Chapter 9

Intestinal nematode infections

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Introduction

Effective control of the major intestinal nematode infections of humans involves relatively low-cost interventions (Savioli, Bundy & Tomkins 1992). Informed decisions about the need for investment in control programmes, however, also require useable estimates of the scale of morbidity (Guyatt & Evans 1992).

Direct estimates of morbidity would be preferred, but the currently available techniques suffer from major limitations, examples of which follow. Active case detection can be useful at the local level (Pawlowski & Davis 1989), but demands a level of resources that makes its widespread use impractical. Passive case detection, which has more appropriate resource demands (Guyatt & Evans 1992), is unreliable for geohelminthiases because the symptoms are non-specific; in one prospective study of trichuris colitis, only 2 per cent of cases observed in the community had self-presented to the local health services (Cooper, Bundy & Henry et al. 1986). Furthermore, there is increasing evidence that the most common and potentially important consequences of infection are insidious effects on nutritional status (Nesheim 1989, Tomkins & Watson 1989) and on physical and intellectual development (Stephenson 1987, Cooper et al. 1990, Nokes et al. 1992a, 1992b). Such effects are unlikely to result in self-presentation to passive case detection clinics, and will be grossly underestimated by survey procedures based on the active detection of clinical signs. This is especially so, as the infections are ubiquitous; both passive and active detection are usually based on deviations from local norms, which may be greatly influenced by the infections.

There are no direct estimates of the community morbidity caused by intestinal helminths. Instead, most studies have focused on estimating the prevalence of infections, only a fraction of which will be associated with disease. Perhaps the first estimate of the global prevalence of intestinal nematode infections was presented by Stoll (1947). His technique

of extrapolation from survey data has proven robust and has been used to derive many of the more recent estimates which suggest that there are some billion infections with *Ascaris lumbricoides* and only slightly fewer infections with hookworm (both *Necator americanus* and *Ancyclostoma duodenale*) and *Trichuris trichiura* (World Health Organization 1987, Crompton 1988, 1989, Bundy & Cooper 1989). In the absence of reliable procedures for estimating disease directly, estimates of burden have been based on extrapolation from the infection prevalence data to provide an estimate of the proportion of infections that are likely to be associated with disease (Warren et al. 1993, Chan et al. 1994). This requires a careful and conservative approach because of the ubiquity of infection; extrapolating from such large numbers has the consequence that even small errors in estimating the disability attributable to individual cases can result in considerable inaccuracy in estimating the total burden. Because of the inherent potential for error in the use of any extrapolation procedure, the major aims of this chapter are to encourage independent scrutiny of the methodology and to highlight areas that particularly warrant further empirical study.

This chapter builds on the studies of Chan et al. (1994) and Warren et al. (1993), and attempts to provide improved estimates of burden of disease based on extrapolation from observed estimates of prevalence of infection. The size of the population at risk of disability is estimated using epidemiological methods developed to describe the relationship between prevalence and mean intensity, and between intensity and potential morbidity (Guyatt et al. 1990, Lwambo, Bundy & Medley 1992), but modified to incorporate the heterogeneity between communities and age classes (Chan et al. 1994). The disability per case at risk is estimated using procedures described elsewhere in this series (Murray & Lopez 1996), and the regional and global burden of disease is obtained by extrapolation from these estimates.

Basic biological characteristics of intestinal nematodes

The analyses presented here focus on the four species of intestinal nematode that are of circumglobal distribution and occur at high prevalence: *Ascaris lumbricoides*, *Trichuris trichiura*, and the two major hookworm species, *Necator americanus* and *Ancylostoma duodenale*.

A. lumbricoides is the large roundworm (15 cm) and lies free in the human duodenum where it feeds on lumenal contents (see Crompton, Nesheim & Pawlowski (1989) for further details of the biology of this parasite). Like all the other nematodes considered here, the worms are dioecious, which is to say that they exist as male and female. The female produces some 100 000 eggs per day which pass out in the faeces of the host and embryonate externally at a rate determined by local environmental factors. The eggs hatch on ingestion, releasing a larva that undergoes a

tissue migration involving the cardiovascular and pulmonary systems. The larva moults as it migrates and ultimately is coughed up from the lungs, swallowed, and becomes established as the adult in the small intestine. The cycle from egg deposition to female patency, when the female is able to produce eggs, has a duration of some 50 days.

T. trichiura, the human whipworm, is a much smaller worm (25 mm) and inhabits the colon (Bundy & Cooper 1989). The anterior two-thirds of the worm is thin and thread-like and is laced through the mucosal epithelium, upon which the worm is believed to feed, leaving the blunt posterior projecting into the colonic lumen for excretion and oviposition. The female produces some 2000 eggs per day which pass out in the host faeces and embryonate externally. The infectious eggs hatch on ingestion and undergo a specifically local migration, via the crypts of Lieberkühn to the mucosal surface. The development cycle takes some 60 days.

The two major hookworm species, which are of similar magnitude to the whipworm, inhabit the small intestine, where they attach to villi with biting mouthparts (Schad & Warren 1990). The worms feed on host blood and move frequently to new sites, leaving multiple, bleeding petechial haemorrhages on the mucosal surface. *A. duodenale* is believed to be more voracious, consuming some 0.14–0.40 ml of blood per day compared with 0.01–0.10 ml by *N. americanus*. The eggs pass out in host faeces and embryonate. Unlike the roundworm and whipworm, the eggs hatch externally releasing a mobile infective larva that actively infects the human host by dermal penetration. *A. duodenale* is also able to infect by the oral route, and there is evidence for vertical transmission of this species either transplacentally or in maternal milk. Having entered the host, the larva undergoes a tissue migration to the lungs and is coughed up and swallowed to moult to the adult in the small intestine. The cycle takes approximately 60 days for both species. *A. duodenale* is apparently able to extend this period by arresting development to the adult stage; a mechanism which may allow avoidance of seasonally hostile external conditions.

Basic epidemiological characteristics of intestinal nematodes

Understanding the epidemiology of helminth infections requires a fundamentally different approach from that required for all other infectious agents. Each worm's establishment in a host is the result of a separate infection event, and the number of infective stages shed (the infectiousness of the host) is a function of the number of worms present. In population dynamic terms this implies that the individual worm is the unit of transmission for helminths, while the individual host is the unit for microparasites (Anderson & May 1982). The size of the worm burden (the intensity of infection) is therefore a central determinant of helminth transmission dynamics, and is also the major determinant of morbidity since the pathology is related to the size of the worm burden, usually in

a non-linear fashion (Stephenson 1987, Cooper & Bundy 1987, 1988). Since the size of the worm burden varies considerably between individuals, and infection implies only that worms are present, a population of "infected" people will exhibit considerable variation in the severity of disease manifestations. The intuitive assumption that all infections are equal may help to explain the historical confusion over the pathogenicity and public health significance of helminth infection (Bundy 1988, Cooper and Bundy 1989). From these considerations it is apparent that an understanding of helminth epidemiology centres around an understanding of the patterns of infection intensity.

Worm burden distributions

Worm burdens are neither uniformly nor randomly distributed amongst individuals, but are highly over-dispersed such that most individuals have few worms while a few hosts harbour disproportionately large worm burdens. This pattern has been described for *Ascaris lumbricoides* (Croll et al. 1982), both species of hookworm (Schad & Anderson 1985) and *Trichuris trichiura* (Bundy et al. 1985). Most studies suggest that approximately 70 per cent of the worm population is harboured by 15 per cent of the host population. These few heavily infected individuals—the "wormy persons" described by Croll & Ghadirian (1981)—are simultaneously at highest risk of disease and the major source of environmental contamination.

Studies of reinfection suggest that individuals are predisposed to a high or low intensity of infection; the size of the worm burden reacquired after successful treatment is positively associated with the intensity of infection before treatment. This association has been shown for all the major geohelminths (Anderson 1986, Elkins, Haswell-Elkins & Anderson 1986, Bundy & Cooper 1988, Holland et al. 1989), and persists over at least two reinfection periods (Chan, Kan & Bundy 1992). Longitudinal studies of *T. trichiura* (Bundy et al. 1988) and *A. lumbricoides* (Forrester et al. 1990) confirm that this positive association reflects a direct relation between the rate of reinfection and initial infection status. Thus in an endemic community it appears that there is a consistent trend for an individual to have an above (or below) average intensity of infection. This trend is more apparent in children with *A. lumbricoides* (Haswell-Elkins, Elkins & Anderson 1987) and *T. trichiura* (Bundy & Cooper 1988) infection, and more apparent in adults with *Necator americanus* (Bradley & Chandiwana 1990) infection, perhaps reflecting the different age-intensity patterns of these species. This pattern is also apparent at the family level (Chai et al. 1985, Forrester et al. 1988, 1990, Chan, Bundy & Kan 1994).

Worm burden and age of host

Over-dispersed distributions, where the highest intensity infections are aggregated in a few individuals of infection intensity, are observed in the community as a whole and also in individual age-classes. The degree of over-dispersion, however, shows some age-dependency. In hookworm

infection the distribution becomes more over-dispersed in adults (Bradley & Chandiwana 1990), while in *A. lumbricoides* and *T. trichiura* there is evidence that dispersion increases to a peak in the child age groups (Bundy et al. 1987b) and then declines in adults (Chan, Kan & Bundy 1992). These changes reflect age-specific trends in the proportion infected (the size of the zero class in the frequency distribution) and in the mean intensity of infection (the mean of the distribution).

The age-dependent pattern of infection prevalence is generally rather similar amongst the major helminth species, exhibiting a rise in childhood to a relatively stable asymptote in adulthood. Maximum prevalence is usually attained before 5 years of age for *A. lumbricoides* and *T. trichiura*, and in young adults with hookworm infection. In *A. lumbricoides* there is often a slight decline in prevalence during adulthood, but this is less common with the other major nematode species.

Prevalence data indicate the proportion of individuals infected and do not provide a simple indication of the number of worms harboured. The marked non-linearity of this relationship is a direct statistical consequence of the over-dispersed pattern of intensity (Guyatt et al. 1990). If worm burdens were normally distributed, there would be a linear relationship between prevalence and intensity (Anderson & May 1985). This is an important relationship since it is central to the method of extrapolation from infection prevalence to infection intensity described in this chapter. It is worth emphasising, therefore, that the relationships are firmly based on empirical studies of the major species of intestinal helminths (Guyatt et al. 1990, Lwambo et al. 1992, Booth 1994).

The lack of simple correspondence between prevalence and intensity has the consequence that the observed age-prevalence profiles provide little indication of the underlying profiles of age-intensity. For most helminth species the initial rise in intensity with age closely mirrors that of prevalence but occurs at a slightly slower rate. Maximum intensity occurs at a host age which is parasite species-specific and dependent on parasite longevity, but independent of local transmission rates (Anderson 1986). For *A. lumbricoides* and *T. trichiura* maximum worm burdens occur in human populations at 5–10 years of age and for hookworms at 20–25 years.

