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Chapter 13

Mass Deworming Programs in Middle Childhood and Adolescence

Donald A. P. Bundy, Laura J. Appleby, Mark Bradley, Kevin Croke, T. Deirdre Hollingsworth, Rachel Pullan, Hugo C. Turner, and Nilanthi de Silva



INTRODUCTION

The current debate on deworming presents an interesting public health paradox. Self-treatment for intestinal worm infection is among the most common self-administered public health interventions, and the delivery of donated drugs through mass drug administration (MDA) programs for soil-transmitted helminths (STHs) exceeds 1 billion doses annually. The clinical literature, especially the older historical work, shows significant impacts of intense STH infection on health; a burgeoning economics literature shows the long-run consequences for development (see, for example, chapter 29 in this volume, Ahuja and others 2017; Fitzpatrick and others 2017). Yet, the literature on clinical trials shows conflicting results, and the resulting controversy has been characterized as the *worm wars*.

The two previous editions of *Disease Control Priorities* contain chapters on STH and deworming programs (Hotez and others 2006; Warren and others 1993). Much of the biological and clinical understanding reflected in those chapters remains largely unchanged. This chapter presents current estimates of the numbers infected and the disease burden attributable to STH infections to illuminate current program efforts, advances in the understanding of epidemiology and program design, and the controversy regarding the measurement of impact.

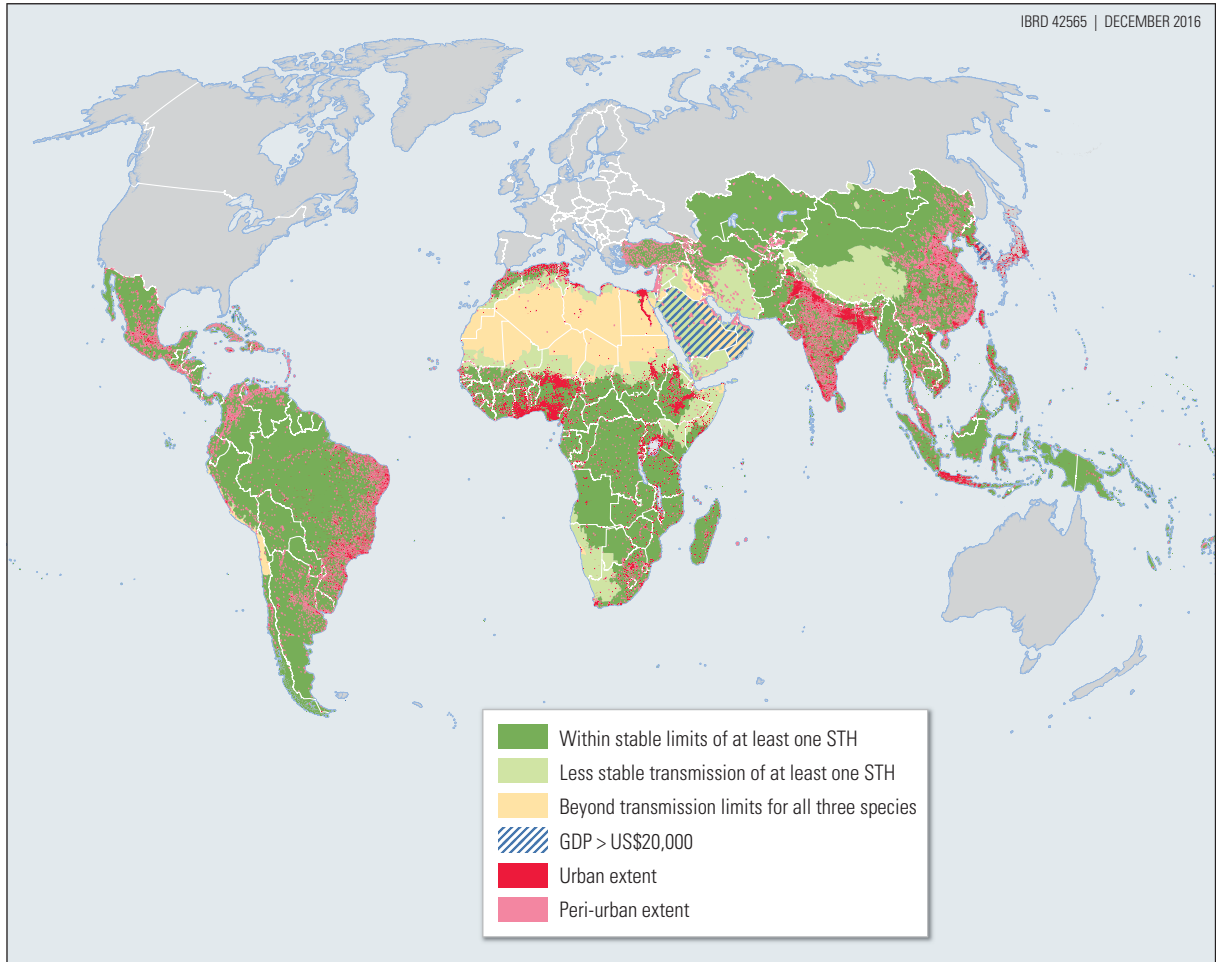
Definitions of age groupings and age-specific terminology used in this volume can be found in chapter 1 (Bundy, de Silva, and others 2017).

ESTIMATED NUMBER OF INFECTIONS AND DISEASE BURDEN

Three types of STH commonly infect humans: roundworm (*Ascaris lumbricoides*), hookworm (comprising two species, *Ancylostoma duodenale* and *Necator americanus*), and whipworm (*Trichuris trichiura*). Recent use of geographic information systems and interpolated climatic data have identified the distributional limits of STHs on the basis of temperature and rainfall patterns as well as socioeconomic factors (Pullan and Brooker 2012). Globally, in 2010 an estimated 5.3 billion people, including 1 billion school-age children, lived in areas stable for transmission of at least one STH species; 69 percent of these individuals lived in Asia.

Map 13.1 is based on clear limiting relationships observed between infection and climatic factors for each species. For example, experimental and observational findings suggest that transmission is implausible in extremely hot, arid, or cold environments, particularly in Africa and the Middle East (Brooker, Clements, and

Map 13.1 Distribution of Soil-Transmitted Helminth Infection Risk, Applying Climatic Exclusion Limits



Source: Adapted from Pullan and Brooker 2012.

Note: Analysis includes only regions considered endemic for STHs. GDP = gross domestic product; STH = soil-transmitted helminth.

Bundy 2006; Brooker and Michael 2000; Pullan and Brooker 2012). Relationships are less clear in Asia, especially for roundworm, for which positive survey data exist even in extremely hot and arid regions of India and Pakistan, perhaps because resistant transmission stages allow for seasonal transmission in environments otherwise hostile for much of the year.

Several attempts have been made to estimate worldwide prevalence of STHs since the first estimates assembled by Norman Stoll in the seminal paper titled “This Wormy World” (Stoll 1947); this section provides revised estimates of the burden of disease for STHs in 2013. The number of persons infected with STHs is generated by applying the revised estimates from 2010 (Pullan and others 2014) to age-stratified population estimates for 2013. These estimates build on a modeling framework that exploits relationships

between infection prevalence, intensity, and potential morbidity originally proposed by Chan and Bundy (1999) for use in the first Global Burden of Disease study (Chan 1997). In brief, the age-stratified mean prevalence was estimated for all endemic regions at subnational scales. The approach used to map the mean prevalence of infection within the boundaries of transmission differed by region, determined by the progress in control, environmental associations, and data availability considerations. For Asia, Latin America and the Caribbean, the Middle East and North Africa, and Oceania, empirical estimates were generated directly from the data. For countries within Sub-Saharan Africa—where detailed data were lacking for several countries but where relationships between infection patterns and environmental factors were clearer—a geostatistical space-time modeling

framework was used to predict the prevalence of each infection across the continent, following the approach of Hay and others (2009).

