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THE GLOBAL BURDEN OF DISEASE DUE TO SCHISTOSOMIASIS

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EXECUTIVE SUMMARY

- There are two main sources for global and regional estimates of schistosomiasis burden: the Global Burden of Disease and the WHO Expert Committee on the Prevention and Control of Schistosomiasis and Soil-Transmitted Helminthiasis. These two sources agree on four major points:
 1. Quantifying the burden of disease is important, as it is being increasingly used for policy decisions regarding the allocation of resources;
 2. Both mortality and morbidity burden should be taken into account;
 3. Morbidity represents the largest share of schistosomiasis burden; and
 4. More accurate estimates of schistosomiasis burden would be highly desirable.
- The two sources disagree on their assessments of both mortality and morbidity. Mortality estimates have a tenfold difference, which is largely explained by the level of constraints within very different estimation methods. Morbidity estimates are not directly comparable due to different parameters chosen to quantify morbidity. Estimates of the total number of prevalent cases of schistosomiasis infection were relatively consistent for the two sources.
- This assessment concludes that schistosomiasis burden may have been underestimated in the GBD of 1990, although data problems make it difficult to demonstrate the degree of underestimation.
- Sensitivity analysis on key variables suggests that it is unlikely that more accurate estimates would significantly change the ranking of schistosomiasis burden, in contrast to the expectations of the WHO Expert Committee. A one and a half to two-fold increase in schistosomiasis burden is most likely. This revision could make schistosomiasis the largest source of burden of disease among tropical diseases (not including malaria).
- Schistosomiasis certainly represents a major cause of burden in some geographic areas. Neither of the two approaches developed by the GBD and the WHO Expert Committee provide ways of dealing with the focal nature of schistosomiasis infection. Better epidemiological data are needed in all countries. GIS and RS have the potential to better model the heterogeneity of schistosomiasis within countries.
- Better estimates of the schistosomiasis mortality and morbidity burden are needed, and should include a more detailed assessment of different sequelae contributing to schistosomiasis burden, as well as separate estimates for each of the three major schistosoma strains (*S. mansoni*, *S. haematobium*, and *S. japonicum*). New methods for assessing morbidity related to schistosomiasis are under development and should help improve accuracy in future estimates of burden.
- Information to further illuminate disease progression could strengthen the ability to target populations at highest risk for severe disability.

THE GLOBAL BURDEN OF DISEASE DUE TO SCHISTOSOMIASIS

I. INTRODUCTION

The WHO Expert Committee on the Prevention and Control of Schistosomiasis and Soil-Transmitted Helminthiasis (WHO Expert Committee) stated in its most recent report that “the calculated figure for DALYs lost to schistosomiasis represents a serious underestimate and should be revised”(WHO, 2002a). It conveys the view of leading experts that the burden of disease estimates for schistosomiasis, in the Global Burden of Disease (GBD) of 1996 and subsequent revisions, has not fully captured the true magnitude of the disease. This paper examines whether the global burden of diseases for schistosomiasis has indeed been underestimated and discusses whether current estimates should be revised.

The DALY (disability-adjusted life year) is the metric developed to quantify the global burden of disease (GBD) in the early 1990s. It is a summary measure of population health, which combines in a single indicator years lost from premature death (YLL) and years of life lived with disability (YLD). One DALY can be thought of as one lost year of ‘healthy life’. The burden of disease measures the gap between the current health status and an ideal situation where everyone lives into old age free of disease and disability. Detailed accounts of methods and findings were published in two volumes: the *Global Burden of Disease* and *Global Health Statistics* (Murray and Lopez, 1996a and 1996b).

The classification developed for the global burden of disease (GBD) is based on the International Classification of Disease (ICD). It follows a ‘tree-structure’, which clusters diseases and conditions into three broad groups of causes, which are both exhaustive and mutually exclusive:

1. Group I – Communicable, maternal, perinatal and nutritional conditions
2. Group II – Noncommunicable diseases
3. Group III – Injuries

Each group has been further divided into several major sub-categories of disease and injury. Infectious and parasitic diseases are included in Group I, and were sub-divided into seven groupings: HIV/AIDS, diarrhoeal diseases, childhood diseases, malaria, tuberculosis, tropical diseases and intestinal nematode infections. The tropical disease cluster includes lymphatic filariasis, leishmaniasis, schistosomiasis, trypanosomiasis, onchocerciasis and Chagas disease. Intestinal nematode infections comprise hookworm disease, trichuriasis and ascariasis.

According to the GBD, schistosomiasis caused the loss of 1.7 million disability-adjusted life years (DALYs) worldwide in 2001, of which 82 percent (1.4 million DALYs) were lost in sub-Saharan Africa (SSA) alone. Schistosomiasis was the third largest cause of the tropical disease cluster burden (which does not include malaria) worldwide (Table 1). In SSA, schistosomiasis caused one quarter of the tropical disease cluster burden (Table 2).

Schistosomiasis is often examined along with intestinal nematodes in health policy discussions, because both infections are most prevalent among school-age children; often occur simultaneously, causing anemia, affecting growth and cognitive development; and respond well to simple and affordable drug treatments that can be provided in school-based programs. The relative importance of schistosomiasis and intestinal nematodes infections was greater in SSA than it was other regions. The global schistosomiasis burden was about equal to that due to hookworm disease, whereas in SSA it was double the combined burden of hookworm disease, trichiuriasis and ascariasis.

Schistosomiasis burden, nevertheless, represented only a small fraction of the total burden of disease - 0.1 percent of global burden of disease, and 0.4 percent of total burden in sub-Saharan Africa (SSA), as it is dwarfed by the immense burden due to HIV/AIDS, malaria, childhood diseases, diarrhoeal diseases and tuberculosis.

According to the WHO information fact sheets, schistosomiasis infects more than 200 million people, and approximately 10 percent of the world's population (over half a billion people) is at risk of infection. Given that so many people are infected, the very small share of the estimated schistosomiasis burden is surprising.

Table 1: Global burden of infectious and parasitic diseases, 2001

Conditions	DALYs (000)	% total	% Tropical diseases
All	1,467,257	100	
Infectious and parasitic diseases	359,377	24.5	
HIV/AIDS	88,429	6.0	
Diarrhoeal diseases	62,451	4.3	
Childhood diseases	48,268	3.3	
Malaria	42,280	2.9	
Tuberculosis	36,040	2.5	
Tropical diseases	12,994	0.9	100
<i>Of which</i>			
Lymphatic filariasis	5,644	0.4	43.4
Leishmaniasis	2,357	0.2	18.1
Schistosomiasis	1,760	0.1	13.5
Trypanosomiasis	1,598	0.1	12.3
Onchocerciasis	987	0.1	7.6
Chagas disease	649	0.0	5.0
Intestinal nematode infections	4,709	0.3	
Hookworm disease	1,825	0.1	
Trichiuriasis	1,649	0.1	
Ascariasis	1,181	0.1	

Source: WHO World Health Report, 2002

Table 2: Burden of infectious and parasitic diseases in SSA, 2001

Conditions	DALYs (000)	% total	% Tropical diseases
All	357,883		100
Infectious and parasitic diseases	189,047	35.7	
HIV/AIDS	67,460	18.8	
Malaria	36,012	10.1	
Childhood diseases	24,997	7.0	
Diarrhoeal disease	21524	6.0	
Tuberculosis	8,941	2.5	
Tropical diseases	6,251	1.7	100
<i>Of which</i>			
Lymphatic flariasis	1,933	0.5	30.9
Trypanosomiasis	1,557	0.4	24.9
Schistosomiasis	1,421	0.4	22.7
Onchocerciasis	937	0.3	15.0
Leishmaniasis	402	0.1	6.43
Intestinal nematode infections	674	0.2	
Hookworm disease	427	0.1	
Trichuriasis	123	0.03	
Ascariasis	121	0.03	

Source: WHO World Health Report, 2002

The publication of the GBD sparked debate regarding three major issues, namely: (i) strategies to fill information gaps, (ii) methods to quantify the severity of disability, and (iii) basic assumptions of the DALY (age-weighting and discounting). Issues pertaining to information gaps and measurement of disability are central to this review of schistosomiasis burden estimates. GBD estimates were revised for several diseases, for the year 2000 and beyond (WHO, 2003). Schistosomiasis was not included in the first round of revisions, but might be revised in the future.

In recent years there has been considerable interest in summary measures of population health, such as the DALY, to inform policy (Field et al., 1998; Murray et al., 2001, Murray et al, 2003). The magnitude of disease burden has indeed become an important consideration in setting funding priorities for research and control programmes (Gross CP et al., 1999, Remme et al., 2002). In this context, the possible underestimation of the global burden of schistosomiasis relative to other diseases matters a great deal, as it may influence decisions on resource allocation.

The next sections review (i) the main differences in the schistosomiasis burden of disease between GBD estimates and estimates from other sources; (ii) how the burden of schistosomiasis was calculated in the GBD; and (iii) ways to improve estimates of the schistosomiasis burden by using new knowledge gained over the past 10 years combined with disease models. The last section discusses whether the schistosomiasis burden was “seriously underestimated” in the GBD with a small sensitivity study, and considers implications for research and programs.

II. METHODS AND DATA SOURCES

This paper is based on the detailed review of published papers relating to:

- a)** Estimates of schistosomiasis burden;
- b)** Conceptual frameworks and analytical methods developed by different groups to generate burden estimates;
- c)** Research advances and findings that will contribute to better schistosomiasis burden estimates in the future.

In order to assess the extent of possible underestimation of schistosomiasis burden relative to other causes we first compared detailed GBD estimates for schistosomiasis with estimates for other conditions, and second, conducted a sensitivity analysis to illustrate changes in burden estimates that would result under different hypothetical scenarios. This analysis builds on existing GBD spreadsheets to calculate the number of years of life lost to premature deaths (YLL) and the number of years lived with a disability (YLD).

No new data were collected for this analysis and no attempt was made to recalculate burden.