The most important differences in the age-intensity profiles of these species become apparent after peak intensity has been attained. *A. lumbricoides* and *T. trichiura* both exhibit a marked decline in intensity to a low level which then persists throughout adulthood. Age-profiles based on egg density in stool had suggested that there was considerable variation in the patterns seen in hookworm (Behnke 1987, Bundy 1990), but it now appears, from studies where burdens have been enumerated by anithelminthic expulsion, that the intensity attains a stable asymptote, or rises marginally, in adulthood (Pritchard et al. 1990, Bradley et al. 1992).

Thus, for those species with convex age-intensity profiles, but asymptotic age-prevalence profiles, a similar proportion of children and adults are infected but the adults have substantially smaller worm burdens. With

hookworm infection, where both prevalence and intensity are asymptotic, more adults are infected and they have larger worm burdens.

Definition and measurement

For most helminthiases, the relationship between infection and disease is likely to be non-linear and complex. If we accept, for the moment, the simple premise that only heavy worm burdens cause disability, then it is apparent that disability will have an age-dependent distribution, since intensity is age-dependent, and also that disability will have an over-dispersed pattern even within the susceptible age-classes. The relationship is further complicated by the non-linear relationship between the severity of disease and the intensity of infection, and by the interaction between symptomatology and the chronicity of infection. Helminthic infection does not inevitably lead to disease: a failure to appreciate this has led to apparently contradictory results from morbidity studies and may be the major contributor to the under-recognition of the public health significance of helminthiasis (Cooper & Bundy 1987, 1988).

An essential prerequisite, therefore, to assessing the global burden of disease is the estimation of the sub-population of the infected population that has a sufficiently large worm burden to put them at risk of disability. This requires some method of relating prevalence of infection data, which are available from empirical studies in all geographical regions, to intensity of infection data, which are not. In this section we describe procedures for extrapolating intensity from prevalence survey data, and for partitioning the risk of disability.

Worm burdens and morbidity

There is a general acceptance of the simple view that very intense infection results in illness, a view that reflects both clinical experience of overwhelming infection and, perhaps equally importantly, an atavistic repugnance at the insidious invasion of the body by large numbers of worms. Such extremes of infection result in the severe anaemia of necatoriasis and the intestinal obstruction of ascariasis (Stephenson 1987), and the chronic colitis of classical trichuris dysentery syndrome (Cooper & Bundy 1988). That helminth morbidity is dependent on infection intensity is, from this perspective, uncontroversial. An understanding of the pattern of the relationship between infection intensity and clinical signs has proven more elusive. This appears to be the result of two main factors.

First, intensity and pathogenesis are non-linearly related. Studies of the anaemia associated with hookworm infection indicate that there is a disproportionate reduction in plasma haemoglobin concentration after some threshold worm burden is exceeded. Although profound anaemia is associated with thousands of worms, clinically significant anaemia can be induced by a few hundred worms, the precise threshold depending on the host's iron status (Lwambo, Bundy & Hedley 1992). Note that this

occurs despite the constant per capita blood loss attributable to hookworm feeding (Martinez-Torres et al. 1967), which might intuitively be expected to give a linear relationship between burden and anaemia. Studies of protein-losing enteropathy in trichuriasis also indicate a non-linear relationship with worm burden (Cooper et al. 1990). The rate of gut clearance of a-1-antitrypsin at first rises rapidly with increasing worm burden to a threshold and rises more slowly thereafter. The relationship is markedly non-linear. This implies that significant intra-lumenal leakage of protein can occur with *T. trichiura* burdens of a few hundred worms. The clinical consequences of this loss will be determined by the nutritional and dietary status of the host and by the chronicity of infection (Cooper, Bundy & Henry 1986). In one study, children with the classical Trichuris Dysentery Syndrome had all experienced mucoid dysentery and rectal prolapse for more than three years (Cooper & Bundy 1987, 1988).

The second reason for the lack of understanding of the relationship between intensity and disease is the difficulty of measuring and attributing morbidity. This is in part the classical epidemiological problem of identifying specific morbidity in an endemic population subjected to multiple insults (Walsh 1984). It is exacerbated for helminth infection, however, by the absence of pathognomonic signs in moderate, but clinically significant, infection. This problem has been addressed by intervention trials using specific antihelminthic therapy. Such studies have shown, for example, significant improvements in linear growth after treatment of moderately infected and stunted children with hookworm, *A. lumbricoides* or *T. trichiura* infection (Stephenson 1987, Stephenson et al. 1990, Cooper et al. 1990). Even more subtle consequences of infection are suggested by recent double-blind placebo trials, which show significant improvement after antihelminthic treatment in the cognitive ability of school-children moderately infected with *T. trichiura* (Nokes et al. 1991, 1992a). These results suggest that even moderate helminthic infection may have insidious consequences that are unlikely to be attributed to helminthiasis in public health statistics. In one study of a village population with hyperendemic geohelminthiasis (Cooper, Bundy & Henry 1986), only 2 per cent of actual morbidity had been reported to the health authorities.

Some insights into the relationship between infection and disability can be provided by data analysis (Guyatt et al. 1990, Lwambo, Bundy & Medley 1992). Empirical studies can provide estimates of the threshold number of worms associated with risk of disability (see above). Then, using models which describe the empirical relationship between infection intensity and prevalence, it is possible to estimate the proportion of individuals in whom the threshold worm burden is exceeded (and are thus are likely to suffer disability) at a given prevalence of infection. Non-linear relationships of this form have been shown in studies of schistosome infections, for which adequate country based morbidity data are available (Jordan & Webbe 1982). There is a need to obtain similar data for intestinal nematodes, but this is currently confounded by the difficulties in estimating morbidity

directly for these infections. One important conclusion of this analysis, however, is that the threshold need not be precisely defined, since the form of the relationship between infection and disease is relatively insensitive to the threshold value, provided the value is relatively large (> 20 worms).

These analyses indicate that the proportion at risk of disability increases dramatically as infection prevalence rises. For example, if 25 *A. lumbricoides* worms are associated with disease, then 20 per cent of the population will be at risk at an infection prevalence of 80 per cent, and less than 2 per cent at an infection prevalence of 70 per cent. It is worth noting that both these infection prevalences could reasonably be considered to be high, which may help explain why studies of helminth morbidity in "high" prevalence areas often reach very different conclusions about the public health significance of helminthiasis (for example, Keusch 1982).

The relationships described here form the basis for the extrapolation procedure developed in this chapter. This procedure involves the use of infection prevalence survey data from individual countries to give an estimate of regional and global prevalence of infection. Empirical data are then used to estimate the fraction of this infected population which is at risk of disability. The following sections describe this procedure and discuss the validity of its assumptions.

Estimation of risk of disability from infection prevalence data

The risk of disability is estimated on the basis of the relationship between worm burden and prevalence of infection. The frequency distribution of worm burdens between individuals has been consistently shown to be highly over-dispersed. Within a community, the majority of people have few or no worms and a few people have very high worm burdens. Observed distributions can be represented empirically by a negative binomial distribution (Anderson & Medley 1985, Guyatt et al. 1990, Lwambo, Bundy & Medley 1992, Bundy & Medley 1992). This theoretical distribution has two parameters, the mean worm burden, m, and the aggregation parameter, k (see Anderson and Medley, 1985 for explanation of this parameter). General values used in this study are $k = 0.54$ for *A. lumbricoides* (Guyatt et al. 1990), $k = 0.23$ for *T. trichiura* (Booth 1994) and $k = 0.34$ for hookworms (Lwambo, Bundy & Medley 1992). These values are estimated from empirical data from field surveys that estimated the distribution of intensity in human populations.

The basis for estimating potential disability is that a) the risk of disability is higher in individuals with higher worm burdens and b) there is some threshold worm burden above which disability is more likely to occur (Table 9.1). The proportion of the population with worm burdens higher than this threshold can then be estimated from the negative binomial distribution (Guyatt & Bundy 1995, Lwambo, Bundy & Medley

Table 9.1 Worm burden thresholds for morbidity used in the model

Species	*Age (years)*	*Higher estimate, lower threshold*	*Lower estimate, higher threshold*
A. lumbricoides	0–4	10	20
	5–9	15	30
	10–14	20	40
	15+	20	40
T. trichiura	0–4	90	250
	5–9	130	375
	10–14	180	500
	15+	180	500
Hookworms	0–4	20	80
	5–9	30	120
	10–14	40	160
	15+	40	160

Note: The lower thresholds are based on empirical observations of worm numbers associated with developmental deficits. The higher thresholds are a more conservative value intended to provide a lower bound to the estimate of morbidity. The thresholds were estimated for children in the 5–10 year age group, and then adjusted for other age group using the procedure described in the text. The lower threshold estimate for *Ascaris lumbricoides* assumes that 30 000 eggs per gram (epg) is associated with deficits in growth and fitness (see Stephenson et al. 1989, 1990) and that worm fecundity is equivalent to approximately 3000 epg for female worm. The higher threshold assumes that morbidity is associated with twice this burden. The *Trichuris trichiura* lower threshold is taken from studies of growth stunting in 5–10 year old children (Cooper et al. 1990), while the higher threshold is estimated from studies of clinical colitis (ES Cooper, personal communication). The hookworm thresholds are based on upper and lower bound estimates of the relationship between infection intensity and anaemia (Lwambo, Bundy & Medley 1992).

1992, Medley, Guyatt & Bundy 1993). This approach is necessarily an approximation, since the effects of a given worm burden on an individual will be modified by that individual's condition (e.g. nutritional status and concurrent infections) and the chronicity of the infection.

Studies indicate that developmental effects of infection (e.g. cognitive and growth deficits) occur at lower worm burdens than the more serious clinical consequences. We therefore use two sets of thresholds for each species, where the lower threshold corresponds to a higher estimate of potential disability from cognitive and growth deficits. These thresholds are shown in Table 9.1. The thresholds for *A. lumbricoides* and *T. trichiura* correspond to those given by Chan et al. 1994. The thresholds for hookworm have been adjusted downwards. This reflects the analyses presented by Crompton & Whitehead (1993), and the observation that the thresholds reviewed by Lwambo, Bundy & Medley (1992) apply to adults rather than children, as had been assumed in the previous calculations. Because children are smaller than adults, it is assumed that a similar worm burden is associated with more morbidity in children.

There is a lack of data on the relationship between disability threshold and age. However, since a given worm burden is more likely to cause disability in children than in adults, the use of a single, age-independent threshold would tend to considerably overestimate the potential disability.

