ICREC_8_2_2, EC No. 03.36, R&D No. 03/SB/003E) and the ethical review boards of the Ministries of Health of the six countries provided ethical approval for use of these data. The US Centers for Disease Control and Prevention was determined to be a non-engaged research partner. In all countries, meetings were held with teachers and parents to inform them about participation in these programs. In Mali, verbal consent from community leaders was obtained as this was the most accepted form of consent at the time. In all other countries, written informed consent was obtained from head teachers at each school. Agreements from parents or guardians were obtained as well as assent from children.

6.3.6 Role of the funding sources

The sponsors of this study played no role in the design, collection, analysis, interpretation, or composition of this report. All authors contributed to the decision to submit for publication.

6.4 Results

6.4.1 *Schistosoma haematobium*

The numbers of schools and participants that contributed *S. haematobium* morbidity data ranged from 7 to 59 schools and 861 to 7,766 participants per PHI category in a survey (Supplementary Table 6.1). Prevalence of infection and PHI decreased at follow-up surveys as compared to baseline (Figure 6.1, row A, left). Overall decreases in prevalence were also experienced for most morbidities (Figure 6.1, row B; Supplementary Figure 6.1).

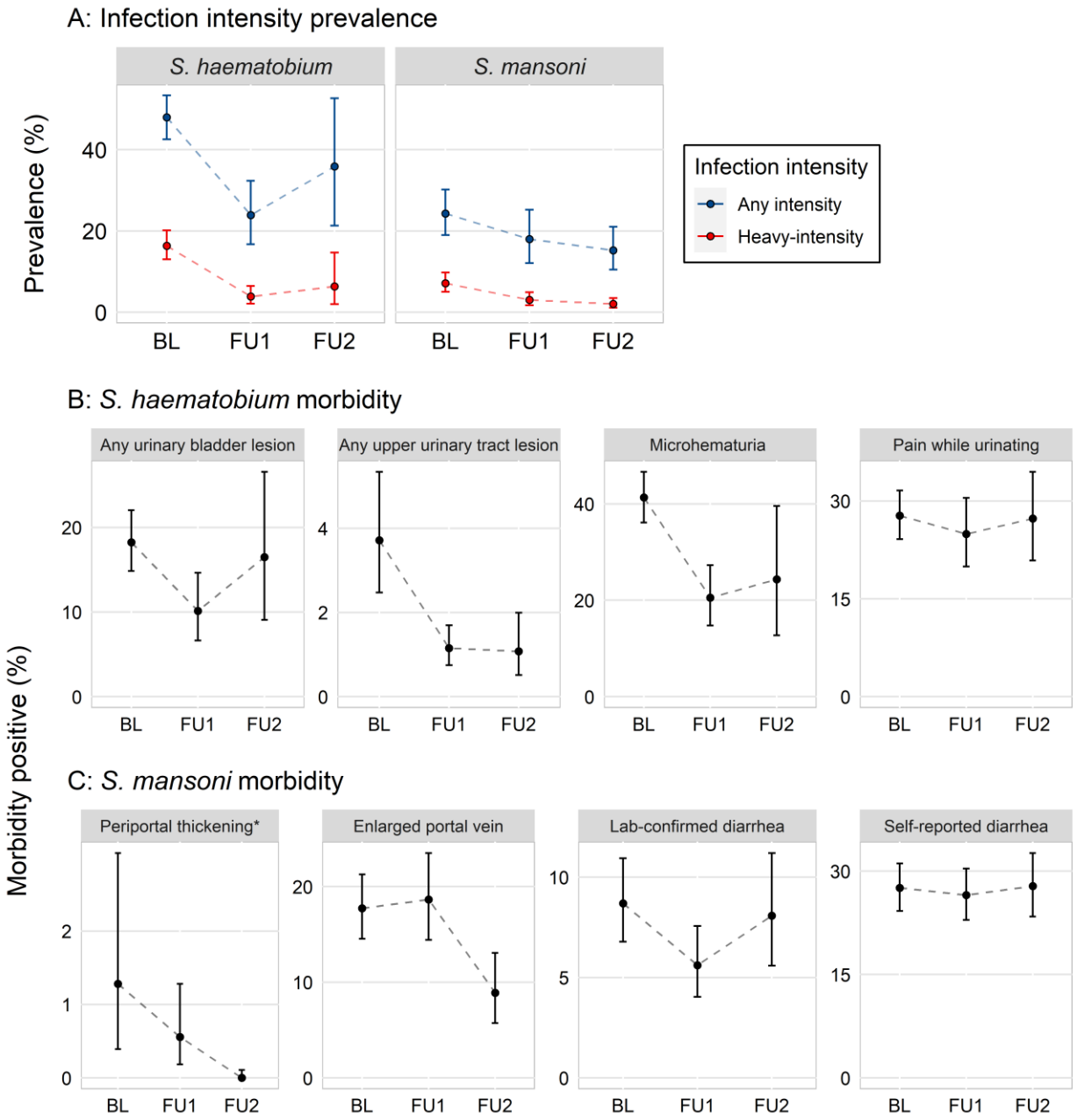
Modeling results found that participants in schools with PHI<1% and 1-5% PHI had lower odds of most morbidities as compared to participants from schools with PHI≥5% (Table 6.1). For participants in schools with PHI<1% compared to participants in schools with PHI≥5%, odds were lower at each survey for any bladder lesion, microhematuria, and pain while urinating. For participants in schools with 1-5% PHI compared to participants from schools with PHI≥5%, odds were lower at each survey for microhematuria. Results were similar to other models (Supplementary Table 6.2).

Participants in schools with PHI<1% had lower odds of microhematuria as compared to participants in 1-5% PHI schools in all three surveys. For other measures, whether aggregated (Figure 6.2; Table 6.1) or individually (Supplementary Figure 6.2; Supplementary Table S2), the differences between morbidity in participants in schools with PHI<1% and participants in schools with 1-5% PHI schools was inconsistent, and for some urinary bladder indicators, morbidity was greater in participants in schools with PHI<1%.

The raw results (Figure 6.2 and Supplementary Figure 6.2) differed at times from the modeled results, likely due to between country variability. For example, the prevalence of any urinary bladder lesion varied at

baseline between countries (Supplementary Figure 6.3). Regression models controlled for country-level differences which accounts for the differences between the raw and modeled results.

Figure 6.1. Line graphs of the prevalence of 6-15 year-old school children who were *Schistosoma* infection and heavy-intensity positive (row A), *S. haematobium* morbidity positive (row B), and *S. mansoni* morbidity positive (row C) at each survey year (BL=baseline, FU1=follow up 1, FU2=follow up 2). *S. haematobium* infections were assessed by urine filtration and *S. mansoni* infections by Kato-Katz. Plots of individual ultrasound indicators for *S. haematobium* and additional morbidity indicators for both species are included in Supplementary Figures 6.1 and 6.2.



* Periportal thickening as measured by irregular image patterns of C, D, E, or F.

Figure 6.2. Line graphs of *Schistosoma haematobium*-related morbidity positive prevalence. Heavy-intensity prevalence category determined at the school-level. Participants were enrolled between 2003-2008 at each survey year (BL=baseline, FU1=follow up 1, FU2=follow up 2). Clustering by school accounted for in 95% confidence bands. Infections were assessed by urine filtration. Model-based tests comparisons are included in Table 6.1. Plots of individual indicators and model-based comparisons are included in Supplemental Figure 6.3 and Table 6.2, respectively.

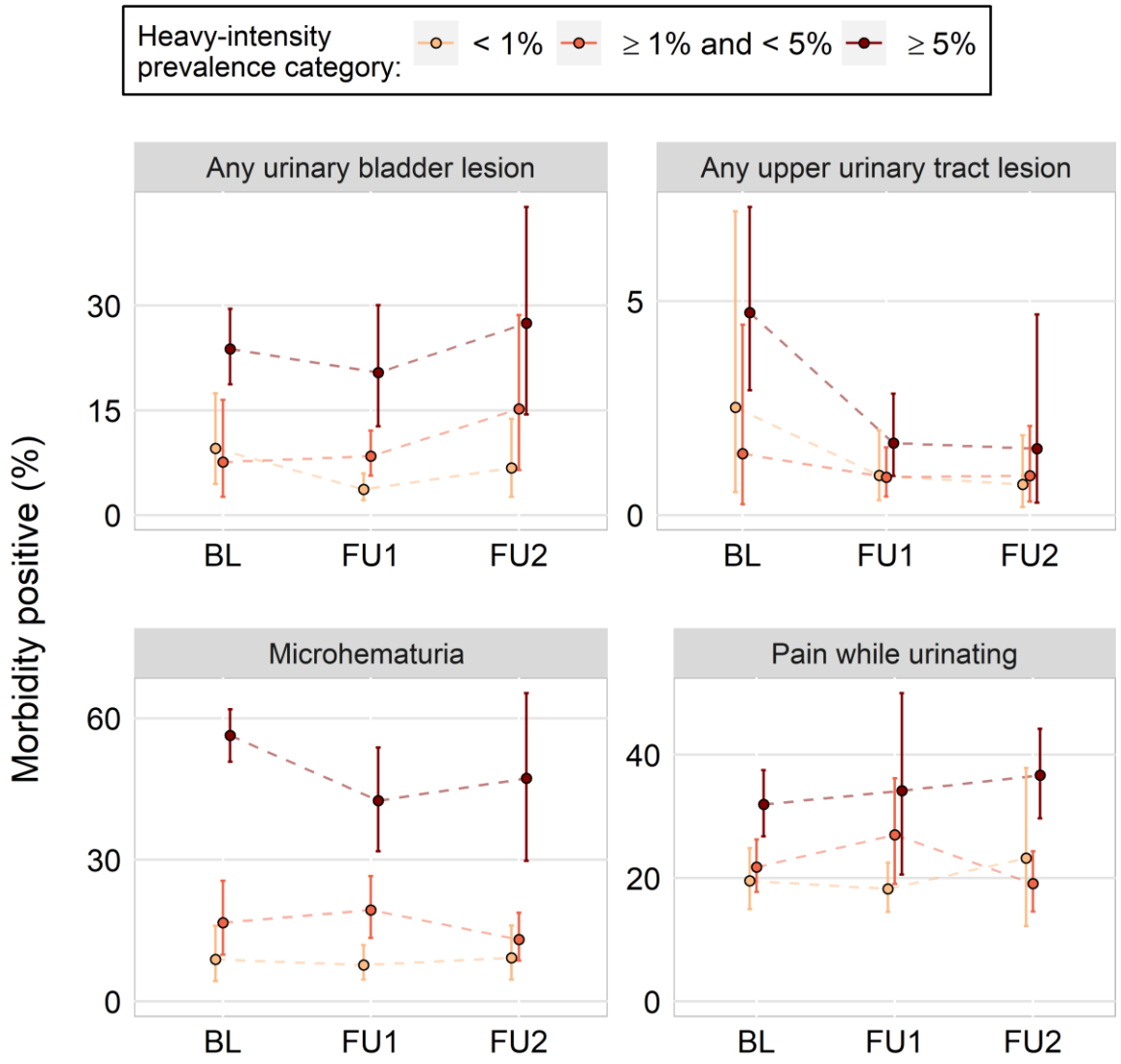


Table 6.1. Odds ratios and 95% credible intervals from Bayesian logistic regression models comparing morbidity positive proportions between heavy-intensity prevalence categories within surveys for *S. haematobium*-related morbidities.

Morbidity	Survey	< 1% vs. ≥ 5%	1-5% v. ≥ 5%	< 1% v. 1-5%
Any urinary bladder lesions	Baseline	**0.27 (0.21, 0.34)**	**0.43 (0.33, 0.54)**	**0.63 (0.47, 0.85)**
	Follow up 1	**0.22 (0.18, 0.28)**	**0.52 (0.42, 0.63)**	**0.43 (0.34, 0.55)**
	Follow up 2	**0.30 (0.22, 0.40)**	**0.31 (0.22, 0.43)**	0.98 (0.67, 1.44)
Any upper urinary tract Lesions	Baseline	0.90 (0.56, 1.45)	0.77 (0.47, 1.22)	1.18 (0.67, 2.07)
	Follow up 1	0.67 (0.41, 1.10)	0.83 (0.51, 1.34)	0.81 (0.46, 1.42)
	Follow up 2	0.61 (0.25, 1.36)	0.36 (0.09, 1.07)	1.68 (0.47, 7.52)
Microhematuria	Baseline	**0.12 (0.10, 0.15)**	**0.27 (0.23, 0.31)**	**0.45 (0.37, 0.56)**
	Follow up 1	**0.14 (0.11, 0.16)**	**0.77 (0.65, 0.92)**	**0.18 (0.15, 0.21)**
	Follow up 2	**0.22 (0.18, 0.28)**	**0.40 (0.31, 0.51)**	**0.56 (0.43, 0.73)**
Pain while urinating	Baseline	**0.62 (0.52, 0.73)**	**0.67 (0.58, 0.78)**	0.92 (0.77, 1.11)
	Follow up 1	0.95 (0.80, 1.13)	1.28 (1.06, 1.55)	**0.74 (0.62, 0.89)**
	Follow up 2	**0.69 (0.56, 0.85)**	**0.70 (0.55, 0.90)**	0.99 (0.77, 1.27)

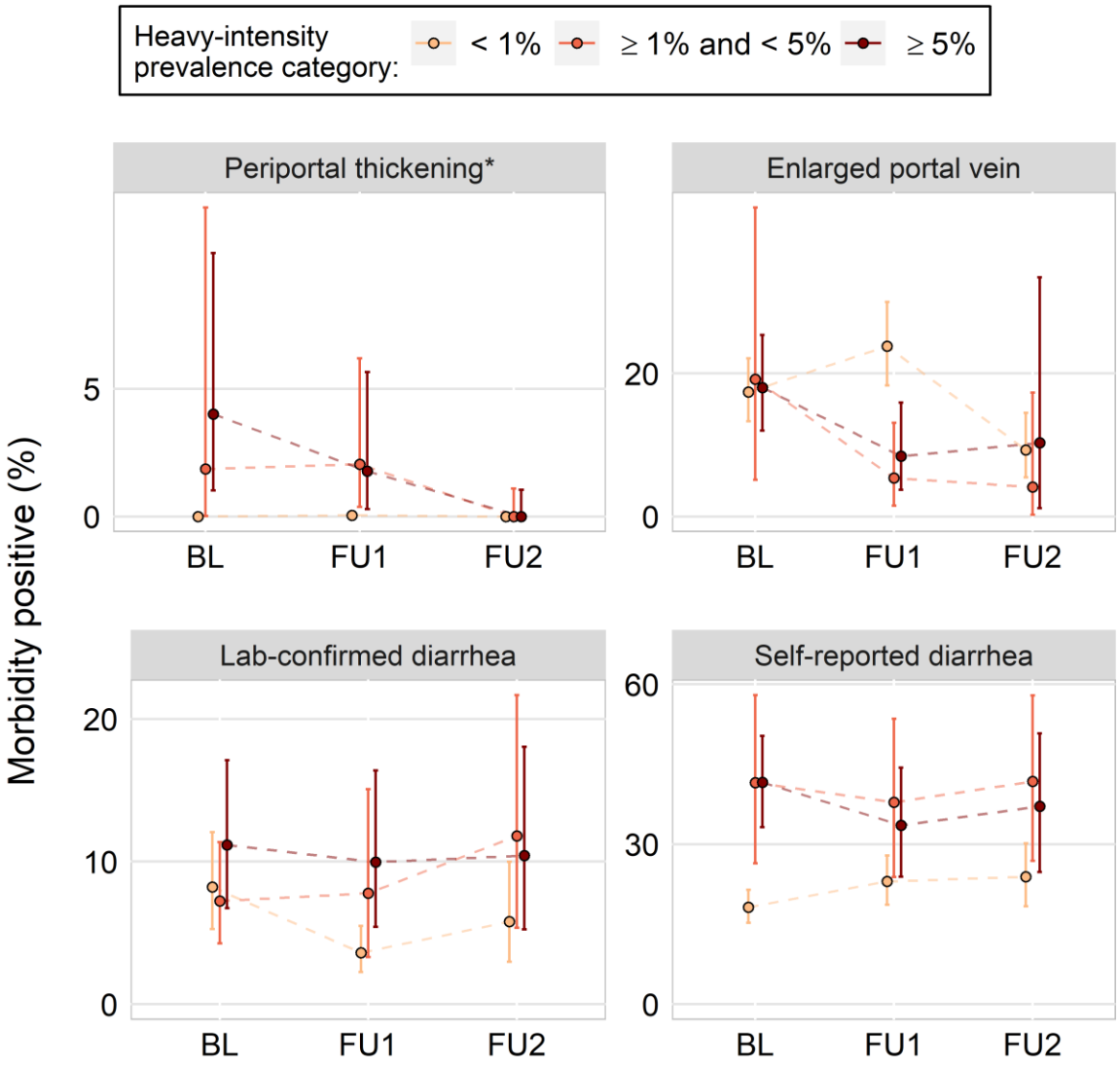
Notes: Bold font indicates the 95% Bayesian credible interval does not contain one. Participants are school-aged children, aged 6-15 years, and enrolled between 2003-2008. Plots of unmodeled estimates are included in Figure 6.2.

6.4.2 *S. mansoni*

For *S. mansoni*, the results from 5 to 65 schools with between 439 and 8,890 participants per PHI category were analyzed (Supplementary Table 6.3). Overall prevalence of *S. mansoni* was lower than *S. haematobium*, and, as with *S. haematobium*, infection prevalence decreased in follow up surveys, though this reduction was smaller than *S. haematobium* (Figure 6.1, row A, right); the prevalence of most *S. mansoni* morbidities experienced decreases during follow up surveys (Figure 6.1, row C; Supplementary Figure 6.4).

As observed for *S. haematobium*, participants in schools with PHI<1% had lower odds of *S. mansoni*-associated morbidities than participants in schools with PHI≥5% (Figure 6.3 and Supplementary Figure 6.5; Table 6.2). At each survey, odds were lower for participants in schools with PHI<1% compared to participants in schools with PHI≥5% for laboratory-confirmed diarrhea. Periportal thickening (as measured by irregular image pattern C, D, E, or F) was lower at baseline, but not at the first follow up 1. There was more self-reported diarrhea in participants in schools with PHI≥5% compared to participants in schools with PHI<1% at baseline. In the unmodeled data, a greater proportion of children with an enlarged portal vein at the first follow up in participants in schools with PHI<1%, though this was largely driven by between country variability, especially the

Figure 6.3. Line graphs of *Schistosoma mansoni*-related morbidity percentages. Heavy-intensity prevalence category determined at the school-level. Participants were enrolled between 2003 and 2008 at each survey year (BL=baseline, FU1=follow up 1, FU2=follow up 2). Clustering by school accounted for in 95% confidence bands. Infections were assessed by Kato-Katz thick smears. Model-based tests comparisons are included in Table 6.2. Plots of additional indicators and model-based comparisons are included in Supplemental Figure 6.4 and Supplemental Table 6.4, respectively.



*Periportal thickening as measured by image pattern C-F.

much higher prevalence in Niger (Supplementary Figure 6.6). Since country level differences are accounted for in the modeling, the estimated odds of enlarged portal vein are lower in participants in <1% PHI schools than participants in schools with PHI≥5% (baseline: OR=0.41, 95% BCI=0.32-0.52; follow up 1: OR=0.61, 95% BCI=0.45-

Table 6.2. Odds ratios and 95% credible intervals from Bayesian logistic regression models comparing morbidity positive proportions between heavy-intensity prevalence categories within surveys for *S. mansoni*-related morbidities.

Morbidity	Survey	< 1% vs. ≥ 5%	1-5% v. ≥ 5%	< 1% v. 1-5%
Image pattern C-F	Baseline	**0.02 (0.00, 0.28)**	0.79 (0.29, 2.11)	**0.03 (0.00, 0.37)**
	Follow up 1	0.20 (0.01, 1.79)	1.80 (0.72, 4.55)	0.11 (0.01, 1.06)
	Follow up 2		Non-estimable*	
Enlarged portal vein	Baseline	**0.41 (0.32, 0.52)**	**0.59 (0.42, 0.82)**	**0.70 (0.51, 0.96)**
	Follow up 1	**0.61 (0.45, 0.83)**	0.82 (0.51, 1.28)	0.75 (0.48, 1.19)
	Follow up 2	**0.57 (0.38, 0.86)**	**0.51 (0.27, 0.94)**	1.10 (0.66, 1.94)
Laboratory-confirmed diarrhea	Baseline	**0.43 (0.35, 0.54)**	**0.42 (0.33, 0.54)**	1.01 (0.81, 1.28)
	Follow up 1	**0.38 (0.30, 0.50)**	**0.63 (0.47, 0.85)**	**0.61 (0.46, 0.80)**
	Follow up 2	**0.63 (0.45, 0.87)**	1.37 (0.97, 1.94)	**0.46 (0.34, 0.62)**
Self-reported diarrhea	Baseline	**0.73 (0.65, 0.82)**	1.08 (0.95, 1.23)	**0.68 (0.60, 0.77)**
	Follow up 1	0.87 (0.75, 1.00)	**0.71 (0.60, 0.85)**	**1.22 (1.04, 1.43)**
	Follow up 2	0.93 (0.78, 1.11)	1.01 (0.81, 1.25)	0.92 (0.78, 1.10)

Bold font indicates the 95% credible interval does not contain one. Participants are school-age children (6-15 years) enrolled between 2003 and 2008. Plots of unmodeled estimates are included in Figure 6.3.

* The odds ratios for image pattern C-F at follow up 2 were highly variable due to the prevalence being close to zero. We chose to omit this effect due to its instability.

0.83; follow up 2: OR=0.57, 95% BCI=0.38-0.86). However, comparisons between participants in schools with 1-5% PHI and participants in schools with PHI≥5% produced inconsistent conclusions across surveys. For example, as expected, participants in schools with 1-5% PHI were at lower odds of lab-confirmed diarrhea than participants in schools with PHI≥5% at baseline (OR=0.42, 95% BCI=0.33-0.54) and follow-up 1 (OR=0.63, 95% BCI=0.47-0.85). But at follow up 2, the relationship was reversed (OR=1.37, 95% BCI=0.97-1.94).

Findings were also inconsistent when comparing participants in schools with PHI<1% to participants in schools with 1-5% PHI. Participants in schools with PHI<1% compared to participants in schools with 1-5% PHI were at lower odds of enlarged portal vein at baseline (OR=0.70, 95% BCI=0.51-0.96) but at increased odds at follow-up 2 though with considerable variability in the point estimate (OR=1.10, 95% BCI=0.66-1.94). For lab-confirmed diarrhea, participants in schools with PHI<1% were at similar odds at baseline compared to participants in schools with 1-5% PHI (OR=1.01, 95% BCI=0.81-1.28) but at lower odds otherwise (follow-up 1: OR=0.61, 95% BCI=0.46-0.80; follow-up 2: OR=0.46, 95% BCI=0.34-0.62).

6.5 Discussion

In general, children in schools with PHI ≥5% displayed higher morbidity than children in schools with PHI<1% and 1-5% PHI, though the extent differed by species, and was generally non-linear where participants in schools with PHI≥5% had considerably higher rates. For *S. haematobium*, participants in schools with PHI<1% or 1-5% PHI had consistently lower odds of morbidity compared to participants in schools with PHI≥5%. Thus, a targeted area with a prevalence of <5% *S. haematobium* heavy-intensity infections among school-age children is expected to have less morbidity than a targeted area with >5% heavy-intensity infections. For *S. mansoni*, while participants in schools with PHI<1% consistently had decreased odds of morbidity compared to participants in PHI≥5% schools, this was not true for participants in schools with 1-5% PHI compared to participants in schools with PHI≥5%. Participants in schools with 1-5% PHI sometimes had decreased odds of morbidity compared to participants in schools with PHI≥5% and sometimes had increased odds. Therefore, for the *S. mansoni* morbidities that we measured, only participants in schools with PHI<1% category have less morbidity than participants in schools with PHI≥5%.

Microhematuria was the only morbidity for which there was a consistent difference between participants in schools with PHI 1-5% versus participants in schools with PHI<1%. These analyses underscore the correlation of microhematuria and *S. haematobium* infection. The WHO 2021-2030 neglected tropical disease roadmap (WHO 2020b) suggests defining an indicator for measuring morbidity of schistosomiasis as a critical action for achieving program goals within the next decade. Microhematuria, which has been used as a proxy for community-level *S. haematobium* prevalence for approximately 40 years (Krauth et al. 2015) due to the two measures being correlated (King et al. 2013), would appear to be an ideal candidate for that species specific indicator because reducing microhematuria to a prevalence consistent with non-schistosomiasis causes might indicate that urogenital schistosomiasis has been eliminated as a public health problem.

Other differences in morbidity between participants in schools with 1-5% PHI and PHI<1% were rare and often inconsistent. Occasional ORs greater or less than one were detected, but these associations were not

realized at all surveys. There were also instances where participants in schools with PHI<1% had increased odds of morbidity compared to participants in schools with 1-5% PHI, such as the baseline presence of any upper urinary tract lesions for *S. haematobium* and follow-up 2 for periportal thickening for *S. mansoni*. Clearly, the PHI thresholds of 1% and 5% do not appear to correlate well with different levels of schistosomiasis morbidity across the two species for multiple morbidity indicators.

These analyses have some limitations and shortcomings. First, a single urine or stool sample was used in multiple countries, meaning the potential for diagnostic misclassification was higher than if more samples had been taken (Lamberton et al. 2014). This is especially true for *S. mansoni* since the overall prevalence was lower, meaning a small number of missed heavy infections would have a greater impact on the PHI. This could explain some of the confusing results when comparing participants in schools with different PHI categories. In addition, our results are limited to morbidity in children. For some ultrasound-detectable morbidities, especially liver fibrosis for *S. mansoni,* substantial pathology does not appear until individuals have been infected for at least 10-15 years. More work is needed to better understand morbidity control in adults, especially as recent modeling studies have found utility in collecting adult data for both species (Toor et al. 2018b; Kura et al. 2020). Reflecting the challenges associated with collecting field-based ultrasound data, many *S. mansoni* ultrasound components were not collected. A more complete ultrasound picture, especially including hepatomegaly and splenomegaly, would have allowed us to evaluate indicators of *S. mansoni* morbidity that are more common in children. Data for other schistosomiasis-associated morbidities often described for children, such as anemia, stunting, wasting, exercise intolerance and delay in cognitive development were not consistently collected by these control programs. If we had access to reliable data for these measures, we may have detected a relationship between PHI categories and morbidity in children. Another limitation was that for *S. mansoni*, most PHI≥5% schools were in Uganda, potentially causing bias for comparisons involving the PHI≥5% category. Although we cannot formally assess the bias, there is the potential that, if the prevalence of morbidity indicators among children in these PHI≥5% Ugandan schools are higher than for children in other PHI≥5% schools, differences between participants in PHI≥5% schools and those in PHI<5% schools are larger than they should be.

Our findings suggest the global effort to control and eliminate schistosomiasis would benefit from revisiting how these goals are defined and operationalized. Given the lack of precision of current morbidity tools, especially in the context of low schistosomiasis prevalence, changes are needed for monitoring and evaluating schistosomiasis. Having two programmatic thresholds for schistosomiasis does not appear to have an empirical basis and a single, elimination as a public health problem target for determining when to stop mass annual preventive chemotherapy, such as is done with trachoma (WHO 2017), would better suit schistosomiasis control programs. The recommended public health actions for countries that have controlled morbidity (1-5% PHI) are similar to countries that have not controlled morbidity (≥ 5% PHI) (WHO 2013). Only when a country is eligible for elimination as a public health problem (PHI<1%) do the public health actions change, which suggests the control of morbidity category (1-5% PHI) is redundant. This is reflected in the current road map which only mentions PHI<1% (WHO 2020b). In addition, most programs have initiated treatment or are currently below 5% PHI (Deol et al. 2019). Still, it is somewhat disappointing that PHI<1% and 1-5% PHI rarely show useful significant differences.

A different measure is needed for morbidity control. Most programs only collect prevalence data for decision-making on frequency of preventive chemotherapy and do not calculate PHI. PHI is rarely utilized in practice and, since these results demonstrate a lack of association between PHI and morbidity indicator levels, morbidity categorization by PHI may be superfluous. Because morbidity may be experienced by people with all infection intensities (King et al. 2005; King 2015), utilizing prevalence of any infection may better predict the morbidity status of a school or community.

Any new measure for morbidity control or elimination as a public health problem needs to have evidence-based targets that better align with actual morbidity (French et al. 2018) and hopefully new targets can be developed. Development of guidelines for elimination of schistosomiasis as a public health needs deeper thought into which morbidity indicators should be used and operationalized. There is a wide array of possible indicators, and it is unclear whether pegging program targets to a single indicator is optimal or whether an aggregate measure would provide greater utility. Chosen indicators should be tailored towards the specific age

groups sampled and be clinically meaningful, readily measured (preferably in the field), easily interpreted by control programs, and prevalent in the age groups that are sampled. A limiting factor in ultrasonic indicators is that they are difficult to collect in the field, but advances in technology are making ultrasound evaluations more practical (Straily et al. 2021) and may mean these indicators can be used to assess morbidity control.

Finally, even though microhematuria appears as a good candidate for monitoring *S. haematobium* morbidity in school-age children, it is the sole example. This demonstrates the need for a comprehensive exploration of the associations between community-level infection and morbidity after initiation of MDA. Such explorations of measuring morbidity should be undertaken, with an emphasis on estimating the background levels of morbidity and quantifying the relationship between school and community infection and morbidity levels. One such pilot initiative has begun in an *S. haematobium* endemic area and an *S. mansoni* endemic area (Neglected Tropical Diseases Support Center 2019), but hopefully identical or similar study designs can be performed in different countries and ecologic archetypes, especially foci with mixed *S. haematobium* and *S. mansoni* infections and *S. japonicum* endemic areas, as well as different age groups. Finally, while some information exists on how an infected child's ultrasound evaluation changes over time (Hatz et al. 1998), greater knowledge of people's ultrasound indicator progression post-infection, especially in older age groups.

6.6 Conclusion

The success of schistosomiasis programs is tied to the WHO categorizations for morbidity control. Those categories are based on PHI, which our analyses demonstrate, often have similar and overlapping levels of morbidity. Thus, the usefulness of PHI in defining control status is limited and indicates that, for the goal of elimination as a public health problem outlined in the WHO 2021-2030 neglected tropical disease roadmap (WHO 2020b) to be met, community measurements must be better aligned with schistosomiasis-related morbidity levels. A reconfiguration of these morbidity categories is warranted.

6.7 Declaration of interests

The authors declare that they do not have any commercial or other association that might pose a conflict of interest.

6.8 Acknowledgments

The Schistosomiasis Control Initiative was supported by the Bill and Melinda Gates Foundation (grant 13122).

We thank all the school and community participants in the surveys of the national control programs; the staff of the national ministries of health for managing and implementing these programs; the ministries of health for granting the authors permission to access and reanalyze these data for the study; and the past and present staff from the Schistosomiasis Control Initiative (SCI Foundation) team. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the CDC.

6.9 Supplemental Materials

6.9.1 Statistical Methods

Our outcome in all models was the presence of a morbidity, y_i, where

$$y_i = \begin{cases} 0, \text{if negative} \\ 1, \text{if positive} \end{cases}.$$

We assume

$$y_i \sim \text{Bernoulli}(p_i)$$

where i denotes an observation. p_i is forced to be bounded on $[0,1]$. For the logistic model, we assume a logit transform of the linear predictor, specifically

$$p_i = \frac{e^{\eta_i}}{1 + e^{\eta_i}}$$

where η_i is the linear predictor. The form of η_i depends on whether participant was sampled in multiple waves. We had n observations in the dataset, where $i = 1, \ldots, n_1$ come from children who were only sampled once during these three surveys and $i = n_1 + 1, \ldots, n_2$ come from children who were only sampled more than once. For $i = 1, \ldots, n_1$,

$$\begin{aligned} \eta_i = {} & \beta_0 + \beta_1 * \text{COM}_i + \beta_2 * \text{EPHP}_i + \beta_3 * \text{FU1}_i + \beta_4 * \text{FU2}_i + \beta_5 * \text{COM}_i * \text{FU1}_i + \beta_6 * \text{COM}_i * \text{FU2}_i + \beta_7 \\ & * \text{EPHP}_i * \text{FU1}_i + \beta_8 * \text{EPHP}_i * \text{FU2}_i + \beta_{9_1} * \text{age}_{1,i} + \cdots + \beta_{9_j} * \text{age}_{j,i} + \beta_{10} * \text{female}_i + \beta_{11_1} \\ & * \text{country}_{1,i} + \cdots + \beta_{11_j} * \text{country}_{j,i} + \gamma_{1,k} \end{aligned}$$

and for $i = n_1 + 1, \ldots, n_2$,

$$\eta_i = \beta_0 + \beta_1 * \mathrm{COM}_i + \beta_2 * \mathrm{EPHP}_i + \beta_3 * \mathrm{FU1}_i + \beta_4 * \mathrm{FU2}_i + \beta_5 * \mathrm{COM}_i * \mathrm{FU1}_i + \beta_6 * \mathrm{COM}_i * \mathrm{FU2}_i + \beta_7 * \mathrm{EPHP}_i * \mathrm{FU1}_i + \beta_8 * \mathrm{EPHP}_i * \mathrm{FU2}_i + \beta_{9_1} * \mathrm{age}_{1,i} + \cdots + \beta_{9_j} * \mathrm{age}_{j,i} + \beta_{10} * \mathrm{female}_i + \beta_{11_1} * \mathrm{country}_{1,i} + \cdots + \beta_{11_j} * \mathrm{country}_{j,i} + \gamma_{1,k} + \gamma_{2,l}$$

In these equations,

- β's are the coefficient estimates (on the log odds scale),
- COM_i is an indicator variable denoting whether observation i is from a school that has PHI≤5% and PHI>1%,
- EPHP_i is an indicator variable denoting whether observation i is from a school that has PHI≤1%,
- $\mathrm{FU1}_i$ equals 1 when observation i was ascertained in follow up 1,
- $\mathrm{FU2}_i$ equals 1 when observation i was ascertained in follow up 2,
- age_i is an indicator variable for the age of the participant treated as a category with 6 as the reference category to ages 7 to 15,
- female_i is an indicator variable for whether participant is a female with male as the reference category,
- $\mathrm{country}_i$ is an indicator variable for the country of the observation with j countries in each model where j depends on the morbidity studied, and
- $\gamma_{1,k}$ and $\gamma_{2,l}$ are random effects for school and person, respectively, where an observation is from school k and person l, with the latter only for $i = n_1 + 1, \ldots, n_2$.

All β's have a Cauchy prior distribution with a center of zero and a scale of 2.5.(Gelman et al. 2008) For the random effect for school, $\gamma_{1,k} \sim \mathrm{Normal}(0, \tau_1)$ where $\tau_1 = {\rho_1}^{-2}$ and ρ_1 is given a scaled Gamma prior with 1 degree of freedom and a scale of 25. This is equivalent to the standard deviation being distributed as a half-t distribution.(Gelman 2006) The random effect for person follows similarly.

Binomial models are fit in the same way, except $y_i \sim Bn(t_i, p_i)$ where y_i is the number of morbidity indicators present and t_i is the total number of morbidity indicator tests completed for observation i.

Specific estimates for the three PHI categories (PHI < 1%; PHI ≥ 1% and < 5%; and PHI ≥ 5%) by survey are then estimated by contrast statements.

6.9.2 Implementation

Models were fit via Markov Chain Monte Carlo using JAGS (Plummer 2003) and CODA (Plummer et al. 2006) in R via the rjags package (Plummer 2019). Three chains were fit with an adaptive phase of 20,000 iterations per chain. For the final model, the iterations from the adaptive phase were discarded and each chain was run for another 100,000 iterations. After completing the 100,000 iterations, graphical displays of the trace and densities functions were used to determine if any chains or a subset of iterations should be discarded. Results were then summarized.

6.9.3 JAGS model code for logistic model

```
model {
 for (i in 1:n.single) {
  y.1[i] ~ dbin(p.bound.1[i], 1)
  p.bound.1[i] <- max(0, min(1, p.1[i]))
  logit(p.1[i]) <- eta.1[i]

  eta.1[i] <- inprod(b[1:P], X.1[i,1:P]) + gamma1[school[i]]
 }

 for (i in 1:n.multi) {
  y.2[i] ~ dbin(p.bound.2[i], 1)
  p.bound.2[i] <- max(0, min(1, p.2[i]))
  logit(p.2[i]) <- eta.2[i]

  eta.2[i] <- inprod(b[1:P], X.2[i,1:P]) + gamma1[school[i]] + gamma2[multi.person[i]]
 }

 # setting up random effect 1
 for (j in 1:n.school) {
  gamma1[j] ~ dnorm(0, tau1)
 }

 tau1 <- pow(rho1, -2)
 rho1 ~ dscaled.gamma(25, 1)

 # setting up random effect 2
```

```
 for (j in 1:n.multi.person) {
  gamma2[j] ~ dnorm(0, tau2)
 }

 tau2 <- pow(rho2, -2)
 rho2 ~ dscaled.gamma(25, 1)


 # priors for fixed effects
 for (f in 1:P) {
   b[f] ~ dt(0, pow(2.5,-2), 1)
 }

 # contrasts
 c[1] <- b[4]
 c[2] <- b[4] + b[6]
 c[3] <- b[4] + b[7]
 c[4] <- b[5]
 c[5] <- b[5] + b[8]
 c[6] <- b[5] + b[9]
 c[7] <- b[5] - b[4]
 c[8] <- b[5] + b[8] - b[4] - b[6]
 c[9] <- b[5] + b[9] - b[4] - b[7]
 c[10] <- b[2]
 c[11] <- b[3]
 c[12] <- b[3] - b[2]
 c[13] <- b[2] + b[6]
 c[14] <- b[3] + b[7]
 c[15] <- b[3] + b[7] - b[2] - b[6]
 c[16] <- b[2] + b[8]
 c[17] <- b[3] + b[9]
 c[18] <- b[3] + b[9] - b[2] - b[8]

 # exceedence probabilities
 for (g in 1:P) {
  pr.b[g] <- step(b[g])
 }
 for (h in 1:18) {
  pr.c[h] <- step(c[h])
 }
}
```

6.9.4 JAGS model code for binomial model

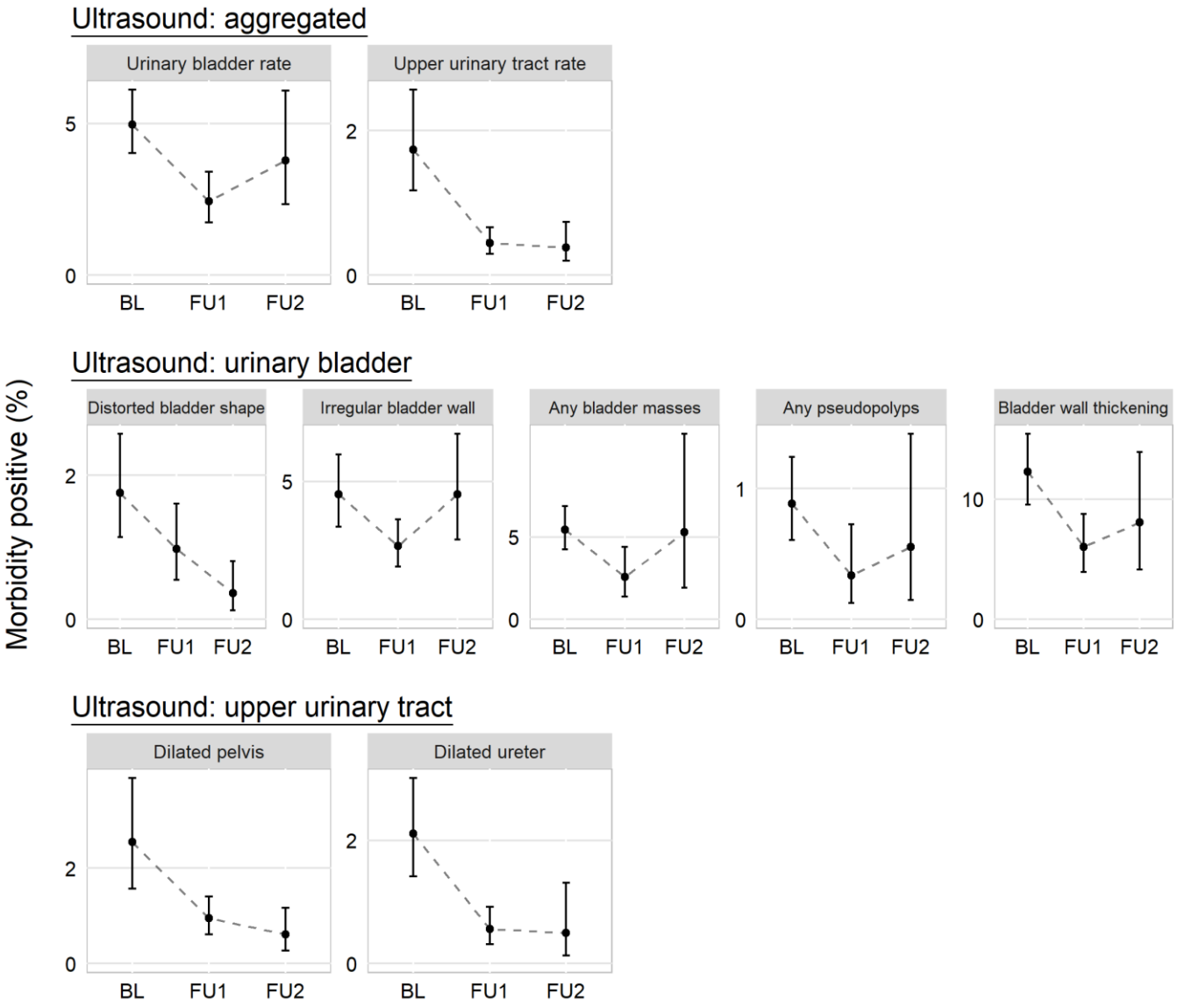
```
model {
 for (i in 1:n.1) {
  y.1[i] ~ dbin(p.1[i], n.tests.1[i])
  logit(p.1[i]) <- eta.1[i]
model {
 for (i in 1:n.single) {
```

```
  y.1[i] ~ dbin(p.1[i], t.1[i])
  logit(p.1[i]) <- eta.1[i]

  eta.1[i] <- inprod(b[1:P], X.1[i,1:P]) + gamma1[school[i]]
}

for (i in 1:n.multi) {
  y.2[i] ~ dbin(p.2[i], t.2[i])
  logit(p.2[i]) <- eta.2[i]

  eta.2[i] <- inprod(b[1:P], X.2[i,1:P]) + gamma1[school[i]] + gamma2[multi.person[i]]
}

# setting up random effect 1
for (j in 1:n.school) {
  gamma1[j] ~ dnorm(0, tau1)
}

tau1 <- pow(rho1, -2)
rho1 ~ dscaled.gamma(25, 1)

# setting up random effect 2
for (j in 1:n.multi.person) {
  gamma2[j] ~ dnorm(0, tau2)
}

tau2 <- pow(rho2, -2)
rho2 ~ dscaled.gamma(25, 1)


# priors for fixed effects
for (f in 1:P) {
   b[f] ~ dt(0, pow(2.5,-2), 1)
}

# contrasts
c[1] <- b[4]
c[2] <- b[4] + b[6]
c[3] <- b[4] + b[7]
c[4] <- b[5]
c[5] <- b[5] + b[8]
c[6] <- b[5] + b[9]
c[7] <- b[5] - b[4]
c[8] <- b[5] + b[8] - b[4] - b[6]
c[9] <- b[5] + b[9] - b[4] - b[7]
c[10] <- b[2]
c[11] <- b[3]
c[12] <- b[3] - b[2]
c[13] <- b[2] + b[6]
c[14] <- b[3] + b[7]
```

```
  c[15] <- b[3] + b[7] - b[2] - b[6]
  c[16] <- b[2] + b[8]
  c[17] <- b[3] + b[9]
  c[18] <- b[3] + b[9] - b[2] - b[8]

  # exceedence probabilities
  for (g in 1:P) {
    pr.b[g] <- step(b[g])
   }
  for (h in 1:18) {
    pr.c[h] <- step(c[h])
  }
}
```

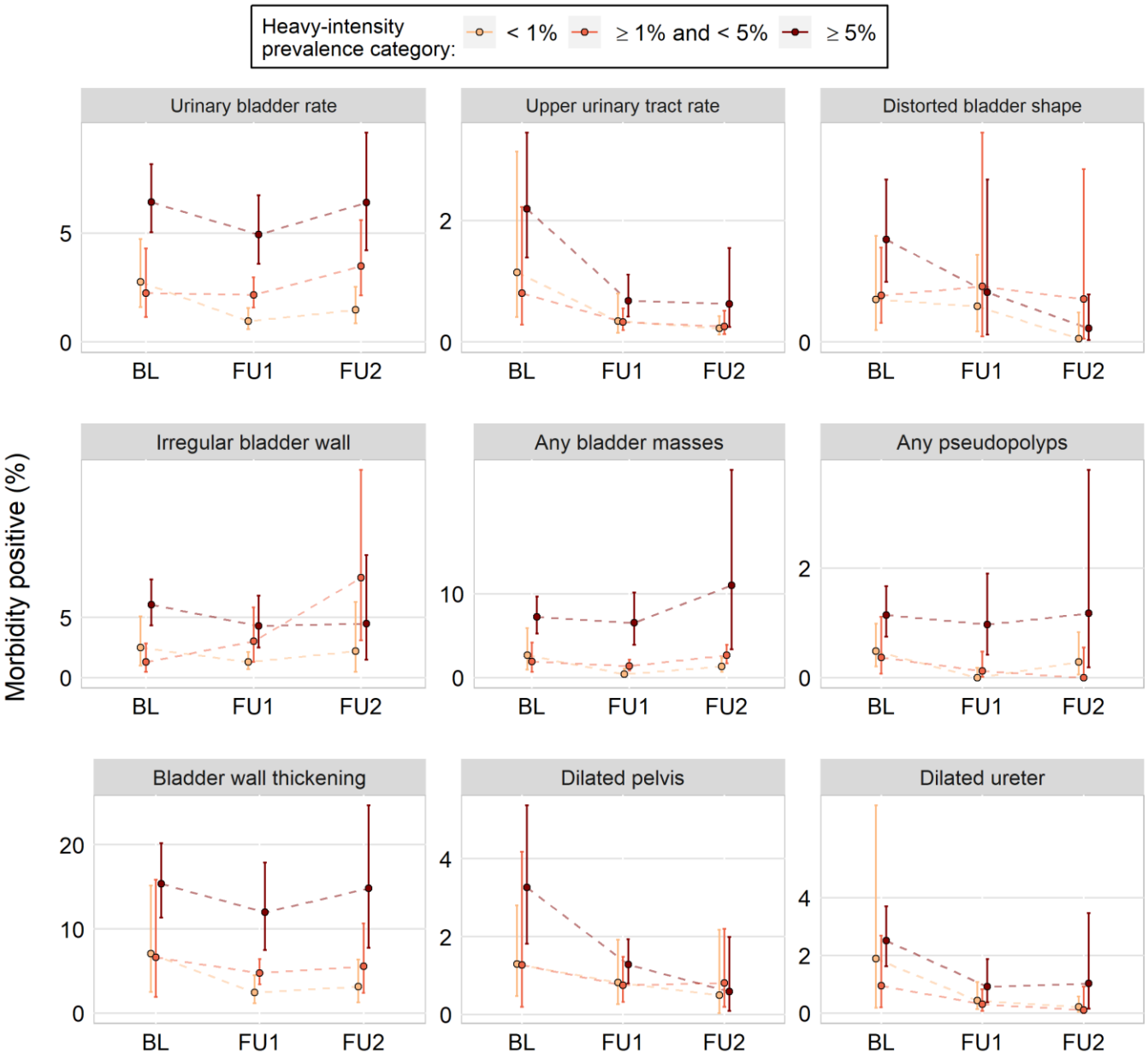
6.9.5 Supplemental Figures

Supplemental Figure 6.1. Line graphs of the percentage of 6-15 year-old school children who were *Schistosoma haematobium*-related morbidity positive at each survey year (BL=baseline, FU1=follow up 1, FU2=follow up 2) not included in Figure 6.1, row B. Clustering by school accounted for in 95% confidence bands.



