CHAPTER 2

LITERATURE REVIEW

2.1 SOIL-TRANSMITTED HELMINTH (STH)

Soil-transmitted helminth (STH) are a group of intestinal parasitic nematode worms which cause human infections through contact with their eggs (i.e., indirect ingestion) or larvae (i.e., skin penetration) that live in the warm and moist soil (Bethony et al, 2006). The four main species that infect humans are large roundworm (*Ascaris lumbricoides*), whipworm (*Trichuris trichiura*) and the two anthropophilic species of hookworm (*Necator americanus* and *Ancylostoma duodenale*). It is common for a single individual, who live in a less developed country to be chronically infected with all three worms (Bethony et al, 2006). In many cases, STH infections rarely cause death, instead, they are considered as one of the world's most leading cause of malnutrition, growth stunting, cognitive and educational deficits and intellectual retardation particularly among vulnerable group such as children and women of reproductive age (Anon, 2002; 2005).

STH infections are one of the world's most prevalent afflictions of humans who live in areas of poverty in the tropical and subtropical countries (Hotez, 2008a). Although the greatest numbers of infections occur in Asia including China, India and Southeast Asia as well as sub-Saharan Africa and Latin America, these infections do not occur exclusively in developing countries (Hotez, 2008a). These infections also affect impoverished and under-represented minority populations even in wealthy developed countries (Hotez, 2008b). For example, STH infections also occur predominantly in poor communities in the Mississippi Delta, in the United States-Mexico borderlands, as

well as in certain immigrant populations and disadvantaged white populations living in Appalachia (Hotez, 2008b).

To date, approximately, 2 billion people or 24% of the world's population are infected with at least one species of STH worldwide, with *A. lumbricoides* infecting 1.2 billion people, *T. trichiura* 800 million, hookworm 600 million (de Silva et al, 2003; Bethony et al, 2006). It is estimated that annual death from STH infections varies widely, from 12,000 to as many as 135,000 deaths annually (Anon, 2002; Anon, 2005). Given that it is uncommon for STH infections to cause fatality to their host, citing mortality figures provides only a small window on their health impact (Hotez et al, 2009). Instead, the worldwide disease burden is typically assessed by disability-adjusted life years (DALYs) as STH infections cause more disability than death (Murray & Lopez, 1996). The total global disease burden due to STH infections is estimated around 39 million DALYs (Hotez et al, 2009). This means that the combined disease burden of STH infections is as great as tuberculosis (37.4 million DALYs) and malaria (46.5 million DALYs) (Chan, 1994a; Liese et al, 2010).

The World Health Organization (WHO) has recognized STH infections as one of the most important causes of physical and intellectual retardation among school-aged children (Anon, 2002; 2005). Nonetheless, despite their significant public health importance, they remain largely neglected by the medical and international community (Bethony et al, 2006). This neglect occurs due to several factors such as the most affected people belongs to the poorest and disadvantages communities who often live in remote, rural areas, urban slums or in conflict zones (Bethony et al, 2006; Hotez, 2009). With little political voice in these disadvantaged communities, STH infections have a low profile and status in public health priorities. They are not highly visible and do not cause explosive outbreaks that attract public and media attention (Hotez, 2009).

Although they cause great and permanent despair, they do not kill large numbers of people. In addition, the quantification of their consequence on economic development and education is difficult to assess (Bethony et al, 2006; Hotez, 2009).

In recent years, however, there has been renewed concern from the international community recognizing the importance of STH infections (Hotez et al, 2009). This interest occurs after the revised DALYs estimation showed that the combined disease burdens due to STH infections are as significant as those of tuberculosis and malaria (Chan, 1994a; Liese et al, 2010). Several studies have showed the profound effect of STH infections on performance and attendance of school children as well as future economic productivity (Bleakley, 2003; Miguel & Kremer, 2004; Muller et al, 2011). The World Health Assembly has passed a resolution urging its members to contribute in the control program aimed to reduce morbidity through mass deworming program especially among school-aged children in developing countries. This resolution has led to a one of the largest worldwide health initiative ever undertaken in combating this neglected tropical diseases (Horton, 2003). Moreover, there are also evidences to indicate that infected individuals with these nematode worms might increase their susceptibility to other important diseases such as malaria (Nacher, 2011), tuberculosis (Potian et al, 2011) and human immunodeficiency virus (HIV) infection (Friedrich, 2012).

2.1.1 The parasite

The life cycle of nematode worms consists of several stages such as the egg, larvae (i.e., which undergo several molts) and adults. The worms can inhabit for several years in the gastrointestinal tract of their hosts. Adult hookworms inhabit the upper part of the

human intestine, while adult *A. lumbricoides* live in the small intestine (i.e., jejunum) and *T. trichiura* whipworms parasitize the large intestine (i.e., colon). The parasites vary greatly in size with female worms usually larger than males. After mating, each adult worm is able to produce thousands of eggs per day, which leave the body in the feces (Table 2.1).

Table 2.1: Characteristics of the soil-transmitted helminth (STH)

Soil-Transmitted Helminth (STH)	Length (mm)	Daily egg output per female worm	Location in host	Lifespan (years)
Roundworm				
A. lumbricoides	150-400	200,000	Small intestine	1
Whipworm				
T. trichiura	30-50	3,000-5,000	Large intestine	1.5-2
Hookworms				
N. americanus	7-13	9,000-10,000	Upper small intestine	5-7
A. duodenale	8-13	25,000-30,000	Upper small intestine	5-7

Sources: Crompton, 1989; Cooper, 1995

2.1.1.1 *Ascaris lumbricoides*

Ascaris lumbricoides is a member of the nematode super family of Ascarididae and closely related to the swine species, namely *Ascaris suum*. *A. lumbricoides* is the largest intestinal roundworm which causes ascariasis. The adult worm is cylindrical-shaped, pinkish or creamy in color with the male being smaller (150 to 250 mm) than the female (200 to 400 mm). The adult worm lives in the small intestine (i.e., jejunum) where it orientates with the head facing the direction of the intestinal flow (Makidono, 1956). A mature adult female worm can produce up to 200,000 eggs per day. The egg has a thick and transparent hyaline shell with a relatively thick outer layer that acts as a supporting

layer. Eggs excreted in the feces require a period of maturation in the soil. When an egg is passed into the environment, the embryo molts within the eggs shell under optimal condition such as warm temperature and moist shaded soil (Crompton, 1989). The infective stage is a third stage larva within the egg. The period of development in the soil depends on the temperature and can range from 2 weeks to several months. Infections with *A. lumbricoides* occur by the accidental ingestion of completely developed embryonated eggs. After ingestion, the egg hatches. The larva which emerges from the egg penetrate the intestinal wall and enter the liver then the lungs after an obligatory extraintestinal migration, before passing over the trachea to re-enter the gastrointestinal tract. It takes about 10 to 12 weeks for eggs to be produced by a mature adult worm from the time an infective egg is ingested. The adult worm has a life span of about a year (Crompton, 1989).