In order to approximate this age effect, in the absence of empirical data, the same proportional changes with age are used for all worm species. The threshold for children under 5 years of age was taken as 50 per cent of that for adults (i.e. adults require twice the worm burden of pre-school children before suffering ill effects), for 5–9 year old children it was taken as 75 per cent of that for adults, and the adult threshold was used for 10–14 year old children (Table 1). These estimates are, we believe, conservative; but they are not firmly based on empirical observation.

Other age-dependent differences are also incorporated into the model. *A. lumbricoides* and *T. trichiura* infections are usually more prevalent in children, whereas hookworm infections are more prevalent in adults. For simplicity, a single age-prevalence relationship (one for each species) was used, based on the typical age-prevalence relationship observed in field studies (Table 9.2). The use of different prevalences for different age groups implies that a separate negative binomial distribution must be calculated for each age group. In order to ensure that the overall prevalence remains unchanged by this procedure, the observed demographic age distribution of the population must be taken into account. The effect of host age on the aggregation parameter (k) remains undefined, and the present framework uses a single (species-specific) aggregation parameter for all age groups.

Incorporating geographical heterogeneity

The prevalence of infection is non-linearly related to the mean intensity of infection in a community, such that the proportion of the population potentially suffering morbidity is disproportionately greater at higher levels of prevalence (Guyatt & Bundy 1991). If the average prevalence among communities is used as a basis for estimating intensity (and potential disability) for a geographical region, this will grossly underestimate the actual morbidity. It is therefore necessary to incorporate geographical

Table 9.2 Age weights for prevalences used in the model

Species	*Age (years)*	*Age weight*
A. lumbricoides	0–4	0.75
	5–9	1.2
	10–14	1.2
	15+	1
T. trichiura	0–4	0.75
	5–9	1.2
	10–14	1.2
	15+	1
Hookworms	0–4	0.2
	5–9	0.5
	10–14	0.9
	15+	1

heterogeneity in prevalence within the estimation procedure (Chan et al. 1994). Spatial heterogeneity in intestinal nematode infection is a relatively neglected area of study (Bundy et al. 1991, Booth & Bundy 1992) but its potential importance has been convincingly demonstrated for microparasitic infections (Anderson 1982, May & Anderson 1984).

Heterogeneity was considered at several geographical levels in the extrapolation procedure. The highest level is the regional level, as defined for the eight World Bank regions. Two regions (EME and FSE) were excluded from the analysis since the prevalences of intestinal nematode infections are very low. The remaining six regions were then divided into "population units" of 20 to 100 million people for which mean prevalence values, based on empirical data, were input into the model. Generally these population units coincide with politically defined countries (which is the unit for which prevalence data are most readily available) but some countries with exceptionally large populations, especially China and India, were subdivided into smaller units based on states or provinces for prevalence estimates.

The subdivision of a region into population units captures some geographical heterogeneity, but this does not include the heterogeneity within the population unit (or country). Literature searches yielded suitable data for examining intra-country variation in the six geographical regions. The level of heterogeneity among communities within the same country was assessed using community-level estimates of prevalence from different studies. Variation in prevalence within countries was estimated for 9 countries for *A. lumbricoides*, 8 countries for *T. trichiura*, and 10 countries for hookworm. The number of prevalence surveys available within each country ranged from 21 to 115. A total of 1600 prevalence surveys were examined in this analysis. The within-country distributions differed between worm species and between countries but were not markedly skewed or asymmetrical. Good correspondence was found between the data and the theoretical normal distribution which was therefore used.

Highly significant positive correlations between mean and standard deviation were observed for *A. lumbricoides* and *T. trichiura* distributions. Therefore, an estimate of "typical" geographical heterogeneity within a population unit could be estimated for these species from the regression. Hookworm distributions show a wider range of standard deviations and there was no significant correlation between these and the means. This may reflect the fact that the hookworm data include undifferentiated estimates for two quite different parasite species (*A. duodenale* and *N. americanus*). This additional source of variation was captured by taking the mean of the standard deviations as an estimate of heterogeneity within the population unit.

These estimates of the geographical variation in prevalence within a population unit were assumed characteristic of each species and were incorporated in the model for all subsequent calculations.

Summary of estimation procedure assumptions

The framework for estimation of the population at risk of disability involves a set of assumptions about the patterns of infection observed at both the community and the regional level.

Community-level assumptions

- *Worm burden frequency distributions are adequately described by the negative binomial distribution.* This probability distribution is the most widely accepted empirical description of observed worm burden distributions (Anderson & May 1991). However, it has been shown in some parasite species to underestimate the proportion of very low worm burdens and thus, potentially, overestimate the number of people in the higher worm burden classes. This could lead to an overestimation of the population at risk.
- *The frequency distribution of worm burdens is species-specific and largely independent of geographical region, infection prevalence or age group.* Analyses of the available empirical data suggest that the degree of aggregation, as assessed by the negative binomial parameter, k, is remarkably consistent between studies and largely independent of geographical region for all the nematode species considered here (Guyatt et al. 1990, Lwambo, Bundy & Medley 1992, Booth 1994). There is some evidence that k increases slightly with prevalence of *A. lumbricoides* (Guyatt et al. 1990) and even more marginally with hookworm prevalence (Lwambo, Bundy & Meadley 1992). Exclusion of this effect would lead to overestimation of potential morbidity. There is conflicting and limited evidence for the relationship between worm burden distribution and age, with some studies showing an increase and others a decrease in aggregation with age (Bundy et al. 1987b). The current assumption of an age-independent distribution could lead to either overestimation or underestimation of potential morbidity.
- *Disability occurs above a worm burden threshold that is higher for adults than children.* Thresholds were estimated from empirical data (Table 9.1). Two sets of thresholds were used for each species. An overestimate of the threshold worm burden would lead to an underestimate of potential morbidity and vice versa. No information is available on the variation of the threshold with age.
- *The age prevalence profile can be generalized between communities.* A similar general pattern is seen when age prevalence profiles from different studies of the same species are compared (Anderson & May 1985). The effect on the estimates of changing the shape of the age-prevalence profile are likely to be complex but, in general, the larger the differences in prevalence between different age groups, the higher the estimate of population at risk.

Regional-level assumptions

- *Infection prevalences between communities in the same country are normally distributed.* Examination of the actual distributions suggested that a normal approximation would be appropriate (Chan et al. 1994). The use of a symmetrical distribution is the most conservative assumption since with a skewed distribution with the same mean (such as the negative binomial distribution), the frequency of very high prevalences will be increased. The current assumption may therefore tend to underestimate the population at risk.
- *The standard deviations of these normal distributions increase linearly with the mean prevalence for* A. lumbricoides *and* T. trichiura *and are independent of mean prevalence for hookworms.* These assumptions are the best available estimates of the effect of spatial heterogeneity on the prevalence distribution, and are based on data presented by Chan et al. (1994).
- *The mean standard deviation relationship is the same in different geographical regions of the world.* The data available suggest a consistent relationship but there are insufficient data to assess this relationship by region. It is not known if there are any regional differences nor whether these might increase or decrease the estimates.
- *A population unit of 20 to 100 million people is a sufficiently fine-grained spatial stratification to capture geographical variation in a population of 4.1 billion people.* The size of this unit is constrained by the availability of empirical data. Larger units would reduce the precision of the estimates of potential morbidity.

Estimation procedure

The method used for estimation is essentially an integration of all the processes described in the text. Fuller details are given by Chan et al. (1994). In summary, the procedure involved the following steps.

1. Country (or other population unit) prevalence data were obtained and divided into prevalence classes. Five prevalence classes were defined and an intermediate prevalence value (S) was used for calculation purposes. These classes are shown in Table 9.3. In this round of calculations the highest two prevalences classes were combined and the set prevalence of the lower class was used for estimation (67 per cent) of community morbidity. This was necessary because with very high prevalences, the negative binomial distribution greatly overestimates potential morbidity. This calculation is not exactly equivalent to merging the two highest prevalence classes since countries in class 5 have a different distribution of community prevalences with a greater proportion in the class 4+5. The estimated morbidity for these countries will therefore be higher.

Table 9.3 Prevalence classes and reference (set) prevalences used in the model

Class	*Prevalence range (percentage)*	*Reference prevalence (percentage)*
1	< 25	10
2	25–45	35
3	45–60	52
4	60–75	67
5	75–100	80
4+5[a]	60–100	67

a. Combined classes 4 and 5 were used for community prevalence distribution.

2. The total populations in each prevalence class were multiplied by the transition matrix (M) to give an estimated community distribution of prevalences for the region (C). The matrix is derived using the following procedure. For each reference prevalence class in the estimation, a normal distribution for the individual community prevalence class distribution in the countries concerned was calculated. For *A. lumbricoides* and *T. trichiura* a standard deviation that increased with mean was used, whereas with hookworms a constant standard deviation given by the average standard deviation of the data sets was used. The regional community distribution of prevalences can then be obtained by multiplying a vector of the country mean prevalence distribution with a species-specific transition matrix which consists of the calculated normal distributions: $C = R.M$.

   The community prevalence distribution has one zero prevalence class and four non-zero-prevalence classes equivalent to the four lower prevalence classes of the country prevalence distribution (Table 9.3). Note that in the previous estimation (Chan et al. 1994) a fifth prevalence class (> 75 per cent) was included. This is now considered to over-emphasize the top end of the prevalence range and thus to overestimate the population at risk, and was therefore not used in the present calculations.

   The transition matrices used for each of the species are shown respectively, in Tables 4a, 4b and 4c.

3. Using regional demographic data, the population is divided into classes of community prevalence and age group and the age-weighted prevalence is calculated for each of these classes. The age weights (A) are shown in Table 9.2. Given a community prevalence s_i for prevalence class i, the prevalence in adults ($p_{i,15+}$) is given by:

$$p_{i,15+} = \frac{s_i}{\sum_j (a_j d_j)}$$

Table 9.4a Transition matrix for *Ascaris lumbricoides*

	Community prevalence distribution				
Reference class	*0*	*1*	*2*	*3*	*4+5*
1	0.251	0.590	0.149	0.010	0
2	0.081	0.264	0.310	0.186	0.159
3	0.057	0.149	0.214	0.175	0.405
4	0.021	0.081	0.149	0.169	0.580
5	0	0.048	0.097	0.133	0.722

Note: A zero class community distribution denotes a prevalence of 0%.

Table 9.4b Transition matrix for *Trichuris trichiura*

	Community prevalence distribution				
Reference class	*0*	*1*	*2*	*3*	*4+5*
1	0.288	0.509	0.177	0.026	0
2	0.097	0.259	0.288	0.180	0.176
3	0.068	0.153	0.200	0.170	0.409
4	0.028	0.087	0.149	0.157	0.579
5	0.011	0.047	0.101	0.125	0.716

Note: A zero class community distribution denotes a prevalence of 0%.

