ORIGINAL ARTICLE

Schistosomiasis — Assessing Progress toward the 2020 and 2025 Global Goals

Arminder K. Deol, Ph.D., Fiona M. Fleming, Ph.D., Beatriz Calvo-Urbano, Ph.D., Martin Walker, Ph.D., Victor Bucumi, M.D., Issah Gnandou, M.D., Edridah M. Tukahebwa, Ph.D., Samuel Jemu, M.Sc., Upendo J. Mwingira, M.D., Abdulhakeem Alkohlani, M.D., Mahamadou Traoré, M.D., Eugene Ruberanziza, M.D., Seydou Touré, M.D., Maria-Gloria Basáñez, Ph.D., Michael D. French, Ph.D., and Joanne P. Webster, Ph.D.

ABSTRACT

BACKGROUND

With the vision of "a world free of schistosomiasis," the World Health Organization (WHO) set ambitious goals of control of this debilitating disease and its elimination as a public health problem by 2020 and 2025, respectively. As these milestones become imminent, and if programs are to succeed, it is important to evaluate the WHO programmatic guidelines empirically.

METHODS

We collated and analyzed multiyear cross-sectional data from nine national schistosomiasis control programs (in eight countries in sub-Saharan Africa and in Yemen). Data were analyzed according to schistosome species (*Schistosoma mansoni* or *S. haematobium*), number of treatment rounds, overall prevalence, and prevalence of heavy-intensity infection. Disease control was defined as a prevalence of heavy-intensity infection of less than 5% aggregated across sentinel sites, and the elimination target was defined as a prevalence of heavy-intensity infection of less than 1% in all sentinel sites. Heavy-intensity infection was defined as at least 400 eggs per gram of feces for *S. mansoni* infection or as more than 50 eggs per 10 ml of urine for *S. haematobium* infection.

RESULTS

All but one country program (Niger) reached the disease-control target by two treatment rounds or less, which is earlier than projected by current WHO guidelines (5 to 10 years). Programs in areas with low endemicity levels at baseline were more likely to reach both the control and elimination targets than were programs in areas with moderate and high endemicity levels at baseline, although the elimination target was reached only for *S. mansoni* infection (in Burkina Faso, Burundi, and Rwanda within three treatment rounds). Intracountry variation was evident in the relationships between overall prevalence and heavy-intensity infection (stratified according to treatment rounds), a finding that highlights the challenges of using one metric to define control or elimination across all epidemiologic settings.

CONCLUSIONS

These data suggest the need to reevaluate progress and treatment strategies in national schistosomiasis control programs more frequently, with local epidemiologic data taken into consideration, in order to determine the treatment effect and appropriate resource allocations and move closer to achieving the global goals. (Funded by the Children's Investment Fund Foundation and others.)

From the Schistosomiasis Control Initiative (A.K.D., F.M.F., B.C.-U.), the London Centre for Neglected Tropical Disease Research (A.K.D., F.M.F., M.W., M.-G.B., J.P.W.), the Department of Infectious Disease Epidemiology, School of Public Health, Faculty of Medicine (St. Mary's Campus), Imperial College London (A.K.D., F.M.F., M.W., M.-G.B., J.P.W.), and the Royal Veterinary College, the Department of Pathobiology and Population Sciences, University of London (M.W., J.P.W.) — all in London; the Ministry of Health Burundi, Bujumbura (V.B.); the Ministry of Health Niger, Niamey (I.G.); the Ministry of Health Uganda, Vector Control Division, Kampala (E.M.T.); the Ministry of Health Malawi, Lilongwe (S.J.); the Ministry of Health Tanzania and the National Institute for Medical Research, Dar es Salaam (U.J.M.); the Ministry of Health Yemen, Sana'a (A.A.); the Ministry of Public Health and Hygiene Mali, Bamako (M.T.); the Neglected Tropical Diseases Unit, Malaria and Other Parasitic Diseases Division, Institute of HIV–AIDS, Disease Prevention, and Control, Rwanda Biomedical Center, Ministry of Health, Kigali (E.R.); the National Schistosomiasis Program, Ministry of Health, Ouagadougou, Burkina Faso (S.T.); and RTI International, Washington, DC (M.D.F.). Address reprint requests to Dr. Deol at the Department of Infectious Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, Keppel St., Bloomsbury, London WC1E 7HT, United Kingdom, or at arminder.deol@lshtm.ac.uk.

