REVIEW ARTICLE

CURRENT CONCEPTS

Hookworm Infection

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Hookworm infection in humans is caused by an infection with the helminth nematode parasites *Necator americanus* and *Ancylostoma duodenale* and is transmitted through contact with contaminated soil. It is one of the most common chronic infections, with an estimated 740 million cases in areas of rural poverty in the tropics and subtropics.[1] Because hookworm infection occurs predominantly among the world's most impoverished people,[1] it holds a unique place in modern history. For example, the reputation of pre-1949 China as the "sick man of Asia" was partly a result of the high prevalence and intensity of infection with hookworm.[2] Mohandas Gandhi had hookworm infection in the last years of his life.[3] Hookworm was also a contributing factor in the slowing of economic development during the early part of the 20th century in the southern United States.[4] Today, hookworm infection is among the most important tropical diseases in humans; the use of disability-adjusted life years as a quantitative measure of the burden of disease reveals that this infection outranks African trypanosomiasis, dengue, Chagas' disease, schistosomiasis, and leprosy.[5]

The greatest number of hookworm cases occur in Asia, followed by sub-Saharan Africa.[1] In China alone, approximately 190 million people are infected, an estimate based on a nationwide study involving the examination of fecal specimens obtained from almost 1.5 million people between 1988 and 1992.[2] *N. americanus* is the most common hookworm worldwide, whereas *A. duodenale* is more geographically restricted. In contrast to these major anthropophilic species, three species of zoonotic hookworm are minor causes of disease in humans. *A. ceylanicum* infects dogs and cats and can also infect humans but is not considered an important pathogen. The dog hookworm *A. caninum* causes human eosinophilic enteritis in northeastern Australia,[6] and *A. braziliense* causes cutaneous larva migrans.

PATHOPHYSIOLOGY AND CLINICAL DISEASE

LARVAL INVASION OF TISSUE

Some of the highest rates of hookworm transmission occur in the world's coastal regions, where infective third-stage larvae can migrate freely in sandy soils and where temperatures and moisture are optimal for viability of larvae.[7] In these areas, repeated exposure to third-stage larvae of *N. americanus* or *A. duodenale* results in a local pruritic, erythematous, papular rash known as "ground itch." Although the entire body surface is vulnerable, ground itch appears most frequently on the hands and feet, which are the major sites of entry for third-stage larvae. In contrast to ground itch, skin invasion by zoonotic *A. braziliense* third-stage larvae results in cutaneous larva migrans, or "creeping eruption," a self-limited dermatologic condition characterized by serpiginous burrows, 1 to 5 cm long. Created by third-stage larvae migrating in the epidermis, the burrows appear on the feet in 39 percent of cases (Fig. 1), the buttocks in 18 percent, and

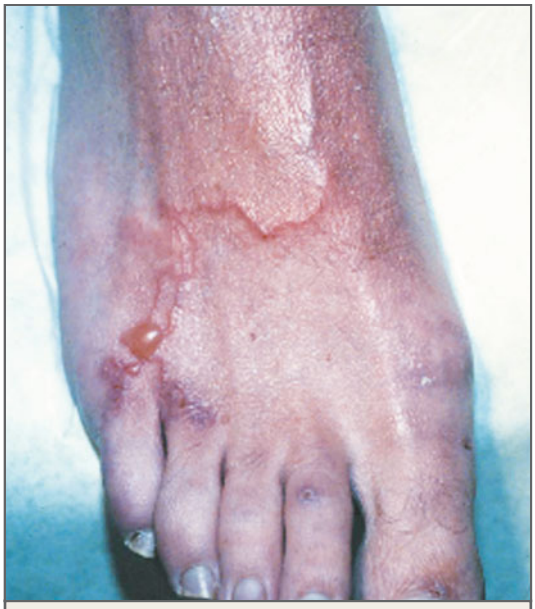

Figure 1. Cutaneous Larva Migrans Caused by *Ancylostoma braziliense*.
Reprinted from Despommier et al.,[8] with the permission of the publisher.

