Chapter 11
Soil-Transmitted Helminths: The Neglected Parasites

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Abstract  Soil-transmitted helminth (STH) infections are still considered to be the most prevalent infections of humankind. STH, traditionally endemic in rural areas, are increasingly becoming a public health concern in urban slums of cities in tropical and subtropical developing countries in Southeast Asia, sub-Saharan Africa and Central and South America. These helminths, *Ascaris lumbricoides*, hookworm (*Ancylostoma duodenale* and *Necator americanus*), *Trichuris trichiura* and *Strongyloides stercoralis*, can live in silence as chronic infections with prominent morbidity amongst children and mothers of childbearing age. The main impact of STH infections is their associations with malnutrition, vitamin A deficiency (VAD), iron-deficiency anaemia (IDA), intellectual retardation and cognitive and educational deficits. The devastating consequences of these helminths during childhood may continue into adulthood with effects on the economic productivity which trap the communities at risk of infections in a cycle of poverty, underdevelopment and disease. Hence, the WHO regarded the control of STH amongst the top five health priorities within the global massive effort to eradicate poverty. Moreover, controlling STH infections has significant positive impacts on the nutritional status and educational performance of the vulnerable children in endemic communities.
11.1 Introduction

Soil-transmitted helminths (STH) (or geohelminths) are nematodes with round, non-segment elongated cylindrical bodies. The species of medical importance include *Ascaris lumbricoides* (roundworms), *Trichuris trichiura* (whipworms), *Ancylostoma duodenale* and *Necator americanus* (hookworms) and *Strongyloides stercoralis* (threadworm). They are classified as ‘soil-transmitted helminths’ because the eggs/larvae passed in faeces need about 3 weeks to mature in the soil before they become infective.

Infections by STH or soil-transmitted helminthiasis are the most common infections of humankind. Recent global estimates suggest that *A. lumbricoides* infects 1.2 billion people, *T. trichiura* infects 800 million, hookworms infect 750 million and *S. stercoralis* infects 100 million people [1]. Moreover, an estimated 5.3 billion people, including 1 billion school-aged children are at risk of infection with at least one STH species, with 69% of them living in Asia, 22% in Africa and the Middle East and 9% in Latin America and the Caribbean [2]. Together with schistosomiasis, STH infections represent more than 40% of the disease burden caused by all tropical diseases except malaria [3]. By using a metric measurement known as DALY (disability-adjusted life year, i.e. the numbers of years lost from premature death or disability), STH results in 40 million DALYs lost annually which accounts for about 20% of DALYs lost due to infectious diseases globally [4]. The most important reasons for high DALY values due to STH were based on the association of hookworm with anaemia, ascariasis with growth stunting and trichuriasis with decreased school performance [5]. Although STH infections rarely cause death, recent estimates attributed 65,000 annual deaths to hookworm infections, 60,000 annual deaths to ascariasis and 10,000 annual deaths to trichuriasis [6]. However, the morbidity caused by STH is most commonly associated with infections of moderate to heavy intensities [7]. Certain groups of people including preschool children, school-aged children and women of childbearing age are more susceptible to higher morbidity and mortality rates than others [8]. Hence, STH infections are amongst the greatest challenges to health and economic development of developing countries.

Despite the fact that STH infections are highly prevalent, disability-inducing and poverty-promoting, they are classified amongst the neglected tropical diseases (NTDs) [1]. These diseases are classified as ‘neglected’ because they persist exclusively in the poorest populations often living in remote, rural areas, in urban slums or in conflict zones and have been largely eliminated in developed countries and thus are often forgotten.
11.2 Aetiology and Burden of STH Infections

11.2.1 Ascaris Infections

Ascaris lumbricoides is probably the first etiologic agent of infection ever described in humans with descriptions of the parasite going back to ancient times and the first scientific description dating back to 1683 [9]. The adult stage of A. lumbricoides is a cylindrical pink- or cream-coloured worm of the family Ascarididae and the superfamily Ascaridoidea. Ascaris is the largest intestinal nematodes infecting humans with male being smaller (120–250 mm in length and 3–4 mm in width) than the female (200–400 mm in length and 5–6 mm in width). The adult worm preferentially resides in the jejunum where it orients with the head facing the direction of the intestinal flow [10]. Mature female A. lumbricoides worms produce 100,000–200,000 fertilised or unfertilised eggs per day. Eggs excreted in stool require a period of maturation in soil. The period of development in the soil is temperature dependent and may range from 2 weeks to several months. The infective stage is a second stage larva within the egg. The larvae that emerge from ingested eggs in the jejunum penetrate the intestinal wall and migrate through hepatic venules to the right side of the heart and the pulmonary circulation, where they penetrate into the alveolar spaces and undergo two further molts. From the alveoli, the 1.5 mm long larvae ascend to the trachea and are swallowed, undergo a last molt in the small intestine and develop to adults. From ingestion of infective eggs to the production of eggs by mature adult worms, development takes about 10–12 weeks and the adult worm has a life span of about a year.

During early infections, the invasive larval stages of Ascaris will elicit a host eosinophilic inflammatory response in the liver (hepatitis) and lung (Loeffler’s pneumonitis). The phase of larval migration is a distinctive type of pneumonitis known as Loeffler’s syndrome (simple pulmonary eosinophilia) characterised by mild group of symptoms, a scarcity of physical signs, a blood eosinophilia varying from less than 10–60 %, a benign course and spontaneous healing within a period of 2–3 weeks and transient pulmonary infiltration. There are very few reports of Loeffler’s syndrome in Southeast Asia despite the fact that ascariasis is common in this region [11]. Moreover, intestinal and bile duct obstructions are the most common complications associated with ascariasis [12].

11.2.2 Trichuris Infections

Trichuris trichiura is a member of the nematode superfamily Trichiuroidea and therefore related to the pathogen Trichinella spiralis [13]. The adult worm is approximately 4 cm long; its whip-like shape refers to the wider posterior section and the long, finely attenuated anterior end [13]. Eggs passed in the faeces of an infected individual have a classic barrel shape with a plug at each pole. After
embryonation in the soil, a process that requires 2–4 weeks, a larva develops. Human transmission occurs by the ingestion of the embryonated eggs, which release larvae that moult and burrow into the colonic mucosa upon arrival into the large intestine. The larva buries its entire body in the epithelium of large intestine forming a tunnel. As the worm matures, its posterior end is extruded from the tunnel and hangs freely in the lumen of intestine.