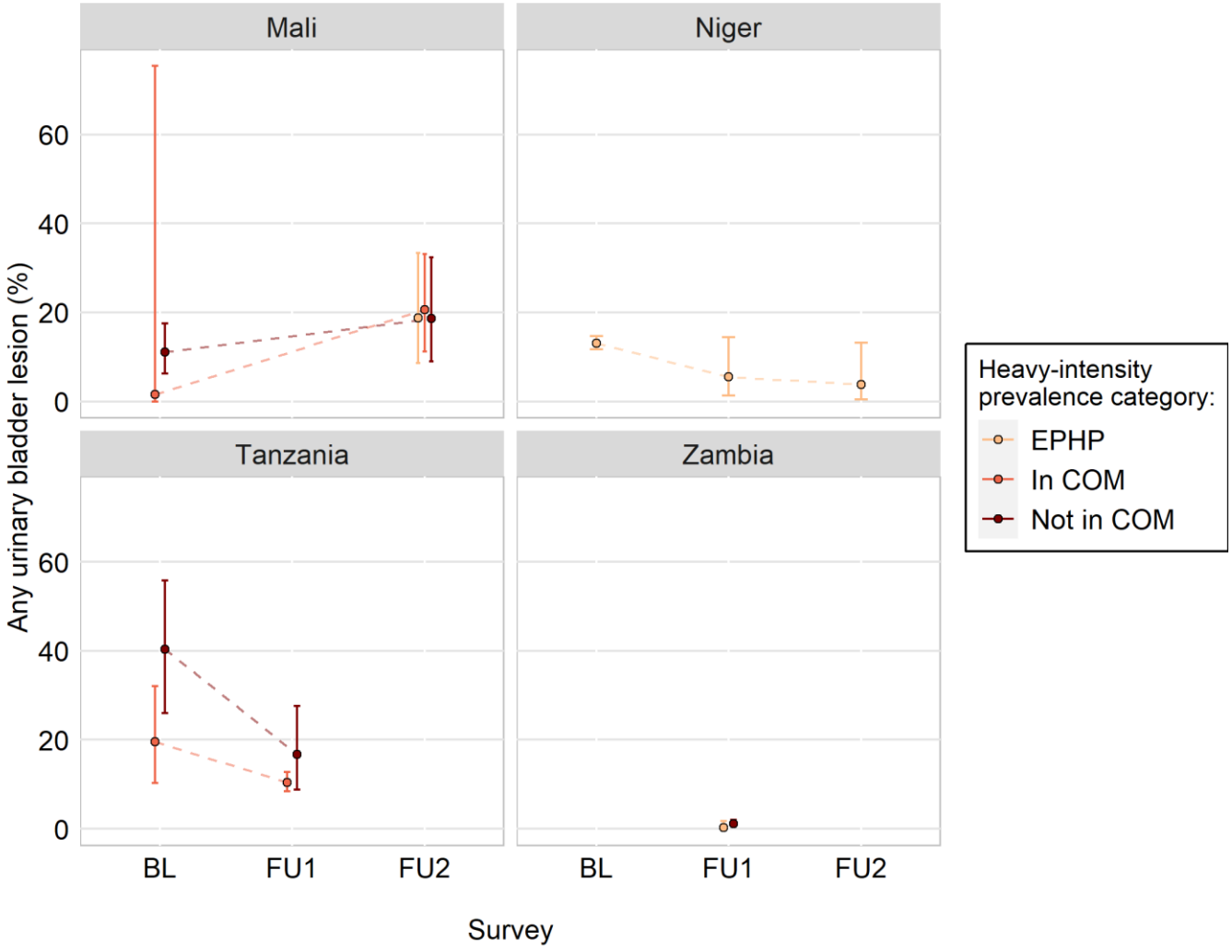
Note: Aggregated ultrasound measures include both dilated left and right pelvis and both dilated left and right ureters, but results shown for dilated pelvis and dilated ureter combine the left and right indicators into a single, binary variable of present in either or not present in either.

Supplemental Figure 6.2. Line graphs of *Schistosoma haematobium*-related morbidity percentages not included in Figure 6.1. Heavy-intensity prevalence category determined at the school-level. Participants were enrolled between 2003 and 2008 at each survey year (BL=baseline, FU1=follow up 1, FU2=follow up 2). Clustering by school accounted for in 95% confidence bands. Infections were assessed by urine filtration. Model-based tests comparisons are included in Supplemental Table 6.2. Plots of aggregated indicators, microhematuria, and self-reported pain while urinating are included in Figure 6.2.

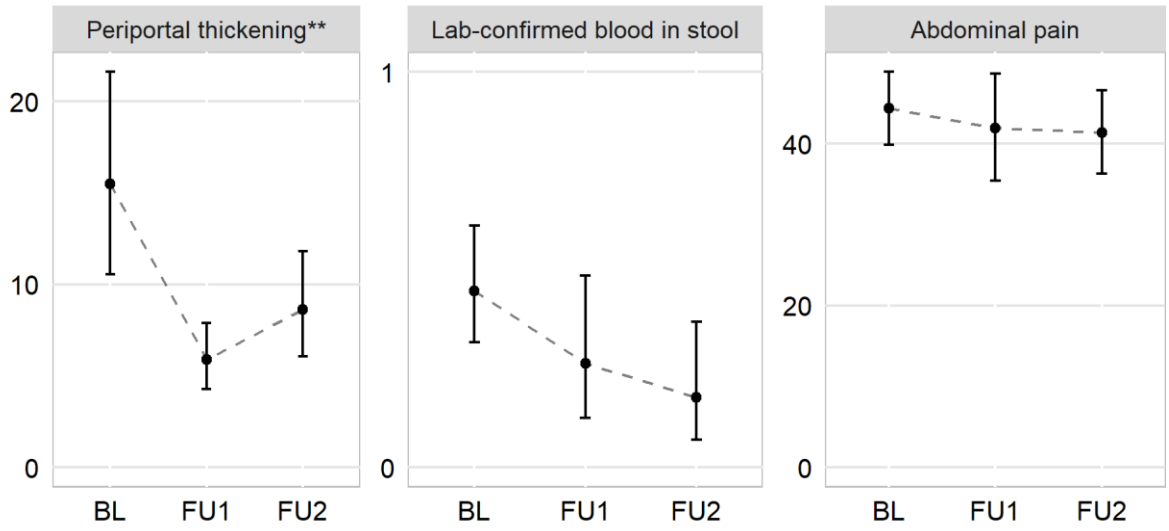


Note: Aggregated ultrasound measures include both dilated left and right pelvis and both dilated left and right ureters, but results shown for dilated pelvis and dilated ureter combine the left and right indicators into a single, binary variable of present in either or not present in either.

Supplemental Figure 6.3. Line graphs of any urinary bladder lesion percentage by heavy intensity prevalence category by country across three surveys (baseline, BL; follow-up 1, FU1; follow-up2, FU2). Participants were enrolled between 2003 and 2008. Clustering by school accounted for in 95% confidence bands. Infections were assessed by urine filtration.

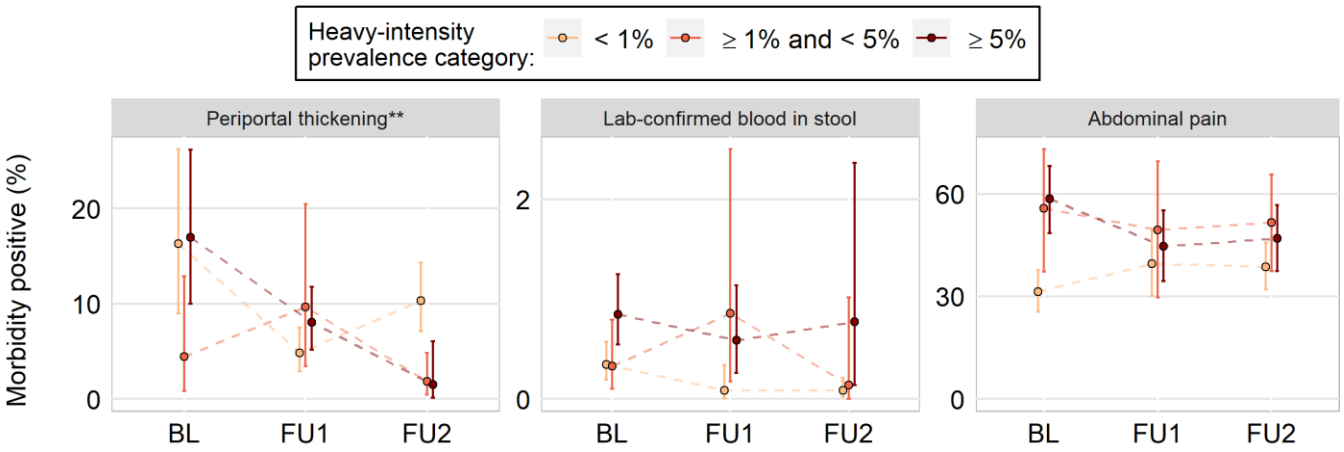


Supplemental Figure 6.4. Line graphs of the percentage of 6-15 year-old school children who were *Schistosoma mansoni*-related morbidity positive at each survey year (BL=baseline, FU1=follow up 1, FU2=follow up 2). Clustering by school accounted for in 95% confidence bands. Selected indicators here are included in Figure 6.1, row C.



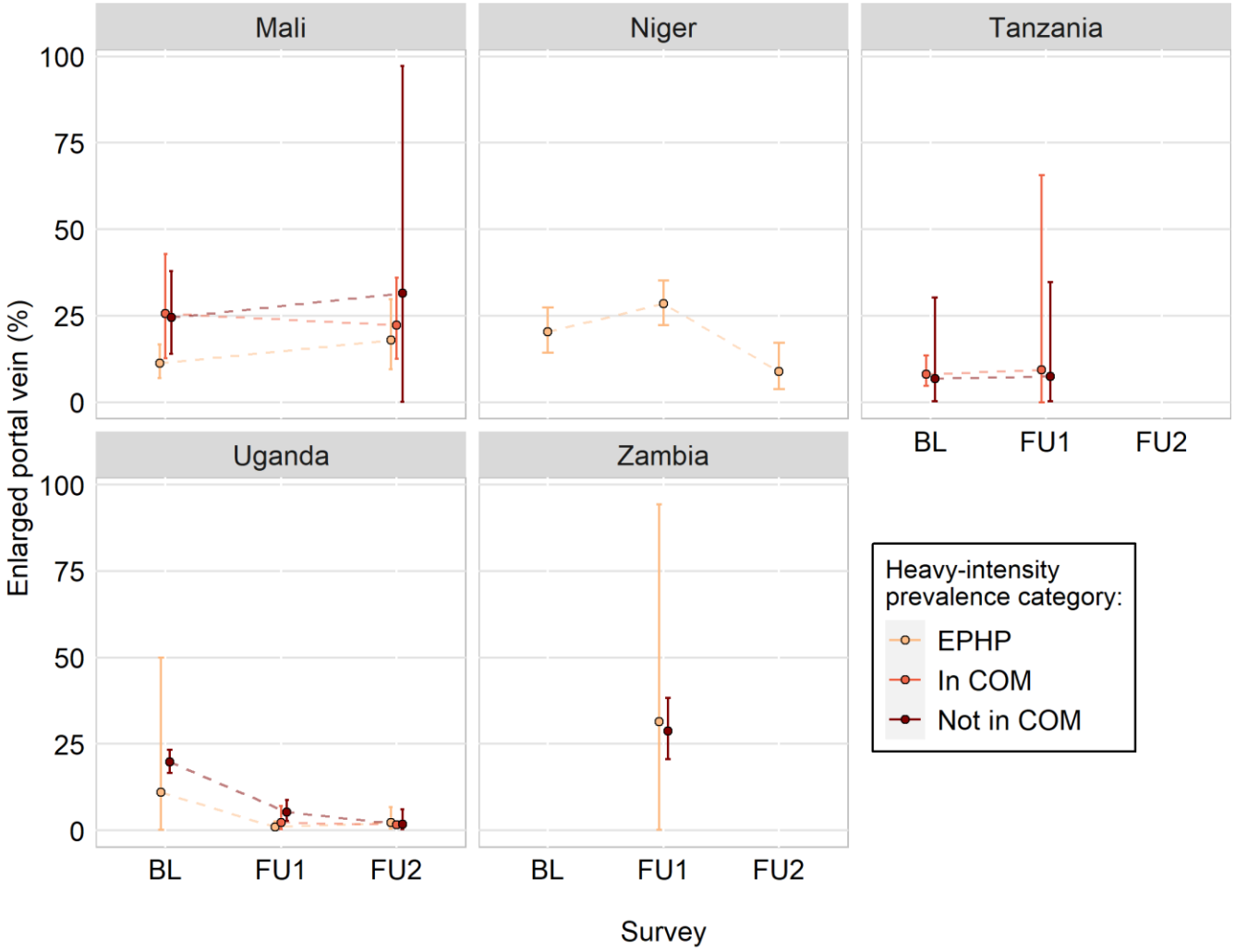
**Periportal thickening is measured by any one of image pattern B, C, D, E, or F.

Supplemental Figure 6.5. Line graphs of Schistosoma mansoni-related morbidity percentages. Heavy-intensity prevalence category determined at the school-level. Participants were enrolled between 2003 and 2008 at each survey year (BL=baseline, FU1=follow up 1, FU2=follow up 2). Clustering by school accounted for in 95% confidence bands. Infections were assessed by Kato-Katz thick smears. Model-based tests comparisons are included in Supplemental Table 6.4. Plots of other indicators are included in Figure 6.3.



**Periportal thickening is measured by any one of image pattern B, C, D, E, or F.

Supplemental Figure 6.6. Line graphs of enlarged portal vein percentage by heavy intensity prevalence category by country across three surveys (baseline, BL; follow-up 1, FU1; follow-up2, FU2). Participants were enrolled between 2003 and 2008. Clustering by school accounted for in 95% confidence bands. Infections were assessed by Kato-Katz thick smears.



6.9.6 Supplemental Tables

Supplemental Table 6.1. Sample sizes of schools and participants in *S. haematobium* analyses. Frequencies are broken down by morbidity and heavy-intensity prevalence category. Cells contain the number of schools with the number of participants in parentheses. Participants are school-age children, with morbidity and infection data, 6-15 years, and enrolled between 2003 and 2008.

		Schools (Participants)		
Morbidity	Survey	Heavy-intensity prevalence < 1%	Heavy-intensity prevalence ≥ 1% and < 5%	Heavy-intensity prevalence ≥ 5%
Ultrasound: aggregated				
Any urinary bladder lesions	Baseline	12 (1635)	12 (1887)	44 (6186)
	Follow up 1	16 (2704)	9 (1586)	11 (1957)
	Follow up 2	7 (1395)	8 (861)	7 (1343)
Any upper urinary tract lesions	Baseline	12 (1628)	12 (1882)	44 (6172)
	Follow up 1	16 (2692)	9 (1589)	11 (1957)
	Follow up 2	7 (1398)	8 (867)	7 (1350)
Urinary bladder rate	Baseline	12 (1752)	12 (1909)	44 (6275)
	Follow up 1	16 (2814)	9 (1660)	11 (1980)
	Follow up 2	7 (1420)	8 (875)	7 (1363)
Upper urinary tract rate	Baseline	12 (1752)	12 (1904)	44 (6267)
	Follow up 1	16 (2813)	9 (1662)	11 (1980)
	Follow up 2	7 (1421)	8 (876)	7 (1363)
Ultrasound: urinary bladder				
Distorted bladder shape	Baseline	16 (2707)	9 (1586)	11 (1957)
	Follow up 1	7 (1400)	8 (864)	7 (1345)
	Follow up 2	12 (1641)	12 (1892)	44 (6213)
Irregular bladder wall	Baseline	16 (2708)	9 (1592)	11 (1957)
	Follow up 1	7 (1400)	8 (865)	7 (1355)
	Follow up 2	12 (1642)	12 (1894)	44 (6219)
Any bladder masses	Baseline	16 (2707)	9 (1592)	11 (1957)
	Follow up 1	7 (1399)	8 (865)	7 (1355)
	Follow up 2	12 (1641)	12 (1893)	44 (6213)
Any pseudopolyps	Baseline	16 (2706)	9 (1592)	11 (1957)
	Follow up 1	7 (1400)	8 (866)	7 (1356)
	Follow up 2	12 (1642)	12 (1893)	44 (6210)
Bladder wall thickening	Baseline	16 (2708)	9 (1592)	11 (1957)
	Follow up 1	7 (1400)	8 (865)	7 (1356)
	Follow up 2	16 (2707)	9 (1586)	11 (1957)
Ultrasound: upper urinary tract				

Dilated left or right pelvis	Baseline	12 (1629)	12 (1886)	44 (6187)
	Follow up 1	16 (2692)	9 (1592)	11 (1957)
	Follow up 2	7 (1400)	8 (867)	7 (1353)
Dilated left or right Ureter	Baseline	12 (1641)	12 (1888)	44 (6195)
	Follow up 1	16 (2705)	9 (1591)	11 (1957)
	Follow up 2	7 (1400)	8 (867)	7 (1353)
Laboratory and self-report				
Microhematuria	Baseline	15 (1963)	14 (2147)	59 (7766)
	Follow up 1	19 (3221)	10 (1725)	11 (1969)
	Follow up 2	7 (1409)	8 (894)	7 (1369)
Pain while urinating	Baseline	15 (1953)	14 (2130)	49 (6918)
	Follow up 1	19 (3208)	10 (1719)	11 (1961)
	Follow up 2	7 (1403)	8 (869)	7 (1365)

Supplemental Table 6.2. Odds ratios and 95% credible intervals from Bayesian logistic regression models comparing morbidity positive proportions between heavy-intensity prevalence categories within surveys for *S. haematobium*-related morbidities not presented in Table 6.1. Bold font indicates the 95% credible interval does not contain one. Participants are school-age children (6-15 years) enrolled between 2003 and 2008. Corresponding plots of unmodeled morbidity prevalence are in Figure 6.2 and Supplemental Figure 6.3.

Morbidity	Survey	< 1% vs. ≥ 5%	1-5% v. ≥ 5%	< 1% v. 1-5%
Ultrasound: aggregated				
Urinary bladder rate	Baseline	**0.42 (0.35, 0.51)**	**0.65 (0.53, 0.79)**	**0.65 (0.52, 0.82)**
	Follow up 1	**0.43 (0.37, 0.51)**	**0.75 (0.64, 0.88)**	**0.58 (0.48, 0.69)**
	Follow up 2	0.36 (0.28, 0.46)	**0.41 (0.31, 0.53)**	0.89 (0.64, 1.22)
Upper urinary tract rate	Baseline	1.43 (0.97, 2.10)	1.30 (0.90, 1.86)	1.10 (0.72, 1.67)
	Follow up 1	**0.61 (0.41, 0.90)**	1.01 (0.68, 1.49)	**0.61 (0.39, 0.95)**
	Follow up 2	**0.38 (0.18, 0.77)**	0.61 (0.30, 1.15)	0.63 (0.26, 1.50)
Ultrasound: urinary bladder				
Distorted bladder shape	Baseline	**0.22 (0.13, 0.36)**	**0.48 (0.32, 0.73)**	**0.46 (0.25, 0.81)**
	Follow up 1	**0.29 (0.16, 0.52)**	**0.46 (0.25, 0.81)**	0.64 (0.32, 1.26)
	Follow up 2	0.43 (0.10, 1.64)	0.61 (0.14, 2.33)	0.70 (0.13, 3.87)
Irregular bladder wall	Baseline	**0.36 (0.24, 0.53)**	**0.52 (0.35, 0.75)**	0.70 (0.43, 1.12)
	Follow up 1	**0.41 (0.27, 0.61)**	0.87 (0.61, 1.24)	**0.47 (0.31, 0.71)**
	Follow up 2	**0.49 (0.31, 0.77)**	**0.37 (0.20, 0.63)**	1.35 (0.73, 2.56)
Any bladder masses	Baseline	**0.40 (0.26, 0.60)**	**0.62 (0.41, 0.94)**	0.64 (0.39, 1.06)
	Follow up 1	**0.20 (0.13, 0.29)**	**0.34 (0.23, 0.48)**	**0.59 (0.37, 0.93)**
	Follow up 2	**0.31 (0.18, 0.50)**	**0.40 (0.22, 0.69)**	0.77 (0.38, 1.58)
Any pseudopolyps	Baseline	**0.35 (0.14, 0.76)**	**0.30 (0.11, 0.69)**	1.18 (0.38, 3.79)
	Follow up 1	**0.20 (0.08, 0.43)**	**0.39 (0.18, 0.79)**	0.51 (0.18, 1.34)
	Follow up 2	**0.00 (0.00, 0.16)**	**0.15 (0.01, 0.75)**	0.02 (0.00, 2.32)
Bladder wall thickening	Baseline	**0.24 (0.18, 0.32)**	**0.48 (0.36, 0.63)**	**0.50 (0.35, 0.70)**
	Follow up 1	**0.28 (0.22, 0.37)**	**0.64 (0.50, 0.81)**	**0.45 (0.33, 0.59)**
	Follow up 2	**0.27 (0.18, 0.39)**	**0.25 (0.15, 0.40)**	1.05 (0.60, 1.89)
Ultrasound: upper urinary tract				
Dilated left or right pelvis	Baseline	0.69 (0.38, 1.24)	0.72 (0.43, 1.17)	0.97 (0.49, 1.87)
	Follow up 1	0.62 (0.35, 1.09)	0.63 (0.34, 1.12)	1.00 (0.51, 1.97)
	Follow up 2	0.88 (0.28, 2.47)	0.90 (0.25, 2.72)	0.98 (0.24, 4.11)
Dilated left or right ureter	Baseline	1.10 (0.63, 1.93)	0.67 (0.36, 1.19)	1.65 (0.84, 3.31)
	Follow up 1	0.69 (0.36, 1.31)	0.80 (0.42, 1.51)	0.86 (0.41, 1.81)
	Follow up 2	**0.27 (0.06, 0.85)**	**0.01 (0.00, 0.28)**	*

* The odds ratio for this effect was highly variable due to the prevalence at both surveys being close to zero. We chose to omit this effect due to its uncertainty.

Supplemental Table 6.3. Sample sizes of schools and participants in *S. mansoni* analyses. Frequencies are broken down by morbidity and heavy-intensity prevalence category. Cells contain the number of schools with the number of participants in parentheses. Participants are school-age children, with morbidity and infection data, aged 6-15 years, and enrolled between 2003 and 2008.

Morbidity	Survey	Heavy-intensity prevalence < 1%	Heavy-intensity prevalence ≥ 1% and < 5%	Heavy-intensity prevalence ≥ 5%
Ultrasound				
Image pattern	Baseline	24 (3225)	5 (429)	16 (1423)
	Follow up 1	22 (3889)	7 (537)	12 (959)
	Follow up 2	24 (3631)	6 (434)	7 (454)
Enlarged portal vein	Baseline	24 (3164)	5 (464)	16 (1501)
	Follow up 1	19 (3296)	7 (537)	12 (960)
	Follow up 2	24 (3637)	6 (435)	7 (456)
Laboratory				
Lab-confirmed blood in stool	Baseline	57 (8080)	17 (2421)	22 (2718)
	Follow up 1	50 (8166)	12 (1400)	17 (1871)
	Follow up 2	26 (4731)	6 (709)	8 (776)
Lab-confirmed diarrhea	Baseline	46 (6290)	17 (2418)	22 (2715)
	Follow up 1	42 (5537)	12 (1400)	17 (1858)
	Follow up 2	18 (2213)	7 (847)	9 (815)
Self-report				
Self-reported diarrhea	Baseline	65 (8890)	20 (2627)	29 (3319)
	Follow up 1	50 (8111)	12 (1368)	17 (1840)
	Follow up 2	36 (5355)	8 (890)	11 (946)
Abdominal pain	Baseline	35 (4457)	15 (1685)	25 (2724)
	Follow up 1	24 (4597)	9 (986)	13 (1365)
	Follow up 2	36 (5349)	8 (889)	11 (946)

Supplemental Table 6.4. Odds ratios and 95% credible intervals from Bayesian logistic regression models comparing morbidity positive proportions between heavy-intensity prevalence categories within surveys for *S. mansoni*-related morbidities not presented in Table 6.2. Bold font indicates the 95% credible interval does not contain one. Participants are school-age children (6-15 years) enrolled between 2003 and 2008. Corresponding plots of unmodeled morbidity prevalence are in Figure 6.3 and Supplemental Figure 6.4.

Morbidity	Survey	< 1% vs. ≥ 5%	1-5% v. ≥ 5%	< 1% v. 1-5%
Ultrasound				
Image pattern C-F	Baseline	**0.12 (0.03, 0.38)**	**0.00 (0.00, 0.18)**	**0.00 (0.00, 0.02)**
	Follow up 1	**0.20 (0.05, 0.61)**	**0.31 (0.02, 2.62)**	**0.06 (0.00, 0.43)**
	Follow up 2	**0.00 (0.00, 0.28)**	Non-estimable*	**0.01 (0.00, 0.07)**
Image pattern B-F	Baseline	**0.48 (0.35, 0.64)**	**0.28 (0.15, 0.48)**	1.72 (0.99, 3.11)
	Follow up 1	**0.32 (0.23, 0.45)**	1.06 (0.70, 1.58)	**0.30 (0.20, 0.46)**
	Follow up 2	**0.62 (0.41, 0.93)**	**0.18 (0.07, 0.37)**	**3.52 (1.74, 8.22)**
Enlarged portal vein	Baseline	**0.31 (0.25, 0.39)**	**0.52 (0.37, 0.71)**	**0.60 (0.46, 0.80)**
	Follow up 1	**0.75 (0.58, 0.98)**	0.88 (0.57, 1.34)	0.85 (0.58, 1.28)
	Follow up 2	0.95 (0.63, 1.46)	1.82 (0.99, 3.31)	**0.52 (0.32, 0.87)**
Laboratory				
Lab-confirmed blood in stool	Baseline	**0.32 (0.15, 0.67)**	**0.37 (0.14, 0.88)**	0.88 (0.38, 2.26)
	Follow up 1	**0.12 (0.04, 0.32)**	1.44 (0.58, 3.60)	**0.08 (0.03, 0.22)**
	Follow up 2	**0.06 (0.02, 0.17)**	**0.10 (0.00, 0.64)**	0.57 (0.07, 16.69)
Lab-confirmed diarrhea	Baseline	**0.74 (0.59, 0.92)**	**0.50 (0.39, 0.64)**	**1.48 (1.17, 1.88)**
	Follow up 1	**0.32 (0.25, 0.42)**	**0.66 (0.48, 0.89)**	**0.49 (0.37, 0.65)**
	Follow up 2	**0.33 (0.24, 0.44)**	**1.41 (1.01, 1.95)**	**0.23 (0.17, 0.32)**
Self-report				
Self-reported diarrhea	Baseline	**0.51 (0.45, 0.58)**	0.97 (0.84, 1.11)	**0.53 (0.47, 0.60)**
	Follow up 1	1.06 (0.92, 1.23)	1.18 (0.99, 1.40)	0.90 (0.78, 1.05)
	Follow up 2	0.88 (0.75, 1.02)	1.23 (1.00, 1.50)	**0.71 (0.60, 0.85)**
Abdominal pain	Baseline	**0.68 (0.59, 0.78)**	**0.70 (0.60, 0.82)**	0.97 (0.84, 1.12)
	Follow up 1	**1.56 (1.33, 1.83)**	**0.79 (0.65, 0.96)**	**1.97 (1.66, 2.34)**
	Follow up 2	**1.31 (1.10, 1.56)**	**1.51 (1.22, 1.86)**	0.87 (0.73, 1.04)

* The odds ratio for this effect was highly variable due to the prevalence at both surveys being close to zero. We chose to omit this effect due to its uncertainty.

7 Urogenital schistosomiasis infection prevalence targets to determine elimination as a public health problem based on microhematuria prevalence in school-age children

Ryan E. Wiegand[1,2,3*], Fiona M. Fleming[4], Anne Straily[1], Susan P. Montgomery[1], Sake J. de Vlas[5], Jürg Utzinger[2,3], Penelope Vounatsou[2,3], W. Evan Secor[1]

[1] *Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America*

[2] *Swiss Tropical and Public Health Institute, Basel, Switzerland*

[3] *University of Basel, Basel, Switzerland*

[4] *SCI Foundation, London, United Kingdom*

[5] *Department of Public Health, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands*

*Corresponding author

Email: rwiegand@cdc.gov

[This manuscript has published in *PLOS Neglected Tropical Diseases* (2021) 15(6): e0009451; https://doi.org/10.1371/journal.pntd.0009451.]

7.1 Abstract

Background: Recent research suggests that schistosomiasis targets for morbidity control and elimination as a public health problem could benefit from a reanalysis. These analyses would define evidence-based targets that control programs could use to confidently assert that they had controlled or eliminated schistosomiasis as a public health problem. We estimated how low *Schistosoma haematobium* infection levels diagnosed by urine filtration in school-age children should be decreased so that microhematuria prevalence was at or below a "background" level of morbidity.

Methodology: Data obtained from school-aged children in Burkina Faso, Mali, Niger, Tanzania, and Zambia who participated in schistosomiasis monitoring and evaluation cohorts were reanalyzed before and after initiation of preventive chemotherapy. Bayesian models estimated the infection level prevalence probabilities associated with microhematuria thresholds ≤ 10%, 13%, or 15%.

Principal findings: An infection prevalence of 5% could be a sensible target for urogenital schistosomiasis morbidity control in children as microhematuria prevalence was highly likely to be below 10% in all surveys. Targets of 8% and 11% infection prevalence were highly likely to result in microhematuria levels less than 13% and 15%, respectively. By contrast, measuring heavy-intensity infections only achieves these thresholds at impractically low prevalence levels.

Conclusions/significance: A target of 5%, 8%, or 11% urogenital schistosomiasis infection prevalence in school-aged children could be used to determine whether a geographic area has controlled or eliminated schistosomiasis as a public health problem depending on the local background threshold of microhematuria.

Funding: The Schistosomiasis Control Initiative was supported by the Bill and Melinda Gates Foundation (grant 13122).

7.2 Author Summary

For urogenital schistosomiasis, targets for morbidity control and elimination as a public health problem are based on the percentage of school-age children with a heavy intensity infection in a set of sentinel schools. These targets are not tied to specific morbidity indicators and should be reevaluated due to the recognition that all infections have an impact on people's health. Multiple studies have shown a strong association between urogenital schistosomiasis infection and microhematuria. In these analyses, data from children aged 6-15 years in monitoring and evaluation cohorts from five African countries were used to determine whether infection and heavy intensity infection targets could be developed based on a prevalence of microhematuria in a school without schistosomiasis infections before and after initiation of a deworming program. Results indicate that targets of 5%, 8%, or 11% urogenital schistosomiasis infection prevalence in school-aged children can be used to reliably conclude that a school is below a microhematuria prevalence of 10%, 13%, or 15%, respectively. These targets could be used by control program managers as guide to determine whether morbidity has been controlled or eliminated as a public health problem.

7.3 Introduction

The primary goal of the World Health Organization (WHO) schistosomiasis control program guidelines since the early 2000's has been to reduce morbidity (WHO 2002). For most of sub-Saharan Africa, the primary control intervention currently employed is the distribution of praziquantel as preventive chemotherapy (French et al. 2018). Due to limited praziquantel availability when the guidelines were developed, WHO focused on reducing the most severe morbidities caused by schistosomiasis. Based on limited data showing associations between severe morbidities and heavy intensity infections (≥ 50 *Schistosoma haematobium* eggs per 10 ml of urine) (WHO 1987), control of morbidity was defined as a <5% prevalence of heavy intensity infections (PHI) and elimination of schistosomiasis as a public health problem was defined as <1% PHI (WHO 2013). Recent analyses suggest the prevalence of morbidity associated with these PHI targets for morbidity control and

elimination as a public health problem may not be distinguishable from each other (Chapter 6), drawing into question their programmatic usefulness. Furthermore, WHO guidance for frequency of preventive chemotherapy is based on infection prevalence (WHO 2002). This results in most country programs only measuring prevalence and creates a disconnect between the stated program goals and implementation of interventions to achieve them.

Praziquantel donations from Merck KGaA have increased the number of people treated globally nearly 10-fold from 2006 to 2017 (WHO 2018). Concurrently, there has been an increased appreciation of more subtle manifestations of schistosomiasis morbidity (King et al. 2005; King 2015; Freer et al. 2018). Thus, there is interest in refocusing schistosomiasis guidelines on morbidity control (French et al. 2018) with calls to create more detailed and specific targets (Lo et al. 2017). A robust, evidence-based target that identifies the point at which schistosomiasis is eliminated as a public health problem will be crucial to meet the goal to approximately double the number of countries validated as having eliminated schistosomiasis as a public health problem by 2023 (WHO 2020b).

Microhematuria is strongly associated with *S. haematobium* infections and has been used in place of egg detection to estimate community-level prevalence (Krauth et al. 2015). A meta-analysis of the use of dipstick-detected microhematuria for the diagnosis of *S. haematobium* infection found 81% (95% confidence interval (CI) 79-83%) sensitivity and 89% (95% CI 87-92%) specificity across different locations and subgroups (King et al. 2013). Analyses of data from multiple, national schistosomiasis control programs found microhematuria prevalence correlated well with PHI (Chapter 5) and WHO's infection intensity categories (Chapter 6). Therefore microhematuria would appear to be a strong candidate as a morbidity indicator that can be reduced to a threshold level that is locally acceptable (WHO 2020b).

Because identifying an indicator for eliminating schistosomiasis as a public health problem is critical to the success of control programs for the next 10 years (WHO 2020b), we investigated *S. haematobium* infection prevalence levels and their likelihood to be the same as or lower than "background" microhematuria levels, i.e., the prevalence of microhematuria in an area with no cases of schistosomiasis. We utilized literature on the expected background prevalence of microhematuria (Krauth et al. 2015; Ochodo et al. 2015) to determine potential threshold levels. Evaluations were performed using control program data before and after one and two years of annual preventative chemotherapy with praziquantel from five African countries supported through the Schistosomiasis Control Initiative (SCI) (Fenwick et al. 2009).

7.4 Methods

7.4.1 Ethics statement

The Imperial College Research Ethics Committee (ICREC_8_2_2, EC No. 03.36, R&D No. 03/SB/003E) and each country's ethical review boards located in the Ministries of Health approved the use of these data. The US Centers for Disease Control and Prevention (CDC) was determined to be a non-engaged research partner. Meetings were held with teachers and parents to inform them about participation in these programs. Verbal consent from community leaders in Mali was given since this was the standard consent at the time. For the other countries, head teachers provided written informed consent. Parents or guardians provided consent and children provided assent. Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

7.4.2 Study design and data collection

Data for these analyses come from national control programs for schistosomiasis and soil-transmitted helminthiasis in Burkina Faso (Koukounari et al. 2007; Garba et al. 2009), Mali (Garba et al. 2009), Niger (Garba et al. 2009), Tanzania (Kabatereine et al. 2006), and Zambia (Kabatereine et al. 2006). Briefly, countries began a national program scale-up including distribution of praziquantel (for schistosomiasis) and albendazole (for soil-transmitted helminthiasis) to treat endemic populations based

on WHO guidance (Montresor et al. 2002). Two monitoring and evaluation cohorts were used in these analyses. First, a longitudinal cohort of children aged 6-12 years in primary schools that were randomly selected from various endemic settings. Schools were treated every year and followed for two more years with the following exceptions: Burkina Faso did not treat schools between baseline and follow-up 1; some schools in Mali were treated twice between baseline and follow up 1 and some schools were treated annually but no data were collected at follow-up 1; Tanzanian schools were not treated between follow-up 1 and 2; and Zambia did not collect data after follow up 1. When a school failed to be treated once annually, that school was removed from subsequent surveys We also included any children aged 6-15 years from a second community cohort and pooled with the children from the longitudinal cohort for school-level estimates. The second cohort mostly contained adults, but had a range of persons aged 4-88 years.

Both cohorts were sampled for the same number of years at approximately the same time. These surveys were performed approximately one year apart and are referred to as baseline, follow-up 1, and follow-up 2. Participants were required to be above 94 cm in height and not currently ill. Praziquantel and albendazole were distributed to consenting participants each year. The baseline survey occurred pre-treatment; the two follow-up surveys each occurred immediately before the annual praziquantel dose.

7.4.3 Infection and microhematuria data

The presence of *S. haematobium* was determined by urine filtration. School-age children from Burkina Faso, Tanzania, and Zambia were evaluated with a single urine sample and single filtration; Nigerien school-age children were evaluated by two filtrations from a single urine sample. In Mali, school-age children were evaluated with single filtrations of two urine samples collected on consecutive days. Approximately 10 ml of urine were passed through a filter, stained, and microscopically examined for *S. haematobium* eggs. If any eggs were detected in a urine sample, that participant was deemed

positive. School-age children with 50 or more *S. haematobium* eggs per 10 ml of urine were deemed to have a heavy intensity infection. Microhematuria was assessed with Hemastix (Bayer Diagnostics; Basingstoke, United Kingdom) dipsticks according to manufacturer instructions. School-age children with a positive or trace-positive (hemolyzed or non-hemolyzed) reading were considered positive.

