Morbidity and infection with schistosomes or soil-transmitted helminths.

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Summary

We investigated the relationship between presence of helminth infection and morbidity in human populations, with the aim to estimate the number of individuals with helminth related morbidity. The results will be used in the *WHO Global Burden* initiative to predict the health burden for endemic countries/regions on the basis of parasitological information available. The work was a joint activity of (1) Department of Public Health, Erasmus University Rotterdam, Netherlands (2) Parasitic Diseases and Vector Control, WHO, Geneva, Switzerland, and (3) Department of Infectious Disease Epidemiology, Imperial College School of Medicine, London, UK.

Helminths are predominant human parasites of the tropical zone. Schistosomiasis (by *Schistosoma mansoni*, *S. japonicum* and *S. haematobium*) and infection by the soil transmitted helminths hookworm (*Necator americanus* and *Ancylostoma duodenale*), roundworm (*Ascaris lumbricoides*) and whipworm (*Trichuris trichiura*) can be a significant burden to the health in human populations. Although death from helminth infection is relatively rare, various (complex) pathological processes cause a wide spectrum of morbidity in the human host, ranging from acute mild symptoms to chronic severe disease after many years of (intense) infection. Appendix A1-A3 lists the various sequelae mentioned by various experts in the field of schistosomiasis and soil transmitted helminths.
Briefly, schistosomiasis causes morbidity by eggs that are deposed in the small venules of the mesenteric circulation (*S. mansoni* and *S. japonicum*) or in the vesical venules (*S. haematobium*). They induce a granulomatous response. For *S. mansoni* and *S. japonicum* this will result in symptoms such as intermittent (sometimes bloody) diarrhoea or blood in stool and abdominal pain starting early after infection. Later on, eggs disposed in the liver can cause hepatomegaly and splenomegaly due to periportal fibrosis. The resulting periportal hypertension can eventually induce ascitis and hematemesis. Eggs in ectopic locations can cause convulsions and paralysis (Jordan *et al.*, 1993).
The *S. haematobium* eggs trapped in the bladder wall will give rise to inflammation of the bladder mucosa, haemorrhages and ulcerations, which result in haematuria and dysuria. In a later stage, granulomas around eggs in the ureter can cause mechanical obstruction of the ureter resulting in hydro-ureter and also hydro-nephrosis. The obstruction can eventually result in a non-functioning kidney and death. Other sequelae related to *S. haematobium* infection are squamous cell type bladder carcinoma and changes in the genital organs.
S. haematobium eggs can also migrate to the skin, central nervous system and the spinal cord and cause ectopic lesions such as papular and nodular lesions in the skin, convulsions and paralysis (Jordan *et al.*, 1993).
The main morbidity related to hookworm infection is anemia caused by the feeding activities of fourth stage larvae (L_4) and adult worms on the gastrointestinal mucosa and the subsequent bleeding from the wounds so produced (Pritchard *et al.*, 1990).
Morbidity caused by *Ascaris lumbricoides* can be divided in two groups: 1) subtle morbidity, e.g. growth reduction, impaired cognitive development and reduced physical fitness and 2) clinically overt, acute disease mainly caused by a high number of worms (intestinal obstruction) or worms that migrated to the biliary or pancreatic duct or the appendix (de Silva *et al.*, 1997a).

All published and unpublished articles on field studies relating helminth infection and morbidity were collected after extensive literature search (Appendix A4) and all quantitative information was stored in a common database (Appendix A5). If possible, the data were aggregated by means of the mathematical expression representing the prevalence of morbidity P_{morb} as a function of the prevalence of infection P_{inf} in a community:

$$P_{morb} = (a + b \cdot P_{inf}^{c}) / (1 + b \cdot P_{inf}^{c})$$

Here, a denotes the prevalence of morbidity resulting from other causes than the infection studied ($P_{inf} \rightarrow 0$); parameters b and c ($c > 0$) determine the increase of disease with rising prevalence of infection. Subsequently, the expression

$$P_{morb} = (b \cdot P_{inf}^{c}) / (1 + b \cdot P_{inf}^{c})$$

is used to predict the prevalence of disease in any (sub)community with known prevalence of infection. A justification of the use of the above expressions can be found in Appendix A6. In some cases, the data did not justify the use of above expression and the relationship was considered non-conclusive. For instance, if anything, abdominal pain seemed to decrease with *S. mansoni* infection. Sometimes the lack of sufficient data from high *S. japonicum* prevalence areas urged us to partially base relationships on the findings for *S. mansoni*. In case of insufficient data on advanced sequelae, but consensus on the relevance of a particular association, morbidity or mortality was predicted through a simple association with expected prevalence of high egg excreters (see the specific chapters of Appendix B).

As many studies report different ways of expressing the same kind of morbidity (e.g. diarrhoea by questionnaire or directly observed, and during the past day or the past month, etc.), it was necessary to make the following general decisions (Appendix A7):

- In case of diarrhoea and blood in stool or urine, the results of questionnaires were preferred to direct observations.
- The period closest to two weeks was used if different recall periods were reported.
- Diarrhoea and blood in stool were used for the calculations of morbidity from intestinal schistosomiasis; to prevent overlap, bloody diarrhoea was not considered.
- The measurement of hepatomegaly at mid-sternal level (MSL) was used for the analysis as it is thought to be more related to infection with intestinal schistosomes than mid-clavicular level (MCL).
- In case of different hemoglobin cut-off values to define anemia from hookworm, the most conservative cut-off value was used.

In addition, to make data from different sources comparable and to reduce bias, it was necessary to process prevalences of infection in two ways:

- Prevalences had to be standardised to a default sensitivity of parasitological diagnosis (i.e. a single 41.7 mg Kato-Katz stool examination for *S. mansoni* and *S. japonicum*; the other infections did not require such standardisation) by means of a stochastic model on egg count variation (Appendix A8).
- The relationship between prevalence of infection and disease had to be adjusted for heterogeneity in infection levels of communities within countries, as only mean prevalences for countries were available (Appendix A9).

Table 1 summarises the estimates of the number of individuals with specific morbidity from *S. haematobium*, *S. mansoni* and hookworm using the above procedure (see Appendix A10 for parameter values used). Given the data available, we believe that most of the morbidity estimates are adequate for use in global burden calculations. For estimates of severe morbidity (including death), more systematic data collection is necessary. Furthermore, the methodology developed is potentially useful for policy making.

Table 1: Summary of the estimated total number (in millions) of individuals with morbidity due to *S. haematobium*, *S. mansoni* and hookworm infection. Appendix C gives estimates per WHO Region (Afr D, Afr E and Emr D) and by age group (pre-school, school and adults). Where possible a 90% confidence interval is given.

	Estimated total number (5%-95%)
S. haematobium	
At risk of infection	*452*
Infected	*111*
Haematuria in last 2 weeks	70 (53-82)
Dysuria in last 2 weeks	24 (17-55)
Minor bladder morbidity (US)	76 (67-92)
Major bladder morbidity (US)	24 (15-30)
Moderate hydronephrosis (US)	9.1#
Major hydronephrosis (US)	9.5#
Non-functioning kidney	[1.7]
Non-functioning kidney (deaths/year)	[0.15]
Bladder cancer, males (deaths/year)	[0.011]
Bladder cancer, females (deaths/year)	[0.0023]
S. mansoni	
At risk of infection	*409*
Infected	*54*
Diarrhoea in last 2 weeks	0.81 (0.0-7.8)
Blood in stool in last 2 weeks	4.4 (3.0-8.5)
Hepatomegaly (MSL)	8.5#
Splenomegaly	[6.4]
Ascitis	[0.081]
Hematemesis ever	[0.43]
Hematemesis (deaths/year)	[0.060]
Hookworm	
At risk of infection	*632*
Infected	*163*
Anemia	45 (19-58)

Confidence intervals could not be calculated

[ ] Use with caution, see remarks in Appendix B

Appendix A: Methods and data

A1 Identification of sequelae

Global burden of disease definition of sequelae is "a condition which causes loss of welfare".

To identify the main sequelae we studied:
Progress in assessment of morbidity due to *Schistosoma mansoni* infection: A review of recent literature (WHO/SCHISTO/88.97)
Progress in assessment of morbidity due to *Schistosoma haematobium* infection: A review of recent literature (WHO/SCHISTO/88.91)
Progress in assessment of morbidity due to *Schistosoma japonicum* infection: A review of recent literature (WHO/SCHISTO/88.95)
M.G. Chen and Kenneth E. Mott: Progress in assessment of morbidity due to *Schistosoma japonicum* infection: A review of the recent literature (1988) Tropical Diseases Bulletin, Vol 85, No 6, P.R1-R45
A. Montresor *et al.*: Helminth control in school-age children, a guide for managers of control programmes
M. Kruijshaar, S.J. de Vlas: Modelling the development of schistosomiasis morbidity
P.E.C. Manson Bar & D.R. Bel: Manson's Tropical Diseases nineteenth edition 1987, William Clowes Ltd, Beccles and Londen

This information was used to prepare a list with the main sequelae per species. The lists were send by email to experts in schistosomiasis and morbidity and soil-transmitted helminth (STH) and morbidity.