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Schistosomiasis is a parasitic neglected tropical disease that is estimated to currently infect more than 140 million persons.[1,2] Ninety percent of the disease burden is in sub-Saharan Africa, where the main species that cause schistosomiasis in humans are *Schistosoma mansoni* (intestinal schistosomiasis) and *S. haematobium* (urogenital schistosomiasis), which are transmitted through feces and urine, respectively.[3,4] Symptoms of schistosomiasis include anemia, stunting, fever, genital lesions, and irreversible organ damage.[5-7] Preventive chemotherapy with praziquantel is the strategy recommended by the World Health Organization (WHO) for the control of schistosomiasis; this therapy is distributed primarily to school-age children 5 to 15 years of age, who have the highest infection burden and who can be reached efficiently through schools.[8] The preventive chemotherapy strategy is determined according to the prevalence of the infection (estimated by initial parasitologic assessment) at the implementation unit level (usually the district). A prevalence of infection below 10% entails the administration of preventive chemotherapy every 3 years; 10 to 49%, treatment every 2 years; and 50% or greater, treatment annually.[9]

The initial success of disease control in some countries[10] has led to the more ambitious WHO vision of "a world free of schistosomiasis."[11] The WHO thus set goals for controlling schistosomiasis morbidity (referred to here as disease control; defined as a prevalence of heavy-intensity infection of <5% aggregated across sentinel sites) by 2020 and achieving the elimination of schistosomiasis as a public health problem (referred to here as elimination; defined as a prevalence of heavy-intensity infection of <1% in all sentinel sites) by 2025 in all countries where schistosomiasis is endemic. The complete interruption of transmission is also a target in selected regions by 2025 (Fig. 1).[11-13] The WHO strategic plan provides guidance on how programs can progress from control of schistosomiasis to elimination and interruption of transmission.[11]

One may predict that the timelines for transitioning between goals will not be uniform across all countries, owing to their epidemiologic and endemicity heterogeneities (Fig. 1). Hence, there exists a need to analyze quantita-

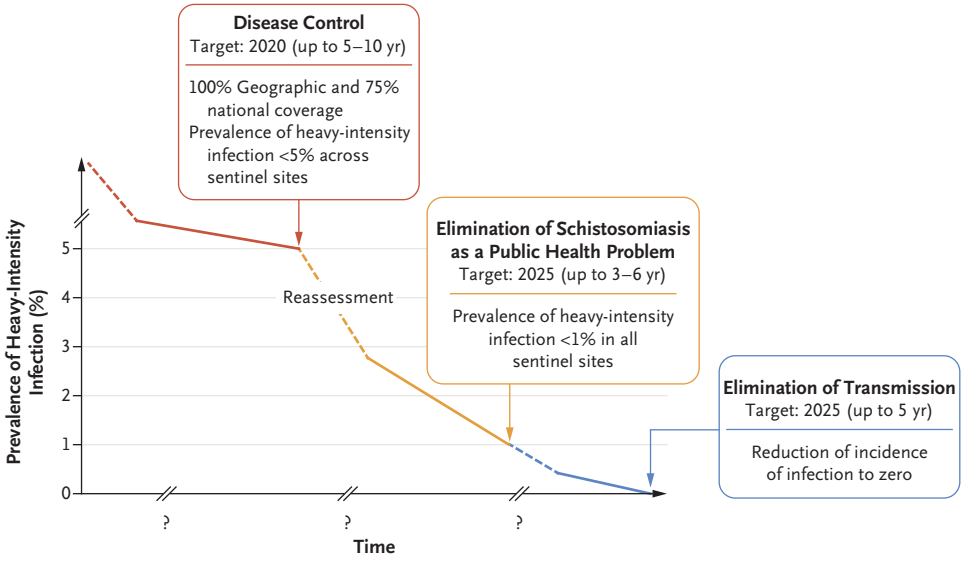

Figure 1. Schematic Representation of Program Progression toward Elimination of Schistosomiasis and Proposed Timelines from the World Health Organization (WHO).

Recommended WHO strategies include the control of the disease by means of preventive chemotherapy, with the use of complementary interventions where possible, and the elimination of the disease as a public health problem by means of adjusted preventive chemotherapy, with the use of complementary interventions being strongly recommended. The elimination of transmission by means of intensified preventive chemotherapy in residual areas of transmission and complementary interventions is considered to be essential.[11]