7.4.4 Data analysis methods

R version 4.0.3 was used for analyses. A binomial, Bayesian, errors in variables (Durbin 1954; Carroll et al. 1984) model was used to assess the relationship between infection and microhematuria prevalence. This approach accounts for uncertainty in the prevalence of microhematuria and prevalence of infection by assuming both are binomially distributed. For each microhematuria prevalence threshold, infection measurement (all infection prevalence or PHI), and survey, four models were fit. The first three models used linear, quadratic, and cubic functions of infection prevalence, respectively, to predict morbidity prevalence. The fourth used a function utilized by van der Werf and de Vlas (van der Werf et al. 2004) for associating community infection prevalence and morbidity indicator prevalence. Models were fit via Markov chain Monte Carlo (MCMC) methods using the rjags package (Plummer 2019). Full details on the statistical and MCMC methods are included in the supplemental materials along with results from all models. Best fitting models were determined by the smallest deviance information criterion (DIC) (Plummer 2002) (Supplemental Table 7.1).

We explored three microhematuria prevalence thresholds. Thresholds of 13% and 15% were based on the results of Krauth and colleagues (Krauth et al. 2015) who found the prevalence of microhematuria unrelated to *S. haematobium* infection to be approximately 13% or 15-20% after incorporating data from a systematic review (Ochodo et al. 2015). They estimated about 3.4% of those infections to be missed infections post-treatment, suggesting 10% could be a more appropriate estimate.

Results are presented as the percent chance that a school's *S. haematobium* infection prevalence had a microhematuria prevalence less than the threshold of 10%, 13%, or 15%. A depiction of the relationship between infection prevalence, microhematuria prevalence, and the percent chance is included in the supplement (Supplemental Figure 7.1). From these curves, one chooses an appropriate percent chance to determine the infection prevalence. The highest infection prevalence that is predicted to result in a microhematuria prevalence below the morbidity threshold is then referred to as the target prevalence. The same approach was used for modeling PHI, where the results are reported as the percent chance that a school with a given PHI target is below the threshold.

7.5 Results

A total of 91 schools were analyzed at baseline, 41 at follow-up 1, and 22 at follow-up 2. The median (and range) for *S. haematobium* infection prevalence was 44.4% (0.0-99.0%) at baseline, 11.3% (0.0-83.5%) at follow-up 1, and 31.2% (2.8-89.2%) at follow-up 2. For microhematuria prevalence, the median and range was 38.5% (0.8-94.7%) at baseline, 11.3% (0.0-60.4%) at follow-up 1, and 14.8% (4.0-71.6%) at follow-up 2.

A grid of scatter plots with each model fit shows only slight differences in the models (Figure 7.1), which was also true when considering the fit statistics (Supplemental Table 7.1) and the model predictions in the range most relevant to these analyses (Supplemental Figure 7.2).

Best fitting curves of infection prevalence and the percent chance of a school falling below the three microhematuria thresholds were largely similar across surveys, with the baseline curve falling between the two follow-up curves (Figure 7.2). Curves from all models were largely consistent, though at follow up 2 the function utilized by van der Werf and de Vlas (van der Werf et al. 2004) failed to reach a 90% chance of achieving the microhematuria threshold (Supplemental Figure 7.3). In best fitting models, infection prevalence targets ≤ 5%, 8%, and 11% provided a 90% chance that the microhematuria

Figure 7.1. Scatter plots of Schistosoma haematobium infection prevalence and microhematuria prevalence of children aged 6-15 years from Burkina Faso, Mali, Niger, Tanzania, and Zambia participating in schistosomiasis control program activities between 2003 and 2008. Points are scaled based on the number of school-age children with *S. haematobium* infection data. Black line indicates model fits and gray shading indicates 95% Bayesian credible intervals (BCIs) from errors in variables model. The dashed line denotes 10% microhematuria prevalence.

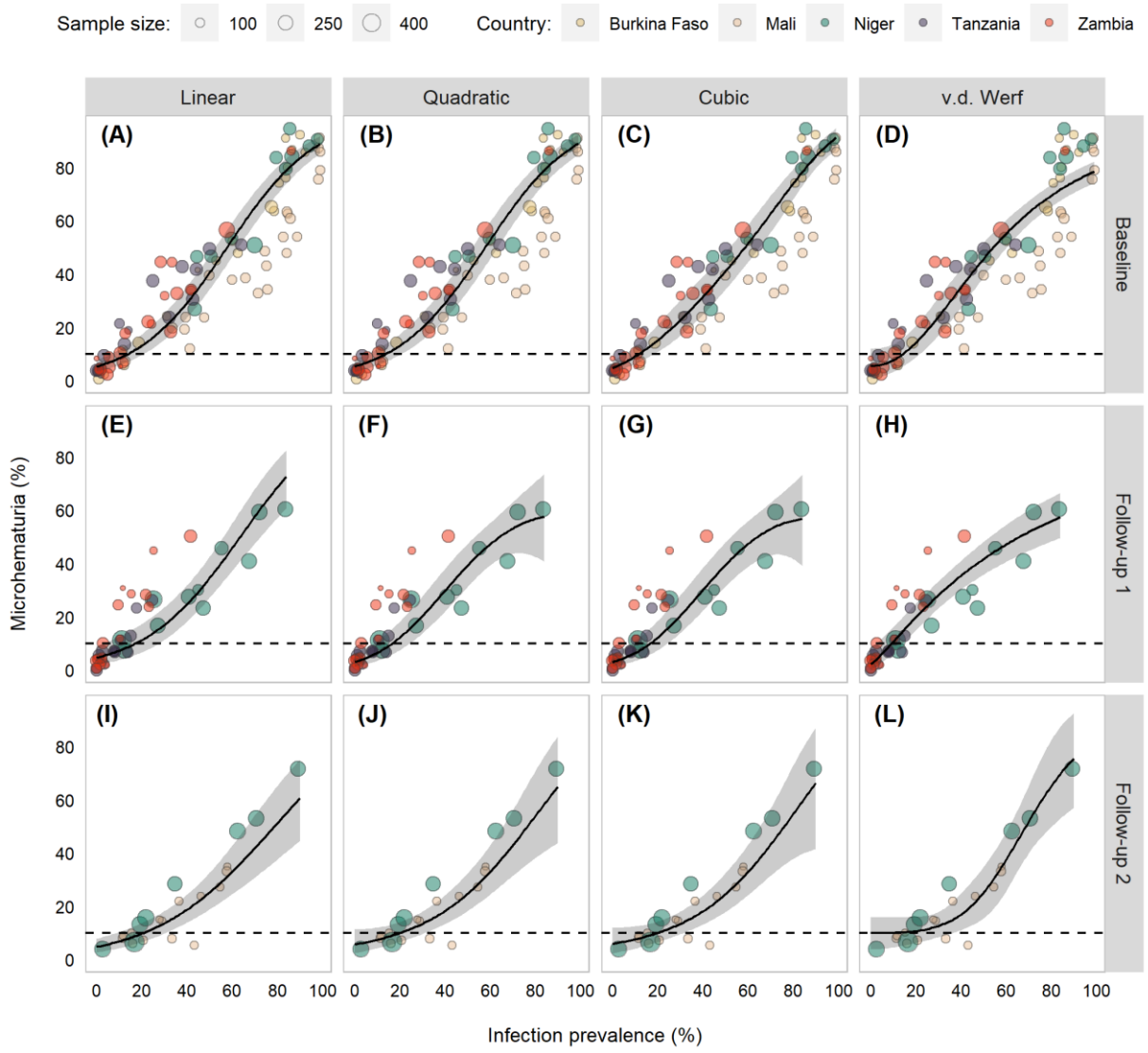
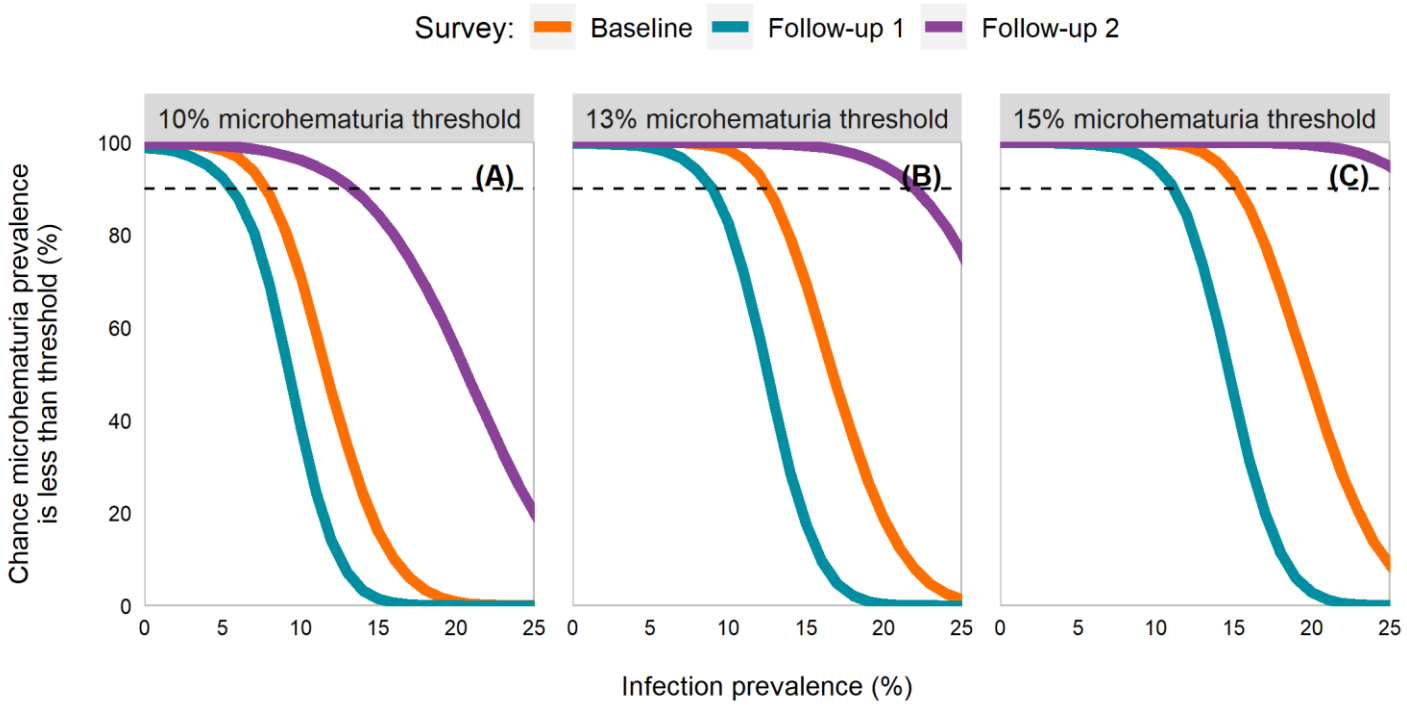


Figure 7.2. Line plots by survey of the percent chance a school with a given *Schistosoma haematobium* infection prevalence is below the microhematuria threshold. Panel A is for a 10% microhematuria threshold ; panel B for 13%; and panel C for 15%. Estimates utilized children aged 6-15 years from Burkina Faso, Mali, Niger, Tanzania, and Zambia participating in schistosomiasis control program activities between 2003 and 2008. Full description of the methods is in the supplementary materials. The dashed line indicates a 90% chance of being below the threshold.



thresholds of 10%, 13%, and 15%, respectively, would be met. The 8% and 11% were very close to having a 95% chance of reaching the 10% and 15% thresholds, respectively, but the percent chance estimate at follow up 1 was slightly less than 95% (94.0% for the 8% target and 94.8% for the 11% target; Supplemental Table 7.2).

The median and range of PHI in schools studied was 9.1% (0.0-79.8%) at baseline, 1.5% (0.0-20.7%) at follow up 1, and 1.8% (0.0-33.8%) at follow up 2. Model fits differed some at the low end (Supplemental Figure 7.4) and high end (Figure 7.3) at baseline but were largely similar for the follow up surveys. At baseline, PHI targets of 0%, 1%, and 2% provided a 97.2%, 98.3%, and 96.0% chance, respectively, that the microhematuria thresholds of 10%, 13%, and 15% would be met (Figure 7.4; Supplemental Table 7.3). At follow up 1, no PHI-based target was able to achieve above a 16.4% chance of reaching any of the thresholds. At follow up 2, a PHI target of 0% was estimated to have a 92.0% chance of reaching the 15% threshold.

7.6 Discussion

Our study examined the relationship between microhematuria and *S. haematobium* infection prevalence. The results suggest different infection prevalence targets that are realistic and measurable for evaluating whether microhematuria has reached or passed below a background level threshold and therefore schistosomiasis is eliminated as a public health problem. Based on these results, national control programs could choose one of the three microhematuria thresholds (10%, 13%, or 15%) and a percent chance of achieving it to determine an infection prevalence target based on the follow-up survey results. We presented targets of 5%, 8%, and 11% infection prevalence since these had a high (90%) chance that they would result in a school possessing a microhematuria prevalence below the thresholds of 10%, 13%, and 15%, respectively. Though, programs could choose a different certainty. For instance, a 15% threshold with an 80% chance of achieving the threshold suggests an infection prevalence target of ≤ 12%.

The results were largely consistent across the three surveys, which gave us confidence in the robustness of these target values. The consistency was especially true at the lower prevalence targets when certainty was high. This could be due to the inclusion of schools from five countries with different ecologic archetypes, thus, giving us a broad representation of different endemic areas. There were some differences between the baseline and follow-up surveys. For instance, as the infection prevalence target increased at follow-up 1, the percent chance tended to decrease much

Figure 7.3. Scatter plots of Schistosoma haematobium prevalence of heavy intensity infections (PHI) and microhematuria prevalence of children aged 6-15 years from Burkina Faso, Mali, Niger, Tanzania, and Zambia participating in schistosomiasis control program activities between 2003 and 2008. Points are scaled based on the number of school-age children with *S. haematobium* infection data. Black line indicates model fits and gray shading indicates 95% Bayesian credible intervals (BCIs) from errors in variables model. The dashed line denotes 10% microhematuria prevalence.

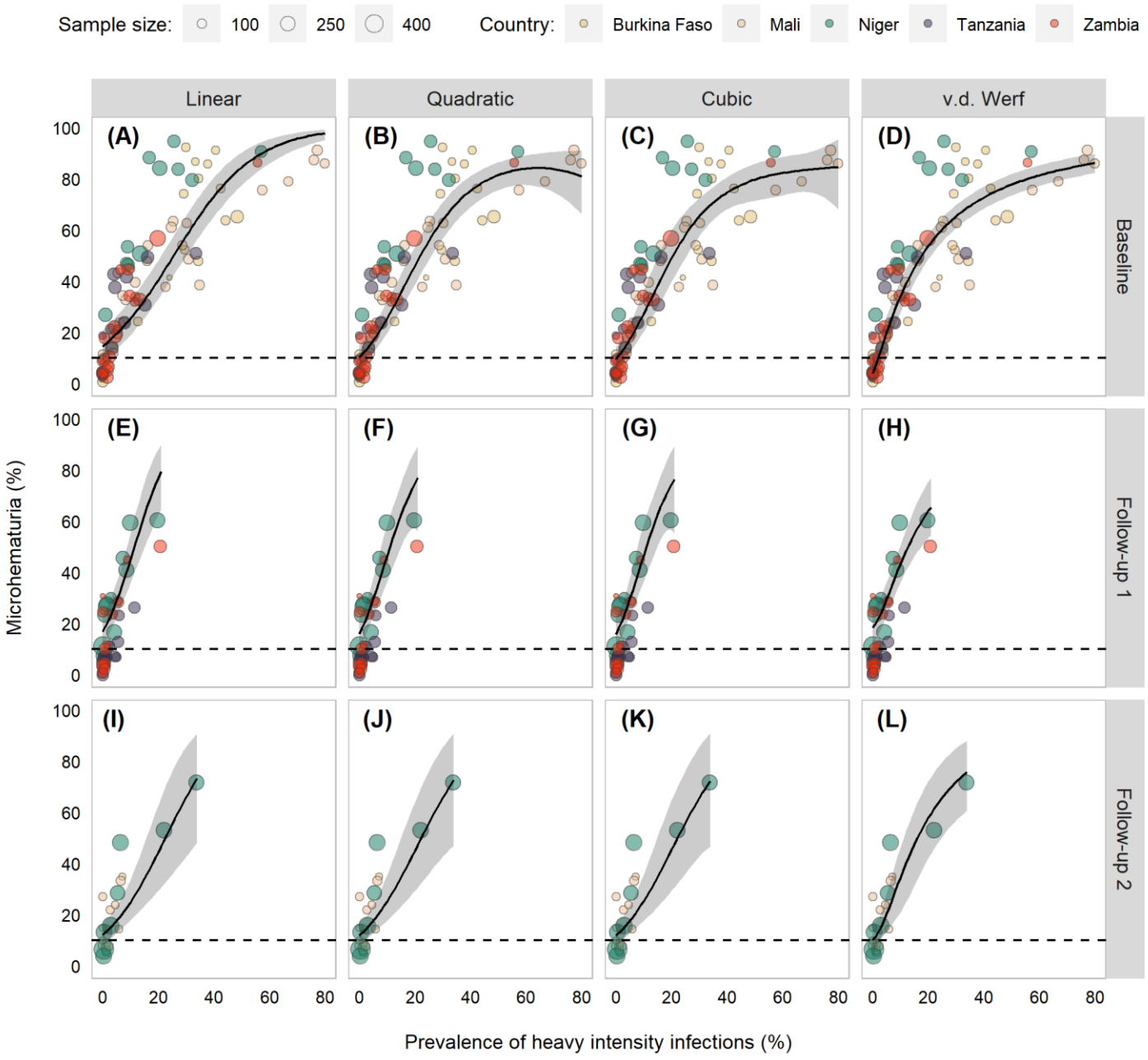
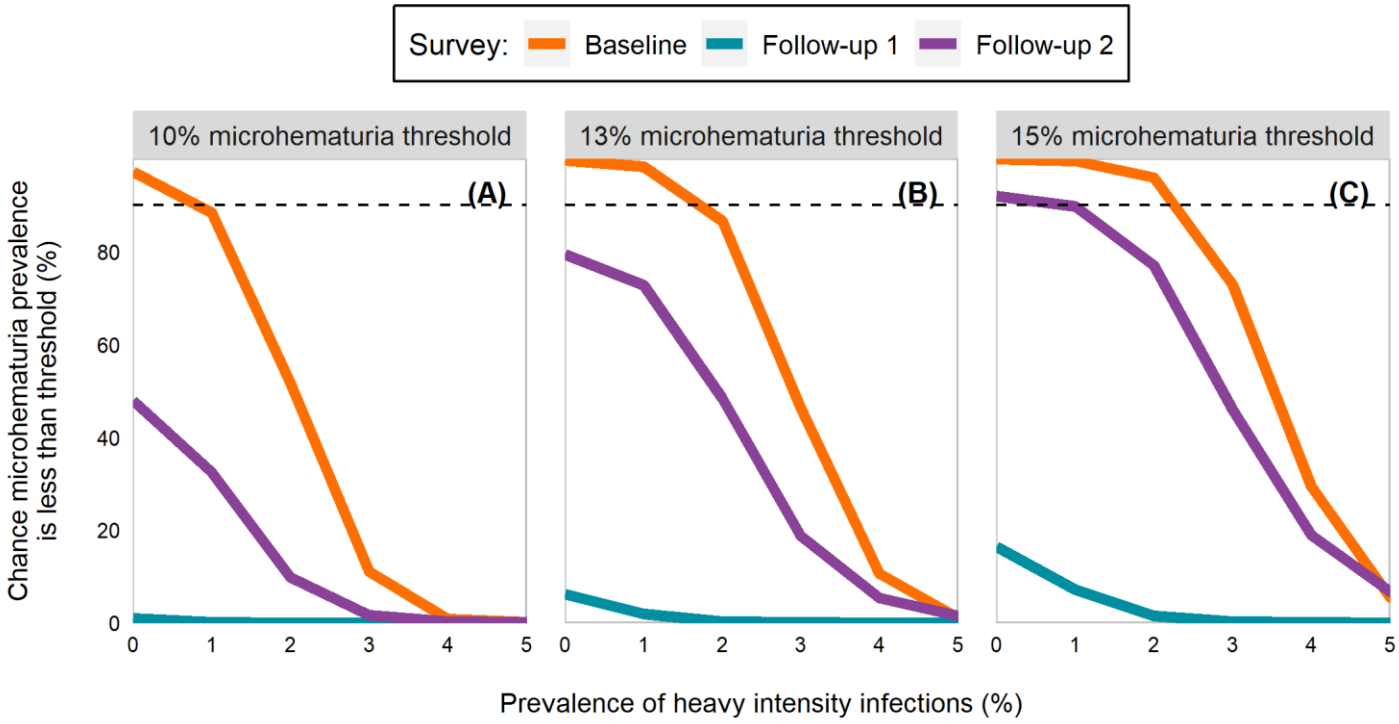


Figure 7.4. Line plots by survey of the percent chance a school with a given *Schistosoma haematobium* prevalence of heavy intensity infections is below the microhematuria threshold. Panel A is for a 10% microhematuria threshold, panel B for 13%, and panel C for 15%. Estimates utilized children aged 6-15 years from Burkina Faso, Mali, Niger, Tanzania, and Zambia participating in schistosomiasis control program activities between 2003 and 2008. Full description of the methods is in the supplementary materials. The dashed line indicates a 90% chance of being below the threshold.



quicker. At a 9% infection prevalence target, the percent chance of falling below the 10% microhematuria threshold was 81% at baseline and 97.2% at follow-up 2 but only 54.5% at follow-up 1. Typically, the follow-up 2 survey consistently had higher certainty. Some of this difference could be attributed to changes in the distributions of infection and microhematuria prevalence post-preventive chemotherapy administration, though bias may have been introduced since many schools were lost to follow-up or excluded due to not being treated once in the preceding year. The heterogeneity between schools was much larger at baseline since far more schools had higher infection prevalence and microhematuria percentages (Figure 7.1).

By contrast, PHI-derived targets provided minimal adaptability and could be prone to misclassification. For 10% microhematuria, there was at least a 90% chance that a school was below the morbidity threshold only at baseline, when PHI was 0%. No prevalence could achieve a 99% chance of meeting the 10% threshold. This includes the current WHO target of 1% PHI, which was unable to reach a 90% chance of meeting the 10% threshold in any survey. For baseline and follow-up 2, there was a steep drop in the percent chance of meeting the threshold usually after 2%, suggesting a small number of missed heavy-intensity infections could easily cause a misclassification.

The overarching goal of this study was to discover readily measurable and well-defined program targets for urogenital schistosomiasis in school-age children. An evidence-based target is crucial for schistosomiasis programs to achieve elimination as a public health problem, which is the stated goal of the WHO 2021-2030 neglected tropical disease (NTD) roadmap (WHO 2020b). Other NTDs have based their validation process around countries falling below defined prevalence targets (WHO 2016; 2017). Defined targets are necessary for program managers as they allow them to determine the efficacy of control efforts, identify when problematic issues such as poor coverage or infection "hotspots" occur, or when to consider switching goals from elimination as a public health problem to interruption of transmission. Current PHI-based targets are unable to ensure that microhematuria is reduced to a background level and are highly sensitive to small changes, whereas the targets proposed here appear robust and can be adapted to different situations.

Our results are specific to *S. haematobium* infections in school-age children and may not be appropriate for older age groups. However, because the prevalence and intensity of schistosome infections are highest in this population and most national programs are based on preventive chemotherapy of school-age children, we believe these targets provide great value for schistosomiasis morbidity control. Furthermore, because the more severe manifestations of schistosomiasis morbidity result from multiple years of infection, effective programs for this school-age group will eventually reduce *S. haematobium* infection-associated morbidity in older individuals as well. For example, Kenyan adults who had received preventive chemotherapy as children demonstrated an 11-fold reduction of bladder wall pathologies compared to previously untreated individuals despite having similar infection levels as adults (Subramanian et al. 1999).

Our results are limited by a few factors. There are individual-level factors which influence the background level of microhematuria, such as the age of first menses in girls. Our assumption is that evaluations of morbidity control and elimination as a public health problem are done at an aggregate level and that a random sample, i.e., one that draws children across sexes and ages, is ascertained. The effect of deviations from a random sample should be studied so the effect on the evaluation is known. The level of certainty of our results may vary by location due to the wide variability of microhematuria prevalence previously noted (Krauth et al. 2015). This could be due to measurement error or variations in the presence of other concomitant phenomena such as menses or concurrent conditions such as urinary tract infections (van der Werf et al. 2004; King et al. 2013). An evaluation's sample size and design could also play a role in an appropriate target. The target may also depend on the dipstick manufacturer utilized. Data in these analyses used Hemastix dipsticks, the same that were used in the study by Krauth and colleagues (Krauth et al. 2015). These results are also not immediately applicable to programs focused on control of *S. mansoni* and new research is still needed to identify a robust morbidity indicator for intestinal schistosomiasis species (Chapter 6). In addition, further work will be necessary to identify target infection levels in other age groups as morbidity can manifest differently in older individuals with more chronic infections. Efforts to identify species-specific morbidity markers are underway (Neglected Tropical Diseases Support Center 2019).

We believe our modeling approach provides a useful framework for defining morbidity-related targets. This modeling approach can be utilized for other diseases which need to set a target based on a morbidity marker. For schistosomiasis, this method can be used again when a suitable intestinal schistosomiasis marker is identified or when improved diagnostics become available and targets need to be recalibrated. Since different thresholds can be evaluated simultaneously and the Bayesian methodology allows for the computation of probability-based measures, this allows for targets to be computed for locations based on program needs.

7.7 Conclusion

These analyses present empirically-based infection targets for urogenital schistosomiasis that utilize the association between infection prevalence and microhematuria prevalence. Our findings can be used by schistosomiasis control programs as targets to reduce microhematuria prevalence below an established background level, and could be adopted to meet the goals in the current road map (WHO 2020b). Current targets based on PHI are not set low enough for control of schistosomiasis-related microhematuria and cannot be reliably used by control programs for this purpose.

7.8 Declaration of interests

The authors declare that they do not have any commercial or other association that might pose a conflict of interest.

7.9 Acknowledgments

The Schistosomiasis Control Initiative (now the SCI Foundation) was supported by the Bill and Melinda Gates Foundation (grant 13122). We thank all the school and community participants in the surveys of the national control programs; the staff of the national ministries of health for managing and implementing these programs; the ministries of health for granting the authors permission to access and reanalyze these data for the study; and the past and present staff from the Schistosomiasis Control Initiative team. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the CDC.

7.10 Supplemental Materials

The goal of this modeling is to identify a *Schistosoma haematobium* infection target or heavy-intensity infection prevalence target where microhematuria prevalence is kept below a level that is assumed to represent when schistosomiasis is eliminated as a public health problem.

In these analyses, the term "threshold" refers to the microhematuria prevalence which is assumed to represent when schistosomiasis is eliminated as a public health problem. From previous research (Krauth et al. 2015; Ochodo et al. 2015), 10%, 13%, or 15% where chosen as potential targets. The term "target" defines the *S. haematobium* infection prevalence or prevalence of heavy intensity infection (PHI), where the percent chance of reaching the target is above an accepted percent change (or probability). In these analyses, all integer infection prevalence values from 0% to 100% were considered.

Since each school or community will have different numbers of people ascertained, a binomial distribution was a natural choice for describing the variation in microhematuria prevalence. Since the prevalence of infection or PHI will also follow a binomial distribution, an errors in variables model (Durbin 1954; Carroll et al. 1984) was used. Bayesian methods were chosen since direct estimates of the percent chance that microhematuria prevalence falls below the target is desired.

7.10.1 Model Details

We aggregated all individual data to the school or community level. This largely concurs with programmatic schistosomiasis evaluations since usually no individual level covariates are included in analyses. If the inclusion of individual level covariates is desired, then a different modeling approach is needed. Nevertheless, with data aggregated to the school or community level, we assume the frequency of the morbidity indicator, *y*, is binomially distributed in the following way

$$y_i \sim Bn(n_i, p_i)$$

where *i* denotes a school or community, n_i is the number of participants evaluated for the morbidity, and p_i is the probability a participant has microhematuria. The probability of microhematuria is assumed to be Beta distributed where

$$p_i \sim \text{Beta}(\phi\mu_i, \phi[1-\mu_i]).$$

The parameter ϕ is used to control the spread of the Beta distribution. Based on testing with the microhematuria data, ϕ was given a $\mathrm{Gamma}(20,1)$ prior for all analyses. Finally, $\mu_i$is the estimate from the standard logit transform. For the cubic model,

$$\mu_i = \frac{e^{\beta_o + \beta_1 r_i + \beta_2 {r_i}^2 + \beta_3 {r_i}^3 + \beta_{4_1}\mathrm{country}_1 + \cdots + \beta_{4_k}\mathrm{country}_k}}{1 + e^{\beta_o + \beta_1 r_i + \beta_2 {r_i}^2 + \beta_3 {r_i}^3 + \beta_{4_1}\mathrm{country}_1 + \cdots + \beta_{4_k}\mathrm{country}_k}}$$

where the β's are estimated by the model and all have Cauchy prior distributions with a center of zero and a scale of 2.5 (Gelman et al. 2008). β_0 is the intercept and the others are the coefficients for each power of the predictor variable, r_i. r_i is the true infection risk of participants with a *S. haematobium* infection (or when heavy-intensity infections are used, the proportion of participants with a heavy intensity infection). The quadratic and linear functions utilize the same approach but remove the cubic (for quadratic) and cubic and quadratic (for linear) terms to estimate μ_i. Indicator variables are included for each of the *k* countries included in each analysis. The observed frequency x_i is the number of participants with an *S. haematobium* infection in school or community *i* where a total of m_i participants were evaluated for *S. haematobium*. Thus,

$$x_i \sim Bn(m_i, r_i)$$

and r_i has $\mathcal{U}(0,1)$ distribution. The inclusion of r_i instead of using ${x_i}/{m_i}$ allows the proportion to vary in the Markov Chain Monte Carlo (MCMC) simulations according to the size of m_i.

We also used a function utilized by van der Werf and colleagues (van der Werf et al. 2002; van der Werf et al. 2003b; van der Werf et al. 2004) to associate community prevalence of *S. haematobium* with the prevalence of morbidity indicators, specifically

$$\mu_i = \frac{a + b * {r_i}^c + \beta_1 \mathrm{country}_1 + \cdots + \beta_k \mathrm{country}_k}{1 + b * {r_i}^c},$$

where $0 \leq a \leq 1$, $b > 0$ and $c > 1$. In this function, a is the morbidity prevalence due to other diseases, and b and c describe the association between r_i and μ_i. Prior distributions for these parameters followed these bounds where

$a \sim \mathcal{U}(0.001,1)$, $b \sim \mathcal{U}(0.01,100)$, $c \sim \mathcal{U}(1.01,100)$, and $\beta_j \sim \text{Cauchy}(0, 2.5)$. As before, μ_i is used to estimate the proportion of participants with the morbidity in question through the Beta distribution.

7.10.2 Model Implementation

Models were fit via MCMC using JAGS (Plummer 2003) and CODA (Plummer et al. 2006) in R via the rjags package (Plummer 2019). Three chains were fit with an adaptive phase of 20,000 iterations per chain. The iterations from the adaptive phase were discarded and each chain was run for another 100,000 iterations.

After completing the 100,000 iterations, graphical displays of the trace and densities functions were used to determine if any chains or a subset of iterations should be discarded. The deviance information criterion (DIC) as defined by Plummer (Plummer 2002), was used to evaluate model fit and the model with the smallest value was chosen as the final model (Supplemental Table 7.1). Predicted values are calculated as the median of the posterior distribution and 95% credible intervals are the 2.5% and 97.5% percentiles of the posterior distribution. Finally, we calculated the percentage of empirically sampled values below the microhematuria threshold at each chosen infection prevalence target. A graphical example of this calculation is included in the supplementary figures for infection prevalence thresholds with a threshold of 10% (Supplemental Figure 7.1). These are the posterior distributions from a cubic model of infection prevalence from the baseline survey. Each infection prevalence has its own posterior distribution and the shading indicates the percentage of the distribution that is below the threshold of 10% (blue) and the proportion that is above the threshold of 10% (red). The more the distribution is colored blue, the greater the likelihood that a school at that infection prevalence will fall below the threshold. The solid black lines at the middle of the distribution indicate the median. If the points at the bottom of the median line were connected, this is the curve that appears in panel C of Figure S2 and shows the connection between the plots in Supplemental Figures 7.2 and 7.3 to Figure 7.1.

7.10.3 JAGS model code for cubic function

```
model{
  for (i in 1:N){
    # Likelihood
    x[i] ~ dbinom(r[i], m[i])
    r[i] ~ dunif(0, 1)

    y[i] ~ dbinom(p[i], n[i])
    p[i] ~ dbeta(alpha[i], beta[i]) T(0.001,0.999)
```

```
  alpha[i] <- phi * mu[i]
  beta[i] <- phi * (1 - mu[i])

  logit(mu[i]) <- b[1] + b[2] * r[i] + b[3] * r[i]^2 + b[4] * r[i]^3 + inprod(cty[1:Q], X[i,1:Q])

  resid[i] <- y[i]/n[i] - p[i]
  residp[i] <- step(resid[i])
 }

 # priors
 for (f in 1:P) {
   b[f] ~ dt(0, pow(2.5,-2), 1)
 }
 for (g in 1:Q) {
    cty[g] ~ dt(0, pow(2.5,-2), 1)
  }
 phi ~ dgamma(20, 1)

 # predicted prevalence and exceedance prob
 for (j in 1:n.pred.x) {
  pred[j] <- ilogit(b[1] + b[2] * pred.x1[j] + b[3] * pred.x2[j] + b[4] * pred.x3[j])
  exprob10[j] <- step(.1-pred[j])
 }
}
```

7.10.4 JAGS model code for van der Werf and colleagues' function

```
model{
 for (i in 1:N){
  # Likelihood
  x[i] ~ dbinom(r[i], m[i])
  r[i] ~ dunif(0, 1)

  y[i] ~ dbinom(p[i], n[i])
  p[i] ~ dbeta(alpha[i], beta[i]) T(0.001,0.999)
  alpha[i] <- phi * mu[i]
  beta[i] <- phi * (1 - mu[i])

  mu[i] <- (a + b * (r[i]^c) + inprod(cty[1:Q], X[i,1:Q])) / (1 + b * (r[i]^c))

  resid[i] <- y[i]/n[i] - p[i]
  residp[i] <- step(resid[i])
 }

 # priors
 a ~ dunif(0.001, 1)
 b ~ dunif(0.01, 1)
 c ~ dunif(1.01, 10)
 for (g in 1:Q) {
   cty[g] ~ dt(0, pow(2.5,-2), 1)
 }
```

```
  phi ~ dgamma(20, 1)

  # predicted prevalence and exceedance prob
  for (j in 1:n.pred.x) {
    pred[j] <- (a + b * (((j-1)/100)^c)) / (1 + b * (((j-1)/100)^c))
    exprob10[j] <- step(.1-pred[j])
  }
}
```

7.10.5 Supplemental Tables

Supplemental Table 7.1. Deviance information criterion (DIC) values for all models fit. Bold font indicates lowest DIC value for a dataset and infection prevalence measure (any infection or heavy-intensity infection).

Model	Linear	Quadratic	Cubic	v.d. Werf
Microhematuria and any infection				
Baseline	1146.871	1147.571	**1143.903**	1164.832
Follow up 1	502.5347	498.2412	497.9989	**497.8581**
Follow up 2	**287.6194**	287.669	287.883	288.2922
Microhematuria and heavy-intensity infection				
Baseline	1115.552	1108.235	1106.894	**1098.904**
Follow up 1	447.5615	446.4221	446.3236	**441.1899**
Follow up 2	245.8518	245.6101	245.6344	**242.9806**

Supplemental Table 7.2. Estimated percent chance of falling below 10%, 13% and 15% microhematuria thresholds for infection prevalence targets between 0 and 25% percent. Values in this table are plotted in Figure 7.1.

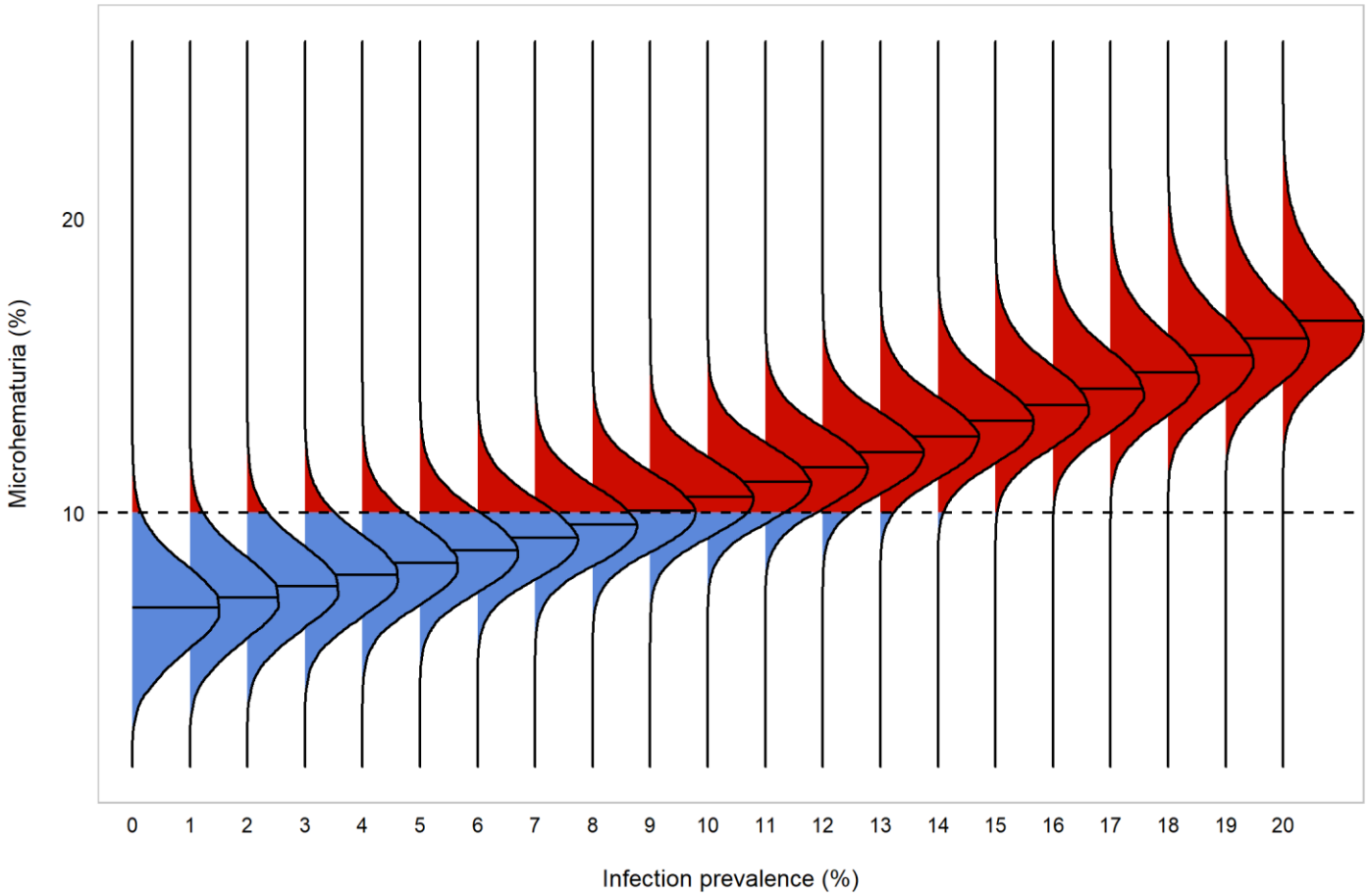
Infection Prevalence (%)	10% microhematuria threshold			13% microhematuria threshold			15% microhematuria threshold		
	Baseline	Follow up 1	Follow up 2	Baseline	Follow up 1	Follow up 2	Baseline	Follow up 1	Follow up 2
0	99.92	98.81	99.83	100	99.84	100	100	99.97	100
1	99.86	98.51	99.77	100	99.79	100	100	99.95	100
2	99.75	97.91	99.69	100	99.69	100	100	99.93	100
3	99.54	96.88	99.58	100	99.54	99.99	100	99.89	100
4	99.12	95.14	99.41	99.99	99.30	99.99	100	99.83	100
5	98.31	92.35	99.21	99.98	98.86	99.99	100	99.70	100
6	96.69	87.84	98.90	99.95	98.02	99.98	100	99.51	100
7	93.71	80.51	98.50	99.88	96.56	99.97	100	99.15	100
8	88.77	69.30	97.95	99.69	94.03	99.95	99.99	98.46	100
9	81.28	54.50	97.19	99.26	89.77	99.93	99.96	97.17	100
10	71.02	38.50	96.19	98.35	82.67	99.89	99.85	94.81	100
11	58.91	24.45	94.83	96.39	71.90	99.85	99.61	90.73	99.99
12	46.16	13.97	93.10	92.85	57.97	99.77	99.07	83.97	99.98
13	34.35	7.14	90.82	87.20	42.75	99.67	97.89	73.66	99.97
14	24.19	3.31	87.98	79.27	28.61	99.49	95.54	60.36	99.96
15	16.03	1.41	84.38	69.31	17.46	99.24	91.60	45.58	99.93
16	10.07	0.57	80.05	58.32	9.60	98.88	85.74	31.37	99.90
17	5.97	0.20	74.92	46.97	4.80	98.35	77.81	19.81	99.85
18	3.34	0.06	69.01	36.25	2.20	97.58	68.40	11.36	99.75
19	1.74	0.02	62.41	26.68	0.95	96.48	58.21	5.91	99.61
20	0.84	0.01	55.23	18.70	0.38	94.93	47.62	2.84	99.37
21	0.38	0	47.70	12.42	0.14	92.80	37.33	1.27	99.01
22	0.17	0	40.20	7.85	0.05	89.96	28.04	0.53	98.49
23	0.08	0	32.86	4.65	0.01	86.29	20.09	0.21	97.67
24	0.03	0	26.10	2.57	0	81.67	13.65	0.07	96.49
25	0.01	0	20.05	1.31	0	76.08	8.81	0.02	94.77

Supplemental Table 7.3. Estimated percent chance of falling below 10%, 13% and 15% microhematuria thresholds for heavy intensity infection prevalence (PHI) targets between 0 and 5% percent. Values in this table are plotted in Figure 7.2.