2.1.1.2 *Trichuris trichiura*

Trichuris trichiura is a member of the nematode super family Trichuroidea, and therefore related to the *Trichinella spiralis. T. trichiura* causes a parasitic disease known as trichuriasis. The adult worm is pinkish-white in color and approximately 30 to 50 mm long with whip-like shape. As for *T. trichiura*, female is also larger than male (i.e., approximately 35 to 50 mm long compared to 30 to 45 mm). The adult worm inhabits the small intestine of their host. A female worm has a productive capacity of 3,000 to 10,000 eggs daily. The characteristic egg is brown in color and barrel-shaped with pug at each pole (Cooper, 1995). A fertilized egg is un-segmented when passes through feces. After embryonation in a favorable environment, infective first stage larva is produced within 3 weeks. Human become infected by ingesting the fully developed

eggs. When the embryonated egg is ingested by human, the infective larva escapes from the egg shell in the upper small intestine and migrates to the large intestine (colon) where they burrow into the intestinal mucosa and further develop into adult worms. The developmental period from the ingested egg to ovipositing adult takes about 12 weeks, while its life span is usually between 1 to 2 years (Cooper, 1995).

2.1.1.3 Hookworms (*Necator americanus* and *Ancylostoma duodenale*)

Hookworms are nematodes belonging to the family Ancylostomatidae, a part of the super family Strongyloidea. The two major species that affect humans are *Necator americanus* and *Ancylostoma duodenale*. Both species can be differentiated by the presence of oral cutting organs in the adult stages. The adult worm is small, cylindrical, fusiform and grayish white in color. The female (i.e., 9 to 13 mm) is larger than male (i.e., 7 to 11 mm). The egg has blunt rounded ends and a single thin transparent hyaline shell. The adult worm usually resides in the small intestine. The egg hatches in soil within 24 to 48 hours under optimal conditions. The rhabditiform larva feeds on bacteria or fecal matter, molting twice to become an infective third stage larva which is non-feeding. The third stage larva (i.e., infective larvae) is motile seeking higher ground to improve the chance of contact with human skin (Cooper, 1995).

After skin penetration, the larva is carried out through the blood vessels to the heart and then to the lungs. From the lungs, the larvae migrate up to the trachea to be swallowed and reach the small intestine, where they mature into an adult. It takes about 5 to 9 weeks from skin penetration until the development of an egg-laying adult (Hoagland & Schad, 1978). The adult worm has a life span of about 5 to 7 years (Cooper, 1995). Unlike *N. americanus* which only infects human through skin

penetration, *A. duodenale* can also be transmitted through oral ingestion of the infective larvae (Hotez, 1989) and lactogenic transmission during breastfeeding (Yu et al, 1995). *A. duodenale* is considered to be the more 'opportunistic parasite' because of its ability to survive in more extreme environmental conditions, its oral infectivity, greater fecundity and higher virulence with regards to higher blood loss (Hoagland & Schad, 1978).

2.1.2 Clinical manifestation of STH infections

In general, STH infections are usually asymptomatic. The clinical manifestation of STH infections generally can be categorized into two features; first, the acute clinical symptoms resulting from early larvae migration through the human skin and viscera and second, the acute and chronic symptoms associated with the intestinal parasitism by adult worm (Table 2.2).

2.1.2.1 Early larvae migration

In the early phase (i.e., early larvae migration) of *A. lumbricoides* infection, migration of larvae to the lungs can cause respiratory symptoms. *Ascaris lumbricoides* larvae that die during migration through lungs can cause eosinophilic granulomas (Kaplan et al, 2001). Classically, heavy infection may also result in verminous pneumonia (i.e., Loeffler's syndrome), a condition which is usually associated with wheezing, dyspnoea, non productive cough and fever with blood-tinged sputum (Loeffler, 1956). In contrast to *A. lumbricoides*, *T. trichiura* life cycle does not involve any pulmonary migration and thus, no pulmonary symptom occurs. As for hookworm infections, several cutaneous

symptoms may occur from penetration of the larvae through skin such as ground itch, a local erythematous and papular rash along with pruritus on the hand and feet due to the continuous exposure to infective larvae (i.e., third stage larvae) (Hotez et al, 2005). Additionally, infection with zoonotic hookworm species such as *A. braziliense* can result in cutaneous larva migrans (CLM) or 'creeping eruptions', a condition characterized by the sign of serpiginous tracks on the feet, buttocks and abdomen (Bowman et al, 2010). In some cases, the migration of third stage larvae from skin to the lung can leads in pneumonitis, though is not as great as in *A. lumbricoides* infection (Hotez et al, 2005). Additionally, oral ingestion of *A. duodenale* larvae also sometimes results in Wakaka syndrome, a condition associated with nausea, vomiting, pharyngeal irritation, cough, dyspnoea and hoarseness (Hotez et al, 2005).

2.1.2.2 Intestinal parasitism by adult worm

During the late phase (i.e., intestinal phase) of STH infections, gastrointestinal symptoms occur typically due to the mechanical effect of high parasite loads. As for *A. lumbricoides* infection, the most severe manifestations are the physical obstruction in intestinal tract by adult worms and migration of adult worm into the biliary tree (O' Hanley & Pool, 1995). Hepatobiliary and pancreatic ascariasis (HPA) occurs when adult worm in the duodenum enter and block bile duct, leading to biliary colic, cholecytitis, cholangitis, pancreatic and hepatic abscess (Khuroo et al, 1990). Chronic *A. lumbricoides* infection also has impacts on their host nutritional status such as increased fecal nitrogen loss, reduction in the ability to digest lactose (i.e., lactose intolerance) and vitamin A malabsorption (Crompton & Nesheim, 2002). In most cases of the chronic infections especially among children, they may experience abdominal pain, nausea and

digestive disturbance and these would significantly increase absenteeism and reduce attention span in school (Crompton & Nesheim, 2002).

As for *T. trichiura*, the adult parasites can cause inflammation and colitis at the site of attachment in the large intestine (MacDonald et al, 1994). Longstanding colitis produces a clinical disorder that resembles inflammatory bowel disease, including chronic abdominal pain, diarrhea and finger clubbing (Cooper, 1995). The most severe manifestation of heavy infection is the *Trichuris* dysentery syndrome (TDS), characterized by chronic dysentery, rectal prolapse, vitamin A deficiency, anaemia and growth stunting particularly in children (Robertson et al, 1992; Cooper, 1995). Heavy *T. trichiura* infections have also been associated with intellectual and cognitive impairments in children (Drake et al, 1994).