the abdomen in 16 percent; in the remainder of cases, the burrows appear predominantly in the lower legs, arms, and face.[9] In the United States, cutaneous larva migrans is seen commonly in military personnel, in travelers returning from resorts that have sandy beaches, and in residents of Florida and the Gulf Coast; it is treated successfully with short oral courses of either albendazole or ivermectin.[10,11]

While in the soil, third-stage larvae are in a state of developmental arrest; development resumes after the larvae enter the human host.[12] In humans, entry through the skin is followed within 10 days by larval migration to the lungs (Fig. 2), resulting in cough and sore throat. Pulmonary hookworm infection resembles Löffler's syndrome because of its association with eosinophilia in the lung. In rare cases, pneumonitis accompanies cutaneous larva migrans. Hookworm pneumonitis is usually not severe, although it may last for more than a month, until the larvae leave the lungs and enter the gastrointestinal tract. It is not commonly recognized that *A. duodenale* third-stage larvae infect humans both by the oral route and through the skin. When infection with *A. duodenale* occurs by the oral route, the early migrations of third-stage larvae cause a syndrome known as Wakana disease, which is characterized by nausea, vomiting, pharyngeal irritation, cough, dyspnea, and hoarseness. Increased circulating levels of IgE occur in response to migrations of third-stage larvae in the lungs and intestines.[13]

CLINICAL DISEASE

The major hookworm-related injury in humans occurs when the adult parasites cause intestinal blood loss.[14-16] The term "hookworm disease" refers primarily to the iron-deficiency anemia that results from moderate or heavy infection. Blood loss occurs when the worms use their cutting apparatus to attach themselves to the intestinal mucosa and submucosa and contract their muscular esophagi to create negative pressure, which sucks a plug of tissue into their buccal capsules (Fig. 3). Capillaries and arterioles are ruptured not only mechanically but also chemically, through the action of hydrolytic enzymes.[14] To ensure blood flow, the adult hookworms release anticlotting agents.[17,18] (One of these, a novel factor VIIa/tissue factor inhibitor, is being developed as a therapeutic agent to block the coagulopathy of fulminant infection with Ebola virus.[19]) The hookworm ingests a portion of the extravasated blood. Some red cells undergo lysis, thereby releasing hemoglobin, which is digested by a cascade of hemoglobinases that line the gut of the parasite.[20]

The major clinical manifestations of hookworm disease are the consequences of chronic intestinal blood loss. Iron-deficiency anemia occurs and hypoalbuminemia develops when blood loss exceeds the intake and reserves of host iron and protein.[15] Depending on the status of host iron, a hookworm burden (i.e., the intensity of infection, or number of worms per person) of 40 to 160 worms is associated with hemoglobin levels below 11 g per deciliter.[21,22] However, other studies have shown that anemia may occur with a lighter hookworm burden.[23] Because infection with *A. duodenale* causes greater blood loss than does infection with *N. americanus*, the degree of iron-deficiency anemia induced by hookworms depends on the species.[16] For instance, in Zanzibar, among children who were infected only with *N. americanus* hookworms, the prevalence of hypoferritinemia (ferritin level, <12 μg per liter) was 33.1 percent, whereas in children who were also infected with *A. duodenale* hookworms, the prevalence was 58.9 percent.[24] When iron stores in the host become depleted, there is a direct correlation between the intensity of hookworm infection (typically measured by quantitative egg counts) and