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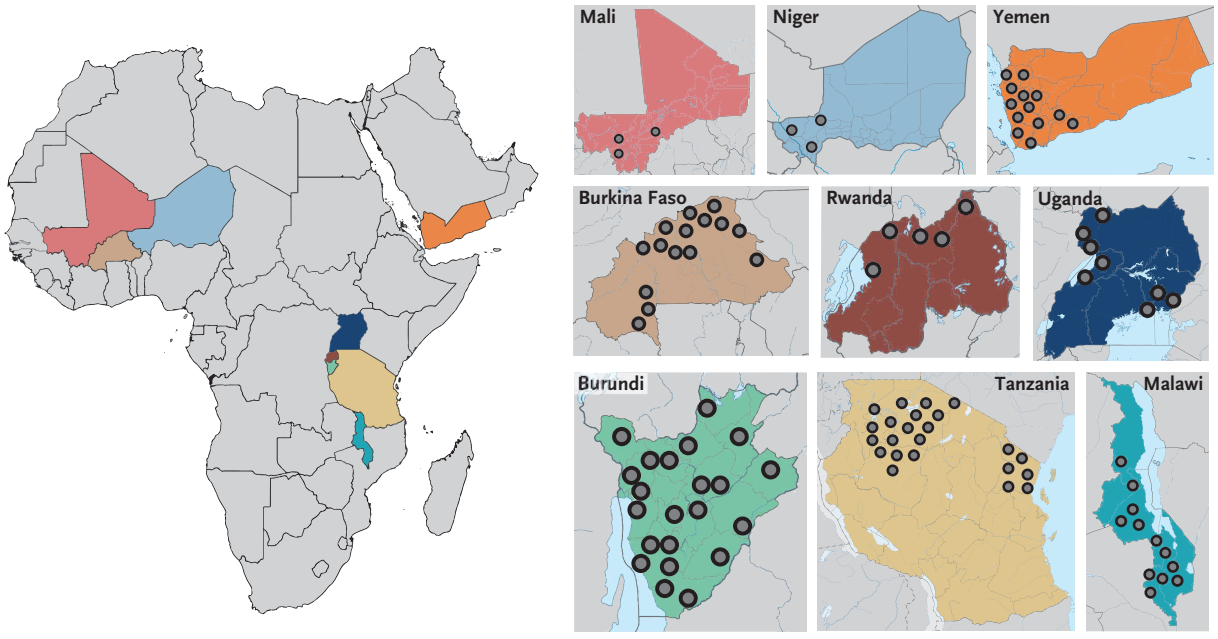

Figure 2. Countries from Which Data Were Analyzed.

The map on the left shows the locations of countries within Africa as well as the location of Yemen. Dots on the maps on the right indicate the areas from which the selected sentinel sites were chosen according to the inclusion criteria. From left to right, starting in the top left square, the total numbers of sentinel sites were as follows: 21 in Mali, 8 in Niger, 36 in Yemen, 16 in Burkina Faso, 6 in Rwanda, 39 in Uganda, 31 in Burundi, 21 in Tanzania, and 22 in Malawi. Burundi and Mali were split into two segments in this study; in Burundi, surveys began in different years in the pilot program and national program, and in Mali, different treatment strategies were implemented in the Segou region and the Bamako and Koulikoro regions.

tive data, captured by means of program monitoring, in order to validate and update these guidelines. Recent theoretical modeling projects that the 2020 goal of disease control inherent in the current treatment guideline is probably obtainable in areas in which prevalence is low or moderate but that the goal will be missed in areas in which prevalence is high.[14]

We aimed to elucidate empirically whether countries have already reached the 2020 and 2025 goals, to investigate how many treatment rounds were necessary to reach these targets (if met), and to assess whether a one-size-fits-all approach would be appropriate for guiding schistosomiasis treatment strategies to reach the WHO-defined threshold criteria for disease control and elimination. Nationally representative cross-sectional epidemiologic data regarding both *S. mansoni* and *S. haematobium* were made available by the national ministries of health in nine countries where schistosomiasis is endemic.

METHODS

DATA COLLATION

Parasitologic data (parasite egg counts from stool and urine samples) were collated from the Schistosomiasis Control Initiative–supported multiyear, cross-sectional sentinel-site surveys in nine countries, which assessed the reduction in prevalence and intensity of schistosomiasis among school-age children after treatment. The inclusion criteria were the following: countries in which ministries of health were supported by the Schistosomiasis Control Initiative; status of having more than 2 years of sentinel-site survey data after baseline; and cross-sectional data for school-age children 5 to 15 years of age. The countries that were included and information about the programs are shown in Figure 2 and in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

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Surveys took place approximately 6 weeks before the next treatment round (i.e., just under 1 year after the last treatment round for annual preventive chemotherapy programs and just under 2 years after the last treatment round for programs with preventive chemotherapy administered every 2 years). The first year of treatment (baseline treatment) varied — ranging from 2003 to 2012 — among countries where treatment was provided depending on schistosomiasis prevalence levels.

The data used in this study were collected as part of the monitoring and evaluation activities of the schistosomiasis control programs taking place in these countries where the disease is endemic. Ethics approval was granted by the St. Mary's Hospital Local Ethics Research Committee, research and development office (part of the Imperial College Research Ethics Committee), as a constituent part of the ongoing Schistosomiasis Control Initiative activities, and by the ministry of health ethical review boards in these countries.

Figure 3 (facing page). Changes in Prevalence of *Schistosoma mansoni* Infection over Time among School-Age Children.