*Trichuris* causes host injury both through direct effects by invading the colonic mucosa and through the systemic effects of infection. The cecum is the preferential site for invasion although heavy infections will extend throughout the colon and even distally to the rectum. Contact of the anterior end of the adult worm with the mucosa of large intestine causes inflammation resulting in the disruption of the normal colonic architecture [8]. In severe chronic infection, the mucosa becomes oedematous and friable which leads to rectal bleeding (whipworm dysentery) with abdominal pain and rectal tenesmus. Frequent straining as a result of rectal tenesmus causes rectal prolapse. Several investigators have pointed out the clinical similarities between the paediatric colitis caused by *Trichuris* infection and the more established causes of inflammatory bowel disease such as Crohn’s disease and ulcerative colitis.

### 11.2.3 Hookworm Infections

Hookworms are nematodes belonging to the family Ancylostomatidae, a part of the superfamily Strongyloidea. The two major genera that affect humans, *Necator* and *Ancylostoma*, are characterised by the presence of oral cutting organs in the adult stages [14]. The major representative of the genus *Ancylostoma* to infect and complete development in humans is *Ancylostoma duodenale*. In contrast to the major human (anthropophilic) species, *Ancylostoma ceylanicum*, a parasite of dogs and cats, is also infective to humans in some regions of Asia, but it is not considered a major pathogen [14]. Other canine and feline hookworms such as *Ancylostoma caninum* and *Ancylostoma braziliense* cause zoonotic diseases in humans, for example, eosinophilic enteritis and cutaneous larva migrans (CLM), respectively [15, 16].

There are significant pathobiological differences between the two major human hookworms. Unlike *N. americanus*, which can complete its life cycle in humans only after skin penetration by filariform larvae, *A. duodenale* is also transmitted by oral ingestion of the infective larvae. *N. americanus* is smaller than *A. duodenale* and produces fewer eggs and causes less blood loss.

The adult worms live in the small intestine (particularly in jejunum) of man, attaching themselves to the intestinal epithelium by means of their mouth part. Hookworm induces blood loss directly through mechanical rupture of host capillaries and arterioles followed by the release of pharmacologically active polypeptides including anticoagulants, antiplatelet agents and antioxidants [17]. Chronic intestinal bleeding causes hookworm-induced protein loss and iron-deficiency
anaemia. In addition, hookworm-associated iron deficiency during childhood is partly responsible for its physical and mental growth retardation effects [18]. The growth stunting effects of hookworm were well documented by the early part of the twentieth century [19], as were some of the effects of hookworm on intelligence quotient.

Studies of the association of anaemia with hookworm blood loss indicate that there is a disproportionate reduction in plasma haemoglobin concentration after some threshold worm burden is exceeded [20]. Although the adult hookworms elicit most of the pathology attributed to hookworm, the infective larval stages also release macromolecules upon host entry that contribute to morbidity. These include hookworm-derived allergens and tissue invasive enzymes [17]. Some of these molecules contribute to the pathogenesis of dermatitis (ground itch) and hookworm pneumonitis.

### 11.2.4 Strongyloides Infections

*Strongyloides stercoralis*, known as threadworms, is an opportunistic nematode. Adult worms reside in the intestinal wall of the small intestine. The adult female is parthenogenetic (self-fertilising), rarely seen in stool and is approximately 2 mm in length. It has a short buccal cavity and a long, thin oesophagus. Male worm is shorter and broader than the female [21].

The female is ovoviviparous. The embryonated eggs hatch in the mucosa of the intestine release the noninfective rhabditiform larvae in the host intestine and these are usually detected in stool samples. The rhabditiform larvae passed in stool is approximately 200–400 $\mu$m long and 15–20 $\mu$m wide and have a short buccal cavity and a prominent genital primordium. While in the lumen of the intestine, the rhabditiform larvae metamorphose into filariform larvae; they may penetrate the intestinal epithelium, causing internal autoinfection, or carried down the intestine and penetrate the perianal and perineal skin, causing external autoinfection. The length of filariform larva is up to 680 $\mu$m with a longer oesophagus than the hookworm and a notched, rather than a pointy, tail. The rhabditiform larva may be voided with the faeces and may undergo development in the soil through direct or indirect cycle. In direct cycle, the rhabditiform larva metamorphoses in 3–4 days into filariform larva. In the indirect cycle, also known as the free-living phase, the rhabditiform larvae develop into free-living male and female adults in the course of 24–30 h.

Strongyloidiasis is transmitted by penetration of the skin by the infective filariform larvae in contaminated soil. Although some itching is common during skin penetration, there are few other symptoms associated with this stage of disease and allergic reactions may also occur. Pulmonary symptoms may be present during the migratory phase of the filariform larvae in the lungs. Diarrhoea and abdominal pain caused by the adult worms frequently accompany the intestinal phase of the disease [8].
In immunocompromised individual, autoinfection may lead to the hyperinfection syndrome, which may occur years after the initial infection. Characteristic clinical features of hyperinfection syndrome are larva currens (dermatitis caused by penetration of filariform larvae around the perianal and perineal skin) and dissemination of filariform larvae to the extraintestinal organs. During autopsy, larvae have been found in many organs such as liver, lungs, heart, kidneys and brain. Sepsis and meningitis, often polymicrobial, may develop with the spreading of enteric bacteria from intestine to the circulation [8].

11.3 Epidemiology and Dynamic Transmission of STH Infections in the Southeast Asian Region

Southeast Asia represents one region of the world in which STH are considered to be highly endemic and where these infections constitute a significant public health risk.

