Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm

Jeffrey Bethony, Simon Brooker, Marco Albonico, Stefan M Geiger, Alex Loukas, David Diemert, Peter J Hotez

The three main soil-transmitted helminth infections, ascariasis, trichuriasis, and hookworm, are common clinical disorders in man. The gastrointestinal tract of a child living in poverty in a less developed country is likely to be parasitised with at least one, and in many cases all three soil-transmitted helminths, with resultant impairments in physical, intellectual, and cognitive development. The benzimidazole anthelmintics, mebendazole and albendazole, are commonly used to remove these infections. The use of these drugs is not limited to treatment of symptomatic soil-transmitted helminth infections, but also for large-scale prevention of morbidity in children living in endemic areas. As a result of data showing improvements in child health and education after deworming, and the burden of disease attributed to soil-transmitted helminths, the worldwide community is awakening to the importance of these infections. Concerns about the sustainability of periodic deworming with benzimidazole anthelmintics and the emergence of resistance have prompted efforts to develop and test new control tools.

Lancet 2006; 367: 1521–32

Department of Microbiology, Immunology, and Tropical Medicine, The George Washington University, Washington DC, 20037 USA (J Bethony PhD, S M Geiger PhD, Prof P J Hotez MD)**; Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK** (S Brooker DPhil)**; Fondazione Ivo de Carneri, Torino, Italy** (M Albonico MD)**; Fundação Oswaldo Cruz, Centro de Pesquisa René Rachou, Belo Horizonte, Brazil** (J Bethony, S Geiger)**; Queensland Institute of Medical Research, Brisbane, Australia** (A Loukas PhD)**; and Albert B Sabin Vaccine Institute, Washington DC, USA** (D Diemert MD, Prof P J Hotez)

Correspondence to:
Prof Peter J Hotez
mtmpjh@gwumc.edu

Introduction

The soil-transmitted helminths are a group of parasitic nematode worms causing human infection through contact with parasite eggs or larvae that thrive in the warm and moist soil of the world's tropical and subtropical countries. As adult worms, the soil-transmitted helminths live for years in the human gastrointestinal tract. More than a billion people are infected with at least one species (table 1).[1] Of particular worldwide importance are the roundworms (*Ascaris lumbricoides*), whipworms (*Trichuris trichiura*), and hookworms (*Necator americanus* or *Ancylostoma duodenale*). They are considered together because it is common for a single individual, especially a child living in a less developed country, to be chronically infected with all three worms. Such children have malnutrition, growth stunting, intellectual retardation, and cognitive and educational deficits.[1]

The soil-transmitted helminths are one of the world's most important causes of physical and intellectual growth retardation. Yet, despite their educational, economic, and public-health importance (panel), they remain largely neglected by the medical and international community. This neglect stems from three features: first, the people most affected are the world's most impoverished, particularly those who live on less than US$2 per day; second, the infections cause chronic ill health and have insidious clinical presentation; and third, quantification of the effect of soil-transmitted helminth infections on economic development and education is difficult. Over the past 5 years, however, the worldwide community has begun to recognise the importance of these infections after revised estimates showed that their combined disease burden might be as great as those of malaria or tuberculosis.[2] Studies have also highlighted the profound effect of soil-transmitted helminth infection on school performance and attendance and future economic productivity.[3,4] Such infections might also increase host susceptibility to other important illnesses such as malaria, tuberculosis, and HIV infection.[5,6] In 2001, the World Health Assembly passed a resolution urging member states to control the morbidity of soil-transmitted helminth infections through large-scale use of anthelmintic drugs for school-aged children in less developed countries. A response to this resolution could establish one of the

Search strategy and selection criteria

Data for this review were identified by a search of PubMed without date restriction for the items "geohelminth", "soil-transmitted helminths", "hookworms", "*Necator americanus*", "*Ancylostoma duodenale*", "*Ascaris lumbricoides*", and "*Trichuris trichiura*". We also made widespread use of WHO publications on soil-transmitted helminths and chapters of books from the authors. When more than one paper illustrated a specific point, the most representative paper was chosen. We selected papers published in English.

	Disease	Estimated population infected (millions)	Geographic region
Major worldwide pathogens			
Ascaris lumbricoides	Common roundworm infection	807–1221	
Trichuris trichiura	Whipworm infection	604–795	
Necator americanus and *Ancylostoma duodenale*	Hookworm infection	576–740	
Strongyloides stercoralis	Threadworm infection	30–100	
Enterobius vermicularis	Pinworm infection	4–28% of children	
Toxocara canis and *Toxocara cati*	Visceral and ocular larva migrans	2–80% of children	
Pathogens of minor or local importance			
Ancylostoma brazilienese	Cutaneous larva migrans		Coastal regions worldwide
Uncinaria stenocephala	Cutaneous larva migrans		Coastal regions worldwide
Ancylostoma caninum	Eosinophilia enteritis		Australia
Ancylostoma ceylanicum	Hookworm infection		Asia
Baylisascaris procyonis	Eosinophilic meningitis		North America
Oesophagostomum bifurcum	Nodular worm infection		West Africa
Strongyloides fuelleborni	Swollen belly syndrome		Papua New Guinea
Ternidens diminutus	False hookworm infection		Southern Africa

Table 1: **Soil-transmitted helminth infections of human beings**

Panel: **Major websites on biology and public-health effect of soil-transmitted helminths**

WHO partners for parasite control
http://www.who.int/wormcontrol

Focusing resources on effective school health
http://www.freshschools.org

Soil-transmitted helminth genome-sequencing projects
http://www.nematode.net
http://www.sanger.ac.uk/Projects/Helminths/

largest worldwide health initiatives ever undertaken.[7] However, such widespread and frequent use of anthelmintics could lead to drug resistance or at least a decline in effectiveness of these front-line drugs in the long-term battle with soil-transmitted helminths.[8,9]

The parasites

Adult hookworms of the genera *Necator* and *Ancylostoma* parasitise the upper part of the human small intestine, whereas ascaris roundworms parasitise the entire small intestine and adult trichuris whipworms live in the large intestine, especially the caecum (table 2).[10] The parasites can live for several years in the human gastrointestinal tract. Human beings are regarded as the only major definitive host for these parasites, although in some cases ascaris infections can also be acquired from pigs.[11] The soil-transmitted helminths vary greatly in size, and female worms are larger than males (figure 1).[10] After mating, each adult female produces thousands of eggs per day (figure 2), which leave the body in the faeces.

People become infected with *T trichiura* and *A lumbricoides* by ingesting the fully developed eggs. After ingestion of trichuris eggs, the released larvae moult and travel to the colon where they burrow into the epithelia and develop into adult whipworms within about 12 weeks.[10] Ascaris larvae penetrate the intestinal mucosa and after an obligatory extraintestinal migration, they enter the liver then the lungs, before passing over the epiglottis to re-enter the gastrointestinal tract and develop into egg-laying adult worms about 9–11 weeks after egg ingestion.[12]

Species	Length (mm)	Daily egg output per female worm	Location in host	Lifespan (years)
Large common roundworm				
Ascaris lumbricoides	150–400	200 000	Small intestine	1
Whipworm				
Trichuris trichiura	30–50	3000–5000	Caecum and colon	1·5–2·0
Hookworms				
Necator americanus	7–13	9000–10 000	Upper small intestine	5–7
Ancylostoma duodenale	8–13	25 000–30 000	Upper small intestine	5–7

Table 2: **Characteristics of the soil-transmitted helminths: adult worms of greatest public-health significance**

N americanus and *A duodenale* hookworm eggs hatch in soil. The larvae moult twice to become infective third-stage larvae, which are non-feeding but motile organisms that seek out higher ground to improve the chance of contact with human skin. After skin penetration, they enter subcutaneous venules and lymphatic vessels to access the host's afferent circulation. Ultimately, the larvae become trapped in pulmonary capillaries, enter the lungs, pass over the epiglottis, and migrate into the gastrointestinal tract.[13] About 5–9 weeks are needed from skin penetration until development of egg-laying adults. *A duodenale* larvae are also orally infective, and lactogenic transmission during breastfeeding has been postulated. Soil-transmitted helminths do not reproduce within the host. This feature is crucial for understanding of the epidemiology and clinical features of soil-transmitted helminth infections, as well as the approaches to their control.