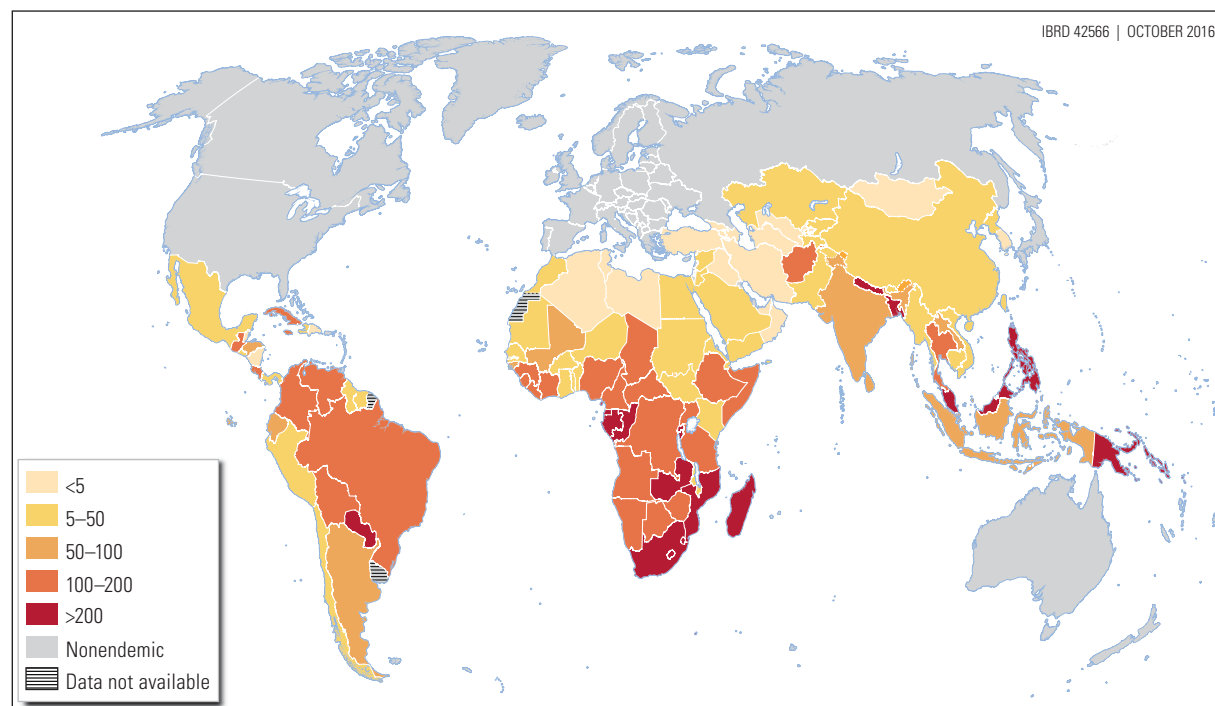
For STHs, prevalence alone does not provide a useful measure of potential morbidity because only a small number of infections will be associated with ill health. Instead, morbidity is related to the intensity of infection, with the most intense infections occurring in only a minority of infected individuals (Bundy and Medley 1992). As prevalence increases, the prevalence of high-intensity infections increases at a higher rate, such that high-prevalence communities experience disproportionate amounts of morbidity (Chan and others 1994). Heterogeneity between communities within subnational areas was therefore approximated using modeled distributions, and the number of persons with infection intensities greater than age-dependent thresholds was estimated indirectly for each species. The frequency distributions of worms, and thus the numbers exceeding these thresholds, were estimated using negative binomial distributions that assumed general species-specific aggregation parameters based on data from Brazil, Kenya, and Uganda (Pullan and others 2014). The Institute for Health Metrics and Evaluation then used these estimates to

estimate disability-adjusted life years (DALYs) for 2013 (Murray and others 2015).

In 2013, an estimated 0.4 billion children under age 15 years worldwide were infected with at least one species of intestinal nematode, resulting in 1.46 million DALYs. Although the greatest number of DALYs occur in Sub-Saharan Africa and Latin America (map 13.2), a large at-risk population means that the vast majority of total infections occur in Asia, where at least one-fourth of preschool and school-age children are host to at least one STH species (table 13.1). The most important STH infection globally for children is roundworm, reflecting the age distribution of infection. Roundworm is of particular concern for preschool-age children in Sub-Saharan Africa, resulting in 143 DALYs per 100,000 population (table 13.2)—mostly attributable to wasting resulting from high-intensity infections. These figures are substantially lower than previous estimates (de Silva and others 2003), attributable in part to several methodological improvements:

- Limitation of populations at risk to areas suitable for transmission
- Increased availability of contributing survey data
- Generation of estimates at higher spatial resolutions.

Map 13.2 Distribution of DALYs for Soil-Transmitted Helminth Infections, per 100,000 Population



Sources: IHME (Institute for Health Metrics and Evaluation). 2014. "Global Burden of Disease Study 2013: Age-Specific All-Cause and Cause-Specific Mortality 1990–2013." IHME, Seattle, Washington.

Note: DALY = disability-adjusted life year. Soil-transmitted helminths include hookworm, roundworm, and whipworm.

Table 13.1 Total Population, Number of Infected Persons, and Overall Prevalence, 2015

Indicator	Total population (millions)	Number of Persons Infected (millions) (95% CI)				Overall Prevalence (95% CI)			
		Hookworm (millions)	Roundworm (millions)	Whipworm (millions)	Any STH (millions)	Hookworm	Roundworm	Whipworm	Any STH
<i>Preschool age (younger than age five years)</i>									
Middle East and North Africa	55.6	0.3 (0.2–0.3)	1.9 (1.2–2.8)	0.6 (0.4–1.0)	2.5 (1.7–3.7)	0.5 (0.3–0.6)	3.4 (2.2–4.9)	1.2 (0.8–1.7)	4.6 (3.1–6.6)
Latin America and the Caribbean	54.5	1.7 (1.1–2.6)	5.3 (3.1–8.4)	4.6 (2.9–7.1)	10.1 (6.3–14.8)	3.2 (2.0–4.8)	9.7 (5.7–15.4)	8.5 (5.3–13.0)	18.4 (11.6–27.2)
Sub-Saharan Africa	210.7	12.5 (7.7–19.1)	17.8 (10.6–27.8)	13.4 (7.7–21.5)	37.4 (23.1–55.3)	5.9 (3.7–9.1)	8.4 (5.0–13.2)	6.4 (3.7–10.2)	17.7 (11.0–26.3)
East Asia and Pacific	151.0	14.6 (8.9–22.6)	13.4 (7.0–22.5)	12.5 (6.8–20.2)	34.1 (20.2–51.6)	9.6 (5.9–14.9)	8.8 (4.7–14.9)	8.1 (4.5–13.4)	22.6 (13.4–34.2)
South Asia	172.4	7.5 (4.8–11.1)	20.0 (11.8–30.6)	6.8 (4.0–11.0)	30.0 (18.4–43.6)	4.4 (2.8–6.4)	11.6 (6.8–17.8)	4.0 (2.3–6.4)	17.3 (10.7–25.3)
Total	644.2	36.6 (22.7–55.7)	58.4 (33.9–93.0)	37.9 (21.7–60.8)	114.1 (70.0–170.0)	5.7 (3.5–8.7)	9.1 (5.3–14.4)	5.9 (3.4–9.4)	17.8 (10.9–26.4)
<i>School age (ages 5–14 years)</i>									
Middle East and North Africa	94.4	0.7 (0.4–0.9)	5.0 (3.4–7.2)	1.8 (1.2–2.6)	6.8 (4.6–9.6)	0.7 (0.5–1.0)	5.3 (3.6–7.6)	1.9 (1.2–2.8)	7.2 (4.9–10.2)
Latin America and the Caribbean	107.0	4.5 (2.9–6.8)	15.0 (9.4–22.6)	13.0 (8.5–19.2)	27.3 (18.1–38.4)	4.2 (2.7–6.3)	14.0 (8.8–21.1)	12.2 (7.9–17.9)	25.5 (16.9–35.9)
Sub-Saharan Africa	354.3	34.0 (21.6–50.4)	47.2 (30.0–70.1)	36.4 (22.2–55.5)	94.8 (62.7–131.0)	9.6 (6.1–14.2)	13.3 (8.4–19.8)	10.3 (6.3–15.7)	26.7 (17.7–37.0)
East Asia and Pacific	294.0	44.3 (27.8–63.2)	34.2 (18.5–55.8)	32.0 (18.7–50.8)	88.0 (55.1–127.1)	15.1 (9.4–21.5)	11.6 (6.3–19.0)	10.9 (6.4–17.3)	30.0 (18.7–43.2)
South Asia	343.0	24.7 (16.3–35.4)	63.0 (39.1–91.5)	21.7 (12.8–33.7)	90.5 (59.5–124.3)	7.2 (4.7–10.3)	18.3 (11.4–26.7)	6.3 (3.7–9.8)	26.4 (17.3–36.2)
Total	1,192.8	108.2 (68.0–156.6)	164.4 (100.6–249.2)	105.0 (63.3–161.9)	307.4 (200.7–432.4)	8.9 (5.7–13.1)	13.9 (8.4–20.9)	8.8 (5.3–13.6)	25.9 (16.8–36.2)

Source: Adapted from Pullan and others 2014.