Shown are the temporal changes in the prevalence of *S. mansoni* infection among school-age children according to sentinel site for each country (light blue lines) and aggregated (mean value) across sentinel sites from each country (colored lines); the number of sentinel sites is shown for each country or its programs. Dashed lines show the 5% prevalence cutoff for heavy-intensity infection, indicating disease control; dotted lines show the 1% prevalence cutoff for heavy-intensity infection, indicating the elimination of schistosomiasis as a public health problem. The aggregated mean line must be under the 5% cutoff to show disease control; all the lines (each representing a sentinel site) must be under the 1% cutoff to indicate elimination. Columns represent the overall prevalence, the prevalence of moderate-intensity plus heavy-intensity infection, and the prevalence of heavy-intensity infection. The I bars indicate 95% confidence intervals that were calculated by accounting for clustering of the data according to sentinel site. The y axes are not proportional; the axis area of lower prevalence is expanded to show detail. In Burundi, data were available from 12 sentinel sites for the pilot program and from 19 sentinel sites for the national program; in Mali, data were available from 10 sentinel-site schools in the Segou region and from 11 sentinel-site schools in the Bamako and Kouli-koro regions (combined).

STATISTICAL ANALYSIS

Sample-size calculations for each country program followed standardized procedures used at the Schistosomiasis Control Initiative that have been described in detail elsewhere (references shown in Table S1). These procedures provided information about the number of sentinel sites (schools) and children to be sampled within each site, and the analysis was powered to detect a preset difference in prevalence at a given administrative level for the country, with accounting for clustering (a design effect) at the sentinel-site level. Survey methods were standardized across countries.

Standard Kato–Katz and urine filtration methods were used to detect *S. mansoni* and *S. haematobium* infection, respectively. The infection intensity category with a 95% confidence interval was calculated according to treatment round, schistosome species, and country program.[9] For *S. mansoni* infection, the infection intensity — the proportion of persons with a given number of schistosome eggs per gram of feces — was defined as follows: light intensity, 1 to 99 eggs per gram; moderate intensity, 100 to 399 eggs per gram; and heavy intensity, at least 400 eggs per gram. For *S. haematobium* infection, the infection intensity — the proportion of persons with a given number of eggs per 10 ml of urine — was defined as follows: light intensity, 1 to 50 eggs per 10 ml; and heavy intensity, more than 50 eggs per 10 ml.

The mean prevalence and 95% confidence intervals were calculated to account for the clustering of data at the sentinel-site level, with the use of the R survey package.[15] The point (mean) prevalence estimates were used for the comparison with WHO guidelines, since the guidelines do not require calculations of 95% confidence intervals. We assessed whether the mean prevalence of heavy-intensity infection across sentinel sites decreased to less than 5%, which would be indicative of disease control, and decreased to less than 1% in all sentinel sites, which would be indicative of elimination.[11] The overall prevalence and the prevalence of moderate-intensity plus heavy-intensity infection (*S. mansoni* only) were also estimated and compared with trends of heavy-intensity infection prevalence. Although the WHO guidelines use the prevalence of heavy-intensity infection as an indirect measure of morbidity (assuming that morbidity is proportional to infection intensity), we included the combined measure

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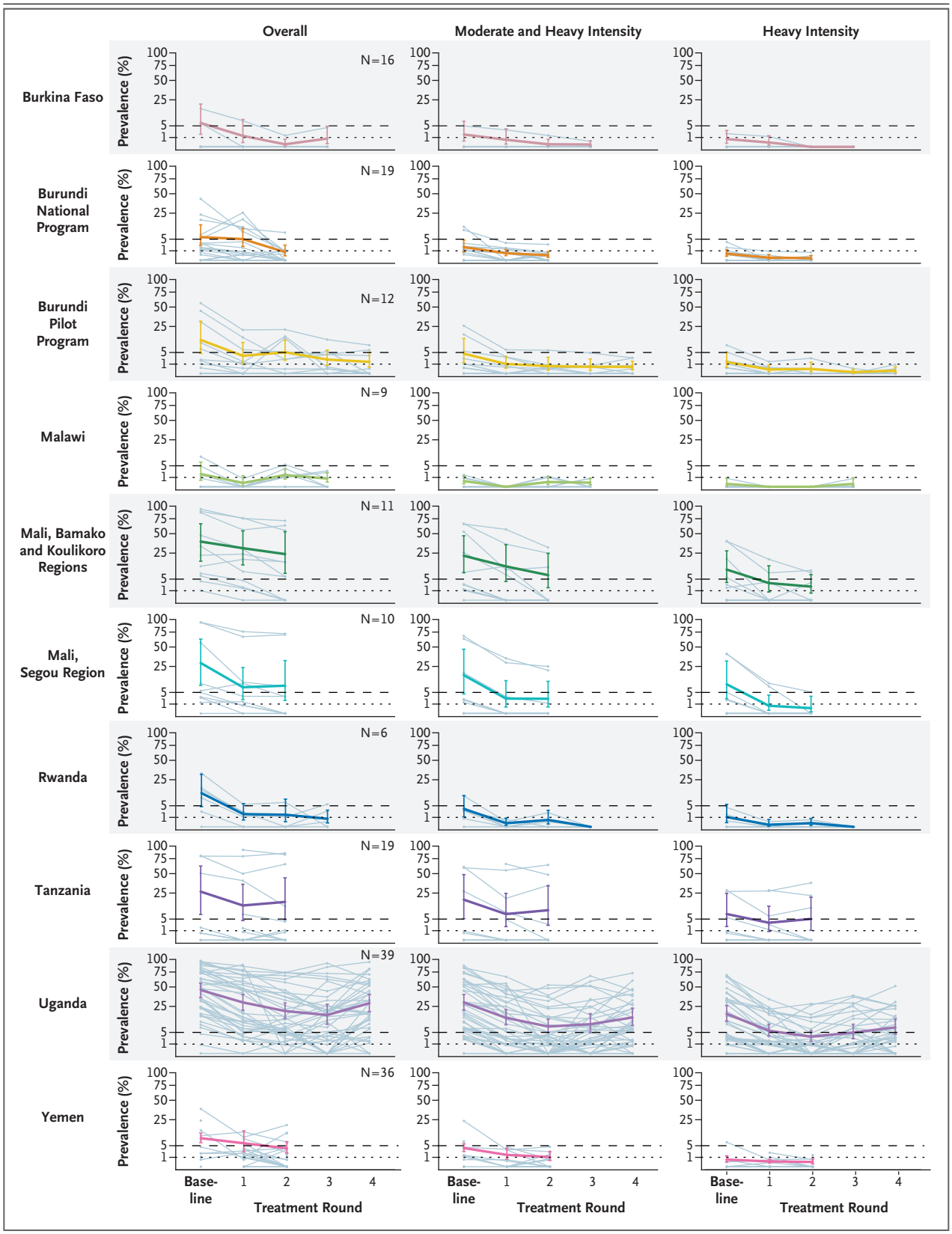