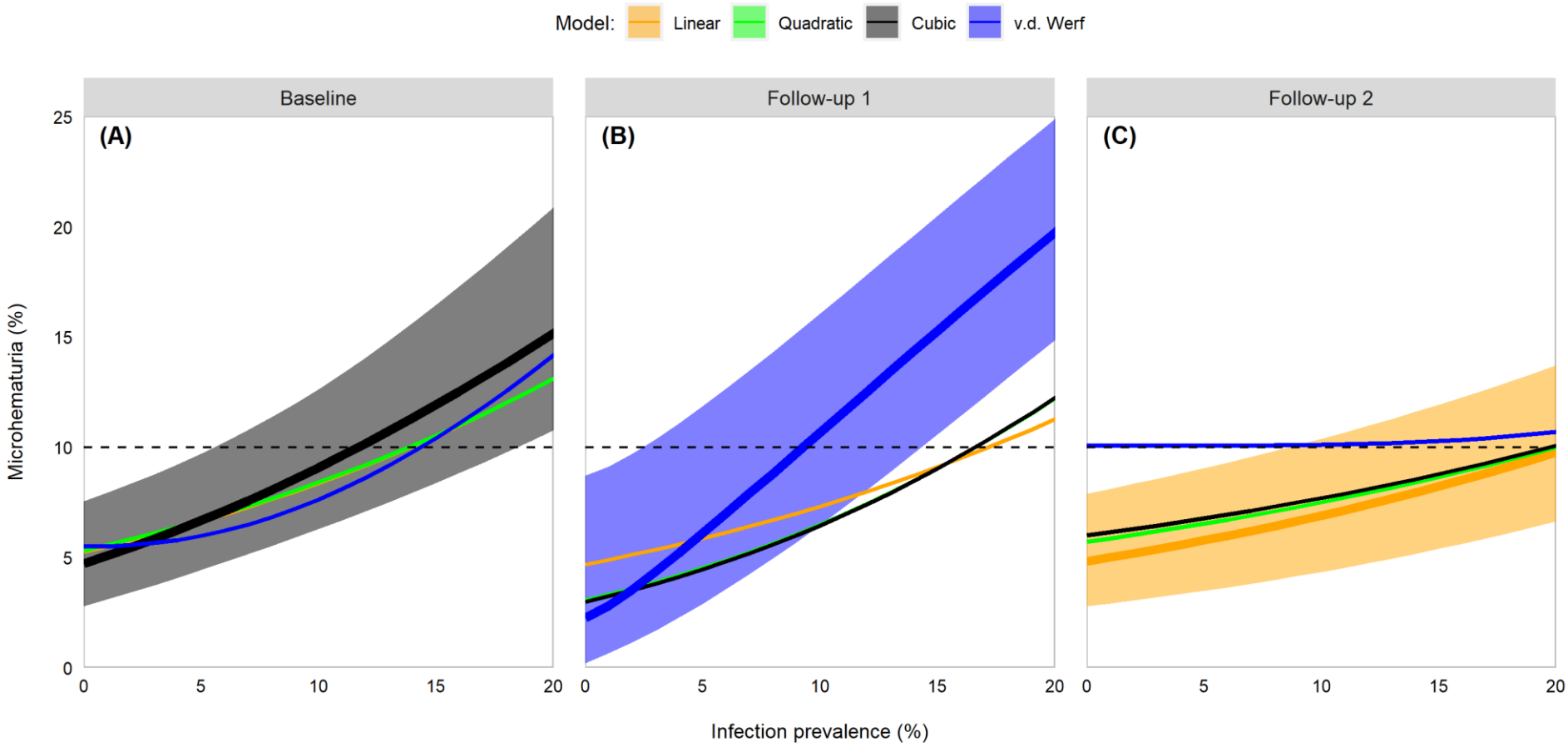
PHI (%)	10% microhematuria threshold			13% microhematuria threshold			15% microhematuria threshold		
	Baseline	Follow up 1	Follow up 2	Baseline	Follow up 1	Follow up 2	Baseline	Follow up 1	Follow up 2
0	97.24	0.86	47.82	99.67	6.20	79.42	99.94	16.44	91.97
1	88.34	0.11	32.41	98.27	1.82	72.74	99.63	7.13	89.71
2	51.58	0	9.69	86.58	0.23	48.37	95.96	1.49	77.07
3	10.94	0	1.57	46.35	0.01	18.80	72.88	0.17	45.98
4	0.80	0	0.24	10.52	0	5.37	29.32	0.01	18.89
5	0.02	0	0.05	1.03	0	1.52	5.42	0	6.74

7.10.6 Supplemental Figures

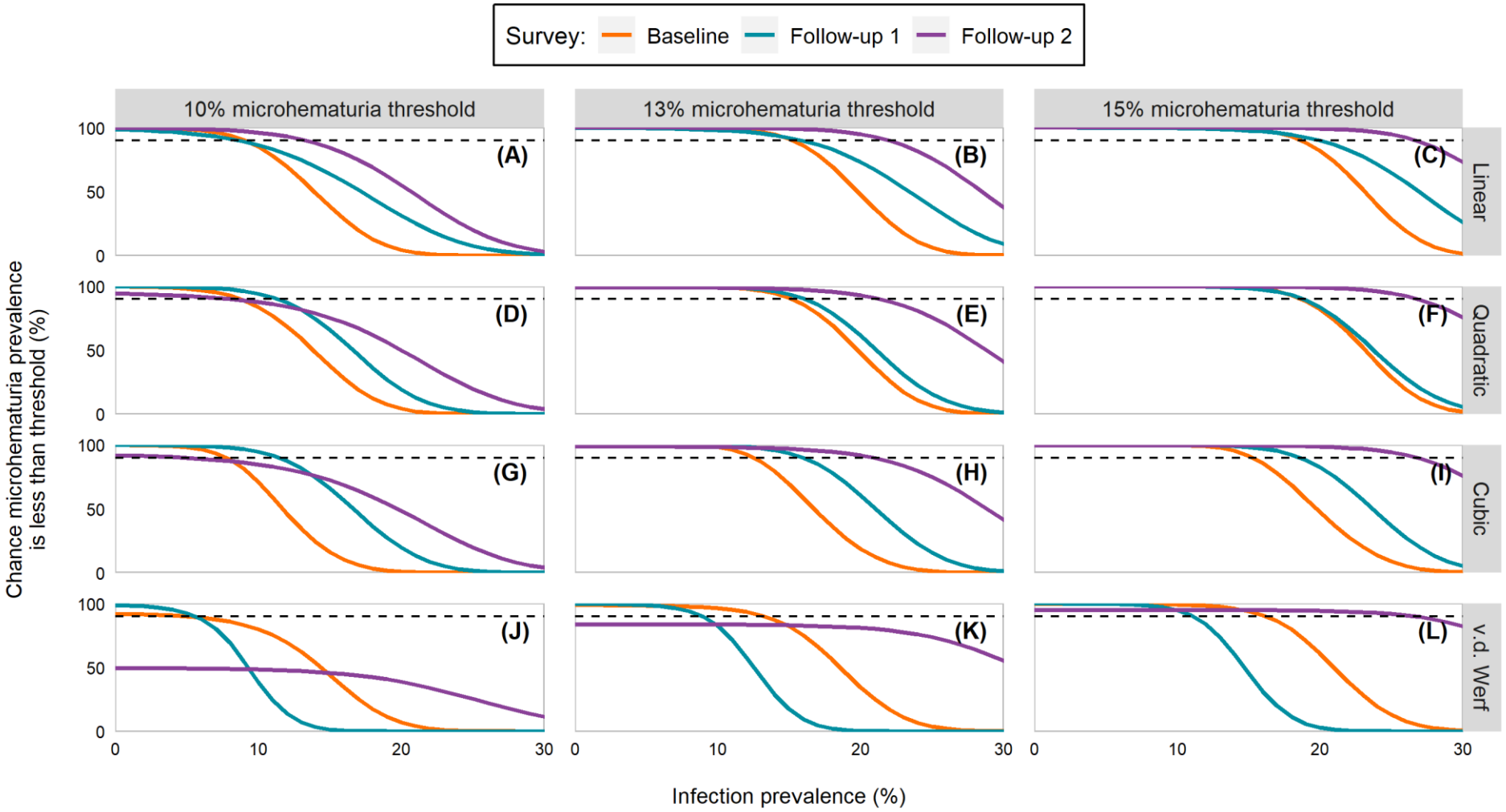
Supplemental Figure 7.1. Posterior distributions of each infection prevalence at the baseline survey as determined by a cubic model with shading for the proportion of the distribution which falls above and below the microhematuria threshold of 10%. Blue indicates the proportion that is above the threshold. The medians correspond to the curve in panel C of Supplemental Figure 7.2.



Supplemental Figure 7.2. Focused version of Figure 7.2 with only model fits confined to the range 0-20% infection intensity prevalence. Best fitting models (see Supplemental Table 7.1 for DIC values which were used to determine best fitting) are represented by thicker line and shaded bands representing 95% credible intervals.

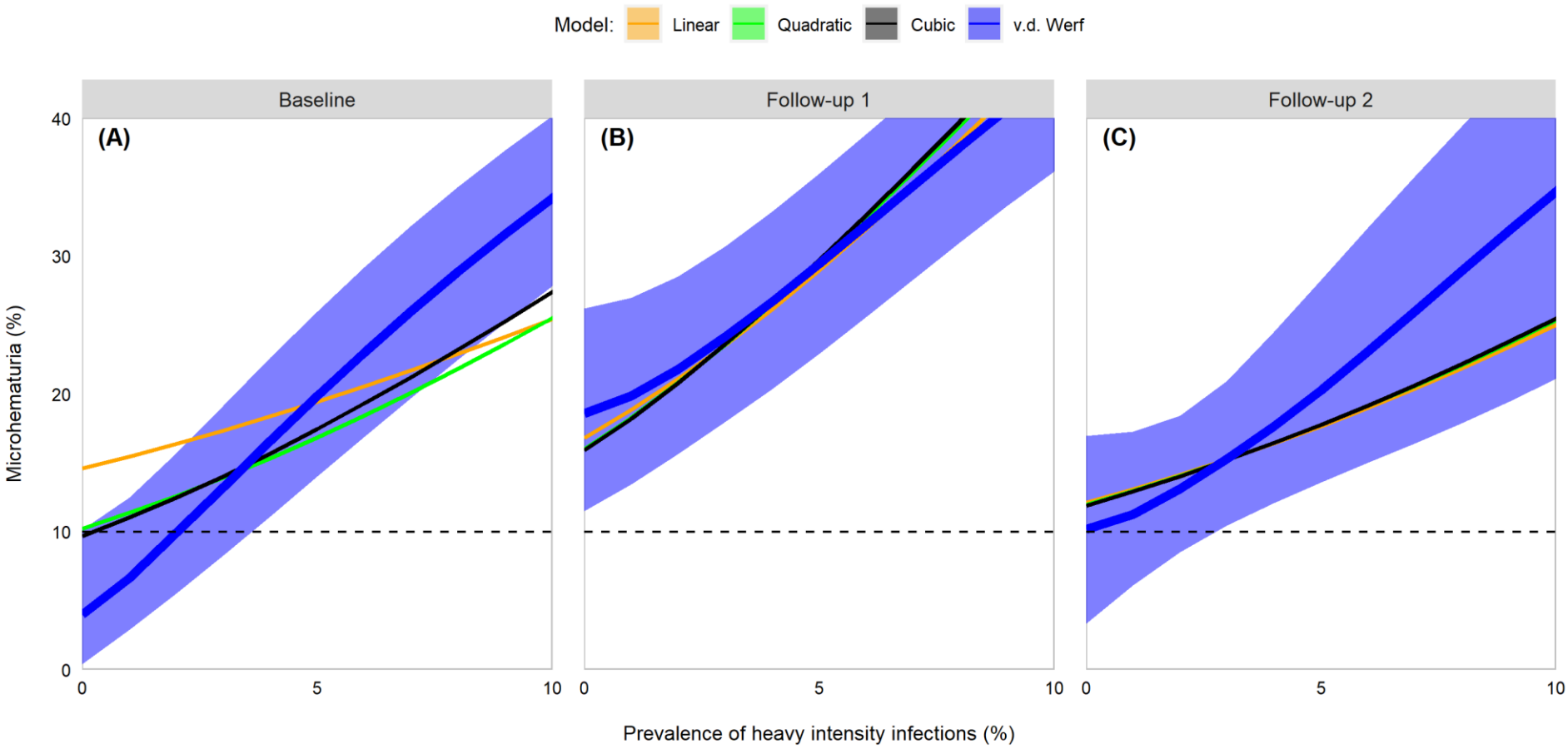


Supplemental Figure 7.3. Line plots of the percentage chance a school with a given *Schistosoma haematobium* infection prevalence will fall below a microhematuria threshold for all models considered. Thresholds of 10%, 13%, and 15% were considered. Estimates utilized children age 6-15 years from Burkina Faso, Mali, Niger, Tanzania, and Zambia participating in schistosomiasis control program activities between 2003 and 2008. Predictions were based on errors in variable Bayesian models. Models were fit separately for each survey

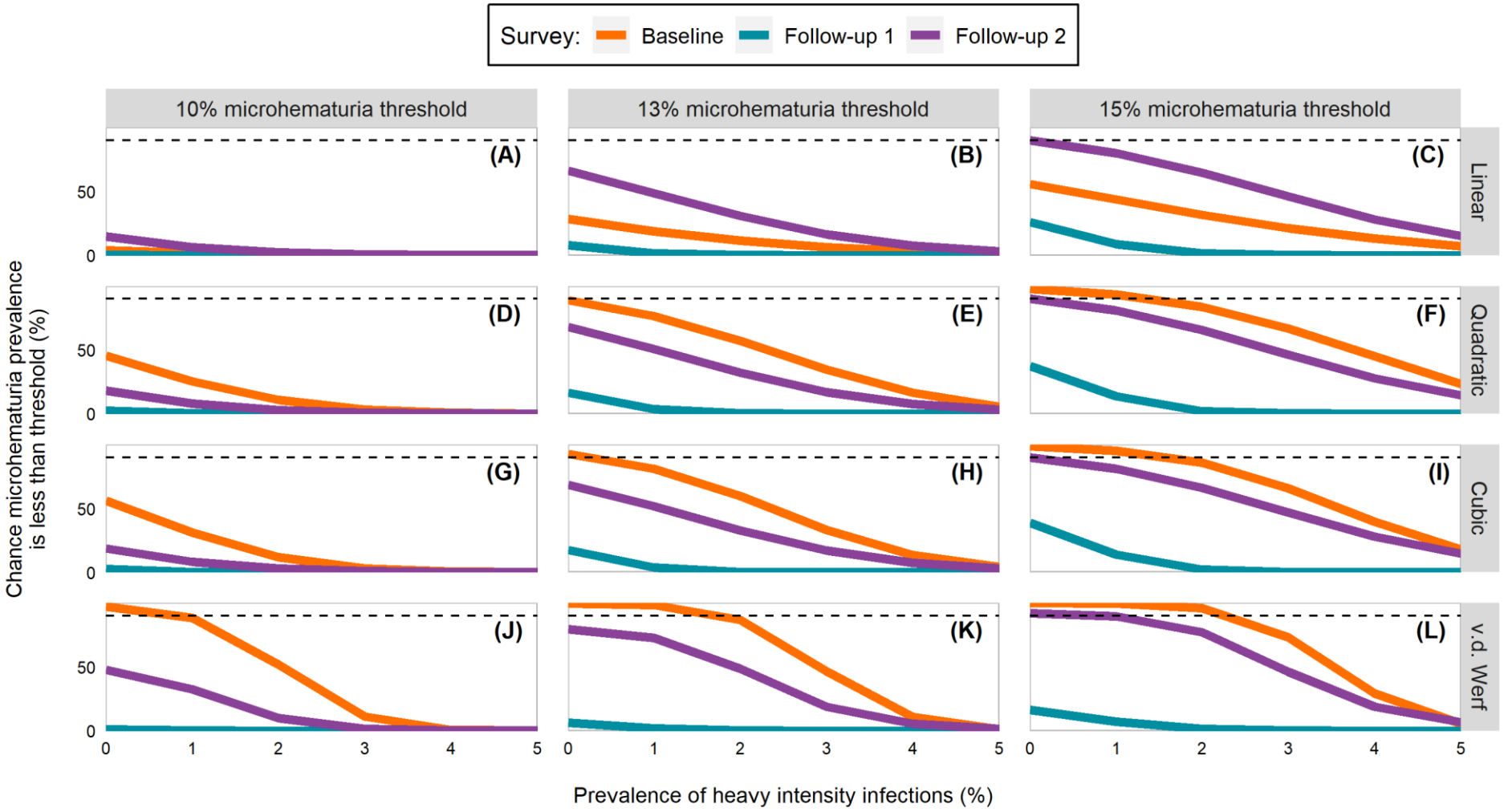


.

Supplemental Figure 7.4. Focused version of Figure 7.4 with only model fits confined to the range 0-5% prevalence of heavy intensity infections. Best fitting models are represented by thicker line and shaded bands representing 95% credible intervals.



Supplemental Figure 7.5. Line plots of the percentage chance a school with a given Schistosoma haematobium prevalence of heavy intensity infections will fall below a microhematuria threshold for all models considered. Thresholds of 10%, 13%, and 15% were considered. Estimates utilized children aged 6-15 years from Burkina Faso, Mali, Niger, Tanzania, and Zambia participating in schistosomiasis control program activities between 2003-2008. Predictions were based on errors in variable Bayesian models. Models were fit separately for each survey.



8 Use of a tablet-based system to perform abdominal ultrasounds in a field investigation of schistosomiasis-related morbidity in western Kenya

Anne Straily*[1], Alfred O. Malit A[2], Dollycate Wanja[2], Emmy Kavere[2], Rono Kiplimo[2], Rose Aera[2], Caroline Momanyi[2], Solomon Mwangi[2], Sarah Mukire[2], Ashley A. Souza[3], Ryan E. Wiegand[1,4,5], Susan P Montgomery[1], William E. Secor[1], Maurice Odiere[2,6]

[1] *Parasitic Diseases Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, Georgia*

[2] *Safe Water and AIDS Project, Kisumu, Kenya*

[3] *Task Force for Global Health, Atlanta, Georgia*

[4] *Swiss Tropical and Public Health Institute, Basel, Switzerland*

[5] *University of Basel, Basel, Switzerland*

[6] *Centre for Global Health Research, Kenya Medical Research Institute, Kisumu, Kenya*

* Corresponding author

E-mail: yzv2@cdc.gov

[This manuscript has been published in *The American Journal of Tropical Medicine and Hygiene* (2021) 104(3):898-901; https://doi.org/10.4269/ajtmh.20-1175]

8.1 Abstract

Chronic intestinal schistosomiasis can cause severe hepatosplenic disease and is a neglected tropical disease of public health importance in sub-Saharan Africa, including Kenya. Although the goal of control programs is to reduce morbidity, milestones for program performance focus on reductions in prevalence and intensity of infection, rather than actual measures of morbidity. Using ultrasound to measure hepatosplenic disease severity is an accepted method of determining schistosomiasis-related morbidity; however, ultrasound has not historically been considered a field-deployable tool because of equipment limitations and unavailability of expertise. A point-of-care tablet-based ultrasound system was used to perform abdominal ultrasounds in a field investigation of schistosomiasis-related morbidity in western Kenya; during the study, other pathologies and pregnancies were also identified via ultrasound, and participants referred to care. Recent technological advances may make it more feasible to implement ultrasound as part of a control program and can also offer important benefits to the community.

8.2 Short Report

Intestinal schistosomiasis, caused by *Schistosoma mansoni*, is estimated to affect 54 million persons in sub-Saharan Africa, with more than 50% of the resultant morbidity found around the great African Lakes, including in Kenya (van der Werf et al. 2003b). Adult *S. mansoni* worms reside in the mesenteric venules in infected humans; female worms release eggs that become trapped in the tissues, primarily the liver, where their presence elicits a granulomatous inflammatory reaction that can result in morbidity. Severe morbidity due to intestinal schistosomiasis is characterized by hepatosplenic disease, including periportal fibrosis, and develops over 5–15 years of infection (Colley et al. 2014a). Advanced periportal fibrosis and resultant portal hypertension can lead to development of esophageal varices, which are rapidly fatal when ruptured. Although the WHO's goal for control programs is to reduce morbidity, evaluation measures focus on reductions in prevalence and infection intensity, rather than actual measures of morbidity (WHO 2013). This is largely because of challenges in measuring severe

morbidity in the field and because symptoms associated with less severe schistosomiasis morbidity can result from other causes (King et al. 2008b). Country control programs need morbidity indicators that can be reliably measured, and the WHO has designated identification of these markers as a critical action to achieve elimination of schistosomiasis as a public health problem (WHO 2020b). In 2019, the Morbidity Operational Research for Bilharziasis Implementation Decisions (MORBID) pilot study was launched in an *S. mansoni*-endemic area of western Kenya to identify better methods to detect morbidity for control programs. Morbidity was assessed by several methods, one of which was ultrasound of the liver and spleen. The full project, including methods and results, will be further described in a future manuscript.

Ultrasound is a useful diagnostic modality to directly visualize the liver and spleen. It is noninvasive, relatively simple to perform, generally has high community acceptance, rapidly provides results, and can distinguish between fibrosis caused by *S. mansoni* infection and other causes of hepatic disease (e.g. cirrhosis or viral hepatitis) (Cerri et al. 1984; Fataar et al. 1984; Homeida et al. 1988a; Homeida et al. 1988b; Abdel-Wahab et al. 1989; Kariuki et al. 2001). However, ultrasound has not been considered a feasible, field-deployable tool for routine use in control programs because of costs and limitations of machines and availability of ultrasonographic expertise. Older models of ultrasound machines were heavy, bulky, and required an external power source, i.e., a generator and fuel, which greatly affected transportation needs, personnel, logistics and costs. For example, during the Schistosomiasis Control Operational Research and Evaluation (SCORE) morbidity studies, the ultrasound machine used in Kenya was a refurbished Aloka SSD-900 portable model[1] (Aloka, Tokyo, Japan) (Sircar et al. 2018). It weighed approximately 14.5kg and required a generator and gasoline for field use. That model could not store images electronically, so they were printed on special thermal paper after each

[1] Use of trade names and commercial sources is for identification only and does not constitute endorsement by the Centers for Disease Control and Prevention or the US Department of Health and Human Services.

examination for further study and review; however, the thermal paper images faded quickly, making them nearly impossible to evaluate retrospectively (Secor 2020b). When the Aloka unit was purchased in 2011, it cost $11,000 USD with an additional $800 USD for the printer (not including cost of shipping unit to Kenya). Updated clinical machines with equivalent features now cost anywhere from $22,000 to $36,000[2] putting them financially out of reach of many country control programs or field studies.

Very recently, tablet-based ultrasound systems consisting of a transducer connected to a compatible smart device have become available. We evaluated whether such a system would be useful to assess hepatosplenic disease related to intestinal schistosomiasis in a field study setting. We used the Lumify system by Philips Medical Imaging[1] (Bothell, WA, USA), consisting of the C5-2 MHz broadband curved array transducer and compatible Android tablets with the Lumify app installed. The Lumify system is ideal for field applications: it consists simply of the transducer and tablet and is therefore light, easily transportable, and does not require an external power source to perform the ultrasound. The display has excellent resolution, comparable to that of a clinical ultrasound machine. High-definition images and short videos can be saved on the tablet for later review. The transducers can be leased for a period of time, which reduces costs. For the Kenya MORBID pilot study, four broadband curved array transducers were leased and four compatible tablets were purchased.

The MORBID sonographers were recent graduates of a medical imaging training program in Nairobi, Kenya. They were proficient in conducting ultrasound exams but needed additional training to identify different patterns of schistosomiasis-specific hepatosplenic disease as standardized by WHO (Richter et al. 2000). In June of 2019, the team traveled to the Kabatereine Schistosomiasis Research Centre at Bugoigo Field Station in Buliisa District, Uganda to undergo an intensive three-day training in schistosomiasis-specific ultrasonography based on the Niamey protocol (Richter et al. 2000). Bugoigo Field Station is situated close to Lake Albert where intestinal schistosomiasis is endemic and morbidity is

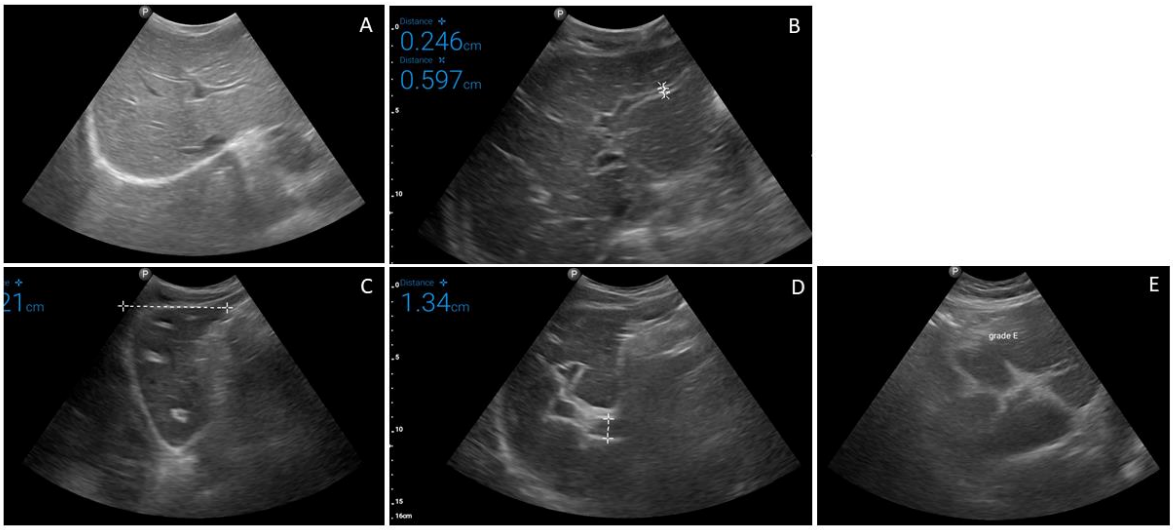
[2] Price as of 8/21/2020 when quote was obtained.

common, enabling the trainees to observe ultrasound patterns associated with advanced schistosomiasis.

The MORBID study protocol was reviewed and approved by the Institutional Review Board of Maseno University, Kisumu, Kenya (Protocol # MSU/DRPI/MUERC/00675/19), and by the Office of the Associate Director for Science in the Center for Global Health, CDC, CDC investigators were considered to be nonengaged with human subjects. The MORBID study was conducted in 45 villages with approximately 200 residents recruited from each village. In total 6,483 participants received an abdominal ultrasound. Between 20-25 participants were examined each day. Images were viewed in real time and saved electronically to the tablet. Each afternoon, upon returning from the field, images were downloaded and saved onto an external hard drive and the tablets recharged. Images were reviewed and scored for schistosomiasis-related hepatosplenic pathology according to standardized guidelines (Figure 1) (Richter et al. 2000). Study morbidity findings will be summarized elsewhere (Odiere et al. 2021)

Although the study's objective was to identify hepatosplenic pathologies associated with schistosomiasis, each participant was given a complete abdominal ultrasound examination. In addition, non-schistosomiasis-associated pathologies were thereby identified, including uterine fibroids, polycystic kidney disease, hydronephrosis, prostatic hypertrophy, fatty liver, and liver cysts. Many areas of Kenya lack this type of advanced imaging capability, and these pathologies may otherwise have gone undiagnosed. Where further evaluation by a physician was needed, the sonographer generated a report and worked with local community health volunteers to refer the participant to a local hospital. For example, an adult male participant with severe lower limb edema was found to have advanced prostatic hyperplasia causing venous occlusion. He reported that he had been variously treated for other potential causes of his lower limb edema but had never received any imaging studies. Twenty-one pregnancies were diagnosed in women, some of whom were not aware that they were pregnant; the

Figure 8.1. Examples of schistosomiasis-related ultrasound liver texture patterns, as defined by WHO's Niamey protocol (Richter et al. 2000), observed during the Morbidity Operational Research for Bilharziasis Implementation Decisions study. (**A**) normal liver parenchyma; (**B**) "starry sky"; (**C**) "rings" (seen here) and "pipe stems", which correspond to the "rings" seen in a scan perpendicular to the one where pipe stems are seen; (**D**) highly echogenic "ruff" seen around the portal bifurcation and main stem; (**E**) highly echogenic "patches" extending from main portal vein and branches into parenchyma.



sonographers were able to determine gestational age, expected delivery date, and fetal sex. Participants taking medication for an abdominopelvic condition were able to receive feedback, for example, whether the condition was resolving, and were provided a report to take to their physician. One participant was identified with situs inversus, a rare congenital condition whereby the major visceral organs are reversed from their normal positions; this individual displayed no symptoms or complications.

A tablet-based ultrasound system offers several advantages over a standard ultrasound machine for assessing schistosomiasis morbidity. The battery life was sufficient to perform 25 ultrasounds per day (the number of abdominal ultrasounds that one sonographer could comfortably perform) and did not require recharging while in the field. The images were stored electronically on the device, negating the need to print the images at the time of the exam as was carried out in previous studies. The device's memory was sufficient to store the images for all study participants examined that day. The tablet and transducer were very easy to transport to, from, and within field sites. This system is also significantly

more affordable than a standard ultrasound machine. To rent four Lumify transducers for 6 months ($1,200 USD) and purchase four tablets ($15,000 KES without VAT or $140 USD each) was about half the cost of purchasing the Aloka in 2011 for the SCORE studies. The Lumify system includes the transducer, app, and access to technical support and telemedicine capabilities, but not a smart device. A comparable standard ultrasound machine retails for $22,000-36,000 USD[3] and still requires an external power source to perform the examination. Another limitation of performing ultrasound in the field is the expertise needed to conduct the examination and interpret the images. We found that contracting recent graduates of a medical imaging training program and providing them with additional training necessary to identify schistosomiasis-specific pathologic changes was an effective solution for meeting this need. Another potential strategy is to develop focused point-of-care ultrasound applications which target only specific findings necessary for diagnosis and treatment decisions and provide training to clinicians already working in affected communities (Bélard et al. 2016).

Measuring severity of hepatosplenic disease is an accepted method of determining schistosomiasis-related morbidity. Recent advances in ultrasound technology make it more feasible to incorporate this technology into a country control program and can also offer significant ancillary benefits to the community, such as the potential to identify other pathologies and refer people to care, as described here. Integrating ultrasound into control programs will help countries both reduce schistosomiasis morbidity and achieve WHO's vision of universal health coverage by providing communities with access to advanced health services (WHO 2020b).

[3] Price as of 8/21/2020 when quote was obtained.

9 Discussion

The thinking of policy makers in the late 1980s and early 1990s was to focus on treating the worst infections. At that time, treatment with praziquantel was too expensive for preventive chemotherapy (King et al. 1989; Stothard et al. 2009a). To achieve morbidity control, this was a sensible strategy, especially given the demonstrated correlation between intensity and severe morbidity (WHO 1987; 1988). Nevertheless, despite the effectiveness of distribution of praziquantel via field trials (Kardaman et al. 1983; King et al. 1992; Kitange et al. 1993), praziquantel was not being widely used and the schistosomiasis burden continued to increase as few infected people were being treated with an effective and save medicine despite the cost of that medicine dropping to as little as USD 0.08 per tablet (Hotez et al. 2009a). The situation looked bleak in the late 2000's (Hotez et al. 2010).

Since then, much has changed with schistosomiasis and other neglected tropical diseases (Molyneux et al. 2017; Hotez et al. 2018). DALYs for NTDs were beginning to drop in the mid 2000's and have continued to do so for over a decade (Global Burden of Disease Collaborative Network 2020). Praziquantel costs have remained low and increases in donations from Merck KGaA have continued. National control programmes were formed and have contributed significantly to this success (Deol et al. 2019). Extensive work in the People's Republic of China has brought *S. japonicum* infection largely under control (Xu et al. 2016). Economic development in Caribbean has meant that schistosomiasis in the region has likely been eliminated in many countries though this has yet to be certified (Secor et al. 2018; Hewitt et al. 2019). Global elimination has crept into the discussion (Fenwick et al. 2016).

Unfortunately, these changes have not been reflected in schistosomiasis guidelines. Our knowledge of schistosomiasis has advanced since the initial research suggested morbidity is only caused by heavy-intensity infections (WHO 1987; 1988; 1989). The conclusions drawn (Mott 2004) and frameworks developed (WHO 2002; 2011b; 2013) from those reports are now outdated.

The goals of this PhD thesis were to improve components of the monitoring and evaluation framework for schistosomiasis. To that end, this thesis achieved the following:

- Furthered the knowledge that praziquantel-mediated declines in *S. mansoni* and *S. haematobium* infections are associated with declines in children in schistosomiasis-associated and some non-specific morbidity indicators as well as increases in self-reported quality-of-life;
- Provided initial evidence that preventive chemotherapy is associated with improved behaviour at school for egg-positive and egg-negative children;
- Aggregated available evidence to show that untreated children or children with active infection had lower attendance and achievement compared to children treated with praziquantel or uninfected children;
- Evaluated the WHO's infection intensity categories to show that *S. haematobium* categories have different levels of morbidity across a range of indicators whereas *S. mansoni* categories do not;
- Demonstrated that, for *S. haematobium*, children in schools below the elimination as a public health problem threshold (<1% PHI) and those with below the control of morbidity threshold (<5% PHI) had lower morbidity levels than children in schools above the control of morbidity threshold (≥5% PHI) but did not have different levels of morbidity between them, except for microhaematuria;
- Showed that, for *S. mansoni*, children in schools below the elimination as a public health problem threshold (<1% PHI) had consistently lower morbidity levels compared to children in schools above the control of morbidity threshold (≥5% PHI) for observable fibrosis and laboratory-confirmed diarrhea but not for other indicators and not between

children in schools who have supposedly controlled morbidity (<5% PHI) and those that have not (≥5% PHI);

- Found robust *S. haematobium* prevalence targets that control microhaematuria; and
- Demonstrated that a tablet-based ultrasound system could allow control programmes to collect morbidity indicators more easily.

The findings in this thesis contribute to schistosomiasis control efforts by utilizing innovative approaches to address monitoring and evaluation questions, validating research findings in real world monitoring and evaluation programmes, learning how the application of established interventions affects morbidity, and suggesting the application of new approaches can better evaluate the effect of control programs (Table 9.1).

9.1 Implications for monitoring & evaluation programmes

There are many potential improvements that could be made to the monitoring and evaluation framework and this section will summarize the potential improvements evaluated in this dissertation.

9.1.1 Heavy-intensity prevalence targets are inadequate for control and elimination as a public health problem

The analyses carried out in chapter 3 demonstrated that, on average, children infected with *S. mansoni* in areas undergoing preventive chemoprophylaxis experience reductions in a wide array of morbidity indicators regardless of whether treatment was annual or every two years. Wasting and elevated portal vein diameter were significantly decreased from year 1 to year 5. Mean scores on the PedsQL measure increased on every domain and overall. Though, there were conflicting results with stunting and VO_2 max which increased and decreased, respectively, on the aggregate, though the effect for VO_2 max was moderated by arm. In addition, a meta-analysis summarized in chapter 4 showed

Table 9.1. Contributions based on the Swiss Tropical and Public Health Institute principles.

Chapter	Manuscript	Innovation	Validation	Application
3	Five-Year Impact of Different Multi-Year Mass Drug Administration Strategies	Tested whether morbidity indicators change over time in a cohort		
4	SCORE Studies on the Impact of Drug Treatment on Morbidity		Summary of SCORE studies which measured the impact of preventative chemotherapy on morbidity	
5	Associations between infection intensity categories and morbidity prevalence	Evaluated the associations between intensity categories and morbidity indicator levels	Strong associations for *S. haematobium*, but a lack of association for *S. mansoni*	
6	Control and elimination of schistosomiasis as a public health problem thresholds fail to differentiate schistosomiasis morbidity prevalence in children	Evaluated the associations between program targets and morbidity indicator levels	Very strong association between *S. haematobium* and microhaematuria, but not for other morbidity indicators; lack of associations for *S. mansoni*	Microhematuria levels could be used to determine infection targets
7	Urogenital schistosomiasis infection prevalence threshold for elimination as a public health problem	Determined the probability that a school-based infection prevalence will reduce morbidity to background level	Infection prevalence provides a more robust and sensitive target than heavy-infection prevalence	Once a location decides on the certainty with which they want to reduce to background morbidity, a threshold can be determined
8	Use of a tablet-based system to perform abdominal ultrasounds	Provided a proof-of-concept that a tablet-based ultrasound system could be used in the field by control programs.		Utilized the technology for the MORBID study

aggregate decreases in morbidity levels associated with drug treatment. Other studies from the SCORE project summarized in chapter 4 demonstrated that infections are associated with worse learning outcomes and that treatment can improve some of these deficits.

Though, the reductions realized in chapter 3 were in a sample of children who largely had light and moderate infections. Using weighted averages from multiply imputed datasets, 64.4% of children were egg positive at year 1 with 10.0% of those children possessing heavy-intensity infections. At year 5,

those weighted averages dropped to 45.6% and 2.1%. Infection levels dropped by about a third while heavy infection levels dropped by approximately three-fourths. *S. mansoni* specific ultrasound-derived measures were at low levels by year 5. Based on the WHO's targets for morbidity control and elimination as a public health problem, the two communities in chapter 3 would be considered to have controlled morbidity because they fell below the 5% PHI target. This is despite over 45% of children being egg positive after five years of observation.

The PHI targets in WHO's guidelines were directly assessed in chapter 6. The only morbidity indicator for which PHI targets had consistently different levels of morbidity was microhaematuria for *S. haematobium*. There were some general trends, but the PHI categories could not reliably and consistently differentiate morbidity levels for any other indicator.

Finally, the relationship between microhaematuria prevalence and PHI categories was analyzed in further depth in chapter 7 to determine whether a target PHI that aligned with microhaematuria prevalence could be estimated. For the microhaematuria thresholds of 10%, 13%, and 15%, a target of 0% PHI had percent chances of 97.2%, 99.7%, and 99.9% at baseline, respectively, but results differed at follow up surveys. At follow up 1, the target of 0% PHI had percent chances of 0.9%, 6.2%, and 16.4%. These same percent chances increased at follow up 2 to 47.8%, 79.4%, and 92.0%, respectively. Some of this volatility may be caused by schools dropping out of the study, but the same schools dropped out in the infection prevalence analyses and those targets were much more robust than for PHI.

These chapters suggest that the prevalence of heavy-intensity infections is not a good representation of the morbidity status of a group of children. One reason for this from a statistical perspective, is the WHO's interpretation of the aggregation of research up to the mid-1980s (WHO 1987; 1988; 1989), which considered a nonsignificant statistical test to prove similarity, an incorrect interpretation. Concluding similarity from a nonsignificant superiority test is incorrect (Altman et al.

1995). Superiority tests have a null hypothesis of no difference and an alternate hypothesis of a difference. Proper testing to support the WHO's conclusion would have flipped the null and alternate hypotheses, meaning the alternate hypothesis should be of no difference. Only with equivalence or non-inferiority testing could their conclusion been achieved. In addition, significance tests do not take into account the practical importance of such a difference (Gelman et al. 2006).

Another flaw in WHO's misinterpretations of the historical results was not taking into account the insensitivity of the diagnostic tests (King 2015). Those studies largely used one stool or urine specimen. Since both urine filtration and Kato-Katz thick smear tests have the likelihood of missing light intensity infections, many of the participants deemed negative may have had light infections, possibly as many as 20-40% (King 2015; Bärenbold et al. 2017). As a result, no eggs may be found from a single filtration or stool examination taken from a person with a light or potentially moderate infection. Thus, the lack of difference observed by WHO may be because people with light or even moderate infections were misclassified as uninfected, thus inflating the morbidity estimate for uninfected people and contributing to the non-significant findings (King 2015).

As mentioned in the introduction, treatment leads to less pathology (King et al. 2005), especially severe pathology (Richter 2003; Mutapi et al. 2017; Wilson 2020). Since defining the control and elimination as a public health problem thresholds by PHI, studies have found that less clinically severe manifestations, which can occur even with light infections and are common in children, have a greater impact on DALYs lost compared to the most severe pathologies (King et al. 2005). Since any *Schistosoma* infection can cause morbidity (King et al. 2008b; King 2009; 2015; King et al. 2020b), focusing on severe pathologies does not address most of the disease burden experienced around the world and, potentially, ignores the populations most vulnerable to the effects of *Schistosoma* infections.

9.1.2 Targets based on morbidity

In chapter 7 we used the results from chapter 6 to determine whether, via statistical modelling, a robust infection prevalence could be estimated for microhaematuria. Microhaematuria was the indicator which showed the most promise for defining a target because of the strong association with PHI-based categories. Also, given the long history of reporting on the relationship between microhaematuria and *S. haematobium* infection, there is empirical evidence of the proportion of microhaematuria that is not caused by *S. haematobium* infection. We utilized that information to set threshold levels of microhaematuria to estimate potential targets. Our results were largely consistent across surveys, where egg positive prevalence targets of ≤ 5%, 8%, and 11% provided a chance of 95% or more that a school would fall below the microhaematuria thresholds of 10%, 13%, and 15%, respectively.

These analyses were successful at determining a robust target for control programmes, but it remains unclear whether this target will control other pathology. Other morbidities, such as bladder fibrosis or female genital schistosomiasis, may also be controlled or become control at such prevalence levels, but further evaluation is needed. In addition, background levels for those pathologies or other morbidity indicators are not well established and are needed for such an analytic approach.

The lack of knowledge regarding background levels of morbidity for other morbidity indicators means defining morbidity targets is challenging. Taking the results from chapter 3 as an example, the two communities in chapter 3 would have controlled morbidity because they fell below WHO's 5% PHI target. Stunting (11.2%), wasting (8.3%), and anemia (41.9%) remained high at year 5, though schistosomiasis is not the only cause of growth retardation and anemia. Since confounding factors could be causing the elevated levels, it's not possible to determine whether all morbidity due to schistosomiasis has been removed. Ultrasonic measures considered to be *S. mansoni* specific were at low levels by year 5. The prevalence of enlarged portal vein diameter decreased from 9.9% in year 1 to

1.4% by year 5 while hepatic fibrosis as measured by image pattern C or worse was consistent from baseline to endline. Research is needed to establish how much morbidity is caused by schistosomiasis and determine appropriate thresholds which are aligned with these background levels.

Once background levels are established, analyses like those done in chapter 7 can be performed on multiple morbidity targets. That way, targets can be established based on a suite of morbidity indicators instead of a single indicator. The severity and typical onset could also be factored into the calculation as well using a decision theoretic approach.

9.1.3 Changes are needed for *S. mansoni* assessment

The analyses in chapter 5 found minimal correlation between an individual's morbidity and infection intensity categories across the three surveys. In chapter 6, analyses of school-level PHI categories found morbidity levels overlapped between the PHI categories, especially for children in schools between 1 and 5% PHI and schools ≥5% PHI. These chapters suggest a reassessment of *S. mansoni* evaluation is needed. Currently, a robust target based on morbidity cannot be determined since associations between morbidity levels and infection are lacking.

As mentioned in chapter 6, there are many potential reasons for the lack of association. Analyses in chapter 6 explored the possibility of reducing the number of intensity categories to three instead of four, but those analyses did not see improvement in the association. Other reasons might be the variability in fecal count measures (Polman et al. 1998; Utzinger et al. 2001), age of the participants (Boisier et al. 1998; King et al. 2003; Booth et al. 2004), or reversion of morbidity due to a long period post-treatment (Doehring-Schwerdtfeger et al. 1992a; Boisier et al. 1998). In addition, since prolonged treatment will result in less severe pathology (Richter 2003; Mutapi et al. 2017; Wilson 2020), the severe complications of hepatosplenic disease will become increasingly rare.