Hookworms harm their host by causing intestinal blood loss as a result of adult parasite invasion and attachment to the mucosa and submucosa of the small intestine leading to anaemia, iron deficiency anaemia (IDA) and protein malnutrition (Crompton & Nesheim, 2002). In heavy hookworm infections, the chronic protein loss can cause hypoproteinaemia and anasarca (Albonico et al, 1999), particularly in high risk group such as children and women of reproductive age due to their increase demand of iron for growth and losses during menstruation (Bundy et al, 1995). Severe IDA due to hookworm infection during pregnancy can have adverse effects on the mother, the fetus and the neonate (Christian et al, 2004).

Table 2.2: Specific and general clinical manifestation of soil-transmitted helimnth infection (STH) infections

Soil-Transmitted Helminth (STH)	Clinical features/manifestation		General features of Soil-Transmitted Helminth (STH) infections
	Early migration (larvae)	**Gastrointestinal parasitism (adult)**	
Roundworm			
A. lumbricoides	Eosinophilic granulomas Verminous pneumonia (Loeffler's Syndrome)	Intestinal obstruction Vitamin A malabsorption Lactose intolerance Hepatobiliary and Pancreatic Ascariasis (HPA)	Growth stunting Cognitive deficits Educational deficits Intellectual deficits Reduction in school attendance and performance
Whipworm			
T. trichiura	None (no pulmonary migration)	*Trichuris* Dysentery Syndrome (TDS) Colitis Dysentery Rectal prolapse Vitamin A deficiency Anaemia	
Hookworm			
N. americanus / *A. duodenale*	Ground itch Pnuemonitis Wakaka syndrome	Intestinal blood loss Iron-deficiency anemia Protein malnutrition	

Sources: Loeffler, 1956; Khuroo et al, 1990; Robertson et al, 1992; Drake et al, 1994; MacDonald et al, 1994; Bundy et al, 1995; Cooper, 1995; Albonico et al, 1999; Kaplan et al, 2001; Crompton & Nesheim, 2002; Christian et al, 2004; Hotez et al, 2005; Bowman et al, 2010

2.1.3 Risk factors of STH infections

Several factors such as host-specific and environmental determinants may affect the risk of acquiring and harboring STH infections.

2.1.3.1 Soil and climate

Given that STH eggs only mature in the soil, environmental factors such as tropical climate with warm temperature and adequate moisture are important determinants for the successful transmission of STH (Crompton, 1989). For example, *A. lumbricoides* and *T. trichiura* eggs are hardier than hookworm and therefore survive better in drier climate (Brooker & Michael, 2000). Both *A. lumbricoides* and *T. trichiura* eggs can develop much better in less permeable clay soils, with survivability increasing with the soil depth (Crompton, 1989). It has been postulated that clay soils may prevent egg dispersal by water (Crompton, 1989). As for hookworm, moisture is especially important. Hookworm eggs hatch in soil and give rise to first stage larvae, which molt to infective third stage larvae (L3) only under precise conditions. Egg development in the soil is dependent upon a number of factors including temperature (20 to 30^{o}C), adequate shade and moisture. As infective L3 migrate along films of moisture, the presence of moisture will then allow L3 to migrate vertically in the soil, mainly at night (Komiya & Yasuraoka, 1966).

It has also been suggested that rainfall patterns may affect the distribution of STH infections (Brooker & Michael, 2000). Study conducted along the coastal plains of South Africa found that transmission of *A. lumbricoides* significantly correlate with annual rainfall and temperature data (Appleton et al, 1999). Similarly, Brooker and

Michael (2000) demonstrated a minimum of 1400 mm annual rainfall is essential for *A. lumbricoides* infection to exceed 10%. Likewise, associated changes in temperature and humidity due to altitude may also affect STH transmission. Survey in South Africa found that *A. lumbricoides* infection occurred at altitude up to 1700 meter above sea level (Appleton & Gouws, 1996). In an extensive study carried out among 1,273 individuals from 7 subgroups of Orang Asli living in different forest altitude in Malaysia, it was found that the groups living at higher and cooler elevations have fewer STH infections (Dunn, 1972). This is partly because the lower soil temperature reduces the embryonation rate of eggs. In contrast, groups that live in warmer lowland forest acquired STH more rapidly as the soil conditions are more favorable to embryonation of eggs (Dunn, 1972).

Several studies using geographical information system (GIS) and satellite sensor data (Remote Sensing, RS) has identified the distributional limits of STH infections on the basis of their ecological limit such as temperature, elevation and vegetation index. For example, findings in Cameroon, Chad and Uganda suggest that *A. lumbricoides* and *T. trichiura* most unlikely to occur in areas where maximum land surface temperature (LST) exceeds 37^{o}C (Brooker et al, 2002a; 2002b). Similar study in Southeast Asia countries (i.e., Thailand, Vietnam, Laos, Cambodia and Myanmar) also observed that prevalence of *A. lumbricoides* and *T. trichiura* infections was low (i.e., less than 10%) in areas where maximum LST is above 37^{o}C (Brooker et al, 2003). More recently, mapping and modeling of STH infections across Kenya by Pullan and co-workers (2011) reported that the odd of *A. lumbricoides* infections was significantly lower with maximum LST.

2.1.3.2 Poverty, sanitation and urbanization

STH infections depend for transmission on environments contaminated with egg-carrying feces (Hotez et al, 2006a). As a result, STH are closely associated with poverty, poor environmental sanitation and lack of clean water supply. In such conditions, STH species are commonly co-endemic (de Silva et al, 2003). Essentially, improvement in sanitation and provision of safe water supply are necessary for effective control of STH infections. Although STH infections are occur predominantly in rural areas, these infections can also found in urban areas particularly in slum or squatter settlements where the social and environmental conditions are ideal for the STH transmission. Many studies have shown a high prevalence of STH infections especially *A. lumbricoides* and *T. trichiura* infections in slums, shanty town and squatter settlements (Crompton & Savioli, 1993; Hotez et al, 2006a).

2.1.3.3 Behavior and occupation

Specific occupation and behaviors may influence the prevalence and intensity of STH infections (Bethony et al, 2001). As high rate of hookworm infection has been found among adults, specific occupation probably has a greater impact on hookworm epidemiology. Engagement in agricultural activities, for instance remains an important denominator for hookworm infection (Brooker et al, 2004). A nationwide survey of STH infections (i.e., 1988 to 1992) in China showed that the highest prevalence of hookworm infection is among vegetable growers and farmers indicating a significant association between the infection and close contact with soil (Hotez et al, 1997). Sanitary behavior and type of occupation that interact with environmental factors

through their effect on water and soil contact can lead to the variation of STH transmission (Hotez et al, 2006a).