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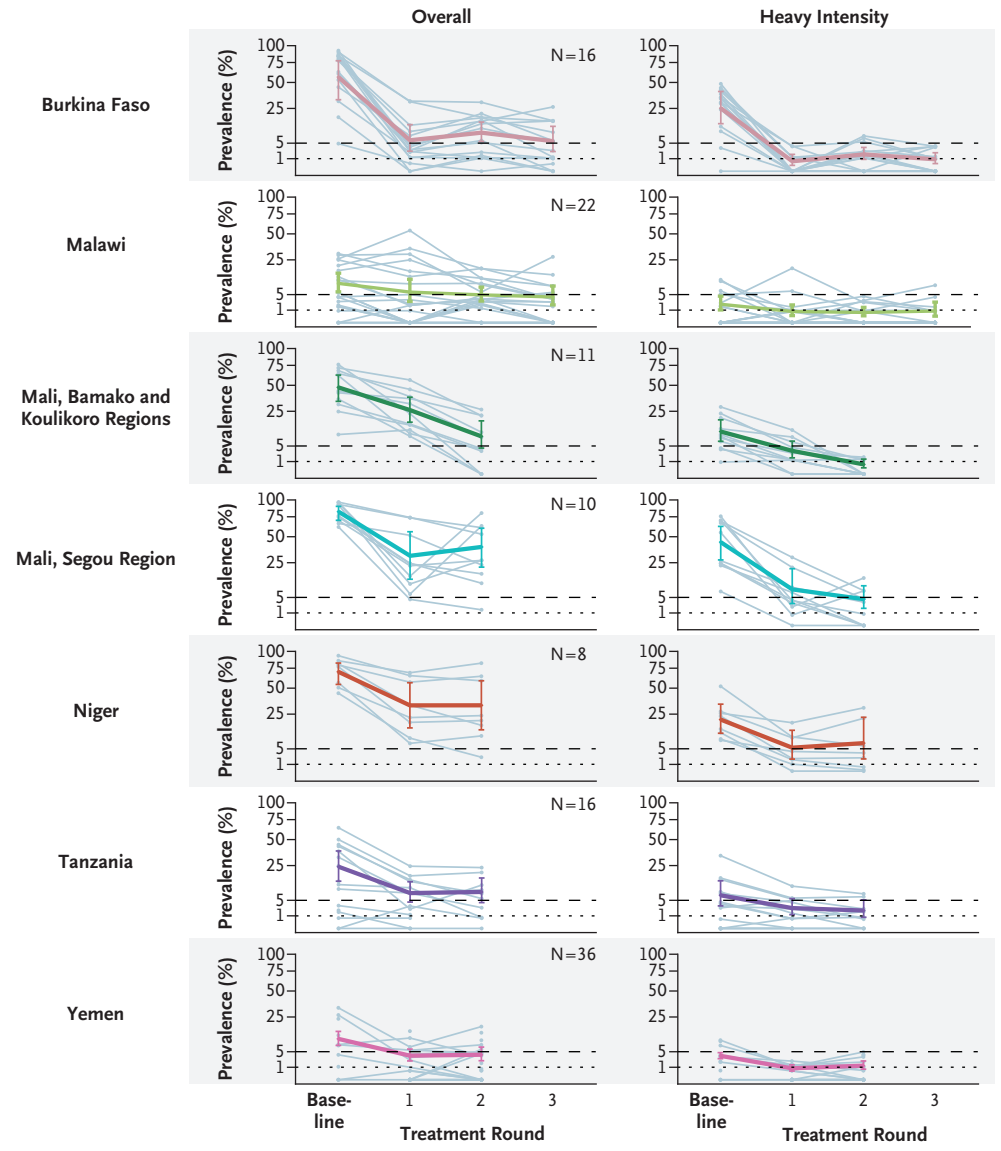