Experts contacted for schistosomiasis:
B. Gryseels
E. Doehring
J. Richter
C. Hatz
H. Feldmeier
R. Lambertucci
Chen Ming Gang

Experts contacted for STH:
D. Crompton
R. Stoltzfus
F. Curtale
L. Stephenson
M. Albonico
D. Bundy
R. Olds

The replies were combined with the information from the literature to produce a list with main sequelae for schistosomiasis and soil-transmitted helminth infections (see appendix A2 & A3).

A2 Sequelae due to schistosomiasis

Schistosoma haematobium

	Pathology	Morbidity
Stage of invasion		– Cercarial dermatitis – Pneumonia
Early	Bladder lesions (hyperaemia, sandy patches, granuloma, ulcer, nodules, polyps, calcification)	– Haematuria (macroscopic) – Dysuria – Urinary frequency
Early and late		– Anemia
Late	Bladder cancer	
	Obstructive uropathy without hydronephrosis Obstructive uropathy with hydronephrosis	
	Genital lesions (female: vulva, vagina, cervix)	– Pain – Pruritis – Bleeding – Purulent discharge
	Ectopic lesions (CNS)	– Convulsions, paralysis
	General	– Reduction of growth – Impaired school and work performance
Subtle		– Reduction of growth – Impaired cognitive development – Reduced physical fitness
Mortality	Renal failure	
	Bladder cancer	

The experts on *S. haematobium* morbidity mentioned the following morbidity, which is not included in the table.

H. Feldmeier:
Secondary pyelonephritis
Hepatosplenomegaly
Periportal fibrosis
Appendicitis
Alterations of the rectosigmoid colon (inflammation, polyps)
Pulmonary artheritis, pulmonary hypertension, cor pulmonale
Males: enlargement and inflammation of the prostrate, the seminal vesicles, the vas deferens, hydrocele, enlargement of epididymis
Females: various types of alterations in the tubes and ovaries (obstruction, enlargement, cysts), infertility (primary, secondary), ectopic pregnancy, pregnancy complication (abortion, stillbirth, preterm delivery), vesico-vaginal fistula

C. Hatz:
Septicaemia

Schistosoma mansoni

	Pathology	Morbidity
Stage of invasion		– Cercarial dermatitis – Pneumonia
Acute	Due to foreign antigens and metabolites excreted when egg production starts	Katayama fever: fever, chills, weakness, weight loss, headache, anorexia, nausea, vomiting, diarrhoea, dry cough, hepatosplenomegaly, bloody diarrhoea, urticaria, peri-orbital oedema, bronchospasm
Early	Colonic polyposis Focal fibrosis Granulomatous inflammation	– (Bloody) diarrhoea – Blood in stool – Abdominal pain
Early and late		– Anemia
Late	Portal hypertension	– Ascites – Oedema – Oesophageal varices – Hematemesis
	Ectopic lesions (CNS)	– Convulsions, paralysis
Subtle		– Reduction of growth – Impaired cognitive development – Reduced physical fitness
Mortality	Liver failure	
	Cor pulmonale	
	Oesophageal bleeding/hematemesis	

The experts on *S. mansoni* morbidity mentioned the following morbidity, which is not included in the table.

H. Feldmeier:
Bladder alterations
Obstructive uropathy
Schistosomal nephropathy
Chronic carrier status of Salmonella and other gram-negative enterobacteriaceae

J. R. Lambertucci:
Association with Salmonella
Pyogenic liver abscess
Myelopathy
Glomerulonephritis
Ectopic lesions, skin involvement
Sepsis (Salmonella, E. coli, Staphylococ)

Schistosoma japonicum

	Pathology	Morbidity
Stage of invasion		– Cercarial dermatitis – Pneumonia
Acute	Due to foreign antigens and metabolites excreted when egg production starts	Katayama fever: fever, chills, weakness, weight loss, headache, anorexia, nausea, vomiting, diarrhoea, dry cough, hepatosplenomegaly, bloody diarrhoea, urticaria, peri-orbital oedema, bronchospasm
Early	Colonic polyposis Focal fibrosis Granulomatous inflammation	– (Bloody) diarrhoea – Blood in stool – Abdominal pain
Early and late		– Anemia
Late	Portal hypertension	– Ascites – Oedema – Oesophageal varices – Hematemesis
	Pulmonary hypertension	– Fatigue – Cough – Dyspnoe
	Ectopic lesions (CNS)	– Convulsions, paralysis
Subtle		– Reduction of growth – Impaired cognitive development – Reduced physical fitness
Mortality	Acute infection	
	Liver failure	
	Cor pulmonale	
	Oesophageal bleeding / hematemesis	

The experts on *S. japonicum* morbidity mentioned the following morbidity, which is not included in the table.

H. Feldmeier:
Bladder alterations
Obstructive uropathy
Schistosomal nephropathy
Chronic carrier status of Salmonella and other gram-negative enterobacteriaceae
Rectal cancer
Liver cancer

A3 Sequelae due to soil transmitted helminth infections

Hookworm (*Ancylostoma duodenale* and *Necator americanus*)
- Anemia (hypochromic microcytic)
- Subtle morbidity: growth reduction, impaired cognitive development, reduced physical fitness

The experts on hookworm morbidity mentioned also the following morbidity:

R. J. Stoltzfus:
Low birth weight infants (if the mother is infected)

L. S. Stephenson:
Reduced appetite
In pregnancy (combined with severe anemia) increased maternal and foetal morbidity and mortality

M. Albonico:
Blood in stool (cause of anemia)
Protein loss enteropathy

Ascaris lumbricoides
- Acute disease: intestinal obstruction, volvulus, intussusception
- Subtle morbidity: growth reduction, impaired cognitive development, reduced physical fitness

The experts on Ascaris morbidity mentioned also the following morbidity:

F. Curtale:
Xerophthalmia (in areas where vitamin A deficiency is prevalent)

D. W. T. Crompton:
Malabsorption

Trichuris trichiura
- Dysentry
- Rectal prolapse
- Anemia
- Subtle morbidity: growth reduction, impaired cognitive development, reduced physical fitness

A4 Literature searched and studied for information on morbidity

1) Pubmed search (24 July 2000):

- Schistosomiasis and cancer (835 hits)
- Schistosomiasis and anemia or anaemia or blood loss (494 hits)
- Schistosomiasis and dysuria, schistosomiasis and abdominal pain, schistosomiasis and haematura or hematuria, schistosomiasis and ultrasound, schistosomiasis and echographique, schistosomiasis and hydronephrosis, schistosomiasis and diarrhoea, schistosomiasis and hepatomegaly (4707 hits)
- Hookworm and anemia or anaemia (374 hits)
- Hookworm and morbidity, trichuris and morbidity, ascaris and morbidity, trichuris and dysentry, trichuris and prolapse, trichuris and anemia or anaemia, ascaris and malnutrition, ascaris and obstruction (172 hits)

2) Cabhealth search (see for keywords Pubmed search)

3) Articles form "Collected papers on the control of Soil Transmitted Helminthiases" (The Asian Parasite Control Organisation).

4) Selection of articles from collection of Simon Brooker, University of Oxford, department of zoology. The collection contained articles collected for:

- GIS studies on schistosomiasis and prevalence
- hookworm and anaemia study
- study on iron deficiency anemia in African school-aged children: The contribution of parasitic infections (S. Brooker & H. Guyatt)
- study on prevalence and intensity of STH infection, whole community studies
- school health and cognitive/educational achievement (www.ceid.ox.ac.uk/schoolhealth/bibliography/)
- school health and anthropometric status/growth (www.ceid.ox.ac.uk/schoolhealth/bibliography/)
- school health and iron & anemia (www.ceid.ox.ac.uk/schoolhealth/bibliography/)

5) Articles on schistosomiasis and morbidity available at CERMES library, list provided by Jean Christoph Ernould.

6) Published and unpublished literature from the country maps available at Parasitic Diseases and Vector Control, CPE, WHO (Geneva).

7) Articles from references of copied articles.

Not collected:

- Case reports
- Studies on *S. haematobium* infection and microscopic haematuria

We entered all copied articles in an endnote file. This file contains information on the authors, the year of publication, the title, the name of the journal, volume and issue of the journal and page numbers. The articles received a unique identifier composed of the year of publication and a serial number (e.g. 89005, article number 5, published in 1989).

In total more than 600 articles on schistosomiasis and morbidity and soil-transmitted helminths and morbidity were collected.