A reassessment may involve sampling from a different population to better assess the presence of morbidity. In addition, a deeper look at the reversion of pathology while under treatment may be beneficial. For subtle pathology, treatment for many years may be needed for symptoms to disappear. Potentially, cohorts may be more useful to track changes in morbidity over time and determine treatment effectiveness. Other morbidity indicators may hold greater utility than those indicative of severe pathology. Potentially, self-reported data could be utilized (Brooker et al. 2001; Lengeler et al. 2002a; 2002b). This has been popular with urogenital schistosomiasis (Ansell et al. 1997; Poggensee et al. 2000; Lengeler et al. 2002a; Clements et al. 2008; Bogoch et al. 2012; Okeke et al. 2014) likely because responses for *S. haematobium* have better reliability than for *S. mansoni* (Lengeler et al. 2002b).

9.1.4 Lack of incentives to collect heavy-intensity infection data

Since prevalence dictates the preventive chemotherapy frequency (WHO 2011b) and the differences in recommended interventions are vague for control of morbidity and elimination as a public health problem categories (WHO 2013), there is little incentive to collect quantitative egg counts. Also, collecting a binary positive or negative value likely saves time. For Kato Katz, a trained microscopist may take approximately 15 minutes per slide to count all eggs but this could be as short as 30 seconds to determine positive or negative (Secor 2020a).

9.1.5 Use of technology to improve programme goals

Ultrasonic evaluation is considered the standard for measuring pathology that is specific to *Schistosoma* infection. Unfortunately, ultrasound use is laborious and cumbersome due to the portability challenges. This is possible for research studies, such as SCORE (Sircar et al. 2018), but impractical for programmes.

In chapter 8, a new instrument incorporating a tablet and a special probe was described. This instrument increases the portability of ultrasound by negating the need for transporting a large

machine, generator, and fuel to study locations. In addition, the tablet allows the operator to save images for future review. Study staff were able to review 20-25 participants per day, suggesting that multiple probes and teams may allow for comprehensive assessment in an area within a short period of time.

Any new technology needs to be affordable, usable, and ethical to be beneficial for control programmes. Costing will need to be studied to determine whether tablets and the specialized probes are economically viable for programmes. Training will be required for staff to administer and read ultrasound images, which may require specialized training. For instance, geospatial techniques have been used extensively for schistosomiasis (Raso et al. 2005; Clements et al. 2006; Brooker 2007; Schur et al. 2011; Schur et al. 2012; Woodhall et al. 2013; Chammartin et al. 2014; Scholte et al. 2014; Lai et al. 2015; Manyangadze et al. 2015) and other NTDs, but their use remains largely confined to research studies and rarely by in country control programmes. Using drones to map snail habitats could be useful for targeting interventions (Chamberlin et al. 2021), but, similarly, use is led by research organizations. More demonstrations and more detailed analysis of the tablet-based ultrasound data are needed to fully characterize the usefulness of this technology and how it compares to traditional ultrasound. Finally, ethical guidelines need to be developed to protect participants against harm. Ultrasound can detect other pre-existing conditions and control programmes will need clear guidance on handling these situations.

9.2 Limitations

Participants in all studies were from areas endemic for multiple NTDs, which have the potential to confound relationships between schistosomiasis and morbidity markers. Efforts were made to focus on schistosomiasis-specific morbidity indicators, but these are difficult to collect, may not present the entire range of morbidity caused by *Schistosoma* infection, and may have associations with other

diseases (Davis et al. 2015), which could lead to measurement error of *Schistosoma* morbidity indicators.

The possibility of measurement error of *Schistosoma* infections is highly likely given the varied number of urine samples or stools evaluated. *S. mansoni* data included in chapters 3 and 4 used multiple stool samples, but those in chapters 5, 6, and 7 used one or two stool samples. Although modelling suggests that single-slide Kato-Katz thick smear testing may be sufficient for monitoring in moderate- and high-prevalence areas (Coffeng et al. 2020), there is a recognition that current diagnostics will not be sufficient after the initiation of a control programme (Stothard et al. 2014; Utzinger et al. 2015; Knopp et al. 2018). Once a schistosomiasis control programme becomes a late-stage control programme, the sensitivity and specificity will need to be at least 99% (Utzinger et al. 2015; King et al. 2020d), neither of which are achieved with a single urine filtration or Kato-Katz thick smear. Approaches to improve this, such as multiple samples over multiple days (Lamberton et al. 2014; Utzinger et al. 2015), incorporating multiple tests (Joseph et al. 1995), or adjusting the prevalence for the diagnostic test characteristics (Reiczigel et al. 2010; Diggle 2011) are not feasible for control programmes.

In addition, multiple datasets did not include evaluations of the more severe manifestations of *S. mansoni* infections, such as hepatomegaly and splenomegaly. This did not enable us to evaluate the utility of these indicators. Though, as endemic areas receive more rounds of preventive chemotherapy, the likelihood of severe disease manifestations will decrease, suggesting these indicators may not be as useful in the future.

9.3 Future directions

9.3.1 Correlations between prevalence in 9-12 year olds and adults post-treatment

Currently, the treatment strategy for schistosomiasis is determined by the prevalence in school-age children (WHO 2013). High-risk adults are also to be treated in high- and moderate-risk communities, but they do not contribute data to the assessment. A modelling study demonstrated that,

in areas with a high-prevalence of school-aged children, the optimal treatment strategy depends on the prevalence of adults (Toor et al. 2018b), suggesting that the evaluation of adults is needed to optimize the treatment strategy. Inclusion of adults has also shown to be a beneficial adaptation for meeting program goals in some *S. haematobium* scenarios (Kura et al. 2020). Though, a prior study explored the correlations between 9-12 year old, 5-8 year old, and adult participants at one SCORE site prior to the initiation of praziquantel dissemination and found reasonably good correlation between community level 9-12 year old prevalence and adult prevalence (Mwinzi et al. 2015b). If this association holds and is strong post-treatment, then there may not be a need to collect information from adults.

9.3.2 Longitudinal correlations between macrohaematuria and microhaematuria

Self-reported macrohaematuria provides similar diagnostic performance to microhaematuria evaluated via reagent strips (van der Werf et al. 2004) or when used in combination to improve the diagnosis for urogenital schistosomiasis (Bassiouny et al. 2014; Okeke et al. 2014). Self-reporting of macrohaematuria does not appear to be affected by the recall period (van der Werf et al. 2003a) and has been shown to be a cost-effective tool for identifying high-risk schools (Ansell et al. 2002). Though, none of these studies evaluated self-reported macrohaematuria and microhaematuria longitudinally to see if the correlation changes pre- and post-initiation of praziquantel treatment or if remains consistent for those with and without urogenital schistosomiasis infection.

9.3.3 Microhaematuria targets by age

Chapter 7 found infection prevalence targets that could keep microhaematuria below particular thresholds. Those analyses controlled for age and sex since microhaematuria prevalence varies by age and sex in school-aged children in areas with (Akinneye et al. 2018) and without (Dodge et al. 1976) endemic schistosomiasis. Though, these targets should be explored further to determine if targets should be adjusted to match the age and sex distribution of the sample.

9.3.4 Individual intensity level that reduces microhaematuria to a background level

The focus of chapter 7 was on school-level infection and microhaematuria prevalence. A different approach could be to determine the best estimate of the intensity level that reduces microhaematuria to a background level.

9.3.5 Ultrasound scoring utility and longitudinal changes

A body of literature exists on the evolution of ultrasound-measured pathology in school-aged children (Richter 2000), though a deeper understanding of changes in specific pathology may be warranted, especially related to the ultrasound scoring. Although a scoring system is included in the schistosomiasis ultrasound guidelines (Richter et al. 2000), it does not appear to be widely used. A better understanding of the scale and especially changes over time may facilitate the interpretation of the scale and promote its utility.

10 Conclusions

WHO's 2021-2030 NTD Roadmap is targeting an increase in the number of countries validated for elimination as a public health problem from 26 in 2020 to 49 in 2023, 69 in 2025, and 78 in 2030 (WHO 2020b). To achieve these goals, a robust monitoring and evaluation framework is needed to measure progress and validate whether geographic areas have eliminated schistosomiasis as a public health problem. The research presented in this thesis provides some evidence of potential improvements to the schistosomiasis monitoring and evaluation framework, specifically:

- *S. mansoni* infection intensity categories do not align with morbidity indicators and are a poor summary of the morbidity afflicting a sample of children;
- *S. haematobium* infection intensity categories are associated with the prevalence of morbidity indicators and provide a good summary of the morbidity afflicting a sample of children;
- Existing targets for control of morbidity and elimination as a public health problem based on the prevalence of heavy-intensity infections do not consistently correlate with morbidity levels except for microhaematuria for *S. haematobium* infections;
- *S. haematobium* infection targets based on controlling microhaematuria prevalence to a prespecified level provide a high likelihood of success and are sensitive to changes;
- *S. haematobium* heavy-intensity infection targets based on controlling microhaematuria do not provide the same level of certainty as any infection targets and are not sensitive enough to detect slight changes in microhaematuria status;
- Control of morbidity and elimination as a public health problem targets based on the prevalence of heavy-intensity *S. mansoni* infections do not associate with morbidity indicators;
- There are a lack of incentives to collect heavy-intensity data; and
- Control programmes should explore the use of technology, especially tablet-based ultrasound systems, to collect data on schistosomiasis morbidity.

11 References

Abdel-Latif Z, Abdel-Wahab MF, El-Kady NM (1981). Evaluation of portal hypertension in cases of hepatosplenic schistosomiasis using ultrasound. *J Clin Ultrasound,* 9(8), 409-412.

Abdel-Wahab M, Abdel-Latif Z, El-Kady N, Arafa N (1978). *The use of ultrasonography in diagnosis of different schistosomal-syndromes.* Paper presented at the Proceedings of the third international workshop on diagnostic ultrasound imaging.

Abdel-Wahab MF, Esmat G, Milad M, Abdel-Razek S, Strickland GT (1989). Characteristic sonographic pattern of schistosomal hepatic fibrosis. *Am J Trop Med Hyg,* 40(1), 72-76.

Abdel-Wahab MF, Esmat G, Ramzy I, Fouad R, Abdel-Rahman M, Yosery A, Narooz S, Strickland GT (1992a). *Schistosoma haematobium* infection in Egyptian schoolchildren: demonstration of both hepatic and urinary tract morbidity by ultrasonography. *T Roy Soc Trop Med Hyg,* 86(4), 406-409.

Abdel-Wahab MF, Ramzy I, Esmat G, El Kafass H, Strickland GT (1992b). Ultrasound For detecting *Schistosoma haematobium* urinary tract complications: comparison with radiographic procedures. *J Urol,* 148(2 Part 1), 346-350.

Adriko M, Faust CL, Carruthers LV, Moses A, Tukahebwa EM, Lamberton PH (2018). Low praziquantel treatment coverage for *Schistosoma mansoni* in Mayuge District, Uganda, due to the absence of treatment opportunities, rather than systematic non-compliance. *Trop Med Infect Dis,* 3(4), 111.

Akinneye J, Fasidi M, Afolabi O, Adesina F (2018). Prevalence of urinary schistosomiasis among secondary school students in Ifedore local government, Ondo state, Nigeria. *Int J Trop Dis,* 1(004).

Akpata R, Neumayr A, Holtfreter MC, Krantz I, Singh DD, Mota R, Walter S, Hatz C, Richter J (2015). The WHO ultrasonography protocol for assessing morbidity due to *Schistosoma haematobium*. Acceptance and evolution over 14 years. Systematic review. *Parasitol Res,* 114(4), 1279-1289.

Alpino P (1591). *De medicina Aegyptiorum: libri IV.* Venice, Italy: Apud Franciscum de Franciscis Senensem.

Altman DG, Bland JM (1995). Statistics notes: absence of evidence is not evidence of absence. *BMJ,* 311(7003), 485.

Anastasiou E, Lorentz KO, Stein GJ, Mitchell PD (2014). Prehistoric schistosomiasis parasite found in the Middle East. *Lancet Infect Dis,* 14(7), 553-554.

Andrade G, Bertsch DJ, Gazzinelli A, King CH (2017). Decline in infection-related morbidities following drug-mediated reductions in the intensity of *Schistosoma* infection: a systematic review and meta-analysis. *PLoS Negl Trop Dis,* 11(2), e0005372.

Andrade ZA, Santana S, Rubin E (1962). Hepatic changes in advanced schistosomiasis. *Gastroenterol,* 42(4), 393-400.

Andrade ZA, Andrade SG (1970). Pathogenesis of schistosomal pulmonary arteritis. *Am J Trop Med Hyg,* 19(2), 305-310.

Andrade ZA, Cheever AW (1971). Alterations of the intrahepatic vasculature in hepatosplenic schistosomiasis mansoni. *Am J Trop Med Hyg,* 20(3), 425-432.

Andrade ZA, Rocha H (1979). Schistosomal glomerulopathy. *Kidney Int,* 16(1), 23-29.

Anonymous (1980). Praziquantel: a new hope for schistosomiasis. *Lancet,* 315(8169), 635-636.

Ansell J, Guyatt H, Hall A, Kihamia C, Kivugo J, Ntimbwa P, Bundy D (1997). The reliability of self-reported blood in urine and schistosomiasis as indicators of *Schistosoma haematobium* infection in school children: a study in Muheza District, Tanzania. *Trop Med Int Health,* 2(12), 1180-1189.

Ansell J, Guyatt HL (2002). Comparative cost-effectiveness of diagnostic tests for urinary schistosomiasis and the implications for school health programmes. *Ann Trop Med Parasit,* 96(2), 145-153.

Arap Siongok TK, Mahmoud AAF, Ouma JH, Warren KS, Muller AS, Handa AK, Houser HB (1976). Morbidity in schistosomiasis mansoni in relation to intensity of infection: study of a community in Machakos, Kenya. *Am J Trop Med Hyg,* 25(2), 273-284.

Arnesen T, Nord E (1999). The value of DALY life: problems with ethics and validity of disability adjusted life years. *BMJ,* 319(7222), 1423.

Arnold BF, Scobie HM, Priest JW, Lammie PJ (2018). Integrated serologic surveillance of population immunity and disease transmission. *Emerg Infect Dis,* 24(7), 1188-1194.

Arnold BF, Kanyi H, Njenga SM, Rawago FO, Priest JW, Secor WE, Lammie PJ, Won KY, Odiere MR (2020). Fine-scale heterogeneity in *Schistosoma mansoni* force of infection measured through antibody response. *P Natl Acad Sci USA,* 117(37), 23174–23181.

Ashton RA, Stewart BT, Petty N, Lado M, Finn T, Brooker S, Kolaczinski JH (2011). Accuracy of circulating cathodic antigen tests for rapid mapping of *Schistosoma mansoni* and *S. haematobium* infections in Southern Sudan. *Trop Med Int Health,* 16(9), 1099-1103.

Assis AMO, Barreto ML, Prado MS, Reis MG, Parraga IM, Blanton RE (1998). *Schistosoma mansoni* infection and nutritional status in schoolchildren: a randomized, double-blind trial in northeastern Brazil. *Am J Clin Nutr,* 68(6), 1247-1253.

Attia OM (1962). A critical study of bilharziasis of the uterus. *J Obstet Gynaecol Brit Em,* 69(2), 334-336.

Ayad N (1956). Bilharziasis survey in British Somaliland, Eritrea, Ethiopia, Somalia, the Sudan, and Yemen. *Bull World Health Organ,* 14(1), 1-117.

Baird S, Hicks JH, Kremer M, Miguel E (2016). Worms at work: long-run impacts of a child health investment. *Q J Econ,* 131(4), 1637-1680.

Baker MC, Mathieu E, Fleming FM, Deming M, King JD, Garba A, Koroma JB, Bockarie M, Kabore A, Sankara DP, Molyneux DH (2010). Mapping, monitoring, and surveillance of neglected tropical diseases: towards a policy framework. *Lancet,* 375(9710), 231-238.

Bärenbold O, Raso G, Coulibaly JT, N'Goran EK, Utzinger J, Vounatsou P (2017). Estimating sensitivity of the Kato-Katz technique for the diagnosis of *Schistosoma mansoni* and hookworm in relation to infection intensity. *PLoS Negl Trop Dis,* 11(10), e0005953.

Bärenbold O, Garba A, Colley DG, Fleming FM, Haggag AA, Ramzy RMR, Assaré RK, Tukahebwa EM, Mbonigaba JB, Bucumi V, Kebede B, Yibi MS, Meité A, Coulibaly JT, N'Goran EK, Tchuem Tchuenté L-A, Mwinzi P, Utzinger J, Vounatsou P (2018). Translating preventive chemotherapy prevalence thresholds for *Schistosoma mansoni* from the Kato-Katz technique into the point-of-care circulating cathodic antigen diagnostic test. *PLoS Negl Trop Dis,* 12(12), e0006941.

Barsoum RS (2013). Urinary schistosomiasis: review. *J Adv Res,* 4(5), 453-459.

Barsoum RS, Esmat G, El-Baz T (2013). Human schistosomiasis: Clinical perspective: review. *J Adv Res,* 4(5), 433-444.

Bartsch H, Kuroki T, Malaveille C, Loprieno N, Barale R, Abbondandolo A, Bonatti S, Rainaldi G, Vogel E, Davis A (1978). Absence of mutagenicity of praziquantel, a new, effective, anti-schistosomal drug, in bacteria, yeasts, insects and mammalian cells. *Mutat Res-Genet Tox,* 58(2), 133-142.

Bassiouny HK, Hasab AA, El Nimr NA, Al Shibani LA, Al Waleedi AA (2014). Rapid diagnosis of schistosomiasis in Yemen using a simple questionnaire and urine reagent strips. *E Mediterr Health J,* 20(4), 242-249.

Batzinger RP, Bueding E (1977). Mutagenic activities in vitro and in vivo of five antischistosomal compounds. *J Pharmacol Exp Ther,* 200(1), 1-9.

Begg RC (1920). Bilharzia disease: some prevalent misconceptions. *S Afr Med J,* 18(14), 239-241.

Bélard S, Tamarozzi F, Bustinduy AL, Wallrauch C, Grobusch MP, Kuhn W, Brunetti E, Joekes E, Heller T (2016). Point-of-care ultrasound assessment of tropical infectious diseases—A review of applications and perspectives. *Am J Trop Med Hyg,* 94(1), 8-21.

Belleli V (1886). *La Bilharzia haematobia. Osservazioni an atomo-pathologiche e cliniche*. Milan, Italy: Gazetta degli Ospitali.

Berberian DA, Paquin HO, Fantauzzi A (1953). Longevity of *Schistosoma hematobium* and *Schistosoma mansoni*: observations based on a case. *J Parasitol,* 39(5), 517-519.

Berggren WL, Weller TH (1967). Immunoelectrophoretic demonstration of specific circulating antigen in animals infected with *Schistosoma mansoni*. *Am J Trop Med Hyg,* 16(5), 606-612.

Bey H (1938). Proposal to establish a schistosomiasis commission. *League of Nations Health Organization*. Geneva.

Biays S, Stich AHR, Odermatt P, Long C, Yersin C, Men C, Saem C, Lormand JD (1999). Foyer de bilharziose à *Schistosoma mekongi* redécouvert au Nord du Cambodge: I. Perception culturelle de la maladie; description et suivi de 20 cas cliniques graves. *Trop Med Int Health,* 4(10), 662-673.

Biggs HEJ, Grantier I (1960). A preliminary list of mollusca of Ras Tanura, Persian Gulf. *J Conchol,* 24, 379.

Bilharz T (1852). Ein Beitrag zur *Helminthographia humana*, aus brieflichen Mittheilungen des Dr. Bilharz in Cairo, nebst Bemerkungen von Professor C.Th.v. Siebold in Breslau. *Z wiss Zool,* 4, 53-76.

Bilharz T (1853). Fernere Mittheilungen über *Distomum haematobium*. *Z wiss Zool,* 4, 454-456.

Bilharz T (1856). *Distomum haematobium* und sein Verhältnis zu gewissen pathologischen Vetänderungen der menschlichen Harnorgane. *Wien Med Wochenschr,* 6, 49–52, 65–68.

Binder S, Campbell CH, Castleman JD, Kittur N, Kinung'hi SM, Olsen A, Magnussen P, Karanja DMS, Mwinzi PNM, Montgomery SP, Secor WE, Phillips AE, Dhanani N, Gazzinelli-Guimaraes PH, Clements MN, N'Goran EK, Meite A, Utzinger J, Hamidou AA, Garba A, Fleming FM, Whalen CC, King CH, Colley DG (2020). Lessons learned in conducting mass drug administration for schistosomiasis control and measuring coverage in an operational research setting. *Am J Trop Med Hyg,* 103(1_Suppl), 105-113.

Blackie WK (1932). *A Helminthological Survey of Southern Rhodesia* (Vol. 5). London: London School of Hygiene & Tropical Medicine, Keppel Street, Gower Street, W.C.I.

Blair DM (1956). Bilharziasis survey in British West and East Africa, Nyasaland, and the Rhodesias. *Bull World Health Organ,* 15(1-2), 203-273.

Blanton RE, Abdel Salam E, Kariuki HC, Magak P, Silva LK, Muchiri EM, Thiongo F, Abdel-Meghid IE, Butterworth AE, Reis MG, Ouma JH (2002). Population-based differences in *Schistosoma mansoni*- and Hepatitis C-induced disease. *J Infect Dis,* 185(11), 1644-1649.

Bocanegra C, Pintar Z, Mendioroz J, Serres X, Gallego S, Nindia A, Aznar ML, Soriano-Arandes A, Salvador F, Gil E, Sikaleta N, Moreno M, Molina I (2018). Ultrasound evolution of pediatric urinary schistosomiasis after treatment with praziquantel in a highly endemic area. *Am J Trop Med Hyg,* 99(4), 1011-1017.

Bogoch II, Andrews JR, Dadzie Ephraim RK, Utzinger J (2012). Simple questionnaire and urine reagent strips compared to microscopy for the diagnosis of *Schistosoma haematobium* in a community in northern Ghana. *Trop Med Int Health,* 17(10), 1217-1221.

Boisier P, Ramarokoto C-E, Ravaoalimalala VE, Rabarijaona L, Serieye J, Roux J, Esterre P (1998). Reversibility of *Schistosoma mansoni*-associated morbidity after yearly mass praziquantel therapy: ultrasonographic assessment. *T Roy Soc Trop Med Hyg,* 92(4), 451-453.

Boisier P, Ramarokoto C-E, Ravoniarimbinina P, Rabarijaona L, Ravaoalimalala VE (2001). Geographic differences in hepatosplenic complications of schistosomiasis mansoni and explanatory factors of morbidity. *Trop Med Int Health,* 6(9), 699-706.

Bonnard P, Boutouaba S, Diakhate I, Seck M, Dompnier J-P, Riveau G (2011). Learning curve of vesico-urinary ultrasonography in *Schistosoma haematobium* infection with WHO practical guide: a "Simple to Learn" examination. *Am J Trop Med Hyg,* 85(6), 1071-1074.

Booth M, Vennervald BJ, Kabatereine NB, Kazibwe F, Ouma JH, Kariuki CH, Muchiri E, Kadzo H, Ireri E, Kimani G, Mwatha JK, Dunne DW (2004). Hepatosplenic morbidity in two neighbouring communities in Uganda with high levels of *Schistosoma mansoni* infection but very different durations of residence. *T Roy Soc Trop Med Hyg,* 98(2), 125-136.

Boros DL (1989). Immunopathology of *Schistosoma mansoni* infection. *Clin Microbiol Rev,* 2(3), 250.

Bradley DJ, McCullough FS (1973). Egg output stability and the epidemiology of *Schistosoma haematobium* Part II. An analysis of the epidemiology of endemic *S. haematobium*. *T Roy Soc Trop Med Hyg,* 67(4), 491-500.

Brooker S, Donnelly CA, Guyatt HL (2000). Estimating the number of helminthic infections in the Republic of Cameroon from data on infection prevalence in schoolchildren. *Bull World Health Organ,* 78, 1456-1465.

Brooker S, Miguel EA, Waswa P, Namunyu R, Moulin S, Guyatt H, Bundy DAP (2001). The potential of rapid screening methods for *Schistosoma mansoni* in western Kenya. *Ann Trop Med Parasit,* 95(4), 343-351.

Brooker S (2007). Spatial epidemiology of human schistosomiasis in Africa: risk models, transmission dynamics and control. *T Roy Soc Trop Med Hyg,* 101(1), 1-8.

Burki A, Tanner M, Burnier E, Schweizer W, Meudt R, Degrémont A (1986). Comparison of ultrasonography, intravenous pyelography and cystoscopy in detection of urinary tract lesions due to *Schistosoma haematobium*. *Acta Trop,* 43(2), 139-151.

Burnim M, Ivy JA, King CH (2017). Systematic review of community-based, school-based, and combined delivery modes for reaching school-aged children in mass drug administration programs for schistosomiasis. *PLoS Negl Trop Dis,* 11(10), e0006043.

Bustinduy AL, King CH (2009). Parasitic Helminths. In Fratamico PM, Smith JL, Brogden KA (Eds.), *Post-Infectious Sequelae and Long-Term Consequences of Infectious Diseases* (pp. 291-329). Washington: American Society for Microbiology Press.

Bustinduy AL, Thomas CL, Fiutem JJ, Parraga IM, Mungai PL, Muchiri EM, Mutuku F, Kitron U, King CH (2011). Measuring fitness of Kenyan children with polyparasitic infections using the 20-meter shuttle run test as a morbidity metric. *PLoS Negl Trop Dis,* 5(7), e1213.

Bustinduy AL, Parraga IM, Thomas CL, Mungai PL, Mutuku F, Muchiri EM, Kitron U, King CH (2013). Impact of polyparasitic infections on anemia and undernutrition among Kenyan children living in a *Schistosoma haematobium*-endemic area. *Am J Trop Med Hyg,* 88(3), 433-440.

Bustinduy AL, King CH (2014). Schistosomiasis. In Farrar J, Hotez PJ, Junghanns T, Kang G, Lalloo DG, White NJ (Eds.), *Manson's Tropical Diseases 23rd edition* (23rd ed., pp. 698-725). Philadelphia: Elsevier Saunders.

Bustinduy AL, Friedman JF, Kjetland EF, Ezeamama AE, Kabatereine NB, Stothard JR, King CH (2016). Expanding praziquantel (PZQ) access beyond mass drug administration programs: paving a way forward for a pediatric PZQ formulation for schistosomiasis. *PLoS Negl Trop Dis,* 10(9), e0004946.

Bustinduy AL, Stothard JR, Friedman JF (2017a). Paediatric and maternal schistosomiasis: shifting the paradigms. *Brit Med Bull,* 123(1), 115-125.

Bustinduy AL, Wright S, Joekes EC, Kabatereine NB, Reinhard-Rupp J, King CH, Stothard JR (2017b). One hundred years of neglect in paediatric schistosomiasis. *Parasitol,* 144(12), 1613-1623.

Caffrey CR (2007). Chemotherapy of schistosomiasis: present and future. *Curr Opin Chem Biol,* 11(4), 433-439.

Caldas IR, Campi-Azevedo AC, Oliveira LFA, Silveira AMS, Oliveira RC, Gazzinelli G (2008). Human schistosomiasis mansoni: immune responses during acute and chronic phases of the infection. *Acta Trop,* 108(2), 109-117.

Campbell SJ, Savage GB, Gray DJ, Atkinson J-AM, Soares Magalhães RJ, Nery SV, McCarthy JS, Velleman Y, Wicken JH, Traub RJ, Williams GM, Andrews RM, Clements ACA (2014). Water, sanitation, and hygiene (WASH): a critical component for sustainable soil-transmitted helminth and schistosomiasis control. *PLoS Negl Trop Dis,* 8(4), e2651.

Campbell SJ, Biritwum N-K, Woods G, Velleman Y, Fleming F, Stothard JR (2018). Tailoring water, sanitation, and hygiene (WASH) targets for soil-transmitted helminthiasis and schistosomiasis control. *Trends Parasitol,* 34(1), 53-63.

Carroll RJ, Spiegelman CH, Lan KKG, Bailey KT, Abbott RD (1984). On errors-in-variables for binary regression models. *Biometrika,* 71(1), 19-25.

Carter JP, Diab AS, Nasiff S, Sanborn WR, Grivetti LE, Davies JA (1970). Bacteriological and urinary findings in adolescent Egyptian males with and without urinary schistosomiasis. *J Trop Med Hyg,* 73(9), 211-217.

Cavalcanti MG, Cunha AFA, Peralta JM (2019). The advances in molecular and new point-of-care (POC) diagnosis of schistosomiasis pre- and post-praziquantel use: in the pursuit of more reliable approaches for low endemic and non-endemic areas. *Front Immunol,* 10(858).

Cerri GG, Alves VA, Magalhães A (1984). Hepatosplenic schistosomiasis mansoni: ultrasound manifestations. *Radiol,* 153(3), 777-780.

Chabasse D, Bertrand G, Leroux J, Gauthey N, Hocquet P (1985). Bilharziose à *Schistosoma mansoni* évolutive découverte 37 ans après l'infestation. *B Soc Pathol Exot,* 78(5), 643-647.

Chamberlin AJ, Jones IJ, Lund AJ, Jouanard N, Riveau G, Ndione R, Sokolow SH, Wood CL, Lafferty KD, De Leo GA (2021). Visualization of schistosomiasis snail habitats using light unmanned aerial vehicles. *Geospatial Health,* 15(2).

Chami GF, Kontoleon AA, Bulte E, Fenwick A, Kabatereine NB, Tukahebwa EM, Dunne DW (2016). Profiling nonrecipients of mass drug administration for schistosomiasis and hookworm infections: a comprehensive analysis of praziquantel and albendazole coverage in community-directed treatment in Uganda. *Clin Infect Dis,* 62(2), 200-207.

Chammartin F, Houngbedji CA, Hürlimann E, Yapi RB, Silué KD, Soro G, Kouamé FN, N'Goran EK, Utzinger J, Raso G, Vounatsou P (2014). Bayesian risk mapping and model-based estimation of *Schistosoma haematobium–Schistosoma mansoni* co-distribution in Côte d'Ivoire. *PLoS Negl Trop Dis,* 8(12), e3407.

Cheever AW, Andrade ZA (1967). Pathological lesions associated with *Schistosoma mansoni* infection in man. *T Roy Soc Trop Med Hyg,* 61(5), 626-639.

Cheever AW (1968). A quantitative post-mortem study of schistosomiasis mansoni in man. *Am J Trop Med Hyg,* 17(1), 38-64.

Cheever AW, Young SW, Shehata A (1975). Calcification of *Schistosoma haematobium* eggs: relation of radiologically demonstrable calcification to eggs in tissues and passage of eggs in urine. *T Roy Soc Trop Med Hyg,* 69(4), 410-414.

Cheever AW, Kamel IA, Elwi AM, Mosimann JE, Danner R (1977). *Schistosoma mansoni* and *S. haematobium* infections in Egypt: II. Quantitative parasitological findings at necropsy. *Am J Trop Med Hyg,* 26(4), 702-716.

Cheever AW, Ismail K, A., Elwi AM, Mosimann JE, Danner R, Sippel JE (1978). *Schistosoma mansoni* and *S. haematobium* infections in Egypt: III. Extrahepatic pathology. *Am J Trop Med Hyg,* 27(1), 55-75.

Cheever AW, Duvall RH, Minker RG (1980). Extrahepatic pathology in rabbits infected with Japanese and Philippine strains of *Schistosoma japonicum*, and the relation of intestinal lesions to passage of eggs in the feces. *Am J Trop Med Hyg,* 29(6), 1316-1326.

Cheever AW, Duvall RH (1982). *Schistosoma japonicum*: migration of adult worm pairs within the mesenteric veins of mice. *T Roy Soc Trop Med Hyg,* 76(5), 641-645.

Cheever AW, Macedonia JG, Mosimann JE, Cheever EA (1994). Kinetics of egg production and egg excretion by *Schistosoma mansoni* and *S. japonicum* in mice Infected with a single pair of worms. *Am J Trop Med Hyg,* 50(3), 281-295.

Cheever AW, Hoffmann KF, Wynn TA (2000). Immunopathology of schistosomiasis mansoni in mice and men. *Immunol Today,* 21(9), 465-466.

Christie JD, Crouse D, Pineda J, Anis-Ishak E, Smith JH, Kamel IA (1986a). Patterns of *Schistosoma haematobium* egg distribution in the human lower urinary tract: I. Noncancerous lower urinary tracts. *Am J Trop Med Hyg,* 35(4), 743-751.

Christie JD, Crouse D, Smith JH, Pineda J, Ishak E-A, Kamel IA (1986b). Patterns of *Schistosoma haematobium* egg distribution in the human lower urinary tract: II. Obstructive uropathy. *Am J Trop Med Hyg,* 35(4), 752-758.

Christinet V, Lazdins-Helds JK, Stothard JR, Reinhard-Rupp J (2016). Female genital schistosomiasis (FGS): from case reports to a call for concerted action against this neglected gynaecological disease. *Int J Parasitol,* 46(7), 395-404.

Cioli D, Pica-Mattoccia L (2003). Praziquantel. *Parasitol Res,* 90(1), S3-S9.

Clark E, Graef I (1935). Chronic pulmonary arteritis in schistosomiasis mansoni associated with right ventricular hypertrophy: report of a case. *Am J Pathol,* 11(4), 693-706.

Clements ACA, Lwambo NJS, Blair L, Nyandindi U, Kaatano G, Kinung'hi S, Webster JP, Fenwick A, Brooker S (2006). Bayesian spatial analysis and disease mapping: tools to enhance planning and implementation of a schistosomiasis control programme in Tanzania. *Trop Med Int Health,* 11(4), 490-503.

Clements ACA, Barnett AG, Nyandindi U, Lwambo NJS, Kihamia CM, Blair L (2008). Age and gender effects in self-reported urinary schistosomiasis in Tanzania. *Trop Med Int Health,* 13(5), 713-721.

Clements MN, Corstjens PLAM, Binder S, Campbell CH, de Dood CJ, Fenwick A, Harrison W, Kayugi D, King CH, Kornelis D, Ndayishimiye O, Ortu G, Lamine MS, Zivieri A, Colley DG, van Dam GJ (2018). Latent class analysis to evaluate performance of point-of-care CCA for low-intensity *Schistosoma mansoni* infections in Burundi. *Parasit Vector,* 11(1), 111.

Clennon JA, King CH, Muchiri EM, Kariuki HC, Ouma JH, Mungai P, Kitron U (2004). Spatial patterns of urinary schistosomiasis infection in a highly endemic area of coastal Kenya. *Am J Trop Med Hyg,* 70(4), 443-448.

Cobbold TS (1859). {XXVII.} On some new forms of *Entozoa*. *Trans Linn Soc Lond,* 22(4), 363-366.

Cobbold TS (1872). On the development of bilharzia hæmatobia: together with remarks on the ova of another urinary parasite (the so-called *Trichina Cystica* of Dr. Salisbury) occurring in a case of hæmaturia from Natal. *BMJ,* 2(604), 89-92.

Coffeng LE, Malizia V, Vegvari C, Cools P, Halliday KE, Levecke B, Mekonnen Z, Gichuki PM, Sayasone S, Sarkar R, Shaali A, Vlaminck J, Anderson RM, de Vlas SJ (2020). Impact of different sampling schemes for decision making in soil-transmitted helminthiasis control programs. *J Infect Dis,* 221(Supplement_5), S531-S538.

Coker CM, Lichtenberg F (1956). A revised method for isolation of *Schistosoma mansoni* eggs for biological experimentation. *P Soc Exp Biol Med,* 92(4), 780-782.

Colebunders R, Verstraeten T, Van Gompel A, Van den Ende J, De Roo A, Polderman A, Visser L (1995). Acute schistosomiasis in travelers returning From Mali. *J Travel Med,* 2(4), 235-238.

Colley DG, Garcia AA, Lambertucci JR, Parra JC, Katz N, Rocha RS, Gazzinelli G (1986). Immune responses during human schistosomiasis. XII. Differential responsiveness in patients with hepatosplenic disease. *Am J Trop Med Hyg,* 35(4), 793-802.

Colley DG, Binder S, Campbell C, King CH, Tchuem Tchuenté L-A, Goran EK, Erko B, Karanja DMS, Kabatereine NB, van Lieshout L, Rathbun S (2013). A five-country evaluation of a point-of-care

circulating cathodic antigen urine assay for the prevalence of *Schistosoma mansoni*. *Am J Trop Med Hyg,* 88(3), 426-432.

Colley DG, Bustinduy AL, Secor WE, King CH (2014a). Human schistosomiasis. *Lancet,* 383(9936), 2253-2264.

Colley DG, Secor WE (2014b). Immunology of human schistosomiasis. *Parasite Immunol,* 36(8), 347-357.

Colley DG, Fleming FM, Matendechero SH, Knopp S, Rollinson D, Utzinger J, Castleman JD, Kittur N, King CH, Campbell CH, Kabole FM, Kinung'hi S, Ramzy RMR, Binder S (2020a). Contributions of the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) to schistosomiasis control and elimination: key findings and messages for future goals, thresholds, and operational research. *Am J Trop Med Hyg,* 103(1_Suppl), 125-134.

Colley DG, Jacobson JA, Binder S (2020b). Schistosomiasis Consortium for Operational Research and Evaluation (SCORE): its foundations, development, and evolution. *Am J Trop Med Hyg,* 103(1_Suppl), 5-13.

Colley DG, King CH, Kittur N, Ramzy RMR, Secor WE, Fredericks-James M, Ortu G, Clements MN, Ruberanziza E, Umulisa I, Wittmann U, Campbell CH (2020c). Evaluation, validation, and recognition of the point-of-care circulating cathodic antigen, urine-based assay for mapping *Schistosoma mansoni* infections. *Am J Trop Med Hyg,* 103(1_Suppl), 42-49.

Cook JA, Baker ST, Warren KS, Jordan P (1974). A controlled study of morbidity of schistosomiasis mansoni in St. Lucian children, based on quantitative egg excretion. *Am J Trop Med Hyg,* 23(4), 625-633.

Corstjens PLAM, van Lieshout L, Zuiderwijk M, Kornelis D, Tanke HJ, Deelder AM, van Dam GJ (2008). Up-converting phosphor technology-based lateral flow assay for detection of *Schistosoma* circulating anodic antigen in serum. *J Clin Microbiol,* 46(1), 171.

Corstjens PLAM, de Dood CJ, Knopp S, Clements MN, Ortu G, Umulisa I, Ruberanziza E, Wittmann U, Kariuki T, LoVerde P, Secor WE, Atkins L, Kinung'hi S, Binder S, Campbell CH, Colley DG, van Dam GJ (2020). Circulating anodic antigen (CAA): a highly sensitive diagnostic biomarker to detect active *Schistosoma* infections—improvement and use during SCORE. *Am J Trop Med Hyg,* 103(1_Suppl), 50-57.

Cort WW (1928). Schistosome dermatitis in the United States (Michigan). *JAMA,* 90(13), 1027-1029.

Coulibaly JT, Knopp S, N'Guessan NA, Silué KD, Fürst T, Lohourignon LK, Brou JK, N'Gbesso YK, Vounatsou P, N'Goran EK, Utzinger J (2011). Accuracy of urine circulating cathodic antigen (CCA) test for *Schistosoma mansoni* diagnosis in different settings of Côte d'Ivoire. *PLoS Negl Trop Dis,* 5(11), e1384.

Coulibaly JT, Panic G, Silué KD, Kovač J, Hattendorf J, Keiser J (2017). Efficacy and safety of praziquantel in preschool-aged and school-aged children infected with *Schistosoma mansoni*: a randomised controlled, parallel-group, dose-ranging, phase 2 trial. *Lancet Glob Health,* 5(7), e688-e698.

Coulibaly JT, Ouattara M, Barda B, Utzinger J, N'Goran EK, Keiser J (2018). A rapid appraisal of factors influencing praziquantel treatment compliance in two communities endemic for schistosomiasis in Côte d'Ivoire. *Trop Med Infect Dis,* 3(2), 69.

Coutinho A (1968). Hemodynamic studies of portal hypertension in schistosomiasis. *Am J Med,* 44(4), 547-556.

Cowper SG (1953). Schistosomiasis in Mauritius. *T Roy Soc Trop Med Hyg,* 47(6), 564-579.

Crellen T, Walker M, Lamberton PHL, Kabatereine NB, Tukahebwa EM, Cotton JA, Webster JP (2016). Reduced efficacy of praziquantel against *Schistosoma mansoni* is associated with multiple rounds of mass drug administration. *Clin Infect Dis,* 63(9), 1151-1159.

Cribb DM, Clarke NE, Doi SAR, Vaz Nery S (2019). Differential impact of mass and targeted praziquantel delivery on schistosomiasis control in school-aged children: a systematic review and meta-analysis. *PLoS Negl Trop Dis,* 13(10), e0007808.

Crombie JA, Anderson RM (1985). Population dynamics of *Schistosoma mansoni* in mice repeatedly exposed to infection. *Nature,* 315(6019), 491-493.

Dabo A, Bary B, Kouriba B, Sankaré O, Doumbo O (2013). Factors associated with coverage of praziquantel for schistosomiasis control in the community-direct intervention (CDI) approach in Mali (West Africa). *Infect Dis Poverty,* 2(1), 11.

Danso-Appiah A, Stolk WA, Bosompem KM, Otchere J, Looman CWN, Habbema JDF, de Vlas SJ (2010). Health seeking behaviour and utilization of health facilities for schistosomiasis-related symptoms in Ghana. *PLoS Negl Trop Dis,* 4(11), e867.

Davis A, Biles JE, Ulrich AM (1979a). Initial experiences with praziquantel in the treatment of human infections due to *Schistosoma haematobium*. *Bull World Health Organ,* 57(5), 773-779.

Davis A, Wegner DH (1979b). Multicentre trials of praziquantel in human schistosomiasis: design and techniques. *Bull World Health Organ,* 57(5), 767-771.

Davis A, Biles JE, Ulrich AM, Dixon H (1981). Tolerance and efficacy of praziquantel in phase II A and II B therapeutic trials in Zambian patients. *Arzneimittel-Forsch,* 31(3a), 568-574.

Davis SM, Wiegand RE, Mulama F, Kareko EI, Harris R, Ochola E, Samuels AM, Rawago F, Mwinzi PM, Fox LM, Odiere MR, Won KY (2015). Morbidity associated with schistosomiasis before and after treatment in young children in Rusinga Island, western Kenya. *Am J Trop Med Hyg,* 92(5), 952-958.

Dawaki S, Al-Mekhlafi HM, Ithoi I, Ibrahim J, Abdulsalam AM, Ahmed A, Sady H, Nasr NA, Atroosh WM (2015). The menace of schistosomiasis in Nigeria: knowledge, attitude, and practices regarding schistosomiasis among rural communities in Kano State. *PLoS ONE,* 10(11), e0143667.