Figure 4. Changes in Prevalence of *S. haematobium* Infection over Time among School-Age Children.

Shown are the temporal changes in the prevalence of *S. haematobium* infection among school-age children according to sentinel site for each country (light blue lines) and aggregated (mean value) across the sentinel sites from each country (colored lines); the number of sentinel sites is shown for each country or its programs. Dashed lines show the 5% prevalence cutoff for heavy-intensity infection, indicating disease control; dotted lines show the 1% prevalence cutoff for heavy-intensity infection, indicating the elimination of schistosomiasis as a public health problem. Columns represent the overall prevalence and the prevalence of heavy-intensity infection. The I bars indicate 95% confidence intervals that were calculated by accounting for clustering of the data according to sentinel site. The y axes are not proportional; the axis area of lower prevalence is expanded to show detail.

of the prevalence of moderate-intensity plus heavy-intensity infection because of uncertainty in the appropriateness of egg-count thresholds for intensity and because some degree of morbidity is believed to be caused by lighter infections.[16]

RESULTS

BASELINE RESULTS

Endemicity at baseline varied according to schistosome species and country. The prevalence of

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Table 1. Rounds of Treatment to Reduce Prevalence of *Schistosoma mansoni* and *S. haematobium* Infection to Reach World Health Organization (WHO) Goals.*

Country and Program, According to Species	Baseline Endemicity Level	Baseline Prevalence (95% CI)		Frequency of Treatment	Treatment Rounds to Reach Disease-Control Goal		Treatment Rounds to Reach Elimination Goal	
		Mean	Heavy-Intensity Infection		After Baseline	For Moderate- plus Heavy-Intensity Prevalence	After Baseline	For Moderate- plus Heavy-Intensity Prevalence
		percent			*number of rounds administered*			
S. mansoni								
Burkina Faso	Low	6.5 (1.8–20.7)	0.7 (0.2–3.0)	Every 2 yr	0	0	2	3
Burundi national program	Low	6.0 (2.4–14.2)	0.5 (0.2–1.3)	Annual	0	0	2	NR
Burundi pilot program	Low	12.7 (4.6–30.9)	1.5 (0.4–4.9)	Annual	0	0	3	NR
Malawi	Low	1.9 (0.5–6.9)	0.1 (0.0–0.9)	Annual	0	0	0	1
Rwanda	Low	12.9 (4.6–31.2)	1.1 (0.2–5.7)	Annual	0	0	1	1
Yemen	Low	9.2 (6.4–13.0)	0.6 (0.3–1.2)	Every 2 yr	0	0	NR	NR
Mali, Segou region	Moderate	28.8 (8.9–62.6)	9.6 (2.5–27.5)	Annual	1	1	NR	NR
Mali, Bamako and Koulikoro regions	Moderate	38.8 (17.2–66.0)	10.6 (3.6–27.5)	Mixed	1	NR	NR	NR
Tanzania	Moderate	26.6 (7.4–62.1)	7.7 (2.1–24.7)	Annual	1	NR	NR	NR
Uganda	Moderate	45.4 (35.6–55.7)	17.7 (11.7–25.8)	Annual	2	NR	NR	NR
S. haematobium								
Malawi	Low	9.8 (6.0–15.5)	2.2 (1.0–4.5)	Annual	0	NA	NR	NA
Tanzania	Moderate	24.1 (14.1–38.0)	6.9 (3.2–14.4)	Annual	1	NA	NR	NA
Yemen	Moderate	10.6 (6.5–16.8)	3.6 (2.1–6.3)	Every 2 yr	0	NA	NR	NA
Burkina Faso	High	56.2 (32.4–77.4)	25.2 (14.3–40.3)	Every 2 yr	1	NA	NR	NA
Niger	High	70.0 (54.2–82.2)	20.8 (12.1–33.5)	Annual	NR	NA	NR	NA
Mali, Segou region	High	82.1 (70.1–90.0)	44.0 (27.3–62.3)	Annual	2	NA	NR	NA
Mali, Bamako and Koulikoro regions	High	47.6 (33.5–62.1)	11.5 (6.8–18.6)	Mixed	1	NA	NR	NA