A5 Data file

The information from the articles is entered in Excel to enable us to use the information for studying the relationship between prevalence and intensity of infection with schistosomiasis or soil-transmitted helminths and the morbidity caused by these infections.

The information from the articles is entered in three different files.

- Morb-anemia.xls, information on prevalence and intensity of infection of hookworm and prevalence of anemia or mean value of hemoglobin
- Morb-haematuria.xls, information on prevalence and intensity of *S. haematobium* infection and prevalence of haematuria and dysuria
- Morb-general.xls, information on prevalence and intensity of infection of *S. mansoni* and *S. japonicum* and information on diarrhoea, bloody diarrhoea, blood in stool, abdominal pain, splenomegaly and hepatomegaly.

Appendix D1 lists the codes of the variables used. Not all sequelae were included in the Excel files. We have chosen to enter information of sequelae from which a considerable number of articles is available and that are presented in a format which can be entered in the Excel file.

A6 Relating morbidity to infection

To obtain an association between morbidity and infection it is necessary to correct for the morbidity due to other causes than the infection studied (base-line morbidity). The best way to do this for acute morbidity is by showing morbidity prevalences in different intensity groups within a community, as this would allow for different baseline levels for different communities. However, there is a limited amount of such studies and finding an adequate method to obtain a statistical relationship between prevalence of morbidity and intensity of infection is complex. Moreover, for chronic morbidity this approach is not valid, as current infection is not the same as history of infection.
In appendix B, we nevertheless show graphs for each combination of morbidity and intensity of infection group (e.g. figure 1.1.1). They were used to indicate associations between type of morbidity and infection with schistosomiasis. These graphs have also been used to judge whether or not to differentiate between e.g. children and adults.

In our analysis, predictions of the number of individuals with morbidity were based on the direct relation between prevalence of morbidity and prevalence of infection on population level. The morbidity in communities with the lowest prevalence of infection then gives information on the base-line morbidity. It should be noted that this is only an "average" base line, so that any functional relationship may to some extent be diluted. The method of relating prevalences has the advantage that more studies are available. Also, most studies based on intensity groups can be included. It is however necessary to standardise for the different sensitivities of the diagnostic techniques used in the studies (see Appendix A8).

An expression related to the logistic regression curve was used to describe the relationship between prevalence of infection (x-axis) and prevalence of morbidity (y-axis). The requirements for this equation are:

1. the possibility of a baseline morbidity due to other causes, defined by parameter a ($a \geq 0.0$)
2. a horizontal start of the curve at $x = 0$ and $y = a$, so first derivative = 0.0 in $(0,a)$
3. the curve should rise monotonously and be able to finally (but not necessarily) reach a prevalence of morbidity of 1.0
4. the curve should show a biologically realistic association between prevalence of infection and prevalence of morbidity, so no steep increase before $x = 0.5$ and thereafter a levelling off. A realistic point of inflection (where the curve is steepest, so second derivative equals 0.0) should usually be on the righthand side of prevalence $x = 0.5$. This condition forces a horizontal start of the curve, which prevents the prediction of substantial morbidity at low prevalence of infection

An equation $y = a + (1 - a) \cdot \exp(f_x) / (1 + \exp(f_x)) = (a + \exp(f_x)) / (1 + \exp(f_x))$ covers the area between a (base-line morbidity) and 1. In normal logistic regression f_x is the linear predictor, e.g. $f_x = B + C \cdot x$. Due to requirement 2, we decided to use $f_x = B + C \cdot \log x$ ($C > 1$). The resulting equation $y = (a + \exp(B) \cdot x^C) / (1 + \exp(B) \cdot x^C)$ has a derivative of $y' = 0$ when $x \rightarrow 0$.

By replacing $\exp(B)$ with b ($b > 0$) and C with c ($c > 1$) this leads to the following expression between prevalence of infection (P_{inf}) and prevalence of morbidity ($P_{morb,exp}$):

$$P_{morb,exp} = (a + b \cdot P_{inf}^c) / (1 + b \cdot P_{inf}^c)$$

We have used a Systat program to fit this standard expression to all the data points of each combination of morbidity and infection. The fit was determined by assuming a binomial distribution and considering each data point equally important. The latter assumption can easily be made, since the vertical location is supposed to be determined by many more phenomena (e.g. the community base-line morbidity) than the size of the population alone. So, we have maximised the log-likelihood

$$\Sigma \{P_{morb,obs} \cdot \log(P_{morb,exp}) + (1 - P_{morb,obs}) \cdot \log(1 - P_{morb,exp})\}$$

for all observed combinations of $P_{morb,obs}$ and P_{inf}.

In case condition 4 was not met, we have chosen an alternative two parameter curve [which is a special case of standard equation $P_{morb,exp} = (a + b \cdot P_{inf}^{c}) / (1 + b \cdot P_{inf}^{c})$] with point of inflection at 1.0 (depending on the data points)

$$x_{infl} = ((c - 1) / (b \cdot (c + 1))^{1/c} = 1.0$$

so

$$b_{1.0} = (c - 1) / (c + 1) \text{ if point of inflection at } 1.0$$

In Appendix B, we present a, b and c for the best fitting standard curve, if applicable (see point 4 above). If the point of inflection is chosen at 1.0, b is presented as $b_{1.0}$.

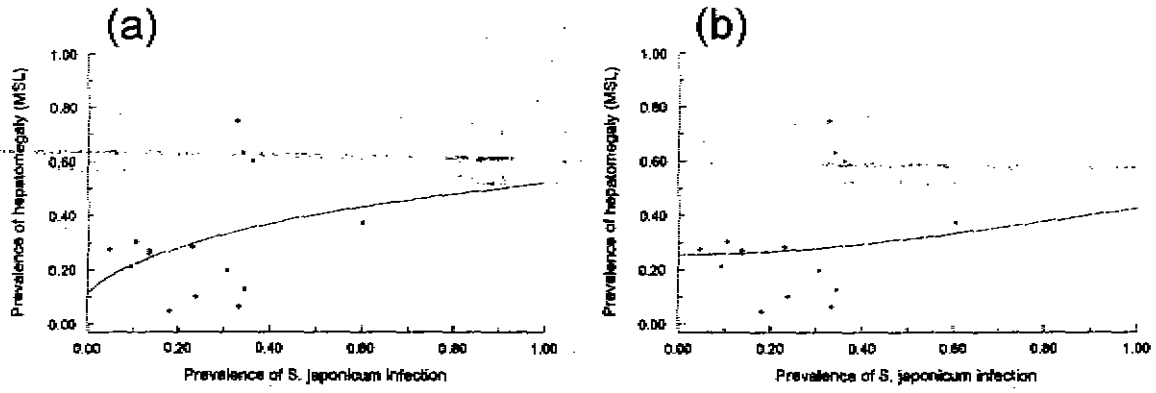

Figure 1: Example of prevalence of *S. japonicum* infection and hepatomegaly (MSL), (a) *standard curve* in which point of inflection < 0.5, and (b) *alternative curve* with point of inflection at 1.0. Curve (a) rises considerably for low prevalences of infection whereas curve (b) remains rather flat for low prevalences of infection. As many endemic populations show prevalences of infection between 0.10 and 0.30, curve (a) will give unrealistic high predictions of morbidity.

From the fitted expression, the curve

$$P_{morb,exp} = (b \cdot P_{inf}^{c}) / (1 + b \cdot P_{inf}^{c}),$$

or its alternative with $b = b_{1.0} = (c - 1) / (c + 1)$ can subsequently be used to make predictions for any community on the prevalance of morbidity in the group not yet affected by the disease

from other causes. To estimate maximum impact of schistosome infection on morbidity, we have assumed all individuals at risk of infection to be potentially at risk of morbidity.

It must be noted that, given the non-linear character of the expression, it can only be used to make inferences on the population level. In case of predictions on the level of countries, it is necessary to consider heterogeneity in prevalences within the country (see Appendix A9).

A7 Measurements of morbidity

7.1 Questionnaire or inspection method and recall period

Most information was available on signs and symptoms of early infection (diarrhoea, haematuria etc.), hepatomegaly and splenomegaly and urinary tract morbidity. These are the main signs and symptoms studied in field surveys. Researchers investigate (a random selection of) communities or school populations by using questionnaires, clinical examination or ultrasound. They examine every individual for hepatomegaly, splenomegaly, ascitis and anemia and ask if they have had (bloody) diarrhoea, blood in stool, abdominal pain, hematemesis, haematuria or dysuria in a certain period. The length of this recall period differs widely between studies. In some studies it can be as short as one day (the last 24 hours) or it can be as long as one year. More than a quarter of the studies does even not specify the period.
Diarrhoea, blood in stool and haematuria can also be studied by inspection of urine or feces. Researchers examine stool and urine specimens for composition and presence of blood. As most early symptoms are intermittent, they will not be present in every stool or urine sample and the prevalence will be lower compared to the results of the questionnaire, see figure 2.