Dayan AD (2003). Albendazole, mebendazole and praziquantel. Review of non-clinical toxicity and pharmacokinetics. *Acta Trop,* 86(2), 141-159.

De Cock KM (1986). Hepatosplenic schistosomiasis: a clinical review. *Gut,* 27(6), 734-745.

de Vlas SJ, Gryseels B (1992a). Underestimation of *Schistosoma mansoni* prevalences. *Parasitol Today,* 8(8), 274-277.

de Vlas SJ, Gryseels B, Van Oortmarssen GJ, Polderman AM, Habbema JDF (1992b). A model for variations in single and repeated egg counts in *Schistosoma mansoni* infections. *Parasitol,* 104(3), 451-460.

de Vlas SJ, van Oortmarssen GJ, Gryseels B (1992c). Validation of a model for variations in *Schistosoma mansoni* egg counts. *T Roy Soc Trop Med Hyg,* 86(6), 645-645.

de Vlas SJ, Engels D, Rabello AL, Oostburg BF, Van Lieshout L, Polderman AM, Van Oortmarssen GJ, Habbema JD, Gryseels B (1997). Validation of a chart to estimate true *Schistosoma mansoni* prevalences from simple egg counts. *Parasitol,* 114 (Pt 2), 113-121.

Deelder AM, Kornelis D, Van Marck EAE, Eveleigh PC, Van Egmond JG (1980). *Schistosoma mansoni*: characterization of two circulating polysaccharide antigens and the immunological response to these antigens in mouse, hamster, and human infections. *Exp Parasitol,* 50(1), 16-32.

Degremont A, Burnier E, Meudt R, Burki A, Schweizer W, Tanner M (1985). Value of ultrasonography in investigating morbidity due to *Schistosoma haematobium* infection. *Lancet,* 325(8430), 662-665.

Delgado-Rodríguez M, Llorca J (2004). Bias. *J Epidemiol Commun Health,* 58(8), 635-641.

Deol AK, Fleming FM, Calvo-Urbano B, Walker M, Bucumi V, Gnandou I, Tukahebwa EM, Jemu S, Mwingira UJ, Alkohlani A, Traoré M, Ruberanziza E, Touré S, Basáñez M-G, French MD, Webster JP (2019). Schistosomiasis — assessing progress toward the 2020 and 2025 global goals. *N Engl J Med,* 381(26), 2519-2528.

Depaquit J, Akhoundi M, Haouchine D, Mantelet S, Izri A (2019). No limit in interspecific hybridization in schistosomes: observation from a case report. *Parasite,* 26, 10.

Des Ligneris MJA (1921). A case of schistosomiasis of the female pelvic genitalia with subsequent tubal pregnancy and abortion. *Med J S Afr,* 17(3), 46-48.

Dew HR (1923). Observations on the pathology of schistosomiasis (S. hæmatobium and S. mansoni) in the human subject. *J Pathol Bacteriol,* 26(1), 27-39.

Dewhurst KE (1949). The tribal distribution of bilharzia in east Africa. *J Trop Med Hyg,* 52(3), 60-61.

Di Bella S, Riccardi N, Giacobbe DR, Luzzati R (2018). History of schistosomiasis (bilharziasis) in humans: from Egyptian medical papyri to molecular biology on mummies. *Pathog Glob Health,* 112(5), 268-273.

Diehl JC, Oyibo P, Agbana T, Jujjavarapu S, Van GY, Vdovin G, Oyibo W (2020, 2020). *Schistoscope: smartphone versus Raspberry Pi based low-cost diagnostic device for urinary schistosomiasis.* Paper presented at the 2020 IEEE Global Humanitarian Technology Conference (GHTC).

Diggle PJ (2011). Estimating prevalence using an imperfect test. *Epidemiol Res Int,* 2011, 608719.

Dittrich M, Thomas AK, Stelma FF, Talla I, Niang M, Decam C, Sow S, Mbaye A, Gryseels B, Ehrich JHH, Doehring E (1994). Preliminary ultrasonographical observations of intestinal lesions in a community with heavy *Schistosoma mansoni* infection in Richard Toll, Senegal. *Acta Trop,* 58(3), 331-336.

Dixon H (1987). *Statistical Methods Applicable to Schistosomiasis Control Programmes*. (WHO/SCHISTO/85.81 Rev.1 (1987)). Geneva: World Health Organization.

Dodge WF, West EF, Smith EH, Bunce H (1976). Proteinuria and hematuria in schoolchildren: epidemiology and early natural history. *J Pediatr,* 88(2), 327-347.

Doehring-Schwerdtfeger E, Abdel-Rahim IM, Kardorff R, Kaiser C, Franke D, Schlake J, Richter J, Elsheikh M, Mohamed-Ali Q, Ehrich JHH (1992a). Ultrasonographical investigation of periportal fibrosis in children with *Schistosoma mansoni* infection: reversibility of morbidity twenty-three months after treatment with praziquantel. *Am J Trop Med Hyg,* 46(4), 409-415.

Doehring-Schwerdtfeger E, Kaiser C, Franke D, Kardorff R, Ali QM, Abdel-Rahim IM (1992b). Inter-observer variance in ultrasonographical assessment of *Schistosoma mansoni*-related morbidity in young schoolchildren. *Acta Trop,* 51(1), 85-88.

Doehring E, Ehrich JHH, Bremer HJ (1986). Reversibility of urinary tract abnormalities due to *Schistosoma haematobium* infection. *Kidney Int,* 30(4), 582-585.

Doenhoff MJ, Cioli D, Utzinger J (2008). Praziquantel: mechanisms of action, resistance and new derivatives for schistosomiasis. *Curr Opin Infect Dis,* 21(6), 659-667.

Dunn MA, Kamel R (1981). Hepatic schistosomiasis. *Hepatol,* 1(6), 653-661.

Dunne DW, Pearce EJ (1999). Immunology of hepatosplenic schistosomiasis mansoni: a human perspective. *Microbes Infect,* 1(7), 553-560.

Durbin J (1954). Errors in variables. *Rev Inst Int Stat,* 22(1/3), 23-32.

Duval D, Galinier R, Mouahid G, Toulza E, Allienne JF, Portela J, Calvayrac C, Rognon A, Arancibia N, Mitta G, Théron A, Gourbal B (2015). A novel bacterial pathogen of *Biomphalaria glabrata*: a potential weapon for schistosomiasis control? *PLoS Negl Trop Dis,* 9(2), e0003489.

Edington GM, Von Lichtenberg F, Nwabuebo I, Taylor JR, Smith JH (1970). Pathologic effects of schistosomiasis in Ibadan, Western State of Nigeria. I. Incidence and intensity of infection; distribution and severity of lesions. *Am J Trop Med Hyg,* 19(6), 982-995.

El-Alamy MA, Habib MA, McNeeley DF, Cline BL (1981). Preliminary results of chemotherapy using praziquantel on a large scale in Qalyub Bilharziasis Project where simultaneous infection with S. mansoni and S. haematobium exists. *Arzneimittel-Forsch,* 31(3a), 612-615.

El-Rooby A (1985). Management of hepatic schistosomiasis. *Semin Liver Dis,* 5(03), 263-276.

el Scheich T, Holtfreter MC, Ekamp H, Singh DD, Mota R, Hatz C, Richter J (2014). The WHO ultrasonography protocol for assessing hepatic morbidity due to *Schistosoma mansoni*. Acceptance and evolution over 12 years. *Parasitol Res,* 113(11), 3915-3925.

Elem B (1984). Urinary calculus in Zambia: its incidence and relationship to *Schistosoma haematobium* infection and vesicovaginal fistula. *Brit J Urol,* 56(1), 44-47.

Engels D, Sinzinkayo E, Gryseels B (1996). Day-to-day egg count fluctuation in *Schistosoma mansoni* infection and its operational implications. *Am J Trop Med Hyg,* 54(4), 319-324.

Ezeamama AE, McGarvey ST, Acosta LP, Zierler S, Manalo DL, Wu H-W, Kurtis JD, Mor V, Olveda RM, Friedman JF (2008). The synergistic effect of concomitant schistosomiasis, hookworm, and *Trichuris* Infections on children's anemia burden. *PLoS Negl Trop Dis,* 2(6), e245.

Ezeamama AE, He C-L, Shen Y, Yin X-P, Binder SC, Campbell CH, Rathbun S, Whalen CC, N'Goran EK, Utzinger J, Olsen A, Magnussen P, Kinung'hi S, Fenwick A, Phillips A, Ferro J, Karanja DMS, Mwinzi PNM, Montgomery S, Secor WE, Hamidou A, Garba A, King CH, Colley DG (2016). Gaining and sustaining schistosomiasis control: study protocol and baseline data prior to different treatment strategies in five African countries. *BMC Infect Dis,* 16(1), 229.

Ezeamama AE, Bustinduy AL, Nkwata AK, Martinez L, Pabalan N, Boivin MJ, King CH (2018). Cognitive deficits and educational loss in children with schistosome infection—a systematic review and meta-analysis. *PLoS Negl Trop Dis,* 12(1), e0005524.

Fairley NH (1919). Bilharziasis: some recent advances in our knowledge. *Lancet,* 193(4998), 1016-1020.

Fairley NH (1920). A comparative study of experimental bilharziasis in monkeys contrasted with the hitherto described lesions in man. *J Pathol Bacteriol,* 23(3), 289-314.

Farid Z, Bassily S, Schulert AR, Zeind AS, McConnell E, Abdel Wahab MF (1968). Urinary blood loss in *Schistosoma haematobium* infection in Egyptian farmers. *T Roy Soc Trop Med Hyg,* 62(4), 496-500.

Fataar S, Bassiony H, Satyanath S, Vassileva J, Hanna RM (1984). Characteristic sonographic features of schistosomal periportal fibrosis. *Am J Roentgenol,* 143(1), 69-71.

Fenwick A, Webster JP, Bosque-Oliva E, Blair L, Fleming FM, Zhang Y, Garba A, Stothard JR, Gabrielli AF, Clements AC, Kabatereine NB, Toure S, Dembele R, Nyandindi U, Mwansa J, Koukounari A (2009). The Schistosomiasis Control Initiative (SCI): rationale, development and implementation from 2002-2008. *Parasitol,* 136(13), 1719-1730.

Fenwick A, Savioli L (2011). Schistosomiasis elimination. *Lancet Infect Dis,* 11(5), 346.

Fenwick A, Jourdan P (2016). Schistosomiasis elimination by 2020 or 2030? *Int J Parasitol,* 46(7), 385-388.

Ferguson AR (1913). The lesions of bilharzial disease. *Glasgow Med J,* 79(1), 14-23.

Ferrari TCA, Moreira PRR (2011). Neuroschistosomiasis: clinical symptoms and pathogenesis. *Lancet Neurol,* 10(9), 853-864.

Fisher AC (1934). A study of the schistosomiasis of the Stanleyville district of the Belgian congo. *T Roy Soc Trop Med Hyg,* 28(3), 277-306.

Foo KT, Blackstock AJ, Ochola EA, Matete DO, Mwinzi PNM, Montgomery SP, Karanja DMS, Secor WE (2015). Evaluation of point-of-contact circulating cathodic antigen assays for the detection of *Schistosoma mansoni* infection in low-, moderate-, and high-prevalence schools in western Kenya. *Am J Trop Med Hyg,* 92(6), 1227-1232.

Fornace KM, Fronterrè C, Fleming FM, Simpson H, Zoure H, Rebollo M, Mwinzi P, Vounatsou P, Pullan RL (2020). Evaluating survey designs for targeting preventive chemotherapy against *Schistosoma haematobium* and *Schistosoma mansoni* across sub-Saharan Africa: a geostatistical analysis and modelling study. *Parasit Vector,* 13(1), 555.

Forsyth DM, Bradley DJ (1964). Irreversible damage by *Schistosoma hæmatobium* in schoolchildren. *Lancet,* 284(7352), 169-171.

Forsyth DM, MacDonald G (1965). Urological complications of endemic schistosomiasis in school-children: part 1. Usagara School. *T Roy Soc Trop Med Hyg,* 59(2), 171-178.

Forsyth DM, MacDonald G (1966). Urological complications of endemic schistosomiasis in schoolchildren Part 2. Donge school, Zanzibar. *T Roy Soc Trop Med Hyg,* 60(5), 568-578.

Foster R, Teesdale C, Poulton GF (1960). Trials with a new molluscicide. *Bull World Health Organ,* 22(5), 543-548.

Freer JB, Bourke CD, Durhuus GH, Kjetland EF, Prendergast AJ (2018). Schistosomiasis in the first 1000 days. *Lancet Infect Dis,* 18(6), e193-e203.

French MD, Rollinson D, Basáñez M-G, Mgeni AF, Khamis IS, Stothard JR (2007). School-based control of urinary schistosomiasis on Zanzibar, Tanzania: monitoring micro-haematuria with reagent strips as a rapid urological assessment. *J Pediatr Urol,* 3(5), 364-368.

French MD, Evans D, Fleming FM, Secor WE, Biritwum NK, Brooker SJ, Bustinduy A, Gouvras A, Kabatereine N, King CH, Rebollo Polo M, Reinhard-Rupp J, Rollinson D, Tchuem Tchuente LA, Utzinger J, Waltz J, Zhang Y (2018). Schistosomiasis in Africa: improving strategies for long-term and sustainable morbidity control. *PLoS Negl Trop Dis,* 12(6), e0006484.

Fu C-L, Odegaard JI, Herbert DBR, Hsieh MH (2012). A novel mouse model of *Schistosoma haematobium* egg-induced immunopathology. *PLoS Path,* 8(3), e1002605.

Fujinami A (1904). Further discussion of the Katayama Disease and its causative parasite. *Kyoto Med J,* 1, 201-213.

Fujinami A (1909). On "Katayama-ki" written by Dr. Fuji-nami 60 years ago. *Chugai Iji Shinpo,* 691, 55-56.

Fujinami A, Nakamura H (1909). The route of infection, the development of the parasite of Katayama Disease and its infection in animals. *Kyoto Med J,* 6(4), 224-252.

Fulford AJC, Butterworth AE, Ouma JH, Sturrock RF (1995). A statistical approach to schistosome population dynamics and estimation of the life-span of *Schistosoma mansoni* in man. *Parasitol,* 110(3), 307-316.

Galappaththi-Arachchige HN, Holmen S, Koukounari A, Kleppa E, Pillay P, Sebitloane M, Ndhlovu P, van Lieshout L, Vennervald BJ, Gundersen SG, Taylor M, Kjetland EF (2018). Evaluating diagnostic indicators of urogenital *Schistosoma haematobium* infection in young women: a cross sectional study in rural South Africa. *PLoS ONE,* 13(2), e0191459.

Garba A, Toure S, Dembele R, Boisier P, Tohon Z, Bosque-Oliva E, Koukounari A, Fenwick A (2009). Present and future schistosomiasis control activities with support from the Schistosomiasis Control Initiative in West Africa. *Parasitol,* 136(13), 1731-1737.

Gashaw F, Erko B, Teklehaymanot T, Habtesellasie R (2008). Assessment of the potential of competitor snails and African catfish (*Clarias gariepinus*) as biocontrol agents against snail hosts transmitting schistosomiasis. *T Roy Soc Trop Med Hyg,* 102(8), 774-779.

Gaspard J, Usey MM, Fredericks-James M, Sanchez-Martin MJ, Atkins L, Campbell CH, Corstjens PLAM, van Dam GJ, Colley DG, Secor WE (2020). Survey of schistosomiasis in Saint Lucia: evidence for interruption of transmission. *Am J Trop Med Hyg,* 102(4), 827-831.

GBD 2017 Collaborators (2017). Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2013;2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet,* 390(10100), 1211-1259.

GBD 2017 Disease and Injury Incidence and Prevalence Collaborators (2018). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet,* 392(10159), 1789-1858.

Gelfand M, Davis GB (1940). Bilharzial lesions of the testis. *S Afr Med J,* 14(17), 334-335.

Gelfand M, Ross WF (1953). II. The distribution of schistosome ova in the genito-urinary tract in subjects of bilharziasis. *T Roy Soc Trop Med Hyg,* 47(3), 218-220.

Gelman A (2006). Prior distributions for variance parameters in hierarchical models. *Bayesian Anal,* 1(3), 515-533.

Gelman A, Stern H (2006). The difference between “significant” and “not significant” is not itself statistically significant. *Am Stat,* 60(4), 328-331.

Gelman A, Jakulin A, Pittau MG, Su Y-S (2008). A weakly informative default prior distribution for logistic and other regression models. *Ann Appl Stat,* 2(4), 1360-1383.

Giboda M, Bergquist NR (1999). Post-transmission schistosomiasis. *Parasitol Today,* 15(8), 307-308.

Gibson RWB (1925). Bilharziasis of the female genital tract. *Med J S Afr,* 21(2), 44-45.

Gilbert B (1943). Schistosomiasis (bilharziasis) of the female genital tract and neighbouring tissues. *J Obstet Gynaecol Brit Em,* 50(5), 317-336.

Global Burden of Disease Collaborative Network (2020). Global Burden of Disease Study 2019 (GBD 2019) Results Retrieved December 22, 2020, 2020, from http://ghdx.healthdata.org/gbd-results-tool

Goldberg EM, Pigott D, Shirude S, Stanaway J, Hay SI, Vos T (2018). Underestimation of the global burden of schistosomiasis–Authors' reply. *Lancet,* 391(10118), 308.

Gonçalves EC, Fonseca AP, Pittella JE (1995). Frequency of schistosomiasis mansoni, of its clinicopathological forms and of the ectopic locations of the parasite in autopsies in Belo Horizonte, Brazil. *J Trop Med Hyg,* 98(5), 289-295.

Gönnert R, Andrews P (1977). Praziquantel, a new broad-spectrum antischistosomal agent. *Z Parasitenkd,* 52(2), 129-150.

Gouda I, Mokhtar N, El-Bolkainy T, El-Bolkainy MN, Bilal MD (2007). Bilharziasis and bladder cancer: a time trend analysis of 9843 patients. *J Egypt Nat Cancer Inst,* 19(2), 158-162.

Gray DJ, McManus DP, Li Y, Williams GM, Bergquist R, Ross AG (2010). Schistosomiasis elimination: lessons from the past guide the future. *Lancet Infect Dis,* 10(10), 733-736.

Griesinger W (1854). Klinische und anatomische Beobachtungen über die Krankheiten von Egypten. In Gresinger W, Roser W, Wunderlich CA (Eds.), *Archiv für Physiologische Heilkunde* (Vol. 13, pp. 528-575). Stuttgart: Ebner & Seubert.

Grimes JET, Croll D, Harrison WE, Utzinger J, Freeman MC, Templeton MR (2014). The relationship between water, sanitation and schistosomiasis: a systematic review and meta-analysis. *PLoS Negl Trop Dis,* 8(12), e3296.

Grimes JET, Croll D, Harrison WE, Utzinger J, Freeman MC, Templeton MR (2015). The roles of water, sanitation and hygiene in reducing schistosomiasis: a review. *Parasit Vector,* 8(1), 156.

Gryseels B, Polderman AM (1987). The morbidity of schistosomiasis mansoni in Maniema (Zaire). *T Roy Soc Trop Med Hyg,* 81(2), 202-209.

Gryseels B, de Vlas SJ (1996). Worm burdens in schistosome infections. *Parasitol Today,* 12(3), 115-119.

Gryseels B, Mbaye A, de Vlas SJ, Stelma FF, Guissé F, Van Lieshout L, Faye D, Diop M, Ly A, Tchuem-Tchuenté LA, Engels D, Polman K (2001). Are poor responses to praziquantel for the treatment of *Schistosoma mansoni* infections in Senegal due to resistance? An overview of the evidence. *Trop Med Int Health,* 6(11), 864-873.

Hairston NG (1965). An analysis of age-prevalence data by catalytic models. A contribution to the study of bilharziasis. *Bull World Health Organ,* 33(2), 163-175.

Hall SC, Kehoe EL (1970). Prolonged survival of *Schistosoma japonicum*. *Calif Med,* 113(2), 75-77.

Handzel T, Karanja DMS, Addiss DG, Hightower AW, Rosen DH, Colley DG, Andove J, Slutsker L, Secor WE (2003). Geographic distribution of schistosomiasis and soil-transmitted helminths in western Kenya: implications for antihelminthic mass treatment. *Am J Trop Med Hyg,* 69(3), 318-323.

Harnett W (1988). The anthelmintic action of praziquantel. *Parasitol Today,* 4(5), 144-146.

Harris ARC, Russell RJ, Charters AD (1984). A review of schistosomiasis in immigrants in Western Australia, demonstrating the unusual longevity of *Schistosoma mansoni*. *T Roy Soc Trop Med Hyg,* 78(3), 385-388.

Hatz C, Mayombana C, de Savigny D, MacPherson CNL, Koella JC, Degrémont A, Tanner M (1990). Ultrasound scanning for detecting morbidity due to *Schistosoma haematobium* and its

resolution following treatment with different doses of praziquantel. *T Roy Soc Trop Med Hyg,* 84(1), 84-88.

Hatz CF, Vennervald BJ, Nkulila T, Vounatsou P, Kombe Y, Mayombana C, Mshinda H, Tanner M (1998). Evolution of *Schistosoma haematobium*-related pathology over 24 months after treatment with praziquantel among school children in southeastern Tanzania. *Am J Trop Med Hyg,* 59(5), 775-781.

Hewitt R, Willingham AL (2019). Status of schistosomiasis elimination in the Caribbean region. *Trop Med Infect Dis,* 4(1), 24.

Hiatt RA, Cline BL, Ruiz-Tiben E, Knight WB, Berrios-Duran LA (1980). The Boqueron Project after 5 years: a prospective community-based study of infection with *Schistosoma mansoni* in Puerto Rico. *Am J Trop Med Hyg,* 29(6), 1228-1240.

Hoekstra PT, Casacuberta-Partal M, van Lieshout L, Corstjens PLAM, Tsonaka R, Assaré RK, Silué KD, Meité A, N'Goran EK, N'Gbesso YK, Amoah AS, Roestenberg M, Knopp S, Utzinger J, Coulibaly JT, van Dam GJ (2020). Efficacy of single versus four repeated doses of praziquantel against *Schistosoma mansoni* infection in school-aged children from Côte d'Ivoire based on Kato-Katz and POC-CCA: an open-label, randomised controlled trial (RePST). *PLoS Negl Trop Dis,* 14(3), e0008189.

Hofstraat K, van Brakel WH (2016). Social stigma towards neglected tropical diseases: a systematic review. *Int Health,* 8(suppl_1), i53-i70.

Holford TR, Hardy RJ (1976). A stochastic model for the analysis of age-specific prevalence curves in schistosomiasis. *J Chron Dis,* 29(7), 445-458.

Holmström O, Linder N, Ngasala B, Mårtensson A, Linder E, Lundin M, Moilanen H, Suutala A, Diwan V, Lundin J (2017). Point-of-care mobile digital microscopy and deep learning for the detection of soil-transmitted helminths and *Schistosoma haematobium*. *Glob Health Action,* 10(sup3), 1337325.

Homeida M, Abdel-Gadir AF, Cheever AW, Bennett JL, Arbab BMO, Ibrahium SZ, Abdel-Salam IM, Dafalla AA, Nash TE (1988a). Diagnosis of pathologically confirmed Symmers' periportal fibrosis by ultrasonography: a prospective blinded study. *Am J Trop Med Hyg,* 38(1), 86-91.

Homeida M, Ahmed S, Dafalla A, Suliman S, Eltom I, Nash T, Bennett JL (1988b). Morbidity associated with *Schistosoma mansoni* infection as determined by ultrasound: a study in Gezira, Sudan. *Am J Trop Med Hyg,* 39(2), 196-201.

Horák P, Mikeš L, Lichtenbergová L, Skála V, Soldánová M, Brant SV (2015). Avian schistosomes and outbreaks of cercarial dermatitis. *Clin Microbiol Rev,* 28(1), 165-190.

Hornstein L, Lederer G, Schechter J, Greenberg Z, Boem R, Bilguray B, Giladi L, Hamburger J (1990). Persistent *Schistosoma mansoni* infection in Yemeni immigrants to Israel. *Israel J Med Sci,* 26(7), 386-389.

Hotez P (2011). Enlarging the "Audacious Goal": elimination of the world's high prevalence neglected tropical diseases. *Vaccine,* 29, D104-D110.

Hotez PJ, Fenwick A (2009a). Schistosomiasis in Africa: an emerging tragedy in our new global health decade. *PLoS Negl Trop Dis,* 3(9), e485.

Hotez PJ, Kamath A (2009b). Neglected tropical diseases in sub-Saharan Africa: review of their prevalence, distribution, and disease burden. *PLoS Negl Trop Dis,* 3(8), e412.

Hotez PJ, Engels D, Fenwick A, Savioli L (2010). Africa is desperate for praziquantel. *Lancet,* 376(9740), 496-498.

Hotez PJ, Alvarado M, Basáñez M-G, Bolliger I, Bourne R, Boussinesq M, Brooker SJ, Brown AS, Buckle G, Budke CM, Carabin H, Coffeng LE, Fèvre EM, Fürst T, Halasa YA, Jasrasaria R, Johns NE, Keiser J, King CH, Lozano R, Murdoch ME, O'Hanlon S, Pion SDS, Pullan RL, Ramaiah KD, Roberts T, Shepard DS, Smith JL, Stolk WA, Undurraga EA, Utzinger J, Wang M, Murray CJL, Naghavi M

(2014). The Global Burden of Disease Study 2010: interpretation and implications for the neglected tropical diseases. *PLoS Negl Trop Dis,* 8(7), e2865.

Hotez PJ, Fenwick A, Ray SE, Hay SI, Molyneux DH (2018). "Rapid impact" 10 years after: the first "decade" (2006–2016) of integrated neglected tropical disease control. *PLoS Negl Trop Dis,* 12(5), e0006137.

Hubley JH (1986). Barriers to health education in developing countries. *Heath Educ Res,* 1(4), 233-245.

Hulse EV (1971). Joshua's curse and the abandonment of ancient Jericho: schistosomiasis as a possible medical explanation. *Med Hist,* 15(4), 376-386.

Hussain S, Hawass ND, Zaidi AJ (1984). Ultrasonographic diagnosis of schistosomal periportal fibrosis. *J Ultrasound Med,* 3(10), 449-452.

Hutchison HS (1928). The pathology of bilharziasis. *Am J Pathol,* 4(1), 1-16.11.

Ibrahim AB (1923). Bilharziasis of the ureter. *Lancet,* 202(5231), 1184-1186.

Inobaya MT, Chau TN, Ng S-K, MacDougall C, Olveda RM, Tallo VL, Landicho JM, Malacad CM, Aligato MF, Guevarra JB, Ross AG (2018). Mass drug administration and the sustainable control of schistosomiasis: an evaluation of treatment compliance in the rural Philippines. *Parasit Vector,* 11(1), 441.

Ishida K, Hsieh MH (2018). Understanding urogenital schistosomiasis-related bladder cancer: an update. *Front Med,* 5, 223.

Ishii A, Tsuji M, Tada I (2003). History of Katayama disease: schistosomiasis japonica in Katayama district, Hiroshima, Japan. *Parasitol Int,* 52(4), 313-319.

Ishizaki T, Kamo E, Boehme K (1979). Double-blind studies of tolerance to praziquantel in Japanese patients with *Schistosoma japonicum* infections. *Bull World Health Organ,* 57(5), 787-791.

Ivy JA, King CH, Cook JA, Colley DG (2018). Historical perspective: revisiting the St. Lucia Project, a multi-year comparison trial of schistosomiasis control strategies. *PLoS Negl Trop Dis,* 12(1), e0006223.

Jamison DT, Breman JG, Measham AR, Alleyne G, Claeson M, Evans DB, Jha P, Mills A, Musgrove P (Eds.). (2006). *Disease Control Priorities in Developing Countries* (2 ed.). New York: Oxford University Press.

Jauréguiberry S, Paris L, Caumes E (2010). Acute schistosomiasis, a diagnostic and therapeutic challenge. *Clin Microbiol Infec,* 16(3), 225-231.

Jia-Gang G, Vounatsou P, Chun-Li C, Utzinger J, Hong-Qing Z, Anderegg D, Rong Z, Zhan-Ying H, Dong L, Fei H, Ming-Gang C, Tanner M (2005). A geographic information and remote sensing based model for prediction of *Oncomelania hupensis* habitats in the Poyang Lake area, China. *Acta Trop,* 96(2), 213-222.

Joseph L, Gyorkos TW, Coupal L (1995). Bayesian estimation of disease prevalence and the parameters of diagnostic tests in the absence of a gold standard. *Am J Epidemiol,* 141(3), 263-272.

Joyce PR, Blackwell JB, Charters AD (1972). Schistosomiasis in gynaecology - two cases in immigrants in Western Australia. *Aust NZ J Obstet Gynaecol,* 12(2), 137-141.

Kabatereine N, Fleming F, Thuo W, Tinkitina B, Tukahebwa EM, Fenwick A (2014). Community perceptions, attitude, practices and treatment seeking behaviour for schistosomiasis in L. Victoria islands in Uganda. *BMC Res Notes,* 7(1), 900.

Kabatereine NB, Fleming FM, Nyandindi U, Mwanza JCL, Blair L (2006). The control of schistosomiasis and soil-transmitted helminths in East Africa. *Trends Parasitol,* 22(7), 332-339.

Kabatereine NB, Brooker S, Koukounari A, Kazibwe F, Tukahebwa EM, Fleming FM, Zhang Y, Webster JP, Stothard JR, Fenwick A (2007). Impact of a national helminth control programme on infection and morbidity in Ugandan schoolchildren. *Bull World Health Organ,* 85(2), 91-99.

Kalinda C, Mindu T, Chimbari MJ (2021). A systematic review and meta-analysis quantifying schistosomiasis infection burden in pre-school aged children (PreSAC) in sub-Saharan Africa for the period 2000–2020. *PLoS ONE,* 15(12), e0244695.

Kamel IA, Elwi AM, Cheever AW, Mosimann JE, Danner R (1978). *Schistosoma mansoni* and *S. haematobium* infections in Egypt. IV. Hepatic lesions. *Am J Trop Med Hyg,* 27(5), 931-938.

Kane CA, Most H (1948). Schistosomiasis of the central nervous system: experiences in World War II and a review of the literature. *Arch Neurol Psychiatr,* 59(2), 141-183.

Kane RA, Southgate VR, Rollinson D, Littlewood DTJ, Lockyer AE, Pagès JR, Tchuem Tchuenté LA, Jourdane J (2003). A phylogeny based on three mitochondrial genes supports the division of *Schistosoma intercalatum* into two separate species. *Parasitol,* 127(2), 131-137.

Kapito-Tembo AP, Mwapasa V, Meshnick SR, Samanyika Y, Banda D, Bowie C, Radke S (2009). Prevalence distribution and risk factors for *Schistosoma hematobium* infection among school children in Blantyre, Malawi. *PLoS Negl Trop Dis,* 3(1), e361.

Karanja DMS, Hightower AW, Colley DG, Mwinzi PNM, Galil K, Andove J, Secor WE (2002). Resistance to reinfection with *Schistosoma mansoni* in occupationally exposed adults and effect of HIV-1 co-infection on susceptibility to schistosomiasis: a longitudinal study. *Lancet,* 360(9333), 592-596.

Kardaman MW, Amin MA, Fenwick A, Cheesmond AK, Dixon HG (1983). A field trial using praziquantel (Biltricide) to treat *Schistosoma mansoni* and *Schistosoma haematobium* infection in Gezira, Sudan. *Ann Trop Med Parasit,* 77(3), 297-304.

Kardorff R, Traoré M, Doehring-Schwerdtferger E, Vester U, Ehrich JHH (1994). Ultrasonography of ureteric abnormalities induced by *Schistosoma haematobium* infection before and after praziquantel treatment. *Brit J Urol,* 74(6), 703-709.

Kardorff R, Gabone RM, Mugashe C, Obiga D, Ramarokoto CE, Mahlert C, Spannbrucker N, Lang A, Günzler V, Gryseels B, Ehrich JHH, Doehring E (1997). *Schistosoma mansoni*-related morbidity on Ukerewe Island, Tanzania: clinical, ultrasonographical and biochemical parameters. *Trop Med Int Health,* 2(3), 230-239.

Kariuki HC, Mbugua G, Magak P, Bailey JA, Muchiri EM, Thiongo FW, King CH, Butterworth AE, Ouma JH, Blanton RE (2001). Prevalence and familial aggregation of schistosomal liver morbidity in Kenya: evaluation by new ultrasound criteria. *J Infect Dis,* 183(6), 960-966.

Kato K, Miura M (1954). Comparative examinations. *Jpn J Parasitol,* 3(35), 382-391.

Katsurada F (1904a). Supplemental report on schistosomiasis japonica. *Tokyo Med J,* 1381, 1876-1882.

Katsurada F (1904b). On the endemic disease in Yamanashi Prefecture. *Okayama Med J,* 173, 217-260.

Katsurada F (1904c). *Schistosomum japonicum*, ein neuer menshlicher Parasit durch welchen eine endemisch Krankheit in verschiedenen Genenden Japans verusacht wird. *Annot Zool Japon,* 5, 147-160.

Katsurada F, Hasegawa T (1909). Research on the development of *Schistosoma japonicum*. *Okayama Med J,* 235, 433-443.

Katz N, Chaves A, Pellegrino J (1972). A simple device for quantitative stool thick-smear technique in schistosomiasis mansoni. *Rev Inst Med Trop SP,* 14(6), 397-400.

Katz N, Rocha RS, Chaves A (1979). Preliminary trials with praziquantel in human infections due to *Schistosoma mansoni*. *Bull World Health Organ,* 57(5), 781-785.

Katz N (2008). The discovery of schistosomiasis mansoni in Brazil. *Acta Trop,* 108(2), 69-71.

Kayuni S, Lampiao F, Makaula P, Juziwelo L, Lacourse EJ, Reinhard-Rupp J, Leutscher PDC, Stothard JR (2019). A systematic review with epidemiological update of male genital schistosomiasis (MGS): a call for integrated case management across the health system in sub-Saharan Africa. *Parasite Epidemiol Control,* 4, e00077.

Khalaf I, Shokeir A, Shalaby M (2012). Urologic complications of genitourinary schistosomiasis. *World J Urol,* 30(1), 31-38.

Khieu V, Sayasone S, Muth S, Kirinoki M, Laymanivong S, Ohmae H, Huy R, Chanthapaseuth T, Yajima A, Phetsouvanh R, Bergquist R, Odermatt P (2019). Elimination of schistosomiasis mekongi from

endemic areas in Cambodia and the Lao People's Democratic Republic: current status and plans. *Trop Med Infect Dis,* 4(1), 30.

King CH, Keating CE, Muruka JF, Ouma JH, Houser H, Siongok TKA, Mahmoud AAF (1988). Urinary tract morbidity in schistosomiasis haematobia: associations with age and intensity of infection in an endemic area of Coast Province, Kenya. *Am J Trop Med Hyg,* 39(4), 361-368.

King CH, Mahmoud AAF (1989). Drugs five years later: praziquantel. *Ann Intern Med,* 110(4), 290-296.

King CH, Muchiri EM, Ouma JH (1992). Age-targeted chemotherapy for control of urinary schistosomiasis in endemic populations. *Mem I Oswaldo Cruz,* 87, 203-210.

King CH (2001). Disease Due to *Schistosoma mekongi*, *S. intercalatum* and Other Schistosome Species. In Mahmoud AAF (Ed.), *Schistosomiasis* (Vol. 3, pp. 391-412). London: Imperial College.

King CH, Magak P, Salam EA, Ouma JH, Kariuki HC, Blanton RE (2003). Measuring morbidity in schistosomiasis mansoni: relationship between image pattern, portal vein diameter and portal branch thickness in large-scale surveys using new WHO coding guidelines for ultrasound in schistosomiasis. *Trop Med Int Health,* 8(2), 109-117.

King CH, Dickman K, Tisch DJ (2005). Reassessment of the cost of chronic helmintic infection: a meta-analysis of disability-related outcomes in endemic schistosomiasis. *Lancet,* 365(9470), 1561-1569.

King CH, Bertino A-M (2008a). Asymmetries of poverty: why global burden of disease valuations underestimate the burden of neglected tropical diseases. *PLoS Negl Trop Dis,* 2(3), e209.

King CH, Dangerfield-Cha M (2008b). The unacknowledged impact of chronic schistosomiasis. *Chron Ill,* 4(1), 65-79.

King CH (2009). Toward the elimination of schistosomiasis. *N Engl J Med,* 360(2), 106-109.

King CH (2010). Parasites and poverty: the case of schistosomiasis. *Acta Trop,* 113(2), 95-104.

King CH, Olbrych SK, Soon M, Singer ME, Carter J, Colley DG (2011). Utility of repeated praziquantel dosing in the treatment of schistosomiasis in high-risk communities in Africa: a systematic review. *PLoS Negl Trop Dis,* 5(9), e1321.

King CH, Bertsch D (2013). Meta-analysis of urine heme dipstick diagnosis of *Schistosoma haematobium* infection, including low-prevalence and previously-treated populations. *PLoS Negl Trop Dis,* 7(9), e2431.

King CH (2015). It's time to dispel the myth of "asymptomatic" schistosomiasis. *PLoS Negl Trop Dis,* 9(2), e0003504.

King CH, Bertsch D (2015a). Historical perspective: snail control to prevent schistosomiasis. *PLoS Negl Trop Dis,* 9(4), e0003657.

King CH, Sutherland LJ, Bertsch D (2015b). Systematic review and meta-analysis of the impact of chemical-based molluscicide for control of *Schistosoma mansoni* and *S. haematobium* transmission. *PLoS Negl Trop Dis,* 9(12), e0004290.

King CH, Galvani AP (2018). Underestimation of the global burden of schistosomiasis. *Lancet,* 391(10118), 307-308.

King CH, Bertsch D, Andrade GN, Burnim M, Ezeamama AE, Binder S, Colley DG (2020a). The Schistosomiasis Consortium for Operational Research and Evaluation Rapid Answers Project: systematic reviews and meta-analysis to provide policy recommendations based on available evidence. *Am J Trop Med Hyg,* 103(1_Suppl), 92-96.

King CH, Binder S, Shen Y, Whalen CC, Campbell CH, Wiegand RE, Olsen A, Secor WE, Montgomery SP, Musuva R, Mwinzi PNM, Magnussen P, Kinung'hi S, Andrade GN, Ezeamama AE, Colley DG (2020b). SCORE studies on the impact of drug treatment on morbidity due to *Schistosoma mansoni* and *Schistosoma haematobium* infection. *Am J Trop Med Hyg,* 103(1_Suppl), 30-35.

King CH, Kittur N, Binder S, Campbell CH, N'Goran EK, Meite A, Utzinger J, Olsen A, Magnussen P, Kinung'hi S, Fenwick A, Phillips AE, Gazzinelli-Guimaraes PH, Dhanani N, Ferro J, Karanja DMS,

Mwinzi PNM, Montgomery SP, Wiegand RE, Secor WE, Hamidou AA, Garba A, Colley DG (2020c). Impact of different mass drug administration strategies for gaining and sustaining control of *Schistosoma mansoni* and *Schistosoma haematobium* infection in Africa. *Am J Trop Med Hyg,* 103(1_Suppl), 14-23.

King CH, Kittur N, Wiegand RE, Shen Y, Ge Y, Whalen CC, Campbell CH, Hattendorf J, Binder S (2020d). Challenges in protocol development and interpretation of the Schistosomiasis Consortium for Operational Research and Evaluation intervention studies. *Am J Trop Med Hyg,* 103(1_Suppl), 36-41.

Kinung'hi S, Magnussen P, Kaatano G, Olsen A (2016). Infection with *Schistosoma mansoni* has an effect on quality of life, but not on physical fitness in schoolchildren in Mwanza Region, north-western Tanzania: a cross-sectional study. *PLoS Negl Trop Dis,* 10(12), e0005257.

Kitange HM, Swai AB, McLarty DG, Alberti KG (1993). Schistosomiasis prevalence after administration of praziquantel to school children in Melela village, Morogoro region, Tanzania. *East Afr Med J,* 70(12), 782-786.

Kittur N, Castleman JD, Campbell CH, King CH, Colley DG (2016). Comparison of *Schistosoma mansoni* prevalence and intensity of infection, as determined by the circulating cathodic antigen urine assay or by the Kato-Katz fecal assay: a systematic review. *Am J Trop Med Hyg,* 94(3), 605-610.

Kittur N, Binder S, Campbell CH, King CH, Kinung'hi S, Olsen A, Magnussen P, Colley DG (2017). Defining persistent hotspots: areas that fail to decrease meaningfully in prevalence after multiple years of mass drug administration with praziquantel for control of schistosomiasis. *Am J Trop Med Hyg,* 97(6), 1810-1817.

Kjetland EF, Ndhlovu PD, Mduluza T, Gomo E, Gwanzura L, Mason PR, Kurewa EN, Midzi N, Friis H, Gundersen SG (2005). Simple clinical manifestations of genital *Schistosoma haematobium* infection in rural Zimbabwean women. *Am J Trop Med Hyg,* 72(3), 311-319.

Kjetland EF, Ndhlovu PD, Kurewa EN, Midzi N, Gomo E, Mduluza T, Friis H, Gundersen SG (2008). Prevention of gynecologic contact bleeding and genital sandy patches by childhood anti-schistosomal treatment. *Am J Trop Med Hyg,* 79(1), 79-83.

Kjetland EF, Leutscher PDC, Ndhlovu PD (2012). A review of female genital schistosomiasis. *Trends Parasitol,* 28(2), 58-65.

Kjetland EF, Norseth HM, Taylor M, Lillebø K, Kleppa E, Holmen SD, Andebirhan A, Yohannes TH, Gundersen SG, Vennervald BJ, Bagratee J, Onsrud M, Leutscher PDC (2014). Classification of the lesions observed in female genital schistosomiasis. *Int J Gynecol Obstet,* 127(3), 227-228.

Kloetzel K (1962). Splenomegaly in schistosomiasis mansoni. *Am J Trop Med Hyg,* 11(4), 472-476.

Kloos H (1995). Human behavior, health education and schistosomiasis control: a review. *Soc Sci Med,* 40(11), 1497-1511.

Knopp S, Stothard JR, Rollinson D, Mohammed KA, Khamis IS, Marti H, Utzinger J (2013). From morbidity control to transmission control: time to change tactics against helminths on Unguja Island, Zanzibar. *Acta Trop,* 128(2), 412-422.

Knopp S, Corstjens PLAM, Koukounari A, Cercamondi CI, Ame SM, Ali SM, de Dood CJ, Mohammed KA, Utzinger J, Rollinson D, van Dam GJ (2015). Sensitivity and specificity of a urine circulating anodic antigen test for the diagnosis of *Schistosoma haematobium* in low endemic settings. *PLoS Negl Trop Dis,* 9(5), e0003752.