* Shown are the numbers of rounds of treatment that were required to reduce the prevalence of *S. mansoni* and *S. haematobium* infections to reach WHO goals of disease control (<5% prevalence of heavy-intensity infection, aggregated across all sentinel sites) and the elimination of schistosomiasis as a public health problem (<1% prevalence of heavy-intensity infection in all sentinel sites). The baseline endemicity levels refer to the WHO prevalence category at the country level, and 95% confidence intervals were calculated by accounting for clustering of the data at the level of the sentinel sites. Burundi and Mali were split into two segments in this study; in Burundi, surveys began in different years in the pilot program (data from 12 sentinel sites) and national program (data from 19 sentinel sites), and in Mali, different treatment strategies were implemented in the Segou region (10 sentinel-site schools) and the Bamako and Koulikoro regions (combined; 11 sentinel-site schools). NA denotes not applicable, and NR not reached (during the time period studied).

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S. mansoni ranged from 1.9% (95% confidence interval [CI], 0.5 to 6.9) in Malawi to 45.4% (95% CI, 35.6 to 55.7) in Uganda. The prevalence of *S. haematobium* ranged from 9.8% (95% CI, 6.0 to 15.5) in Malawi to 82.1% (95% CI, 70.1 to 90.0) in the Segou region of Mali.[9] Despite this heterogeneity, the infection intensity in all countries decreased after the first round of treatment to below or within 0.8 percentage points of the 5% prevalence for the heavy-intensity threshold for control of *S. mansoni* infection and within 3.3 percentage points for *S. haematobium* infection (Figs. 3 and 4 and Figs. S1 and S2).

Treatment reduced the prevalence of heavy-intensity infection by both species to below 5% in all countries except Niger (5.4%; 95% CI, 2.0 to 13.8), which only marginally missed the metric for *S. haematobium* infection in the first treatment round (Figs. 3 and 4 and Table 1). The more ambitious target of elimination of schistosomiasis as a public health problem was achieved only for *S. mansoni* infection and only in half the country programs. Moreover, Malawi had already reached the elimination target for *S. mansoni* infection at baseline.

S. MANSONI INFECTION

All 10 country programs reached the disease-control target (prevalence of heavy-intensity infection of <5%) after two rounds of treatment or fewer (Fig. 3 and Table 1 and Fig. S1). This included Uganda, which had a relatively high prevalence at baseline. However, a subsequent gradual increase in the prevalence of heavy-intensity infection to just over the 5% threshold was observed in Uganda after the third and fourth treatment rounds. Burkina Faso, Burundi (pilot and national programs), Malawi, and Rwanda reached the elimination target after three rounds of treatment or fewer (but these sites had a baseline mean prevalence of heavy-infection intensity that was already below the 5% disease-control threshold).

According to the more conservative criteria of an overall prevalence of moderate-intensity plus heavy-intensity infection of less than 5% to represent disease control and of less than 1% to represent elimination (*S. mansoni* infection only), 6 country programs were already below the threshold of less than 5% prevalence at baseline, and 1 country program (in the Segou region of Mali) met this target after one round of treatment (Fig. 3 and Table 1). Three country programs (Burkina Faso, Malawi, and Rwanda) achieved elimination, and according to the currently available data, 3 of the 10 country programs did not reach any target (disease control or elimination) in the relatively short treatment period that included the data currently available.

S. HAEMATOBIUM INFECTION

All the countries except Malawi and Yemen had a baseline prevalence of heavy-intensity *S. haematobium* infection of more than 5%. By the second treatment round, all the countries except Niger were below this threshold, thus meeting the disease-control criteria (Fig. 4 and Table 1 and Fig. S2). The prevalence of heavy-intensity infection in Niger decreased from 20.8% (95% CI, 12.1 to 33.5) at baseline to 5.4% (95% CI. 2.0 to 13.8) after a single treatment round, just missing the disease-control target.

Although three country programs reached a prevalence of less than 1% for heavy-intensity infection aggregated across sentinel sites (Fig. 4), no countries reached this threshold in every sentinel site with regard to *S. haematobium* infection. Thus, the elimination goal was not met.

DISCUSSION

The WHO provides guidance on the expected number of years of treatment to reach schistosomiasis control and the elimination of schistosomiasis as a public health problem (5 to 10 years for control, plus an additional 3 to 6 years for elimination). These data show that these thresholds are often reached sooner, whether treatment occurs annually or every 2 years. With the exception of *S. haematobium* infection in Niger, all the programs reached the disease-control target in two or fewer treatment rounds (i.e., between 1 and 2 years, depending on treatment frequency). However, six country programs started with a prevalence of heavy-intensity infection of less than 5% for *S. mansoni* infection, which indicated that they were already within the disease-control target at baseline. With regard to *S. mansoni* infection, the goal of elimination of schistosomiasis as a public health problem was reached by five programs with the use of three or fewer treatment rounds. This prompts the question as to what strategy to adopt in cases in which the baseline prevalence of heavy-intensity infection already meets the threshold target. The