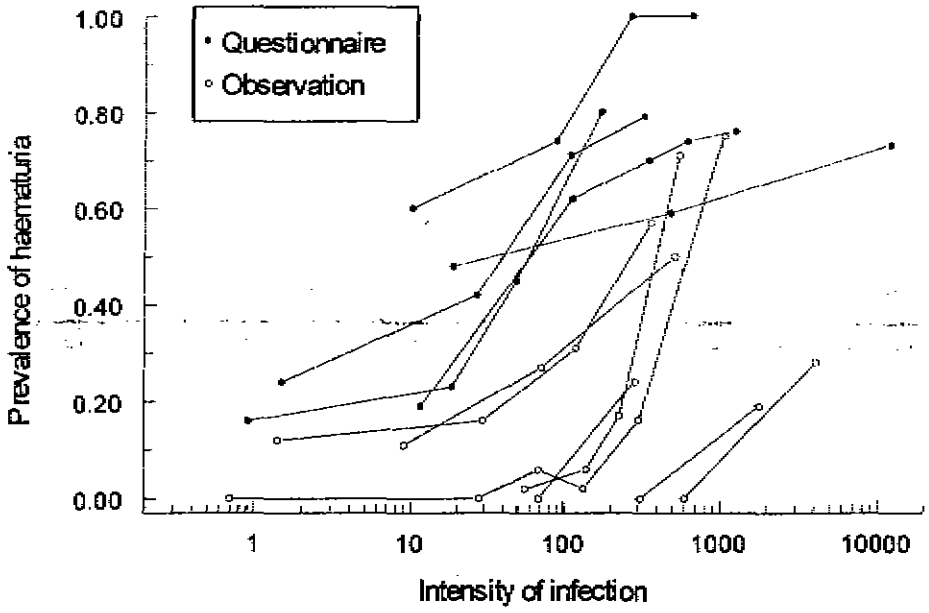

Figure 2: Prevalence of haematuria for different intensity of *S. haematobium* infection groups measured by using questionnaire or by inspection of the urine. Points from the same study are connected.

There are two disadvantages of the questionnaire method: 1) recall bias, 2) the interpretation of the question "did you have diarrhoea, blood in stool, abdominal pain, haematuria or dysuria" can differ between and within study populations.
If the interviewer asks the respondent to report symptoms, which occurred long ago, this might pose problems. It can be difficult for someone to remember if he/she had a certain symptom in the last two or more months. Therefore, the number of persons reporting signs and symptoms in the last two months might be an underestimate of the real number. It is also

possible that people do remember that they had one of the symptoms not too long ago and report that this was within the last two months although it might have been more than two months, this gives an overestimation of the prevalence of the symptom. Also, if the recall period is long, an individual can have had more than one episode of the symptom. This is normally not registered by the investigators. Long recall periods will therefore most likely give an underestimation of the real prevalence of the symptom.
The second problem is the interpretation of the questions by the respondent. The medical definitions of the different signs and symptoms normally differ from the layman's interpretation. Also the interpretation of one study population might differ from the interpretation of another which makes it difficult to compare the results (cultural difference).
Considering all advantages and disadvantages, we decided to use the results of the questionnaires for the calculation of the morbidity estimates, rather than results from direct observation (for example appendix B, figure 1.1.2 and 1.1.3). If prevalences were reported for more than one recall period we chose the recall period nearest to two weeks.

7.2 Overlap between diarrhoea, bloody diarrhoea and blood in stool

Diarrhoea, bloody diarrhoea and blood in stool are all reported as measured morbidity in the literature on intestinal schistosomiasis and morbidity. The difference between the three symptoms is gradual and probably difficult to distinguish. Most studies that report prevalence of bloody diarrhoea do not report prevalence of blood in stool and vice versa.
For the calculations of intestinal morbidity, we will concentrate on diarrhoea and blood in stool and not bloody diarrhoea. Diarrhoea and blood in stool are relatively easy to distinguish, whereas there will be overlap between diarrhoea and bloody diarrhoea and blood in stool and bloody diarrhoea. We also chose for blood in stool because it is considered to be the most specific symptom related to intestinal schistosomiasis.
Due to lack of information we were not able to calculate the relation between prevalence of blood in stool and prevalence of *S. japonicum* infection. Therefore, we assumed that the shape of the curve for the relation between prevalence of blood in stool and prevalence of infection will be the same for *S. mansoni* and *S. japonicum*, only the start of the curve is fitted at a different level (Appendix B, figure 2.1.4 and 2.1.8 and figure 2.1.6 and 2.1.9).

7.3 Hepatomegaly measured at mid-sternal level or mid-clavicular level

The prevalence of hepatomegaly is measured by clinical examination or by ultrasound. For this analysis we only used the results of studies that reported hepatomegaly by clinical examination.
Hepatomegaly can be measured in mid-sternal level (MSL) or mid-clavicular level (MCL). Enlargement at the MSL level is considered to be related to schistosomiasis infection and was therefore used for the estimations. The cut-off points for defining hepatomegaly differed between the studies (MSL: from palpable to > 5cm, MCL: from palpable to > 4 cm). Some studies reported prevalence of hepatomegaly for more than one cut-off point. The results of the lowest reported cut-off point (i.e. palpable) for the mid-sternal level were used for the analysis (Appendix B2.3).

7.4 Cut-off level for anemia

Studies on hookworm infection and prevalence of anemia used different cut-off levels below which a person is diagnosed with anemia. The values of the cut-off levels range from 7 gr/dl haemoglobin to 14 gr/dl. Sometimes one study uses different cut-off values for men, women and children. If a study reported prevalence of anemia for different cut-off levels than the results obtained by using the most conservative cut-off level were used for the calculations.

A8 Standardisation of prevalence and intensity of infection

In community or school surveys, the prevalence of infection is determined by examination of stool or urine, or by antibody or antigen detection. These diagnostic techniques will give different levels of prevalence. Very sensitive techniques will identify most infected individuals. Less sensitive techniques will leave (many) individuals with (light) infection undetected. To be able to compare prevalences obtained by different diagnostic techniques we decided to only use studies based on stool or urine examination. In addition, for intestinal schistosomiasis we have tried to standardise prevalences according to the expected outcome of a default diagnostic technique (i.e. a single 41.7 mg Kato-Katz faecal sample for *S. mansoni* and *S. japonicum*).
It is also difficult to compare intensity groups between different studies. The zero group as identified by a poor sensitive technique may contain several infected individuals who would have been part of the second category in a study with better diagnostics. Moreover, the mean egg count of individuals in an intensity group depends on the level of infection in the whole population. For instance in a low endemic situation, individuals with zero eggs in their stool or urine are most likely really uninfected. On the other hand, in a high endemic situation, zero counts are more likely to be the result of (lightly) infected individuals whose eggs were missed that particular day. It is therefore necessary to have an adequate expression of the real intensity of infection in a particular intensity of infection group. We chose to express the morbidity data as a function of the *expected* (geometric) mean intensities in each intensity group.

Both, calculation of standardised prevalences and expected mean intensities has been done by using an existing model. De Vlas *et al.* (De Vlas *et al.*, 1992) showed that the distribution of *S. mansoni* egg counts in human populations can adequately be described by a stochastic model. This model assumes repeated individual egg counts as a representation of an underlying distribution of worm (pair) burdens. The number of worms n is assumed to follow a negative binomial distribution NegBin (M, k) with mean worm load M and aggregation parameter k. The smaller the value of k, the more the worms are concentrated in a small, highly infected part of the population. High values of k mean that all individuals have about the same chance of being infected, approximating a Poisson distribution. The worm pair distribution is the result of applying a mating process to the distribution of worms. If n_m and n_f represent the number of male and female worms ($n_m + n_f = n$), then x = Minimum (n_m, n_f) is considered to be the number of worm pairs; n_m follows from a binomial distribution with parameters n and p. We assumed a value of $p = 0.5$, which means a ratio of male to female worms of 1:1.
The faecal egg counts for a given number of worms are assumed to follow a negative binomial distribution NegBin (f_x, r) with mean egg counts being a proportional function $f_x = h \cdot x$ of the worm pair number x, and an aggregation parameter r. Parameter h relates worm pair burdens to the expected number of eggs and therefore depends on the total amount of stool investigated ($h = 0.001 \cdot$ *mg stool*). For *S. mansoni*, for example, $h = 0.05$ (50 mg of stool) and $h = 0.042$ (42 mg of stool).
Repeated individual egg counts could vary between day-to-day stool specimens, e.g. due to changes in stool size and consistency, and within one specimen, e.g. due to clustering of eggs. These mechanisms become more important as the interval between examinations increases or the amount of stool examined decreases, respectively. The value of r is therefore determined by two components of aggregation: r_1 depends on the number of specimens and the duration between successive measurements and has been estimated at $1.27 \cdot$ *number of specimens* for about month-to-month variation in *S. mansoni*; r_2 depends on the total amount of stool examined and has been estimated at $0.0896 \cdot$ *mg stool*, so that $r_2 = 4.48$ for 50 mg stool samples. The overall aggregation parameter r can be described conveniently using the expression $1/r = 1/r_1 + 1/r_2$ (De Vlas, PhD thesis, 1996).