Previous studies in Thailand demonstrated that STH infections appear to be largely controlled in urban populations, with prevalence amongst urban school children being as low as 0.3 % for hookworms and 0.05 % for Ascaris [22]. However, high-risk urban populations do remain, and these include immunocompromised people (with an STH prevalence of 3.8–13.3 % [23]) as well as many patients in institutionalised care (1.1–29.7 % [24]), indicating that the surveillance and control of STH in urban Thai populations is still critical. Most recently, a case of biliary ascariasis-induced acute pancreatitis with cholangitis without imaging support was discovered in a patient coming from an urban area. The investigation results showed no eosinophilia and no Ascaris eggs in stool examination; however, the parasite was found when an endoscopic retrograde cholangiopancreatography was performed [25]. In contrast, control efforts have progressed more slowly in Thailand’s remote and rural areas, and disease burdens remain high. For example, a study of 1,010 school children in remote communities in northern Thailand (Nan Province) revealed prevalence of 21.7 % for Ascaris, 18.5 % for hookworm and 16.3 % for Trichuris [26]. Similarly, high prevalence of STH infections (5.7 %, 18.0 % and 28.5 % for Ascaris, hookworm and Trichuris, respectively) has been reported in rural/remote communities in Nakhon Si Thammarat province in southern Thailand [27]. Recently, molecular tools targeting the internal transcribed spacer 1 (ITS1)-5.8S-ITS2 region of the ribosomal RNA gene identified N. americanus as the most common hookworm. However, A. duodenale and A. ceylanicum were also detected [28].

In Malaysia, STH diseases are not notifiable and are considered to be largely controlled [29]. However, foci of high endemicity (with prevalence of 5.5–98.2 % for Trichuris, 8.0–67.8 % for Ascaris and 3.0–44.7 % for hookworms) still persist in underprivileged or minority communities such as Orang Asli (aborigine) children [30–33], amongst Indians living in estates [34], amongst multiracial communities
living in the squatter areas [35] and in poor Malay living in traditional villages [36, 37] in which sanitation is often poor. However, it is important to note that reinfec-
tions are also a major issue, with evidence that prevalence can return to near
pretreatment levels just 6 months following deworming [38]. This information
emphasises the need for improved integrated control measures (including routine
treatment, diagnosis and effective health education) as well as enhanced infrastruc-
ture and economic development in underprivileged or disadvantaged communities.
Although effective control programmes are imperative, the availability of advanced
diagnostics is equally crucial. Recently, a multiplex real-time polymerase chain
reaction assay for the detection of various species of STH was developed providing
a more specific and sensitive diagnostic tool for the detection of these helminth
species in epidemiological studies and monitoring of treatment programmes
[39]. Meanwhile, identification of human and animal hookworm species was
achieved with the utilisation of the real-time PCR coupled with high-resolution
melting (HRM) analysis targeting the second internal transcribed spacer (ITS-2) of
nuclear ribosomal DNA as the genetic marker providing a rapid and straightforward
method for the diagnosis, identification and discrimination of five human hook-
worms [40]. Molecular tools have enabled confirmation that *N. americanus* and
*A. ceylanicum* are found in Malaysia with the former being more common [41] and
that *A. ceylanicum* transmission dynamic in endemic areas in Malaysia is height-
ened by the close contact of human and domestic animal (i.e. dogs and cats)
populations [42].

Clinical features of severe STH infections have been described in previous
studies carried out in Malaysia. It has been reported that ascariasis was responsible
for 42 % and 41 % of all acute abdominal emergencies and intestinal obstruction,
respectively, in children 7 years and below admitted to a hospital in Kuala Lumpur
[43]. Moreover, previous studies amongst aboriginal children in Selangor and
Pahang states strongly indicated that ascariasis is associated with protein-energy
malnutrition and vitamin A deficiency [44, 45]. On the other hand, rectal prolapse
occurred in 50 % of children with severe trichuriasis which was also identified as
the main predictor of stunting and iron-deficiency anaemia amongst Orang Asli
children in Malaysia [45–47].

Although *Strongyloides stercoralis* infection is not very commonly reported in
Malaysia compared to other parasitic infections, it is common in immunosuppres-
sive patients and may present with hyperinfection. Recently, a case of *S. stercoralis*
hyperinfection was reported in a diabetic patient [48], a known case of
non-Hodgkin lymphoma (NHL) presenting with recurrent NHL stage IV and had
undergone salvage chemotherapy and a case of angioimmunoblastic T-cell lym-
phoma (AITL) in a patient with lymphadenopathy and bulky neck mass who
eventually succumbed following multi-organ failure [49]. Interestingly,
*S. stercoralis* rhabditiform larvae were identified in water samples used to wash
pegaga, kesum and water spinach, and the number of larvae observed were
152, 9 and 16, respectively. Analysis by real-time PCR confirmed the microscopic
observation of this helminth highlighted that vegetables and herbs may be likely
sources of *S. stercoralis* infection in Kota Bharu, Kelantan [50]. More recently,
serological and molecular approaches were used to investigate *S. stercoralis* infection amongst an Orang Asli (indigenous) community following a preliminary detection by microscopic examination of faecal samples. Of the 54 samples, 17 samples were positive via enzyme-linked immunosorbent assay (ELISA) and 3 yielded *S. stercoralis* DNA amplification. Given the high ELISA positive results, false positivity is suspected. Hence, PCR method should be considered as an alternative diagnostic tool for the detection of *S. stercoralis* infection [51].

In the Philippines, STH infections are still a major human health problem, with the WHO estimating an overall prevalence of >50 % and a regional prevalence of 47.5–92.5 % as of 2004 [29]. Recently, a large-scale study was initiated to evaluate the impact of STH control programmes in endemic regions. The study included 3,373 school children in six provinces and recorded prevalences of 21.0–51.7 % for *Ascaris*, 14.5–59.8 % for *Trichuris* and 0.5–7.5 % for hookworms [52]. A study amongst indigenous individuals reported higher risk of morbidity due to helminth infections in these groups of people [53]. Belizario et al. [52] also recommended a reassessment of existing helminth control strategies to focus on semiannual mass treatment programmes, associated with improved educational campaigns, enhanced environmental sanitation and ongoing surveillance. There is no doubt that the fragmented geography of the Philippines, as a large archipelago, presents major logistical and epidemiological challenges that are likely to have substantial effects on the success of any treatment programmes against STH. Despite this, the WHO currently estimates that the Philippines had reached the 75 % treatment threshold-level for school-aged children established by Resolution 54.19 in 2007 and 2008 [54].