III. COMPARATIVE ANALYSIS OF GLOBAL AND REGIONAL MORTALITY AND MORBIDITY ESTIMATES

Sources

The two main sources providing global and regional estimates of schistosomiasis mortality and morbidity are both within the World Health Organization (WHO):

- The Global Burden of Disease project in the WHO cluster on Evidence and Information for Policy; and
- The Parasitic and Vector Control unit (PVC), in the WHO cluster of Communicable Diseases.

Mortality and burden of disease estimates by sex, cause, and WHO region, have been published as Annexes to the WHO World Health Reports since 1999. The WHO Expert Committee provided estimates of total number of people with morbidity and mortality due to schistosomiasis infection in SSA in its latest report (WHO 2002). It includes findings of research commissioned by PVC to estimate schistosomiasis morbidity (van der Werf et al. 2002, 2003). In the text, tables, and figures of this paper, we refer to these two sources of estimates as i) GBD and ii) WHO Expert Committee.

Key findings

Estimates of the total number of people infected in SSA provided by each source were relatively consistent, ranging between 165 million (WHO Expert Committee) and 218 million (GBD). Estimates of the number of deaths, on the other hand, differed by an order of magnitude, ranging between 15 thousand in all endemic regions (GBD) and 150-200 thousand deaths in SSA (WHO Expert Committee). The large variance between these estimates underscores the high degree of uncertainty that persists with regard to the public health impact of schistosomiasis. Other estimates provided by each source are not directly comparable as they use different units of measurement (Table 3).

Table 3: Global and regional estimates of schistosomiasis mortality and morbidity, GBD and WHO Expert Committee

INDICATOR	GLOBAL BURDEN OF DISEASE (GBD), 2001 (1)	WHO EXPERT COMMITTEE (2,3)
DALYs (millions)		
Global total	1.7	
SSA	1.4	
Prevalent cases (millions)		
Global total	238	193
SSA	218	166
<i>Of which</i>		
	S.haematobium	112
	S.mansoni	54
Mortality estimates		
Number of deaths (000s)		
Global total	15	
SSA	5	200
<i>Of which</i>		
	Renal failure	150
	Bladder cancer	13
	Haematemesis	[130]
Morbidity estimates S.mansoni		
Cases (millions)	Diarrhea (previous 2weeks)	0.8
	Dysuria (previous 2 weeks)	4.4
	Hepatomegaly	8.5
	Splenomegaly	[6.3]
	Ascites	[0.3]
	Haematemesis (ever)	[0.9]
Morbidity estimates S.haematobium		
Cases (millions) (90% CI)	Haematuria (previous 2 weeks)	71 (52-89)
	Dysuria	32 (17-55)
	Minor bladder morbidity (US)	76 (67-92)
	Major bladder morbidity (US)	24 (15-31)
	Moderate hydronephrosis	9.6
	Major hydronephrosis	9.6

Source: Prevention and Control of Schistosomiasis and Soil-Transmitted Helminthiasis, WHO 2002; WHO, World Health Report, 2002. Figures in square brackets [] should be interpreted with caution.

Estimation strategies

- (1) Mortality: cause of death models; morbidity GBD epidemiological model (DisMod)
- (2) Prevalence: extrapolation from historical prevalence data
- (3) Morbidity and mortality estimates were derived from results of mathematical models that quantified the relationship between (i) prevalence of infection and (ii) prevalence of selected morbid outcomes (van der Werf et al., 2002, 2003a)

Discussion

Direct comparison of estimates provided by each of the two main sources is limited as they differed in:

- (i) the aims of research;
- (ii) the units of measurement; and
- (iii) the levels of data disaggregation.

Aims of research

The contexts, in which estimates of schistosomiasis mortality and morbidity were made, were quite different. The GBD 1990 broke new paths and provided the first comparable global estimates of more than a hundred causes of disease and injury. It had three explicit aims (Murray and Lopez, 1996c):

- i) To incorporate non-fatal conditions into assessments of health status;
- ii) To disentangle epidemiology from advocacy in order to produce objective, independent and demographically plausible assessments of the burdens of particular conditions and diseases; and
- iii) To measure disease and injury in a currency that can also be used to assess the cost-effectiveness of interventions, in terms of cost per unit of disease averted.

Almost a decade later, the WHO Expert Committee addressed specific limitations of GBD schistosomiasis burden estimates, seeking to better convey the full impact of schistosomiasis infection, and draw renewed attention to the need to revise GBD estimates.

Units of measurement

The WHO Expert Committee provided number of deaths and number of people affected by different signs and symptoms. The GBD quantified burden as YLL, YLD and DALYs, which take into account not only the number of deaths or people affected, but also the age at which death or disability occur.

Levels of data disaggregation

The GBD included estimates for each sex and five different age groups, thus taking into account changes in the distribution and severity of disease over the life span. It did not provide separate estimates for different schistosoma strains.

The WHO Expert Committee, on the other hand, did not include age and sex specific estimates, but provided estimates for each of the two schistosoma strains found in SSA (*S.mansoni*, and *S.haematobium*).

In spite of these notable differences, there is complete agreement on four key points:

- a) Quantifying the burden of disease is important;
- b) Both mortality and morbidity burden should be taken into account;
- c) Morbidity represents the largest share of schistosomiasis burden; and
- d) More detailed estimates would be highly desirable in future revisions of the GBD.

The next section presents differences in the methods of calculation of mortality and morbidity estimates for schistosomiasis, with attention to (i) analytical frameworks; (ii) available empirical evidence, and (iii) estimation strategies used to overcome the limitation of current knowledge regarding the distribution, severity, and duration of non-fatal health outcomes of schistosomiasis infection.

IV. ESTIMATION STRATEGIES TO FILL KNOWLEDGE GAPS

The main difficulty hampering accurate estimation of schistosomiasis burden stems from shortcomings in the available empirical data, so that indirect estimation strategies are required to fill information gaps. Approaches chosen to overcome data limitations are the root cause of the great variance observed in published estimates.

IV.1. Analytical frameworks

1. The GBD analytical framework

The analytical framework developed for the GBD is complex. The assessment of the burden of disease for any cause includes two key components – mortality and morbidity. It requires information about the number of deaths by cause; the epidemiology of the disease (incidence, prevalence, remission rates, and case fatality rates); and disease progression. Successive analytical steps seek to ensure that epidemiological estimates are internally consistent¹ and the severity of non-fatal health outcomes comparable across a wide range of conditions.

2. The WHO Expert Committee analytical framework

The WHO Expert Committee did not develop a new analytical framework. Instead, its approach addresses one of the major limitations of current GBD estimates of schistosomiasis morbidity burden – namely, the absence of details regarding specific

¹ An epidemiological disease model (DisMod), which quantifies relationships between people at risk in the general population, incidence and remission rates, case fatality rates and overall mortality was developed to check the internal consistency and plausibility of all available empirical data, from different sources;

components that were included in YLD estimates. It provided estimates of the number of people suffering from specific clinical manifestations.

Even though no attempt was made to further quantify the severity of selected outcomes, the WHO Expert Committee recommended that specific disability weights be assigned to each clinical manifestation, as a means to address shortcomings of GBD estimates of morbidity burden (WHO Expert Committee, 2002).

IV. 2. Available empirical data and estimation strategies

A systematic review of available empirical evidence and estimation strategies developed to fill information gaps is a first step in the effort to generate better estimates of schistosomiasis mortality and morbidity burdens (Table 4).

Table 4: Schistosomiasis burden – data requirements and limitations

Data type	Parameters	Available data / Comments
Epidemiological parameters	Incidence	NA – insidious beginning of infection
	Prevalence	At least one estimate is available, for a subset of the population, in all endemic countries
	Remission rates	NA
	Case fatality rates	Limited to a few small population-based studies
	Deaths by cause	Incomplete reporting of deaths due to schistosomiasis in most countries
Disease progression	Major sequelae	Only partially defined – no consensus yet
	Age at onset	Small number of epidemiological studies
	Duration	Poorly documented
	Severity	GBD disability weights

A. Schistosomiasis Mortality

Case definition

Mortality estimates provided in the GBD follow the International Classification of Disease (ICD) rules for cause of death attribution. Accordingly, the case definition for schistosomiasis in the GBD specified that mortality estimates were limited to direct mortality from schistosomiasis and did not include mortality from bladder cancer, renal failure, cirrhosis or colon cancer that may be related to schistosomiasis. Estimates provided by the WHO Expert Committee considered the full impact of schistosomiasis on mortality, and thus included direct mortality from schistosomiasis as well as deaths from bladder cancer, for which schistosomiasis infection is a risk factor (Ross et al., 2002; el-Mawla, 2001; Mostafa et al., 1999, Cohen et al. 1992).

Available data

Reporting of deaths and causes of deaths in most developing countries is incomplete, particularly in SSA.

Estimation strategies

The GBD combined demographic methods and cause-of-death models to estimate the number of deaths by cause, age and sex in different regions (Murray and Lopez, 1996a). Estimates provided in the WHO Expert Committee Report were based on extrapolation from the prevalence of selected clinical manifestations (van der Werf et al., 2002, 2003a) (Table 5).

Table 5. Mortality caused by schistosomiasis infection: estimation strategies

	Empirical database	Estimation strategies	Model constraints	Criteria for cause of death attribution
GBD	Reported deaths (Egypt) and small number of epidemiological studies providing CFR	Two step process: 1) Demographic models for all cause mortality; 2) Epidemiological models for cause-specific mortality, derived from all cause mortality	Number of deaths constrained by all cause mortality 15,000 deaths	Limited to direct mortality from S. Did not include mortality from bladder cancer, cirrhosis and colon cancer that may be related to S.
WHO Expert Committee	Epidemiological studies	Extrapolation from results of mathematical models formalizing the relationship between (i) prevalence of infection and (ii) prevalence of selected signs and symptoms	No constraints 150,000-200,000 deaths	Includes deaths due bladder cancer related to schistosomiasis infection and other consequences

The estimated 13,000 deaths due to bladder cancer included by the WHO Expert Committee take into account that schistosomiasis is a risk factor for bladder cancer and should certainly be included to represent its full impact. The inclusion of bladder cancer deaths, however, does not explain the tenfold difference in mortality estimates between GBD and WHO Expert Committee (Table 3). Rather, they result from constraints (or the lack thereof) imposed on indirect estimations. GBD mortality estimates were constrained by age and sex specific estimates of total deaths for all causes combined, so that the sum of cause-specific deaths could not exceed the total number of deaths.