Epidemiology and burden of disease

Soil-transmitted helminth infections are widely distributed throughout the tropics and subtropics (table 3). Climate is an important determinant of transmission of these infections, with adequate moisture and warm temperature

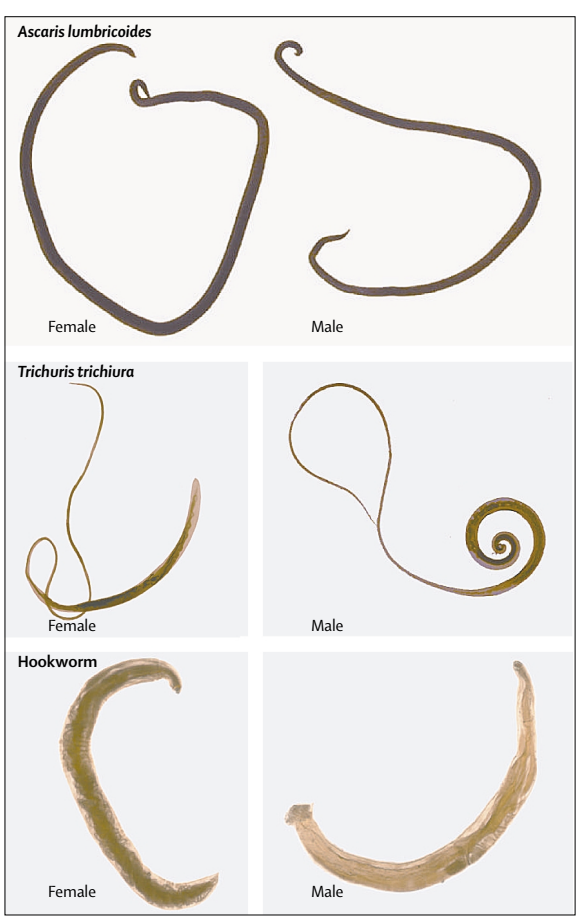

Figure 1: **Adult male and female soil-transmitted helminths**
Reproduced with permission.[10]

essential for larval development in the soil.[15,16] Equally important determinants are poverty and inadequate water supplies and sanitation.[14] In such conditions, soil-transmitted helminth species are commonly coendemic. There is evidence that individuals with many helminth infections have even heavier infections with soil-transmitted helminths.[17] Because morbidity from these infections and the rate of transmission are directly related to the number of worms harboured in the host,[18] intensity of infection is the main epidemiological index used to describe soil-transmitted helminth infection. Intensity of infection is measured by the number of eggs per gram of faeces, generally by the Kato-Katz faecal thick-smear technique.[19] For *A lumbricoides* and *T trichiura*, the most intense infections are in children aged 5–15 years, with a decline in intensity and frequency in adulthood. Whether such age dependency indicates changes in exposure, acquired immunity, or a combination of both remains controversial.[20] Although heavy hookworm infections also occur in childhood, frequency and intensity commonly remain high in adulthood, even in elderly people.[21] Soil-transmitted helminth infections are often referred to as being "overdispersed" in endemic communities, such that most worms are harboured by a few individuals in an endemic area.[22] There is also evidence of familial and household aggregation of infection.[23,24] with the relative contribution of genetics and common household environment debated.

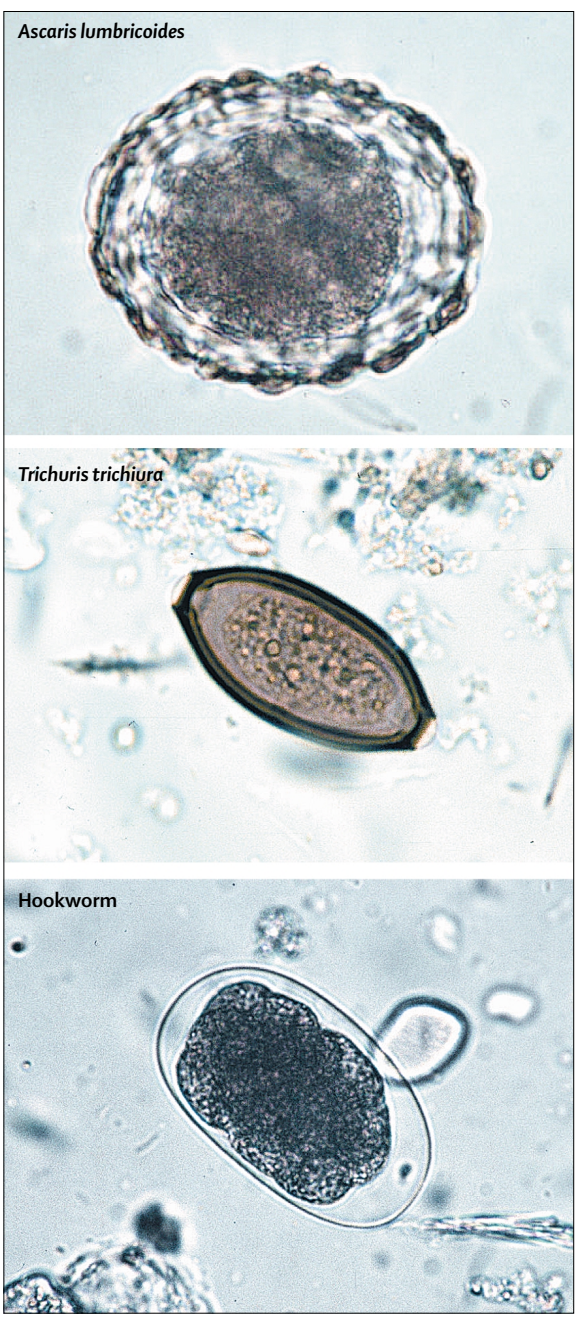

Figure 2: **Soil-transmitted helminth eggs**
Reproduced with permission.[10]

Estimates of annual deaths from soil-transmitted helminth infection vary widely, from 12 000[25] to as many as 135 000.[26] Because these infections cause more disability than death, the worldwide burden, as for many neglected tropical diseases, is typically assessed by disability-adjusted life years (DALY).[27] Since the first DALY estimates were provided, there has been much variability in quoted estimates (table 4),[26–28] partly because of different emphases on the cognitive and health effects. The lower estimates assume that most hookworm cases do not result in severe anaemia or pronounced protein loss by the host, whereas the higher estimates show the long-term results of infection such as malnutrition and delayed cognitive development, especially in children.[29] For these reasons, school-aged children have been the major targets for anthelmintic treatment, and the scale of disease in this age group was pivotal in leveraging support for school-based control.[30, 31]

	LAC	SSA	MENA	SAS	India	EAP	China*	Total
Ascariasis	84	173	23	97	140	204	86	807
Trichuriasis	100	162	7	74	73	159	29	604
Hookworm	50	198	10	59	71	149	39	576

LAC=Latin America and Caribbean; SSA=sub-Saharan Africa; MENA=middle east and north Africa; SAS=south Asia; EAP=east Asia and the Pacific Islands. *New Chinese data derived from Report on the National Survey on Current Situation on Major Human Parasitic Diseases in China, Ministry of Health, PRC, and National Institute of Parasitic Diseases, China CDC, May, 2005

Table 3: **Worldwide estimates of number of soil-transmitted helminth infections by region (millions of cases)[14]**

Infection	1990[27]	1990[28]	2001[25]
Ascariasis	1·8	10·5	1·2
Trichuriasis	1·8	6·4	1·6
Hookworm	1·5	22·1	1·8
Total	5·0	39·0	4·7

Table 4: **Estimates of DALY lost to soil-transmitted helminth infections**

There is evidence to support the high disease-burden estimates from soil-transmitted helminth infections, and highlight the importance of hookworm as a threat to maternal and child health. For example, cross-sectional evidence from Africa and Asia shows that 30–54% of moderate to severe anaemia in pregnant women is attributable to hookworm,[32,33] and intervention studies suggest that antenatal anthelmintics substantially increase maternal haemoglobin concentrations as well as birthweight and infant survival.[34] In childhood, hookworm contributes to moderate and severe anaemia in school-aged children,[35] and there is increasing recognition of a similar contribution in preschool children.[36,37] These features of hookworm disease need to be better incorporated into DALY estimates. Because hookworms are the most widespread species of soil-transmitted helminth in sub-Saharan Africa,[16] where iron stores are low, this consequence of infection could substantially alter the perception of the public-health importance of hookworm. In light of their nutritional and educational effects, soil-transmitted helminth infections clearly need to be reassessed, as has lately been done for schistosomiasis.[38]

Host-parasite interactions

Despite their large size and ability to elicit potent immune responses, soil-transmitted helminths are refractory to host immunity, establishing chronic infections during the host's life, and, in the case of hookworm, intensity of infection actually rises with the age of the host.[21] These organisms have complex life cycles within the human host, undergoing a succession of developmental stages, which can carry stage-specific antigens, and pass through a range of host tissues (skin, lungs, and gut).[39] Soil-transmitted helminths are thought to survive within the host not just by warding off immune attack, but instead by aggressively subverting the host immune response to create niches that optimise successful residence, feeding, and reproduction.[40] Soil-transmitted helminths induce production of cytokines (interleukin-4, interleukin-5, interleukin-10, and interleukin-13), parasite-specific immunoglobulin, and non-specific immunoglobulin E, and expansion and mobilisation of mast cells, eosinophils, and basophils.[41] This constellation of responses is known as the T-helper-2 (Th2) immune response. It is important in allergy and clinical immunology in general.[42] Whether the Th2 response brings about the elimination or the maintenance of the parasite is debated. The functional effector mechanisms driven by the Th2 response to infection with soil-transmitted helminths include eosinophil-mediated larval killing, production of specific and polyclonal immunoglobulin E, mast-cell degranulation, goblet-cell hyperplasia, and increased mucus secretion.[43] Different subsets of effector cells might operate against different nematode species;[43,44] for example, mast cells seem to be central to protective responses against hookworm and ascaris but not in the expulsion of trichuris.[43] Although immunity to hookworm at the population level is not apparent, a negative association between concentrations of interleukin-5 and the likelihood of being reinfected with *N americanus* after anthelmintic treatment has been found, suggesting that the effect of interleukin-5 (probably mediated by eosinophils) is directed against incoming larvae.[45,46] Similarly, inverse associations between secretion of interleukin-5 and interleukin-13 and susceptibility to reinfection were noted in patients infected with *A lumbricoides* or *T trichiura* infections.[47–49]