Note: CI = confidence interval; STH = soil-transmitted helminth. Numbers in parentheses indicate range at 95 percent confidence interval.

Table 13.2 DALYs per 100,000 Population, by Region and Type of Soil-Transmitted Helminth

	DALYs per 100,000		
	Hookworm	Roundworm	Whipworm
<i>Preschool age (younger than age 5 years)</i>			
Middle East and North Africa	4.2 (2.4–6.4)	14.3 (9.9–19.7)	0.0 (0.0–0.1)
Latin America and the Caribbean	21.8 (13.1–34.1)	34.1 (24.6–46.1)	8.2 (4.3–15.2)
Sub-Saharan Africa	39.7 (25.3–59.7)	143.2 (117.6–173.7)	6.5 (3.7–10.6)
East Asia and Pacific	21.7 (13.4–34.2)	19.7 (13.3–28.9)	7.3 (3.3–14.0)
South Asia	19.3 (11.4–29.8)	43.1 (32.2–58.0)	2.0 (0.9–3.8)
<i>School age (ages 5–14 years)</i>			
Middle East and North Africa	7.3 (4.4–11.0)	4.8 (2.7–8.2)	0.1 (0.0–0.3)
Latin America and the Caribbean	73.7 (47.0–107.7)	19.2 (10.7–31.8)	16.9 (8.7–30.2)
Sub-Saharan Africa	80.7 (51.8–120.2)	33.7 (22.5–49.6)	18.1 (10.0–30.2)
East Asia and Pacific	52.7 (34.0–78.5)	11.6 (6.0–20.9)	14.4 (6.3–28.5)
South Asia	38.1 (22.8–58.4)	36.6 (21.4–60.6)	5.2 (2.5–9.5)

Source: Institute for Health Metrics and Evaluation, Global Health Data Exchange, <http://ghdx.healthdata.org/>.

Note: CI = confidence interval. Numbers in parentheses indicate range at 95 percent CI.

Results are still limited by the paucity of recent data, especially for much of Asia. These prevalence estimates were informed by a comprehensive review of population-based surveys conducted between 1980 and 2010. However, a number of coordinated efforts have been underway recently to scale up and complete the mapping for neglected tropical diseases (NTDs), including STHs. It will be important to ensure that future revisions of the Global Burden of Diseases, Injuries, and Risk Factors Study incorporate these new prevalence estimates when producing revised DALYs for STHs.

Map 13.3 shows the current distribution of STH infections. These infections were historically prevalent in many parts of the world where they are now uncommon. These areas include parts of Europe; Japan; the Republic of Korea; Taiwan, China; and the Caribbean and North America (Mexico and the United States), where sustained control efforts and economic development have led to their elimination, at least as a public health problem (Hong and others 2006; Kobayashi, Hara, and Kajima 2006; Tikasingh, Chadee, and Rawlins 2011). The distribution of worm species also reflects social and environmental factors, with greater transmission of hookworm infection in rural areas, and greater prevalence of roundworm and whipworm in periurban environments (Pullan and Brooker 2012).

The distribution of STH infection is declining, partially as a result of global economic development, declining poverty, and greater access to health services and

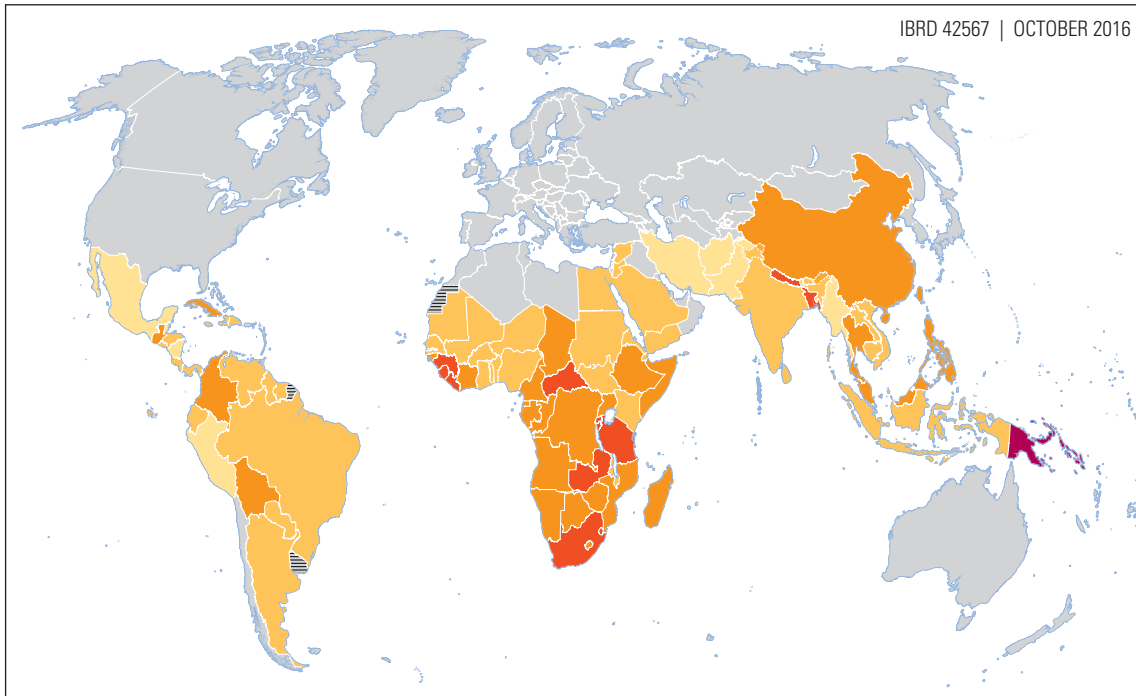
sanitation programs, especially in poor communities. It seems probable that the targeting of more than 1 billion deworming treatments a year in poor communities has also contributed. More contemporary surveys and joined-up databases are needed for reliable estimates, but crude estimates suggest that the number of school-age children living with worm infection was cut in half from 2010 to 2015.