Before and early 2000, studies in Indonesia revealed prevalences of 10.0–96.6 % for *Ascaris*, 1.0–98.0 % for *Trichuris* and 0.6–39.7 % for hookworm [55–57]. Since 1975, when the nationwide helminth control programmes were initiated till 1999, control programmes have been inconsistent [58, 59]. Presently, the WHO estimates that, as of 2007 and 2008 data, just 2 % of preschool-aged children and 3 % of school-aged children received regular anthelmintic therapy in Indonesia [54]. Although it is likely that this is, in large part, a consequence of the remote and disparate geography of much of Indonesia, clearly significant focus on expanded national deworming programmes in this region should be considered a major priority. The current status of the efficacy and effectiveness of albendazole and mebendazole for the treatment of *Ascaris lumbricoides* in northwestern Indonesia showed no evidence of drug resistance so far. In addition, although both drugs showed incomplete oxicidal effects, single-dose albendazole is better than mebendazole in sterilising *A. lumbricoides* eggs [60]. There was also a report of the occurrence of an atypical invasive *S. stercoralis* infection of the stomach mucosa in an elderly female patient from Bangka Island, northwestern Indonesia, associated with acute interstitial nephritis. The patient showed rapid improvement after treatment with mebendazole [61].

Data indicated that Vietnam has high prevalence of STH (~40.1–44.4 % of the total population is infected with *Ascaris*, 17.5–23.1 % with *Trichuris* and 22.1–28.6 % with hookworm) [29, 62–67]. This may be due to the common practice
of using human excreta as fertiliser in agricultural practices as a recent report has highlighted the presence of *A. lumbricoides* and *T. trichiura* infections associated with wastewater and human excreta use in agriculture in Vietnam [68]. Recent data indicate significant geographic variation in STH prevalence levels: highest (i.e. 75–85 % for *Ascaris*, 38–40 % for *Trichuris* and 27–28 % for hookworm infections) in the north [63] and substantially lower (i.e. <20.0 %), albeit still significant, in the south [69]. These differences in prevalence have been interpreted to be attributable to variation in climate, agricultural practices and/or socio-economic development [70, 71].

For Cambodia, mass anthelmintic treatment has been expanded substantially in recent years. Montresor et al. [72] highlighted Cambodia as one of the few SEA countries with high endemicity of STH to have reached the WHO’s target of delivering treatment to 75 % of school-aged children. As of 2006, anthelmintic treatment reached 98 % of school (~2.8 million) and 74 % of preschool (~1.75 million) children [72]. A recent large-scale study [73] showed reductions in helminth prevalence levels in several villages in the provinces of Kratie and Stung Treng from 1997 to 2005, following mass treatment, and reported substantial reductions in the prevalence of *Ascaris* (from 9.5–69.8 % to 0.0–5.4 %), *Trichuris* (from 1.6–9.5 % to 0.0–2.0 %) and hookworm infection (from 45.1–86.0 % to 6.1–26.0 %). Subsequently, a 2006–2011 evaluation on 16,372 faecal samples detected parasites in 3,121 (19.1 %) samples and most common were *Giardia lamblia* (8.0 % of samples; 47.6 % disease episodes), hookworm (5.1 %; 30.3 %) and *S. stercoralis* (2.6 %; 15.6 %). The proportion of infected children increased, and the number of disease episodes effectively treated with a single dose of mebendazole decreased over the 5-year period [74]. However, for *Strongyloides* infection, ivermectin is highly efficacious against *S. stercoralis* but prohibitive costs render the drug inaccessible to most Cambodians [75]. Recently, a sensitive novel real-time PCR assays were developed to detect *Strongyloides* spp. and hookworms providing an alternative in the diagnosis of STH infections in Cambodia [76].

In Lao PDR, broadscale deworming programmes have also been highly successfully. A large, national survey conducted in 2003 [77] examined ~30,000 school children. The overall prevalence of STH infections was estimated at 61.9 % (27.2–96.2 % prevalence by province), with a mean prevalence of 34.9 % (1.6–81.9 % by province), 25.8 % (5.4–71.0 % by province) and 19.1 % (3.0–45.1 % by province) for *Ascaris*, *Trichuris* and hookworms, respectively. This information provided the impetus for the initiation of large national deworming programmes [72, 78] yielding one of the most comprehensive datasets with which to evaluate their effectiveness. This deworming programme, targeting school-aged children, were initiated in 2005 and rapidly expanded to reach ~1 million children (~99 % of the school-aged population) by 2007 [29, 72]. A previous study [78] assessed the impact of this programme (which included one to two treatment/s with mebendazole [500 mg] each year, public awareness campaigns and the training of health professionals) and reported substantial decreases in the prevalence of STH (60–20 % for *Ascaris* and 42–31 % for *Trichuris*). These
data are suggestive of substantial reductions in morbidity associated with helminthiasis, in concert with direct decreases in prevalence, as a result of the national deworming programmes. However, a study in Mekong River basin found that multiple species of intestinal parasite infections were common with 86.6 % of 669 studied participants harbouring at least two and up to seven different parasites concurrently. Amongst nematode infections, hookworm was the most prevalent species (76.8 %), followed by *A. lumbricoides* (31.7 %) and *T. trichiura* (25 %) [79]. Another recent study also highlighted that 28.4 % of children studied had monoparasitic infection and 9.3 % had a polyparasitic infection [80]. With regard to hookworm infection, a study found 30 % (61/203 samples) of people infected in Lahanam Village, Savannakhet Province, Lao PDR. Copro-PCR with specific primers for hookworms and *Trichostrongylus* spp. and sequencing discovered *N. americanus*, *A. duodenale* and also the animal hookworms, *A. caninum*, *A. ceylanicum* and *Trichostrongylus colubriformis* [81]. Another study found that dogs in northern Lao PDR have a role in human hookworm transmission as both *N. americanus* and *A. ceylanicum* were both found in humans and dogs [82].

In Myanmar, the majority of clinical manifestations of ascariasis in children responsible for hospital admission were due to intestinal obstruction with the next most common manifestation was intestinal colic [83]. A previous study also highlighted that 7.5 % of laparotomies were due to complications of ascariasis [84]. In 2002–2003, a small-scale survey of children in selected schools (representing the major climatic zones within the country) was conducted by the WHO and the Myanmar Ministry of Health, and estimated mean prevalences of 57.5 % (range from 1.4 to 91.6 %) for *Trichuris*, 48.5 % (18.2–69.1 %) for *Ascaris* and 6.5 % (0.0–17.2 %) for hookworm [85] were reported. Moreover, ~18.2 % (range from 0.9 to 50.3 %) of infected people had ‘moderate’ to ‘heavy’ infection intensity, and 22.1 % (range from 9.3 to 34.9 %) of people tested were anaemic [85]. A pilot programme, targeting 25,000 school-aged children, was undertaken to assess mass treatment with albendazole at a dose of 400 mg and cost of ~$0.05 per child [85]. In early 2004, this programme was extended by the Ministry of Health to include a total of 1 million school-aged children in the worst affected regions of Myanmar (representing ~15 % of the countries school-aged children considered ‘at high risk’ of STH infection). The proportion of children receiving anthelmintic therapy has since expanded to 23 % of school-aged and 19 % of preschool-aged individuals [54].