2.1.3.4 Age and household clustering

Many epidemiological studies were also focused on heterogeneity in the intensity of STH infections by age (Crompton, 2000). Although STH can infect all members of a population, it is clear that there are specific groups who are at greater risk of heavy infections. The distribution of STH infections is strongly age dependent (Chan et al, 1994b). For example, children aged 5 to 15 years have the most severe infection (i.e., high worm burden and frequency) particularly *A. lumbricoides and T. trichiura* infections, but declines significantly in adulthood (Gilles, 1996). In contrast, hookworm frequently exhibits a steady rise in intensity and frequency of infection with age, peaking in adulthood (Crompton, 2000). Family size also influences the epidemiology of STH infections. It has been observed that STH infections tend to be distributed in cluster (Forrester et al, 1988; Chan et al, 1994b). In order words, when one child in a family is infected, the siblings are also likely to be infected. One possible explanation is that more eggs would be expected in the vicinity of a household with heavily infected individuals and as such, household with infected members would function as transmission loci (Forrester et al, 1988; Chan et al, 1994b).

2.1.3.5 Genetics

To date, no gene that control STH infections in human have been identified (Hotez et al, 2006a). However, preliminary study among Nepalese population has identified some possible role of chromosome 1 and chromosome 13 in controlling intensity of *A.*

lumbricoides infection. This provides the first evidence that individual quantitative trait loci may influence variation in STH burden (Williams-Blangero et al, 2002).

2.1.4 Global control strategies of STH infections

One aspect of STH control that has changed in recent years is the perceived objectives of control. In the past, the objective is to eradicate the infections, leading to 'eradication campaigns' in many parts of the world. However, it is now a general consensus that STH infections are difficult to eliminate, for both practical and ecological reasons (Savioli et al, 1992). As of now, there are three main intervention strategies for controlling of STH infections namely anthelminthic drug treatment, improved sanitation and health education (Hotez et al, 2006a). Rather than eradication, the primary objectives are to reduce morbidity by decreasing the worm burden for the survival and healthy development of high risk groups (Savioli et al, 1992). Today, periodic deworming at regular intervals with inexpensive anthelminthic drugs stands out as the most cost-effective means to control and reduce the morbidity associated with STH infections in endemic areas. The World Health Organization (WHO) recommends both albendazole and mebendazole as the drug of choice to be used in public health program for controlling STH infections, although older drugs such as pyrantel pamoate and levamisole are also occasionally used particularly in some developing countries (Anon, 2002; 2005). With a dose of benzimidazole costing only US$ 0.02 (Anon, 2005), deworming drugs are almost irresistibly affordable.

While STH can infect all age groups, it is clear that school-aged children, women of child-bearing age including adolescent girl are the most vulnerable groups who are at the greater risk of morbidity and suffers the most intense consequences due

to the infections (Anon, 2005). Studies demonstrated that regular deworming among school-aged children has significantly improved their physical and cognitive outcomes, nutritional status, physical fitness, appetite, growth and intellectual development (Crompton, 2000; Crompton & Nesheim, 2002; Drake et al, 2000; Stephenson et al, 2000; Miguel & Kremer, 2004). Another positive outcome is the regularity of children attending school by reducing school absenteeism up to 25% (Crompton & Nesheim, 2002; Bleakley, 2003). When compared with other measures for improving school attendance, deworming is ranked by far as the most cost effective (Anon, 2005). It has also been reported that when pregnant women in endemic areas were treated once or twice during their pregnancy, there were substantial improvement in maternal survival (Christian et al, 2004).

Although periodic deworming can significantly reduce the number of adult worms in the gastrointestinal tract which is also reflected in reduced egg counts, there are some obstacles that diminish the effectiveness of the drug. Factor such as low efficacy of the anthelminthic drug, for example, single dose albendazole or mebendazole are ineffective against hookworm and *T. trichiura* infections (Bennett & Guyatt, 2000; Albonico et al, 2002; Adam et al, 2004). Likewise, high re-infection rates after treatment especially in highly endemic area (Albonico et al, 1995) and diminished efficacy with frequent and repeated use (i.e., possibly due to drug resistance) are some other factors that may lead to ineffectiveness of anthelminthic treatment (Chan et al, 1992; Albonico et al, 2003). Moreover, concerns of the anthelmintic resistance have been reported in veterinary medicine (Conder & Campbell, 1995; Geerts et al, 1997).

Improvement of sanitation that intended at controlling transmission by reducing soil and water contamination is another way for STH interventions (Hotez et al, 2006a). Sanitation is the only definitive intervention to control STH infections. In order for this

intervention to be fully effective, it should cover a high percentage of population at broad scale. Thus, implementation of such strategy to control STH infections is difficult particularly when the resources are finite and limited (Asaolu & Ofoezie, 2003). Likewise, if improved sanitation were to be used as the main control intervention, it can take years or even decades for sanitation to be successfully effective (Brooker et al, 2006).

Health education is another major intervention in controlling STH infections aimed at reducing transmission and re-infections by promoting healthy behaviors such as encouraging the use of latrines and hygienic behavior (Hotez et al, 2006a). Without a change in sanitary behaviors, regular deworming cannot achieve a significant reduction in STH transmission (Brooker et al, 2006). In addition, health education can be offered simply and economically by decreasing cost, increasing levels of knowledge and decreasing re-infections rate (Lansdown et al, 2002). Likewise, it does not involve any contraindications or risk. Its benefit goes beyond the control of STH infections as it can build trust and engage communities, which are essential aspects to the successfulness of public health initiatives (Hotez et al, 2006a).

2.1.5 Vaccination - The long-term prospects for new control tools

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 (Devaney, 2005). This project has been funded mainly by the Bill & Melinda Gates Foundation and has additional support from

the Dutch Ministry of Foreign Affairs, the Brazilian Ministry of Health, Texas Children's Hospital and the Children's National Clinical and Translational Science Institute (Anon, 2012). 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 (Hotez et al, 2006b). For example, a study in Brazil and China showed a significant association between individuals producing IgE against *ASP-2,* protecting them from high intensity of hookworm infection (Bethony et al, 2005). In addition, studies on vaccinated dogs and hamsters also showed that *ASP-2* vaccine partially protects them (i.e., vaccinated dogs and hamsters) after infections with *A. caninum* (Bethony et al, 2005) and *A. ceylanicum* (Mendez et al, 2005) in terms of blood lost and worm loads in both adult worm and egg stages. 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 (Diemert et al, 2012).