The survival of soil-transmitted helminths suggests that they succeed by achieving some form of balanced parasitism, in which transmission is maintained and acute morbidity avoided. This ideal homoeostatic state almost certainly needs an environment rich in regulatory mechanisms. Interleukin-10 is the most abundantly produced regulatory cytokine in soil-transmitted helminth infection. However, its role in maintaining the chronicity of soil-transmitted helminth infection is unclear.[40] Geiger and colleagues,[50] reported that interleukin-10 responses to crude ascaris antigen were high in individuals infected with ascaris or trichuris. Whereas Turner and co-workers[49] reported that interleukin-10 concentrations declined with intensity of ascaris infection in older individuals, Jackson and colleagues[48] showed that higher interleukin-10 concentrations correlated with heavier ascaris infection in older people. These downregulatory immune mechanisms might also benefit the host by blocking progression to atopic reactions.[51] The immune response to these infections has long been known to share key features with the allergic response, especially the enhanced Th2 response. In view of these immunological features and the complementary geographic distribution of soil-transmitted helminth infection and allergic disease, many studies have investigated whether the Th2 response to soil-transmitted helminths protects or pre-empts the host from developing allergic manifestations linked to Th2, a theory known as the hygiene hypothesis.[51]

Much of the survival success of soil-transmitted helminths can be attributed to their secretomes, which interact with host tissues and maintain the parasitic existence (table 5). Of particular importance are the secretions that modulate the host's immune response. As helminth proteomes are being matched to increasing gene sequence datasets,[74,75] a molecular snapshot of the mixture released into host tissues by these parasites is being gradually revealed. One constituent, natural-killer-cell-binding protein, is secreted by adult *N americanus* and binds specifically to natural-killer cells and induces them to secrete interferon-γ.[57] This finding is the first evidence of a pathogen-derived protein that binds selectively to natural-killer cells and the first report of a nematode-derived product that induces abundant secretion of cytokines from natural-killer cells. The researchers suggested that interferon-γ production in the gut would counteract the development of a potentially host-protective Th2 response that might eliminate the parasite.[57] Other secreted proteins from adult hookworms

Species	Molecule	Known or putative function	Therapeutic potential	Reference
Hookworms	ASP2	Pathogenesis-related protein of unknown function but secreted on host entry by third-stage larvae	Hookworm vaccine antigen	52–54
		Similar structure to chemokines; possible protease		
		Antiserum blocks third-stage larvae migration		
	NIF	Binds CD11b/CD18 and blocks neutrophil migration	Treatment for cerebral ischaemia	55,56
	NKBP	Binds natural killer cells and induces interferon-γ production	Potential adjuvant	57
	Haemoglobinases	Cascade of mechanistically distinct proteases that digest haemoglobin in the worm's gut	Hookworm vaccine antigens	58–60
	HPI	Pathogenesis-related protein that inhibits platelet activation and adhesion by blocking function of gpIIb/IIIa and gpIa/IIa	Potential hookworm vaccine candidate	61,62
	AcAPs	Novel and potent anticoagulant that inhibit factor Xa, factor VIIa, and tissue factor VIIa/TF	Thrombosis and disseminated intravascular coagulation	63–65
	Eotaxin-cleaving protease	Secreted metalloprotease that digests eotaxin and prevents eosinophil recruitment	..	66
	Haemolysin	Haemolytic protein that forms pores in erythrocyte membranes allowing hemoglobin to be released	Potential hookworm vaccine candidate	67
Ascaris	PI-3	Pepsin inhibitor that protects worms from digestion	..	68
	PC	Phosphorylcholine linked to secreted glycoconjugates suppress lymphocyte proliferation	..	69
Trichuris	TT47	Forms pores in caecal epithelial cells, allowing parasite to keep anterior end in syncytial environment	..	70
	ES products	Promote Th2/Treg response that dampens intestinal inflammation	Therapy for Crohn's disease and ulcerative colitis	71,72
	TsMIF	Inhibits migration of PBMCs by competing with host macrophage inhibitory factor	..	73

ASP-2=*Ancylostoma*-secreted protein 2; NIF=neutrophil inhibitory factor; NKBP=natural-killer-cell-binding protein; HPI=hookworm platelet inhibitor; AcAPs=Ancylostoma caninum anticoagulant peptides; PI-3=pepsin inhibitor 3; PC=phosphoryl choline; TT47=*Trichuris trichiura* 47; ES products=excretory secretory products; TsMIF=*Trichinella spiralis* macrophage inhibitory factor; gpIIb/IIIa=glycoprotein IIb/IIIa ; gpIa/IIa=glycoprotein Ia/IIa ; PBMCs=peripheral blood mononuclear cells.

Table 5: **Selected molecules secreted by soil-transmitted helminths, their known or putative functions and their potentials as anti-helminth vaccines or therapies for other disorders (experimentally proven or suggested by the cited authors)**

modulate immune responses. The dog hookworm, *A caninum*, secretes neutrophil inhibitory factor, which binds to the integrins CD11b/CD18 and blocks adhesion of activated human neutrophils to vascular endothelial cells as well as the release of hydrogen peroxide from activated neutrophils.[55] This protein is in the pathogenesis-related protein superfamily, cysteine-rich secreted proteins that are abundantly expressed by all parasitic nematodes investigated so far. They seem to have diverse roles in nematode parasitism by binding to host cells. Other hookworm pathogenesis-related proteins combat haemostasis by binding to platelets and inhibiting their activation.[61] The observations that these proteins are released by third-stage larvae after stimulation with human serum suggests their importance during the early stages of larval invasion in the host.[76] The crystal structure of *Na* ASP-2,[52] a pathogenesis-related protein from *N americanus* with potential as a hookworm vaccine antigen,[53,77,78] revealed a structural fold that presented a similar charge distribution to that of some chemokines.[52] Serum from laboratory animals vaccinated with ASP-2 blocks larval migration through tissue,[53,78] although the exact mechanism is not known. *N americanus* secretes a metalloprotease that degrades eotaxin, providing a potential strategy to prevent recruitment and activation of eosinophils at the site of infection.[66] The molecules that *Ancylostoma* secrete to inhibit host coagulation and ensure blood flow and continuous bleeding at the site of parasite attachment, including novel inhibitors of factor Xa and VIIa/tissue factor, have also been described in detail,[79] as has a multienzyme cascade involved in host red-blood-cell lysis and haemoglobin digestion.[58]

A lumbricoides has been the focus of much study because of the ease with which large quantities of biological material can be obtained from *A suum* (a close relative that infects swine). Several secreted molecules of *A suum* have been biochemically characterised. Ascaris secretes from its body wall a pepsin inhibitor that is thought to protect maturing worms from digestive enzymes in the stomach before they reach the small intestine. The crystal structure of the pepsin inhibitor from *A suum* complexed with porcine pepsin has been reported,[68] and homologous inhibitors from other soil-transmitted helminths have since been described.[80] The non-proteinaceous secreted nematode molecules are also of interest because of their immunomodulatory properties as pathogen-associated molecular patterns. For example, soil-transmitted helminths secrete phosphorylcholine that is linked to glycoprotein glycans or glycolipids.[81] Phosphorylcholine-bearing molecules interfere with key signalling pathways involved in lymphocyte proliferation could be involved in

the suppression of lymphocyte responses in ascariasis[69] and filarial nematode infections.[82] Moreover, secreted ascaris glycosphingolipids inhibit lipopolysaccharide-induced production of Th1 cytokines such as interferon-γ in a phosphorylcholine-dependent manner,[69] further highlighting the diverse molecular interactions of the immunmodulatory secretory products of the soil-transmitted helminths.

T trichiura secretes large amounts of a protein called TT47 that forms ion-conducting pores in lipid bilayers,[70] allowing the parasite to invade the host gut and maintain its anterior end in a syncytial environment in the caecal epithelium. Unlike *T trichiura*, the swine whipworm *T suis* does not develop to maturity in people, although the larvae can briefly colonise individuals without causing disease. The secreted products of trichuris are potent inducers of anti-inflammatory cytokines.[71] This attribute has led to the use of *T suis* to treat proinflammatory autoimmune disorders such as Crohn's disease,[72] in which helminth larvae are thought to create an anti-inflammatory local environment in the gut that combats the proinflammatory (Th1-biased) immune response associated with this disease. The specific secreted molecules in *T suis* that induce the anti-inflammatory response are unknown, although potential candidates include one that mimics the effects of the human chemokine, macrophage migration inhibitory factor.[73]

Clinical features

The clinical features of soil-transmitted helminth infections can be classified into the acute manifestations associated with larval migration through the skin and viscera, and the acute and chronic manifestations resulting from parasitism of the gastrointestinal tract by adult worms (table 6).