SCALE OF DEWORMING PROGRAMS

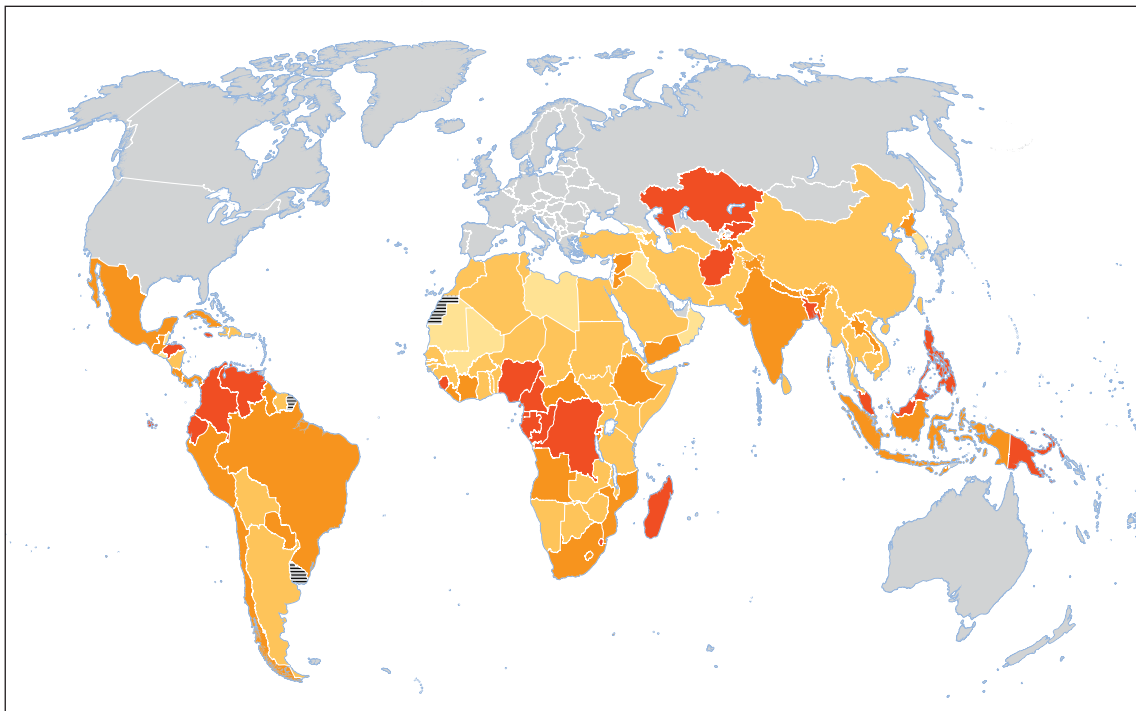
Deworming programs have long been popular with public health teams and the people exposed to infection. Norman Stoll's "This Wormy World" provided a clear vision of the ubiquity of infection and the scale of deworming programs in the then-endemic areas, including the U.S. South (Stoll 1947). Since the beginning of the twentieth century, schools have been viewed as the natural base for programs because they provide an existing infrastructure to reach the age group for whom infection is often most intense and who might benefit the most from deworming at a stage when they are still learning and growing (Bundy, Schultz, and others 2017, chapter 20 in this volume). In Dakar in 2000, at the World Education Forum that relaunched the Education for All program, the role of schools in delivering health programs, including deworming, was reinvigorated by the launch of the global partnership Focusing Resources on Effective School Health (FRESH).

Map 13.3 Distribution of Soil-Transmitted Helminth Infection Prevalence for Children Younger than Age 15 Years, by Species, 2015

a. Hookworm



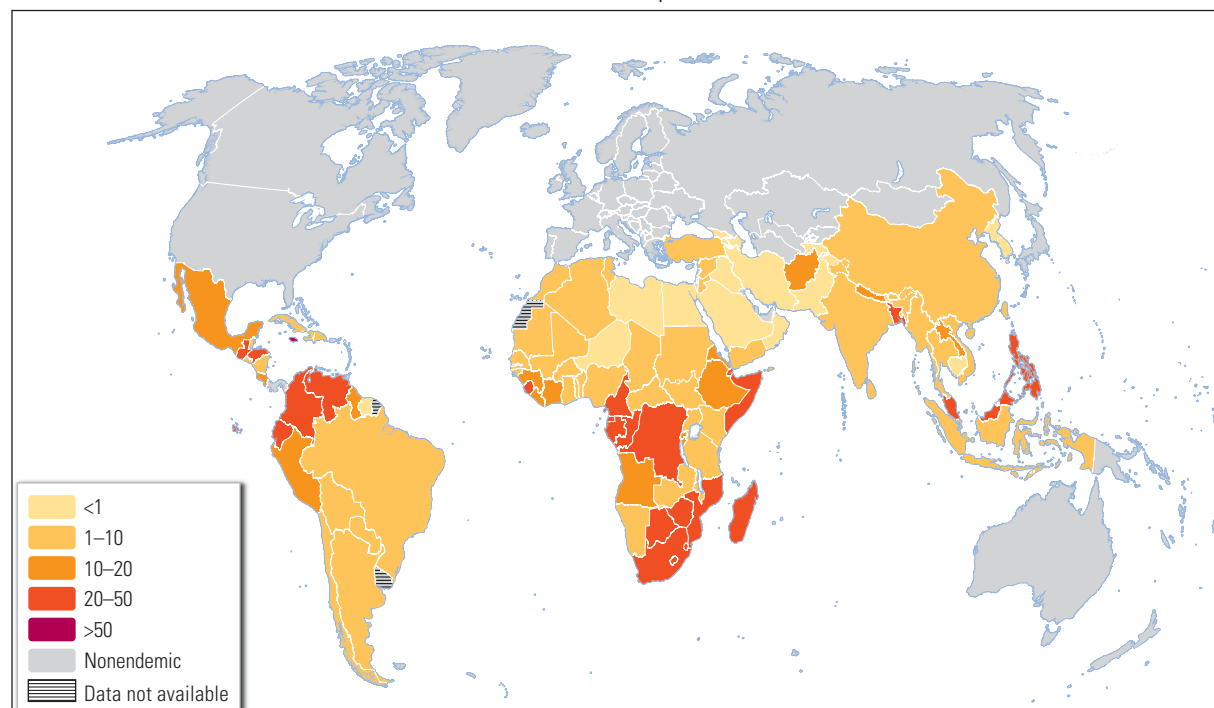
b. Roundworm



map continues next page

Map 13.3 Distribution of Soil-Transmitted Helminth Infection Prevalence for Children Younger than Age 15 Years, by Species, 2015 (continued)

c. Whipworm



Source: Adapted from Pullan and others 2014 and updated to 2015.
 Note: Based on geostatistical models for Sub-Saharan Africa and empirical data for all other regions.

FRESH was given greater vitality a year later when the World Health Assembly endorsed a target of deworming 75 percent of schoolchildren in member states with endemic STH infections. The FRESH principles continue to guide school health programs and are still being used and cited, for example, in the strategic plan for national deworming announced in Ethiopia in 2012.

From these beginnings, deworming, especially school-based deworming, has become a major public health program. In the London Declaration on Neglected Tropical Diseases announced in 2012, 14 pharmaceutical companies committed to donating medicines for 10 of the most prevalent NTDs, including STHs. The specific donations for STHs are targeted at school-age children and comprise 400 million treatments of albendazole (GlaxoSmithKline) and 200 million treatments of mebendazole (Johnson & Johnson). Medicines donated for other purposes, such as ivermectin for onchocerciasis and lymphatic filariasis, are also effective against STHs, and additional albendazole is donated specifically for lymphatic filariasis.

This progress adds up to a substantial volume of treatments efficacious against STHs. In 2015, the latest date for which treatment data are available for all

three commonly used anthelmintics, the World Health Organization (WHO) reports that approximately 564 million children (150 million preschool-age children and 416 million school-age children) were treated with albendazole or mebendazole for STHs (WHO 2015a) (table 13.3). While 556.2 million persons (including approximately 36 million preschool-age children and 139 million school-age children) were treated with albendazole under MDA programs targeting elimination of lymphatic filariasis (WHO 2015b), approximately 113.2 million persons were treated with ivermectin under the onchocerciasis elimination program in Africa (WHO 2015a). These figures suggest that in 2015, more than 1 billion persons were treated with drugs that are efficacious against STHs during the course of just one year.