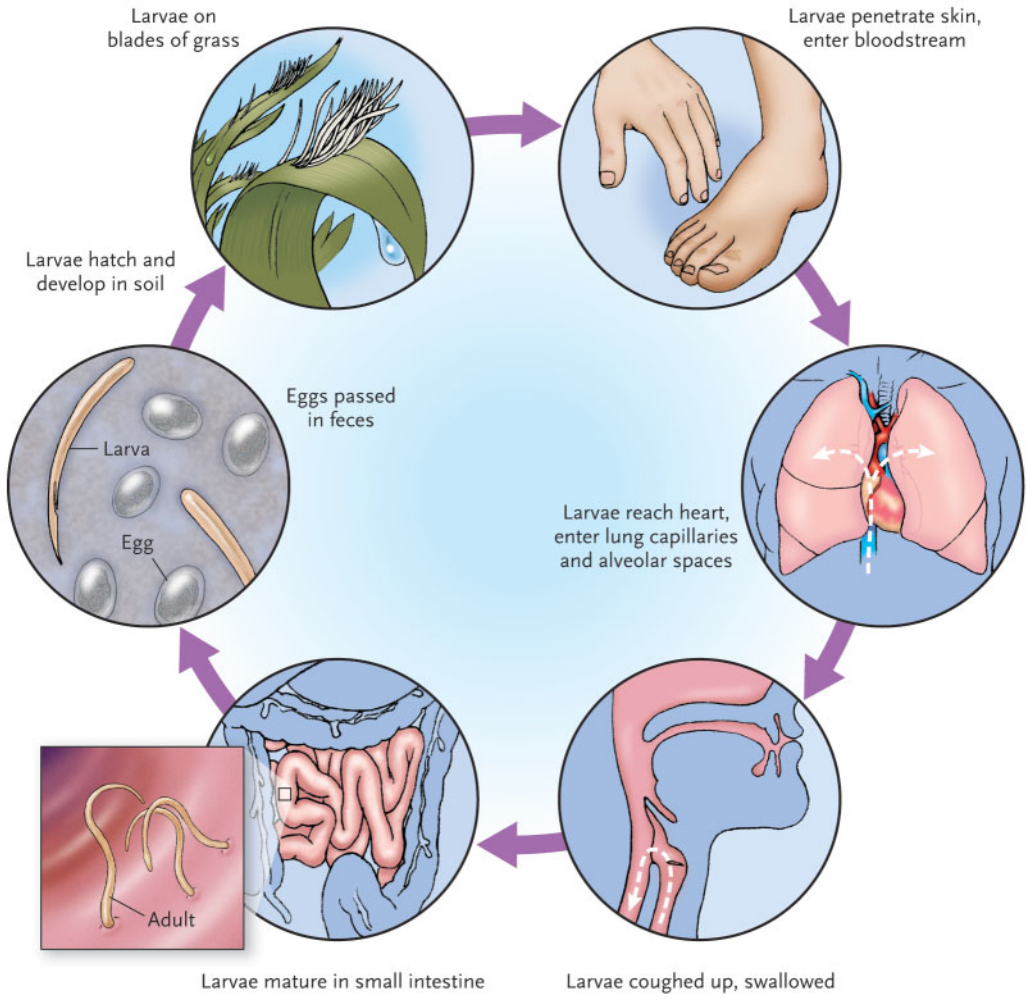

Figure 2. The Life Cycles of *Necator americanus* and *Ancylostoma duodenale*.

Humans acquire hookworm when third-stage infective larvae in soil either penetrate the skin (as do both *N. americanus* and *A. duodenale*) or when they are ingested (*A. duodenale* only). The larvae are each approximately 600 μm long and are developmentally arrested. After entering the host, the larvae receive a host-derived signal that causes them to resume development.[12] The larvae then migrate through the vasculature and are swept by the afferent circulation to the right side of the heart and then to the pulmonary vasculature. From the lung capillaries, the larvae rupture and enter the parenchyma, where they ascend the alveoli, bronchioles, bronchi, and trachea. After being coughed up and swallowed, the larvae enter the gastrointestinal tract, where they molt twice and develop to the adult stage. Approximately six to eight weeks pass from the time the larvae first infect humans until they reach sexual maturity and mate. Each female hookworm produces thousands of eggs daily. Intestinal blood loss in the host begins just before egg production and release and continues for the life of the hookworm. Hookworm eggs exit the body in feces. When deposited in soil, with adequate warmth, shade, and moisture, the eggs hatch within 24 to 48 hours and develop into first-stage larvae. These larvae molt twice as they develop to the third stage. The larvae are nonfeeding organisms that can live for several weeks in the soil, until they exhaust their lipid metabolic reserves. Transmission of hookworm is most prevalent in areas where there is high moisture and appropriate soil conditions. Sandy soils containing silt (i.e., "sandy loam") are most favored and account for the high prevalence of hookworm infection in coastal areas.[7] (Adapted from Despommier et al.[8])