Table 9.4c Transition matrix for hookworms

	Community prevalence distribution				
Reference class	*0*	*1*	*2*	*3*	*4+5*
1	0.309	0.464	0.187	0.04	0
2	0.040	0.269	0.382	0.203	0.106
3	0	0.089	0.274	0.292	0.345
4	0	0.018	0.118	0.227	0.637
5	0	0	0.040	0.119	0.841

Note: A zero class community distribution denotes a prevalence of 0%.

where a_j is the age weight for age group j and d_j is the proportion of the population in age group j. The age specific prevalence in the other age groups are then given by:

$$p_{ij} = p_{i,15+} a_j \quad .$$

4. For each of the classes, using the species-specific aggregation parameter (k) and age specific morbidity threshold (t_j), the potential morbidity estimate (e_{ij}) is calculated using the negative binomial distribution. This theoretical distribution has two parameters, the mean worm burden μ, and the aggregation parameter k. These are related to the prevalence (P) in the following way:

$$P = 1 - (1 + \frac{\mu}{k})^{-k}$$

The basis for the estimation of the population at risk of disability is that morbidity is mainly confined to the fraction of the population with high worm burdens. A threshold worm burden (T) is defined over which morbidity effects are potentially observed (Table 9.1). The individual terms of the negative binomial, $p(x)$,(the proportion of individuals with x worms) are given by:

$$\pi(x) = \left(1 + \frac{\mu}{k}\right)^{-k} \left(\frac{\Gamma(k+x)}{x!\ \Gamma(k)}\right) \left(\frac{\mu}{\mu + k}\right)^{x}$$

where Γ represents the gamma function. The proportion of the population with more than (T) worms (the morbidity function $Morb(P,T)$) is therefore given by:

$$Morb(P,T) = 1 - \sum_{x=0}^{x=T} \pi(x)$$

The potential morbidity estimate (e_{ij}) is obtained by multiplying the morbidity function by the population in each class (n_{ij}):

$$e_{ij} = n_{ij}\ Morb(p_{ij}, t_j)$$

5. The above estimates are summed to give the age specific population at risk estimates for each region (f_j):

$$f_j = \sum_i e_{ij}$$

These procedures were followed for each of the parasitic infections under consideration.

Estimates of population infected and at risk of disability

The estimates of population infected and at risk or disability are shown in Tables 9.5 to 9.7. For each nematode species, these estimates are given for different age classes and for different geographical regions. Two estimates of population at risk were used for each infection, based on different estimates of worm burden thresholds. Both thresholds are based on empirical data and were chosen to be relatively conservative. The lower estimate of worm burden reflects probable developmental consequences of infection such as impaired growth or fitness, while the higher estimate is intended to reflect the likelihood of more serious consequences of infection.

The estimates of population infected are all slightly lower than those presented by Chan et al. (1994), because of the exclusion of the highest reference prevalence class from the present extrapolation procedure. This has had an even greater effect on reducing the estimated size of the

Table 9.5a Estimates of numbers infected and at risk of disability for *Ascaris lumbricoides*, by World Bank region

Region	Population (millions)	Infections (millions)	Infections (as a percentage)	Population at risk (millions)	Population at risk (percentage)
SSA	512	104	20.25	3.04 0.78	0.59 0.15
LAC	441	171	38.76	8.04 1.92	1.82 0.44
MEC	503	96	19.15	2.94 0.74	0.58 0.15
IND	850	188	22.13	6.60 1.62	0.78 0.19
CHN	1 160	532	45.85	25.32 5.72	2.18 0.49
OAI	654	291	44.53	16.38 3.99	2.50 0.61
Total	4 120	1 382		62.32 14.76	

Table 9.5b Estimates of numbers infected and at risk of disability for *Ascaris lumbricoides*, by age group

Age group (years)	Population (millions)	Infections (millions)	Infections (percentage)	Population at risk (millions)	Population at risk percentage)
0–4	553	130	24	1.84 0.05	0.33 0.01
5–9	482	182	38	27.81 9.45	5.77 1.96
10–14	437	169	39	17.99 4.65	4.12 1.06
15+	2 647	901	34	14.68 0.61	0.55 0.02
Total	4 120	1 382	34	62.32 14.76	1.51 0.36

population at risk of disability from ascariasis and trichuriasis, and on the estimated population above the high threshold for hookworm infection. The estimated population above the lower threshold of hookworm burdens has, however, increased as a result of the change in threshold.

The estimates for *A. lumbricoides* are shown in Table 9.5. The estimated total number of *A. lumbricoides* infections is 1382 million, slightly higher than estimates from other sources (World Health Organization 1987, Crompton 1988, Bundy 1990). The number at risk of morbidity is estimated in the range 15–63 million. The overall infection prevalence is 34 per cent in the exposed population while the prevalence of those at risk

Table 9.6a Estimates of numbers infected and at risk of disability for *Trichuris trichiura*, by World Bank region

Region	*Population (millions)*	*Infections (millions)*	*Infections (percentage)*	*Population at risk (millions)*	*Population at risk (percentage)*
SSA	512	85	16.57	2.21	0.43
				0.97	0.19
LAC	441	146	33.16	7.27	1.65
				2.97	0.67
MEC	503	64	12.64	0.04	0.01
				0.00	0.00
IND	850	134	15.78	3.02	0.36
				1.25	0.15
CHN	1 160	340	29.29	17.29	1.49
				6.65	0.57
OAI	654	238	36.41	15.70	2.40
				6.54	1.00
Total	4 120	1 007	24.43	45.53	1.11
				18.39	0.45

Table 9.6b Estimates of numbers infected and at risk of disability for *Trichuris trichiura*, by age group

Age group (years)	*Population (millions)*	*Infections (millions)*	*Infections (percentage)*	*Population at risk (millions)*	*Population at risk (percentage)*
0–4	553	96	17.38	0.04	0.01
				0.00	0.00
5–9	482	135	28.04	19.92	4.13
				10.40	2.16
10–14	437	125	28.60	15.93	3.65
				7.69	1.76
15+	2 647	650	24.57	9.63	0.36
				0.30	0.01
Total	4 120	1 007	24.43	45.53	1.11
				18.39	0.45

in the exposed population is between 0.4 per cent and 1.5 per cent. The highest prevalences are found in China and the Other Asia and Islands region.

The model assumes that prevalence of *A. lumbricoides* infection is slightly higher in children of 5 to 15 years old than in adults and younger children (Anderson & May 1985). The results show that this difference is greatly magnified in the estimates of population at risk, such that potential morbidity is significantly higher in school age children than in any other

Table 9.7a Estimates of numbers infected and at risk of disabililty for hookworm, by World Bank region

Region	Population (millions)	Infections (millions)	Infections (percentage)	Population at risk (millions)	Population at risk (percentage)
SSA	512	138	26.93	18	2.46
				8	1.06
LAC	441	130	29.40	15	3.44
				3	0.70
MEC	503	95	18.81	8	1.54
				2	0.47
IND	850	306	36.00	47	5.48
				11	1.32
CHN	1 160	340	29.29	29	2.47
				3	0.24
OAI	654	242	37.04	35	5.29
				8	1.29
Total	4 120	1 250	30.34	151	3.66
				36	0.87

Table 9.7b Estimates of numbers infected and at risk of disability for hookworm, by age

Age group (years)	Population (millions)	Infections (millions)	Infections (percentage)	Population at risk (millions)	Population at risk (percentage)
0–4	553	41	7.35	0	0.00
				0	0.00
5–9	482	89	18.54	0	0.00
				0	0.00
10–14	437	145	33.31	10	2.29
				1	0.16
15+	2 647	975	36.81	141	5.33
				35	1.32
Total	4 120	1 250	30.34	151	3.67
				36	0.87

age group. This is a result of the non-linear relationship between prevalence of infection and potential morbidity (Guyatt et al. 1990).

The estimates for *T. trichiura* are shown in Table 9.6. The totals show a lower number of infections than for *A. lumbricoides*, there being 1007 million infections resulting in a global prevalence of 24 per cent. The total population at risk is also lower for *T. trichiura*, in the range 18–45 million. As with *A. lumbricoides*, the highest prevalences of disability risk are found in Other Asia and Islands, in China and in children of school age.

The estimates for hookworm infections are shown in Table 9.7. There

are an estimated 1250 million hookworm infections and between 36 million and 151 million people at risk of disability. The distributions of infection and morbidity, both by age and region, are different from those for *A. lumbricoides* and *T. trichiura*. The disability risk attributable to hookworm infections is much higher in adults. The regional distribution is also different, with the highest prevalence of estimated disability in India.

Review of empirical databases by region

Direct estimates of the community morbidity attributable to intestinal helminthiases are unavailable. Hence the disability-adjusted life year (DALY) estimates are based on extrapolating the population at risk (intensely infected) from empirical observations of the proportion of the population infected.

The data on prevalence of infection used in the current estimation are from a database held at Oxford University, derived from field survey data compiled for a UNESCO report on global prevalence of helminth infection (Bundy & Guyatt 1990). They are based on an extensive search of the original literature and, as far as possible, represent data collected within the last 20 years; older data were used only if no other data were available for a particular country. Additional criteria for data selection include large sample size and community-based studies (i.e. not hospital records or institutional data). The number of studies available for each country varied, hence the reliability of the estimate for mean prevalence also varies. For the majority of countries, the sample size was at least several thousand individuals. Note that the data presented in Table 9.8 exclude a substantial number of unpublished surveys used in the actual analysis.

The survey estimates are based on the microscopic detection of parasite eggs in faecal specimens. While *A. lumbricoides* and *T. trichiura* eggs can be readily identified, the eggs of the two hookworm species, *Ancyclostoma duodenale* and *Necator americanus*, cannot be distinguished by normal diagnostic methods and are recorded here as the combined prevalence of both species. The stool examination procedure also fails to detect light infections, particularly when single examinations are made as in the case of field surveys (Hall 1982). Furthermore, the procedure will not detect non-fecund infections (e.g. single worm or single sex) which may represent a significant minority of infections (Guyatt 1992, Guyatt & Bundy 1995). Thus the survey data are conservative and underestimate the true prevalence of infection.