Early larval migration

Migrating soil-transmitted helminth larvae provoke reactions in many of the tissues through which they pass. For example, ascaris larvae that die during migration through the liver can induce eosinophilic granulomas.[83] In the lungs, ascaris larval antigens cause an intense inflammatory response consisting of eosinophilic infiltrates that can be seen on chest radiographs. The resulting verminous pneumonia is commonly accompanied by wheezing, dyspnoea, a non-productive cough, and fever, with blood-tinged sputum produced during heavy infections. Children are more susceptible to pneumonitis, and the disease is more severe on reinfection. In some regions—such as Saudi Arabia—verminous pneumonia is seasonal and occurs after spring rains.[84] Small numbers of affected children develop status asthmaticus, leading to the idea that *A lumbricoides* and its zoonotic counterpart, *Toxocara canis*, are occult environmental causes of asthma.[85,86]

Several cutaneous syndromes result from skin-penetrating larvae. Repeated exposure to *N americanus* and *A duodenale* hookworm third-stage larvae results in ground itch, a local erythematous and papular rash accompanied by pruritus on the hands and feet.[13] By contrast, when zoonotic hookworm third-stage larvae—typically *A braziliense*—enter the skin, they produce cutaneous larva migrans, which is characterised by the appearance of serpiginous tracks on the feet, buttocks, and abdomen.[87] After skin invasion, hookworm third-stage larvae travel through the vasculature and enter the lungs, although the resulting pneumonitis is not as great as in ascaris infection.[13,88] Oral ingestion of *A duodenale* larvae can result in Wakana syndrome, which is characterised by nausea, vomiting, pharyngeal irritation, cough, dyspnoea, and hoarseness.[13]

	Specific clinical features/syndromes		General features
	Larval migration	Adult gastrointestinal parasitism	
Ascariasis	Verminous pneumonia	Lactose intolerance	Impaired growth
		Vitamin A malabsorption	Impaired physical fitness
		Intestinal obstruction	Impaired cognition
		Hepatopancreatic ascariasis	Reductions in school attendance and performance
Trichuriasis	None	Colitis	
		Trichuris dysentery syndrome	
		Rectal prolapse	
Hookworm	Ground itch	Intestinal blood loss	
	Cough	Iron-deficiency anaemia	
	Wakana disease	Protein malnutrition	

Table 6: **Specific and general clinical features or syndromes of the soil-transmitted helminth infections of major medical importance**

Intestinal parasitism

Generally only soil-transmitted helminth infections of moderate and high intensity in the gastrointestinal tract produce clinical manifestations, with the highest-intensity infections most common in children.[28] The numerical threshold at which worms cause disease in children has not been established, because it depends on the underlying nutritional status of the host. Each of the major soil-transmitted helminths produces characteristic disease syndromes.

Ascariasis

The presence of large numbers of adult ascaris worms in the small intestine can cause abdominal distension and pain (figure 3). They can also cause lactose intolerance and malabsorption of vitamin A and possibly other nutrients,[89] which might partly cause the nutritional and growth failure. In young children, adult worms can aggregate in the ileum and cause partial obstruction because the lumen is small.[90,91] Various grave consequences can ensue, including intussusception, volvulus, and complete obstruction,[90] leading to bowel infarction and intestinal perforation. The resulting peritonitis can be fatal, although if the child survives, the wandering adult worms can die and cause a chronic

granulomatous peritonitis. Typically, a child with obstruction because of ascaris has a toxic appearance with signs and symptoms of peritonitis. In some cases, a mass can be felt in the right lower quadrant.[92] Adult worms can enter the lumen of the appendix, leading to acute appendicular colic and gangrene of the appendix tip, resulting in a clinical picture indistinguishable from appendicitis. Adult ascaris worms also tend to move in children with high fever, resulting in the emergence of worms from the nasopharynx or anus. Hepatobiliary and pancreatic ascariasis results when adult worms in the duodenum enter and block the ampullary orifice of the common bile duct, leading to biliary colic, cholecystitis, cholangitis, pancreatitis, and hepatic abscess.[90] By contrast with intestinal obstruction, hepatobiliary and pancreatic ascariasis occurs more commonly in adults—especially women—than in children, presumably because the adult biliary tree is large enough to accommodate an adult worm.[90]

Trichuriasis

Adult whipworms live preferentially in the caecum, although in heavy infections, whipworms can be seen throughout the colon and rectum. The adult parasite leads both an intracellular and an extracellular existence, with the anterior end embedded in epithelial tunnels within the intestinal mucosa and the posterior end located in the lumen. Inflammation at the site of attachment from large numbers of whipworms results in colitis. Longstanding colitis produces a clinical disorder that resembles inflammatory bowel disease, including chronic abdominal pain and diarrhoea, as well as the sequelae of impaired growth, anaemia of chronic disease, and finger clubbing.[93] Trichuris dysentery syndrome is an even more serious manifestation of heavy whipworm infection, resulting in chronic dysentery and rectal prolapse.[93] Whipworm infection can also exacerbate colitis caused by infection with *Campylobacter jejuni*.[94]

Hookworm infection

In hookworm infection, the appearance of eosinophilia coincides with the development of adult hookworms in the intestine.[95] The major pathology of hookworm infection, however, results from intestinal blood loss as a result of adult parasite invasion and attachment to the mucosa and submucosa of the small intestine.[13] Hookworm disease occurs when the blood loss exceeds the nutritional reserves of the host, thus resulting in iron-deficiency anaemia. The presence of more than 40 adult worms in the small intestine is estimated to be sufficient to reduce host haemoglobin concentrations below 11 g/dL,[96] although the exact number depends on several factors including the species of hookworm—*A duodenale* causes more blood loss than *N americanus*—and the host iron reserves.[13,97] The clinical manifestations of hookworm disease resemble those of iron-deficiency anaemia from other causes. The chronic protein loss from heavy hookworm infection can result in hypoproteinaemia and anasarca.[13] Because children and women of reproductive age have reduced iron reserves, they are at particular risk of hookworm disease. The severe iron-deficiency anaemia that can arise from hookworm disease during pregnancy can have adverse results for the mother, the fetus, and the neonate.[34]

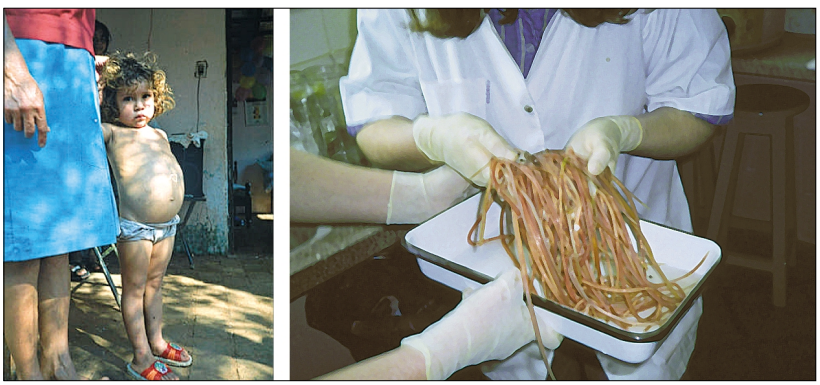

Figure 3: **Girl from Paraguay with heavy ascaris infection before deworming and worms extracted**
Photographs courtesy of Dr Nora Labiano-Abello (left image) and reproduced with permission reference 10 (right image).

Diagnosis and treatment

In their definitive host, each adult female whipworm or hookworm produces thousands of eggs per day, and each female ascaris worm produces upwards of 200 000 eggs daily (table 2). Because many soil-transmitted helminth infections present without specific signs and symptoms, the clinician typically needs some index of suspicion, such as local epidemiology or country of origin, to request a faecal examination. In some cases, especially of hookworm infection, persistent eosinophilia is a common presenting finding.[98] Several egg concentration techniques—eg, formalinethyl acetate sedimentation—can detect even light infections.[12] The Kato-Katz faecal-thick smear and the McMaster method are used to measure the intensity of infection by estimating the number of egg counts per gram of faeces.[99,100] Ultrasonography and endoscopy are useful for diagnostic imaging of the complications of ascariasis, including intestinal obstruction and hepatobiliary and pancreatic involvement.[90,101]

The treatment goal for soil-transmitted helminth infections is to remove adult worms from the gastrointestinal tract (table 7). The drugs most commonly used for the removal of soil-transmitted helminth infections are mebendazole and albendazole. These benzimidazole drugs bind to nematode β-tubulin and inhibit parasite microtubule polymerisation,[104] which causes death of adult worms through a process that can take several days. Although both albendazole and mebendazole are deemed broad-spectrum anthelmintic agents, important therapeutic differences affect their use in clinical practice. Both agents are effective against ascaris in a single dose. However, in hookworm, a single

	Infection	Drug	Dose
		Adult	Child
Ascariasis	Albendazole†	400 mg once	400 mg once
	Mebendazole	100 mg twice a day for 3 days	100 mg twice a day for 3 days
		500 mg once	500 mg once
	Pyrantel pamoate	11 mg/kg (maximum dose 1 g) for 3 days	11 mg/kg (maximum dose 1 g) for 3 days
	Levamisole	2·5 mg/kg once	2·5 mg/kg once
Hookworm	Albendazole*	400 mg once	400 mg once
	Mebendazole	100 mg twice a day for 3 days	100 mg twice a day for 3 days
	Pyrantel pamoate	11 mg/kg (maximum dose 1 g) for 3 days	11 mg/kg (maximum dose 1 g) for 3 days
	Levamisole	2·5 mg/kg once; repeat after 7 days in heavy infection	2·5 mg/kg once; repeat after 7 days in heavy infection
Trichuriasis	Mebendazole	100 mg twice a day for 3 days	100 mg twice a day for 3 days
		500 mg once	500 mg once
	Albendazole*	400 mg for 3 days	400 mg for 3 days

*Modified from the *Medical Letter on Drugs and Therapeutics, Drugs for Parasitic Infections*.[102] †In children of 1–2 years the dose of albendazole is 200 mg instead of 400 mg, based on a recommendation in the Report of the WHO informal consultation on the use of praziquantel during pregnancy and lactation and albendazole/mebendazole in children under 24 months.[103]

Table 7*: Treatment of soil-transmitted helminth infections

dose of mebendazole has a low cure rate and albendazole is more effective.[105,106] Conversely, a single dose of albendazole is not effective in many cases of trichuriasis.[107] For both trichuriasis and hookworm infection, several doses of benzimidazole anthelmintic drugs are commonly needed. Another important difference between the two drugs is that mebendazole is poorly absorbed from the gastrointestinal tract so its therapeutic activity is largely confined to adult worms. Albendazole is better absorbed, especially when ingested with fatty meals, and the drug is metabolised in the liver to a sulphoxide derivative, which has a high volume of distribution in the tissues.[108] For this reason, albendazole is used for the treatment of disorders caused by tissue-migrating larvae such as visceral larva migrans caused by *Toxocara canis*. Systemic toxic effects, such as those on the liver and bone marrow, are rare for the benzimidazole anthelmintic drugs in the doses used to treat soil-transmitted helminth infections. However, transient abdominal pain, diarrhoea, nausea, dizziness, and headache commonly occur.