The official estimates of treatment coverage in school-age children continue to show relatively low, albeit rising, levels of coverage, estimated to be about 45 percent in 2014 (figure 13.1 and table 13.3). These estimates are based on the donated drugs provided through WHO mechanisms, expressed as a proportion of the world's school-age children. Both the supply (that is, the numerator) and the demand (that is, the denominator) continue to rise

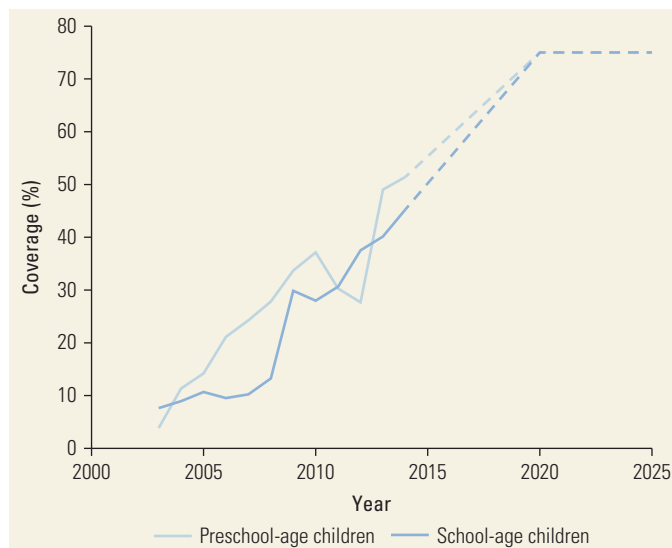
Table 13.3 Total Number of Preschool-Age and School-Age Children Estimated to Require Preventive Chemotherapy for Soil-Transmitted Helminths, by WHO Region, 2009 and 2015

WHO region	2009			2015		
	Requiring PC for STHs (millions)	Receiving PC for STHs (millions)	Regional coverage (%)	Requiring PC for STHs (millions)	Receiving PC for STHs (millions)	Regional coverage (%)
African	283.8	91.0	32	298.0	153.0	51
Americas	45.5	21.1	46	46.9	24.3	52
Eastern Mediterranean	78.0	2.5	3	74.4	17.9	24
European	4.3	0.4	9	2.3	0.5	23
South-East Asia	372.0	144.8	39	354.4	172.1	49
Western Pacific	99.1	14.1	14	75.2	32.4	43
Total	882.7	273.9	31	851.2	400.2	47

Source: WHO 2011, 2016.

Note: PC = preventive chemotherapy; STHs = soil-transmitted helminths; WHO = World Health Organization.

Figure 13.1 Reported Global Coverage of Preschool- and School-Age Children, 2003–14, with a Projection to the 2020 Target of 75 Percent Coverage



Source: Adapted from figure 1 of Trusscott, Turner, and Anderson 2015. The data on reported coverage are from the World Health Organization, "Neglected Tropical Diseases: PCT Databank," http://www.who.int/neglected_diseases/preventive_chemotherapy/lf/en/.

Note: Figure shows the treatment coverage of preschool-age and school-age children up to 2014. The dashed lines are indicative of the change necessary to reach the goal of 75 percent treatment by 2020.

leading to little change in coverage year over year reported by the WHO. These estimates report the number of doses that are donated specifically for school-based deworming (about 379 million tablets in 2015); they do not report the number of other donated drugs that are efficacious against STHs (an additional 900 million doses in 2014) or the large number of nongovernmental organization and

self-administered treatments in the unprogrammed category that go unreported. The scale of actual treatment of schoolchildren in any year could easily be twice that reported in the official statistics.

HEALTH IMPACT OF WORMS AND DEWORMING

Although the WHO recommends MDA for vulnerable groups, such as children and pregnant women, who live in areas with endemic intestinal worm infection, a series of reviews from both the Cochrane Collaboration (most recently, Taylor-Robinson and others [2015]) and the Campbell Collaboration (Welch and others 2016) argues that there is substantial evidence that mass deworming does not produce health benefits and does not support the use of MDA. How can these two views be reconciled?

Substantial Historical Literature on the Clinical Consequences of STH Infection

The clinical literature, gathered over the early part of the last century, shows significant impacts of intense STH infection on health. Through collation of data from several different studies that described the occurrence of *Ascaris*-induced intestinal obstruction in specific regions of endemic countries, and studies on the community prevalence of ascariasis in the same regions, the incidence of *Ascaris*-induced intestinal obstruction was shown to clearly increase, in a nonlinear fashion, as community prevalence of infection increased (de Silva, Guyatt, and Bundy 1997a). Similar data collations

showed patients with acute intestinal obstruction due to ascariasis harbored more than 60 worms in most instances, with a 10-fold higher worm burden in fatal cases. Children younger than age five years were shown to develop obstruction with much smaller worm burdens (de Silva, Guyatt, and Bundy 1997b). A model of the global numbers at risk of morbidity and death due to ascariasis estimated that in 1990, some 11.5 million children were at risk of clinically overt acute illness and that some 200,000 children developed serious complications such as intestinal obstruction, biliary or pancreatic disease, appendicitis, and peritonitis, resulting in about 10,000 deaths each year (de Silva, Chan, and Bundy 1997).

Evidence also points to the effects of *Trichuris* infection on growth and development of infected children, in particular in those children who have a heavy burden of infection. Reports from Jung and Beaver (1951) described dysentery, diarrhea, and colitis in children with *Trichuris* infection; heavily infected children more frequently presented with the more severe symptom of rectal prolapse. This heavy infection can lead to a well-described *Trichuris* dysentery syndrome, characterized by dysentery, anemia, growth retardation, finger clubbing, rectal prolapse, and a specific trichuriasis colitis (Cooper and Bundy 1988). Furthermore, curative treatment for parasite infection leads to rapid alleviation of these symptoms (Cooper and Bundy 1988; Jung and Beaver 1951). Studies have recorded significant catch-up growth in middle childhood—especially ages four to eight years—following curative treatment, with significant increases in height and weight as well as improvements in cognition (Callender and others 1998; Cooper and others 1990; Cooper and others 1995; Nokes and others 1992).

Anemia is associated with trichuriasis colitis and is the defining characteristic of hookworm infection. On maturation and migration to the gut, hookworms attach to the intestinal mucosa and submucosa, rupturing capillaries mechanically as well as through release of anti-clotting agents to maintain blood flow (Hotez and others 2004). The development of anemia is related to infection intensity as well as to the duration of infection and nutritional status of individuals (Crompton and Whitehead 1993; Hall and others 2008). A seminal trial by Stoltzfus and others (1997) showed a significant association between hookworm infection and severe anemia, as well as iron deficiency over and above dietary intake of iron. The authors predicted that eliminating hookworm infections from their study population could lead to a reduction in anemia of 25 percent and severe anemia by as much as 73 percent.

Thus, the pathology for each of these helminth infections can be severe in both immediate effects and

medium-term consequences for growth and development. Furthermore, for each of these infections, curative treatment leads to alleviation of the immediate symptoms as well as to accelerated gains in growth and development, indicating that the pathology of worm infection can largely be reversed if treated in a timely manner.