Currently, no information on STH is available in Timor-Leste. However, STH infections are expected to be a significant problem due to poverty and lack of proper infrastructure, especially in the remote communities. Detailed epidemiological surveys of STH in the populations of this country would provide major insights into the burden of disease and would aid in directing deworming programmes, which are currently estimated to reach approximately one quarter of the children in Timor-Leste [54]. Although there are no known STH monitoring or control programmes in Brunei Darussalam or Singapore [29], considering the high level of transnational travel (e.g. for employment and tourism) between these countries and their neighbours (in which STH are endemic), the potential for
exposure to these helminths remains a medical health risk, which is worthy of continuous consideration. This is evident as in June 2006; of the 118 Singaporean soldiers who visited Brunei Darussalam for jungle training for 10 days, two soldiers had severe diarrhoea and were diagnosed with severe hookworm infection. An epidemiological investigation and case-control study was then initiated amongst these 118 soldiers. Of 103 soldiers completing both the questionnaire and with all the laboratory tests, 42 soldiers (41%) had eosinophilia (>0.6 × 10⁹/l) and 18 (17%) had hookworm infection on microscopy. More than 89% recalled substantial exposure to soil or groundwater, but no exposure was significantly associated with eosinophilia or infection. After adjusting for possible exposures, not wearing footwear during rest periods had a significantly higher odds ratio (2.86) for acquiring hookworm infection or eosinophilia [69].

11.4 Public Health and Economic Consequences of STH

STH infections are global public health problems because of their high prevalence and also because of their consequences. Almost all tropical and subtropical regions are affected by STH infections especially amongst children. Thus, United Nations agencies and other nongovernmental organisations have dedicated their efforts to minimise and eradicate STH amongst the communities at high risk of STH. Despite these efforts and interventions to control STH infections, about 70% of school-aged children at risk of STH infections are still not protected by deworming treatment [86].

Several studies in different Southeast Asian countries including Malaysia, Thailand, Indonesia and Vietnam have revealed a temporal relationship between STH infections and protein-energy malnutrition, iron-deficiency anaemia (IDA), vitamin A deficiency (VAD), poor cognitive functions and poor school participation amongst schoolchildren [45, 87, 88]. The World Health Organization [3] indicated that STH may have a negative impact on the economic development of communities and nations, resulting from failure to treat school-age children who are infected. These children are often physically and intellectually compromised by anaemia, leading to attention deficits, learning disabilities, school absenteeism and higher dropout rates and this may yield a generation of adults disadvantaged by the irreversible sequelae of infections. Hence, benefits of successful STH control programmes extend well beyond eliminating STH as they improve the growth and physical fitness of children as well as contribute to higher educational attainment, labour force participation, productivity and income amongst the most vulnerable populations [89–91]. Previous studies in Indonesia, Vietnam and Malaysia revealed that the level of serum iron, vitamin A and school performance, respectively, were improved after deworming [7, 87, 88].

The negative consequences of STH infections may continue into adulthood with effects on the economic productivity which trap the communities at risk of infections in a cycle of poverty, underdevelopment and disease [89, 92]. It is well
documented that obtaining more education leads to higher adult income, and thus, the effect of mass deworming on school participation should be central to any reasonable policy analysis for the future development of the individual and society. Moreover, several reports from different parts of the world argue that eradication of the most prevalent intestinal helminth infections is a very high return investment [93]. For instance, the gross national product (GNP) increased in Japan just after the successful control of parasitic diseases including STH, and this means that improved public health conditions preceded economic growth [94]. Within this context, the importance of the burden of tropical diseases including STH in impeding economic development of developing nations has received considerable attention in recent years, and there is now broad agreement that they should be a priority for the improved health in large parts of the world population. The WHO regarded the control of schistosomiasis and STH amongst the top five health priorities within the global massive effort against poverty [95].

11.5 Controlling STH Infections

The World Health Organization suggests three main and vital interventions to prevent and control STH infections. These interventions are periodic administration of anthelmintic drug, proper sanitation and effective health education [96]. Anthelmintic drug is aimed at reducing morbidity by decreasing the worm burden. Periodic deworming amongst high-risk groups will reduce the intensity of infection and will frequently result in improvement of child’s health, nutrition and development. Adequate proper sanitation is aimed at controlling transmission by reducing the contamination of soil by faeces of infected individuals. Moreover, health education is aimed at reducing transmission and reinfection by increasing people’s awareness towards STH and promoting healthy behaviours and hygienic practices including the use of toilets [97]. The combination of these three main interventions is essential for a long-term control and elimination of STH. Indeed, without improvements in sanitation and personal hygiene practices, periodic deworming cannot attain a sustainable reduction in transmission. Similarly, improving sanitation may not attain the desired impact without a parallel improvement in hygiene awareness and health-related behaviours in the population [98].

Generally, the prevalence of STH infections in SEA were high (>50 %) especially in the 1970s. In view of this, national helminth control programmes were initiated in Malaysia in 1974 [99], Indonesia in 1975 [58], Thailand in 1980 [100] and Philippines in 1999 [101]. In addition, school-based anthelmintic (i.e. albendazole or mebendazole) control programmes were also instituted in Vietnam [72, 102], Cambodia [103, 104], Lao PDR [77] and Myanmar [85, 105] by the respective country in collaboration with world agencies and/or foreign developed nations. However, there is no known STH monitoring or control in Brunei Darussalam or Singapore [29].
Key policies in the national governmental control programmes which include surveillance, treatment, improved sanitation, better educational awareness and the provision of safe drinking water have produced successful outcomes in many instances [72, 100]. Until now, STH has been successfully controlled in Brunei Darussalam and Singapore [72]. In Malaysia and Thailand, there are still pockets of populations with high prevalences and these are usually concentrated in rural areas where populations are marginalised with high level of poverty, inadequate clean water supply and improper sanitation facilities coupled with low hygiene and substandard nutrition. However, in East Timor, Indonesia, Myanmar and the Philippines, these infections have remained endemic [106].