Knopp S, Person B, Ame SM, Ali SM, Muhsin J, Juma S, Khamis IS, Rabone M, Blair L, Fenwick A, Mohammed KA, Rollinson D (2016). Praziquantel coverage in schools and communities targeted for the elimination of urogenital schistosomiasis in Zanzibar: a cross-sectional survey. *Parasit Vector,* 9(1), 5.

Knopp S, Ame SM, Hattendorf J, Ali SM, Khamis IS, Bakar F, Khamis MA, Person B, Kabole F, Rollinson D (2018). Urogenital schistosomiasis elimination in Zanzibar: accuracy of urine filtration and

haematuria reagent strips for diagnosing light intensity *Schistosoma haematobium* infections. *Parasit Vector,* 11(1), 552.

Kokaliaris C, Garba A, Matuska M, Bronzan RN, Colley DG, Dorkenoo AM, Ekpo U F, Fleming FM, French MD, Kabore A, Mbonigaba JB, Midzi N, Mwinzi PNM, N'Goran EK, Polo MR, Sacko M, Tchuem Tchuenté LA, Tukahebwa EM, Uvon PA, Yang G, Wiesner L, Zhang Y, Utzinger J, Vounatsou P (2021). Effect of preventive chemotherapy on schistosomiasis among school-aged children in sub-Saharan Africa: a temporally explicit geostatistical analysis. *Lancet Infect Dis*.

Komiya Y, Kobayashi A (1966). Evaluation of Kato's thick smear technique with a cellophane cover for helminth eggs in feces. *Jpn J Med Sci Biol,* 19(1), 59-64.

Koonrungsesomboon N, Wadagni AC, Mbanefo EC (2015). Molecular markers and *Schistosoma*-associated bladder carcinoma: a systematic review and meta-analysis. *Cancer Epidemiol,* 39(4), 487-496.

Kosinski KC, Bosompem KM, Stadecker MJ, Wagner AD, Plummer J, Durant JL, Gute DM (2011). Diagnostic accuracy of urine filtration and dipstick tests for *Schistosoma haematobium* infection in a lightly infected population of Ghanaian schoolchildren. *Acta Trop,* 118(2), 123-127.

Koukounari A, Sacko M, Keita AD, Gabrielli AF, Landoure A, Dembele R, Clements AC, Whawell S, Donnelly CA, Fenwick A, Webster JP (2006). Assessment of ultrasound morbidity indicators of schistosomiasis in the context of large-scale programs illustrated with experiences from Malian children. *Am J Trop Med Hyg,* 75(6), 1042-1052.

Koukounari A, Gabrielli AF, Touré S, Bosqué-Oliva E, Zhang Y, Sellin B, Donnelly CA, Fenwick A, Webster JP (2007). *Schistosoma haematobium* infection and morbidity before and after large-scale administration of praziquantel in Burkina Faso. *J Infect Dis,* 196(5), 659-669.

Krauth SJ, Coulibaly JT, Knopp S, Traoré M, N'Goran EK, Utzinger J (2012). An in-depth analysis of a piece of shit: distribution of *Schistosoma mansoni* and hookworm eggs in human stool. *PLoS Negl Trop Dis,* 6(12), e1969.

Krauth SJ, Greter H, Stete K, Coulibaly JT, Traoré SI, Ngandolo BNR, Achi LY, Zinsstag J, N'Goran EK, Utzinger J (2015). All that is blood is not schistosomiasis: experiences with reagent strip testing for urogenital schistosomiasis with special consideration to very-low prevalence settings. *Parasit Vector,* 8(1), 584.

Kura K, Truscott JE, Toor J, Anderson RM (2019). Modelling the impact of a *Schistosoma mansoni* vaccine and mass drug administration to achieve morbidity control and transmission elimination. *PLoS Negl Trop Dis,* 13(6), e0007349.

Kura K, Hardwick RJ, Truscott JE, Toor J, Hollingsworth TD, Anderson RM (2020). The impact of mass drug administration on *Schistosoma haematobium* infection: what is required to achieve morbidity control and elimination? *Parasit Vector,* 13(1), 554.

Kvalsvig JD (1986). The effects of schistosomiasis haematobium on the activity of school children. *J Trop Med Hyg,* 89(2), 85-90.

LaBeaud AD, Nayakwadi Singer M, McKibben M, Mungai P, Muchiri EM, McKibben E, Gildengorin G, Sutherland LJ, King CH, King CL, Malhotra I (2015). Parasitism in children aged three years and under: relationship between Infection and growth in rural coastal Kenya. *PLoS Negl Trop Dis,* 9(5), e0003721.

Lai Y-S, Biedermann P, Ekpo UF, Garba A, Mathieu E, Midzi N, Mwinzi P, N'Goran EK, Raso G, Assaré RK, Sacko M, Schur N, Talla I, Tchuenté L-AT, Touré S, Winkler MS, Utzinger J, Vounatsou P (2015). Spatial distribution of schistosomiasis and treatment needs in sub-Saharan Africa: a systematic review and geostatistical analysis. *Lancet Infect Dis,* 15(8), 927-940.

Lamberton PHL, Kabatereine NB, Oguttu DW, Fenwick A, Webster JP (2014). Sensitivity and specificity of multiple Kato-Katz thick smears and a circulating cathodic antigen test for *Schistosoma mansoni* diagnosis pre- and post-repeated-praziquantel treatment. *PLoS Negl Trop Dis,* 8(9), e3139.

Lambertucci JR, Serufo JC, Gerspacher-Lara R, Rayes AAM, Teixeira R, Nobre V, Antunes CMF (2000). *Schistosoma mansoni*: assessment of morbidity before and after control. *Acta Trop,* 77(1), 101-109.

Lambertucci JR (2010). Acute schistosomiasis mansoni: revisited and reconsidered. *Mem I Oswaldo Cruz,* 105, 422-435.

Lambertucci JR, Drummond SC, Voieta I, de Queiróz LC, Pereira PPN, Chaves BA, Botelho PP, Prata PH, Otoni A, Vilela JF, Antunes CM (2013). An outbreak of acute *Schistosoma mansoni* schistosomiasis in a nonendemic area of Brazil: a report on 50 cases, including 5 with severe clinical manifestations. *Clin Infect Dis,* 57(1), e1-e6.

Lammie PJ, Fenwick A, Utzinger J (2006). A blueprint for success: integration of neglected tropical disease control programmes. *Trends Parasitol,* 22(7), 313-321.

Lammie PJ, Lindo JF, Secor WE, Vasquez J, Ault SK, Eberhard ML (2007). Eliminating lymphatic filariasis, onchocerciasis, and schistosomiasis from the Americas: breaking a historical legacy of slavery. *PLoS Negl Trop Dis,* 1(2), e71.

Lammie PJ, Moss DM, Brook Goodhew E, Hamlin K, Krolewiecki A, West SK, Priest JW (2012). Development of a new platform for neglected tropical disease surveillance. *Int J Parasitol,* 42(9), 797-800.

League of Nations Health Organization (1938). Consultation of experts on bilharziasis (schistosomiasis). Geneva.

Leenstra T, Coutinho HM, Acosta LP, Langdon GC, Su L, Olveda RM, McGarvey ST, Kurtis JD, Friedman JF (2006). *Schistosoma japonicum* reinfection after praziquantel treatment causes anemia associated with inflammation. *Infect Immun,* 74(11), 6398-6407.

Léger L, Lambert J, Goulet A, Rowan C, Dinelle Y (1984). Capacité aérobie des Québécois de 6 à 17 ans - Test navette de 20 mètres avec paliers de 1 minute. *Can J Sport Sci,* 9, 64-69.

Léger LA, Lambert J (1982). A maximal multistage 20-m shuttle run test to predict VO_2 max. *Eur J Appl Physiol O,* 49(1), 1-12.

Léger LA, Mercier D, Gadoury C, Lambert J (1988). The multistage 20 metre shuttle run test for aerobic fitness. *J Sport Sci,* 6(2), 93-101.

Lehman JS, Farid Z, Bassily S, Haxton J, Wahab MFA, Kent DC (1970). Intestinal protein loss in schistosomal polyposis of the colon. *Gastroenterol,* 59(3), 433-436.

Lehman JS, Mott KE, Morrow RH, Muniz TM, Boyer MH (1976). The intensity and effects of infection with *Schistosoma mansoni* in a rural community in northeast Brazil. *Am J Trop Med Hyg,* 25(2), 285-294.

Lehman JS, Jr., Farid Z, Smith JH, Bassily S, El-Masry NA (1973). Urinary schistosomiasis in Egypt: clinical, radiological, bacteriological and parasitological correlations. *T Roy Soc Trop Med Hyg,* 67(3), 384-399.

Leiper RT (1915a). Report on the results of the Bilharzia Mission in Egypt, 1915. Part II: prevention and eradication. *J Roy Army Med Corps,* 25(2), 147-192.

Leiper RT (1915b). Report on the results of the Bilharzia Mission in Egypt, 1915. Part III: development. *J Roy Army Med Corps,* 25(3), 253-267.

Leiper RT (1915c). Report on the results of the Bilharzia Mission in Egypt, 1915. Part I: transmission. *J Roy Army Med Corps,* 25(1), 1-55.

Leiper RT, Thomson JG (1916). Report on the results of the Bilharzia Mission in Egypt, 1915. Part IV: Egyptian mollusca. *J Roy Army Med Corps,* 27(2), 171-190.

Leiper RT (1918). Report on the results of the Bilharzia Mission in Egypt, 1915. Part V: adults and ova. *J Roy Army Med Corps,* 30(3), 235-260.

Lengeler C, Utzinger J, Tanner M (2002a). Screening for schistosomiasis with questionnaires. *Trends Parasitol,* 18(9), 375-377.

Lengeler C, Utzinger J, Tanner M (2002b). Questionnaires for rapid screening of schistosomiasis in sub-Saharan Africa. *Bull World Health Organ,* 80(3), 235-242.

Leutscher PDC, Ramarokoto C-E, Hoffmann S, Jensen JS, Ramaniraka V, Randrianasolo B, Raharisolo C, Migliani R, Christensen N (2008). Coexistence of urogenital schistosomiasis and sexually transmitted infection in women and men living in an area where *Schistosoma haematobium* is endemic. *Clin Infect Dis,* 47(6), 775-782.

Li EY, Gurarie D, Lo NC, Zhu X, King CH (2019). Improving public health control of schistosomiasis with a modified WHO strategy: a model-based comparison study. *Lancet Glob Health,* 7(10), e1414-e1422.

Lo NC, Bogoch II, Blackburn BG, Raso G, N'Goran EK, Coulibaly JT, Becker SL, Abrams HB, Utzinger J, Andrews JR (2015). Comparison of community-wide, integrated mass drug administration strategies for schistosomiasis and soil-transmitted helminthiasis: a cost-effectiveness modelling study. *Lancet Glob Health,* 3(10), e629-e638.

Lo NC, Addiss DG, Hotez PJ, King CH, Stothard JR, Evans DS, Colley DG, Lin W, Coulibaly JT, Bustinduy AL, Raso G, Bendavid E, Bogoch II, Fenwick A, Savioli L, Molyneux D, Utzinger J, Andrews JR (2017). A call to strengthen the global strategy against schistosomiasis and soil-transmitted helminthiasis: the time is now. *Lancet Infect Dis,* 17(2), e64-e69.

Lo NC, Gurarie D, Yoon N, Coulibaly JT, Bendavid E, Andrews JR, King CH (2018). Impact and cost-effectiveness of snail control to achieve disease control targets for schistosomiasis. *P Natl Acad Sci USA,* 115(4), E584-E591.

London Declaration on Neglected Tropical Diseases (2012). Uniting to combat neglected tropical diseases: ending the neglect & reaching the 2020 goals Retrieved 6/25/2019, from https://unitingtocombatntds.org/wp-content/uploads/2017/11/london_declaration_on_ntds.pdf

Looss A (1908). What is *Schistosoma mansoni*, Sambon 1907? *Ann Trop Med Parasit,* 2, 153-191.

Lumley T (2019). survey: analysis of complex survey samples (Version R package version 3.35-1).

Lund AJ, Sam MM, Sy AB, Sow OW, Ali S, Sokolow SH, Bereknyei Merrell S, Bruce J, Jouanard N, Senghor S, Riveau G, Lopez-Carr D, De Leo GA (2019). Unavoidable risks: local perspectives on water contact behavior and implications for schistosomiasis control in an agricultural region of northern Senegal. *Am J Trop Med Hyg,* 101(4), 837-847.

Machemer L, Lorke D (1978). Mutagenicity studies with praziquantel, a new anthelmintic drug, in mammalian systems. *Arch Toxicol,* 39(3), 187-197.

Madden FC (1899). A case of bilharzia of the vagina. *Lancet,* 153(3956), 1716.

Madden FC (1911). Two rare manifestations of bilharziosis. *Lancet,* 178(4593), 754-755.

Magak P, Chang-Cojulun A, Kadzo H, Ireri E, Muchiri E, Kitron U, King CH (2015). Case–control study of posttreatment regression of urinary tract morbidity among adults in *Schistosoma haematobium*–endemic communities in Kwale County, Kenya. *Am J Trop Med Hyg,* 93(2), 371-376.

Magalhães RJS, Clements ACA, Patil AP, Gething PW, Brooker S (2011). Chapter 5 - The Applications of Model-Based Geostatistics in Helminth Epidemiology and Control. In Rollinson D, Hay SI (Eds.), *Adv Parasitol* (Vol. 74, pp. 267-296): Academic Press.

Majid MF, Kang SJ, Hotez PJ (2019). Resolving "worm wars": an extended comparison review of findings from key economics and epidemiological studies. *PLoS Negl Trop Dis,* 13(3), e0006940.

Majima T (1888). A strange case of liver cirrhosis caused by parasitic ova. *Tokyo Med J,* 2, 898-901.

Malhotra I, LaBeaud AD, Morris N, McKibben M, Mungai P, Muchiri E, King CL, King CH (2018). Cord blood antiparasite interleukin 10 as a risk marker for compromised vaccine immunogenicity in early childhood. *J Infect Dis,* 217(9), 1426-1434.

Manson P (1902). Report of a case of bilharzia from the West Indies. *BMJ,* 2(2190), 1894.

Manyangadze T, Chimbari MJ, Gebreslasie M, Mukaratirwa S (2015). Application of geo-spatial technology in schistosomiasis modelling in Africa: a review. *Geospatial Health,* 10(2).

Mao CP (1958). Research on schistosomiasis japonica in China. *Am J Trop Med Hyg,* 7(1), 58-62.

Markel SF, LoVerde PT, Britt EM (1978). Prolonged latent schistosomiasis. *JAMA,* 240(16), 1746-1747.

Martin LK, Beaver PC (1968). Evaluation of Kato thick-smear technique for quantitative diagnosis of helminth infections. *Am J Trop Med Hyg,* 17(3), 382-391.

Matsuura U (1909). Report of investigation concerning the relation between schistosomiasis japonica and dermatitis in the endemic area, and the route of penetration into the human body. *Kyoto Med J,* 6, 253-265.

McCullough FS, Gayral P, Duncan J, Christie JD (1980). Molluscicides in schistosomiasis control. *Bull World Health Organ,* 58(5), 681-689.

Mduluza T, Chimponda TN, Mduluza-Jokonya TL, Choto ET, Mutapi F (2017). Urogenital schistosomiasis—evidence-based benefits of treatment initiated early during childhood. *Curr Clin Microbiol Rep,* 4(4), 192-201.

Mduluza T, Jones C, Osakunor DNM, Lim R, Kuebel JK, Phiri I, Manangazira P, Tagwireyi P, Mutapi F (2020). Six rounds of annual praziquantel treatment during a national helminth control program significantly reduced schistosome infection and morbidity levels in a cohort of schoolchildren in Zimbabwe. *PLoS Negl Trop Dis,* 14(6), e0008388.

Medhat A, Zarzour A, Nafeh M, Shata T, Sweifie Y, Attia M, Helmy A, Shehata M, Zaki S, Mikhail N, Ibrahim S, King C, Strickland GT (1997). Evaluation of an ultrasonographic score for urinary bladder morbidity in *Schistosoma haematobium* infection. *Am J Trop Med Hyg,* 57(1), 16-19.

Meira JA (1949). Schistosomiasis mansoni: a survey of its distribution in Brazil. *Bull World Health Organ,* 2(1), 31-37.

Meltzer E, Schwartz E (2013). Schistosomiasis: current epidemiology and management in travelers. *Curr Infect Dis Rep,* 15(3), 211-215.

Midzi N, Sangweme D, Zinyowera S, Mapingure MP, Brouwer KC, Kumar N, Mutapi F, Woelk G, Mduluza T (2008). Efficacy and side effects of praziquantel treatment against *Schistosoma haematobium* infection among primary school children in Zimbabwe. *T Roy Soc Trop Med Hyg,* 102(8), 759-766.

Miller-Fellows SC, Howard L, Kramer R, Hildebrand V, Furin J, Mutuku FM, Mukoko D, Ivy JA, King CH (2017). Cross-sectional interview study of fertility, pregnancy, and urogenital schistosomiasis in coastal Kenya: documented treatment in childhood is associated with reduced odds of subfertility among adult women. *PLoS Negl Trop Dis,* 11(11), e0006101.

Miller P, Wilson RA (1978). Migration of the schistosomula of *Schistosoma mansoni* from skin to lungs. *Parasitol,* 77(3), 281-302.

Miller P, Wilson RA (1980). Migration of the schistosomula of *Schistosoma mansoni* from the lungs to the hepatic portal system. *Parasitol,* 80(2), 267-288.

Miyagawa Y (1912a). Route of migration of *Schistosomum japonicum* from the skin to the portal vein, and morphology of the young worm at the time of penetrating the skin. *Tokyo Med J,* 26, 3-4.

Miyagawa Y (1912b). Über dem Wandernsweg des *Schistosomum japonicum* von der Haut bis zum Pfortadersystem, und über de Körperkonstitution der jüngsten Würmer zur Zeit deter Hautinvasion. *Centralblatt Bakteriol Parasitenkd Infekt,* 66, 406-416.

Miyagawa Y (1913a). Concerning the cercaria of *Schistosomum japonicum* and the young worm at the time of its penetration into the body of host. *Iji Shinbun,* 890, 1512-1531.

Miyagawa Y (1913b). Concerning the cercaria of *Schistosomum japonicum* and the young worm at the time of its penetration into the body of host. *Iji Shinbun,* 891, 1597-1608.

Miyairi K, Suzuki M (1913). On the development of *Schistosoma japonicum*. *Tokyo Med J,* 1836, 1961-1965.

Mohamed-Ali Q, Doehring-Schwerdtfeger E, Abdel-Rahim IM, Schlake J, Kardorff R, Franke D, Kaiser C, Elsheikh M, Abdalla M, Schafer P, Ehrich JHH (1991). Ultrasonographical investigation of periportal fibrosis in children with *Schistosoma mansoni* infection: reversibility of morbidity seven months after treatment with praziquantel. *Am J Trop Med Hyg,* 44(4), 444-451.

Mohamed I, Kinung'hi S, Mwinzi PNM, Onkanga IO, Andiego K, Muchiri G, Odiere MR, Vennervald BJ, Olsen A (2018). Diet and hygiene practices influence morbidity in schoolchildren living in Schistosomiasis endemic areas along Lake Victoria in Kenya and Tanzania—A cross-sectional study. *PLoS Negl Trop Dis,* 12(3), e0006373.

Molyneux DH, Savioli L, Engels D (2017). Neglected tropical diseases: progress towards addressing the chronic pandemic. *Lancet,* 389(10066), 312-325.

Montero R, Ostrosky P (1997). Genotoxic activity of praziquantel. *Mutat Res,* 387(3), 123-139.

Montgomery S (2020). Schistosomiasis. In Brunette GW, Nemhauser JB (Eds.), *CDC Yellow Book*. New York: Oxford University.

Montresor A, Crompton DWT, Hall A, Bundy DAP, Savioli L (1998). *Guidelines for the evaluation of soil-transmitted helminthiasis and schistosomiasis at community level: a guide for managers of control programmes*. (WHO/CTD/SIP/98.1). Geneva: World Health Organization.

Montresor A, Engels D, Chitsulo L, Bundy DAP, Brooker S, Savioli L (2001). Development and validation of a 'tablet pole' for the administration of praziquantel in sub-Saharan Africa. *T Roy Soc Trop Med Hyg,* 95(5), 542-544.

Montresor A, Crompton DWT, Gyorkos TW, Savioli L (2002). *Helminth control in school-age children: a guide for managers of control programmes*. Geneva: World Health Organization.

Moore DV, Sandground JH (1956). The relative egg producing capacity of *Schistosoma mansoni* and *Schistosoma japonicum*. *Am J Trop Med Hyg,* 5(5), 831-840.

Mostafa MH, Sheweita SA, O'Connor PJ (1999). Relationship between schistosomiasis and bladder cancer. *Clin Microbiol Rev,* 12(1), 97-111.

Mott KE, Dixon H, Osei-Tutu E, England EC (1983). Relation between intensity of *Schistosoma haematobium* infection and clinical haematuria and proteinuria. *Lancet,* 321(8332), 1005-1008.

Mott KE (2004). Schistosomiasis. In Murray CJL, Lopez AD, Mathers CD (Eds.), *The Global Epidemiology of Infectious Diseases* (Vol. IV, pp. 349-391). Geneva: World Health Organization.

Müller I, Coulibaly JT, Fürst T, Knopp S, Hattendorf J, Krauth SJ, Stete K, Righetti AA, Glinz D, Yao AK, Pühse U, N'Goran EK, Utzinger J (2011). Effect of schistosomiasis and soil-transmitted helminth infections on physical fitness of school children in Côte d'Ivoire. *PLoS Negl Trop Dis,* 5(7), e1239.

Murmann P, von Eberstein M, Frohberg H (1976). Zur Vertraglichkeit von Droncit. Zusammenfassung der Versuchsergebnisse. *Vet Med Nachr,* 2, 142-153.

Murray CJ (1996). Rethinking DALYs. In Murray CJ, Lopez AD (Eds.), *The Global Burden of Disease* (pp. 1-98). Cambridge MA: Harvard School of Public Health/World Bank.

Murray CJ, Schroeder SA (2020). Ethical Dimensions of the Global Burden of Disease. In Eyal N, Hurst SA, Murray CJL, Schroeder SA, Wikler D (Eds.), *Measuring the Global Burden of Disease: Philosophical Dimensions* (pp. 24-49). New York: Oxford University.

Murray CJL, Lopez AD (1996). *The Global Burden of Disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020*. Cambridge MA: Harvard School of Public Health/World Bank.

Musuva R, Shen Y, Wei X, Binder S, Ivy JA, Secor WE, Montgomery SP, King CH, Mwinzi PNM (2017). Change in children's school behavior after mass administration of praziquantel for *Schistosoma mansoni* infection in endemic areas of western Kenya: a pilot study using the Behavioral Assessment System for Children (BASC-2). *PLoS ONE,* 12(7), e0181975.

Musuva RM, Awiti A, Omedo M, Ogutu M, Secor WE, Montgomery SP, Alaii J, Mwinzi PNM (2014). Community knowledge, attitudes and practices on schistosomiasis in western Kenya-the SCORE project. *Am J Trop Med Hyg,* 90(4), 646-652.

Mutapi F, Maizels R, Fenwick A, Woolhouse M (2017). Human schistosomiasis in the post mass drug administration era. *Lancet Infect Dis,* 17(2), e42-e48.

Muth S, Sayasone S, Odermatt-Biays S, Phompida S, Duong S, Odermatt P (2010). Chapter 7 - *Schistosoma mekongi* in Cambodia and Lao People's Democratic Republic. In Zhou X-N, Bergquist R, Olveda R, Utzinger J (Eds.), *Adv Parasitol* (Vol. 72, pp. 179-203): Academic Press.

Mwanga JR, Lwambo NJS (2013). Pre- and post-intervention perceptions and water contact behaviour related to schistosomiasis in north-western Tanzania. *Acta Trop,* 128(2), 391-398.

Mwanga JR, Kinung'hi SM, Mosha J, Angelo T, Maganga J, Campbell CH (2020). Village response to mass drug administration for schistosomiasis in Mwanza Region, northwestern Tanzania: are we missing socioeconomic, cultural, and political dimensions? *Am J Trop Med Hyg,* 103(5), 1969-1977.

Mwinzi PNM, Kittur N, Ochola E, Cooper PJ, Campbell CH, King CH, Colley DG (2015a). Additional evaluation of the point-of-contact circulating cathodic antigen assay for *Schistosoma mansoni* infection. *Front Public Health,* 3(48).

Mwinzi PNM, Muchiri G, Wiegand RE, Omedo M, Abudho B, Karanja DMS, Montgomery SP, Secor WE (2015b). Predictive value of school-aged children's schistosomiasis prevalence and egg intensity for other age groups in western Kenya. *Am J Trop Med Hyg,* 93(6), 1311-1317.

Nash TE, Cheever AW, Ottesen EA, Cook JA (1982). Schistosome infections in humans: perspectives and recent findings. *Ann Intern Med,* 97(5), 740-754.

National Center for Biotechnology Information (2020). PubChem Compound Summary for CID 4477, Niclosamide Retrieved December 1, 2020, 2020, from https://pubchem.ncbi.nlm.nih.gov/compound/Niclosamide

Nausch N, Dawson EM, Midzi N, Mduluza T, Mutapi F, Doenhoff MJ (2014). Field evaluation of a new antibody-based diagnostic for *Schistosoma haematobium* and *S. mansoni* at the point-of-care in northeast Zimbabwe. *BMC Infect Dis,* 14(1), 165.

Nayakwadi Singer M, Heath C, Muinde J, Gildengorin V, Mutuku FM, Vu D, Mukoko D, King CL, Malhotra IJ, King CH, LaBeaud AD (2017). Pneumococcal vaccine response after exposure to parasites in utero, in infancy, or mid-childhood. *Pediatrics,* 139(4), e20162781.

Neglected Tropical Diseases Support Center (2019, August 27, 2019). MORBID: Morbidity Operational Research for Bilharziasis Implementation Decisions (Pilot) Retrieved May 20, 2020, from https://www.ntdsupport.org/cor-ntd/ntd-connector/morbid-morbidity-operational-research-bilharziasis-implementation-decisions

Nesi G, Nobili S, Cai T, Caini S, Santi R (2015). Chronic inflammation in urothelial bladder cancer. *Virchows Arch,* 467(6), 623-633.

Njenga SM, Mutungi FM, Wamae CN, Mwanje MT, Njiru KK, Bockarie MJ (2014). Once a year school-based deworming with praziquantel and albendazole combination may not be adequate for control of urogenital schistosomiasis and hookworm infection in Matuga District, Kwale County, Kenya. *Parasit Vector,* 7(1), 74.

Njenga SM, Kanyi HM, Arnold BF, Matendechero SH, Onsongo JK, Won KY, Priest JW (2020). Integrated cross-sectional multiplex serosurveillance of IgG antibody responses to parasitic diseases and vaccines in coastal Kenya. *Am J Trop Med Hyg,* 102(1), 164-176.

NTD Modelling Consortium Schistosomiasis Group (2019). Insights from quantitative and mathematical modelling on the proposed WHO 2030 goal for schistosomiasis. *Gates Open Res,* 3, 1517.

Obermeier J, Frohberg H (1977). Mutagenicity studies with praziquantel, a new anthelmintic drug: tissue-, host-, and urine-mediated mutagenicity assays. *Arch Toxicol,* 38(3), 149-161.

Ochodo EA, Gopalakrishna G, Spek B, Reitsma JB, van Lieshout L, Polman K, Lamberton P, Bossuyt PMM, Leeflang MMG (2015). Circulating antigen tests and urine reagent strips for diagnosis of active schistosomiasis in endemic areas. *Cochrane Db Syst Rev*(3), CD009579.

Odiere MR, Straily A, Secor WE (2021). *MORBID main paper*.

Okeke OC, Ubachukwu PO (2014). Performance of three rapid screening methods in the detection of *Schistosoma haematobium* infection in school-age children in Southeastern Nigeria. *Pathog Glob Health,* 108(2), 111-117.

Olliaro PL, Coulibaly JT, Garba A, Halleux C, Keiser J, King CH, Mutapi F, N'Goran EK, Raso G, Scherrer AU, Sousa-Figueiredo JC, Stete K, Utzinger J, Vaillant MT (2020). Efficacy and safety of single-dose 40 mg/kg oral praziquantel in the treatment of schistosomiasis in preschool-age versus school-age children: an individual participant data meta-analysis. *PLoS Negl Trop Dis,* 14(6), e0008277.

Olsen A, Kinung'hi S, Magnussen P (2018). Comparison of the impact of different mass drug administration strategies on infection with *Schistosoma mansoni* in Mwanza Region, Tanzania—a cluster-randomized controlled trial. *Am J Trop Med Hyg,* 99(6), 1573-1579.

Olsen A, Kinung'hi S, Kaatano G, Magnussen P (2020). Changes in morbidity, physical fitness, and perceived quality of life among schoolchildren following four years of different mass drug administration strategies against *Schistosoma mansoni* infection in Mwanza Region, northwestern Tanzania. *Am J Trop Med Hyg,* 102(1), 100-105.

Olveda DU, McManus DP, Ross AGP (2016a). Mass drug administration and the global control of schistosomiasis: successes, limitations and clinical outcomes. *Curr Opin Infect Dis,* 29(6), 595–608.

Olveda RM, Acosta LP, Tallo V, Baltazar PI, Lesiguez JLS, Estanislao GG, Ayaso EB, Monterde DBS, Ida A, Watson N, McDonald EA, Wu HW, Kurtis JD, Friedman JF (2016b). Efficacy and safety of praziquantel for the treatment of human schistosomiasis during pregnancy: a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet Infect Dis,* 16(2), 199-208.

Omedo M, Ogutu M, Awiti A, Musuva R, Muchiri G, Montgomery SP, Secor WE, Mwinzi P (2014). The effect of a health communication campaign on compliance with mass drug administration for schistosomiasis control in western Kenya—the SCORE project. *Am J Trop Med Hyg,* 91(5), 982-988.

Omer AH, Hamilton PJ, Marshall TF, Draper CC (1976). Infection with *Schistosoma mansoni* in the Gezire area of the Sudan. *J Trop Med Hyg,* 79(7), 151-157.

Omer AHS (1981). Praziquantel in the treatment of mixed *S. haematobium* and *S. mansoni* infections. *Arzneimittel-Forsch,* 31(3a), 605-608.

Ondigo BN, Muok EMO, Oguso JK, Njenga SM, Kanyi HM, Ndombi EM, Priest JW, Kittur N, Secor WE, Karanja DMS, Colley DG (2018). Impact of mothers' schistosomiasis status during gestation on children's IgG antibody responses to routine vaccines 2 years later and anti-schistosome and anti-malarial responses by neonates in western Kenya. *Front Immunol,* 9(1402).

Onkanga IO, Mwinzi PNM, Muchiri G, Andiego K, Omedo M, Karanja DMS, Wiegand RE, Secor WE, Montgomery SP (2016). Impact of two rounds of praziquantel mass drug administration on *Schistosoma mansoni* infection prevalence and intensity: a comparison between community wide treatment and school based treatment in western Kenya. *Int J Parasitol,* 46(7), 439-445.

Ouma JH, King CH, Muchiri EM, Mungai P, Koech DK, Ireri E, Magak P, Kadzo H (2005). Late benefits of 10-18 years after drug therapy for infection with *Schistosoma haematobium* in Kwale District, Coast Province, Kenya. *Am J Trop Med Hyg,* 73(2), 359-364.

Pan C-T (1965). Studies on the host-parasite relationship between *Schistosoma mansoni* and the snail *Australorbis glabratus*. *Am J Trop Med Hyg,* 14(6), 931-976.

Panic G, Barda B, Kovač J, Coulibaly JT, Keiser J (2019). Evaluation of the Clinitek®, a point-of-care urinalysis system for the measurement of clinically significant urinary metabolites and detection

of haematuria in *Schistosoma haematobium* infected children in southern Côte d'Ivoire. *Parasit Vector,* 12(1), 298.

Parraga IM, Assis AMO, Prado MS, Barreto ML, Reis MG, King CH, Blanton RE (1996). Gender differences in growth of school-aged children with schistosomiasis and geohelminth infection. *Am J Trop Med Hyg,* 55(2), 150-156.

Payet B, Chaumentin G, Boyer M, Amaranto P, Lemonon-Meric C, Lucht F (2006). Prolonged latent schistosomiasis diagnosed 38 years after infestation in a HIV patient. *Scand J Infect Dis,* 38(6-7), 572-575.

Pearce EJ, MacDonald AS (2002). The immunobiology of schistosomiasis. *Nature Rev Immunol,* 2(7), 499-511.

Pearson RD, Guerrant RL (1983). Praziquantel: a major advance in anthelminthic therapy. *Ann Intern Med,* 99(2), 195-198.

Pellegrino J, Paulo Marcos ZC (1978). *Schistosoma mansoni*: wandering capacity of a worm couple. *J Parasitol,* 64(1), 181-182.

Person B, Ali SM, A'Kadir FM, Ali JN, Mohammed UA, Mohammed KA, Rollinson D, Knopp S (2016a). Community knowledge, perceptions, and practices associated with urogenital schistosomiasis among school-aged children in Zanzibar, United Republic of Tanzania. *PLoS Negl Trop Dis,* 10(7), e0004814.

Person B, Knopp S, Ali SM, A'kadir FM, Khamis AN, Ali JN, Lymo JH, Mohammed KA, Rollinson D (2016b). Community co-designed schistosomiasis control interventions for school-aged children in Zanzibar. *J Biosoc Sci,* 48(S1), S56-S73.

Peters P, Mahmoud AA, Warren KS, Ouma J, Arap Siongok T (1976a). Field studies of a rapid, accurate means of quantifying *Schistosoma haematobium* eggs in urine samples. *Bull World Health Organ,* 54(2), 159-162.

Peters PA, Warren KS, Adel AFM (1976b). Rapid, accurate quantification of schistosome eggs via nuclepore filters. *J Parasitol,* 62(1), 154-155.

Phillips SM, Lammie PJ (1986). Immunopathology of granuloma formation and fibrosis in schistosomiasis. *Parasitol Today,* 2(11), 296-302.

Pica-Mattoccia L, Cioli D (2004). Sex- and stage-related sensitivity of *Schistosoma mansoni* to in vivo and in vitro praziquantel treatment. *Int J Parasitol,* 34(4), 527-533.

Picquet M, Vercruysse J, Shaw DJ, Diop M, Ly A (1998). Efficacy of praziquantel against *Schistosoma mansoni* in northern Senegal. *T Roy Soc Trop Med Hyg,* 92(1), 90-93.

Pirajá da Silva MA (1908a). Contribuição para o estudo da Schistosomíase na Bahia. Vinte observações. [Contribution to the study of schistosomiasis in Bahia]. *Bras Med,* 22, 451-454.

Pirajá da Silva MA (1908b). La Schistosomose a Bahia. [Contribution to the study of schistosomiasis in Bahia]. *Arch Parasitol,* 13, 281-300.

Pirajá da Silva MA (1908c). Contribuição para o estudo da Schistosomíase na Bahia. [Contribution to the study of schistosomiasis in Bahia]. *Bras Med,* 22, 281-282.

Pirajá da Silva MA (1908d). Contribuição para o estudo da Schistosomíase na Bahia. Dezesseis observações. [Contribution to the study of schistosomiasis in Bahia]. *Bras Med,* 22, 441-444.

Pirajá da Silva MA (1909). Contribution to the study of schistosomiasis in Bahia. [Contribution to the study of schistosomiasis in Bahia]. *Braz J Trop Med Hyg,* 12, 159-164.

Plummer M (2002). Discussion of the paper by Spiegelhalter et al. *J Roy Stat Soc B Met,* 64(4), 620-621.

Plummer M (2003). JAGS: a program for analysis of Bayesian graphical models using Gibbs sampling. In Hornik K, Leisch F, Zeileis A (Eds.), *Proceedings of the 3rd international workshop on distributed statistical computing (DSC 2003)* (Vol. 124, pp. 10). Vienna, Austria: Austrian Science Foundation.

Plummer M, Best N, Cowles K, Vines K (2006). CODA: convergence diagnosis and output analysis for MCMC. *R news,* 6(1), 7-11.

Plummer M (2019). rjags: Bayesian Graphical Models using MCMC (Version R package version 4-10). Retrieved from https://CRAN.R-project.org/package=rjags

Poggensee G, Krantz I, Kiwelu I, Feldmeier H (2000). Screening of Tanzanian women of childbearing age for urinary schistosomiasis: validity of urine reagent strip readings and self-reported symptoms. *Bull World Health Organ,* 78(4), 542-548.

Pointier JP, Jourdane J (2000). Biological control of the snail hosts of schistosomiasis in areas of low transmission: the example of the Caribbean area. *Acta Trop,* 77(1), 53-60.

Polderman AM, Gryseels B, Gerold JL, Mpamila K, Manshande JP (1984). Side effects of praziquantel in the treatment of *Schistosoma mansoni* in Maniema, Zaire. *T Roy Soc Trop Med Hyg,* 78(6), 752-754.

Pollack HM, Banner MP, Martinez LO, Hodson CJ (1981). Diagnostic considerations in urinary bladder wall calcification. *Am J Roentgenol,* 136(4), 791-797.

Polman K, Engels D, Fathers L, Deelder AM, Gryseels B (1998). Day-to-day fluctuation of schistosome circulating antigen levels in serum and urine of humans infected with *Schistosoma mansoni* in Burundi. *Am J Trop Med Hyg,* 59(1), 150-154.

Prata A, Bina JC (1968). Development of the hepatosplenic form of schistosomiasis. (A study of 20 patients observed during a 5 year period.). *Gaz Méd Bahia,* 68(2), 49-60.

Pugh RNH, Jakubowski AW, Gilles HM (1979). Malumfashi Endemic Diseases Research Project, VI. *Ann Trop Med Parasit,* 73(1), 37-44.

R Development Core Team (2018). R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing. Retrieved from https://www.R-project.org/

Randrianasolo BS, Jourdan PM, Ravoniarimbinina P, Ramarokoto CE, Rakotomanana F, Ravaoalimalala VE, Gundersen SG, Feldmeier H, Vennervald BJ, van Lieshout L, Roald B, Leutscher P, Kjetland EF (2015). Gynecological manifestations, histopathological findings, and *Schistosoma*-specific polymerase chain reaction results among women with *Schistosoma haematobium* infection: a cross-sectional study in Madagascar. *J Infect Dis,* 212(2), 275-284.

Raso G, Matthys B, N'Goran EK, Tanner M, Vounatsou P, Utzinger J (2005). Spatial risk prediction and mapping of *Schistosoma mansoni* infections among schoolchildren living in western Côte d'Ivoire. *Parasitol,* 131(1), 97-108.

Reiczigel J, Földi J, Ózsvári L (2010). Exact confidence limits for prevalence of a disease with an imperfect diagnostic test. *Epidemiol Infect,* 138(11), 1674-1678.

Renoult AJ (1808). Notice sur l'hématurie qu'éprouvent les Européens dans la haute Egypte et la Nubie. *J Gén Méd Chir Pharm,* 17, 366-370.

Richter J, Correia Dacal AR, Vergetti Siqueira JG, Poggensee G, Mannsmann U, Deelder A, Feldmeier H (1998). Sonographic prediction of variceal bleeding in patients with liver fibrosis due to *Schistosoma mansoni*. *Trop Med Int Health,* 3(9), 728-735.

Richter J (2000). Evolution of schistosomiasis-induced pathology after therapy and interruption of exposure to schistosomes: a review of ultrasonographic studies. *Acta Trop,* 77(1), 111-131.

Richter J, Hatz C, Campagne G, Bergquist NR, Jenkins JM (2000). Ultrasound in schistosomiasis: a practical guide to the standard use of ultrasonography for assessment of schistosomiasis-related morbidity: Second International Workshop, October 22-26 1996, Niamey, Niger (pp. 49). Geneva: World Health Organization.

Richter J (2003). The impact of chemotherapy on morbidity due to schistosomiasis. *Acta Trop,* 86(2), 161-183.

Righetti AA, Adiossan LG, Ouattara M, Glinz D, Hurrell RF, N'Goran EK, Wegmüller R, Utzinger J (2013). Dynamics of anemia in relation to parasitic infections, micronutrient status, and increasing age in south-central Côte d'Ivoire. *J Infect Dis,* 207(10), 1604-1615.

Rodriguez HF, Garcia-Palmieri MR, Rivera JV, Rodriguez-Molina R (1955). A comparative study of portal and bilharzial cirrhosis. *Gastroenterol,* 29(2), 235-246.

Rollinson D, Stothard JR, Southgate VR (2001). Interactions between intermediate snail hosts of the genus *Bulinus* and schistosomes of the *Schistosoma haematobium* group. *Parasitol,* 123(7), 245-260.

Rollinson D, Knopp S, Levitz S, Stothard JR, Tchuem Tchuente LA, Garba A, Mohammed KA, Schur N, Person B, Colley DG, Utzinger J (2013). Time to set the agenda for schistosomiasis elimination. *Acta Trop,* 128(2), 423-440.

Rosin MP, El Din Zaki SS, Ward AJ, Anwar WA (1994). Involvement of inflammatory reactions and elevated cell proliferation in the development of bladder cancer in schistosomiasis patients. *Mutat Res-Fund Mol M,* 305(2), 283-292.

Ross AG, Vickers D, Olds GR, Shah SM, McManus DP (2007). Katayama syndrome. *Lancet Infect Dis,* 7(3), 218-224.

Ross AGP, Olveda RM, Acosta L, Harn DA, Chy D, Li Y, Gray DJ, Gordon CA, McManus DP, Williams GM (2013). Road to the elimination of schistosomiasis from Asia: the journey is far from over. *Microbes Infect,* 15(13), 858-865.

Ross AGP, Olveda RM, Chy D, Olveda DU, Li Y, Harn DA, Gray DJ, McManus DP, Tallo V, Chau TNP, Williams GM (2015a). Can mass drug administration lead to the sustainable control of schistosomiasis? *J Infect Dis,* 211(2), 283-289.

Ross AGP, Olveda RM, Li Y (2015b). An audacious goal: the elimination of schistosomiasis in our lifetime through mass drug administration. *Lancet,* 385(9983), 2220-2221.

Rubaba O, Chimbari MJ, Soko W, Manyangadze T, Mukaratirwa S (2018). Validation of a urine circulating cathodic antigen cassette test for detection of *Schistosoma haematobium* in Mkhanyakude district of South Africa. *Acta Trop,* 182, 161-165.

Ruberanziza E, Wittmann U, Mbituyumuremyi A, Mutabazi A, Campbell CH, Colley DG, Fleming FM, Ortu G, van Dam GJ, Umulisa I, Tallant J, Kabera M, Semakula M, Corstjens PLAM, Munyaneza T, Lancaster W, Mbonigaba JB, Clements MN (2020). Nationwide remapping of *Schistosoma mansoni* infection in Rwanda using circulating cathodic antigen rapid test: taking steps toward elimination. *Am J Trop Med Hyg,* 103(1), 315-324.