Because the benzimidazole anthelmintic drugs are embryotoxic and teratogenic in pregnant rats, there are concerns about their use in children younger than 12 months and during pregnancy. Overall, the experience with these drugs in children younger than 6 years is scarce, although evidence suggests they are probably safe. A review of the use of the benzimidazole anthelmintic drugs in children aged 12–24 months concluded that they can be used "if local circumstances show that relief from ascariasis and trichuriasis is justified".[109] Both pyrantel pamoate and levamisole are regarded as alternative drugs for the treatment of hookworm and ascaris infections, although the former is not effective for the treatment of trichuriasis and they are administered by bodyweight.

Morbidity control through deworming

The use of anthelmintic drugs nowadays is not restricted to the treatment of symptomatic soil-transmitted helminth infections; the drugs are now used also for large-scale morbidity reduction in endemic communities. Increasing evidence suggests that chronic infection with soil-transmitted helminths results in impaired childhood growth and poor physical fitness and nutritional status. The causal link between chronic infection and impaired childhood development is extrapolated from the recorded improvement in these features after deworming.[110–115] The mechanisms underlying these associations are thought to involve impairment of nutrition, although there is little specific evidence to support this assumption.[112]

Regular treatment with benzimidazole anthelmintic drugs in school-age children reduces and maintains the worm burden below the threshold associated with disease.[31,110] The benefits of regular deworming in this age group include improvements in iron stores,[112] growth and physical fitness,[112,113] cognitive performance,[4] and school attendance.[4] In younger children, studies have shown improved nutritional indicators such as reduced wasting, malnutrition, and stunting, and improved appetite.[111,114] Treated children had better scores for motor and language milestones in their early development,[115] although some investigators still find this relation controversial. Relevant to these findings, administration of anthelmintic drugs to children infected with soil-transmitted helminths from 1 year of age is now deemed appropriate.[116] The patents on anthelmintic drugs recommended by WHO have expired, and the drugs can be produced at low cost by generic manufacturers. The cost of drug delivery is also low because after simple training, teachers could be involved in deworming.[1] If women in endemic areas are treated once or twice during pregnancy, there are substantial improvements in maternal anaemia[117,118] and birthweight and infant mortality at 6 months.[34] In areas where hookworm infections are endemic, anthelmintic treatment is recommended during pregnancy except in the first trimester.[119–121]

An important factor in treatment is reinfection. After community-wide treatment, rates of hookworm infection reach 80% of pretreatment rates within 30–36 months.[122] *A lumbricoides* infection reached 55% of pretreatment rates within 11 months[123] and *T trichiura* infection reached 44% of pretreatment rates within 17 months.[23] Despite reinfection, however, regular treatment to reduce the worm burden consistently could prevent some of the sequelae associated with chronic infection.

Drug resistance against the front-line anthelmintics is widespread in nematodes of livestock as a result of frequent treatment of animals kept in close proximity and with little gene flow. If such conditions were replicated in human nematodes, drug resistance would

soon arise.[124] Human nematodes have longer reproducing times, are subjected to less frequent treatment (the treatment interval is longer than the parasites' generation time), and the treatment is targeted at certain populations, thereby sparing a circulating pool of sensitive alleles, which should reduce selection pressure.[125] Nevertheless, the effectiveness of drugs must be closely monitored, especially in areas where drug pressure is high, such as regions where mass anthelmintic chemotherapy is also administered for the elimination of lymphatic filariasis. Development of sensitive methods for the early detection of anthelmintic resistance are part of the research agenda, with special attention being given to in-vitro tests and molecular biology techniques that could be adaptable to field conditions.[9] Because no new anthelmintic drugs are in late-stage development at present, the effectiveness of available products needs to be preserved.

New control methods

Concerns about the sustainability of periodic deworming with benzimidazole anthelmintic drugs and the emergence of resistance with widespread use have prompted efforts to develop and test new control tools. Nitazoxanide, a nitroimidazole compound that is increasingly used in children with giardiasis and cryptosporodiosis, is also being explored as a broad-spectrum antiparasitic agent with anthelmintic properties.[126] Tribendimidine has low toxicity, yet broad-spectrum activity against many soil-transmitted helminths.[127] In randomised studies in China, tribendimidine was equivalent to mebendazole and albendazole for the treatment of *A lumbricoides*, *T trichiura*, and hookworm infections, and better than these drugs for *N americanus* infection.[127] A study comparing tribendimidine with albendazole for the treatment of hookworm is under way in Africa. Combination therapy with drugs with differing modes of action is an alternative strategy to improve efficacy and lower the risk of resistance.[9] For example, combinations of levamisole with mebendazole and of pyrantel with oxantel are more effective than any single drug.[2,128]

Vaccination remains the method of choice to control soil-transmitted helminth infection, because it offers the possibility of a simple, single step for the interruption of infection, disease, and transmission. Several substantial obstacles impede vaccine development against soil-transmitted helminths,[39] including the lack of good animal models and a poor understanding of the events that permit soil-transmitted helminths to endure for years in their human host in the face of a potent immune response. Nevertheless, a hookworm vaccine consisting of the recombinant larval antigen ASP2 is effective in animal models (dogs and hamsters) and has shown a protective association in immunoepidemiology studies in two continents.[53,78,129,130] The *Na* ASP-2 hookworm vaccine is now undergoing clinical development in human beings.[131]

Conclusions

Soil-transmitted helminth infections in people will remain a worldwide public-health threat for as long as poverty persists in the developing world. The UN agencies have appropriately recognised the health and educational effect of these infections in children, and have taken steps to distribute anthelmintic drugs in schools and to undertake chemotherapy programmes on an unprecedented scale. Large-scale deworming is necessary to reduce the worldwide morbidity of these infections, but without improved water supplies and sanitation this approach cannot be relied on for sustainable reductions in parasite frequency or intensity of infection. The infrastructure that has been established for deworming of children in schools is expected, however, to facilitate introduction of new anthelmintic vaccines and other control tools,[131] and some of the proposed interventions for the integrated control of endemic neglected tropical coinfections such as lymphatic filariasis, onchocerciasis, schistosomiasis, and trachoma.[132] Such strategies could result in substantial reductions in the worldwide disease burden in the years to come.

Conflict of interest statement

P Hotez is an inventor on an international patent application: PCT/US02/33106 (filed Nov 11, 2002) "Hookworm vaccine". The patent was filed in the USA, Brazil, India, China, and Mexico. If awarded, the patent would belong to the George Washington University with an exclusive licence to the Human Hookworm Vaccine Initiative of the Albert B Sabin Vaccine Institute, a non-profit (501c3) organisation devoted to increasing the use of vaccines worldwide. The Human Hookworm Vaccine Initiative is funded mainly by the Bill and Melinda Gates Foundation. Because hookworm is a neglected disease affecting the poorest people in less developed countries, a hookworm vaccine is not expected to have commercial value or income-generating potential. The rationale for filing a patent is to ensure that the vaccine is developed for those who need it and to encourage vaccine manufacturers in less developed countries to work with the Sabin Vaccine Institute for manufacture of the hookworm vaccine. The first-generation hookworm vaccine, the *Na*-ASP-2 vaccine was developed entirely in the non-profit sector through the Human Hookworm Vaccine Initiative of the Albert B Sabin Vaccine Institute. P Hotez is a co-chair of the Scientific Advisory Council of the Albert B Sabin Vaccine Institute, but he receives no compensation for this activity. He is also a member of the academic advisory board for the Pfizer Postdoctoral Fellowship in Infectious Diseases. This provides a postdoctoral fellowship to a highly-qualified infectious diseases specialist conducting basic and translational research in infectious diseases at an academic medical centre. This activity is unrelated to anything discussed in this Seminar. J Bethony is the recipient of an International Research Scientist Award (KO1) from Fogarty International Center of the National Institutes of Health. S Brooker is the recipient of a Wellcome Trust Advanced Research Fellowship (073656). A Loukas is the recipient of an RD Wright Career Development Award from the National Health and Medical Research Council of Australia. M Albonico is supported by the Fondazione Ivo de Carneri. All the authors receive funding from the Bill and Melinda Gates Foundation through the Human Hookworm Vaccine Initiative of the Albert B Sabin Vaccine Institute. No funding source had any role in the writing of this Seminar.

References

1 WHO. Deworming for health and development. Report of the third global meeting of the partners for parasite control. Geneva: World Health Organization, 2005.