11.5.1 Periodic Anthelmintic Drug Distribution

Mass anthelmintic drug administration has been used for generations as the main pillar and the most cost-effective intervention to control STH infections worldwide. It has been considered as the main approach for STH control in areas where infections are heavily transmitted, where resources for disease control are limited and where funding for sanitation is insufficient [107]. In endemic areas, the anthelmintic drug can be distributed to the entire community without prior diagnosis for the infection status (mass treatment) or distributed to certain group of a targeted population, which may be defined by age, sex or any other social characteristics, without prior diagnosis for the infection status (targeted treatment). Moreover, the treatment can only be distributed to the vulnerable people after a diagnosis to detect the most heavily infected people who will be most at risk of long-term consequences of morbidity and mortality. School-based deworming may be particularly a cost-effective approach as it takes advantage of an existing school infrastructure and the fact that schoolchildren are easily accessible through schools. It may also provide an effective way of reaching large portions of an at-risk population, including school personnel, the families of the schoolchildren and other members of the community. Moreover, in highly endemic communities, the periodic distribution of anthelmintic drugs needs to be integrated with programmes which currently deliver health care to children aged between 1 year and school age, such as immunisation programmes, vitamin A capsule distribution programmes and maternal-child health clinics [108].

The WHO recommends four anthelmintic drugs for the control of STH [3]. These drugs are albendazole, mebendazole, levamisole and pyrantel pamoate with albendazole as the drug of choice which is currently used in almost all national control programmes. In addition to these anthelmintic drugs, thiabendazole which has been used for treating strongyloidiasis has been long hampered by low efficacy and high frequency of unpleasant side effects. However, ivermectin, used as a single dose of 150–200 mg/kg against strongyloidiasis, has shown high cure rates [109].
Albendazole is a broad-spectrum anthelmintic agent available in pharmaceutical form as flavoured chewable tablets (200 and 400 mg) and as an oral suspension (100 mg/5 ml) and given in a single dose of 400 mg, reduced to 200 mg for children below 24 months. A single dose of 400 mg is highly effective against ascariasis and hookworm infections. However, strongyloidiasis and heavy trichuriasis may require a 3-day course of treatment [110, 111]. Albendazole, like other benzimidazole derivatives, prevents the formation of microtubules by binding to the nematode β-tubulin and inhibiting the parasite microtubule polymerisation which causes death of adult worms within few days [112, 113]. Moreover, it also interferes with metabolic process by impairing the uptake of glucose, thereby increasing glycogen depletion, and impeding the formation of ATP which is used as the energy source by the helminths [113]. The drug is poorly absorbed by the host and most of its anthelmintic action operates directly in the gastrointestinal tract. However, its absorption can be enhanced several times when ingested with fatty meals.

On the other hand, a low cure rate of a single dose of albendazole drug against trichuriasis has been reported in Malaysia, Thailand, the Philippines, Lao PDR, Vietnam and other countries in the Southeast Asia and Western Pacific regions [38, 72, 114]. Similarly, pyrantel has been extensively used in several STH control programmes, particularly in Southeast Asia. In Malaysia, the national mass deworming programme using a single dose of pyrantel pamoate once or twice a year was discontinued in 1983 due to the low effectiveness of the drug against *Trichuris* and hookworm infections [31].

### 11.5.2 Sanitation

*Sanitation is more important than independence* (Mahatma Gandhi, 1923).

Soil-transmitted helminthiasis is a faecal-borne infection, and transmission occurs when the infective stages passed to soil for developmental process and then infect human either directly (hand-to-mouth or skin penetration) or indirectly (through food and water). Hence, sanitation in the context of economic development is the only definitive intervention that eliminates these infections as it plays an important role in protecting the uninfected individuals and reducing the environmental sources of infections. Globally, 1.1 billion people practise open defecation and 2.6 billion people are still lacking access to sanitation, and at any given time, about half of the urban populations of Africa, Asia and Latin America have a disease associated with poor sanitation, hygiene and water [115]. A mathematical model suggests that 1 g of fresh faeces from an infected person can contain about 106 viral pathogens, 106–108 bacterial pathogens, 104 protozoan cysts or oocysts and 10–104 helminth eggs [116]. Hence, open defecation habit plays a major role in contaminating the soil and spreading of STH infections. However, one of the limiting factor is that the cost of sanitation is always higher when compared to other interventions and implementing this strategy is always difficult where
resources are limited [117]. For instance, the STH control in Vietnam, based on regular deworming, latrine construction and health education, has shown that the cost per child for each latrine was very high (US$7.9) when compared with anthelmintic drug treatment which costs pennies. Moreover, the positive impact of improved sanitation is slow and may take few years to achieve desired benefits.

In SEA, the lack of proper sanitation, particularly in rural areas, has been identified as a significant risk factor amongst aboriginal communities in Malaysia [32, 118], southern Thailand [119], central Lao PDR [120], a low-country tea plantation in Sri Lanka [121], underprivileged areas in Indonesia [122] and amongst a community using both wastewater and human excreta in agriculture and aquaculture in Hanoi, Vietnam [123]. A recent systematic review and meta-analysis study investigating on the association of sanitation with STH infections revealed that the introduction of sanitary system reduces the prevalence of STH by about 30 % [124].

11.5.3 Health Education

Health education that is effective, targeted and simple is often recommended as a first option to create the enabling environment for other strategies to thrive, especially in underprivileged communities [125, 126]. Health education can be provided simply and economically, and its benefits go beyond the control of helminth infections [6]. In general, providing information on the disease and the possible adoption of preventive measures frequently results in an increase in knowledge and awareness of the targeted population towards specific health problem but not necessarily in behavioural change which is somehow more difficult and needs longer time [117]. Health educational materials (posters, leaflets, drama, radio and video messages) with some practical activities on hygienic practices have been traditionally used to transmit and disseminate health-related messages.