This model has been tested extensively for *S. mansoni*. For *S. haematobium* and *S. japonicum*, preliminary studies have shown that the same model can describe field data (not published). In general, both *S. haematobium* and *S. japonicum* show more within-individual variation (i.e. lower r values) than *S. mansoni*. However, the egg production (expressed by h = mean number of eggs/worm pair/sample) is usually higher, so that the sensitivity of standard diagnosis is comparable between the three schistosome species. The applicability of the model to hookworm is questionable: for instance, there is evidence of a density-dependent relation between worm burden and egg production, which would violate our assumption of proportionality. Therefore, we did not do standardisation of hookworm prevalence data.
Table 1 gives the parameter values for the three schistosome species and hookworm, to be used to describe the available data. As only *S. japonicum* and *S. mansoni* show large variation between studies in amount of stool (i.e. number of stool specimens, and number and size of stool samples) used, we have only applied the standardisation of prevalences here. Estimation of the expected geometric mean of each intensity group, on the basis of the model, was applied for all three schistosome species (it was not necessary for hookworm). A user-friendly modelling device, called EpiWorm, was developed to carry out the model fitting and to make the predictions.
In case no information was available on the amount of stool or urine examined, we have assumed the following defaults: a single 41.7 mg Kato-Katz stool sample (*S. mansoni* and *S. japonicum*), 10 ml urine sample (*S. haematobium*) and 10 mg stool sample (hookworm). The same amounts were also used as the defaults to standardise the prevalences.

Table 1: The values of r_1, r_2 and h for *S. haematobium*, *S. mansoni* and *S. japonicum* expressed by $r_1 = R_1 \cdot$ *number of specimens*, $r_2 = R_2 \cdot$ *total stool*(*mg*) or $R_2 \cdot$ *total urine*(*ml*) and $H \cdot$ *total stool*(*mg*) or $H \cdot$ *total urine*(*ml*). *Total stool* or *total urine* equals *number of specimens* · *number of samples per specimen* · *weight*(*mg*) or *volume*(*ml*) *per sample*. These values have been applied in the EpiWorm model.

	R_1	R_2	H
S. haematobium	1.27	0.0346	0.040
S. mansoni	1.27	0.0896	0.001
S. japonicum	1.27	0.0142	0.002

Predictions of standardised prevalences and expected mean egg counts in an intensity group are possible if r_1, r_2 and h are assumed to be universally applicable, and if M (mean worm load) and k (aggregation parameter) are estimated for each population or age group concerned. This means that at least two indicators of the level of infection in a population must be available. There are 3 combinations, which meet this condition:

- prevalence and (geometric) mean egg count (with or without zero counts)
- number of individuals in each intensity group (at least three groups)
- number of individuals in each intensity group (at least two groups) and (geometric) mean egg count in all groups together (with or without zero counts)

The model has been fitted to all studies, which met the above criteria. If only one indicator was provided (i.e. the prevalence of infection), a value of k had to be assumed.
Figure 3 shows the resulting estimations of each combination of parameters M and k (where this was possible) for the three schistosome species. There seems to be a trend (especially for *S. japonicum*) with the value of k increasing with M.

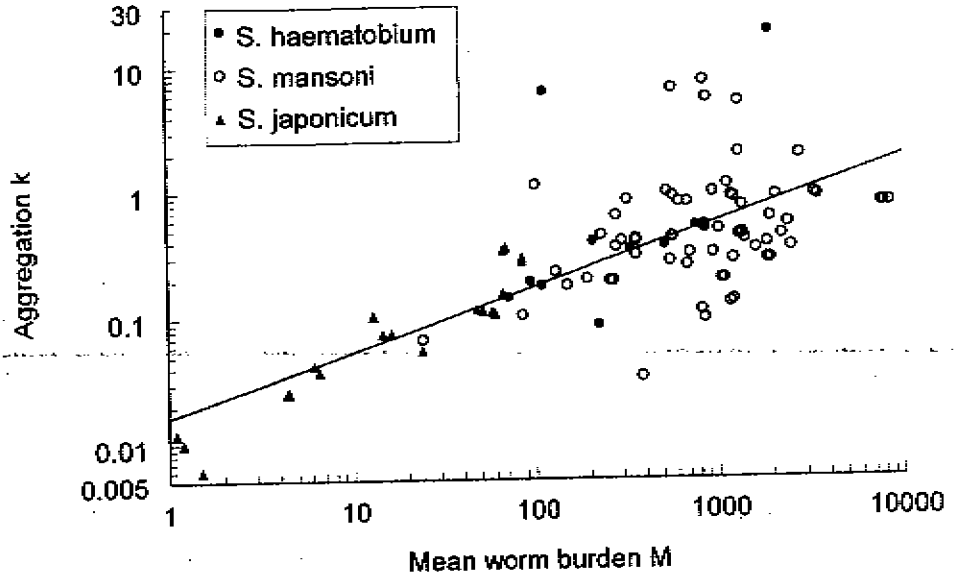

Figure 3: Association between the estimated values of the mean worm burden M and the aggregation parameter k, for *S. haematobium*, *S. mansoni* and *S. japonicum* [curve: $k = 0.0163 \cdot M^{0.514}$. The curves for *S. haematobium*, *S. mansoni* and *S. japonicum* are only borderline significantly different. Data came from studies where k and M could both be estimated (intensity studies with at least three categories, or studies on prevalence and mean egg count).

With known values of all parameters, standardised prevalences for the default amounts (see above) can be predicted by the EpiWorm model.
Figure 4 gives an example of the relation between blood in stool and *S. mansoni*. It is clearly shown how the values from studies based on non-default amounts of stool shift to the left (initially more stool used) or the right (less stool used).

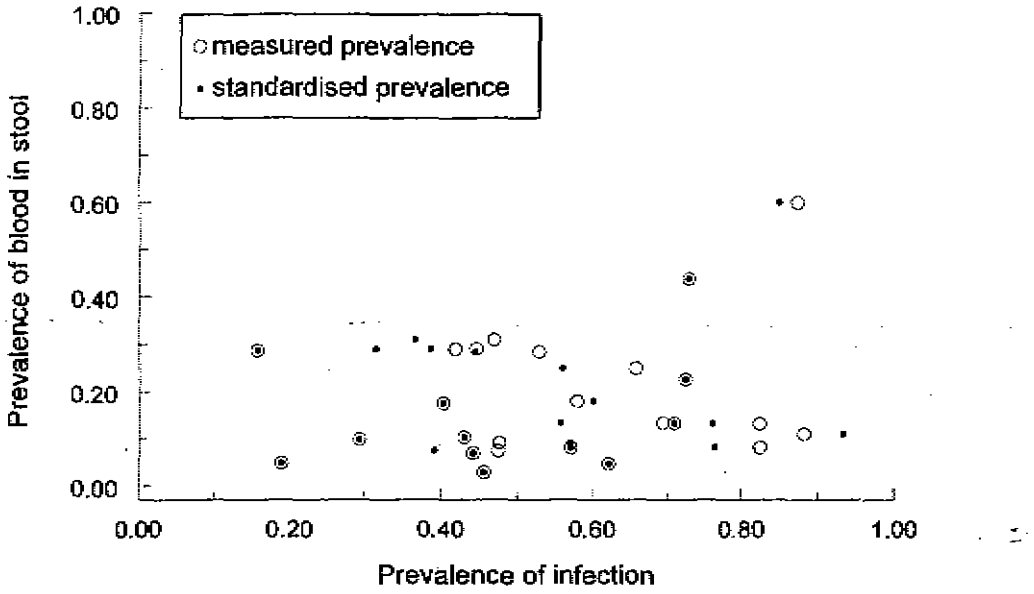

Figure 4: Blood in stool as a function of measured and standardised prevalences of *S. mansoni* infection. Both points overlap if the default amount of stool (single 41.7 mg) was used. Shifted points are located on the same vertical line.

Figure 5 gives an example of the relationship between the prevalence of blood in stool and intensity of infection, as determined by the model (standardised mean egg count) and using an alternative ad-hoc method (measured mean egg count). The latter, simplistic method takes the geometric mean of the upper and lower limit of each intensity group + 1 (expressed in real egg counts). For the last group, which has no upper limit, the ad-hoc method assumes the group to be of equal size as the previous one and calculates the mean egg count accordingly. It can clearly be seen that the model derived points have moved to the middle of the figure. In fact the highest and lowest egg count categories are more the result of outlier egg count values than real low or high worm burdens. This means that after standardisation the relationship between morbidity and infection has become stronger. Without use of the model, the association between infection and disease would have been underestimated as in regression to the mean.