Estimation of DALYs

The analyses to this point have produced estimates of the size of the populations with worm burdens that are likely to result in some form of disability. This section focuses on the estimation of the proportion of the population at risk who are likely to be disabled and the degree of disability, and how

Table 9.8 Summary of prevalence studies of helminth infections, by World Bank region and country or area

Country or area	Sample size	Number of sites	Prevalence estimate (percentage)			Source
			Ascaris	Trichuris	Hookworm[a]	
Sub-Saharan Africa						
Benin	423	1	60			
	135	1		35	N.a = 19	Pampliglione & Ricciardi 1971
Burkina Faso	913	2	0.5			Faucher et al. 1984
Cameroon	27 040	530	45			Ratard et al. 1991
	5 040	18		53	N.a = 49	Carrie 1982, Ripert et al. 1978, Ripert, Leugueun-Ngougbeou & Same-Ekobo 1982
Cape Verde	1 572		72			de Meira, Nogueira & Simoes 1947 Barbosa 1956, Nogueira & Coito1950
Central African Republic	214	5	19	17		Ricciardi 1972
	126	3			N.a = 34	Brumpt et al.,1972
	88	2			A.d = 83	
Ethiopia	32 276	290	40			Tedla & Ayel 1986
	1 059	41		40		Taticheff, Abdulahi & Haile-Meskal 1981
	5 506	95			N.a = 20 A.d = 1	
Gabon	2 684	21	39	68	43	Garin 1978, Richard-Lenoble 1982
Gambia	684	3	29			McGregor & Smith 1952; Marsden 1963
Ghana	422	4	52	30	17	Annan et al. 1986
Liberia	690	8	17	19	60	Sturchler et al. 1980
Madagascar	217	1	61	20	A.d = 30	Cerf, Burgess & Wheeler 1981
Madeira	3 313	2	7	0.5	A.d = 18 N.a = 0.1	Santos 1952

continued

Table 9.8 Summary of prevalence studies of helminth infections, by World Bank region and country or area *(continued)*

Country or area	Sample size	Number of sites	Prevalence estimate (percentage)			Source
			Ascaris	*Trichuris*	*Hookworm*[a]	
Malawi	289	10	4		15	Burgess, Burgess & Wheeler 1973
Mali	2 174	4	0.5			Rougement et al. 1974
	2 974	5		0.5		Ranque 1982
	1 797	3			N.a. = 58	
Nigeria	1 266	6	67	46.5	31	Oduntan 1974
Réunion	2 803	10	49	85	24	Bonnefoy & Lsautier 1978
Senegal	359	4	36	15	N.a = 9	Juminer, Diallo & Laurens 1971
Somalia	556	5	13	34		Bianchini et al. 1981
Sudan	319	3			A.d. = 8	Ilardi et al. 1980, 1981, 1987 Kuntz, Lawless & Mansour 1955
Togo	93 504	6+	7	1	A.d. =7	Lapierre, Tourte-Schaeffer 1982
Uganda	157	3	0	0	38	Sorvillo 1982
United Republic of Tanzania	276	1	2	43	N.a. = 62	Sturrock 1964
Zambia	4 920	17			0	Wenlock & Ash 1977
Zimbabwe	38 484		0.5			Goldsmid et al. 1976
	595			0.5	10	Blackie 1932; Goldsmid 1976
India						
	23 949	59	8		13	Saxena & Prasad 1971
	1 270	48		16		Bidinger, Crompton & Arnold 1981; Arora 1975; Chowdury 1968; Chatterjee & Mukhopadhyay 1985; Mukerji & Mathen 1950; Lane et al. 1917; Bagchi, Prasad & Mathur 1964; Sanyal et al. 1972
China						
	1 477 742	2 843	47	19	17	Yu 1994

Other Asia & Islands						
Indonesia	51 364	77	71	48	29	Cross et al. 1970, 1975, 1976, 1977a & b; Clarke et al. 1973; Carney et al. 1974, 1977; Stafford et al. 1980; Joseph et al. 1978
Republic of Korea	398	1	14	42	0.5	Seo et al. 1983
Lao People's Democratic Republic	2 493	11	49	50	A.d = 41	Sornmani et al. 1974
Malaysia	96 075	30	48	55	49	Kan 1982, 1985; Russell 1928, 1934; Dunn 1972 Sinniah et al. 1978
Papua New Guinea	1 304	33	24			Ashford et al. 1981
	1 023	32		2	72	Shield et al. 1986
Philippines	1 300	4	54.8		22	Cross et al. 1977c
	286	3		69		Tatengco, Marxan & Castro 1972
Singapore	614	7	45	72	37	Desowitz 1963
Taiwan, China	622	7	91	44	7	Bergner 1964; Chang, Sun & Chin 1973
Thailand	67 300	85	6	5.8		Jones 1976
	68 153	101			35	Preuksaraj et al. 1981; Papasarathorn et al. 1975 Sadun 1955
Viet Nam	409	8	33	14	57	Colwell et al. 1971
Latin America & Caribbean						
Brazil	2 511	10	60	36	27	Vinha 1971
Chile	34 799	38	19			Neghme & Silva 1952, 1963, 1983; Schenone et al. 1981; Ramirez et al. 1972; Puga et al. 1980
	90 277	81		26		
Costa Rica	33 161	3	12	28	4	Zamora et al. 1978; Rojas & Zumbado 1980
Dominica	1 000	2	38	92	N.a. = 11	Grell & Zumbado 1981
Ecuador	3 970	14	50	60		Peplow 1982
	1 568	12			33	Ortiz 1969
Guatemala	15 383	1	73	1819		Aguilar 1981
Mexico	604	1	62	67		Stoopen & Beltran 1964
Surinam	854	10	62	45		Asin & van Thiel 1963

continued

Table 9.8 Summary of prevalence studies of helminth infections, by World Bank region and country or area *(continued)*

Country or area	Sample size	Number of sites	Prevalence estimate (percentage)		Hookworm[a]	Source
			Ascaris	Trichuris		
Middle Eastern Crescent						
Algeria	565	6	41	29	13	Pampiglione & Hadjeres 1965
Egypt	41 476	8	16			Mohamed et al. 1985
	39 574	5		17	A.d. = 1	Farag 1985; Tadros 1973; Wells & Blagg 1956; Mohamed et al. 1988; Lawless, Kuntz & Strome 1956;
Iran	1 137	7	22	0.5	A.d = 29	Colett 1966; Nazari & Massoud 1980
Iraq	4 000	16			1.3	Niazi et al. 1975
Morocco	61 995	3	1			Cadi-Soussi et al. 1982
	62 004	3		2		
Pakistan	295	3	61	55	49	Kuntz 1960
Saudi Arabia	835	1	0.1	0.1	0	El-Rahimy et al. 1986
Tunisia	24 047		11			Thiers, Lassoued & Abid 1976

a. *N.a* = Necator americanus; *A.d.* = Aneaslostoma duodenale.

b. For hookworm, *Ancylostoma duodenale* accounts for 50% and *Necator americanus* makes up 2%.

c. Hookworm only among Jasmin workers.

this varies with such factors as age and sex. It also attempts to determine the relatively rare mortality attributed to intestinal nematode infection.

The calculation of disability-adjusted life years (DALYs) is based on the population at risk of disability. It is assumed that there are three sources of DALY loss: *contemporaneous* disability, which occurs in individuals with worm burdens above the higher threshold in Table 9.1 and which persists as long as the individual remains infected; *chronic* disability, which occurs in a small proportion of children with worm burdens above the lower threshold and which is life-long; and life years lost from *mortality*. The sum of these three effects gives the overall DALY estimate.

Population at risk of disability

Estimates of the populations at risk of disability are shown in Tables 9.9 to 9.11. Note that these populations are not the populations infected but some fraction of these which are at risk of disability because their worm burdens exceed a threshold that has been shown to be associated with some disability. For each species there are two populations considered to be at risk, based on two estimates of threshold burden: a larger population with worm burdens exceeding the lower threshold (associated with chronic or developmental disability); and a smaller population with burdens exceeding the higher threshold (associated with acute or contemporaneous disability). The proportion of the population at risk (*not* the prevalence of infection) is given in Tables 9.9 to 9.11.

These estimates have been recalculated and differ from the original estimates (World Bank 1993, Chan et al. 1994). For *A. lumbricoides* and *T. trichiura* they are substantially lower than the earlier estimates as a result of removing the highest prevalence reference class from the extrapolation analysis. This change avoids overemphasis on the highest prevalence classes, which contribute disproportionately to the at risk population, and so gives a more conservative estimate. For the hookworm estimates, there was the same change in procedure but also a change in the worm burden thresholds. The change in thresholds was necessary to correctly assign the thresholds to the appropriate age classes in the light of new information. The effects of these changes for hookworm infection are to substantially reduce the estimated size of the population above the higher threshold and to slightly increase the population above the lower threshold.

Contemporaneous effects of infection

Given that people in endemic areas are continuously infected and reinfected throughout life it can be assumed, for present purposes, that incidence is numerically equivalent to prevalence and that infection duration is one year. The contemporaneous effects are assumed to occur in 100 per cent of the population with worm burdens above the higher threshold, and persist as long as an individual remains infected.

With *A. lumbricoides*, the most common consequences of infection are insidious effects, which are often manifested as effects on development

(reviewed by Crompton, Nesheim & Pawlowski 1989). They are, however, contemporaneous effects in that they can be partially reversed on treatment; that is, they occur only while infection persists. Such effects include reduction in growth rate (height-for-age and weight-for-age), physical fitness and appetite, for school-age and younger children (Stephenson et al. 1989, 1990, 1993). There is also evidence that this infection has consequences for congnitive ability in school-age children.

Cognitive consequences have yet to be sought in adults, but it would be surprising if adults responded differently from children since the effect is on ability rather than development. We assume here that adults with above-threshold worm burdens are affected, although the proportion of adults in this category is very small (0.02 per cent).

Table 9.9 Data for DALY calculation, Ascariasis, both sexes, 1990

		Proportion at risk		*Average age*	*Duration*	*Duration of disability*	
Region	*Age Group*	*Acute*	*Permanent*	*at onset*	*of risk*	*Acute*	*Permanent*
Sub-Saharan Africa	0–4	0	120	2	1	1	81.3
	5–14	525	1 720	10	1	1	71.7
	15–44	10	170	30	1	1	51.9
	45–59	10	170	50	1	1	32.5
	60+	10	170	70	1	1	14.9
Latin America & Caribbean	0–4	10	410	2	1	1	81.3
	5–14	1 790	5 950	10	1	1	71.7
	15–44	20	580	30	1	1	51.9
	45–59	20	580	50	1	1	32.5
	60+	20	580	70	1	1	14.9
Middle Eastern Crescent	0–4	0	120	2	1	1	81.3
	5–14	555	1 815	10	1	1	71.7
	15–44	10	180	30	1	1	51.9
	45–59	10	180	50	1	1	32.5
	60+	10	180	70	1	1	14.9
India	0–4	0	170	2	1	1	81.3
	5–14	770	2 530	10	1	1	71.7
	15–44	10	250	30	1	1	51.9
	45–59	10	250	50	1	1	32.5
	60+	10	250	70	1	1	14.9
China	0–4	20	600	2	1	1	81.3
	5–14	2 810	8 870	10	1	1	71.7
	15–44	40	890	30	1	1	51.9
	45–59	40	890	50	1	1	32.5
	60+	40	890	70	1	1	14.9
Other Asia & Islands	0–4	10	540	2	1	1	81.3
	5–14	2 345	7 850	10	1	1	71.7
	15–44	30	770	30	1	1	51.9
	45–59	30	770	50	1	1	32.5
	60+	30	770	70	1	1	14.9

The disabling consequences of reduced physical fitness and cognitive ability have yet to be empirically quantified, as is the case for many of the morbid effects for which DALY estimation is attempted. We assume here, by default, that the contemporaneous effects of moderate ascariasis result in disability at the lowest disability weight (Class 1) (Murray & Lopez 1996).