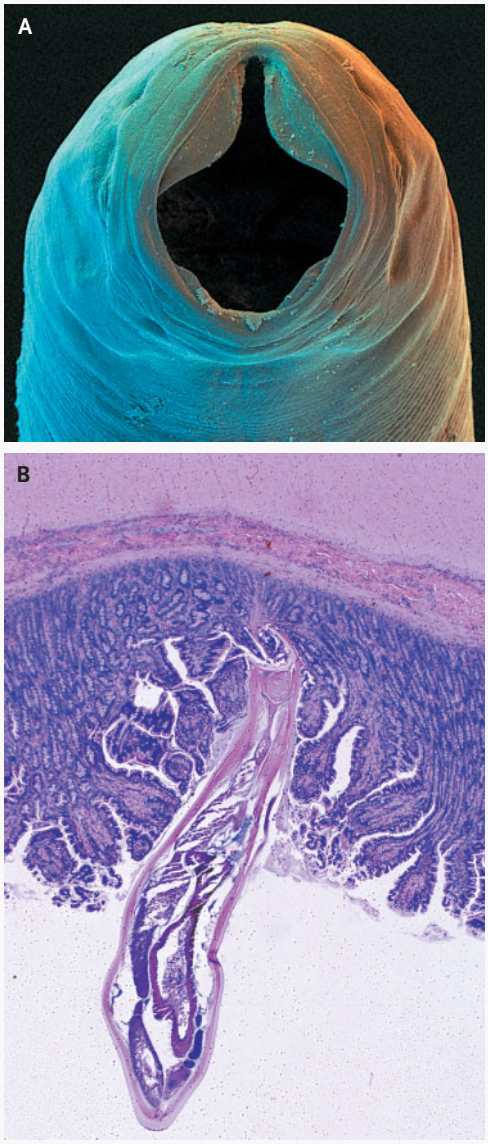

Figure 3. Pathogenesis and Clinical Sequelae of Hookworm Disease.

Panel A shows a scanning electron micrograph of *Necator americanus*. The buccal capsule is characterized by cutting plates, which allow the adult parasite to feed on intestinal mucosa, submucosa, and blood. Each hookworm ranges in length from 5 to 13 mm and causes up to 0.3 ml of blood loss per day. (Photograph by David Scharf; reprinted from Despommier et al.[8] with the permission of the publisher.) Panel B shows an adult hookworm feeding on intestinal mucosa and submucosa (hematoxylin and eosin). (Photograph courtesy of Dr. Bernard Zook, Department of Pathology, George Washington University Medical Center.)

the reduction in hemoglobin, serum ferritin, and protoporphyrin levels (Fig. 4).[15,24]

Most of the physical signs of chronic hookworm infection reflect the presence of iron-deficiency anemia. In addition, anasarca from extensive plasma hypoproteinemia is associated with edema of the face and lower limbs and with potbelly. The skin becomes waxy and acquires a sickly yellowish color (a feature of tropical chlorosis). Hookworm can cause hypothermia that is severe enough to reduce fever caused by malaria.[25] Other than hypochromic microcytic anemia, the most prominent laboratory finding is eosinophilia. Eosinophilia peaks at five to nine weeks after the onset of infection, a period that coincides with the appearance of adult hookworms in the intestine.[13] Patients with a light hookworm burden are usually asymptomatic; however, some patients report subjective clinical improvement after treatment.[26] A moderate or heavy hookworm burden results in recurrent epigastric pain and tenderness, nausea, exertional dyspnea, pain in the lower extremities, palpitations, joint and sternal pain, headache, fatigue, and impotence.[27,28] Some patients crave bulky substances and ingest dirt (pica). In adults, the capacity for work may be adversely affected, and many report an inability to work.[26,29]