This has led Sabin PDP to develop new criteria for the selection of helminth antigens for potential vaccine candidate including skin test and sero-prevalence study in endemic areas (Anon, 2012). Currently, two lead candidate antigens, *Necator americanus*-glutathione-S- transferase-1) (*Na-GST-1*) (Jariwala et al, 2010; Goud et al, 2012) and *Necator americanus*-aspartic protease-1 (*Na-APR-1*) (Williamson et al, 2002) are being developed as potential vaccine candidates. In late 2011, Part I of the Phase I clinical trial on *Na-GST-1* has began in Belo Horizonte, Brazil. The result indicated that no safety issues were reported from healthy participant (i.e., no history of hookworm

infections) (Anon, 2012). 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. Following successful clinical trials in Part I, the Part II of its Phase I clinical trial of the *Na-GST-1* has began in Americaninhas, Brazil in 2012 (Anon, 2012).As for the *Na-APR-1*, the vaccine is undergoing development and pilot "current Good Manufacturing Practices" (cGMP) process (Anon, 2012). 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. The coming decade guarantees to be an exciting one in the history of hookworm control as new and appropriate technologies are folded together to combat hookworm disease (Hotez et al, 2006b). However, additional research is needed to determine how this vaccine can be incorporated into existing control programs and how it would be beneficial for vulnerable groups that are currently not targeted for regular deworming programs. Until these new technologies become available, periodic deworming for high risk population remains the most practical and substantive means to control STH infections (Hotez et al, 2006a).

2.2 HIGH RESOLUTION MELTING (HRM) ANALYSIS

High resolution melting (HRM) analysis is a novel and relatively new post-PCR analysis technique for DNA analysis including genotyping, mutation scanning and sequence matching (Wittwer et al, 2003; Reed et al, 2007). It was first developed in 2002 by collaboration between researchers from the University of Utah, United States of America (USA) and Idaho Technology (Utah, USA) (Wittwer et al, 2003). HRM

analysis allows direct characterization of PCR amplicons in a closed-tube system (Gundry et al, 2003). Simple and fast, this method is a probe-free assay that requires no manual post-PCR analysis as it generates computerized graphic output, thus lowering the risk of contamination (Montgomery et al, 2007). It does not require sophisticated instrument as it can be performed on an existing real-time PCR machine. This is straightforward, yet highly sensitive and accurate alternative method to other conventional molecular investigative applications (Wittwer et al, 2003; Reed et al, 2007). HRM analysis is also much more cost-effective (i.e., low reaction cost) to other assays as it only requires low-cost generic dyes rather than specific labeled probes such as Taqman probes, which are relatively expensive making it ideal for high throughput analysis (Reed & Wittwer, 2004; Reed et al, 2007).

Basically, HRM analysis is based on dissociation techniques of double-stranded DNA (i.e., dsDNA) melt curve. These advances are mainly due to the recent availability of improved dsDNA-binding dyes together with real-time PCR machine and analysis software (Wittwer et al, 2003; Reed et al, 2007). Each double stranded DNA fragments has its own melting behavior characteristic which generally depends on it composition, length, GC content or strand complementarity (Ririe et al, 1997; Wittwer et al, 1997). Any sequence variations or alterations in these characteristics will produce different melting behavior of the DNA fragments (Ririe et al, 1997; Wittwer et al, 1997), making DNA sequences easy to be discriminated (Ririe et al, 1997). Even single nucleotide substitution such as single nucleotide polymorphism (SNP) can be easily identified. It simply generates DNA melt-curve profiles which are sufficiently sensitive and specific for genotyping and species differentiation based on their unique and distinct melting patterns (Wittwer et al, 2003; Montgomery et al, 2007).

2.2.1 Fundamental of DNA Melting Analysis

Standard DNA melting curve analysis coupled with real-time PCR is a post-PCR analysis techniques that analyze the amplified DNA based on their biophysical measurement (Ririe et al, 1997; Wittwer et al, 1997). Historically, such approach has been used for various applications, generally to detect primer dimer or other non-specific PCR by-products (Ririe et al, 1997; Wittwer et al, 1997). HRM analysis begins with region of interest being amplified in the presence of a fluorescent dsDNA-binding dye. This binding dye has high fluorescence when bound to dsDNA than in ssDNA or unbound state (Ririe et al, 1997; Wittwer et al, 2003). After real-time PCR amplification, the amplicon were then subjected to melting step in the same PCR machine. The amplicon is gradually melted at high temperature. During melting (i.e., when the dsDNA dissociates or melts into single strands), the dye is released, causing changes in fluorescence.

The result of HRM is a melting curve that is generated during the fluorescence emission in the melting process through its dissociation temperature (i.e., melting temperature, T_m) (Wittwer et al, 2003). The T_m is defined as the point in the melt curve where half (50%) of the DNA is in double-stranded and single-stranded (i.e., melted) form, respectively (Wittwer et al, 2003). It equivalents the temperature at which the emitted fluorescence is 50%. At this point, it provides information of the amplicon characteristics such as their GC content where Tm is higher in GC-rich amplicons, length and sequence composition (Ririe et al, 1997; Wittwer et al, 1997; 2003). Detection and discrimination of amplicon with different sequence variants rely in the shape of this melting temperature for each melt curve (Wittwer et al, 2003). Amplicon with similar sequence variants are identified as groups that display same melting profile (Wittwer et al, 2003). The resulting melting curve profiles can offer valuable

information in various molecular biology field including genotyping, mutation screening, sequence matching and other investigative applications (Gundry et al, 2003; Wittwer et al, 2003; Montgomery et al, 2007; Reed et al, 2007).

2.2.2 HRM application

2.2.2.1 Genotyping

Currently, there are many methods available for genotyping. However, close-tube genotyping methods have strong advantages compared to other techniques as no processing step is required during the amplification and analysis, thus lowering the risk of contamination (Reed et al, 2007). Traditionally, this method requires allele-specific probes such as fluorescent dye and quencher that separate during amplification by hydrolysis or loss it secondary structure (Lay & Wittwer, 1997). However, two probes are usually needed in order to genotype correctly (Reed et al, 2007). The first high resolution genotyping without probes was reported using fluorescently-labeled primers by Gundry and co-workers (2003). However, genotyping become more complicated when the PCR product size and the distance from the labeled primer increased. This problem was solved by the introduction of fluorescent saturation dye by Wittwer and co-workers (2003). To date, genotyping using HRM analysis with fluorescent saturation dye has been applied to both human and microbial studies. In human clinical studies, it has been used to investigate single base changes (i.e., single nucleotide polymorphism, SNP) in ß-globin (Gundry et al, 2003; Wittwer et al, 2003; Liew et al, 2004), cystic fibrosis (Chou et al, 2005), factor V and prothrombin (Liew et al, 2004), hemochromatosis protein (Palais et al, 2005) and platelet antigen (Liew et al, 2007). In

microbial studies, the targets include bacteria species discrimination (Cheng et al, 2006), identifying *Salmonella* resistance gene (Slinger et al, 2007), *Aspergillus* speciation (Erali et al, 2006) and *Staphylococcus aureus* (Lilliebridge et al, 2011).