There are also more serious consequences of infection, largely associated with obstruction of ducts and intestinal lumen by these large worms. Systematic data on these acute complications are lacking, but the numerous reports based on inpatient records suggest that ascariasis is an important cause of hospitalization in endemic areas (reviewed by Pawlowski & Davies 1989). Ascariasis was the cause of 2.6 per cent of all hospital admissions in Kenya in 1976, and 3 per cent in a children's hospital in Myanmar between 1981 and 1983 (Stephenson, Lathan & Oduori 1980, Thein-Hlaing 1987). Complications resulting from ascariasis accounted for 0.6 per cent of all admissions to a paediatric surgery department in South Africa in 1987, 5.8 per cent of emergency admissions to a hospital in Mexico in 1975, 10.6 per cent of admissions for acute abdominal emergency to a children's hospital in Myanmar, and between 0.8 and 2.5 per cent of admissions in a survey of hospitals in China (Flores & Reynaga 1978, World Health Organization 1987, Thein-Hlaing et al. 1990). The most common abdominal emergencies presenting are intestinal obstruction and biliary ascariasis, the proportions varying geographically, perhaps because of differences in diagnostic procedures (Maki 1972). The classical surgical presentation is in patients between 3 and 10 years of age, although adults also may be affected (Davies and Rode 1982, Chai et al. 1991). Laparotomy attributable to ascariasis was the second most common cause of all laparotomies in 2–4 year old children in Durban, Lishiu and Sao Paulo, and the fifth or sixth cause in adults in Myanmar, China and Nigeria (World Health Organization 1987). Reports using unstandardized indicators indicate that between 0.02 and 0.9 per cent of infections may require hospitalization (Pawlowski & Davies 1989), the proportion presumably varying with the local intensity of infection. Thus of the 4.5 per cent of infected children under 10 years of age who are here estimated to exceed the higher threshold of infection, between 0.4 and 20 per cent are likely to require hospitalization. These children will suffer a severely disabling condition, which may be life-threatening (see below), but which can be alleviated by appropriate clinical management. If it is assumed that such cases are managed appropriately, then the duration of disability is likely to be a few weeks. Complicated ascariasis has a reported history of over 10 days followed by 5 days of management, while the management of biliary ascariasis involves 4–6 weeks of observation before opting for surgical intervention (Davies & Rode 1982). The disability therefore is considered, for the present analyses, to be contemporaneous with infection, to have a duration of 4 weeks, to have a severity of Class III (Murray & Lopez 1996), and to affect 5 per cent of children under 15 years

Table 9.10 Data for DALY calculation, Trichuriasis, both sexes, 1990

		Proportion at risk		Average age	Duration	Duration of disability	
Region	*Age Group*	*Acute*	*Permanent*	*at onset*	*of risk*	*Acute*	*Permanent*
Sub-Saharan Africa	0–4	0	0	2	1	1	81.3
	5–14	680	1 340	10	1	1	71.7
	15–44	0	110	30	1	1	51.9
	45–59	0	110	50	1	1	32.5
	60+	0	110	70	1	1	14.9
Latin America & Caribbean	0–4	0	10	2	1	1	81.3
	5–14	2 855	5 795	10	1	1	71.7
	15–44	10	470	30	1	1	51.9
	45–59	10	470	50	1	1	32.5
	60+	10	470	70	1	1	14.9
Middle Eastern Crescent	0–4	0	0	2	1	1	81.3
	5–14	0	30	10	1	1	71.7
	15–44	0	0	30	1	1	51.9
	45–59	0	0	50	1	1	32.5
	60+	0	0	70	1	1	14.9
India	0–4	0	0	2	1	1	81.3
	5–14	620	1 240	10	1	1	71.7
	15–44	0	100	30	1	1	51.9
	45–59	0	100	50	1	1	32.5
	60+	0	100	70	1	1	14.9
China	0–4	0	10	2	1	1	81.3
	5–14	3 380	6 475	10	1	1	71.7
	15–44	20	570	30	1	1	51.9
	45–59	20	570	50	1	1	32.5
	60+	20	570	70	1	1	14.9
Other Asia & Islands	0–4	0	20	2	1	1	81.3
	5–14	3 980	8 050	10	1	1	71.7
	15–44	20	650	30	1	1	51.9
	45–59	20	650	50	1	1	32.5
	60+	20	650	70	1	1	14.9

of age with burdens exceeding the higher threshold. Note that this is a conservative assumption since it excludes the documented, though rare, occurrence of complications in adults. Furthermore, the case rates for children are based on records from tertiary facilities to which a substantial proportion of the most disadvantaged and heavily infected children may have limited access.

With *T. trichiura* there is evidence that moderate intensity infections result in growth deficits that can be reversed by the antihelminthic removal of the worms (Cooper et al. 1990), and that these infections result in a protein losing enteropathy and anaemia (Cooper et al. 1991, 1992, MacDonald et al. 1991, Ramdath et al. 1995). In young children there are also

Table 9.11a Data for DALY calculation, Hookworm disease, males, 1990

Region	Age Group	Proportion at risk		Average age at onset	Duration of risk	Duration of disability	
		Acute	Permanent			Acute	Permanent
Sub Saharan Africa	0–4	0	0	2	1	1	80.0
	5–14	180	1 260	10	1	1	70.4
	15–44	2 650	5 760	30	1	1	50.5
	45–59	2 650	5 760	50	1	1	31.0
	60+	2 650	5 60	70	1	1	13.6
Latin America & Caribbean	0–4	0	0	2	1	1	80.0
	5–14	30	945	10	1	1	70.4
	15–44	1 090	5 030	30	1	1	50.5
	45–59	1 090	5 030	50	1	1	31.0
	60+	1 090	5 030	70	1	1	13.6
Middle Eastern Crescent	0–4	0	0	2	1	1	80.0
	5–14	30	480	10	1	1	70.4
	15–44	770	2 400	30	1	1	50.5
	45–59	770	2 400	50	1	1	31.0
	60+	770	2 400	70	1	1	13.6
India	0–4	0	0	2	1	1	80.0
	5–14	70	1575	10	1	1	70.4
	15–44	2 070	8150	30	1	1	50.5
	45–59	2 070	8 150	50	1	1	31.0
	60+	2 070	8 150	70	1	1	13.6
China	0–4	0	0	2	1	1	80.0
	5–14	10	540	10	1	1	70.4
	15–44	330	3 260	30	1	1	50.5
	45–59	330	3 260	50	1	1	31.0
	60+	330	3 260	70	1	1	13.6
Other Asia & Islands	0–4	0	0	2	1	1	80.0
	5–14	70	1545	10	1	1	70.4
	15–44	2 060	7 980	30	1	1	50.5
	45–59	2 060	7 980	50	1	1	31.0
	60+	2 060	7 980	70	1	1	13.6

effects on development quotient (Griffiths locomotor subscale), anaemia and growth that are at least partially reversible by antihelmintic therapy (Callender et al. 1994). There is also an increasing body of evidence that both cognitive function (Tables 9.12a and 9.12b) and educational achievement are impaired by moderate intensity infections, and that at least some of these effects can be reversed by antihelmintic treatment (Nokes et al. 1992a, 1992b, Simeon, Grantham-McGregor & Wong 1995, Simeon et al. 1995). As for ascariasis, it is assumed that these are contemporaneous effects of trichuriasis and result in the lowest disability weight (Class 1).

Particularly large burdens of *T. trichiura* may result in the "classical" dysenteric form of trichuriasis, synonymous with Trichuris Dysentery Syn-

Table 9.11b Data for DALY calculation, Hookworm disease, females, 1990

		Proportion at risk		*Average age*	*Duration*	*Duration of disability*	
Region	*Age Group*	*Acute*	*Permanent*	*at onset*	*of risk*	*Acute*	*Permanent*
Sub Saharan Africa	0–4	0	0	2	1	1	82.5
	5–14	180	1 260	10	1	1	73.0
	15–44	2 650	5 760	30	1	1	53.3
	45–59	2 650	5 760	50	1	1	34.0
	60+	2 650	5 760	70	1	1	16.2
Latin America & Caribbean	0–4	0	0	2	1	1	82.5
	5–14	30	945	10	1	1	73.0
	15–44	1 090	5 030	30	1	1	53.3
	45–59	1 090	5 030	50	1	1	34.0
	60+	1 090	5 030	70	1	1	16.2
Middle Eastern Crescent	0–4	0	0	2	1	1	82.5
	5–14	30	480	10	1	1	73.0
	15–44	770	2 400	30	1	1	53.3
	45–59	770	2 400	50	1	1	34.0
	60+	770	2 400	70	1	1	16.2
India	0–4	0	0	2	1	1	82.5
	5–14	70	1 575	10	1	1	73.0
	15–44	2 070	8 150	30	1	1	53.3
	45–59	2 070	8 150	50	1	1	34.0
	60+	2 070	8 150	70	1	1	16.2
China	0–4	0	0	2	1	1	82.5
	5–14	10	540	10	1	1	73.0
	15–44	330	3 260	30	1	1	53.3
	45–59	330	3 260	50	1	1	34.0
	60+	330	3 260	70	1	1	16.2
Other Asia & Islands	0–4	0	0	2	1	1	82.5
	5–14	70	1 545	10	1	1	73.0
	15–44	2 060	7 980	30	1	1	53.3
	45–59	2 060	7 980	50	1	1	34.0
	60+	2 060	7 980	70	1	1	16.2

drome (Ramsey 1962) and Massive Infantile Trichuriasis (Kouri & Valdes Diaz 1952). This typically occurs in children between 3 and 10 years of age and is associated with burdens involving at least several hundreds of worms carpeting the colonic mucosa from ileum to rectum. The colon is inflamed, oedematous and friable, and often bleeds freely (Venugopal et al. 1987). Reviews of case histories suggest that the mean duration of disease at the time of presentation is typically in excess of 12 months and that relapse after treatment frequently occurs (Gilman et al. 1983, Cooper et al. 1990, Callender et al. 1994). The probability of relapse, and of a child experiencing multiple episodes, is greatly enhanced because a proportion of heavily infected children are predisposed to reacquire heavy infection

even after successful treatment (Bundy et al. 1987a, 1987b). The typical signs of the syndrome (see Bundy & Cooper 1989a for a review of 13 studies involving 697 patients) are rectal prolapse, tenesmus, bloody mucoid stools (over months or years), growth stunting, and a profound anaemia, which may lead to a secondary anaemia. The complete spectrum of clinical features associated with the syndrome occurs in some 30 per cent of children with intense trichuriasis. Many of the major clinical effects are reversible by appropriate therapy (Cooper, Bundy & Henry 1986, Gilman et al. 1983), hence the disability is considered here to be a contemporaneous consequence of infection. For the present analyses it is assumed that the disability is contemporaneous with infection, has a duration of over 12 months, has a severity of Class II (Murray & Lopez, 1996), and affects 20 per cent of children under 15 years of age experiencing the higher threshold of intensity.