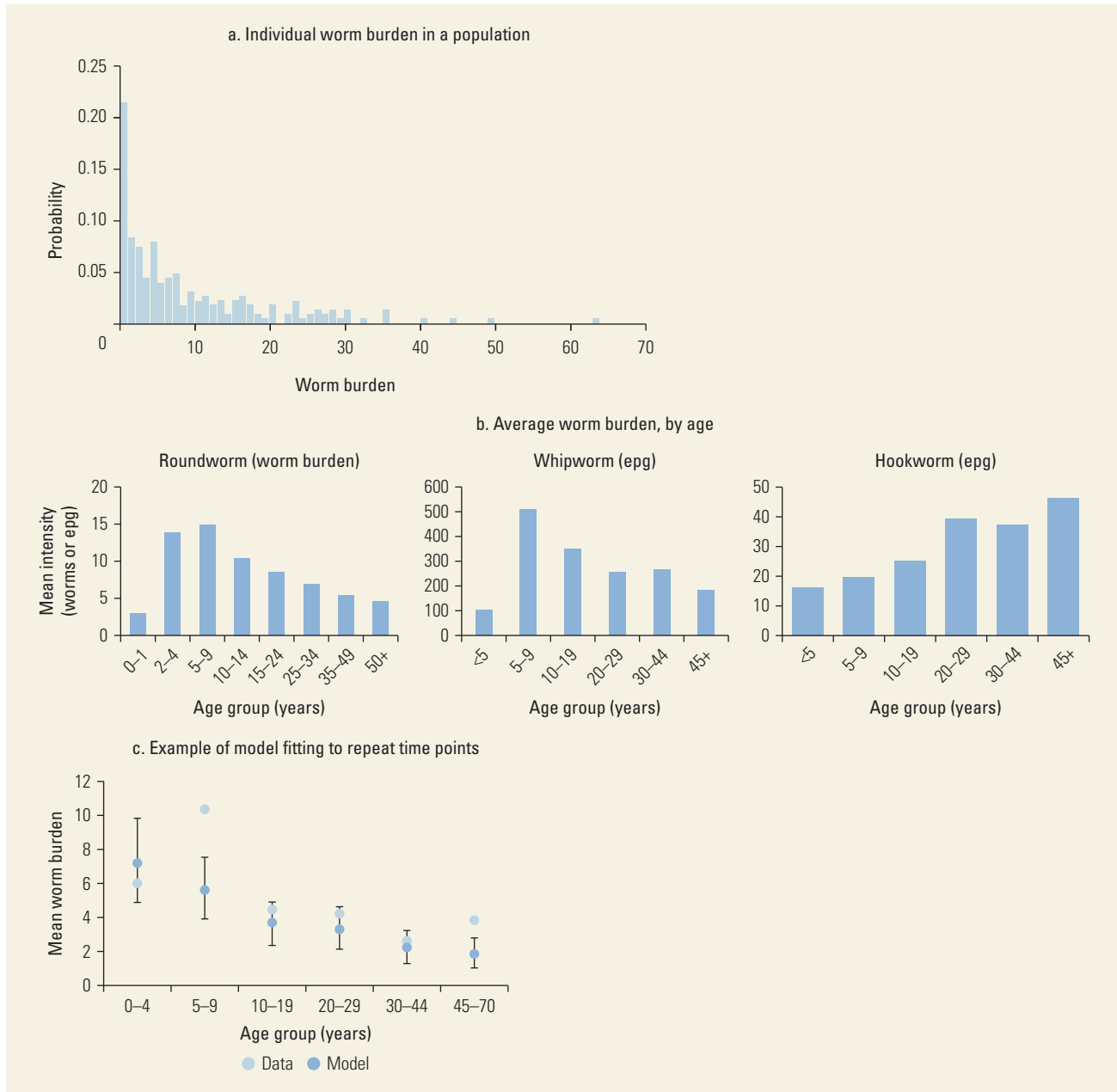
This literature, now largely historical, on clinical trials of patients with known and intense infection compared with untreated controls, offers convincing evidence on both the effect of infection on patients and the benefits of treatment. Such trials should no longer be conducted because it would be unethical to withhold treatment from patients known to be infected.

Impact of Current MDA-Based Trial Design

The majority of deworming trials today are designed quite differently from traditional clinical trials. They are based on the operational design of deworming programs, in which MDA covers all of the target population, usually an age class, living in an area where infection is endemic, with no measure of individual infection status or intensity. Because infection intensity is overdispersed, such that most people have lower-than-average infection and a minority have intense infection (figure 13.2), there will be considerable and unknown variance in the intensity of individual infection. Because the intensity is unknown in any individual, so too is the likelihood of morbidity and the potential scale of benefit from treatment. With the current trial design, the population outcome can only be measured as some average of individual benefits. Even were there to be considerable benefit for the minority of intensely infected individuals, if there is little or no benefit for the majority with light infections then the average effect will be small. The underlying situation across the population is unknowable with current MDA-based trial designs.

To illustrate what the analyses show in practice, we compare two comprehensive analyses drawing on the same small pool of trials available in this area of research. In the first analysis, Taylor-Robinson and others (2015) examined both randomized trials of universal deworming programs, which include children both with and without worms, and studies among groups of infected children already screened and diagnosed. They then conducted formal meta-analysis for eight outcomes: weight, height, middle-upper-arm circumference, triceps skinfold thickness, subscapular skinfold thickness, body mass index, hemoglobin, and school attendance. They concluded that, while *targeted* deworming of infected children may increase weight gain, for mass deworming programs that cover children with and without worms,

Figure 13.2 Distribution of Worm Burden



Sources: Panel a, adapted from Hollingsworth, Truscott, and Anderson 2013; panel b, adapted from Truscott and others 2014; panel c, adapted from Truscott, Turner, and Anderson 2015.
 Note: epg = eggs per gram of stool. Worm burden indicates the expected number of worms harbored by an individual.

“There is now substantial evidence that [mass treatment of all children in endemic areas] does not improve *average* [emphasis added] nutritional status, hemoglobin, cognition, school performance, or survival” Taylor-Robinson and others (2015, 2). They included a maximum of 11 estimates from 10 trials for weight gain, with many fewer trials for most of the other outcome measures.

In the other analysis, Croke and others (2016) augmented Taylor-Robinson and others’ (2015) sample with information from published studies as well as several excluded studies and then conducted meta-analysis on this augmented sample. Focusing on weight gain, for which the number of available studies is greatest, they noted that the appropriate test for the

hypothesis of no treatment effect in all cases is a fixed-effect meta-analysis. Using this model, the hypothesis of zero weight gain from deworming was rejected at the 10 percent level using the original data from the Taylor-Robinson and others (2015) study. Using the augmented sample, they found a 0.111 kilogram weight gain ($p < 0.001$) from deworming in a fixed-effects model and a 0.134 kilogram weight gain ($p = 0.01$) in a random-effects model.

Noting that including trials from settings with minimal STH prevalence and mass deworming is not recommended because such a policy may minimize the estimated impact of deworming, they then estimated positive and statistically significant impacts in settings in which the WHO recommends multiple doses of mass treatment annually (greater than 50 percent prevalence), and in settings where the WHO recommends mass deworming at least once per year (greater than 20 percent prevalence). For high- and medium-prevalence areas (greater than 50 percent prevalence of any single STH species), the fixed-effects estimate was 0.157 kilogram, while the random-effects estimate was 0.182 kilogram. For trials in settings with greater than 20 percent prevalence, the fixed-effects estimate was 0.142 kilogram, while the random-effects estimate was 0.148 kilogram.

Accordingly, while Taylor-Robinson and others (2015) highlighted an apparent contradiction between the evidence on treatment of infected individuals (evidence of benefit) and mass treatment (no evidence of benefit), Croke and others (2016) demonstrated that mass deworming also has evidence of benefit, albeit of smaller magnitude than the effects identified in targeted studies. Evidence for this benefit is particularly strong in high- and medium-prevalence settings. The estimated weight gain in these universal treatment studies is notably smaller than in studies of individuals known to be infected—on the order of 0.13 and 0.75 kilogram, respectively—which would be the logical consequence of averaging across a population with an overdispersed distribution of intensity of infection and probability of morbidity.

The similar results but very different conclusions of these two analyses of the same trial datasets may be helpful for understanding the paradoxical literature in the deworming area. Both analyses found effects with targeted treatment trials, as is well documented in the clinical literature. Both analyses found small effects on weight gain (the measure for which most trials are available for meta-analysis) when exploring the effects across whole populations with unknown distribution of infection intensity—finding these effects significant in one analysis and not significant in the other. Resolving this debate requires exploring the distribution of

individual morbidity and infection intensity. One important point is that the targeted treatment trials are also the earlier trials: detecting average effects in populations will only become more difficult as infection levels continue to decline.

OPTIMIZING PROGRAM DESIGN BY MODELING POPULATION DYNAMICS

Both chapters on deworming in the earlier editions of *Disease Control Priorities* emphasized the importance of understanding population dynamics as a determinant of good program design (Hotez and others 2006; Warren and others 1993). This section explores how the population dynamics modeling is being used to optimize program design and, in particular, what the modeling says about the value of MDA versus screen and treat and of school-based deworming versus universal coverage.

A common epidemiological feature of STH infections is the overdispersed distribution of worms (figure 13.2, panel a): while many people have a medium to low burden of infection, a minority of people have a high burden of infection. Because of the linear relationship between infection intensity and morbidity, individuals with high burdens are most likely to suffer health impacts of STHs, to contribute the largest number of infectious eggs, and to be reinfected following mass treatment, raising the possibility that targeting these individuals would be the most effective way to control both the health impact and the transmission of STHs. However, this approach has some practical challenges.