B. Schistosomiasis Morbidity

Quantifying the morbidity burden is by far the most difficult component of burden estimation for any cause and is particularly challenging for schistosomiasis. It includes four components:

- (1) Descriptive epidemiology – to determine the number of people suffering from disabling non-fatal health outcomes of schistosomiasis;
- (2) Knowledge of disease progression in affected populations – to define the age at onset and duration of major disabling non-fatal health outcomes;
- (3) Selection of sequelae – to define non-fatal health outcomes that should be included in morbidity estimates;
- (4) Choice of disability severity weights – to quantify the severity of selected sequelae, relative to other causes of disability.

Available data and estimation strategies that were developed for each component are presented below.

B.1. Epidemiological parameters

Available data

Schistosomiasis infection² is often asymptomatic, so that incidence (the number of new cases occurring each year) is not known. Prevalence of schistosomiasis infection is, therefore, the only readily available epidemiological parameter (and even that measure is incomplete).

The prevalence and intensity of schistosomiasis infection has been measured in all endemic countries, at least in one population group, at one point in time, over the past twenty years. Multiple estimates are available for most countries. Although the focal nature of schistosomiasis infection and the great heterogeneity in spatial distribution of schistosomiasis infection within a country have been given some attention, these nevertheless, greatly limit the ability to generate reliable national estimates of schistosomiasis prevalence from sub-national prevalence estimates. The exact number of people infected thus remains difficult to quantify, as very few countries have sufficiently detailed mapping of prevalence based on field studies to develop reliable national estimates.

In 1987, the *Atlas of the global distribution of schistosomiasis* was published, based on a compilation of all empirical evidence that was available at the time regarding the prevalence and distribution of major forms of schistosomiasis (Doumenge et al, 1987). It represented the culmination of an effort initiated by the WHO Parasitic Disease Programme in 1976 to assess the global distribution of schistosomiasis. Data sources included surveys reported in the published literature; official reports from WHO Member States; and other unpublished reports from various sources. This Atlas still represents the most comprehensive source of reference currently available, even though the data are at least two decades old. These historical data provide the basis for most national estimates. The total number of people infected with schistosomiasis, based on the average

² The gold standard for diagnosis of schistosomiasis infection is the detection of S. eggs excreted in stools for intestinal strains (*S. mansoni*; *S. japonicum*), and in the urine for urinary strains (*S. haematobium*). The number of eggs excreted measures the intensity of infection. These parameters are easily measured with limited laboratory equipment.

prevalence of infection in each country, were first compiled to quantify global needs for praziquantel treatment – an estimated 200 million people infected worldwide (Utoska et al. 1989).

Estimation strategies

Three main strategies have been used in recent years to estimate national, regional, and global prevalence of schistosomiasis (Table 6):

- 1) Extrapolation from limited epidemiological data (Engels et al. 2002; Chitsulo et al., 2000);
- 2) Epidemiological disease models (GBD, 1990); and
- 3) Models based on geographic information systems (GIS) and remote sensing (RS) (Brooker et al. 2002a, 2000a, 2000c).

Table 6. Prevalence of Schistosomiasis infection: empirical data and estimation strategies

Empirical data	Estimation strategies	Estimates	Main limitations	
1) Average population prevalence of S. infection 2) 1995 population estimates	1) extrapolation from Schistosomiasis Atlas prevalence data and more recent estimates to generate national estimates for each country	Number of prevalent cases – global and by region, for S. M and S.H	No sex distribution. Although age was taken into account, estimates were not published Ignores heterogeneity of spatial distribution	Engels et al., 2002 Chitsulo et al. 2000
1) Most recent S. prevalence data by age and sex for each region (surveys and/or estimates from Natl. S. Control Programs)	2) Epidemiological model to generate regional estimates	Number of prevalent cases, global and by region, by age and sex for all S. strains combined	No estimates for each major schistosoma strains. Ignores heterogeneity of spatial distribution	Mott, 1995
1) S. prevalence data 2) 2000 population density estimates by country	3) GIS/RS combined with prediction models	Spatial distribution of prevalent cases by country and region for SSA	Limited number of validation studies	Brooker & al., 2002a, 2000a, 2000c

1) Extrapolation from historical data

In the absence of accurate epidemiological data, the most recent estimates provided by the WHO Expert Committee were derived through direct extrapolation from estimates developed by Utoska et al. (1989), applied to the 1995 population (Engels et al., 2002; Chitsulo et al., 2000).

2) Epidemiological disease model

GBD estimates for the year 1990 were based on an exhaustive review of the most recent available empirical evidence from community-based surveys and national control programs. Epidemiological parameters provided by different sources were checked for internal consistency, in order to generate the most plausible estimates (Mott, 1995). These have been updated yearly since 1999, to reflect demographic changes only.

3) Models based on geographic information systems (GIS) and remote sensing (RS)

Geographic information systems (GIS) and remote sensing (RS) make it possible to map the heterogeneity of spatial distribution of diseases based on ecological parameters. Neither simple extrapolation from historical data nor disease models fully took into account the heterogeneity of spatial distribution of schistosomiasis infection when assessing prevalence by country or region. GIS and RS have been widely used to map the distribution of malaria in SSA, and have been applied to estimate national prevalence of schistosomiasis infection more accurately in Cameroon, Chad, and Tanzania (Brooker, 2002 b, 2002c, 2001; Beasley 2002). This approach is promising but still needs to be validated through field observation before it can be widely applied to produce revised estimates of *S.* prevalence in SSA.

B.2. Disease progression

In addition to epidemiological parameters, knowledge about the natural history of the disease and the impact of treatment is needed to model disease progression in affected communities. This is particularly important since schistosomiasis infection is not equivalent to schistosomiasis disease. Interactions between the parasite, the host and the environment determine the pace and severity of schistosomiasis disease progression, following infection (Ross et al, 2002).

Invasion, migration and maturation of the parasite first induce an acute disease phase (acute schistosomiasis), followed years later by a chronic disease phase (chronic schistosomiasis). The chronic phase can be further divided into early and late stages of disease. Each successive phase represents the outcome of the host immunological responses to *S.* egg deposition in tissues, which induces pathological changes. These manifest as signs and symptoms. Acute intestinal schistosomiasis (*S. mansoni* and *S. japonicum*) may cause abdominal pain, bloody diarrhea, and tender hepato-splenomegaly. In its chronic form, intestinal strains may cause obstruction to blood flow, splenomegaly, hypersplenism, bleeding from oesophageal varices. Urinary strains (*S. haematobium*) may manifest as dysuria and hematuria in both the acute and chronic stages, and cause renal colic, hydronephrosis, and renal failure in the late stages of disease progression (Table 5).

Table 5: Summary overview of Schistosomiasis disease progression

Schistosomiasis - all forms

	Parasite	Host response	Pathological tissue changes	Signs and symptoms	Resulting morbidity			Disability weight
					<i>S.mansoni</i>	<i>S. japonicum</i>	<i>S. haematobium</i>	
Invasion	1. Cercariae released in water penetrate skin; 2. become schistosomula, migrate through lung, heart, liver; 3. worms mature in the liver; 4. migrate to mesenteric vessels of the bowel or bladder where female lay eggs			rash, dermatitis	none or minimal	none or minimal	none or minimal	No
Acute phase of infection	female parasite laying eggs: some retained in tissues, others excreted in feces or urine	immune reaction	granuloma formation around eggs trapped in the liver and intestinal wall	Katamaya fever: fever, headache, generalized myalgias, abdominal pain, bloody diarrhea; tender hepatomegaly, splenomegaly (30% of cases); Growth retardation and anemia during childhood	none or minimal	moderate, short term	none or minimal	No
Chronic phase of infection: S. mansoni and S. japonicum: Gastrointestinal and liver disease								
Early stages		cellular granulomatous reaction around eggs, in response to antigens eggs secrete	fibrotic deposition in host tissues: intestine and liver (Symmers fibrosis: clay-pipe-stem fibrosis) for S.M and S.J; genitourinary tract for S.H periportal collagen deposits lead to progressive obstruction of blood flow, portal hypertension and varices	Abdominal pain, diarrhea, blood in stool; hepatomegaly				No
Late Stages				Splenomegaly, ascites, and bleeding from oesophageal varices	moderate to severe	moderate to severe		Yes
S. haematobium: Genitourinary disease								
Early stages		cellular granulomatous reaction around eggs, in response to antigens eggs secrete		Dysuria and haematuria				
Late Stages			calcification of the bladder, obstruction of the ureter, hydronephrosis	Dysuria and haematuria proteinuria; renal colic, renal failure (late stage)			moderate to severe	Yes

None of the clinical manifestations of schistosomiasis is specific. They can be due to other causes, in particular intestinal nematode infections and malaria, which often co-exist with schistosomiasis. This compounds the difficulty of assessing disease progression in affected populations. Therefore, although disease progression has been well described in individuals, it has been much less well documented in affected communities.

Available data

Several, often small, population-based studies provide descriptive statistics about the distribution of observed clinical signs and self-reported symptoms in populations with documented schistosomiasis infection of variable prevalence and severity.

The lack of specificity of self-reported and observed clinical manifestations, greatly limit their validity as a tool to assess disease progression. Even though earlier post-mortem studies pointed to a direct relationship between intensity of infection and severity of post-mortem findings, recent studies demonstrated important variations in the severity and time-lag of outcomes between endemic populations with similar prevalence and intensity of infection in Kenya and Egypt (Kariuki et al., 2001). Disease progression has multiple determinants: it is a function of complex interactions between schistosoma strains; genetic and immunological determinants of the human host; and the environment broadly defined (Blanton et al, 2002).

In contrast, pathological changes induced by schistosoma egg deposition in tissues are specific (peri-portal hepatic fibrosis and bladder calcification). Parameters like egg-counts measure the level of infection but do not provide direct evidence about pathological changes. Ultrasonography has replaced invasive techniques (i.e hepatic biopsy, urography) as the gold standard to objectively assess the severity distribution of schistosomiasis disease in communities³. Population-based studies using portable ultrasonography, conducted during the 1990s, have contributed an objective assessment of disease progression in communities (Table 6).