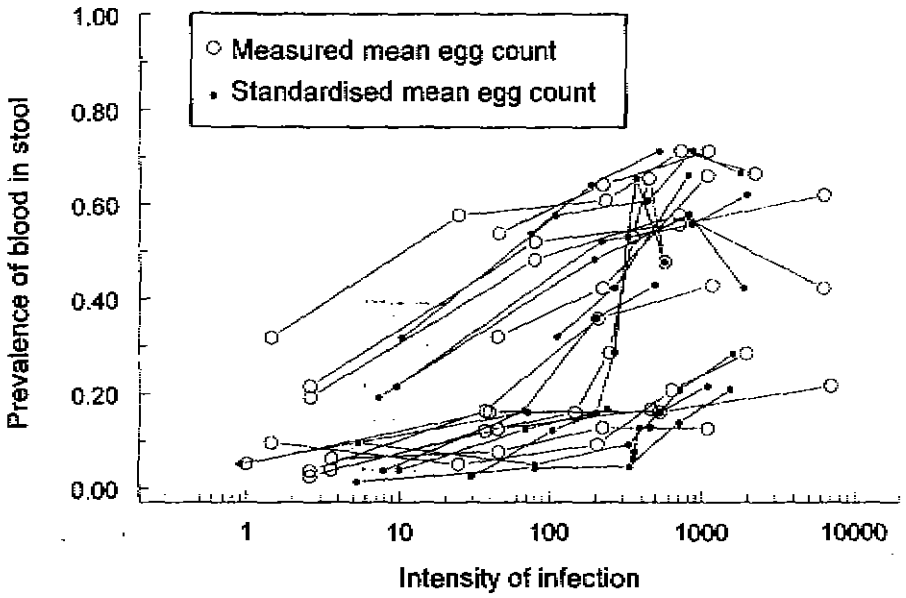

Figure 5: Prevalence of blood in stool by the measured and standardised mean egg count for the intensity of infection group. Points from the same study are connected.

The EpiWorm model can also be used to calculate the percentage of the population that has a intensity of *S. haematobium* infection > 10 eggs/10 ml or > 50 eggs/10 ml (figure 6). Most serious morbidity might be linearly associated with the proportion of individuals with high egg excretion.

The percentage of the population > 10 eggs/10 ml can be higher than observed prevalence of infection (in moderate to high endemic situations). This is due to an insensitive diagnostic technique. Esp. in high endemic situations, most negative cases are actually infected (De Vlas & Gryseels, 1992), of which many may even have a more then 10 eggs/10 ml in repeated examinations.

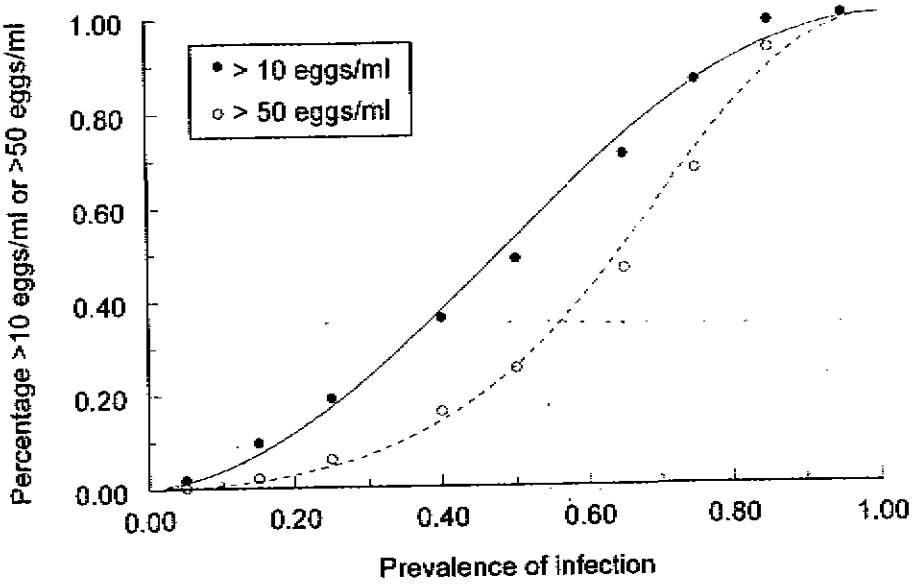

Figure 6: Association between the prevalence of *S. haematobium* infection and the expected percentage of the population with mean egg counts > 10 eggs/10 ml or > 50 eggs/10 ml. Data are from Epiworm calculations. The —— line has the expression *percentage > 10 eggs/10 ml* $= 1/(1.130 \cdot (1/P_{inf} - 1)^{1.545} + 1)$ and the --- line has the expression *percentage > 50 eggs/10 ml* $= 1/(2.927 \cdot (1/P_{inf} - 1)^{1.810} + 1)$

A9 Heterogeneity in infection prevalences within countries

The equations to relate prevalence of morbidity to infection only apply to individual communities (mostly villages). It should be noted that they cannot be used to predict prevalences of morbidity on an aggregated level using a mean prevalence of infection in a given country. Due to the non-linear character of the equation, predictions will be biased and mostly underestimated. Most morbidity will occur in those villages in the country with highest prevalence of infection. However, even countries with a low mean prevalence will have some villages with prevalences high enough to induce some morbidity cases. This process becomes more important if the curve is highly convex.

To get an impression of the variation in prevalences within a region, six data sets were available. Figure 6 shows the cumulative distribution of *S. haematobium* prevalences in Kilombero district of Morogoro Region, Tanzania [Tanzania 1] (Lengeler *et al.*, 1991) and Magu district of Mwanza Region, Tanzania [Tanzania 2] (provided by Guyatt and Brooker (Guyatt *et al.*, 1999)) and *S. mansoni* prevalences in the region of Man, western Côte d'Ivoire (provided by J. Utzinger (Utzinger *et al.*, 2000)), Kafr El Sheikh governorate, Egypt (provided by Barakat (Barakat *et al.*, 1995)), town of Matadi and the administrative zone of Songololo, Congo (Lengeler *et al.*, 2000) and the Rusizi Plain, Burundi (Gryseels & Nkulikyinka, 1988).
We have fitted a normal distribution to the logit transformed $^{10}\log(P_i/(1-P_i))$ prevalences P_i ($i = 1, .., N$) for each data set. For *S. haematobium* areas the values of N are 50 (Tanzania 1) and 52 (Tanzania 2) (figure 6a). The prevalence of Tanzania 1 has mean = 0.16 ("anti-logit" of the mean of logit transformed data) and = 0.54 (logit transformed data). Similarly, Tanzania 2 has mean = 0.58 and = 0.37. For *S. mansoni* areas the values of N are 54 (Congo), 9 (Burundi), 44 (Egypt) and 60 (Côte d'Ivoire) (figure 6b). The prevalence of Congo has mean = 0.20 and = 0.87, Burundi has mean = 0.28 and = 0.45, Egypt has mean = 0.42 and = 0.20 and Côte d'Ivoire has mean = 0.54 and = 0.56. There does not seem to be a trend in mean and .
We assume that the heterogeneity in prevalence in a country is comparable or higher than the heterogeneity in prevalence observed in the described districts. In the absence of comparable data on country level and other infections, we decided to use the s.d. = 0.6 throughout (comparable to Côte d'Ivoire). Lower values of s.d. seem to be more adequate for smaller areas (as Kafr El Sheikh governorate).
Subsequently, the prevalence of morbidity P_{morb} in a region with mean prevalence of infection P_{inf} was predicted by

$$P_{morb,exp} = \int_0^1 \frac{b \cdot P_{inf}^{\ c}}{1 + b \cdot P_{inf}^{\ c}} \cdot \Pr(P_{inf})$$

were $\Pr(P_{inf})$ denotes the probability of a community having prevalence of infection P_{inf}, given a normal distribution of logit transformed prevalences of infection with mean logit(P_{inf}) and s.d. = 0.6 (figure 7). We have used SPSS and MS-Excel to make the calculations.