2 Chan MS. The global burden of intestinal nematode infections: fifty years on. *Parasitol Today* 1997; **13:** 438–43.

3 Bleakley H. Disease and development: evidence from hookworm eradication in American South. *J European Econ Assoc* 2003; **1:** 376–86.

4 Miguel EA, Kremer M. Worms: identifying impacts on education and health in the presence of treatment externalities. *Econometrica* 2003; **72:** 159–217.

5 Fincham JE, Markus MB, Adams VJ. Could control of soil-transmitted helminthic infection influence the HIV/AIDS pandemic? *Acta Trop* 2003; **86:** 315–33.

6 Le Hesran JY, Akiana J, Ndiaye el HM, Dia M, Senghor P, Konate L. Severe malaria attack is associated with high prevalence of *Ascaris lumbricoides* infection among children in rural Senegal. *Trans R Soc Trop Med Hyg* 2004; **98:** 397–99.

7 Horton J. Global anthelmintic chemotherapy programs: learning from history. *Trends Parasitol* 2003; **19:** 405–99.

8 Albonico M, Bickle Q, Ramsan M, Montresor A, Savioli L, Taylor M. Efficacy of mebendazole and levamisole alone or in combination against intestinal nematode infections after repeated targeted mebendazole treatment in Zanzibar. *Bull World Health Organ* 2003; **81:** 343–52.

9 Albonico M, Engels D, Savioli L. Monitoring drug efficacy and early detection of drug resistance in human soil-transmitted nematodes: a pressing public health agenda for helminth control. *Int J Parasitol* 2004; **34:** 1205–10.

10 Despommier D, Gwadz RW, Hotez PJ, Knirsch CA. Parasitic diseases, 5th edn. New York: Apple Tree Production, 2005.

11 Crompton DW. Ascaris and ascariasis. *Adv Parasitol* 2001; **48:** 285–375.

12 Faust EC, Russell PF. Craig and Faust's clinical parasitology. Philadelphia: Lea & Febiger, 1964.

13 Hotez PJ, Brooker S, Bethony JM, Bottazzi ME, Loukas A, Xiao S. Hookworm infection. *N Engl J Med* 2004; **351:** 799–807.

14 de Silva NR, Brooker S, Hotez PJ, Montresor A, Engels D, Savioli L. Soil-transmitted helminth infections: updating the global picture. *Trends Parasitol* 2003; **19:** 547–51.

15 Brooker S, Clements A, Bundy DAP. Global epidemiology, ecology and control of soil-transmitted helminth infections. *Adv Parasitol* 2006; **62:** 223–65.

16 Brooker S, Michael E. The potential of geographical information systems and remote sensing in the epidemiology and control of human helminth infections. *Adv Parasitol* 2000; **47:** 245–88.

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

18 Anderson RM, May RM. Infectious diseases of humans: dynamics and control. Oxford: Oxford University Press, 1991.

19 Katz N, Chaves A, Pellegrino J. A simple device for quantitative stool thick-smear technique in schistosomiasis mansoni. *Rev Inst Med Trop Sao Paulo* 1972; **14:** 397–400.

20 Galvani AP. Age-dependent epidemiological patterns and strain diversity in helminth parasites. *J Parasitol* 2005; **91:** 24–30.

21 Bethony J, Chen J, Lin S, et al. Emerging patterns of hookworm infection: influence of aging on the intensity of *Necator* infection in Hainan Province, People's Republic of China. *Clin Infect Dis* 2002; **35:** 1336–44.

22 Anderson RM, May RM. Helminth infections of humans: mathematical models, population dynamics, and control. *Adv Parasitol* 1985; **24:** 1–101.

23 Chan L, Bundy DA, Kan SP. Aggregation and predisposition to *Ascaris lumbricoides* and *Trichuris trichiura* at the familial level. *Trans R Soc Trop Med Hyg* 1994; **88:** 46–48.

24 Forrester JE, Scott ME, Bundy DAP, Golden MHN. Clustering of *Ascans lumbricoides* and *Trichuris trichiura* infections within households. *Trans Roy Soc Trop Med Hyg* 1988; **82:** 282–88.

25 WHO. World health report: annex table 2: deaths by cause, sex, and mortality stratum in WHO regions and annex table 3: burden of disease in DALYs by cause, sex and mortality stratum in WHO regions. Geneva: World Health Organization, 2002: 186–93.

26 WHO. Prevention and control of schistosomiasis and soil-transmitted helminthiasis. Geneva: World Health Organization, 2004.

27 Murray CJL, Lopez AD. The global burden of disease: a comprehensive assessment of mortality and morbidity from disease, injuries, and risk factors in 1990 and projected to 2020. Cambridge, MA: Harvard University Press, 1996.

28 Chan MS, Medley GF, Jamison D, Bundy DA. The evaluation of potential global morbidity attributable to intestinal nematode infections. *Parasitology* 1994; **109:** 373–87.

29 Bundy DAP, Chan MS, Medley GF, Jamison D, Savioli L. Intestinal nematode infections. In: Murray CJL, Lopez AD, Mathers CD, eds. Global epidemiology of infectious disease: Global burden of disease volume IV. Geneva: World Health Organization, 2004. 243–300. http://whqlibdoc.who.int/publications/2004/9241592303.pdf (accessed Feb 20, 2006).

30 Bundy DA, Shaeffer S, Jukes M, et al. School-based health and nutrition programs. In: Jamison D, Breman J, Meacham A, et al., eds. Disease control priorities in developing countries, 2nd edn. New York: World Bank, World Health Organization, Fogarty International Center of the National Institutes of Health, US Department of Health and Human Services (in press).

31 Savioli L, Stansfield S, Bundy DA, et al. Schistosomiasis and soil-transmitted helminth infections: forging control efforts. *Trans R Soc Trop Med Hyg* 2002; **96:** 577–79.

32 Stoltzfus RJ, Dreyfuss ML, Chwaya HM, Albonico M. Hookworm control as a strategy to prevent iron deficiency. *Nutr Rev* 1997; **55:** 223–32.

33 Navitsky RC, Dreyfuss ML, Shrestha J, Khatry SK, Stoltzfus RJ, Albonico M. *Ancylostoma duodenale* is responsible for hookworm infections among pregnant women in the rural plains of Nepal. *J Parasitol* 1998; **84:** 647–51.

34 Christian P, Khatry SK, West KP Jr. Antenatal anthelmintic treatment, birthweight, and infant survival in rural Nepal. *Lancet* 2004; **364:** 981–83.

35 Crompton DW, Stephenson LS. Hookworm infection, nutritional status, and productivity. In: Schad GA, Warren KS, eds. Hookworm disease: current status and new directions. London: Taylor and Frances, 1990: 231–64.

36 Brooker S, Peshu N, Warn PA, et al. The epidemiology of hookworm infection and its contribution to anaemia among pre-school children on the Kenyan coast. *Trans R Soc Trop Med Hyg* 1999; **93:** 240–46.

37 Stoltzfus RJ, Chwaya HM, Montresor A, Albonico M, Savioli L, Tielsch JM. Malaria, hookworms and recent fever are related to anemia and iron status indicators in 0- to 5-y old Zanzibari children and these relationships change with age. *J Nutr* 2000; **130:** 1724–33.

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

39 Maizels RM, Holland MJ, Falcone FH, Zang XX, Yazdanbakhsh M. Vaccination against helminth parasites: the ultimate challenge for vaccinologists? *Immunol Rev* 1999; **171:** 125–47.

40 Maizels RM, Balic A, Gomez-Escobar N, Nair M, Taylor MD, Allen JE. Helminth parasites: masters of regulation. *Immunol Rev* 2004; **201:** 89–116.

41 Maizels RM, Bundy DA, Selkirk ME, Smith DF, Anderson RM. Immunological modulation and evasion by helminth parasites in human populations. *Nature* 1993; **365:** 797–805.

42 Mosmann TR, Coffman RL. TH1 and TH2 cells: different patterns of lymphokine secretion lead to different functional properties. *Annu Rev Immunol* 1989; **7:** 145–73.

43 Bradley JE, Jackson JA. Immunity, immunoregulation and the ecology of trichuriasis and ascariasis. *Parasite Immunol* 2004; **26:** 429–41.

44 Finkelman FD, Shea-Donohue T, Goldhill J, et al. Cytokine regulation of host defense against parasitic gastrointestinal nematodes: lessons from studies with rodent models. *Annu Rev Immunol* 1997; **15:** 505–33.

45 Maizels RM, Balic A. Resistance to helminth infection: the case for interleukin-5-dependent mechanisms. *J Infect Dis* 2004; **190:** 427–29.

46 Quinnell RJ, Pritchard DI, Raiko A, Brown AP, Shaw MA. Immune responses in human necatoriasis: association between interleukin-5 responses and resistance to reinfection. *J Infect Dis* 2004; **190:** 430–38.

47 Jackson JA, Turner JD, Rentoul L, et al. T helper cell type 2 responsiveness predicts future susceptibility to gastrointestinal nematodes in humans. *J Infect Dis* 2004; **190:** 1804–11.

48 Jackson JA, Turner JD, Rentoul L, et al. Cytokine response profiles predict species-specific infection patterns in human GI nematodes. *Int J Parasitol* 2004; **34:** 1237–44.