Comparative studies of clinical examination of liver and spleen size and ultrasonography findings showed that clinical manifestations were not a reliable indicator of the severity of periportal fibrosis (Lambertucci et al. 2001; Gerspacher-Lara et al. 1998).

Ultrasonographic assessments of the distribution of stages of periportal hepatic fibrosis in several communities where *S.mansoni* was prevalent in Sudan, Northern Senegal, Uganda, Tanzania and Brazil confirmed that a large proportion of the population had no periportal fibrosis (ranging between 30 and 64 percent). The remainder had mostly mild

³ Since it was first introduced in the late 1980s, ultrasonography has been applied in numerous studies to stage the severity of peri-portal fibrosis in communities. The cumulative experience acquired by many investigators has led to the development of successive protocols to standardize measurements, and improve the comparability of findings from different studies (WHO, 2000).

periportal fibrosis, and only 2 percent or less had advanced periportal fibrosis (Mohamed-Ali et al., 1999; Rouquet et al, 1993; Tanabe et al, 1997). Studies that reported the age-specific distribution of the severity of fibrosis demonstrate that, in the absence of treatment, periportal fibrosis progresses over time. For instance, ultrasonographic studies in Tanzania showed that while 70 percent of children below age twenty had no fibrosis and only 0.2 percent had severe fibrosis, the population distribution shifted with age: only 30 percent of adults age 40 and older had no fibrosis and 4 percent had severe fibrosis (Kardorff et al., 1997). A similar progression of the age prevalence of stages of hepatic fibrosis was documented in Sudan (Mohamed-Ali et al., 1999), and in China (Wiest et al., 1993). The population with liver fibrosis decreased sharply in older ages. This could be explained by spontaneous reversal of pathology, but is much more likely due to schistosomiasis mortality following irreversible damage (Table 7).

Table 6: Disease progression: empirical data and estimation strategies from population-based surveys

Empirical data	Estimation strategies	Comments
Self- reported symptoms; observed clinical manifestations	Contributed to the development of mathematical expressions formalizing observed relationships between prevalence of sign and symptoms, and prevalence of infection	None specific for schistosomiasis, but associated;
Ultrasonography assessments of liver fibrosis, and spleen size (S.mansoni and S.japonicum); or bladder and urinary tract (S.haematobium)	The development of model of disease progression for each schistosoma strain is possible, but has not yet been applied to estimate schistosomiasis burden, compatible with GBD methodology.	Periportal hepatic fibrosis and bladder calcifications are pathognomonic; Ultrasonography studies showed limitations of clinical manifestation, as a means to assess disease progression

The slow progressive development of pathology following infection has been well is an important feature of schistosomiasis and has been well documented (Richter, 2000), . There is a long lag time, lasting between 5 and 15 years, between the age at which prevalence is highest, and the age when pathological changes induced by egg deposition cause clinical manifestations. Pathology may progress even in the absence of ongoing infection, so that clinical disease may persist after successful interruption of transmission, referred to as “post-transmission schistosomiasis” (Giboda et al., 2000). For instance, in Japan, several chronic schistosomiasis cases persisted as long as twenty-five years after the end of schistosomiasis transmission in 1977 (Hayashi et al., 2000).

Table 7. Distribution of the prevalence of periportal fibrosis in selected untreated populations affected with S.mansoni

Country (year)	Study population	Prevalence of infection	F0 %	F1 %	F2 %	F3 %
Sudan, Gezira State (98)	Al Tawaheel, entire population, (792)	High prevalence (71%), low intensity (<100 eggs/g)	30.4	58.2	9.2	2.2
Senegal, Northern (93) *	Richard Toll, entire population, (50,000)	High prevalence, moderate intensity, 3 years after introduction of infection	67.0	33.0	0.0	0.0
Brazil, North-East (97)	4 villages, entire population, (573)	High prevalence, moderate intensity	48.0	47.0	5.0	0.0
Uganda, Nile District (91)	Rhino camp and Obongi (10,000)	High prevalence (82%), low intensity (<100 eggs/g)	51.5	29.5	17.0	2.0
Tanzania, Lake Victoria (94)	Ukerewe Island, entire population (1,695),	High prevalence (84%), high intensity(175 eggs/g)	64.0	29.8	5.1	1.1
	<i>of which:</i>					
	10 years or less		86.4	13.3	0.2	0.0
	11-20 years		70.8	25.6	3.3	0.2
	21-40 years		54.9	37.5	6.3	1.3
	>40 years		34.0	49.0	13.0	4.0

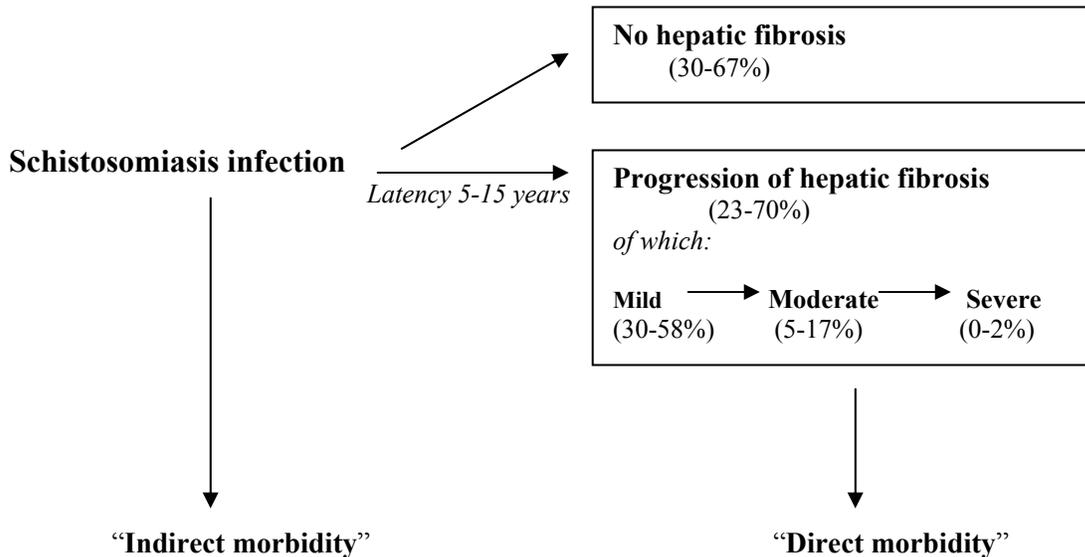
* The very recent introduction of infection explains the absence of more severe fibrosis in this population
 F0: no periportal fibrosis; F1: mild periportal fibrosis; F2: moderate periportal fibrosis; F3: severe periportal fibrosis

It was estimated that approximately 40 percent of the 200 million people infected with schistosomiasis worldwide remain asymptomatic (80 million); 60 percent become symptomatic (120 million), and approximately 10 percent develop severe disease (20 million) (Chitsulo et al., 2002). The empirical evidence and methods from which these estimates were derived were not provided in the paper and therefore are obscure. However, they concur with findings from ultrasonography studies, which show that a significant proportion of the endemic populations did not develop periportal hepatic fibrosis, and that only a small fraction of the population had severe forms of periportal hepatic fibrosis.

Models of disease progression

Estimates from ultrasonography studies in populations with various levels of prevalence and intensity of infection with schistosoma mansoni (Table 7), provide the basis to develop a model of the progression of hepatic fibrosis in those communities (Figure 1). Similar models could be developed for other schistosoma strains.

Figure 1. Model of the progression of hepatic fibrosis following infection with *S. mansoni*



Initial approaches to epidemiological modeling based on microsimulation were not pursued (Habbema et al., 1996). Neither the GBD, nor any other source, has yet developed and applied population-based models of disease progression to estimate the schistosomiasis morbidity burden. Population-based ultrasonography studies of hepatic fibrosis are a recent evaluation tool, which were not widely available at the time when the first GBD estimates of schistosomiasis burden were conducted.

B.3. Selection of sequelae

There is no agreement regarding the list of sequelae that should be included in morbidity assessments. The selection raises issues of definition of morbidity; and desirable levels of aggregation of disabling sequelae. The limited availability of empirical evidence about the population distribution and duration of different non-fatal health outcome has been and remains a strong limiting factor in the final selection of sequelae.

In the GBD, sequelae refer non-fatal health outcomes that cause disability. Disability was defined in the International Classification of Impairments, Disabilities and Handicap as “as any restriction or lack (resulting from an impairment) of ability to perform an activity in the manner or within the range considered normal for a human being” (ICIDH, World Health Organization 1980)⁴. Sequelae resulting from schistosomiasis include:

⁴ The ICDH distinguishes three dimensions of the consequences of disease: impairment, disability and handicap. Disability was defined as any restriction or lack (resulting from an impairment) of ability to perform an activity in the manner or within the range considered normal for a human being.

- a) “direct morbidity” - which refers to non-fatal health outcomes resulting from pathological changes and clinical manifestations induced by schistosomiasis egg deposition in tissues; and
- b) “indirect morbidity”- includes (i) nutritional consequences of schistosomiasis infection (anemia, growth retardation), and (ii) functional consequences (educational impairment and productivity loss). This term used in the literature has not been clearly defined. It includes some ambiguities about boundaries and causal relationships with schistosomiasis in part because they are non-specific and there are complex interactions with other diseases. Causal mechanisms have not been fully elucidated.

“Indirect morbidity” resulting from heavy worm loads of all schistosoma strains potentially represents the largest share of total S. disability burden. It may affect a sizable share of all those infected, even in the absence of any other clinical manifestation. Children and adolescents are the most vulnerable age group. Indirect sequelae are sometimes referred to as “subtle morbidity” because, so far, they have been difficult to quantify, and are based on observed associations rather than established causality. The fact that other widely prevalent worm infections (ascariasis, trichuriasis, and hookworm disease) may result in the same disabling outcomes and often occur simultaneously with schistosomiasis compounds the problem of causality attribution.