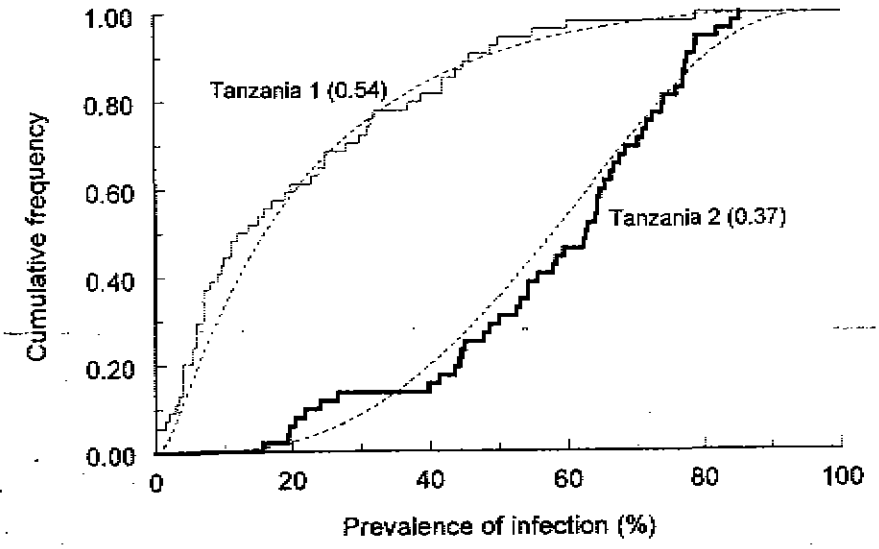

Figure 6a: Cumulative prevalence of *S. haematobium* infection for data from Tanzania (2 data sets kindly provided by resp. Guyatt & Brooker and Lengeler *et al.*). The value between brackets is standard deviation of logit transformed prevalence.

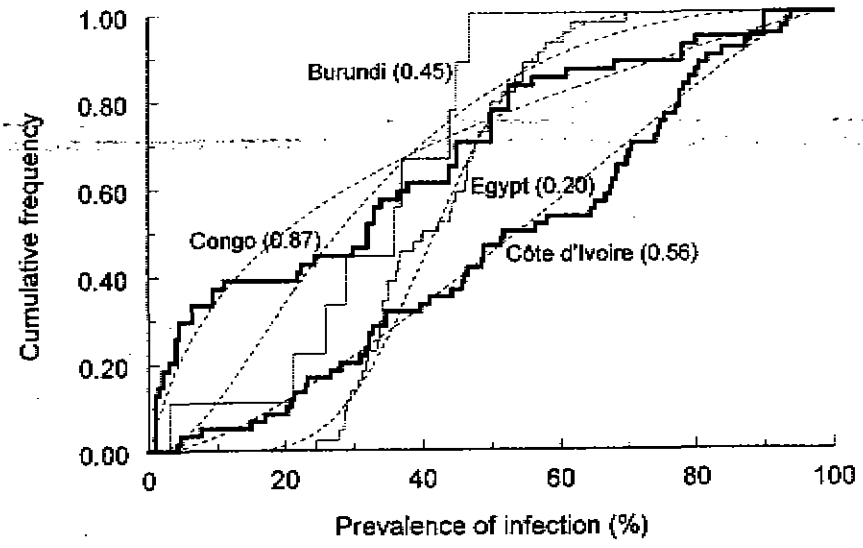

Figure 6b: Cumulative prevalence of *S. mansoni* infection for data from Congo, Burundi, Egypt and Côte d'Ivoire (data kindly provided by resp. Lengeler *et al.*, Gryseels & Nkulikyinka, Barakat *et al.* and Utzinger *et al.*). The value between brackets is standard deviation of logit transformed prevalence.

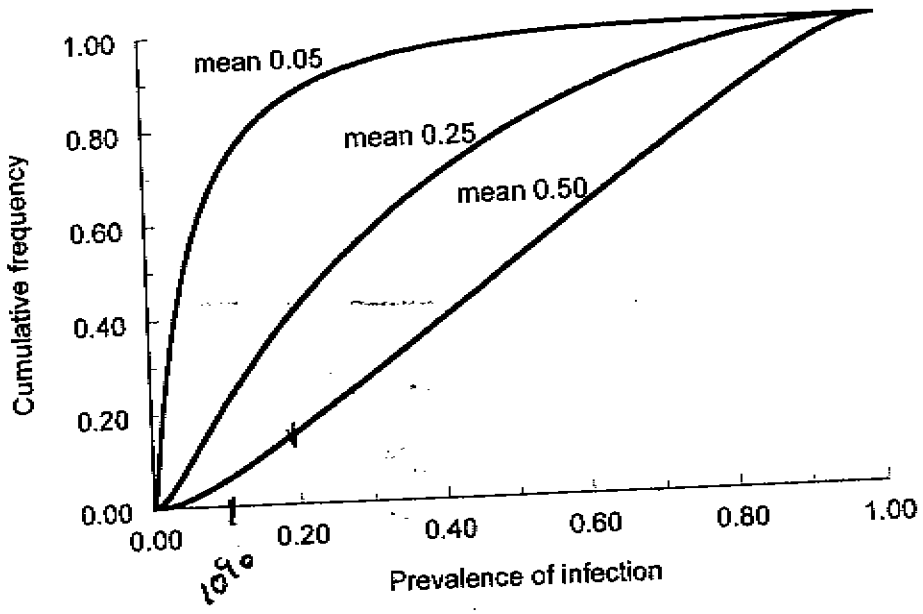

Figure 7: Distribution of prevalence of infection for communities within a country with a mean prevalence of 0.05, 0.25, 0.5, assuming a normal distribution of logit transformed prevalences with standard deviation = 0.6, as used in our calculations.

A10 Predicting morbidity for countries/regions

In summary, the number of individuals with a type of morbidity was calculated for 3 groups (pre-school children, schoolchildren and adults) for 3 WHO regions (Africa D Region, Africa E Region and EMR-D Region). We used the prevalences of infection in the 3 groups by country (provided by D. Engels and S. Brooker, Appendix C). Heterogeneity in community prevalences was taken account of by assuming a standard deviation of 0.6 (Appendix A9).

To calculate the estimated number of individuals with a type of morbidity we used the association between prevalence of infection and morbidity

$$P_{morb,\,exp} = (b \cdot P_{inf}^{\,c}) / (1 + b \cdot P_{inf}^{\,c})$$

or an alternative curve (Appendix A6) with preset point of inflection.

All estimates of acute morbidity (haematuria, dysuria, bladder morbidity, hydronephrosis, diarrhoea, blood in stool, hepatomegaly, splenomegaly and anemia due to hookworm infection) were calculated as described above for all groups. Estimates for major hydronephrosis were calculated for schoolchildren and adults. Numbers of other chronic morbidity (non functioning kidney, bladdercancer, hematemesis and ascitis) were only estimated for adults. Also, some additional calculations were made for non functioning kidney, bladder cancer and hematemesis (Appendix B).

To estimate confidence intervals for the total number of individuals with a type of morbidity, we used the bootstrap method (Efron & Tibshirani, 1993). Bootstrapping replicates the process of sample generation from an underlying population by drawing samples with replacement from the original data set, of the same size as the original data set. In this way the uncertainty of the parameters a, b and c, given the combinations of prevalence of infection and morbidity available, is mimicked by the variability in the set of bootstrap replica's. For each type of morbidity we drew 200 new samples form the original data set. Each bootstrap was processed as described above. We chose to present the 90% interval for the estimated total number of individuals with morbidity (between 5 and 95 percentile) in Appendix C, table 4-6, 10-12 and 16-18. Intervals were calculated for haematuria, dysuria, bladder morbidity, diarrhoea, blood in stool and anemia due to hookworm infection.
Note that this only represents part of the uncertainty (uncertainty in curve parameters). For example, uncertainty in the original combinations of prevalences of infection and morbidity available and the prevalence of infection in countries is not taken account of. Also, the used degree of heterogeneity in community prevalences is subject to uncertainty.

Appendix B: Infection and morbidity associations

B1 Urinary schistosomiasis

1.1 Haematuria

In field studies, the prevalence of haematuria is measured by questionnaire (interviewing individuals and asking for red urine in a specified time period) or by inspection of a urine sample (looking at the collected urine sample and classification of the colour). The time period used by the questionnaire method differs widely between the different field studies (1 day to 4 weeks, often not specified).
Inspection of a urine sample can be compared to the questionnaire method with a very short recall period. Therefore, the prevalence of haematuria by inspection will generally be lower than the prevalence of haematuria by questionnaire method. Figure 1.1.1 shows the difference between the measured prevalence by the two methods.