49 Turner JD, Faulkner H, Kamgno J, et al. Th2 cytokines are associated with reduced worm burdens in a human intestinal helminth infection. *J Infect Dis* 2003; **188:** 1768–75.

50 Geiger SM, Massara CL, Bethony J, Soboslay PT, Carvalho OS, Correa-Oliveira R. Cellular responses and cytokine profiles in *Ascaris lumbricoides* and *Trichuris trichiura* infected patients. *Parasite Immunol* 2002; **24:** 499–509.

51 Yazdanbakhsh M, van den Biggelaar A, Maizels RM. Th2 responses without atopy: immunoregulation in chronic helminth infections and reduced allergic disease. *Trends Immunol* 2001; **22:** 372–77.

52 Asojo OA, Goud G, Dhar K, et al. X-ray structure of Na-ASP-2, a pathogenesis-related-1 protein from the nematode parasite, *Necator americanus*, and a vaccine antigen for human hookworm infection. *J Mol Biol* 2005; **346:** 801–14.

53 Bethony J, Loukas A, Smout M, et al. Antibodies against a secreted protein from hookworm larvae reduce the intensity of hookworm infection in humans and vaccinated laboratory animals. *FASEB J* 2005; **19:** 1743–45.

54 Hawdon JM, Narasimhan S, Hotez PJ. Ancylostoma secreted protein 2: cloning and characterization of a second member of a family of nematode secreted proteins from *Ancylostoma caninum*. *Mol Biochem Parasitol* 1999; **99:** 149–65.

55 Moyle M, Foster DL, McGrath DE, et al. A hookworm glycoprotein that inhibits neutrophil function is a ligand of the integrin CD11b/CD18. *J Biol Chem* 1994; **269:** 10008–15.

56 Jiang N, Chopp M, Chahwala S. Neutrophil inhibitory factor treatment of focal cerebral ischemia in the rat. *Brain Res* 1998; **788:** 25–34.

57 Hsieh GC, Loukas A, Wahl AM, et al. A secreted protein from the human hookworm *Necator americanus* binds selectively to NK cells and induces IFN-γ production. *J Immunol* 2004; **173:** 2699–704.

58 Williamson AL, Lecchi P, Turk BE, et al. A multi-enzyme cascade of hemoglobin proteolysis in the intestine of blood-feeding hookworms. *J Biol Chem* 2004; **279:** 35950–57.

59 Loukas A, Bethony JM, Williamson AL, et al. Vaccination of dogs with a recombinant cysteine protease from the intestine of canine hookworms diminishes the fecundity and growth of worms. *J Infect Dis* 2004; **189:** 1952–61.

60 Loukas A, Bethony JM, Mendez S, et al. Vaccination with recombinant aspartic hemoglobinase reduces parasite load and protects against anemia after challenge infection with blood-feeding hookworms. *PLoS Med* 2005; **2:** e295.

61 Del Valle A, Jones BF, Harrison LM, Chadderdon RC, Cappello M. Isolation and molecular cloning of a secreted hookworm platelet inhibitor from adult *Ancylostoma caninum*. *Mol Biochem Parasitol* 2003; **129:** 167–77.

62 Chadderdon RC, Cappello M. The hookworm platelet inhibitor: functional blockade of integrins GPIIb/IIIa (αIIbβ3) and GPIa/IIa (α2β1) inhibits platelet aggregation and adhesion in vitro. *J Infect Dis* 1999; **179:** 1235–41.

63 Cappello M, Vlasuk GP, Bergum PW, Huang S, Hotez PJ. *Ancylostoma caninum* anticoagulant peptide: a hookworm-derived inhibitor of human coagulation factor Xa. *Proc Natl Acad Sci USA* 1995; **92:** 6152–56.

64 Hotez PJ, Ashcom J, Bin Z, et al. Effect of vaccinations with recombinant fusion proteins on *Ancylostoma caninum* habitat selection in the canine intestine. *J Parasitol* 2002; **88:** 684–90.

65 Stassens P, Bergum PW, Gansemans Y, et al. Anticoagulant repertoire of the hookworm *Ancylostoma caninum*. *Proc Natl Acad Sci USA* 1996; **93:** 2149–54.

66 Culley FJ, Brown A, Conroy DM, Sabroe I, Pritchard DI, Williams TJ. Eotaxin is specifically cleaved by hookworm metalloproteases preventing its action in vitro and in vivo. *J Immunol* 2000; **165:** 6447–53.

67 Don TA, Jones MK, Smyth D, O'Donoghue P, Hotez P, Loukas A. A pore-forming haemolysin from the hookworm, *Ancylostoma caninum*. *Int J Parasitol* 2004; **34:** 1029–35.

68 Ng KK, Petersen JF, Cherney MM, et al. Structural bas is for the inhibition of porcine pepsin by *Ascaris* pepsin inhibitor-3. *Nat Struct Biol* 2000; **7:** 653–57.

69 Deehan MR, Goodridge HS, Blair D, et al. Immunomodulatory properties of *Ascaris suum* glycosphingolipids: phosphorylcholine and non-phosphorylcholine-dependent effects. *Parasite Immunol* 2002; **24:** 463–69.

70 Drake L, Korchev Y, Bashford L, et al. The major secreted product of the whipworm, *Trichuris*, is a pore-forming protein. *Proc Biol Sci* 1994; **257:** 255–61.

71 Parthasarathy G, Mansfield LS. *Trichuris suis* excretory secretory products (ESP) elicit interleukin-6 (IL-6) and IL-10 secretion from intestinal epithelial cells (IPEC-1). *Vet Parasitol* 2005; **131:** 317–24.

72 Summers RW, Elliott DE, Urban JF Jr, Thompson R, Weinstock JV. *Trichuris suis* therapy in Crohn's disease. *Gut* 2005; **54:** 87–90.

73 Tan TH, Edgerton SA, Kumari R, et al. Macrophage migration inhibitory factor of the parasitic nematode *Trichinella spiralis*. *Biochem J* 2001; **357:** 373–83.

74 van Balkom BW, van Gestel RA, Brouwers JF, et al. Mass spectrometric analysis of the *Schistosoma mansoni* tegumental sub-proteome. *J Proteome Res* 2005; **4:** 958–66.

75 Yatsuda AP, Krijgsveld J, Cornelissen AW, Heck AJ, de Vries E. Comprehensive analysis of the secreted proteins of the parasite *Haemonchus contortus* reveals extensive sequence variation and differential immune recognition. *J Biol Chem* 2003; **278:** 16941–51.

76 Hawdon JM, Hotez PJ. Hookworm: developmental biology of the infectious process. *Curr Opin Genet Dev* 1996; **6:** 618–23.

77 Fujiwara R, Loukas A, Mendez S, et al. Vaccination with irradiated *Ancylostoma caninum* third stage larvae induces a Th2 protective response in dogs. *Vaccine* 2006; **24:** 501–09.

78 Goud GN, Bottazzi ME, Zhan B, et al. Expression of the *Necator americanus* hookworm larval antigen *Na*-ASP-2 in *Pichia pastoris* and purification of the recombinant protein for use in human clinical trials. *Vaccine* 2005 **23:** 4754–64.

79 Ledizet M, Harrison LM, Koskia RA, Cappello M. Discovery and pre-clinical development of antithrombotics from hematophagous invertebrates. *Curr Med Chem Cardiovasc Hematol Agents* 2005; **3:** 1–10.

80 Delaney A, Williamson A, Brand A, et al. Cloning and characterisation of an aspartyl protease inhibitor (API-1) from *Ancylostoma* hookworms. *Int J Parasitol* 2005; **35:** 303–13.

81 Lochnit G, Dennis RD, Geyer R. Phosphorylcholine substituents in nematodes: structures, occurrence and biological implications. *Biol Chem* 2000; **381:** 839–47.

82 Goodridge HS, Stepek G, Harnett W, Harnett MM. Signalling mechanisms underlying subversion of the immune response by the filarial nematode secreted product ES-62. *Immunology* 2005; **115:** 296–304.

83 Kaplan KJ, Goodman ZD, Ishak KG. Eosinophilic granuloma of the liver: a characteristic lesion with relationship to visceral larva migrans. *Am J Surg Pathol* 2001; **25:** 1316–21.

84 Gelpi AP, Mustafa A. *Ascaris* pneumonia. *Am J Med* 1968; **44:** 377–89.

85 Chan PW, Anuar AK, Fong MY, Debruyne JA, Ibrahim J. *Toxocara* seroprevalence and childhood asthma among Malaysian children. *Pediatr Int* 2001; **43:** 350–53.

86 Sharghi N, Schantz PM, Caramico L, Ballas K, Teague BA, Hotez PJ. Environmental exposure to *Toxocara* as a possible risk factor for asthma: a clinic-based case-control study. *Clin Infect Dis* 2001; **32:** E111–16.

87 Blackwell V, Vega-Lopez F. Cutaneous larva migrans: clinical features and management of 44 cases presenting in the returning traveller. *Br J Dermatol* 2001; **145:** 434–37.

88 Hotez PJ. Hookworm infections. In: Guerrant RL, Walker DH, Weller PF, eds. Tropical infections diseases: principles, pathogens and, practice, 2nd edn. London: Elsevier-Churchill Livingstone, 2006: 1265–73.

89 Taren DL, Nesheim MC, Crompton DW, et al. Contributions of ascariasis to poor nutritional status in children from Chiriqui Province, Republic of Panama. *Parasitology* 1987; **95:** 603–13.

