Table 1 Ranking by DALYs of Selected Infectious and Tropical Diseases

Disease condition	Disease burden (DALYs) (million)
Lower respiratory infections	91.3
HIV-AIDS	84.5
Diarrheal diseases	62.0
Malaria	46.5
Tuberculosis	34.7
Hookworm infection	22.1
Measles	21.4
Lymphatic filariasis	5.8
Schistosomiasis	4.5
Leishmaniasis	2.1

Abbreviation: SALY, disability adjusted life years.
Source: From Ref. 32.

intensity hookworm infections are at the greatest risk of developing hookworm anemia (3). Age is an important risk factor for heterogeneity. Hookworm infection intensity exhibits a unique age distribution among the soil-transmitted helminth infections and peaks in adulthood, unlike ascariasis and trichuriasis, which intensity peaks in childhood (18–20). Evidence also exists for household and micro-geographical clustering of hookworm-infected individuals (21), and there is evidence that hookworm intensity may carry a heritable pattern (22). Finally, an increasing number of studies have shown that hookworms commonly coinfect individuals with other helminths, especially schistosomes (23,24).

Geographic Distribution

The geographic distribution of hookworm infection reflects two major elements: poverty and an appropriate climate and ecology. The basis for the link between poverty and hookworm infection was reviewed recently (10), and includes associations between increased transmission and inadequate sanitation, including poor housing construction (e.g., dirt floors), as well as a lack of access to essential medicines, especially anthelminthic drugs. Among the important factors related to climate and ecology are high surface temperature (15,25), altitude, soil type, and rainfall (26,27). Today, the greatest number of hookworm cases occur in sub-Saharan Africa (198 million cases), followed by Southeast Asia and the Pacific region (149 million), India and South Asia (130 million), Latin America and the Caribbean (50 million), China (39 million), and the Middle East (10 million) (1,2). With the exception of the Middle East, some areas of China, north of the Yangtze River, northern India, and restricted geographic regions of Africa and South America where *A. duodenale* is found, *N. americanus* is the predominant hookworm in all these regions. In some areas, mixed infections occur (3).

Disease Burden

Studies by Stoltzfus and colleagues (28) reveal that hookworm accounts for a significant percentage of the anemia disease burden in developing countries. Among some populations of sub-Saharan Africa, hookworm infection in children was shown to account for up to 41% of the IDA and 57%of moderate to severe anemia (28); it is also an important cause of anemia in Brazilian (29) and Southeast Asian children. Brooker et al. (30) have recently completed a meta-analysis that confirms that among the estimated 44 million pregnant women infected with hookworms (31), this infection is a major cause of anemia. Although hookworm is not considered a significant cause of mortality in developing countries, such estimates of the contribution of hookworms to anemia translates into a significant impact on global morbidity. Current DALY estimates for hookworm vary widely, ranging from 1.8 to 22.1 million DALYs lost annually (1). The lower estimate is roughly equivalent to that of otitis media whereas the higher estimate suggests that the disease burden of hookworm infection is approximately one-half that of malaria's (3,32). Such variation largely reflects significant differences in assumptions regarding the contribution of hookworm to IDA and protein malnutrition in developing countries (32). However, new meta-analyses for the contribution of hookworm to both childhood and maternal anemia (30) are expected to result in a revision of the DALY estimates caused by hookworm infection.

NATURAL HISTORY AND IMMUNOLOGY OF HOOKWORM INFECTION

The life cycle of *N. americanus* and *A. duodenale* have been reviewed previously (3). Briefly, humans become infected with hookworms when third-stage infective larvae (L3) penetrate through the skin and then migrate into subcutaneous venules and lymphatics before being swept via the afferent circulation and entering the pulmonary capillary bed. From there, the L3 enter the respiratory tree through the alveolae and ascend the bronchioles, bronchi, pass over the epiglottis, and enter the gastrointestinal tract. In the small intestine, the L3 molt twice to become adult male and female hookworms where they can live for five years or more. The adult worms, approximately one centimeter in length, attach to the mucosa and submucosa, lacerate capillaries and arterioles, and then feed on host blood and mucosal tissues. The hookworms mate and produce thousands of eggs that exit the body in the feces. The eggs hatch in soil with adequate moisture and high temperatures and then molt twice to the L3 stage, which seeks higher ground to come into human skin contact. *A. duodenale* is also orally infective.

The immunology of human and animal hookworm infection is complex and has been the subject of several recent papers and reviews (33–36). Briefly, with respect to animal hookworm infections, there are three major laboratory models for studying host immune responses. Unfortunately, no single model adequately or completely reproduces the immune responses to human hookworm infection. Of all of the animal models in current use, *A. caninum* infections in dogs most resemble human hookworm infection, with respect to the ability of adult hookworms to live the longest and in terms of the relationships between number of hookworms and fecundity and blood loss (35). Described below is the use of attenuated and irradiated L3 (irL3), which were used to develop a canine vaccine against hookworm infection. The golden hamster (*Mesocricetus auratus*) has also been used for both *A. ceylanicum* and *N. americanus* infections, both of which are characterized by host blood loss, lymphoproliferation, and host anitbody production during infection (37–39). However, the model also has limitations for purposes of vaccine testing as frequently less than 10% to 20% of the L3 develop to adult hookworms in the hamster gastrointestinal tract (38).

Most of the knowledge of human immunity to hookworms relies on immunoepidemiologic studies of hookworm-infected humans residing in endemic areas (36). These studies are hampered by difficulties in following untreated patients over long periods of time (36). Another valuable source of