HOOKWORM DISEASE IN MOTHERS AND CHILDREN

The overall prevalence and intensity of hookworm infection are higher in males than in females, in part because males have greater exposure to infection. However, women and young children have the lowest iron stores and are therefore most vulnerable to chronic blood loss as the result of hookworm infection.[15,24] In children, chronic hookworm disease retards physical growth,[30] which is sometimes most apparent at puberty. Approximately 80 years ago, an inverse correlation was observed between the hookworm burden and a child's intelligence quotient.[31] More recent evidence suggests that hookworm infection also has subtle yet profound adverse effects on memory, reasoning ability, and reading comprehension in childhood.[32] Most of these effects are probably attributable to the presence of iron-deficiency anemia. Infants and preschool children are particularly vulnerable to the developmental and behavioral deficits caused by iron-deficiency anemia,[33] and two analyses indicate that hookworm infection remains an impor-

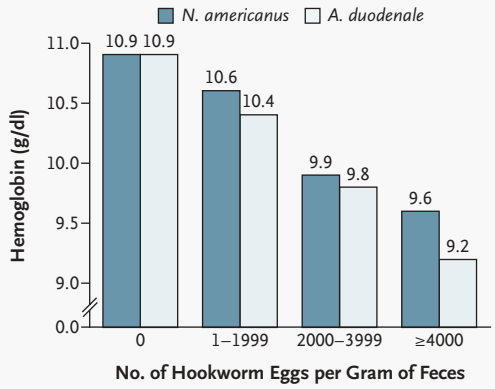

Figure 4. Relationship between the Hookworm Burden and Anemia.

Quantitative egg counts serve as an indirect measure of the adult-hookworm burden (i.e., the number of worms per patient). Hemoglobin levels drop in proportion to infection. (Data are from Albonico et al.[16])

tant contributor to anemia in this age group.[34,35] Hookworm infection in children may reduce school attendance, with subsequent effects on productivity and wage-earning potential in adulthood.[4,29]

Hookworm infection is considered a major health threat to adolescent girls and women of reproductive age, with adverse effects on the outcome of pregnancy.[22,36,37] The World Health Organization estimates that because of increased physiological demands for iron during pregnancy combined with malnutrition, more than half of the pregnant women in developing countries have problems related to iron-deficiency anemia.[37] Severe iron-deficiency anemia during pregnancy has been linked to increased maternal mortality, impaired lactation, and prematurity and low birth weight.[37] An estimated 44 million pregnant women are infected with hookworm worldwide, with 7.5 million in sub-Saharan Africa alone.[22,38] In 1929, A.C. Chandler first pointed out that "pregnancy is a powerful factor in accentuating the effects of hookworm disease, or it might be more accurate to put it vice versa."[39] Estimates in Kenya and Nepal suggest that hookworm infection causes 30 percent and 41 percent, respectively, of moderate or severe cases of anemia among pregnant women (hemoglobin level, <9 g per deciliter).[15] The association between hookworm infection and anemia is greatest in multigravidas.[40,41] It has been conjectured that in China and other regions where *A. duodenale* occurs, hookworm infection during pregnancy could result in vertical transmission to neonates, possibly through ingestion of *A. duodenale* third-stage larvae in milk and colostrum.[42]

In many regions of sub-Saharan Africa, hookworm disease overlaps geographically with falciparum malaria. Since much of the morbidity associated with both diseases results from anemia,[14,15,43] it is possible that hookworm disease exacerbates malarial anemia and vice versa. A potentially promising avenue of research is the further examination of co-endemic infections, such as hookworm infection, malaria, and human immunodeficiency virus (HIV) infection, in which morbidity is due largely or at least in part to anemia.[15,43,44]