With regard to STH transmission, reduction in the faecal contamination of soil can be achieved by promoting the use of latrines and promoting personal/family hygiene measures such as washing hands, periodic cutting of nails, proper food preparation and wearing shoes during outdoor activities. The best example here is community-led total sanitation (CLTS), an innovative communications-based approach for mobilising communities to completely eliminate open defecation and achieving ‘open defecation-free’ status [127]. This approach focuses on the behavioural change needed to ensure real and sustainable improvements via community mobilisation rather than helping individual households to acquire toilets. It was developed and introduced in Bangladesh and uses external facilitators and community volunteers to raise community awareness on contamination of open defecation to the environment, water and food ingested by households. Subsequently, CLTS has spread from South Asia to Africa and South America and reported to be highly successful in certain communities.
Previous studies indicated that when health education was used alone without other interventions, it showed minimum reduction rate in the prevalence of STH [55, 128]. However, higher reduction rates were achieved when health education was introduced with sanitation, and this can be considered as the option of choice for sustaining and prolonging the control outcome of other intervention programmes [129]. In Japan, systematic health education programmes were applied alongside various methods of prevention of STH infection like construction of simple latrines, disinfection of vegetables and the use of chemical fertilisers, and all these measures helped in eradicating ascariasis [130].

11.5.4 Can We Deworm This Wormy World? Stories of Success from Asia

Recent estimates suggest that 5.3 billion people are either infected or at risk of STH infections worldwide as they live in areas stable for transmission of at least one STH species [2]. A further 143 million lived in areas of unstable transmission for at least one STH species. These figures make a target of eradication of STH not possible. Thus, WHO programmes and initiatives focus on the elimination of morbidity not parasites. In the eternal battle of humans against worms/helminths, a few success stories in eliminating and reducing the transmission, prevalence and intensity of STH infections have been documented in several Asian countries, notably Japan, South Korea and Taiwan, with mass deworming, proper sanitation and hygiene education being the main components of control programmes [94, 131].

This success was achieved by using a school-health-based approach which was implemented through triangular cooperation amongst government agencies, nongovernmental organisations and scientific experts. Within this context, the Japan International Cooperation Agency (JICA) proposed the Global Parasite Control Initiative in 1998 and established three research and training centres around the world in order to extend the successful experience in controlling parasitic infections to other countries worldwide [132]. One of these centres, Asian Center of International Parasite Control (ACIPAC), was established in 2000 at Mahidol University, Bangkok. This centre has organised several training courses for the school-health-based control of STH for health personnel and educators. Moreover, JICA has supported small-scale pilot projects using the Japanese model in STH control in Cambodia, Lao PDR, Myanmar and Vietnam.

With regard to the WHO strategic plan of eliminating STH infection as a public health problem in children, Cambodia and Lao PDR were amongst the first countries in the world to achieve 75 % national coverage of preventive chemotherapy in school children and maintain high national coverage [86]. Recently, national STH control programmes in Cambodia have achieved a substantial success in reducing the prevalence rates from 80–90 % to less than 15 % [133].
11.6 Future Directions

11.6.1 Vaccination: The Long-Term Prospects for New Control Tools

To date, national deworming programmes through mass drug administration in SEA countries such as Cambodia, Lao PDR, Myanmar, Thailand and Vietnam have had an important impact on reducing the prevalence of STH infections [134]. However, heavy dependence on such drugs alone is a cause of concern. Unlike ascariasis and trichuriasis, in which the highest intensity usually occurs in school-aged children, heavy infection of hookworm can occur in adults [135]. Thus, the deworming programmes which usually target school-aged children are not expected to reduce hookworm infection significantly while they might have some effect on ascariasis and trichuriasis. In addition, such regular mass anthelmintic treatment often fails against hookworm effectively because of the rapid reinfection in endemic areas [136] and diminished efficacy of the anthelmintic drugs with increased and repeated use [137]. Amongst aboriginal schoolchildren in Malaysia, the reinfection rates of STH were reported to be high and by 6 months after completion of deworming, the prevalence and intensity of infections were similar to pretreatment levels [38].

As a potential threat, the rapid increasing mass distribution of these few anthelmintic drugs raises some concerns about a sustained drug efficacy and the potential threat of emerging resistance as a result of drug pressure and widespread use of these anthelmintic drugs [112]. Moreover, some previous studies have reported a low efficacy of single-dose albendazole and mebendazole. Although both drugs are effective against *A. lumbricoides*, mebendazole is not effective against hookworms, while neither of the drugs is effective against *T. trichiura* unless used with large doses for 3 successive days [126]. In addition, anthelmintic drug resistance is already a serious problem in nematode of veterinary importance [138] and this reality should be taken into consideration when implementing drug-based control strategies against STH.

It is thought that even more efficacious and powerful drug compared to albendazole and mebendazole would not be expected to overcome the occurrence of rapid reinfection after treatment. This has prompted efforts to develop an effective vaccine. Because of its simple, single step for disease, infection and transmission interruption, vaccination remains the method of choice to control STH infections. The Human Hookworm Vaccine (HHV) Initiative was initiated in 2000 by the Sabin Vaccine Institute Product Development Partnership (Sabin PDP) in collaboration with the George Washington University, the Oswaldo Cruz Foundation, the Chinese Institute of Parasitic Diseases, the Queensland Institute of Medical Research and the London School of Hygiene and Tropical Medicine [139]. To date, several candidates of vaccine antigens for hookworm have been successfully identified as having potential for vaccine development. For example,
the *Necator americanus*-Ancylostoma-secreted protein-1 (*Na-ASP-2*) vaccine was the first generation of hookworm vaccine that has advanced into clinical development in human [140, 141]. Despite several evidences showing that *Na-ASP-2* are the promising candidate for vaccine development, the trial was discontinued after their Phase I clinical trial in a hookworm endemic area in Brazil when some participants developed allergic reaction to the *Na-ASP-2* vaccine [142].

This has led Sabin PDP to develop new criteria for the selection of helminth antigens for potential vaccine candidate including skin test and seroprevalence study in endemic areas [143]. Currently, two lead candidate antigens, *Necator americanus*-glutathione S-transferase-1 (*Na-GST-1*) [144, 145] and *Necator americanus*-aspartic protease-1 (*Na-APR-1*) [146] are being developed as potential vaccine candidates with Part I of the Phase I clinical trial on *Na-GST-1* being initiated in Brazil. The result indicated that no safety issues were reported from healthy participant (i.e. no history of hookworm infections) [143]. These promising outcomes were sufficient for the researchers to proceed to the next stage of the trial, in which the vaccine candidate will be given to adults who were exposed to hookworm infections. The Human Hookworm Vaccine that is still under development will ultimately incorporate both the *Na-GST-1* and *Na-APR-1* in a bivalent vaccine in making the goal of first-ever human hookworm vaccine a reality.