90 Khuroo MS, Zargar SA, Mahajan R. Hepatobiliary and pancreatic ascariasis in India. *Lancet* 1990; **335:** 1503–06.

91 Villamizar E, Mendez M, Bonilla E, Varon H, de Onatra S. *Ascaris lumbricoides* infestation as a cause of intestinal obstruction in children: experience with 87 cases. *J Pediatr Surg* 1996; **31:** 201–04; discussion 204–05.

92 Khuroo MS. Ascariasis. *Gastroenterol Clin North Am* 1996; **25:** 553–77.

93 Bundy DAP, Cooper ES. Trichuris and trichuriasis in humans. *Advances in Parasitology* 1989; **28:** 107–73.

94 Shin JL, Gardiner GW, Deitel W, Kandel G. Does whipworm increase the pathogenicity of *Campylobacter jejuni*? A clinical correlate of an experimental observation. *Can J Gastroenterol* 2004; **18:** 175–77.

95 Maxwell C, Hussain R, Nutman TB, et al. The clinical and immunologic responses of normal human volunteers to low dose hookworm (*Necator americanus*) infection. *Am J Trop Med Hyg* 1987; **37:** 126–34.

96 Lwambo NJ, Bundy DA, Medley GF. A new approach to morbidity risk assessment in hookworm endemic communities. *Epidemiol Infect* 1992; **108:** 469–81.

97 Albonico M, Stoltzfus RJ, Savioli L, et al. Epidemiological evidence for a differential effect of hookworm species, *Ancylostoma duodenale* or *Necator americanus*, on iron status of children. *Int J Epidemiol* 1998; **27:** 530–37.

98 Nutman TB, Ottesen EA, Ieng S, et al. Eosinophilia in Southeast Asian refugees: evaluation at a referral center. *J Infect Dis* 1987; **155:** 309–13.

99 Dunn A, Keymer A. Factors affecting the reliability of the McMaster technique. *J Helminthol* 1986; **60:** 260–62.

100 Santos FL, Cerqueira EJ, Soares NM. Comparison of the thick smear and Kato-Katz techniques for diagnosis of intestinal helminth infections. *Rev Soc Bras Med Trop* 2005; **38:** 196–98.

101 Koumanidou C, Manoli E, Anagnostara A, Polyviou P, Vakaki M. Sonographic features of intestinal and biliary ascariasis in childhood: case report and review of the literature. *Ann Trop Paediatr* 2004; **24:** 329–35.

102 Anonymous. Drugs for parasitic infections. *Med Lett Drugs Ther* August, 2004: http://www.themedicalletter.com/restricted/articles/w1189c.pdf (accessed Nov 12, 2005).

103 WHO. Report of the WHO informal consultation on the use of praziquantel during pregnancy/lactation and albendazole/mebendazole in children under 24 months. 8–9 April, 2002. http://whqlibdoc.who.int/hq/2003/WHO_CDS_CPE_PVC_2002.4.pdf.

104 Lacey E. Mode of action of benzimidazoles. *Parasitol Today* 1990; **6:** 112–15.

105 Albonico M, Ramsan M, Wright V, et al. Soil-transmitted nematode infections and mebendazole treatment in Mafia Island schoolchildren. *Ann Trop Med Parasitol* 2002; **96:** 717–26.

106 Bennett A, Guyatt H. Reducing intestinal nematode infection: efficacy of albendazole and mebendazole. *Parasitol Today* 2000; **16:** 71–74.

107 Adams VJ, Lombard CJ, Dhansay MA, Markus MB, Fincham JE. Efficacy of albendazole against the whipworm *Trichuris trichiura*: a randomised, controlled trial. *S Afr Med J* 2004; **94:** 972–76.

108 Dayan AD. Albendazole, mebendazole and praziquantel. Review of non-clinical toxicity and pharmacokinetics. *Acta Trop* 2003; **86:** 141–59.

109 Montresor A, Awasthi S, Crompton DW. Use of benzimidazoles in children younger than 24 months for the treatment of soil-transmitted helminthiasis. *Acta Trop* 2003; **86:** 223–32.

110 Bundy DAP, Michael E, Guyatt H. Epidemiology and control of nematode infection and disease in humans. In: Lee DL, ed. The biology of nematodes. London: Taylor and Francis, 2002: 599–617.

111 Stoltzfus RJ, Dreyfuss ML, Chwaya HM, Albonico M. Hookworm control as a strategy to prevent iron deficiency. *Nutr Rev* 1997; **55:** 223–32.

112 Stephenson LS, Latham MC, Kurz KM, Kinoti SM, Brigham H. Treatment with a single dose of albendazole improves growth of Kenyan schoolchildren with hookworm, *Trichuris trichuria*, and *Ascaris lumbricoides* infections. *Am J Trop Med Hyg* 1989; **41:** 78–87.

113 Stephenson LS, Latham MC, Adams EJ, Kinoti SN, Pertet A. Physical fitness, growth and appetite of Kenyan school boys with hookworm, *Trichuris trichiura* and *Ascaris lumbricoides* infections are improved four months after a single dose of albendazole. *J Nutr* 1993; **123:** 1036–46.

114 Awasthi S, Pande VK, Fletcher RH. Effectiveness and cost-effectiveness of albendazole in improving nutritional status of pre-school children in urban slums. *Indian Pediatr* 2000; **37:** 19–29.

115 Stoltzfus RJ, Kvalsvig JD, Chwaya HM, et al. Effects of iron supplementation and anthelmintic treatment on motor and language development of preschool children in Zanzibar: double blind, placebo controlled study. *BMJ* 2001; **323:** 1389–93.

116 Montresor A, Stoltzfus RJ, Albonico M, et al. Is the exclusion of children under 24 months from anthelmintic treatment justifiable? *Trans R Soc Trop Med Hyg* 2002; **96:** 197–99.

117 Atukorala TM, de Silva LD, Dechering WH, Dassenaeike TS, Perera RS. Evaluation of effectiveness of iron-folate supplementation and anthelminthic therapy against anemia in pregnancy - a study in the plantation sector of Sri Lanka. *Am J Clin Nutr* 1994; **60:** 286–92.

118 Torlesse H, Hodges M. Albendazole therapy and reduced decline in haemoglobin concentration during pregnancy (Sierra Leone). *Trans R Soc Trop Med Hyg* 2001; **95:** 195–201.

119 de Silva NR, Sirisena JL, Gunasekera DP, Ismail MM, de Silva HJ. Effect of mebendazole therapy during pregnancy on birth outcome. *Lancet* 1999; **353:** 1145–49.

120 Savioli L, Crompton DW, Neira M. Use of anthelminthic drugs during pregnancy. *Am J Obstet Gynecol* 2003; **188:** 5–6.

121 WHO. Report of the WHO informal consultation on hookworm infection and anemia in girls and women. Geneva: World Health Organization, 1996.

122 Quinnell RJ, Slater AF, Tighe P, Walsh EA, Keymer AE, Pritchard DI. Reinfection with hookworm after chemotherapy in Papua New Guinea. *Parasitology* 1993; **106:** 379–85.

123 Elkins DB, Haswell-Elkins M, Anderson RM. The importance of host age and sex to patterns of reinfection with *Ascaris lumbricoides* following mass anthelmintic treatment in a South Indian fishing community. *Parasitology* 1988; **96:** 171–84.

124 Geerts S, Coles GC, Gryseels B. Anthelmintic resistance in human helminths: learning from the problems with worm control in livestock. *Parasitol Today* 1997; **13:** 149–51; discussion 156.

125 Savioli L, Montresor A, Bundy D, Albonico M, Renganathan E. Anthelminthic resistance in human helminths: learning from the problem of worm control in livestock-Reply. *Parasitol Today* 1997; **13:** 156.

126 Gilles HM, Hoffman PS. Treatment of intestinal parasite infections: a review of nitazoxaanide. *Trends Parasitol* 2002; **18:** 95–97.

127 Xiao SH, Hui-Ming W, Tanner M, Utzinger J, Chong W. Tribendimidine: a promising, safe and broad-spectrum anthelmintic agent from China. *Acta Trop* 2005; **94:** 1–14.

128 Albonico M, Bickle Q, Haji HJ, et al. Evalutation of the efficacy of pyrantel-oxantel for the treatment of soil-transmitted nematode infections. *Trans R Soc Trop Med Hyg* 2002; **96:** 685–90.

129 Goud GN, Zhan B, Ghosh K, et al. Cloning, yeast expression, isolation, and vaccine testing of recombinant Ancylostoma-secreted protein (ASP)-1 and ASP-2 from *Ancylostoma ceylanicum*. *J Infect Dis* 2004; **189:** 919–29.

130 Mendez S, Valenzuela JG, Wu W, Hotez PJ. Host cytokine production, lymphoproliferation, and antibody responses during the course of *Ancylostoma ceylanicum* infection in the golden Syrian hamster. *Infect Immun* 2005; **73:** 3402–07.

131 Hotez PJ, Bethony J, Bottazzi ME, Brooker S, Buss P. Hookworm: "the great infection of mankind". *PLoS Med* 2005; published online March 29, DOI:10.1371/journal.pmed.0020067

132 Molyneux DH, Hotez PJ, Fenwick A. "Rapid impact interventions": how a health policy of integrated control of Africa's neglected tropical diseases could benefit the poor. *PLoS Med* 2005; published online Oct 11. DOI:10.1371/journal.pmed.0020336