A review conducted by Kenneth Warren for the chapter on Helminth Infection in “*Disease Control Priorities in Developing Countries*” concluded that (a) heavy infection with schistosomiasis was clearly implicated in productivity loss; (b) impaired learning was probably important only in heavy infections; (c) there was no conclusive evidence that schistosomiasis reduced school attendance (Jamison et al., 1993). New data available from large scale studies of combined therapy suggest that deworming improves school attendance (Miguel et al., 2001)

Nutritional consequences: growth retardation and anemia

The association between schistosomiasis infection and nutritional status varies as a function of age and S.strain, intensity of infection, and coinfection with other infectious diseases has been well documented. The most vulnerable age groups are children and adolescents, and the evidence is strongest for S.haematobium and S. japonicum. Heavy infection with S. haematobium and S. japonicum cause growth faltering through protein loss and altered endocrine function in children. Cross-sectional studies conducted in the Philippines (Leyte) and China (Jiangxi province) showed that S.japonicum disrupted nutritional status and growth throughout childhood and adolescence, independent of the

An impairment is any loss or abnormality of psychological, physiological or anatomical structure or function. A handicap is a disadvantage for a given individual resulting from an impairment or disability that limits or prevents the fulfillment of a role that is normal (depending on age, sex, and social and cultural factors) for that individual (ICIDH)

influence of other soil-transmitted infections (Ascaris and Trichuriasis). The studies hypothesized that lost growth potential might result in poorer health, affected cognitive and intellectual functions among children, and reduced productivity among adults (McGarvey et al., 1992; McGarvey et al., 1993).

Only two randomized, double-blind trials were conducted in Northeastern Brazil (Assis et al., 1998) and in the Philippines (McGarvey et al., 1996). Both studies concluded that schistosomiasis infection resulted in poor nutritional status and growth retardation among school age children, independent of infection with other intestinal nematodes infections. Several cross-sectional studies have also demonstrated the existence of a strong association between high intensity schistosomiasis infection and those outcomes (Jukes et al., 2002; Stephenson, 1993; McGarvey, 1992). Children with heavy worm burdens and poor nutritional status were found to be most likely to suffer cognitive impairments.

The long-term impact on growth, nutrition and cognitive development, or the impact of treatment and possible rebound morbidity after discontinuation of control measures has not been established. The longest published longitudinal study was conducted in the Philippines and lasted eight years (Olveda et al, 1996).

The comparison between the list of morbid signs and symptoms provided in a survey of disease experts (van der Werf, 2002) (Table 9), and the list of sequelae that were included in GBD estimates of schistosomiasis, other tropical diseases, and soil transmitted helminthes (Table 10), illustrate some of the complexities underlying the election of sequelae included in morbidity burden estimates for schistosomiasis, as well as between schistosomiasis and other intestinal nematode infections.

B.4. Disability Weights

The GBD included disability weights for over 300 different sequelae in order to quantify and compare their severity. Disability weights ranged between 0 (perfect health) and 1 (equivalent to death), on a continuous scale. These were derived from disability weights that had been formally quantified using a standard protocol for twenty-two indicator conditions, by an international group of health professionals. Validation of the relative rankings of indicator conditions developed by numerous groups of health professionals from a wide array of developed and developing countries, using the same standard protocol, confirmed the robustness of the approach. However, Charles King stated in a recent presentation “recent studies have cast doubt on the ability of experts to reliably predict the life path of patients with chronic infections of low mortality” (King, personal communication).

Schistosomiasis infection is the only sequela, that was included for schistosomiasis in the GBD. It was assigned a disability weight of 0.005 (between ages 5-14) and 0.006 (for all ages 15 years and older) – which imply that, overall, schistosomiasis infection caused only limited disability in endemic populations

The choice of a low disability weight represents the population distribution of severity of S. morbidity, which ranges from no disability at all to severe hepatic and urinary disease. The severity weight represents a weighted average of all possible non-fatal health outcomes triggered by S. infection, and were based on the limited availability of empirical evidence regarding the distribution of disabling outcomes (Murray and Lopez, 1996a).

Table 9: Non-fatal health outcomes of schistosomiasis provided by disease experts and parameters included in WHO Expert Committee estimates of schistosomiasis morbidity

Morbidity (Signs and symptoms from survey of disease experts) <i>Schistosoma hematobium</i>	Morbidity (Signs and symptoms from survey of disease experts) <i>Schistosoma mansonia</i>	Parameters included in estimates
DIRECT MORBIDITY		
Cercarial dermatitis	Cercarial dermatitis	
Pneumonia	Pneumonia	
	Katamaya fever	
Haematuria		<i>For S. Heamatoibium:</i> Haematuria
Dysuria		Dysuria
Urinary frequency		Major bladder pathology
		Hydronephrosis
		<i>For S. Mansoni</i>
	Blood in stools	Blood in stool
	Abdominal pain	Abdomial pain
	Ascites	Splenomagaly
	Oedema	Hepatomegaly
	Oesophagal varices	
	Haematemesis	Haematemesis
<i>Genital lesions</i>		
Pain		
Pruritus		
Bleeding		
Purulent discharged		
<i>Nervous system</i>	<i>Nervous system</i>	
Convulsion, paralysis	Convulsion paralysis	
INDIRECT MORBIDITY		
Anemia	Anemia	
Reduction of growth	Reduction of growth	
Impaired school work and performance		
Impaired cognitive development	Impaired cognitive development	
Reduced physical fitness	Reduced physical fitness	

Source: Van der Werf, 2002

Table 10: Tropical disease cluster and soil transmitted helminths: sequelae included in GBD morbidity burden estimates

Cause	Sequelae
Schistosomiasis	Infection
Ascariasis	High intensity infection Contemporaneous cognitive deficit Cognitive impairment Intestinal obstruction
Trichuriasis	High intensity infection Contemporaneous cognitive deficit Cognitive impairment Massive dysentery syndrome
Ancylostomiasis and necatoriasis	High intensity infection Cognitive impairment Anemia
Chagas disease	Infection Cardiomyopathy without congestive heart failure Cardiomyopathy with congestive heart failure Megaviscera
Leishmaniasis	Visceral Cutaneous
Lymphatic filariasis	Hydrocele >15cm Bancroftar Lymphoedema Bruglar Lymphoedema
Onchocerciasis	Blindness Itching Low vision
Trypanosomiasis	Episodes

Source: Global Health Statistics, 1996

The WHO Expert Committee recommended that the next step should be the development of disability weights for a wider range of specific sequelae. It did not discuss how disability weights should be defined, nor did it suggest specific values, because differences with GBD methodology had not been reconciled.

B.5. Morbidity estimates

Estimation strategies

A review of the major components that should ideally be included in estimates of morbidity burden underscores the complexity of morbidity burden estimation, and important knowledge gaps that have yet to be addressed (Table 11).

Table 11. Morbidity caused by Schistosomiasis infection: empirical data estimation strategies

	Empirical data	Units of measurement	Estimation strategies
GBD	Epidemiological studies	YLD – aggregate estimate only; no sequelae other than infection were specified.	Simplified disease model in which infection lasts one year, and has a low overall disability weight
Van der Werf	Epidemiological studies	Number of people affected with selected signs or symptoms	Mathematical model based on observed relationship between prevalence of infection and selected signs and symptoms.

GBD – simplified disease model

The GBD quantified morbidity burden as disability-adjusted life year - or years lost to disability (YLD). YLD is a time-based measure, which expresses morbidity in terms of numbers of years lived with a disability of defined duration and severity, rather than simply the number of people affected by it. The number of YLD for any non-fatal health outcome is equal to the product of i) number of people affected, ii) time spent in a given health state, and iii) its severity.

A simplified disease model, based on two key basic assumptions, was developed to quantify schistosomiasis morbidity burden in the GBD:

- a) the incidence of S. infection was assumed to have an average duration of one year, and thus was approximately equal to prevalence (incidence of S. infection is not known, whereas prevalence is readily available); and
- b) infection was the only non-fatal health outcome that was specified. The duration of “infection” was arbitrarily set to last one year, and had a single low disability weight, which was applied to all ages and both sexes.

The GBD attributed all disability resulting from schistosomiasis to “schistosomiasis infection” because the empirical evidence was deemed insufficient for the inclusion of any specific sequelae when the first estimates of S. burden were compiled for the GBD during the mid 1990s.

WHO Expert committee - mathematical model

The basic assumption underlying morbidity estimates developed by van der Werf and included in the WHO Expert Committee report, was the existence of a relationship between (i) the prevalence of infection as a proxy for intensity, and (ii) the prevalence of self-reported and observed clinical manifestations of schistosomiasis. This relationship was formalized by a mathematical expression based on pooled results from all available epidemiological studies, which provided estimates for both components. The final list of disabling outcomes was driven by data availability and was also the rationale for falling back on prevalence-base models. Mathematical expressions were applied to estimates of schistosomiasis prevalence in SSA, in order to calculate the total number of people with selected clinical manifestations in the region.

Selected signs and symptoms included:

- a) dysuria, hematuria, bladder morbidity and hydronephrosis for the urinary form of schistosomiasis (*S. haematobium*); and
- b) diarrhea, blood in stool, hepatomegaly, splenomegaly, ascites, and haematemesis for intestinal and hepatosplenic schistosomiasis (*S. mansoni*).

Estimates of mortality due to different causes were based on further extrapolation from estimates of the number of people with selected clinical manifestations.

The two major limitations of this approach are the selection process of outcomes, and the relevance of selected outcomes as indicators of the severity of disease progression. They nevertheless represent a significant improvement, which will certainly contribute to the further development of GBD estimates.

V. SENSITIVITY ANALYSIS

We conducted a small sensitivity study, based on hypothetical distributions of disease progression, to illustrate the direction and magnitude of change in burden estimates under different assumptions of mortality and cognitive development. Simulations were made to test changes in burden estimates that would result from the (a) tenfold increase in number of deaths (WHO Expert Committee) and (b) morbidity assuming that different proportion of endemic populations had permanent cognitive impairments

The first set of estimates simulates different population distributions of cognitive impairment (100%; 50%; 25%), while maintaining GBD mortality estimates (YLL).