However, additional research is needed to determine how this vaccine can be incorporated into existing control programmes and how it would be beneficial for vulnerable groups that are currently not targeted for regular deworming programmes. Until these new technologies become available, periodic deworming for high-risk population remains the most practical and substantive means to control STH infections [141]. The coming decade promises to be an exciting one in the history of STH control as new and appropriate technologies are folded together to combat the STH diseases particularly hookworm infection in SEA and other endemic countries around the world. With the establishment of an extensive infrastructure for biomedical research over the last decades in Singapore and other SEA countries and the enthusiasm for seeing helminthological science translated into new interventions, it is believed that this region has major potential for leadership in the development of new alternative and sustainable integrated control tools of STH infections in the years to come.

### 11.6.2 Using Geographical Information Systems in STH Control

Although it is known that STH is still a major public health problem in many SEA countries, a precise estimate of the total disease burden has not been fully described as collation of systematic information on STH infections is not currently available. Most of the information or record on the prevalence of STH infections is scattered across the literature and not catalogued systematically. These data are seldom
available in an accessible format for policy makers or public health authorities. Hence, previous approach in describing the distribution of STH infections has typically been made at the national level using prevalence data from few available published reports, which are then extrapolated to the country as a whole. Such approach however has limited practical importance to effectively target control efforts. In recent years, there has been renewed interest from the international organisations in the helminth control programme that leads to an increase momentum to attain more comprehensive data, allowing available control resources to be most rational and cost-effectively deployed [147]. As a result of these changes in health priorities, tremendous efforts have been made in the development of methods to map the distribution of diseases, particularly through the use of geographical information system (GIS) and remote sensing (RS) which made data integration and mapping more accessible and reliable [147].

A principal advantage of GIS is that it facilitates regular updating of database and provides a ready basis for mapping and analysis. It also offers us the ability for modelling the spatial distribution of STH infections in relation to the ecological factors which are derived from remote sensed satellite data that are known to influence their distribution pattern, deepening our knowledge and understanding in the biology and epidemiology of the infections [148, 149]. It allows us to predict the distribution of infection and identify endemic areas, thus providing more precise estimates of populations at risk and map their distribution by facilitating the stratification of areas using infection risk probabilities. This can provide basic information on treatment intervention or public health measure delivery systems at broad spatial scale particularly in areas without comprehensive data [148]. Such approach has also the potential in facilitating and assisting the design of sustainable development control programme at realistic scale for national control programme by providing the relevant authorities with relatively low-cost approach for both the upstream (e.g. survey and design) and downstream (e.g. targeting, monitoring and evaluation) control programme, which significantly reduce the cost of practical programme by identifying priority areas or simplifying the monitoring and evaluation processes [148]. Thus, the use of GIS is essential for developing and implementing control measures to those populations in greatest need particularly when the recourses for control programmes are finite and limited.

In addition, the use of remote sensing (RS) satellite data, which provides proxy to environmental data, helps to further enhance the functional capabilities of GIS by predicting the distribution of STH in relation to their ecological limit [147]. The association between the ecological factors such as altitude, climate, temperature and rainfall that influence the distribution pattern of STH has long been acknowledged and observed previously in many studies conducted in SEA. Such association has been observed in several SEA countries including Malaysia [150], Indonesia [151], Myanmar [85], the Philippines [134] and Vietnam [70]. However, such findings were based on the comparative observation prevalence of STH in different ecological zones such as mountain area vs. lowland or northern part of the country vs. southern part.
To date, the GIS and RS tools have been widely used for analysis, mapping and spatial modelling of several parasitic diseases including STH infections [147, 152–159]; however, such approach in STH mapping has been attempted largely in African countries. Only recently, GIS and RS approaches for mapping of STH infections have been extended to Southeast Asia regions including Mekong countries, i.e. Cambodia, Lao PDR, Myanmar, Thailand and Vietnam [156] as well as Indonesia and the Philippines through the support from UNICEF [160]. Findings from the mapping of STH in Mekong countries suggested that *A. lumbricoides* and *T. trichiura* are most unlikely to occur in areas where land surface temperature (LST) exceeds 37 °C particularly in Vietnam where low prevalence of *A. lumbricoides* and *T. trichiura* infections (i.e. less than 10 %) were reported in areas where maximum LST is above 37 °C [156]. Likewise, predictive risk map and disease pattern for the whole Mekong countries have been developed to estimate STH burden in each country at the provincial level. The present examples have also sufficiently proven that if used appropriately, GIS and RS technologies can be used as relevant and important tools to design cost-effective control programme through a more precise and prioritised geographical target population such as school-age children in a high-risk area particularly when the resources for control is finite and limited, using the example and experience in Mekong countries [156].

In order for the potential of GIS and RS to be fully utilised particularly at the identified high-risk areas, it has to be implemented together with the existing appropriate control strategies. One way that this could be achieved is by incorporating and adopting the programme so-called Focus Resources on Effective School Health (FRESH) framework [161]. The FRESH framework was established to provide a consensus approach of good practice for the efficient and successful implementation of health and nutrition services within school-health programme (Anon 2000). Amongst the early international partners together with WHO were UNESCO, UNICEF, World Food Program (WFP), World Bank and Partnership for Child Development (PCD). The framework suggests four core components that have to be considered in designing a cost-effective school-health and nutrition programme which indirectly provides the appropriate mix interventions that can be adopted for STH control programme for the targeted school-age children. However, of course, GIS and FRESH framework do not prescribe the designs of deworming programme in school as such programme is highly variable depending on the specific country. In low-income countries, participation of both public and private sectors is commonly used. For public sector, the Ministry of Health (MoH) can involve in supervising the activity while the Ministry of Education (MoE) assists in the implementation of the activity for intervention programme, particularly through teachers. The participation of public sectors in such approach has been demonstrated to be successful in many low-income countries [148]. As for private sector, the nongovernmental organisation (NGO) bodies can participate and contribute by sponsoring or donating drug for treatment through the MoH and MoE. It has been shown that the involvement of private sector has proven to be sustainable and effective in many middle-income countries such as Indonesia and historically Japan and South Korea by delivering treatment that is paid for the community
Whatever the design, identifying which populations (i.e. schools and communities) are in greatest need for the treatment is a fundamental part of the process of these GIS and RS approaches.

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