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areas where *S. haematobium* was endemic had higher overall infection levels at baseline than *S. mansoni* areas, and none reached the elimination goals within the time frame of this study. Countries where the prevalence is endemically low, which also had a lower prevalence of heavy-intensity infection at baseline (≤1.5% for *S. mansoni* infection), reached the elimination target sooner than was proposed by the guidelines. Our results, which are based on analysis of nationally representative data sets from multiple countries, complement the theoretical modeling that projects that achievement of disease control is possible in areas with low or moderate prevalence and that elimination is possible in areas with low prevalence.[14] We believe that this combination of programmatic data and mathematical models could inform programmatic goals and targets.

The case of Uganda, however, shows that goals may be reached but are reversible. Reasons behind this rebound may reflect factors related in part to the influx of refugees, reduced adherence to treatment, or changes in drug efficacy.[17] Such rebounds are nevertheless particularly relevant wherever program stability is impeded, owing to, for example, civil unrest (as in Burundi) or war (as in Yemen). We also highlight variation among sentinel sites within each country (Figs. 3 and 4); this factor requires consideration when the country-level disease-control targets proposed by the WHO are reviewed. In addition, the effectiveness of program implementation may vary over time. Thus, it is important to define time periods over which control and elimination targets should be sustained in order for success to be declared, and it is also important to be vigilant to recrudescence wherever interruption of transmission has not been achieved.

As expected, we observed a strong positive association between overall infection prevalence and either the prevalence of heavy-intensity infection or the prevalence of moderate-intensity plus heavy-intensity infection (Fig. S3). There was substantial variation of data points among countries and treatment rounds, which was probably caused by the heterogeneity of underlying adult parasite loads (which was perhaps due to variation in exposure among human hosts) such that the intensity of infection and subsequent disease-related sequelae vary substantially among areas with a similar prevalence of infection. The magnitude of the change in the prevalence of infection after treatment varied substantially among country programs. This finding emphasizes the need for research on appropriate morbidity indicators.

Heavy-intensity infections are not the only type of infections that lead to schistosomiasis-related complications[16]; therefore, moderate-intensity plus heavy-intensity infections were combined to form an additional metric of morbidity. In considering the aims of disease control and elimination, since control thresholds may be reached relatively quickly, it would be worth considering this metric in order to adequately accommodate the larger population group that may have schistosomiasis-related complications.

An important limitation of this study is the absence of available data on specific treatment coverage, which can vary substantially among national-scale preventive chemotherapy programs (see the Supplementary Appendix). Other information, such as migration patterns and school enrollment and attendance rates, may also influence the effectiveness of preventive chemotherapy programs and explain variation among study areas. Detailed information on these factors has not been routinely collected. This situation is common in programs regarding neglected tropical diseases, and we recommend that such supplementary operational data collection be integrated into all routine monitoring and evaluation data-collection protocols.

Furthermore, our data serve to highlight several additional key issues that could be clarified in future WHO guidelines. For instance, more than half the programs in our study involved sentinel sites with mixed *S. mansoni* and *S. haematobium* infections. Although we, following the standard WHO guidelines and monitoring and evaluation guidelines, analyzed intestinal and urogenital schistosomiasis independently, it appears to be intuitive that some areas may have had higher levels of infection prevalence when both species were combined or when underlying interactions occurred, which thereby influenced their threshold targets.[18] Similarly, adults and preschool-age children are, in general, absent from routine monitoring and evaluation, so data from school-age children alone are used as a proxy for the situation in the wider community. It appears to be unrealistic to determine whether the targets of disease control, elimination of

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schistosomiasis as a public health problem, and in particular interruption of transmission have been met without the consideration of this unmonitored reservoir. This issue becomes even more apparent when one considers the concurrent role of potential zoonotic reservoirs of schistosomiasis within regions where the disease is endemic, particularly in those areas that are considered to have persistent hot spots.[10]

Finally, what has not yet been adequately addressed is whether there will still be true disease in the community even after the targets have been reached, since schistosomiasis-related complications (e.g., genital schistosomiasis and hepatosplenomegaly) can continue many years after the infection has ceased. True disease control and elimination of the disease as a public health problem require the redefining of disease (morbidity) control (not to be completely dependent on egg output), improved diagnostic tools, and the incorporation of new strategies to address long-term complications.

In countries where the prevalence of heavy-intensity infection is less than 5% at baseline, it is unclear whether they should aim immediately for elimination or continue to treat according to guidelines for 5 to 10 years. The key messages of our study are that countries often achieve disease control after very few treatment rounds and that the universal timeline currently recommended is not appropriate for all programs and will be affected by baseline endemicity, schistosome species, and the context-specific relationship between infection and morbidity, among other extraneous factors.

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