With hookworm the major consequence of infection is anaemia (see Schad & Banwell 1984 and Crompton & Stephenson 1990 for reviews of the extensive literature in this area). Anaemia is associated with: reduced worker productivity; reduced adult and child fitness; reduced fertility in women; reduced intrauterine growth rate, prematurity and low birth weight; and cognitive deficits (Fleming 1982, Stephenson et al.1993, Pollitt et al. 1986, Boivin et al. 1993) (Tables 9.12a and 9.12b). Since the higher threshold for the intensity of hookworm infection was selected on the basis of the development of anaemia, it is here assumed that 100 per cent of those exceeding this threshold suffer at least Class I disability. As discussed elsewhere (World Bank 1993), the consequences of anaemia will be more serious for a subset of the affected population, resulting in Class II and Class III disability. The disability weight distribution for anaemia was used for the present analyses, 70 per cent in Class II, 24 per cent in Class III and 6 per cent in Class IV.

For all species it is assumed here that the effects are independent of host sex. It is also assumed that the disability weight is age-independent since the method of extrapolating the population at risk incorporates age-weights in both the prevalence of infection and the threshold associated with disability by age.

Chronic effects of infection

In addition to the contemporaneous effects of infection, there is evidence that some consequences of infection are irreversible. This is the case for some cognitive deficits (Table 9.12a), some elements of development quotient (Callendar et al. 1994), and some growth effects during childhood (Stephenson et al. 1993). In all studies, some forms of disability in a proportion of children do not respond to therapy. We estimate that in any annual cohort of heavily infected children some 5 per cent suffer these permanent consequences. Studies of reinfection show that children are predisposed to a particular intensity of infection (Keymer & Pagel 1990, Hall, Anwar & Tomkins 1992), such that some 30 per cent of heavily infected children

Table 9.12a Selected studies investigating the effects of parasitic helminth infections on mental processing

Parasite	*Country*	*Study design*	*Sample size*	*Time between baseline and follow-up (if appropriate)*	*Age of subjects (years)*	*Significant effects of helminth infection on mental processing*		*Investigators*
						Baseline differences between infected and uninfected group	*Intervention differences*	
Trichuris trichiura Moderate intensity	Jamaica	Intervention Placebo controlled Albendazole	T = 206 P = 201 C = 206	26 weeks	7–11	* Reading x Spelling * Arithmetic x School Attendance Tests in battery = 4	Treatment interaction effects: • heavily infected and received treatment improved in spelling; • stunted and received treatment improved in school attendance.	Simeon et al. 1994
		Intervention Placebo controlled Albendazole	T = 96 P = 93 C = 100	14 weeks	8–10	x Fluency x French learning (initial) * Letter search Tests in battery = 6	Treatment interaction effects: Underweight children improved in fluency.	Simeon et al. 1994
		Intervention Placebo controlled Albendazole	T = 49 P = 48 C = 48	14 weeks	10–11	* Silly sentences x Letter search Tests in battery = 8	None significant	Baddeley, Meeks-Gardner & Grantham-McGregor 1995
		Intervention Placebo controlled Albendazole	T = 66 P = 67 C = 63	10 weeks	9–11	x Digit-span forwards x Digit-span backwards x Analogical reasoning x Pegboard non-dominant hand Tests in battery = 9	None significant	Sternberg, Powell & McGrane, 1995

Trichuris trichiura Moderate–heavy intensity	Jamaica	Intervention Placebo controlled Albendazole	T = 62 P = 41 C = 56	63 ± 8 days	9–12	Fluency Digit-span forwards Digit-span backwards Arithmetic Coding Comprehension Matching familiar figures: easy Matching familiar figures: hard Tests in battery = 8	Fluency Digit-span forwards Digit-span backwards	Nokes et al.1992a, 1992b
Hookworm presence	Zaire	Intervention, Case control Levamizole + malaria treatment if infected only	T = 47 C = 50	4 weeks	8.75 ± 1.6	Sequential processing, including number recall Word order * Mental processing total Tests in battery = 10	Spatial memory	Boivin et al. 1993
Hookworm + Iron status presence	Zaire	Intervention, placebo controlled Levamizole iron supplements	T + Iron = 17 P + Iron; T only; P only; = 30	4 weeks	Male = 7.7 Fem = 8.0	Not reported Tests in battery = 10	Effect = iron + hookworm trnt Spatial memory Number recall Word order Face recognition Gestalt Matrix analogies Mental processing total Sequential total Simultaneous total	Boivin & Giordani 1993

continued

Table 9.12a Selected studies investigating the effects of parasitic helminth infections on mental processing *(continued)*

Parasite	*Country*	*Study design*	*Sample size*	*Time between baseline and follow-up (if appropriate)*	*Age of subjects (years)*	*Significant effects of helminth infection on mental processing*		*Investigators*
						Baseline differences between infected and uninfected group	*Intervention differences*	
Trichuris trichiura TDS – very heavy intensity	Jamaica	Case control, interventions pair-matched Albenda-zole given to infected children every 4 months	T = 19 C = 19	12 months	3–6	Griffiths DQ subscales Locomotor Eye hand coordination Hearing and speech Performance	Locomotor	Callender et al. 1991
Ascaris lumbricoides Presence (Study actually designed to investigate T. trichiura)	Jamaica	Cross-section, matched for class	Infd = 196 Uninfd = 207 (*Infd* with *T. trichiura* = 409)	—	7–11	* Reading * Spelling * Arithmetic * School attendance Tests in battery = 4		Simeon et al. 1994
Ascaris lumbricoides presence	Ecuador	Cross-section	Infd = 103 Uninfd C = 27	—	9–13	* Stroop words * Peabody raw score * Digit Symbol * Wisconsin Card Sorting Test Interaction with nutrition in	Not done	Levav et al. 1995

						Peabody Test * = controlled for nutrition status All sample had high EEG Tests in battery = 13		
Polyparasitism *A. lumbricoides*, *T. trichiura*, Hookworm intensity	Jamaica	Cross-section	Infd = 473 Uninfd = 170	—	9–11	Academic stream (children streamed by teachers according to academic ability; children with least ability more likely to be infected and heavily infected) Only test in battery	Not done	Nokes et al. 1991
Polyparasitism *A. lumbricoides*, *T. trichiura*, hookworm, Schistosome spp. Protozoa Intensity	South Africa	Cross-section all infected with different spp.	Subjects = 110	—	10	* Sustained attention (pathogenicity of parasitic species more important than prevalence/ intensity at predicting performance) Other test = Memory	Not done (Intervention disrupted by flooding)	Kvalsvig Cooppan & Connolly 1991
Trichuris trichiura Low-Moderate and heavy intensity	Italy	Cross-section	Uninf = 232 Infd = 124	—	6–10	x Lower school grade correlated with intensity. No relationship when controlled for social and hygienic conditions. Other outcome = promotion.	Not done	de Carneri 1968

continued

Table 9.12a Selected studies investigating the effects of parasitic helminth infections on mental processing *(continued)*

Parasite	*Country*	*Study design*	*Sample size*	*Time between baseline and follow-up (if appropriate)*	*Age of subjects (years)*	*Significant effects of helminth infection on mental processing*		*Investigators*
						Baseline differences between infected and uninfected group	*Intervention differences*	
Trichuris trichiura Low–Moderate & heavy Intensity	Italy	Cross-section	Uninf = 125 Infd = 233	—	6–11	x Slower promotion, poor grades correlated with intensity. No relationship when controlled for social and hygienic conditions. Other outcome = absenteeism	Not done	de Carneri Garofano & Grassi 1967
Hookworm Intensity	Australia	Cross-section	Uninfd = 116 Infected: low intensity = 65 Infected: high intensity= 159	—	6.5–15.5	Binet-Simon test and Porteus Mazes correlated with intensity of infection.	Not done	Waite & Neilson 1919
Hookworm presence	United States of America	Cross-section	78	—	6–17	* Grade advancement (deficit of 0.23 grades/year)	Not done	Stiles 1915

Table 9.12b Selected studies investigating the effects of parasitic helminth infections on physical fitness

Parasite	*Country*	*Study design and Measure of activity*	*Sample size*	*Time between baseline and follow-up (if appropriate)*	*Age of subjects (years)*	*Baseline differences between infected and uninfected group*	*Intervention differences*	*Investigators*
Polyparasitism *T. trichiura* *A. lumbricoides* Hookworm Presence	Kenya	Intervention placebo controlled Albendazole Harvard Step Test	T=18 P=15	7 weeks	6–12	Fitness negatively correlated with haemoglobin/iron status.	No change in fitness score and pulse rate in placebo group. Significant improvement in fitness in treatment group. Improvement significantly related to reduction in hookworm and *A. lumbricoides* egg counts.	Stephenson et al.1990
Polyparasitism *T. trichiura* *A. lumbricoides* Hookworm presence	Kenya	Intervention placebo controlled Albendazole Harvard Step Test	T=27 P=26	4 months	7–13	No difference between infected groups.	No change in fitness score and pulse rate in placebo group. Significant improvement in fitness in treatment group. Improvement significantly related to reduction in hookworm, weight gain and increase in energy intake during the 4 month study period.	Stephenson et al.1993

Definitions

Intervention	One group receives treatment. Groups tested pre-intervention and post-intervention.
Placebo controlled	Infected group randomly assigned to treatment or placebo. Groups tested pre-intervention and post-intervention.
Case control	Infected group compared to an uninfected group. Groups matched for age as a minimum. Infected group receives treatment. Uninfected group receives no treatment.
Pair-matched	Infected group and uninfected group pair matched for confounding variables other than just for age.
Cross-section	Infected group compared against uninfected group. Neither group receives treatment. Groups tested at baseline only.
Presence	Subjects selected for the study on the basis of the presence of infection and not on the basis of the intensity of infection.
Intensity	Analysis of results takes into consideration the intensity of infection.
Light, moderate or heavy intensity	The intensity of infection of subjects recruited to the study.

continued

Table 9.12b Selected studies investigating the effects of parasitic helminth infections on physical fitness *(continued)*

Abbreviations

T	Infected group treated with antihelminthic.
P	Infected group treated with antihelminthic placebo.
NoT	Infected group receiving no intervention, i.e. no treatment or no placebo.
C	Uninfected control receiving no treatment or placebo.
Infd	Infected with parasite spp.
Uninfd	Uninfected with parasite spp.