The second set of estimates simulates the effect of the significantly larger (tenfold) WHO mortality estimates and the following scenarios (a) no change in GBD morbidity estimates, and (b) the same different population distributions of cognitive impairment (100%; 50%; 25%) as in the first set of simulations.

The analysis was done using the detailed GBD burden estimation spreadsheets developed to generate schistosomiasis YLL, YLD and DALY for 2002. Estimates of cognitive impairment were calculated using the GBD severity weight of 0.024, the severity weight assigned for cognitive impairments due to other helminthes. Composite disability weights were calculated reflecting the population average disability.

1. GBD YLL and YLD assuming:
 - a) cognitive impairment affecting all cases
(composite disability weight = 0.024)
 - b) cognitive impairment affecting 50 percent of cases, and mild impairment (0.006) affecting the other cases
(composite disability weight = 0.015)
 - c) cognitive impairment affecting 25 percent of cases, and mild impairment (0.006) affecting the other cases
(composite disability weight = 0.011)

2. GBD YLL *10, and YLD assuming:
 - a) GBD estimates for schistosomiasis infection
 - b) cognitive impairment affecting all cases
(disability weight = 0.024)
 - c) cognitive impairment affecting 50 percent of cases, and mild impairment (0.006) affecting the other cases
(composite disability weight = 0.015)
 - d) cognitive impairment affecting 25 percent of cases, and mild impairment (0.006) affecting the other cases
(composite disability weight = 0.011)

The sensitivity analysis shows that schistosomiasis burden would increase two to five times, both globally and in SSA, under the different assumptions (Table 12). The analysis indicates that even the number of deaths was underestimated by a factor of 10 in the GBD, as suggested by the WHO Expert Committee, and that all prevalent cases suffer permanent cognitive impairment it only would produce a five-fold increase in burden. It is more likely that revised estimates would increase by one- to two-fold. This revised estimate would make schistosomiasis the largest cause of burden within the tropical disease cluster, but would not significantly increase its importance relative to other major causes of burden, such as malaria.

There is, however, an important caveat. Estimates were based on the current GBD simplified disease model and thus fail to take into account its major shortcomings. In the absence of better understanding of key determinants of disease progression, the extent to which the inclusion of specific sequelae (which would have higher disability weights, but affect a much smaller proportion of infected people) would change current YLD estimates (based on a large number of people and low disability weight) remains unclear. For instance, assuming that schistosomiasis infection resulted in permanent cognitive impairment in only 10 percent of cases, and that the remaining 90 percent suffered no disability at all, the overall disability weight in the population would be equal to 0.0024 ($0.024 * 0.1$), which is less than the current disability weight of 0.006.

Regardless of possible changes in schistosomiasis burden estimates, there is no doubt that new knowledge gained over the past 10 years should be used to produce revised estimates of burden, and could improve the validity of estimates in the future. For example, the meta-analysis of disability-related outcomes in endemic populations undertaken by Charles King promises to contribute to future burden of disease estimates.

Table 12: Sensitivity analysis of schistosomiasis burden, selected assumption (2002)

Assumptions	Global burden estimates				SSA burden estimates				
	YLL	YLD	DALY	ratio new/GBD	YLL	YLD	DALY	ratio new/GBD	
Current GBD	223,774	1,474,254	1,698,028		119,683	1,340,081	1,459,764		
Deaths = tenfold increase (WHO estimates)	2,237,740	1,474,254	3,711,994	2.2	1,196,830	1,340,081	2,536,911	1.7	
Deaths = GBD estimates									
Cognitive impairment	100%	223,774	6,344,226	6,568,000	3.9	119,683	5,779,983	5,899,666	4.0
Cognitive impairment	50%	223,774	3,965,141	4,188,915	2.5	119,683	3,612,489	3,732,172	2.6
Cognitive impairment	25%	223,774	2,775,599	2,999,373	1.8	119,683	2,528,743	2,648,426	1.8
Deaths = tenfold increase (WHO estimates)									
Cognitive impairment	100%	2,237,740	6,344,226	8,581,966	5.1	1,196,830	5,779,983	6,976,813	4.8
Cognitive impairment	50%	2,237,740	3,965,141	6,202,881	3.7	1,196,830	3,612,489	4,809,319	3.3
Cognitive impairment	25%	2,237,740	2,775,599	5,013,339	3.0	1,196,830	2,528,743	3,725,573	2.6
GBD estimates:									
Lymphatic Filariasis			5,644,000				1,933,000		
Leishmaniasis			2,357,000				1,557,000		
Intestinal Nematodes infection			4,709,000				674,000		
Malaria			42,000,000				36,012,000		

VI. DISCUSSION

The main issues that emerge from this critical review of two main estimation strategies and the available empirical data are as follows:

1. Major shortcomings of current estimates;
2. Uncertainties about the degree to which GBD schistosomiasis captured the full impact of schistosomiasis;
3. Potential contributions of new tools and research findings to future estimates;
4. Implications for research;
5. Implications for programs.

Major shortcomings of current estimates

The large variance between schistosomiasis burden estimates of the GBD and the WHO Expert Committee is disturbing and has to be addressed.

- Although the tenfold difference in estimates of schistosomiasis mortality is the most striking, it was primarily due to the methods applied and could be reconciled. The GBD approach, based on demographic and cause-of-death model, is much more rigorous than the extrapolation from epidemiological estimates that was done to generate estimates of number of deaths included in the WHO Expert Committee Report. It was nevertheless limited by the lack of reliable mortality data.
- Morbidity estimates are much more problematic, and are really at the core of the current controversy regarding the plausibility of GBD estimates of schistosomiasis burden. YLD estimates were calculated by applying a single sequela (schistosomiasis infection); a low disability weight; and assumed one-year duration to all prevalent cases. The absence of further details regarding a) non-fatal health outcomes that were included as “schistosomiasis infection” and b) a low disability weight conveys a lack of transparency about morbidity components that were either included or left out, and thus does not allow one to assess the extent to which GBD morbidity estimates captured the full impact of schistosomiasis.
- The choice of a low disability weight represents the population distribution of severity of schistosomiasis morbidity, which ranges from no disability at all to severe and urinary disease. The final disability weight (0.005/0.006) thus represents a weighted average of all possible non-fatal health outcomes triggered by schistosomiasis infection. Since health outcomes included as “schistosomiasis infection” were not specified, the extent to which they took into account nutritional and functional consequences of infection is difficult to determine. Furthermore, low disability weights also indicate that severe schistosomiasis disease caused premature mortality, but caused little disability prior to death.

Did the GBD underestimate schistosomiasis burden ?

- The limited sensitivity analysis shows that changing assumptions about mortality and morbidity might lead to a five-fold increase in current estimates. Uncertainties that persist regarding the progression and severity distribution of non-fatal health outcomes in endemic populations, however, do not allow us to reliably define the direction and magnitude of changes in burden estimates that would result.
- Another approach to get a partial answer to the question that schistosomiasis burden may have been underestimated relative to other causes is to compare schistosomiasis burden estimates and estimates for intestinal nematode infections that are often co-morbid with schistosomiasis and cause similar outcomes. Several important differences in the computation of the morbidity burden caused by the three major intestinal nematode infections (ascariasis, trichuriasis, and hookworm) and by schistosomiasis are worth noting.

First the range of sequelae specified in morbidity estimates for ascariasis, trichuriasis, and hookworm was much more detailed than it was for schistosomiasis. It included effects of infection on cognitive development (contemporaneous cognitive deficit and cognitive impairment), as well as disability caused by severe pathology (intestinal obstruction; massive dysentery syndrome, and anemia) (Table 11).

Table 11: Sequelae and disability weights for Schistosomiasis and soil-transmitted helminthes

Condition	Sequelae	Disability weight	% cases
Schistosomiasis	Infection	0.005/0.006*	100
Ascariasis	High intensity infection		
	Contemporaneous cognitive deficit	0.006	87.2
	Cognitive impairment	0.024	8.3
Trichuriasis	Intestinal obstruction	0.463	4.3
	High intensity infection		
	Contemporaneous cognitive deficit	0.006	79.7
Ancylostomiasis and nectoriasis	Cognitive impairment	0.024	4.6
	Massive dysentery syndrome	0.138	15.7
	Anemia	0.024	97.8

* under age 15 years/15 years and above

Source: Global Health Statistics, 1996

Disability weights for schistosomiasis infection (0.005/0.006) were equivalent to disability weights assigned to contemporaneous cognitive deficit, which is reversible. Cognitive impairment, which is irreversible, and anemia were assigned the same higher disability weight (0.024). Cognitive impairment caused the largest share of morbidity burden resulting from high intensity infection with ascariasis (85 percent) and trichuriasis (87.4 percent). Higher disability weights were also assigned to major organic sequelae of ascariasis and trichuriasis (intestinal obstruction (0.463), and massive dysentery syndrome (0.138)).

The second important difference worth noting is the selection criteria of severity of infection: only “high intensity infection” was included for intestinal nematodes, whereas schistosomiasis infection comprised all levels of infection intensity (mild, moderate, and severe). These differing criteria limit the direct comparability of resulting disability estimates between schistosomiasis and major intestinal nematode infections

Potential contributions of new tools and research findings to future estimates

- Important advances in the available empirical evidence gathered since schistosomiasis burden estimates were developed for the GBD in the mid-1990s. This new evidence will provide a stronger foundation, to inform future revisions of the schistosomiasis burden:
 - 1) The application of ultrasonography to objectively assess disease progression in communities;
 - 2) Geographic mapping (GIS and RS) coupled with epidemiological assessments to refine estimates of schistosomiasis prevalence;
 - 3) Epidemiological studies in endemic populations, including controlled clinical trials to assess causality of schistosomiasis infection in the development of indirect morbidity, and longitudinal studies to better define the severity and duration of cognitive deficits;
 - 4) The meta-analysis of disability-related outcomes in endemic populations, undertaken to develop an independent estimate of disability due to schistosomiasis, conducted by Charles King, promises to further contribute to a revision of burden estimates (not yet published). It will be interesting to see the degree of concurrence with findings of the thorough review of the literature conducted by van der Werf to develop mathematical models.

Implications for research

Research is needed to inform future revisions of burden estimates includes short-term, as well as medium to long-term objectives.