- First, commonly used diagnostics—wet smear in saline or Kato-Katz examination of stool samples to count eggs—are poor diagnostics of the underlying worm burden because of both variations in egg output and the nonlinear relationship to worm burden (Anderson and Schad 1985).
- Second, selective diagnosis and treatment involves expensive fieldwork, including collecting and analyzing stool samples and finding, reidentifying, and treating highly infected individuals (see next section on costs).
- Third, the nature of the overdispersed distribution means that a large proportion of the population has to be sampled to detect the few who have to be treated.

The few field studies that have been performed have found that selective treatment of persons with high parasite burden is less effective than mass treatment at

reducing population-level prevalence (Asaolu, Holland, and Crompton 1991); that mass treatment is more cost-effective than selective treatment (Holland and others 1996); and that school-based deworming is a highly cost-effective way to reduce anemia (Brooker and others 2008; Guyatt and others 2001) in particular settings, reflecting the results of modeling studies (Guyatt, Bundy, and Evans 1993) and a recent review of costs and cost-effectiveness (Turner and others 2015). Current evidence suggests that the most cost-effective way to reduce high-burden infections in children is through school-based deworming rather than selective treatment.

Epidemiological studies have also found indirect benefits to mass treatment of children, such as reductions in prevalence of infection in untreated adults (Asaolu, Holland, and Crompton 1991; Bundy and others 1990). These indirect effects have been found for roundworm and whipworm, but different effects were found in different settings, reflecting local differences in prevalence and distribution of infection. The population-level impact of a school-based deworming program and the impact on transmission to other members of the community and reinfection after treatment depend on the epidemiology of the parasite, efficacy of the treatments, age distribution of the population, and coverage of the treatment program. For roundworm and whipworm, the highest burden of infection is usually in children (figure 13.2, panel b); therefore, a school-based program covering preschool- and school-age children could have a large impact on transmission, particularly in settings with a high proportion of school-age population, provided the treatment used is effective for whipworm (Chan and others 1994; Turner and others 2016) and prevalence is at moderate to low levels. For hookworm, the burden of infection tends to be higher in adults; therefore, a school-based deworming program is likely to be less effective at reducing both morbidity (Coffeng and others 2015; Truscott, Turner, and Anderson 2015) and transmission at the population level (Anderson, Truscott, and Hollingsworth 2014; Anderson and others 2013; Anderson and others 2015; Chan and others 1994). However, systematically excluding a portion of the community from treatment can undermine elimination programs (Coffeng and others 2015), although it also helps slow the emergence of drug resistance.

Many of these results are from mathematical modeling studies, which have become more complex in recent years. An important development has been the validation of models against repeat time-point data (figure 13.2, panel c); these models are being expanded to include the most recent data (Coffeng and others 2015; Truscott, Turner, and Anderson 2015). Given that coverage of

adults is likely to be required to break transmission, analyses have shown that in many settings the higher cost of coverage is offset by the lower number of rounds required, given that treatment can be stopped when transmission has been permanently interrupted (Lo and others 2015; Turner and others 2015; Turner and others 2016).

This section considers two issues: how treatment can bring down intensity and morbidity, and how treatment might break transmission. Empirical evidence is available for the former, but caution should remain about the latter. Although MDA has proven to be effective with onchocerciasis and lymphatic filariasis, these diseases have much slower epidemic growth rates than do STHs, and both require vectors for transmission rather than fecal contamination of the environment with infective stages.

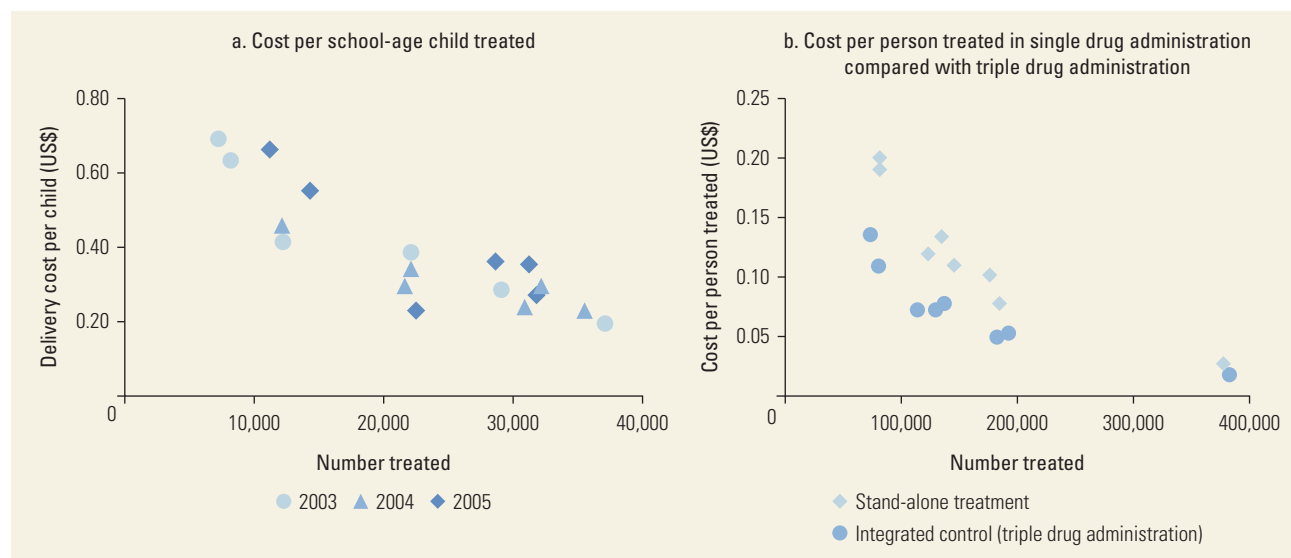
ESTIMATED COST OF MDA

One of the main arguments for deworming, and the basis of the WHO recommendation for the use of MDA, especially school-based deworming, is the cost-effectiveness arising from an exceptionally low-cost intervention delivered infrequently without the need for costly screening. The value for money of this approach for low-income countries has recently been greatly enhanced by the availability of donated treatments. This section explores the costs in more detail.

MDA offers notable economies of scale (Brooker and others 2008; Evans and others 2011) because the cost per treatment decreases as the number treated rises (figure 13.3, panel a). This effect occurs because some of the most significant costs associated with MDA delivery are fixed and do not depend on the number treated: increasing the number treated therefore reduces the average fixed cost per treatment (Turner and others 2016). These economies of scale may account for much of the observed variation in the costs of delivering NTD treatment (Turner and others 2015).

Table 13.4 lists the costs of STHs delivered through a variety of MDA program designs. Integrating STH programs with other NTD programs or indeed other control programs, such as child health days, can produce economies of scope, by which the average cost per treatment declines as a result of delivering two or more interventions at once (figure 13.3, panel b); for example, integrating NTD programs reduces the overall cost between 16 percent and 40 percent (Evans and others 2011; Leslie and others 2013). Furthermore, the incremental cost of adding deworming into established immunization campaigns or child health days

Figure 13.3 Observed Economies of Scale and Scope Associated with Preventive Chemotherapy



Sources: Panel a, data from Brooker and others 2008; panel b, data from Evans and others 2011.

Note: Triple drug administration refers to the co-administration of albendazole, ivermectin, and praziquantel on a single delivery platform in communities where multiple neglected tropical diseases are prevalent.