DIAGNOSIS IN RETURNING TRAVELERS AND IMMIGRANTS

The cutaneous manifestations of hookworm infection must be differentiated from cercarial dermatitis ("swimmer's itch") and creeping eruption from other causes, such as gnathostomiasis, strongyloidiasis, and infection with fly larvae. The pulmonary manifestations are usually not specific enough to link them specifically to hookworm. Persistent eosinophilia in refugees, especially those from Southeast Asia, is commonly associated with active hookworm infection.[45] Abdominal tenderness or the presence of iron-deficiency anemia in immigrants from areas where hookworm is endemic warrants investigation for infection.[27] The microscopical examination of unconcentrated feces is adequate to identify hookworm eggs and to diagnose clinically important infection. Several quantitative techniques are available to estimate the output of hookworm eggs; these techniques are valuable for epidemiologic studies because they provide indirect measures of the worm burden. The eggs of *A. duodenale* and *N. americanus* are indistinguishable, although the polymerase chain reaction and morphologic examination of cultured third-stage larvae can differentiate the two species.[46] Zoonotic hookworm infection does not cause egg-bearing infections in humans.

EPIDEMIOLOGY, TREATMENT, AND PROSPECTS FOR CONTROL

OVERDISPERSION OF AND PREDISPOSITION TO HOOKWORM INFECTION

In all areas where hookworm is endemic, the variation in the worm burden among persons who be-

come infected is large. High-intensity and low-intensity infections have been recorded among subjects living in similar conditions of exposure to the parasite. The distribution of worm burdens among different human hosts is highly overdispersed so that often only 10 percent of the infected population carries 70 percent of the worms.[47] Because most helminths do not replicate in humans, the rate of morbidity from infections with helminths is typically highest among patients with the heaviest worm burdens. There is evidence that some persons are predisposed to a heavy (or light) hookworm burden owing to either genetic or exposure factors.[48,49]

HOOKWORM AND AGE

For many common helminthic infections, including ascariasis, trichuriasis, and schistosomiasis, the intensity of infection usually peaks during childhood and adolescence (Fig. 5).[47] In contrast, there appears to be considerable variation in the age–intensity profile of hookworm infection. Although the hookworm burden may be heavy in children, especially those in sub-Saharan Africa,[30,34] the most commonly recognized pattern is a steady rise in the intensity of infection during childhood, with either a peak or a plateau in adulthood. In China, age accounts for 27 percent of the variation in the intensity of hookworm infection, with the highest intensity among middle-aged persons, or even those over the age of 60 years.[50] Such infection patterns have implications for the world's expanding elderly populations.[2]

The observation that the intensity of hookworm infection increases with age has led to the suggestion that hookworms can either evade or suppress host immune responses.[51,52] To understand how this occurs, several investigators have either described or isolated antiinflammatory and other immunomodulatory molecules from adult hookworms, including a T-cell apoptotic factor, an integrin antagonist of host CD11b and CD18, a retinol-binding protein, a C-type lectin, a tissue inhibitor of metalloproteases, cysteine-rich secretory proteins, and an eotaxin-degrading factor.[53] These bioactive polypeptides may also have systemwide effects that down-regulate host immune responses to other infections. In the process of mining the hookworm genome,[54] researchers are likely to discover additional molecules.[55] Further study of immunomodulating molecules derived from parasites might shed light on the emerging controversy over the question of whether hookworm as well as other helminths promote susceptibility to HIV infection, malaria, tuberculosis, or other infections.[56,57]