Rubin DB (2004). *Multiple Imputation for Nonresponse in Surveys*. New York: John Wiley & Sons.

Ruffer MA (1910). Note on the presence of "bilharzia haematobia" in Egyptian mummies of the Twentieth Dynasty [1250-1000 B.C.]. *BMJ,* 1(2557), 16.

Sabah AA, Fletcher C, Webbe G, Doenhoff MJ (1986). *Schistosoma mansoni*: chemotherapy of infections of different ages. *Exp Parasitol,* 61(3), 294-303.

Sacolo H, Chimbari M, Kalinda C (2018). Knowledge, attitudes and practices on schistosomiasis in sub-Saharan Africa: a systematic review. *BMC Infect Dis,* 18(1), 46.

Sadun EH, von Lichtenberg F, Cheever AW, Erickson DG, Hickman RL (1970). Experimental infection with *Schistosoma haematobium* in chimpanzees. *Am J Trop Med Hyg,* 19(3), 427-458.

Salari P, Fürst T, Knopp S, Utzinger J, Tediosi F (2020). Cost of interventions to control schistosomiasis: a systematic review of the literature. *PLoS Negl Trop Dis,* 14(3), e0008098.

Sambon LW (1907a). New or little known African *Entozoa*. *J Trop Med Hyg,* 10, 117.

Sambon LW (1907b). Remarks on *Schistosoma mansoni*. *J Trop Med Hyg,* 10, 303-304.

Sambon LW (1909). What is *Schistosoma mansoni*. *J Trop Med Hyg,* 12, 1-11.

Samuels AM, Matey E, Mwinzi PNM, Wiegand RE, Muchiri G, Ireri E, Hyde M, Montgomery SP, Karanja DMS, Secor WE (2012). *Schistosoma mansoni* morbidity among school-aged children: a SCORE project in Kenya. *Am J Trop Med Hyg,* 87(5), 874-882.

Sandbach FR (1976). The history of schistosomiasis research and policy for its control. *Med Hist,* 20(3), 259-275.

Sanneh B, Joof E, Sanyang AM, Renneker K, Camara Y, Sey AP, Jagne S, Baldeh I, Ceesay SJ, Sambou SM, Ogoussan K (2017). Field evaluation of a schistosome circulating cathodic antigen rapid test kit at point-of-care for mapping of schistosomiasis endemic districts in The Gambia. *PLoS ONE,* 12(8), e0182003.

Santos AT, Blas BL, Noseñas JS, Portillo GP, Ortega OM, Hayashi M, Boehme K (1979). Preliminary clinical trials with praziquantel in *Schistosoma japonicum* infections in the Philippines. *Bull World Health Organ,* 57(5), 793-799.

Sarant L (2017). Egypt: the flatworm's revenge. *Nature,* 551(7679), S46-S47.

Satayathum SA, Muchiri EM, Ouma JH, Whalen CC, King CH (2006). Factors affecting infection or reinfection with *Schistosoma haematobium* in coastal Kenya: survival analysis during a nine-year, school-based treatment program. *Am J Trop Med Hyg,* 75(1), 83-92.

Satrija F, Ridwan Y, Jastal, Samarang, Rauf A (2015). Current status of schistosomiasis in Indonesia. *Acta Trop,* 141, 349-353.

Savioli L, Hatz C, Dixon H, Kisumku UM, Mott KE (1990). Control of morbidity due to *Schistosoma haematobium* on Pemba Island: egg excretion and hematuria as indicators of infection. *Am J Trop Med Hyg,* 43(3), 289-295.

Scholte RGC, Carvalho OS, Malone JB, Utzinger J, Vounatsou P (2012). Spatial distribution of *Biomphalaria* spp., the intermediate host snails of *Schistosoma mansoni*, in Brazil. *Geospatial Health,* 6(3), S95-S101.

Scholte RGC, Gosoniu L, Malone JB, Chammartin F, Utzinger J, Vounatsou P (2014). Predictive risk mapping of schistosomiasis in Brazil using Bayesian geostatistical models. *Acta Trop,* 132, 57-63.

Schur N, Hürlimann E, Garba A, Traoré MS, Ndir O, Ratard RC, Tchuem Tchuenté L-A, Kristensen TK, Utzinger J, Vounatsou P (2011). Geostatistical model-based estimates of schistosomiasis prevalence among individuals aged ≤20 years in west Africa. *PLoS Negl Trop Dis,* 5(6), e1194.

Schur N, Vounatsou P, Utzinger J (2012). Determining treatment needs at different spatial scales using geostatistical model-based risk estimates of schistosomiasis. *PLoS Negl Trop Dis,* 6(9), e1773.

Schur N, Hürlimann E, Stensgaard A-S, Chimfwembe K, Mushinge G, Simoonga C, Kabatereine NB, Kristensen TK, Utzinger J, Vounatsou P (2013). Spatially explicit *Schistosoma* infection risk in eastern Africa using Bayesian geostatistical modelling. *Acta Trop,* 128(2), 365-377.

Scott JA (1937). The incidence and distribution of the human schistosomes in Egypt. *Am J Epidemiol,* 25(3), 566-614.

Sebastianes PM, Sales DM, Santos JEM, Leão ARdS, Costa JDd, Takemoto K, Capobianco J, Bezerra ASdA, D'Ippolito G (2010). Interobserver variability of ultrasound parameters in portal hypertension. *Mem I Oswaldo Cruz,* 105, 409-413.

Secor WE (2014). Water-based interventions for schistosomiasis control. *Pathog Glob Health,* 108(5), 246-254.

Secor WE (2015). Early lessons from schistosomiasis mass drug administration programs [version 1; peer review: 3 approved]. *F1000 Res,* 4(F1000 Faculty Rev)(1157).

Secor WE, Colley DG (2018). When should the emphasis on schistosomiasis control move to elimination? *Trop Med Infect Dis,* 3(3), 85.

Secor WE (2020a, 12/5/2020). [Reading time of a Kato-Katz slide].

Secor WE (2020b). [Fading of ultrasound images on thermal paper].

Secor WE, Wiegand RE, Montgomery SP, Karanja DMS, Odiere MR (2020). Comparison of school-based and community-wide mass drug administration for schistosomiasis control in an area of western Kenya with high initial *Schistosoma mansoni* infection prevalence: a cluster randomized trial. *Am J Trop Med Hyg,* 102(2), 318-327.

Shane HL, Verani JR, Abudho B, Montgomery SP, Blackstock AJ, Mwinzi PNM, Butler SE, Karanja DMS, Secor WE (2011). Evaluation of urine CCA assays for detection of *Schistosoma mansoni* infection in western Kenya. *PLoS Negl Trop Dis,* 5(1), e951.

Shen Y, King CH, Binder S, Zhang F, Whalen CC, Secor WE, Montgomery SP, Mwinzi PNM, Olsen A, Magnussen P, Kinung'hi S, Phillips AE, Nalá R, Ferro J, Aurelio HO, Fleming F, Garba A, Hamidou A, Fenwick A, Campbell CH, Colley DG (2017). Protocol and baseline data for a multi-year cohort study of the effects of different mass drug treatment approaches on functional morbidities from schistosomiasis in four African countries. *BMC Infect Dis,* 17(1), 652.

Shen Y, Wiegand RE, Olsen A, King CH, Kittur N, Binder S, Zhang F, Whalen CC, Secor WE, Montgomery SP, Mwinzi PNM, Magnussen P, Kinung'hi S, Campbell Jr. CH, Colley DG (2019). Five-year impact of different multi-year mass drug administration strategies on childhood *Schistosoma mansoni*–associated morbidity: a combined analysis from the Schistosomiasis Consortium for Operational Research and Evaluation cohort studies in the Lake Victoria regions of Kenya and Tanzania. *Am J Trop Med Hyg,* 101(6), 1336-1344.

Shiff C (2017). Why reinvent the wheel? Lessons in schistosomiasis control from the past. *PLoS Negl Trop Dis,* 11(10), e0005812.

Shousha AT (1949). Schistosomiasis (Bilharziasis): a world problem. *Bull World Health Organ,* 2(1), 19-30.

Simoonga C, Utzinger J, Brooker S, Vounatsou P, Appleton CC, Stensgaard AS, Olsen A, Kristensen TK (2009). Remote sensing, geographical information system and spatial analysis for schistosomiasis epidemiology and ecology in Africa. *Parasitol,* 136(13), 1683-1693.

Sircar AD, Mwinzi PNM, Onkanga IO, Wiegand RE, Montgomery SP, Secor WE (2018). *Schistosoma mansoni* mass drug administration regimens and their effect on morbidity among schoolchildren over a 5-year period—Kenya, 2010–2015. *Am J Trop Med Hyg,* 99(2), 362-369.

Slootweg R, Malek EA, McCullough FS (1994). The biological control of snail intermediate hosts of schistosomiasis by fish. *Rev Fish Biol Fisher,* 4(1), 67-90.

Smith JH, Kamel IA, Elwi A, von Lichtenberg F (1974). A quantitative post mortem analysis of urinary schistosomiasis in Egypt. I. Pathology and pathogenesis. *Am J Trop Med Hyg,* 23(6), 1054-1071.

Smith JH, Elwi A, Kamel IA, Von Lichtenberg F (1975). A quantitative post mortem analysis of urinary schistosomiasis in Egypt. II. Evolution and epidemiology. *Am J Trop Med Hyg,* 24(5), 806-822.

Smith JH, Kelada AS, Khalil A, Torky AH (1977a). Surgical pathology of schistosomal obstructive uropathy: a clinicopathologic correlation. *Am J Trop Med Hyg,* 26(1), 96-108.

Smith JH, Torky H, Kelada AS, Farid Z (1977b). Schistosomal polyposis of the urinary bladder. *Am J Trop Med Hyg,* 26(1), 85-88.

Smith JH, Christie JD (1986). The pathobiology of *Schistosoma haematobium* infection in humans. *Hum Pathol,* 17(4), 333-345.

Sokolow SH, Huttinger E, Jouanard N, Hsieh MH, Lafferty KD, Kuris AM, Riveau G, Senghor S, Thiam C, N'Diaye A, Faye DS, De Leo GA (2015). Reduced transmission of human schistosomiasis after restoration of a native river prawn that preys on the snail intermediate host. *P Natl Acad Sci USA,* 112(31), 9650–9655.

Sokolow SH, Wood CL, Jones IJ, Lafferty KD, Kuris AM, Hsieh MH, De Leo GA (2018). To reduce the global burden of human schistosomiasis, use 'old fashioned' snail control. *Trends Parasitol,* 34(1), 23-40.

Sonsino P (1884). Ricerche sullo sviluppo della Bilharzia haematobia. *Giornale della R. Accademia di Torino,* 32, 17-21.

Sousa-Figueiredo JC, Betson M, Atuhaire A, Arinaitwe M, Navaratnam AMD, Kabatereine NB, Bickle Q, Stothard JR (2012a). Performance and safety of praziquantel for treatment of intestinal schistosomiasis in infants and preschool children. *PLoS Negl Trop Dis,* 6(10), e1864.

Sousa-Figueiredo JC, Betson M, Stothard JR (2012b). Treatment of schistosomiasis in African infants and preschool-aged children: downward extension and biometric optimization of the current praziquantel dose pole. *Int Health,* 4(2), 95-102.

Southgate VR (1997). Schistosomiasis in the Senegal River Basin: before and after the construction of the dams at Diama, Senegal and Manantali, Mali and future prospects. *J Helminthol,* 71(2), 125-132.

Standley CJ, Mugisha L, Dobson AP, Stothard JR (2012). Zoonotic schistosomiasis in non-human primates: past, present and future activities at the human–wildlife interface in Africa. *J Helminthol,* 86(2), 131-140.

Steinmann P, Keiser J, Bos R, Tanner M, Utzinger J (2006). Schistosomiasis and water resources development: systematic review, meta-analysis, and estimates of people at risk. *Lancet Infect Dis,* 6(7), 411-425.

Stelma FF, Talla I, Verle P, Niang M, Gryseels B (1994). Morbidity due to heavy *Schistosoma mansoni* infections in a recently established focus in northern Senegal. *Am J Trop Med Hyg,* 50(5), 575-579.

Stephenson LS, Latham MC, Kurz KM, Kinoti SN (1989). Single dose metrifonate or praziquantel treatment in Kenyan children. *Am J Trop Med Hyg,* 41(4), 445-453.

Stoll NR (1947). This wormy world. *J Parasitol,* 33(1), 1-18.

Stothard JR, Chitsulo L, Kristensen TK, Utzinger J (2009a). Control of schistosomiasis in sub-Saharan Africa: progress made, new opportunities and remaining challenges. *Parasitol,* 136(13), 1665-1675.

Stothard JR, Sousa-Figueiredo JC, Standley C, Van Dam GJ, Knopp S, Utzinger J, Ameri H, Khamis AN, Khamis IS, Deelder AM, Mohammed KA, Rollinson D (2009b). An evaluation of urine-CCA strip test and fingerprick blood SEA-ELISA for detection of urinary schistosomiasis in schoolchildren in Zanzibar. *Acta Trop,* 111(1), 64-70.

Stothard JR, Sousa-Figueiredo JC, Betson M, Green HK, Seto EYW, Garba A, Sacko M, Mutapi F, Vaz Nery S, Amin MA, Mutumba-Nakalembe M, Navaratnam A, Fenwick A, Kabatereine NB, Gabrielli AF, Montresor A (2011). Closing the praziquantel treatment gap: new steps in epidemiological monitoring and control of schistosomiasis in African infants and preschool-aged children. *Parasitol,* 138(12), 1593-1606.

Stothard JR, Stanton MC, Bustinduy AL, Sousa-Figueiredo JC, Van Dam GJ, Betson M, Waterhouse D, Ward S, Allan F, Hassan AA, Al-Helal MA, Memish ZA, Rollinson D (2014). Diagnostics for schistosomiasis in Africa and Arabia: a review of present options in control and future needs for elimination. *Parasitol,* 141(14), 1947-1961.

Straily A, Malit AO, Wanja D, Kavere EA, Kiplimo R, Aera R, Momanyi C, Mwangi S, Mukire S, Souza AA, Wiegand RE, Montgomery SP, Secor WE, Odiere M (2021). Use of a tablet-based system to perform abdominal ultrasounds in a field investigation of schistosomiasis-related morbidity in western Kenya. *Am J Trop Med Hyg,* 104(3), 898-901.

Subramanian AK, Mungai P, Ouma JH, Magak P, King CH, Mahmoud AA, King CL (1999). Long-term suppression of adult bladder morbidity and severe hydronephrosis following selective population chemotherapy for *Schistosoma haematobium*. *Am J Trop Med Hyg,* 61(3), 476-481.

Sullivan KM, Mei Z, Grummer-Strawn L, Parvanta I (2008). Haemoglobin adjustments to define anaemia. *Trop Med Int Health,* 13(10), 1267-1271.

Symmers WSC (1904). Note on a new form of liver cirrhosis due to the presence of the ova of nilharzia hæmatobia. *J Pathol Bacteriol,* 9(2), 237-239.

Talla I, Kongs A, Verle P, Belot J, Sarr S, Coll AM (1990). Outbreak of intestinal schistosomiasis in the Senegal River Basin. *Ann Soc Belge Méd Trop,* 70(3), 173-180.

Tanaka H, Tsuji M (1997). From discovery to eradication of schistosomiasis in Japan: 1847–1996. *Int J Parasitol,* 27(12), 1465-1480.

Tchuem Tchuenté L-A, Kueté Fouodo CJ, Kamwa Ngassam RI, Sumo L, Dongmo Noumedem C, Kenfack CM, Gipwe NF, Nana ED, Stothard JR, Rollinson D (2012). Evaluation of circulating cathodic antigen (CCA) urine-tests for diagnosis of *Schistosoma mansoni* infection in Cameroon. *PLoS Negl Trop Dis,* 6(7), e1758.

Tchuem Tchuenté L-A, Rollinson D, Stothard JR, Molyneux D (2017). Moving from control to elimination of schistosomiasis in sub-Saharan Africa: time to change and adapt strategies. *Infect Dis Poverty,* 6(1), 42.

Terer CC, Bustinduy AL, Magtanong RV, Muhoho Ne, Mungai PL, Muchiri EM, Kitron U, King CH, Mutuku FM (2013). Evaluation of the health-related quality of life of children in *Schistosoma haematobium*-endemic communities in Kenya: a cross-sectional study. *PLoS Negl Trop Dis,* 7(3), e2106.

The Cairo Working Group (1992). The use of diagnostic ultrasound in schistosomiasis — Attempts at standardization of methodology. *Acta Trop,* 51(1), 45-63.

Thomas AK, Dittrich M, Kardorff R, Talla I, Mbaye A, Sow S, Niang M, Yazdanpanah Y, Stelma FF, Gryseels B, Doehring E (1997). Evaluation of ultrasonographic staging systems for the assessment of *Schistosoma mansoni* induced hepatic involvement. *Acta Trop,* 68(3), 347-356.

Thomas CM, Timson DJ (2018). The mechanism of action of praziquantel: six hypotheses. *Curr Top Med Chem,* 18(18), 1575-1584.

Thomas H, Gönnert R (1977). The efficacy of praziquantel against cestodes in animals. *Z Parasitenkd,* 52(2), 117-127.

Toor J, Alsallaq R, Truscott JE, Turner HC, Werkman M, Gurarie D, King CH, Anderson RM (2018a). Are we on our way to achieving the 2020 goals for schistosomiasis morbidity control using current World Health Organization guidelines? *Clin Infect Dis,* 66(suppl_4), S245-S252.

Toor J, Turner HC, Truscott JE, Werkman M, Phillips AE, Alsallaq R, Medley GF, King CH, Anderson RM (2018b). The design of schistosomiasis monitoring and evaluation programmes: the importance of collecting adult data to inform treatment strategies for *Schistosoma mansoni*. *PLoS Negl Trop Dis,* 12(10), e0006717.

Toor J, Truscott JE, Werkman M, Turner HC, Phillips AE, King CH, Medley GF, Anderson RM (2019). Determining post-treatment surveillance criteria for predicting the elimination of *Schistosoma mansoni* transmission. *Parasit Vector,* 12(1), 437.

Toor J, Rollinson D, Turner HC, Gouvras A, King CH, Medley GF, Hollingsworth TD, Anderson RM (2020). Achieving elimination as a public health problem for *Schistosoma mansoni* and *S. haematobium*: when Is community-wide treatment required? *J Infect Dis,* 221(Supplement_5), S525-S530.

Touré S, Zhang Y, Bosqué-Oliva E, Ky C, Ouedraogo A, Koukounari A, Gabrielli AF, Bertrand S, Webster JP, Fenwick A (2008). Two-year impact of single praziquantel treatment on infection in the national control programme on schistosomiasis in Burkina Faso. *Bull World Health Organ,* 86(10), 780-787.

Tuhebwe D, Bagonza J, Kiracho EE, Yeka A, Elliott AM, Nuwaha F (2015). Uptake of mass drug administration programme for schistosomiasis control in Koome Islands, central Uganda. *PLoS ONE,* 10(4), e0123673.

Utzinger J, N'Goran EK, Ossey YA, Booth M, Traoré M, Lohourignon KL, Allangba A, Ahiba LA, Tanner M, Lengeler C (2000). Rapid screening for *Schistosoma mansoni* in western Côte d'Ivoire using a simple school questionnaire. *Bull World Health Organ,* 78(3), 389-398.

Utzinger J, Booth M, N'Goran EK, Müller I, Tanner M, Lengeler C (2001). Relative contribution of day-to-day and intra-specimen variation in faecal egg counts of *Schistosoma mansoni* before and after treatment with praziquantel. *Parasitol,* 122(5), 537-544.

Utzinger J, Keiser J (2004). Schistosomiasis and soil-transmitted helminthiasis: common drugs for treatment and control. *Expert Opin Pharmaco,* 5(2), 263-285.

Utzinger J, Becker SL, van Lieshout L, van Dam GJ, Knopp S (2015). New diagnostic tools in schistosomiasis. *Clin Microbiol Infec,* 21(6), 529-542.

van Dam GJ, Wichers JH, Ferreira TMF, Ghati D, van Amerongen A, Deelder AM (2004). Diagnosis of schistosomiasis by reagent strip test for detection of circulating cathodic antigen. *J Clin Microbiol,* 42(12), 5458-5461.

van Dam GJ, de Dood CJ, Lewis M, Deelder AM, van Lieshout L, Tanke HJ, van Rooyen LH, Corstjens PLAM (2013). A robust dry reagent lateral flow assay for diagnosis of active schistosomiasis by detection of *Schistosoma* circulating anodic antigen. *Exp Parasitol,* 135(2), 274-282.

van Dam GJ, Odermatt P, Acosta L, Bergquist R, de Dood CJ, Kornelis D, Muth S, Utzinger J, Corstjens PLAM (2015). Evaluation of banked urine samples for the detection of circulating anodic and cathodic antigens in *Schistosoma mekongi* and *S. japonicum* infections: a proof-of-concept study. *Acta Trop,* 141, 198-203.

van der Werf MJ, de Vlas SJ, Looman CW, Nagelkerke NJ, Habbema JD, Engels D (2002). Associating community prevalence of *Schistosoma mansoni* infection with prevalence of signs and symptoms. *Acta Trop,* 82(2), 127-137.

van der Werf MJ, Borsboom GJJM, de Vlas SJ (2003a). No effect of recall period length on prevalence of self-reported haematuria in *Schistosoma haematobium*-endemic areas. *T Roy Soc Trop Med Hyg,* 97(4), 373-374.

van der Werf MJ, de Vlas SJ, Brooker S, Looman CW, Nagelkerke NJ, Habbema JD, Engels D (2003b). Quantification of clinical morbidity associated with schistosome infection in sub-Saharan Africa. *Acta Trop,* 86(2-3), 125-139.

van der Werf MJ, de Vlas SJ (2004). Diagnosis of urinary schistosomiasis: a novel approach to compare bladder pathology measured by ultrasound and three methods for hematuria detection. *Am J Trop Med Hyg,* 71(1), 98-106.

Van Etten L, Kremsner PG, Krijger FW, Deelder AM (1997). Day-to-day variation of egg output and schistosome circulating antigens in urine of *Schistosoma haematobium*-infected school children from Gabon and follow-up after chemotherapy. *Am J Trop Med Hyg,* 57(3), 337-341.

Varni JW, Seid M, Rode CA (1999). The PedsQL™: measurement model for the Pediatric Quality of Life Inventory. *Med Care,* 37(2), 126-139.

Varni JW, Burwinkle TM, Seid M, Skarr D (2003). The PedsQL™* 4.0 as a pediatric population health measure: feasibility, reliability, and validity. *Ambul Pediatr,* 3(6), 329-341.

Varni JW, Burwinkle TM, Seid M (2006). The PedsQLTM 4.0 as a school population health measure: feasibility, reliability, and validity. *Qual Life Res,* 15(2), 203-215.

Vennervald BJ, Kenty L, Butterworth AE, Kariuki CH, Kadzo H, Ireri E, Amaganga C, Kimani G, Mwatha J, Otedo A, Booth M, Ouma JH, Dunne DW (2004). Detailed clinical and ultrasound examination of children and adolescents in a *Schistosoma mansoni* endemic area in Kenya: hepatosplenic disease in the absence of portal fibrosis. *Trop Med Int Health,* 9(4), 461-470.

Verani JR, Abudho B, Montgomery SP, Mwinzi PNM, Shane HL, Butler SE, Karanja DMS, Secor WE (2011). Schistosomiasis among young children in Usoma, Kenya. *Am J Trop Med Hyg,* 84(5), 787-791.

Vermund SH, Bradley DJ, Ruiz-Tiben E (1983). Survival of *Schistosoma mansoni* in the human host: estimates from a community-based prospective study in Puerto Rico. *Am J Trop Med Hyg,* 32(5), 1040-1048.

Viana AG, Gazzinelli-Guimarães PH, Castro VNd, Santos YLdOd, Ruas ACL, Bezerra FSdM, Bueno LL, Dolabella SS, Geiger SM, Phillips AE, Fujiwara RT (2019). Discrepancy between batches and impact on the sensitivity of point-of-care circulating cathodic antigen tests for *Schistosoma mansoni* infection. *Acta Trop,* 197, 105049.

Vieira P, Miranda HP, Cerqueira M, de Lurdes Delgado M, Coelho H, Antunes D, Cross JH, da Costa JMC (2007). Latent schistosomiasis in Portuguese soldiers. *Mil Med,* 172(2), 144-146.

Vinkeles Melchers NVS, van Dam GJ, Shaproski D, Kahama AI, Brienen EAT, Vennervald BJ, van Lieshout L (2014). Diagnostic performance of *Schistosoma* Real-Time PCR in urine samples from Kenyan children infected with *Schistosoma haematobium*: day-to-day variation and follow-up after praziquantel treatment. *PLoS Negl Trop Dis,* 8(4), e2807.

Visser LG, Polderman AM, Stuiver PC (1995). Outbreak of schistosomiasis among travelers returning from Mali, west Africa. *Clin Infect Dis,* 20(2), 280-285.

von Lichtenberg F (1964). Studies on granuloma formation: III. Antigen sequestration and destruction in the schistosome pseudotubercle. *Am J Pathol,* 45(1), 75-93.

von Lichtenberg F, Edington GM, Nwabuebo I, Taylor JR, Smith JH (1971). Pathologic effects of schistomiasis in Ibadan, Western State of Nigeria. II. Pathogenesis of lesions of the bladder and ureters. *Am J Trop Med Hyg,* 20(2), 244-254.

von Lichtenberg F, Erickson DG, Sadun EH (1973). Comparative histopathology of schistosome granulomas in the hamster. *Am J Pathol,* 72(2), 149-178.

Walker M, Mabud TS, Olliaro PL, Coulibaly JT, King CH, Raso G, Scherrer AU, Stothard JR, Sousa-Figueiredo JC, Stete K, Utzinger J, Basáñez M-G (2016). New approaches to measuring anthelminthic drug efficacy: parasitological responses of childhood schistosome infections to treatment with praziquantel. *Parasit Vector,* 9(1), 41.

Wall KM, Kilembe W, Vwalika B, Dinh C, Livingston P, Lee Y-M, Lakhi S, Boeras D, Naw HK, Brill I, Chomba E, Sharkey T, Parker R, Shutes E, Tichacek A, Secor WE, Allen S (2018). Schistosomiasis is associated with incident HIV transmission and death in Zambia. *PLoS Negl Trop Dis,* 12(12), e0006902.

Wallerstein RS (1949). Longevity of *Schistosoma mansoni*: observations based on a case. *Am J Trop Med Hyg,* s1-29(5), 717-722.

Warren KS, Mahmoud AAF, Cummings P, Murphy DJ, Houser HB (1974). Schistosomiasis mansoni in Yemeni in California: duration of infection, presence of disease, therapeutic management. *Am J Trop Med Hyg,* 23(5), 902-909.

Warren KS, Mahmoud AAF, Muruka JF, Whittaker LR, Ouma JH, Siongok TKA (1979). Schistosomiasis haematobia in Coast Province Kenya. *Am J Trop Med Hyg,* 28(5), 864-870.

Warren KS, De-Long S, Zhao-Yue X, Hong-Chang Y, Peters PA, Cook JA, Mott KE, Houser HB (1983). Morbidity in schistosomiasis japonica in relation to intensity of infection. *N Engl J Med,* 309(25), 1533-1539.

Warren KS (1984). The kinetics of hepatosplenic schistosomiasis. *Semin Liver Dis,* 4(04), 293-300.

Webbe G, James C (1977). A comparison of the susceptibility to praziquantel of *Schistosoma haematobium*, *S. japonicum*, *S. mansoni*, *S. intercalatum* and *S. mattheei* in hamsters. *Z Parasitenkd,* 52(2), 169-177.

Webster JP, Koukounari A, Lamberton P, Stothard J, Fenwick A (2009). Evaluation and application of potential schistosome-associated morbidity markers within large-scale mass chemotherapy programmes. *Parasitol,* 136(13), 1789-1799.

White PC, Pimentel D, Garcia FC (1957). Distribution and prevalence of human schistosomiasis in Puerto Rico in 1953. *Am J Trop Med Hyg,* 6(4), 715-726.

Whitty CJM, Mabey DC, Armstrong M, Wright SG, Chiodini PL (2000). Presentation and outcome of 1107 cases of schistosomiasis from Africa diagnosed in a non-endemic country. *T Roy Soc Trop Med Hyg,* 94(5), 531-534.

WHO (1950). Joint OIHP/WHO study-group on bilharziasis in Africa: report on the first session *World Health Organization Technical Report Series*. Geneva: World Health Organization.

WHO (1965). Molluscicide screening and evaluation. *Bull World Health Organ,* 33(4), 567-581.

WHO (1973). *Shistosomiasis control: report of a WHO expert committee*. (No. 515). Geneva: World Health Organization.

WHO (1980). *Epidemiology and control of schistosomiasis: report of a WHO expert committee*. Geneva: World Health Organization.

WHO (1987). *Progress in assessment of morbidity due to Schistsoma haematobium infection: a review of recent literature*. (WHO/SCHISTO/87.91). Geneva: World Health Organization.

WHO (1988). *Progress in assessment of morbidity due to Schistsoma mansoni infection: a review of recent literature*. (WHO/SCHISTO/88.97). Geneva: World Health Organization.

WHO (1989). *Progress in assessment of morbidity due to Schistsoma intercalatum infection: a review of recent literature*. (WHO/SCHISTO/89.101). Geneva: World Health Organization.

WHO (1991). *Meeting on ultrasonography in schistosomiasis: proposal for a practical guide to the standardized use of ultrasound in the assessment of pathological changes*. (TDR/SCH/ULTRASON/91.3). Geneva: World Health Organization.

WHO (1993). *The control of schistosomiasis: second report of the WHO Expert Committee [meeting held in Geneva from 8-15 November 1991]* (Vol. 830). Geneva: World Health Organization.

WHO (2002). *Prevention and control of schistosomiasis and soil-transmitted helminthiasis* (2003/02/21 ed. Vol. 912). Geneva: World Health Organization.

WHO (2006). *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.

WHO (2011a). Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity *Vitamin and Mineral Nutrition Information System* Retrieved 12/12/2020, from http://www.who.int/vmnis/indicators/haemoglobin.pdf

WHO (2011b). *Monitoring and epidemiological assessment of mass drug administration for eliminating lymphatic filariasis: a manual for national elimination programmes*. Geneva: World Health Organization.

WHO (2011c). *Helminth control in school-age children: a guide for managers of control programmes* (2 ed.). Geneva: World Health Organization.

WHO (2012). *A roadmap for implementation: accelerating work to overcome the global impact of neglected tropical diseases*. Geneva: World Health Organization.

WHO (2013). *Schistosomiasis: progress report 2001-2011, strategic plan 2012-2020*. Geneva: World Health Organization.

WHO (2016). *Validation of elimination of trachoma as a public health problem*. (WHO/HTM/NTD/2016.8). Geneva: World Health Organization Retrieved from https://apps.who.int/iris/handle/10665/208901.

WHO (2017). *Validation of elimination of lymphatic filariasis as a public health problem*. (WHO/HTM/NTD/PCT/2017.01). Geneva: World Health Organization Retrieved from https://apps.who.int/iris/bitstream/handle/10665/254377/9789241511957-eng.pdf.

WHO (2018). Schistosomiasis and soil-transmitted helminthiases: numbers of people treated in 2017. *Wkly Epidemiol Rec,* 93(50), 681-692.

WHO (2020a). Genital manifestations of schistosomiasis Retrieved 12/29/2020, 2020, from https://www.who.int/schistosomiasis/genital_schistosomiasis/en/

WHO (2020b). Ending the neglect to attain the sustainable development goals: a road map for neglected tropical diseases 2021–2030. Geneva: World Health Organization.

WHO Expert Committee on the Control of Schistosomiasis (1985). *The control of schistosomiasis: report of a WHO expert committee [meeting held in Geneva from 8 to 13 November 1984]*. (728). Geneva: World Health Organization Retrieved from https://apps.who.int/iris/handle/10665/39529.

WHO Multicentre Growth Reference Study Group, de Onis M (2006). Assessment of differences in linear growth among populations in the WHO Multicentre Growth Reference Study. *Acta Paediatr,* 95(S450), 56-65.

Wickham H (2017). tidyverse: easily install and load the 'tidyverse' (Version R package version 1.2.1). Retrieved from https://CRAN.R-project.org/package=tidyverse

Wiegand RE, Mwinzi PNM, Montgomery SP, Chan YL, Andiego K, Omedo M, Muchiri G, Ogutu MO, Rawago F, Odiere MR, Karanja DMS, Secor WE (2017). A persistent hotspot of *Schistosoma mansoni* infection in a five-year randomized trial of praziquantel preventative chemotherapy strategies. *J Infect Dis,* 216(11), 1425-1433.

Wilke T, Davis GM, Cui-E C, Xiao-Nung Z, Xiao Peng Z, Yi Z, Spolsky CM (2000). *Oncomelania hupensis* (Gastropoda: Rissooidea) in eastern China: molecular phylogeny, population structure, and ecology. *Acta Trop,* 77(2), 215-227.

Wilkins HA, Goll PH, de C. Marshall TF, Moore PJ (1984). Dynamics of *Schistosoma haematobium* infection in a Gambian community. III. Acquisition and loss of infection. *T Roy Soc Trop Med Hyg,* 78(2), 227-232.

Wilson RA (2009). The saga of schistosome migration and attrition. *Parasitol,* 136(12), 1581-1592.

Wilson RA (2020). Schistosomiasis then and now: what has changed in the last 100 years? *Parasitol,* 147(5), 507-515.

Won KY, Kanyi HM, Mwende FM, Wiegand RE, Goodhew EB, Priest JW, Lee Y-M, Njenga SM, Secor WE, Lammie PJ, Odiere MR (2017). Multiplex serologic assessment of schistosomiasis in western Kenya: antibody responses in preschool aged children as a measure of reduced transmission. *Am J Trop Med Hyg,* 96(6), 1460-1467.

Woodhall DM, Wiegand RE, Wellman M, Matey E, Abudho B, Karanja DMS, Mwinzi PMN, Montgomery SP, Secor WE (2013). Use of geospatial modeling to predict *Schistosoma mansoni* prevalence in Nyanza Province, Kenya. *PLoS ONE,* 8(8), e71635.

World Health Assembly (2012). Elimination of schistosomiasis. In World Health Organization (Ed.), *Sixty-Fifth World Health Assembly* (pp. 36-37). Geneva: World Health Organization.

Wynn TA, Thompson RW, Cheever AW, Mentink-Kane MM (2004). Immunopathogenesis of schistosomiasis. *Immunol Rev,* 201(1), 156-167.

Xu J, Steinman P, Maybe D, Zhou XN, Lv S, Li SZ, Peeling R (2016). Chapter One - Evolution of the National Schistosomiasis Control Programmes in The People's Republic of China. In Zhou X-N, Li S-Z, Utzinger J, Bergquist R (Eds.), *Adv Parasitol* (Vol. 92, pp. 1-38): Academic Press.

Yang G-J, Vounatsou P, Tanner M, Zhou X-N, Utzinger J (2006). Remote sensing for predicting potential habitats of *Oncomelania hupensis* in Hongze, Baima and Gaoyou lakes in Jiangsu province, China. *Geospatial Health,* 1(1), 85-92.

Younes A, El-Sherief H, Gawish F, Mahmoud M (2017). Biological control of snail hosts transmitting schistosomiasis by the water bug, *Sphaerodema urinator*. *Parasitol Res,* 116(4), 1257-1264.

Yu JM, de Vlas SJ, Yuan HC, Gryseels B (1998). Variations in fecal *Schistosoma japonicum* egg counts. *Am J Trop Med Hyg,* 59(3), 370-375.

Zhang Z, Jiang Q (2011). Schistosomiasis elimination. *Lancet Infect Dis,* 11(5), 345.

Zhou L-Y, Deng Y, Steinmann P, Yang K (2013). The effects of health education on schistosomiasis japonica prevalence and relevant knowledge in the People's Republic of China: a systematic review and meta-analysis. *Parasitol Int,* 62(2), 150-156.

Zoni AC, Catalá L, Ault SK (2016). Schistosomiasis prevalence and intensity of infection in Latin America and the Caribbean countries, 1942-2014: a systematic review in the context of a regional elimination goal. *PLoS Negl Trop Dis,* 10(3), e0004493.

Zuidema PJ (1981). The Katayama syndrome; an outbreak in Dutch tourists to the Omo National Park, Ethiopia. *Trop Geogr Med,* 33(1), 30-35.

Zwang J, Olliaro PL (2014). 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,* 8(11), e3286.

12 Brief Curriculum Vitae

Ryan E. Wiegand

1600 Clifton Road NE · Mailstop H24-5 · Atlanta, GA 30329 ·(404) 639-2031 · Fax: (404) 718-4816
RWiegand@cdc.gov · ryan.wiegand@gmail.com · ORCID: 0000-0002-9486-1850
https://scholar.google.com/citations?user=_nFoG7gAAAAJ&hl=en

Education:

2002	M.S., Applied Statistics	Purdue University	West Lafayette, IN
2000	B.A. (Cum Laude), Mathematics	St. Olaf College	Northfield, MN
1999	Study abroad	Budapest Semester of Mathematics	Budapest, Hungary

Biographical:

Citizenship: U.S.A.
Language: English (native), Spanish (intermediate), German (basic)

Permanent Positions:

2022-	**Mathematical Statistician**, Division of Viral Diseases, Centers for Disease Control and Prevention	Atlanta, GA
2011-2022	**Mathematical Statistician**, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention	Atlanta, GA
2007-2011	**Mathematical Statistician**, Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention	Atlanta, GA
2005-2007	**Research Associate**, Department of Biostatistics, Bioinformatics and Epidemiology, Medical University of South Carolina	Charleston, SC
2002-2005	**Biostatistician II**, Department of Psychiatry, Indiana University	Indianapolis, IN

Other Positions:

2021	**Statistician**, Vaccine Task Force, COVID-19 Response, Centers for Disease Control and Prevention	Atlanta, GA
2020-2022	**Statistician**, Epidemiology Task Force, COVID-19 Response, Centers for Disease Control and Prevention	Atlanta, GA
2020	**Analyst**, Heath Systems and Worker Safety Task Force, COVID-19 Response, Centers for Disease Control and Prevention	Atlanta, GA
2020	**Team Lead**, Case Surveillance Task Force, COVID-19 Response, Centers for Disease Control and Prevention	Atlanta, GA
2017-2019	**Academic Editor**, *PLOS ONE*	
2016	**Zika Research Studies Statistician**, Division of Global Health Protection, Centers for Disease Control and Prevention	Atlanta, GA
2015-	**Statistical Advisory Board**, *PLOS ONE*	
2013	**Statistician**, Multi-state Outbreak of Cyclosporiasis, Centers for Disease Control and Prevention	Atlanta, GA
2012-2017	**Lead**, Data Management Activity, Centers for Disease Control and Prevention	Atlanta, GA

Selected publications (of 124):

1. Suthar AB, Wang J, Seffren V, Wiegand RE, Griffing S, Zell E (2022). Public health impact of covid-19 vaccines in the US: observational study. *BMJ,* 377, e069317.
2. McNamara LA, Wiegand RE, Burke RM, Sharma AJ, Sheppard M, Adjemian J, et al. (2022). Estimating the early impact of the US COVID-19 vaccination programme on COVID-19 cases, emergency department visits, hospital admissions, and deaths among adults aged 65 years and older: an ecological analysis of national surveillance data. *Lancet,* 399(10320), 152-160
3. Bajema KL, Wiegand RE, Cuffe K, Patel SV, Iachan R, Lim T, et al. (2021). Estimated SARS-CoV-2 seroprevalence in the US as of September 2020. *JAMA Intern Med*, 181(4), 450-460.
4. Oneko M, Steinhardt LC, Yego R, Wiegand RE, Swanson PA, KC N, et al. (2021). Safety, immunogenicity and efficacy of PfSPZ Vaccine against malaria in infants in western Kenya: a double-blind, randomized, placebo-controlled phase 2 trial. *Nat Med,* 27(9), 1636-1645.
5. Secor WE, Wiegand RE, Montgomery SP, Karanja DMS, Odiere MR (2020). Comparison of school-based and community-wide mass drug administration for schistosomiasis control in an area of western Kenya with high initial *Schistosoma mansoni* infection prevalence: a cluster randomized trial. *Am J Trop Med Hyg,* 102(2), 318-327.
6. Wiegand RE, Mwinzi PNM, Montgomery SP, Chan YL, Andiego K, Omedo M, et al. (2017). A persistent hotspot of *Schistosoma mansoni* infection in a five-year randomized trial of praziquantel preventative chemotherapy strategies. *J Infect Dis,* 216(11), 1425-1433.
7. Harris JR, Wiegand RE (2017). Detecting infection hotspots: Modeling the surveillance challenge for elimination of lymphatic filariasis. *PLOS Negl Trop Dis,* 11(5), e0005610.
8. Steinhardt LC, St Jean Y, Impoinvil D, Mace KE, Wiegand R, Huber CS, et al. (2017). Effectiveness of insecticide-treated bednets in malaria prevention in Haiti: a case-control study. *Lancet Glob Health,* 5(1), e96-e103.
9. Wiegand RE, Rose CE, Karon JM (2016). Comparison of models for analyzing two-group, cross-sectional data with a Gaussian outcome subject to a detection limit. *Stat Meth Med Res,* 25(6), 2733-2749.
10. Samuels AM, Clark EH, Galdos-Cardenas G, Wiegand RE, Ferrufino L, Menacho S, et al. (2013). Epidemiology of and impact of insecticide spraying on Chagas disease in communities in the Bolivian Chaco. *PLOS Negl Trop Dis,* 7(8), e2358.
11. Oster AM, Wiegand RE, Sionean C, Miles IJ, Thomas PE, Melendez-Morales L, et al. (2011). Understanding disparities in HIV infection between black and white MSM in the United States. *AIDS,* 25(8), 1103-1112.
12. Wiegand RE (2010). Performance of using multiple stepwise algorithms for variable selection. *Stat Med,* 29(15), 1647-1659.
13. Nurnberger JI, Wiegand R, Bucholz K, O'Connor S, Meyer ET, Reich T, et al. (2004). A family study of alcohol dependence: coaggregation of multiple disorders in relatives of alcohol-dependent probands. *Arch Gen Psychiat,* 61(12), 1246-1256.

Awards:

Excellence in Public Health Protection, CDC/ATSDR (2021)
Larry J. Anderson Award for Outstanding Public Health Science, CDC National Center for Immunization and Respiratory Diseases (2021)
Excellence in Quantitative Sciences, CDC Center for Global Health (2015, 2017, 2020)
Excellence in Epidemiology (International), CDC/ATSDR (2018)
Excellence in Partnering, CDC Center for Global Health (2016)
Excellence in Emergency Response (Domestic), CDC Center for Global Health (2014)
Statistical Science Award, Applied Category, CDC Statistical Advisory Group (2014)