2.2.2.2 Mutation scanning

In contrast to genotyping, mutation scanning is a method to screen the differences between two copies of DNA within the same individuals (Reed et al, 2007). Several techniques has been developed to study the differences in DNA copies including single-strand conformational polymorphism (SSCP) analysis (Orita et al, 1989), denaturing gradient gel electrophoresis (DGGE) (Xiao & Oefner, 2001) and denaturing high pressure liquid chromatography (DHPLC) (Chou et al, 2005). Although sequencing result provides information for genotyping and scanning, such techniques often requires extensive automation, instrumentation and analysis (Reed et al, 2007). These techniques requires post-processing steps such as separation of the sample on a gel or matrix, additional enzymatic and chemical processing, thus increase the risk of contamination. Likewise, some of the techniques are manual and labor intensive, complex and involve specialized equipments (Reed et al, 2007). Thus, the post PCR steps are major limitations for these conventional mutation scanning tools. In contrast, the use of HRM analysis in mutation scanning study does not require any post PCR processing steps, additional enzymatic or chemical reactions or separation process (Reed et al, 2007). It also offers higher sensitivity compared to conventional mutation scanning method such as DHPLC (Chou et al, 2005). Mutation scanning using HRM analysis has been widely used in human clinical studies. It has been used to detect mutation in several cancer specimens (Willmore-Payne et al, 2005; 2006), primary carnitine deficiency

(Dobrowolski et al, 2005), cystic fibrosis gene (Chou et al, 2005), thalassemia (Prathomtanapong et al, 2009), early epileptic encephalopathy (Saitsu et al, 2010) and myotonic dystrophy (Radvansky et al, 2010).

2.2.2.3 Sequence matching

In some cases, determination of DNA sequence matches (i.e., sequence identity) is more important than sequence information of the genotype (i.e., genotyping). This is particularly relevant in certain scenarios such as in organ or tissue transplantation and forensic investigation cases (Reed et al, 2007). One important example is during organ transplantation where donors or siblings are usually screened for human leukocyte antigen (HLA) to determine the best major histocompatibility match. This commonly involves serotyping or genotyping at numerous loci such as HLA A, B, C and DR by often lengthy conventional approaches just in order to find compatible donors with similar HLA sequence identity (Reed et al, 2007). However, sequence matching by HLA is much simpler and fast for accurately identify compatible donor with similar HLA sequence identity at several loci in HLA (Zhou et al, 2004). Recipient and donor with matching sequence identity had the same meting curves while different shape of melting curve are produced if the sequence for both recipient and donor are not compatible (i.e., not identical) (Zhou et al, 2004).

2.2.2.4 HRM application in parasitic studies

The utilization of HRM analysis in parasitic organisms has been rather sporadic. This technique has mainly been used in molecular studies of parasitic protozoa. For example,

it was used to detect point mutations in antimalarial drug resistance study of *Plasmodium falciparum* genes (Andriantsoanirina et al, 2009). Likewise, Mangold and co-workers (2005) has successfully used HRM analysis to differentiate *Plasmodium* spp. infecting humans (i.e., *Plasmodium falciparum, Plasmodium ovale* and *Plasmodium malariae*). Several studies also applied HRM analysis to discriminate *Leishmania* spp. infecting humans including *Leishmania major, Leishmania donovani, Leishmania tropica, Leishmania infantum* and *Leishmania aethiopica* (Nicolas et al, 2002; Nasereddin & Jaffe, 2010; Talmi-Frank et al, 2010). Robinson and co-workers (2006) used HRM analysis to differentiate *Naegleria* spp. by screening the internal ribosomal spacers (ITS) ribosomal RNA gene. Similarly, it has been used for rapid screening of several *Cryptosporidium* spp. (i.e., *Cryptosporidium hominis, Cryptosporidium parvum* and *Cryptosporidium meleagridis*) targeting the ITS-2 gene in human clinical samples (Pangasa et al, 2009). Such approach has also been applied to study the genetic diversity of *Dientamoeba fragilis* of different clinical samples (Hussein et al, 2009) and *Giardia* spp. (Bienz et al, 2001). As for parasitic worms, the used of the HRM analysis has been rather limited. The technique was applied for rapid differentiation of *Brugia malayi* and *Brugia pahangi* (Areekit et al, 2009) and population genetic studies of *Fascioloides magna* (Radvansky et al, 2011).

2.3 GEOGRAPHIC INFORMATION SYSTEM (GIS)

Geographic information system (GIS) is a powerful combination computer system of hardware and software that is capable to store, capture, manipulate, retrieval, analyze and display all forms of geographically referenced information (Burrough, 1986; Anon, 1993). The unique attraction of GIS is not just a database but its ability to add a

geographical dimension such as spatial and map information that can be linked together (Burrough, 1986; Anon, 1993; Clarke et al, 1996). Traditionally, geographical information commonly display on conventional map such as atlas map, large scale topographical map, town planning map or thematic map including those showing land-use, geology, soil and climatic variation that contain almost everything shown on single map (Burrough, 1986; Openshaw, 1996). During the early 1970s, the computer was first applied to geography which makes GIS emerged as a multidisciplinary field as analytical and display tools (Clarke et al, 1996; Openshaw, 1996). Since the reinforcement of GIS through the use of computer in 1970s, geographical information (i.e., cartographic map objects) are store in a digital form, basically in a format of two dimensional map coordinates kwon as longitude (x) and latitude (y) representing the element of points, polygons and lines that maps are built from and can be decomposed into (Burrough, 1986; Anon, 1993; Openshaw, 1996). Several factors lead to the renaissance of GIS development such as the availability and user-friendliness of computer with less cost and the broad accessibility of public domain digital map (Clarke et al, 1996).

2.3.1 GIS functional capabilities

By standard definitions, GIS can bring together the elements needed for problem solving and analysis (Clarke et al, 1996). Data capture involves data that can be imported to the GIS from existing external digital sources. This is particularly relevant, for example in a project where no data is available and such data must be obtained or assembled from other studies, public domain database and images. In other words, GIS has the ability to import the most common data formats such as raster (i.e., image-type)

and vector (i.e., line-type). Secondly, GIS is also able to capture new map data directly. This means that either we scan any traditional map and export it into the GIS database or trace over a map features using a digitizing tablet and input them into the existing GIS map database. Thirdly, like other regular database systems, GIS can do basic data processing such as data entry, editing and update information in the existing database (Burrough, 1986; Clarke et al, 1996).