- Short-term objectives

1. Research to inform the selection of sequelae:

Research is needed to compile all available evidence regarding the distribution and severity of non-fatal health outcomes in endemic populations. This research will inform the selection of sequelae that should be included in revisions of schistosomiasis burden. The meta-analysis undertaken by Charles King is one example of this inquiry.

2. Research to inform the choice and valuation of disability weights.

The framework that was developed to define disability weights for diseases in the Netherlands might provide a strategy that could be applied to develop more detailed disability weights for schistosomiasis. It applied the EQ-5D questionnaire developed by the EuroQol group to value health (Krabbe et al, 1999, Stouthard et al. 1997).

- Medium to long-term

Promising new tools (GIS/RS; ultrasonography; makers of disease progression) still require further development and valuation (GIS/RS; ultrasonography; makers of disease progression).

These new tools should be applied, within the confines of ethically sound studies that do not withhold treatment of those in need, to (i) objectively assess morbidity in endemic populations; (ii) better understand determinants of disease progression; and (iii) monitor and evaluate the impact of interventions on disease progression.

Implications for programs

Disease control programs and burden of disease estimation should be closely linked. Epidemiological data collected by programs will enrich the knowledge base needed to improve burden of disease assessments, and schistosomiasis burden estimates will be important to inform program development, monitoring and evaluation:

- Better estimates of the severity and distribution of schistosomiasis burden may have important implications for program design and evaluation, through better targeting of population groups at highest risk for severe disease progression.
- Burden estimates provide the denominator for the comparative cost-effectiveness analysis of different interventions. Therefore, the development of reliable local burden estimates, coupled with costing analysis, could inform choices to improve the cost-effectiveness of national schistosomiasis control programs.

Praziquantel treatment is currently the cornerstone of schistosomiasis control. It effectively reduces the intensity of schistosomiasis infection, is relatively simple to administer, and is low cost. In spite of these advantages, the prevalence of schistosomiasis remains high in most parts of Sub-Saharan Africa where the disease is endemic. Other reasons that might explain the limited impact of praziquantel treatment in the region is the heterogeneity of schistosomiasis prevalence within countries and affected communities. This means that either the distribution of disease within communities must be known or a large number of individuals, mostly school-age children, have to be treated in order to reach the relatively small number of those who would benefit most from treatment. As a result, the low cost of praziquantel might be offset by the large number of those treated, which may decrease the cost-effectiveness of schistosomiasis control programs. Detailed mapping of the distribution of schistosomiasis within countries, coupled with reliable markers of disease progression, might contribute to better targeting of individuals at highest risk.

- In the absence of long-term follow-up studies of disease progression in treated populations it is difficult to assess the impact of treatment. Of particular concern are the few short-term follow-up studies that have shown the existence of “rebound morbidity” only a few years after treatment ended (Olveda et al., 1996), and the potential development of drug resistance (King et al., 2000; Renganathan et al., 1998; Bindley et al. 1994).
- Finally, the primary focus of schistosomiasis control programs on school-age children leaves out the assessment of curative or palliative interventions that might reduce the severity of outcomes of disease progression and prevent premature death among the small percent of adults with severe disease. Further operational research is needed to improve the effectiveness of passive detection and treatment of patients presenting at health care facilities (van der Werf et al., 2003b). The cost-effectiveness of splenectomy and surgical interventions to prevent bleeding from oesophageal varices might be worthwhile considering, particularly in endemic populations where prevalence and intensity of infection have been successfully reduced. For instance, S. disease is the most frequent underlying cause of splenectomy in Northern Brazil where schistosomiasis mansoni infection persists. Splenectomy and surgical removal of esophageal varices is the intervention of choice to prevent mortality from bleeding in advanced cases of portal hypertension (Lacerda et al., 2002).

VII. MAIN CONCLUSIONS

- There are two main sources for global and regional estimates of schistosomiasis burden: the Global Burden of Disease and the WHO Expert Committee on the Prevention and Control of Schistosomiasis and Soil-Transmitted Helminthiasis. These two sources agree on four major points:
 1. Quantifying the burden of disease is important, as it is being increasingly used for policy decisions regarding the allocation of resources;
 2. Both mortality and morbidity burden should be taken into account;
 3. Morbidity represents the largest share of schistosomiasis burden; and
 4. More accurate estimates of schistosomiasis burden would be highly desirable.
- The two sources disagree on their assessments of both mortality and morbidity. Mortality estimates have a tenfold difference, which is largely explained by the level of constraints within very different estimation methods. Morbidity estimates are not directly comparable due to different parameters chosen to quantify morbidity. Estimates of the total number of prevalent cases of schistosomiasis infection were relatively consistent for the two sources.
- This assessment concludes that schistosomiasis burden may have been underestimated in the GBD of 1990, although data problems make it difficult to demonstrate the degree of underestimation.
- Sensitivity analysis on key variables suggests that it is unlikely that more accurate estimates would significantly change the ranking of schistosomiasis burden, in contrast to the expectations of the WHO Expert Committee. A one and a half to two-fold increase in schistosomiasis burden is most likely. This revision could make schistosomiasis the largest source of burden of disease among tropical diseases (not including malaria).
- Schistosomiasis certainly represents a major cause of burden in some geographic areas. Neither of the two approaches developed by the GBD and the WHO Expert Committee provide ways of dealing with the focal nature of schistosomiasis infection. Better epidemiological data are needed in all countries. GIS and RS have the potential to better model the heterogeneity of schistosomiasis within countries.
- Better estimates of the schistosomiasis mortality and morbidity burden are needed, and should include a more detailed assessment of different sequelae contributing to schistosomiasis burden, as well as separate estimates for each of the three major schistosoma strains (*S. mansoni*, *S. haematobium*, and *S. japonicum*). New methods for assessing morbidity related to schistosomiasis are under development and should help improve accuracy in future estimates of burden.
- Information to further illuminate disease progression could strengthen the ability to target populations at highest risk for severe disability.

REFERENCES

- Beasley M, Brooker S, Ndinaromtan M, Mafjiouroum EM, Baboguel M, DjenguinabeE, Bundy DA (2002) *First nationwide survey of the health of schoolchildren in Chad*. Trop Med Int Health Jul;7(7);625-630.
- Brindley PJ (1994) *Drug resistance to schistosomicides and other anthelmintics of medical significance*. Acta Tropica 56: 213-31.
- Blanton RE, Salam EA, Kariuki HC, Magak P, Silva LK, Muchiri EM, Thiongo F, Abdel-Meghid IE, Butterworth AE, Reis MG, Ouma JH.(2002) *Population-based differences in Schistosoma mansoni- and hepatitis C-induced disease*. J Infect Dis. Jun 1;185(11):1644-9.
- Brooker S. (2002a) *Schistosomes, snail. and satellites*.Acta Trop. May;82(2):207-14.
- Brooker S, Hay SI, Bundy DA.(2002b) *Tools from ecology: useful for evaluating infection risk models?* Trends Parasitol. Feb;18(2):70-4.
- Brooker S, Beasley M, Ndinaromtan M, Madjiouroum EM, Baboguel M, Djenguinabe Hay SI, Bundy DA. (2002c) *Use of remote sensing and a geographical information system in a national heminth control programme in Chad*. Bull World Health Organ. 80(10)783-9.
- Brooker S, Hay SI, Issae W, Hall A, Kihamia CM, Lwambo NJ, Wint W, Rogers DJ, Bundy DA. (2001) *Predicting the distribution of urinary schistosomiasis in Tanzania using satellite sensor data*. Trop Med Int Health.Dec;6(12):998-1007.
- Brooker S, Rowlands M, Haller L, Savioli L, Bundy DA. (2000a) *Towards an atlas of human helminth infection in sub-Saharan Africa: the use of geographical information systems (GIS)*. Parasitol Today. Jul;16(7);303-7.
- Brooker S, Donnelly CA, Guyatt HL. (2000b) *Estimating the number of helminthic infections in the Republic of Cameroon from data on infection prevalence in schoolchildren*. Bull World Health Organ.78(12):1456-65.
- Brooker S, Michael E. (2000c) *The potential of geographical information systems and remote sensing in the epidemiology and control of human helminth infections*. Adv Parasitol. 47:245-88.
- Chitsulo L, Engels D, Montessor A, Savioli L. (2000) *The global status of schistosomiasis control and its control*. Acta Ttop. Oct.23;77(1):41-51.
- Cohen SM, Johansson SL. (1992) *Epidemiology and etiology of bladder cancer*. Urol Clin North Am. August; 19(3):421-28.
- Doumenge JP, Mott KE, Cheung C, Chapuis O, Perrin MF, Reaud-Thomas G. (1987) *Atlas of the global distribution of schsitosomiasis*. CEGET-CNRS/WHO. PUB, Talence.
- Engels D, Chitsulo L, Montresor A, Savioli L. (2002) *The global epidemiological situation of schsitosomiasis and new approaches to control and research*. Acta Trop. May;82(2):139-46.

el-Mawla NG, el-Bolkainy MN, Khaled HM.(2001) *Bladder cancer in Africa: update*. Semin Oncol. Apr;28(2):174-8.

Field MJ, Gold MR,eds.(1998) *Summarizing population health: directions for the development and application of population metrics*. National Academy Press, Washington, DC.

Gerspacher-Lara R, Pinto-Silva RA, Serufo JC, Rayes AA, Drummond SC, Lambertucci JR.(1998) *Splenic palpation for the evaluation of morbidity due to schistosomiasis mansoni*. Mem Inst Oswaldo Cruz.;93 Suppl 1:245-8.

Giboda M, Berquist NR.(2000) *Post-transmission schistosomiasis: a new agenda*. Acta Trop. Oct.23;77(1):3-7.

Gross CP, Anderson GF, Power NR. (1999) *The relation between funding by the National Institutes of Health and the burden of disease*. N Engl J. Med. Jun.17;340(24):1914-5.

Habbema JD, De Vlas SJ, Plaisier AP, Van Oortmarsen GJ. (1996) *The microsimulation approach to epidemiologic modeling of helminthic infections, with special reference to schistosomiasis*. Am J Trop Med Hyg. Nov;55(5 Suppl):165-9.