Table 13.4 Key Preventive Chemotherapy Costing Studies Using Albendazole and Mebendazole

Study	Country	Target of intervention	Primary distribution method	Results
Brooker and others 2008	Uganda	STHs and SCH	School based (annually)	The overall economic cost per child treated in the six districts was US\$0.54, which ranged from US\$0.41 to US\$0.91 (delivery costs: US\$0.19–US\$0.69). The overall financial cost per child treated was US\$0.39. Costs are in 2005 US\$.
Goldman and others 2007	Multicountry study	LF (and STHs indirectly)	Community based (annually)	The financial cost per treatment ranged from US\$0.06 to US\$2.23. Costs are in 2000–03 US\$ (base year 2002).
Evans and others 2011	Nigeria	STHs, SCH, LF, and onchocerciasis	Community based (annually)	In 2008, school-age children in eight local government areas received a single round of ivermectin and albendazole followed at least one week later by praziquantel. The following year, a single round of triple drug administration was given, reducing the programmatic costs for MDA, not including drug and overhead costs, 41 percent (from US\$0.078 to US\$0.046 per treatment). Costs are in 2008–09 US\$.
Goldman and others 2011	Haiti	STHs and LF	School based and community based (annually)	The cost per treatment was US\$0.64, including the value of donated drugs. The program cost, excluding the value of the donated drugs, was US\$0.42 per person treated. Costs are in 2008–09 US\$.
Leslie and others 2011	Niger	STHs and SCH	School based and community based (annually)	The full economic cost of delivering the school-based and community-based treatment was US\$0.76 and US\$0.46, respectively. Including program costs alone, the values were US\$0.47 and US\$0.41, respectively. Costs are in 2005 US\$.
Leslie and others 2013	Niger	STHs, SCH, LF, and trachoma	School based and community based (annually)	The average economic cost of integrated preventive chemotherapy was US\$0.19 per treatment, excluding drug costs. The average financial cost per treatment of the vertical SCH and STH control program (before the NTD programs were integrated) was US\$0.10. Costs are in 2009 US\$.

table continues next page

Table 13.4 Key Preventive Chemotherapy Costing Studies Using Albendazole and Mebendazole (continued)

Study	Country	Target of intervention	Primary distribution method	Results
Boselli and others 2011	Lao PDR	STHs within a child health day campaign	Child health days (annually)	The incremental cost of adding deworming into the national immunization campaign was US\$0.03 per treatment (delivery costs: US\$0.007). The cost per treatment for the vertical school-based national deworming campaign (targeting school-age children) was US\$0.23. Costs are in 2009 US\$.
Fiedler and Semakula 2014	Uganda	STHs within a vitamin A supplementation campaign	Child health days (one round)	The average economic cost per child reached by the child health day program was US\$0.22 (per round). Costs are in 2010 US\$.

Note: LF = lymphatic filariasis; MDA = mass drug administration; NTD = neglected tropical disease; SCH = schistosomiasis; STHs = soil-transmitted helminths. For a more detailed summary of cost data for preventive chemotherapy, see Keating and others (2014) and Turner and others (2015).

with an already developed delivery infrastructure is very small—approximately US\$0.03 per treatment (Boselli and others 2011)—and much lower than delivering treatment through vertical national deworming programs (Turner and others 2015); however, it may target younger children only and not access the age group with intense infection. This possibility highlights the critical need to consider the local context of NTD control programs when comparing the reported costs of MDA.

CONCLUSIONS

STH deworming programs are among the largest public health programs in low- and lower-middle-income countries as measured by coverage. The actual scale of these programs is unknown but is substantial; more than 1 billion donated doses of medicines effective against STHs are delivered by formal programs and supplemented by widespread self-treatment and unprogrammed activities. Deworming is one of the most common self-administered treatments in low-income countries; there is no question that there is strong community demand for this intervention. The large majority of formal MDA programs for STHs is school based.

STH infection is declining worldwide, likely reflecting the influence of improved hygiene and sanitation associated with global declines in poverty. The decline also reflects control efforts during the twentieth century that have largely eliminated STHs as a public health problem

in previously endemic areas of North America (Mexico and the United States), Japan, Korea, and upper-middle-income countries throughout southern and eastern Asia.

This trend accelerated during the past decade, especially in the poorest countries where infection was previously most intense. Estimates are crude, but suggest that infection prevalence in school-age children was halved between 2010 and 2015. Efforts are underway to provide more extensive and more accurate surveys of infection status, supported by the creation of integrated databases that provide contemporary estimates of infection and treatment coverage. Efforts to monitor the potential emergence of drug resistance in treated populations are also increasing.

Much of the treatment is delivered through schools and targets school-age children. In 2015, India had the largest public health intervention ever conducted in a single day, deworming 89 million schoolchildren during the Annual School Deworming Day. The target for 2016 is 270 million schoolchildren. Modeling suggests that expanding programs to include other age groups might break transmission, and studies are exploring the utility of this approach in practice. Increasingly, countries are combining MDA for lymphatic filariasis and STHs since both use the same anthelmintics.

STH infection has been shown to be associated with clinical and developmental outcomes that are largely reversible by treatment (box 13.1). Both historical and contemporary trials of targeted treatment of individuals known to be infected have also demonstrated benefit from treatment.

Box 13.1

WHO Recommendations for the Control of Morbidity Attributable to Soil-Transmitted Helminths

Present recommendations

Since 2001, the World Health Organization (WHO) has recommended, for the prevention and control of the morbidity due soil-transmitted helminth (STH) infection, the implementation of preventive chemotherapy (PC) in the form of periodical, large-scale administration of anthelmintics to population groups at risk of morbidity due to infection.

Children and women of childbearing age are considered the population groups with the highest risk of morbidity from STH infection, because they are in a period of life in which they are particularly vulnerable to nutrient deficiencies associated with infection.

The current recommendation is for treatment once a year when the prevalence of STH infection is more than 20 percent and twice a year when prevalence

exceeds 50 percent. The PC strategy is being implemented worldwide; in 2015, more than 50 percent of preschool children and more than 63 percent of school-age children in areas endemic for STHs were treated with anthelmintics.

Updating the recommendations

A WHO Guideline Review Committee (GRC) comprising independent experts met in Geneva in April 2016 to reassess the WHO recommendations on STHs control in light of scientific and programmatic evidence cumulated during the last 15 years of PC interventions. The conclusions of the GRC are presently being finalized and are expected to be published in early 2017.

Source: WHO 2001.

The findings of a small group of more recent clinical trials based on MDA have been controversial. These trials measure average change in health metrics for the whole population treated, irrespective of the infection status of individuals. Since morbidity is related to intensity, and intensity has an overdispersed distribution in populations, the average change in health metrics likely reflects the outcomes for a majority of people who are lightly infected and may derive limited benefit from treatment and for a minority who are more intensely infected and may derive greater benefit. The actual distribution of intensity and infection in these trial populations is unknown because individual screening is not necessary for MDA. The controversy arises because the change when averaged across the whole population is typically small, and there are insufficient data to determine with confidence whether the small size of the change reflects the underlying population distribution or the scale of benefit. An additional factor is that these more recent trials are conducted against the background of successful control efforts and the correspondingly low intensity of infection in most of the study populations. Studies are now being designed that aim to separate these factors.

The controversy in this area has extended from the results themselves to their policy implications. There is general agreement that STH infection can affect health, but disagreement regarding the circumstances that would justify an MDA program. While this debate continues, demand for MDA is continuing in the endemic countries and self-treatment is continuing on a massive scale. The debate would benefit from quantitative policy analysis setting out the population parameters that would and would not justify an MDA approach (see chapter 29 in this volume, Ahuja and others 2017, for an example of how this analysis has been approached from an economic perspective). The trend toward integrated MDA programs that target both lymphatic filariasis and STHs would also change the policy question being asked.

Looking to the future, we can expect infection levels to continue to decline as a result of the combination of high levels of treatment and continuing economic development trends in poor communities. We can also hope for a resolution of the worm wars as methods for assessing impact improve to reflect epidemiological realities, but this goal may be compromised if levels of impact continue to fall with sustained control.

NOTE

World Bank Income Classifications as of July 2014 are as follows, based on estimates of gross national income (GNI) per capita for 2013:

- Low-income countries (LICs) = US\$1,045 or less
- Middle-income countries (MICs) are subdivided:
 - a) lower-middle-income = US\$1,046 to US\$4,125
 - b) upper-middle-income (UMICs) = US\$4,126 to US\$12,745
- High-income countries (HICs) = US\$12,746 or more.

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