Key

X	Controlled for confounding variables and infection did not remain significant.
*	Controlled for confounding variables and infection remained significant.
No mark	No attempt to control for confounding variables.

in an annual cohort would be expected to reacquire heavy infection. Thus each year the proportion of children exceeding the threshold worm burden will consist of some 70 per cent of individuals who have not previously experienced heavy infection, which implies a cumulative increase in the proportion suffering permanent disability. We therefore assume that each year 3 per cent of newly heavily infected children, and children only, suffer life-long consequences of infection.

The disability attributable to these effects has yet to be empirically determined. Stunted children may be disadvantaged in education (Moock & Leslie 1986, Jamison 1986, Glewwe & Jacoby 1995), as are children with low development quotients or cognitive impairment (Pollitt 1990). On the other hand, physical and mental maturation may eventually compensate, to some degree, for initial retardation (Pollitt et al. 1986). In a recent study of two years nutritional supplementation of stunted children, locomotor development improved in the first year, as seen with antihelminthic treatment of trichuriasis (Callender et al. 1994), while other areas of development did not improve until the second year (Grantham-McGregor et al. 1991). Given this uncertainty we assume that the permanent consequences of infection result in disability at the lowest weight (Class 1). Thus in calculating the DALYs for all the helminth infections it is assumed here that 3 per cent of children experiencing worm burdens above the lower threshold suffer permanent disability of Class 1.

Mortality

This is the weakest area of DALY estimation because of the lack of empirical data. Ascariasis is the best documented helminthiasis in terms of mortality. There are numerous studies of case fatality rates in hospitals (reviewed by Pawlowski & Davies 1989). These indicate that the outcome of acute complications of ascariasis is modified by the general health status of the patient, the intensity of infection and the medical procedure (see Pawlowski & Davies 1989). In one hospital in Sao Paulo, for example, the case fatality rate was 1.35 per cent for conditions which could be managed conservatively, and 26.1 per cent in patients undergoing surgery (Okumura et al. 1974). These studies confirm that death is a not infrequent outcome of complications of ascariasis, but provide little insight into mortality rates in the community. An extrapolation from central hospital data in Myanmar suggests there are 0.008 deaths per 1000 infections per year (Thein-Hliang 1987), but this is considered to be a considerable underestimate since only a small proportion of children with severe complications are likely to have access to the hospital (Pawlowski & Davies 1989). Only two population based estimates are available: one for the Darmstadt epidemic (0.1 deaths per 1000 infected per year) (Krey 1949) and one for Japan prior to national control efforts (0.061 deaths per 1000 infected per year) (Yokogawa 1976). Based on the present estimate of global infection, these rates suggest that between 8 000 and 14 000 children die each year.

The final estimate of global mortality due to ascariasis in the Global

Burden of Disease project was 11 000 concentrated in the age group 5–14 years (Murray and Lopez 1996). Mortality was distributed by region in proportion to the region-specific population at risk (above higher threshold) and to the region-specific probability of dying between birth and 4 years (World Bank 1993). This last quantity was added to take account of regional variations in access to acute medical services.

No population-based mortality estimates have been published for *T. trichiura* infection. Prior to the advent of safe and effective therapy for *T. trichiura* infection in the late 1970s a number of reports described paediatric inpatients with Trichuris Dysentery Syndrome who, despite clinical efforts, died as a result of profuse haemorrhage and secondary anaemia (Wong and Tan 1961, Fisher and Cremin 1970) or of intussusception (Reeder, Astacio & Theros 1968). Although there continue to be reports of the syndrome, a fatal outcome in a clinical setting today would suggest inappropriate management. The picture in the community, however, may be rather different since, in the absence of specific diagnosis, the aetiology of chronic bloody dysentery may be unrecognized. Nevertheless, mortality is undoubtedly a rare consequence of trichuriasis.

The profound anaemia of hookworm infection is life-threatening and has been estimated, although the means of estimation are not described, to result in 65 000 deaths per year (World Health Organization 1992). Again there is a lack of empirical data, presumably in this case because of the difficulty in identifying the etiology of anaemia-related deaths. A figure of 4 300 deaths was used by Murray and Lopez (1996) and was distributed to ascribe the highest proportion of mortality to women of childbearing age (15–44 years) and to older age groups. The distribution of deaths between regions was divided in the same way as for the other infections.

In including these estimates of mortality we recognize that they are unsupported by vital registration statistics. But it should also be recognized that intense infection is most prevalent in the poorest regions of the poorest countries. In such areas mortality may be most likely because of limited access to appropriate management, while both the diagnosis of cause of death and its registration may be least reliable. There is clear evidence that deaths do occur. What is unclear is the extent of this mortality.

Disability

Much of the disability associated with helminth infection is insidious and would be unlikely to be brought to clinical attention. As such it is difficult to compare with the more classical clinical signs. On the other hand, cognitive deficits may have profound consequences for educational outcomes and growth stunting is one of the best characterized correlates with underachievement, so these insidious effects may have far reaching societal consequences. Achieving some realistic balance between the clinical consequences for the individual and developmental consequences for

society goes beyond the scope of the present exercise, and would require a more sophisticated weighting system, if indeed the effects could be quantified. For present purposes, the very low proportional weighting selected for the chronic effects of infection is influenced by the view that the Class 1 disability weight may be an overestimate of the effects of infection from a clinical perspective.

Other considerations in calculating burden

There are three main reasons why the burden of intestinal helminths may not be adequately captured by the present calculations. First, there are no direct measures of morbidity against which the extrapolation procedure could be conclusively validated. Although each step in the extrapolation was independently assessed against empirical data as far as possible, there must remain uncertainty until observed data become available. Second, the mortality data are largely unsubstantiated. Mortality has the potential to significantly alter the overall burden estimates. It is therefore unsatisfactory that mortality data have received so little research attention. Third, there is a particular lack of information on the morbid consequences of infection in young children. It is possible that even very low worm burdens may have disproportionately severe effects on developing physiologies and organ systems. Anecdotal evidence suggests that the current estimates of threshold and disability weights may significantly underestimate the burden in children under 10 years of age, and particularly those under 5 years.

The societal consequences of growth stunting and educational underachievement may be of substantially greater relevance than the disability in the individual.

Intestinal nematode infections as risk factors for other diseases

Intestinal nematode infection is associated with malabsorption and is a potentially important predisposing factor for malnutrition in communities on marginal diets. These effects may relate broadly to protein-energy malnutrition, or to specific deficiencies. For example, *A. lumbricoides* infection has been associated with malabsorption of vitamin A.

Hookworm infection and to a lesser extent trichuriasis are associated with iron loss predisposing to anaemia. It is self evident that the risk of anaemia is dependent on iron balance and thus that infection may be an important contributing factor.

The attributable contribution to global malnutrition is potentially considerable given the ubiquity of infection and its specifically high prevalence in the poorest societies with the least adequate diets.

Burden and intervention

The major intestinal helminth infections can be effectively treated simultaneously with single dose oral therapy. The treatment is widely available, safe, simple and inexpensive. Prevention of reinfection requires reduction in transmission, which can be achieved by synchronized treatment programmes and by improvements in sanitation.

In the absence of currently financed health interventions there would be some increase in the current burden. For example, there would be a greater number of deaths from intestinal obstruction in the absence of operative procedures, and from severe anaemia or malnutrition in the absence of rehabilitation therapy. However, with some important exceptions such as Japan and the Republic of Korea, control of intestinal helminth infections is only rarely a component of national public health programmes.

It could be argued that the entire burden could eventually be avoided by appropriate application of currently available interventions. For example, evidence from the Republic of Korea and Japan indicates that reduction in the prevalence of *A. lumbricoides* infection at the national level results in a significant decline in acute complications of ascariasis requiring hospitalization (Chai et al. 1991) and in ascariasis related mortality (Yokogawa 1976). Curative treatment would mitigate the contemporaneous or acute effects of infection, while measures to control transmission would avoid chronic developmental disability, although neither could reverse the deficits that are already present in the population.

Economic analyses suggest that carefully targeted community treatment programmes are exceptionally cost-effective (Warren et al 1993, Guyatt & Evans 1992, World Bank 1993). This arises because the therapy is inexpensive (US$0.20 or less per dose), is required at infrequent intervals (of the order of one year), can have community-wide effects even if targeted at some fraction of the population which makes the greatest contribution to transmission (such as school-age children), and can be delivered through existing infrastructures (such as schools or the primary health care system).

Conclusions

The global morbidity attributable to intestinal nematode infections, although generally accepted to be large, has proven difficult to quantify. The method presented here provides a framework whereby the potential global burden may be estimated in the absence of any direct measures of morbidity. The estimates are intended to give some indication of the potential burden of intestinal helminthiases rather than to provide absolute values. It would of course be possible to seek further refinement of the approach, but our view is that the most pressing need is to obtain reliable community data on the observed levels of morbidity and on the consequences of disability. The present analyses indicate that even low

levels of individual disability can sum to a considerable burden with such ubiquitous infections; the important question is what this implies for communities in practice. The analysis has revealed important lacunae in our knowledge of these infections and it is hoped that this might guide future applied research.

The present estimates suggest that the potential morbidity attributable to geohelminthiases is much greater than previously supposed. This reflects the inclusion of both the traditionally recognized clinical effects of helminthiases (see World Health Organization 1992) and more recently recognized developmental effects, which rarely result in clinical presentation but which may have major consequences for the individual and the community.

Another general implication of the results arises from the similarity of the age and regional distributions for *A. lumbricoides* and *T. trichiura* infection and morbidity. This observation has been made before for prevalence data (Booth & Bundy 1992), and strong positive correlations between *A. lumbricoides* and *T. trichiura* prevalences in communities have been demonstrated. This suggests that these two infections could be controlled within a single programme. The age distribution of the burden also supports the conclusion that there are particular benefits in targeting control of *A. lumbricoides* and *T. trichiura* infection at school age children (Bundy et al. 1985, Savioli, Bundy & Tomkins 1992).

The results suggest that the vast majority of the morbidity attributable to intestinal nematodes is readily avoidable or reversible using existing and cost-effective approaches, and that the mortality is also a largely avoidable consequence of acute infection. These observations, and the scale of the burden of current disease, argue for greater public health emphasis on the control of intestinal helminthiases.

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