Hayashi S, Ohtake H, Koike M. (2000) *Laparoscopic diagnosis and clinical course of chronic schistosomiasis japonica*. Acta Trop. Oct.23;77(1):133-40.

Jamison DT, Mosley H, Measham AR, Bobadilla JL eds. (1993) *Disease Control Priorities in Developing Countries*, Oxford University Press, New York.

Jukes MC, Nokes CA, Alcock KJ, Lambo JK, Kihamia C, Ngorosho N, Mbise A, Lorri W, Yona E, Mwanri L, Baddeley AD, Hall A, Bundy DA; Partnership for Child Development (2002) *Heavy schistosomiasis associated with poor short-term memory and slower reaction times in Tanzanian schoolchildren* Trop Med Int Health. Feb;7(2):104-17.

Lacerda CM, Freire W, Vieira de Melo PS, Lacerda HR, Carvalho G. (2002) *Splenectomy and ligation of the left gastric vein in schistosomiasis mansoni: the effect on esophageal variceal pressure measured by a non-invasive technique*. Keio J Med. Jun;51(2):89-92.

Lambertucci JR, Cota GF, Pinto-Silva RA, Serufo JC, Gerspacher-Lara R, Costa Drummond S, Antunes CM, Nobre V, Rayes A. (2001) *Hepatosplenic schistosomiasis in field-based studies: a combined clinical and sonographic definition*. Mem Inst Oswaldo Cruz. 96 Suppl:147-50.

Kariuki HC, Mbugua G, Magak P, Bailey JA, Muchiri EM, Thiongo FW, King CH, Butterworth AE, Ouma JH, Blanton RE, 2001. *Prevalence and familial aggregation of schistosomal liver morbidity in Kenya: evaluation by new ultrasound criteria*. J Infect Dis 183: 960-6.

Kardorff R, Gabone RM, Mugashe C, Obiga D, Ramarokoto CE, Mahlert C, Spannbrucker N, Lang A, Gunzler V, Gryseels B, Ehrich JH, Doehring E. (1997) *Schistosoma mansoni-related morbidity on Ukerewe Island, Tanzania: clinical, ultrasonographical and biochemical parameters*. Trop Med Int Health. Mar;2(3):230-9.

- King CH, Muchiri EM, Ouma JH (2000). *Evidence against rapid emergence of praziquantel resistance in Schistosoma haematobium, Kenya*. Emerging Infectious Diseases 6: 585-94.
- Krabbe PF, Stouthard ME, Essink-Bot ML, Bonsel GJ.(1999) *The effect of adding a cognitive dimension to the EuroQol multiattribute health-status classification system*. J Clin Epidemiol. Apr;52(4):293-301.
- McGarvey ST, Aligui G, Graham KK, Peters P, Olds GR, Olveda R (1996). *Schistosomiasis japonica and childhood nutritional status in northeastern Leyte, the Philippines: a randomized trial of praziquantel versus placebo*. Am J Trop Med Hyg. May;54(5):498-502.
- McGarvey ST, Wu G, Zhang S, Wang Y, Peters P, Olds GR, Wiest PM.(1993) *Child growth, nutritional status, and schistosomiasis japonica in Jiangxi, People's Republic of China*. Am J Trop Med Hyg. Apr;48(4):547-53.
- McGarvey ST, Aligui G, Daniel BL, Peters P, Olveda R, Olds GR. (1992) *Child growth and schistosomiasis japonica in northeastern Leyte, the Philippines: cross-sectional results*. Am J Trop Med Hyg. May;46(5):571-81.
- McGarvey ST. (1992) *Nutritional status and child growth in schistosomiasis*. R I Med. 19Apr;75(4):187-90.
- Miguel E., Kremer M.(2001) *Worms: education and health externalities in Kenya*. NBER working paper w8481, Cambridge MA.
- Mohamed-Ali Q, Elwali NE, Abdelhameed AA, Mergani A, Rahoud S, Elagib KE, Saeed OK, Abel L, Magzoub MM, Dessein AJ.(1999) *Susceptibility to periportal (Symmers) fibrosis in human schistosoma mansoni infections: evidence that intensity and duration of infection, gender, and inherited factors are critical in disease progression*. J Infect Dis. Oct;180(4):1298-306.
- Mostafa MH, Sheweita SA, O'Connor PJ (1999) *Relationship between schistosomiasis and bladder cancer*. Clin Microbiol Rev. Jan;12(1):97-111.
- Mott KE (1995) *Schistosomiasis*. Background paper prepared for the Global Burden of Disease. Unpublished
- Murray CJL, Salomon JA, Mathers D, and Lopez AD eds. (2003) *Summary measures of population health: concepts, ethics, measurement and applications*. World Health Organization, Geneva.
- Murray CJL, Salomon JA, Mathers C. (2000) *A critical examination of summary measures of population health*. Bull World Health Organ; 78(8)981-94.
- Murray CJL, Lopez AD eds. (1996a) *The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020*.

Global Burden of Disease and Injury, Vol.1. Harvard School of Public Health on behalf of the World Health Organization and the World Bank Cambridge, MA.

Murray CJL, Lopez AD eds. (1996b) *Global health statistics: a compendium of incidence, prevalence and mortality estimates for over 200 conditions*. Global Burden of Disease and Injury Series, Vol.2. Harvard School of Public Health on behalf of the World Health Organization and the World Bank Cambridge, MA.

Murray CJL, Lopez AD eds. (1996c) *The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020, Summary*. Harvard School of Public Health on behalf of the World Health Organization and the World Bank Cambridge, MA.

Olveda RM, Daniel BL, Ramirez BD, Aligui GD, Acosta LP, Fevidal P, Tiu E, de Veyra F, Peters PA, Romulo R, Domingo E, Wiest PM, Olds GR. (1996) *Schistosomiasis japonica in the Philippines: the long-term impact of population-based chemotherapy on infection, transmission, and morbidity*. J Infect Dis. Jul;174(1):163-72.

Olveda RM, Tiu E, Fevidal P Jr, de Veyra F Jr, Icatlo FC Jr, Domingo EO. (1983) *Relationship of prevalence and intensity of infection to morbidity in schistosomiasis japonica: a study of three communities in Leyte, Philippines*. Am J Trop Med Hyg. 1983 Nov;32(6):1312-21.

Renganathan E, Cioli D (1998). *An international initiative on praziquantel use*. Parasitology Today 14: 390-1.

Remme JH, Blas E, Chitsulo L, Desjeux PM, Engers HD, Kanyok TP, Kengeya Kayondo JF, Kioy DW, Kumaraswami V, Lazdins JK, Nunn PP, Odula A, Ridely RG, Toure YT, Zicker F, Morel CM (2002) *Strategic emphases for tropical diseases research: a TDR perspective*. Trends Parasitol. Oct;18(10):421-6.

Richter J (2000) *Evolution of schistosomiasis-induced pathology after therapy and interruption of exposure to schistosomes: a review of ultrasonographic studies*. Acta Trop. Oct 23;77(1):111-31.

Ross AG, Bartley PB, Sleight AC, Olds GR, Li Y, Williams GM, McManus DP. (2002) *Schistosomiasis*. N Engl J Med April 18;346(16):1212-20.

Rouquet P, Verle P, Kongs A, Talla I, Niang M. (1993) *Hepatosplenic alterations determined by ultrasonography in a population recently infected with Schistosoma mansoni in Richard-Toll, Senegal*. Trans R Soc Trop Med Hyg. Mar-Apr;87(2):190-3.

Stephenson L (1993) *The impact of schistosomiasis on human nutrition*. Parasitology;107 Suppl:S107-23.

Stouthard MEA, Essink-Bok ML, Barendregt JJ, Kramers PGN, van der Water HPA, Gunning-Schepers LJ, van der Maas P (1997) *Disability weights for diseases in the Netherlands*. Department of Public Health, Erasmus U., Rotterdam.

Tanabe M, Goncalves JF, Goncalves FJ, Tateno S, Takeuchi T. (1997) *Occurrence of a community with high morbidity associated with Schistosoma mansoni infection regardless of low infection intensity in north-east Brazil*. Trans R Soc Trop Med Hyg. Mar-Apr;91(2):144-9.

Utroska JA, Chen MG, Dixon H, Yoon S, Helling-Borda M, Hogerzeil HV, Mott KE. (1989) *An estimate of global needs for praziquantel within schistosomiasis control programmes*. World Health Organization WHO/Schisto/89.102.

van der Werf MJ, de Vlas SJ, Brooker S, Looman CW, Nagelkerke NJ, Habbema JD, Engels D. (2003a) *Quantification of clinical morbidity associated with schistosome infection in sub-Saharan Africa*. Acta Trop. May;86(2-3):125-139.

van der Werf MJ, Bosompem KM, de Vlas SJ. (2003b) *Schistosomiasis control in Ghana: case management and means for diagnosis and treatment within the health system*. Trans R Soc Trop Med Hyg. Mar-Apr;97(2):146-52.

van der Werf MJ, de Vlas SJ, Looman CW, Nagelkerke NJ, Habbema JD, Engels D. (2002) *Associating community prevalence of schistoma mansoni infection with prevalence of signs and symptoms*. Acta Trop. May;82(2):127-37.

Wiest PM, Wu G, Zhong S, McGarvey ST, Tan E, Yuan J, Peters P, Olveda RM, Olds GR. (1993) *Schistosomiasis japonica on Jishan Island, Jiangxi Province, People's Republic of China: persistence of hepatic fibrosis after reduction of the prevalence of infection with age*. Trans R Soc Trop Med Hyg. 1993 May-Jun;87(3):290-4.

WHO Expert Committee (2002) *Prevention and Control of Schistosomiasis and Soil Transmitted Helminthiasis*. World Health Organ Tech Rep Ser.;912:i-vi,1-57,back cover.. Geneva.

WHO (World Health Organization) (2002). *The World Health Report 2002 Reducing risks, promoting healthy life*. Geneva

WHO (World Health Organization) (2000) *Ultrasound in Schistosomiasis. A practical guide to the standardized use of ultrasonography for assessment of schistosomiasis-related morbidity*. Workshop Report TDR/STR/SCH/00.1