As for data storage capability, it involves storage of both map and attributes data. Attribute data are frequently stored in a relational database management system in the same GIS and accessed by a spread-sheet or query-driven users interface (Burrough, 1986; Clarke et al, 1996). As for storage, map data must be encoded into a set of numbers so that the geometry of the map is accessible for query and stored digitally in few files. For example, image maps are commonly stored as gridded assay. However, line maps can be stored in various formats, but most commonly by using both the coordinate information and encoded topology in order that the relationship between points, lines and areas can be obtained in advance (Burrough, 1986; Clarke et al, 1996).

In GIS, data records can be retrieved in one of two ways. By using the database manager, it allows the storing data to be searched, reordered and selected on the basis of a characteristic's attributes and their values. This means that the GIS can allow spatial retrieval. In other words, it allows us to select any location of interest by sorting them either according to alphabetically order, regions, latitudes, distance or any attributes. Likewise, GIS also allows combining searches of several data (i.e., layer). For example, vegetations, rivers, roads and village populations can be combined into a single query from these layers using single retrieval combination searches (Burrough, 1986; Clarke et al, 1996). For display function, it includes mostly the making of maps. Tools such as

contours, symbols, shading, choropleth or sized symbols are the common tools for constructing maps.

2.3.2 GIS and spatial analysis

One of the main key advantages of GIS applications in epidemiological field is its ability to execute spatial analysis. In the broadest terms, spatial analysis refers to the ability to manipulate any spatial data into different types and create additional meaning as a result (Burrough, 1986; Anon, 1993). With regards to spatial analysis in epidemiology perspective, there are three types of analysis, namely visualization, exploratory data analysis and modeling (Figure 2.1) (Bailey & Gatrell, 1995). The common objectives of spatial epidemiological analysis are the description of spatial patterns, identification of diseases clusters and explanation or prediction of disease risk (Bailey & Gatrell, 1995; Pfeiffer et al, 2008). Visualization commonly defined as the ability of more advanced statistical analysis software (i.e., program) to explore and display results of other traditional statistical analysis tools in various ways and formats. It is the most commonly used spatial analysis.

In GIS, the main visualization mean is the map. The map is able to assist in displaying and describing any spatial patterns which are useful for stimulating more complex analyses (Bailey & Gatrell, 1995; Pfeiffer et al, 2008). With regards to exploratory data analysis, it is defined as the ability of GIS applications to detect any patterns or irregularities (i.e., anomalies) of the certain process and help to formulate new hypothesis in relation to the process that give rise to the data. In other words, it involves the use of statistical analysis methods to determine whether observed patterns are random in space (Bailey & Gatrell, 1995; Pfeiffer et al, 2008). Meanwhile, modeling

introduces the concept of cause-effect relationships using both spatial and non-spatial data sources in order to explain and predict spatial patterns using statistical or mathematical analysis (Bailey & Gatrell, 1995; Pfeiffer et al, 2008). It involves the techniques to estimate the transmission parameters over the earth surface (Clarke et al, 1996).

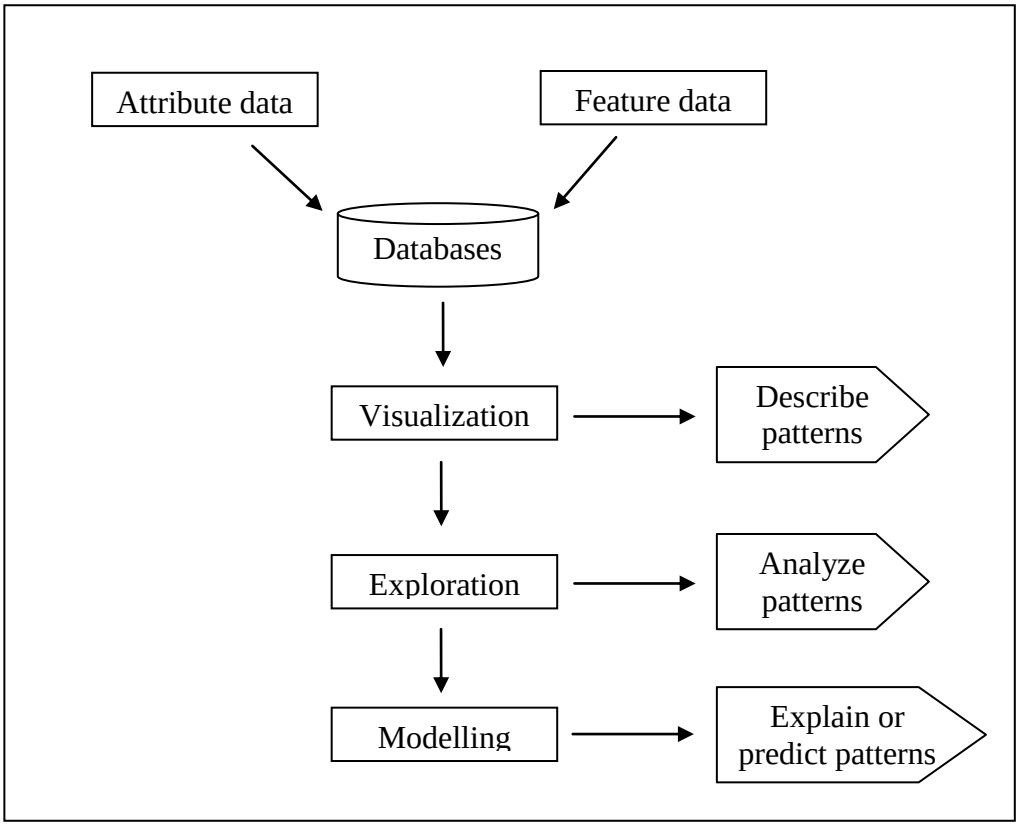

Figure 2.1: Conceptual framework of spatial epidemiology data analysis using geographical information system (GIS) (Bailey & Gatrell, 1995)

2.2.3 GIS application in epidemiology and public health

Generally, GIS has been widely used in various disciplines such as forestry, urban and town planning, transportation, marketing, archeology and many other disciplines (Clarke et al, 1996). Due to its ability to integrate and analyze various spatial data

through spatial analysis tools, GIS has been successfully used to map and analyze epidemiological distribution of various infectious disease and relate it to factors that may influence the distribution patterns such as metrological and ecological factors (Brooker & Michael, 2000). The collection of these environmental data has been greatly enhanced by the used of remote sensing (RS) satellite data that can give proxy to environmental information (Goetz et al, 2000; Hay, 2000). In broad terms, remote sensing (RS) is defined as the acquisition of information of certain object or phenomenon that is not in physical or intimate contact with the object itself using a real-time sensing device such as satellite or airplane (Cline, 1970; Clarke et al, 1996). In the epidemiology of infectious disease (e.g., tropical diseases) context, it refers to the utilization of imaging sensor technologies by means of satellites mainly to obtain the environmental data in order to explore the factor that affect the disease pattern and transmission (Brooker & Michael, 2000; Hay, 2000).