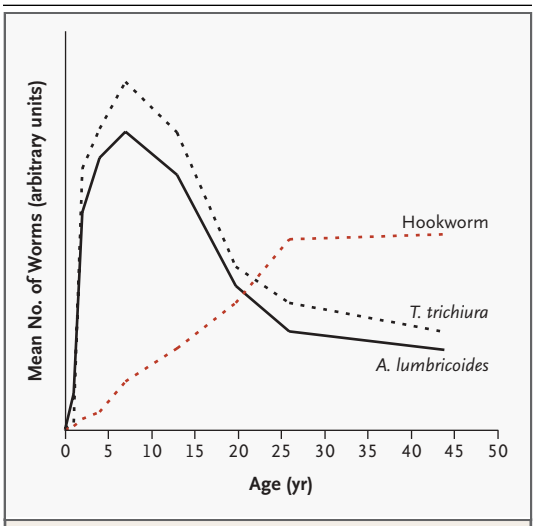

Figure 5. Patterns of Hookworm Infection According to Age.

The hookworm burden increases with age, in contrast to the burden of other soil-transmitted helminths (e.g., *Ascaris lumbricoides* and *Trichuris trichiura*), which is highest in childhood. Worm burden is shown in arbitrary units to emphasize the relative shape of the curves.

SCHOOL-BASED DEWORMING

Although proper sanitation and footwear are often considered important for the control of hookworm, their effect on transmission is frequently either marginal or evident only after decades.[50,53,58] The specific treatment of choice for the removal of hookworms from the intestines is a single dose of a benzimidazole anthelmintic, either albendazole (400 mg) or mebendazole (500 mg).[59] Either agent usually reduces the hookworm burden to a level below the threshold that could result in disease, and both agents are now available generically at low cost. Because of this, a resolution was put forward at the 2001 World Health Assembly urging countries to control schistosomiasis and the soil-transmitted helminthiases — ascariasis, trichuriasis, and hookworm infection. The global target is by 2010 to provide routine treatment for at least 75 percent of all school-age children who are at risk for infection, using a benzimidazole anthelmintic alone or in conjunction with praziquantel.[37] In time, this would become the largest public health program ever attempted.[60] The rationale for focusing on

schools is that school-age children have the highest intensity of ascaris, trichuris, and schistosome infections of any age group, and schools provide a cost-effective way to deliver anthelmintics.[37,61] Either of the benzimidazole anthelmintics can be administered as a single tablet to all children, regardless of their size and age. In communities where infection is common, clinicians can offer treatment to all children without the need to examine each child for the presence of worms. With support from the local health system, teachers can safely administer benzimidazole anthelmintics and praziquantel.[37,61]

School-based deworming offers a number of health-related and other benefits to children, including improvements in iron and hemoglobin status,[62,63] in physical growth,[30,63] in cognition, in educational achievement, and in school absenteeism,[63,64] as well as major advantages for the whole community, including reduced helminth transmission through soil and a lower disease burden, especially for ascariasis and trichuriasis.[61,63,65] It is less obvious, however, what effect school-based deworming will have on reducing the disease burden of hookworm in a community. Because the disease burden is often concentrated among adult populations (including women of reproductive age), and because preschool children are particularly vulnerable to the effects of iron deficiency,[33,34] in many communities school-based programs miss important vulnerable populations that are at risk for hookworm. In contrast to infections with ascaris and trichuris, it is unlikely that school-based deworming will reduce the transmission of hookworm.[66] Moreover, in areas where hookworm is endemic, reinfection often occurs within just a few months after deworming with the use of a benzimidazole anthelmintic.[67] In some cases, treatments are required three times a year to improve the iron status of the host.[63,68] Additional data indicate that the efficacy of treatment with benzimidazole anthelmintics diminishes after periodic therapy.[69] These problems, coupled with theoretical concern about emerging resistance to benzimidazole anthelmintics,[70] have led to efforts among researchers to identify new tools for the control of hookworm.

To date, the reduction of poverty and increased economic development have done more to eliminate hookworm infection in industrialized nations than any other factor, including sanitation, the use of anthelmintics, the use of footwear, and health education.[2] Until such socioeconomic reforms become widespread, the implementation of the World Health Assembly's resolution to reduce infection and the development of a vaccine may help control hookworm infection.

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