Historically, the potential use of the GIS and RS techniques in the epidemiology and control of tropical diseases was first highlighted in the early 1970s (Cline, 1970). Malone and co-workers (1994) were the first to successfully use GIS coupled with RS technologies to map and predict the distribution of human schistosomiasis in Nile delta, Egypt. To date, GIS and RS have been widely used as important means to design and implement practical and low-cost control program of various infectious diseases including tropical diseases (Brooker & Micheal, 2000). For example, such approaches have been contributed to the design and implementation control program of onchocerciasis or river blindness, a tropical disease caused by parasitic filarial worm, *Onchocerca volvulus* in Africa through the development of Rapid Epidemiological Mapping of Onchocerciasis (REMO) by the WHO Tropical Research Group (TDR) (Ngoumou et al, 1994; Katabarwa et al, 1999). REMO has been used as a successful

key to control onchocerciasis by identifying high risk communities especially those living nearby the river basin. Then, these high risk communities are individually screened for the *O. volvulus* worms. Such approach facilitates communities to be categorized into priority areas (i.e., those areas requires ivermectin intervention), non priority areas (i.e., areas that do not require treatment) and possible endemic areas that need additional investigation (Ngoumou et al, 1994; Katabarwa et al, 1999). In addition, findings of REMO have also helped to estimate the number of population that requires drug intervention which has assisted the African Program for Onchocerciasis Control (APOC) to identify population at greatest needs (Noma et al, 2002).

The Schistosomiasis Control Initiative (SCA) is another example of the usefulness of GIS and RS as successful decision-making key tools for national control program of schistosomiasis in Sub-Sahara Africa countries (Brooker et al, 2006). Both approaches have also been used to estimate number of population at risk for schistosomiasis, numbers of requiring treatment and cost of delivering anthelminthic drug by classify the areas into different priority areas in other endemic countries in African continents (Brooker et al, 2002a, 2002b; Kabatereine et al, 2004; Clements et al, 2006; Tchuem Tchuente et al, 2012). In addition, the use of GIS coupled with remotely-sensed environmental data demonstrated that no *Schistosoma mansoni* transmission occurs in areas with total annual rainfall less than 850mm and altitude of more than 400 meter above sea level (Kabatereine et al, 2004). Any community that has been classified and identified lives in high risk areas are screened using any standard parasitological technique thus can prioritize and target schistosomiasis control program quickly and cheaply (Brooker et al, 2004). Besides these two examples, many studies have sufficiently showed the usefulness of GIS and RS in formulating and implementing an effective and sustainable cost-effectiveness tropical diseases control

program, for example filariasis (Sabesan et al, 2000; Gyapong et al, 2002), malaria (Omumbo et al, 2005; Hay & Snow, 2006; Hay et al, 2006), human African trypanosmiasis (Cecchi et al, 2009), onchocerciasis (Ngoumou et al, 1994; Katabarwa et al, 1999; Noma et al, 2000), and loiasis (Diggle et al, 2007; Zoure et al, 2011).

To date, the utilization of GIS and RS approach is increasingly being used to collect, store, map and model the distribution of STH infections (Brooker & Michael, 2000; Brooker et al, 2000; 2002a; 2002b; 2003; 2004, 2009; Knopp et al, 2008; Pullan et al, 2011; Tchuem Tchuente et al, 2012), however such approach in STH mapping has been attempted only in African countries. In recent years, the used of GIS and RS approaches for STH mapping have also been extended to Southeast Asia regions including Mekong countries such as Cambodia, Lao PDR, Myanmar, Thailand and Vietnam (Brooker et al, 2003) as well as Indonesia and the Philippines (Brooker, 2002c). Such approaches provide basic information to investigate the geographical distribution of infection, highlighting where such information is lacking, identify priority areas or populations in greatest needs, estimating the number of target population at high risk and cost of delivering drug interventions (Brooker et al, 2000). On the other hand, the used of remote sensing (RS) satellite data, which provides proxy to environmental data helps to further enhanced the functional capabilities of GIS by predicting the distribution of STH in relation to their ecological limit (Brooker & Michael, 2000).

The renaissance of GIS in STH mapping was started in early 2000 with the aim to obtain and collect any available survey data on STH infections into a standardize GIS platform through the support from WHO (Brooker et al, 2000). As a result to this initiative, Brooker and co-workers (2000) has successfully developed STH atlas and database using GIS for whole Sub-Sahara Africa (i.e., involving 39 countries). Ten

years later, Brooker and co-workers (2009) provided an updated global atlas of STH map for East Africa countries including Brundi, Kenya, Rwanda, Tanzania and Uganda, which provides reliable prevalence map and updated information for cost-effectiveness control program to the communities in greatest need. With regards to the used of GIS and RS applications to map and predict distribution of STH infections, such approaches was first carried in Cameroon (Brooker et al, 2002a). In the same year, Brooker and co-workers extended such approaches to map and estimated number of population at high risk and requiring anthelminthic drug in Chad (Brooker et al, 2002b). More recently, Pullan and colleagues (2011) used GIS and RS approach to map the observed prevalence of STH from one of the largest collection of contemporary survey data in Africa countries from 945 cross-sectional studies conducted between 1974 and 2007 across Kenya. Their findings provided accurate geographical distribution of STH infections across Kenya, estimation number of infected individuals in un-sampled areas that warrant mass drug administration (MDA) and cost of delivering treatment as well as highlighting where future survey or data collections should be carried out in defining infection risks in areas with high uncertainties (Pullan et al, 2011).

The above examples have demonstrated how GIS coupled with RS technologies have led the way in assisting and developing sustainable control programs for various tropical diseases including STH infections. Additionally, as discussed here, such approaches can offer important new insights to predict the infection risk and their transmission patterns over large geographical scale. Prior to this, conventional techniques could not address these issues (Brooker et al, 2006). The present examples have also amply proven that if used appropriately, GIS and RS technologies can be used as relevant and important tools to design cost-effective control program through a more precise and prioritize geographical target population, using the example and experience

of Rapid Epidemiological Mapping of Onchocerciasis (REMO) (Ngoumou et al, 1994; Katabarwa et al, 1999) and Schistosomiasis Control Initiative (SCA) (Kabatereine et al, 2004; Brooker et al, 2006). As of today, the Global Atlas of Helminth Infection (GAHI) project (www.thiswormyworld.org) was initiated by the London School of Hygiene & Tropical Medicine and collaboration with the Partnership for Child Development (PCD), Imperial College London with a primary aim to provide reliable and updated global distribution maps of helminth infection that are essential to prioritize treatment intervention to population in greatest need particularly when the resources for control is finite and limited. It is an open access resources with global information of STH and schistosomiasis distributions (Brooker et al, 2000; 2009).