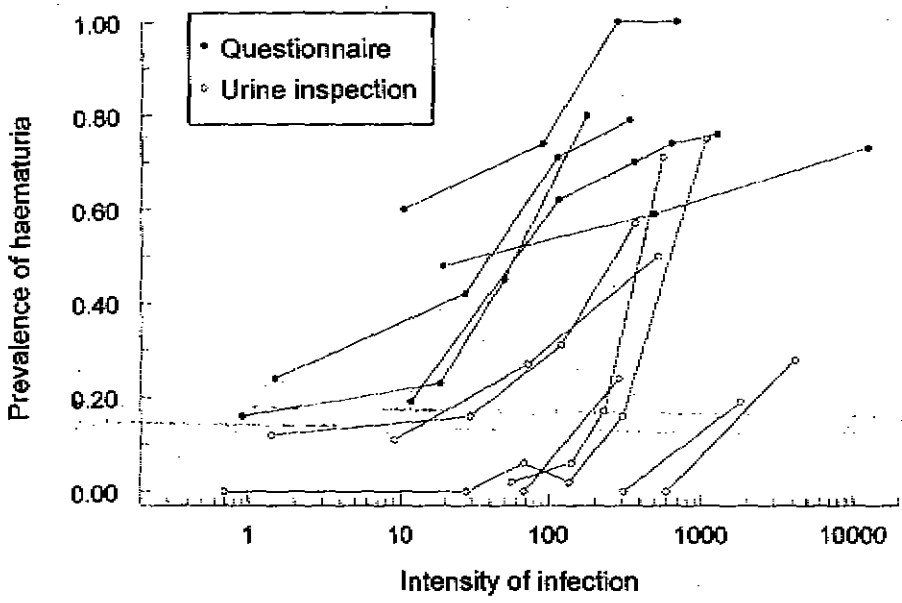

Figure 1.1.1: Prevalence of haematuria by intensity of infection. Points from the same study are connected.

For haematuria by inspection we used the standard curve (point of inflection at 0.53) (Appendix A6), $a = 0.060$, $b = 1.158$ and $c = 3.041$ (figure 1.1.2).

For haematuria by questionnaire method, some studies reported for different recall periods, mostly 1 day and two weeks. For the analysis, we selected the results of the recall periods closest to two weeks (Appendix A7).
Two studies provided most data points, Lengeler *et al.* (1991) 50 data points and Guyatt *et al.* (1999) 52 data points. The shape of the individually fitted curves for the data points from Lengeler *et al.* and Guyatt *et al.* was comparable to the shape of the curve for the other data points. Therefore, a combined curve for all data points was fitted.

For haematuria by questionnaire we used the standard curve, which is represented by $a = 0.113$, $b = 1.039$ and $c = 1.400$ (figure 1.1.3).

The base-line prevalence of haematuria (i.e. haematuria due to other causes) is much higher for the questionnaire method compared to the results from inspection of a urine sample, resp. 0.113 and 0.060. This can be due to the misclassification of dark or brown urine by the patients in the questionnaire method.
The shape of the curve in figure 1.1.2 and 1.1.3 is comparable, indicating that the additional morbidity due to *S. haematobium* infection can be measured both by questionnaire and inspection of urine. The formula for haematuria by questionnaire is used for calculating the number of individuals with haematuria (Appendix A7).

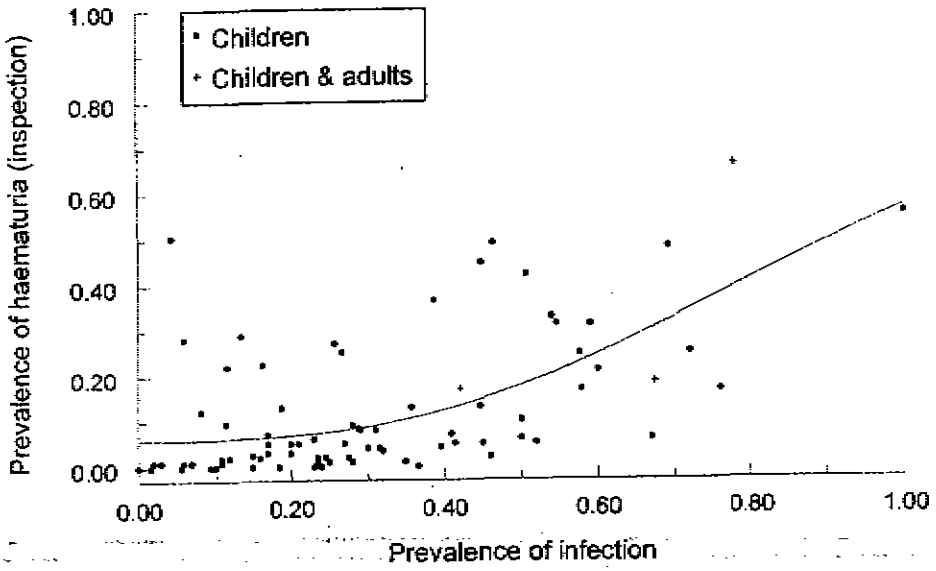

Figure 1.1.2: Prevalence of haematuria measured by inspection of the urine by prevalence of *S. haematobium* infection.

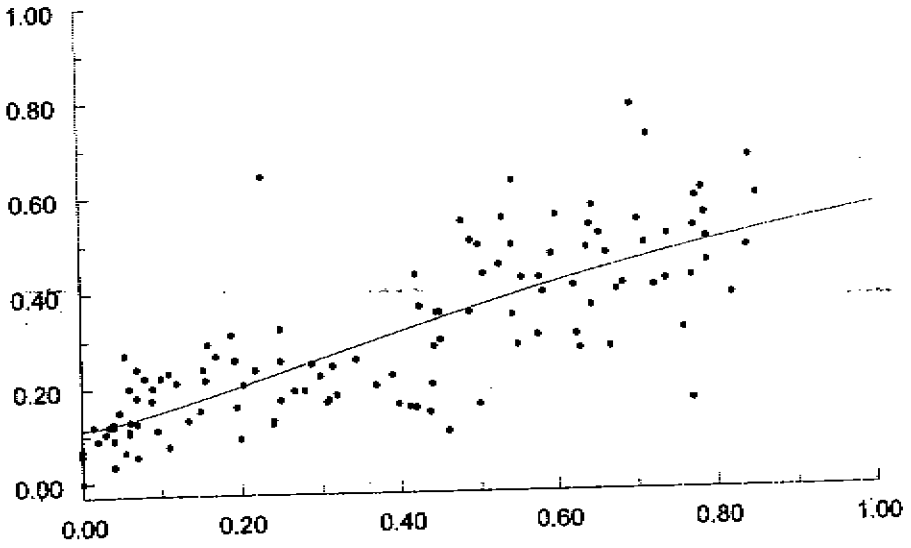

Figure 1.1.3: Prevalence of haematuria measured by questionnaire by prevalence of *S. haematobium* infection.

1.2 Dysuria

Prevalence of dysuria is measured by questionnaire. Individuals are asked if they had dysuria in a certain period. This period varied from 1 day to 4 weeks or was not specified in the articles. Figure 1.2.1 shows that the baseline prevalence of dysuria differs considerably between the different studies.
The fitted curve is represented by $a = 0.295$, $b = 1.944$ and $c = 4.225$ (figure 1.2.2). There seems to be no reason to distinguish adults and children.
The baseline prevalence of dysuria is high, i.e. 0.295. This indicates that dysuria is a symptom often caused by other diseases or overreported.

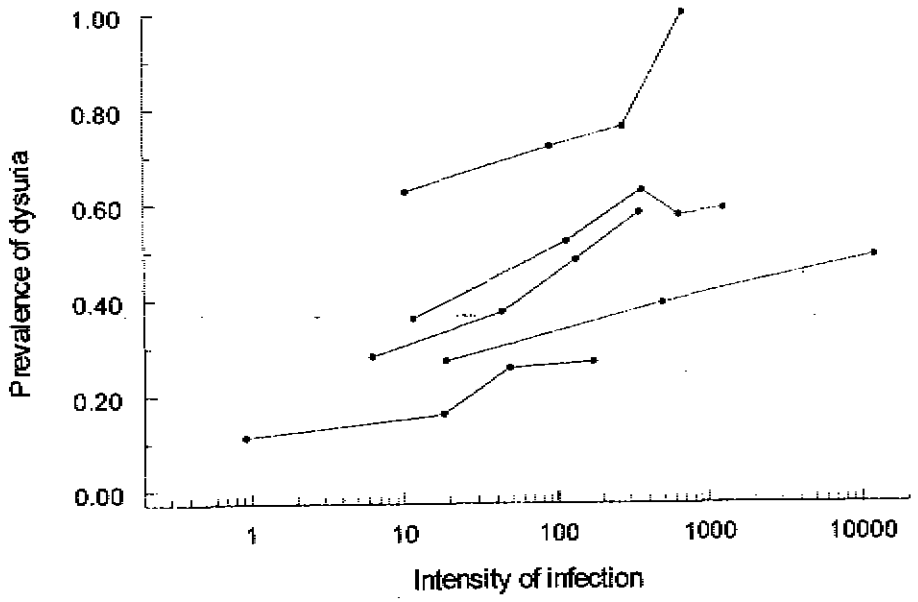

Figure 1.2.1: Prevalence of dysuria by intensity of *S. haematobium* infection. Points from the same study are connected.

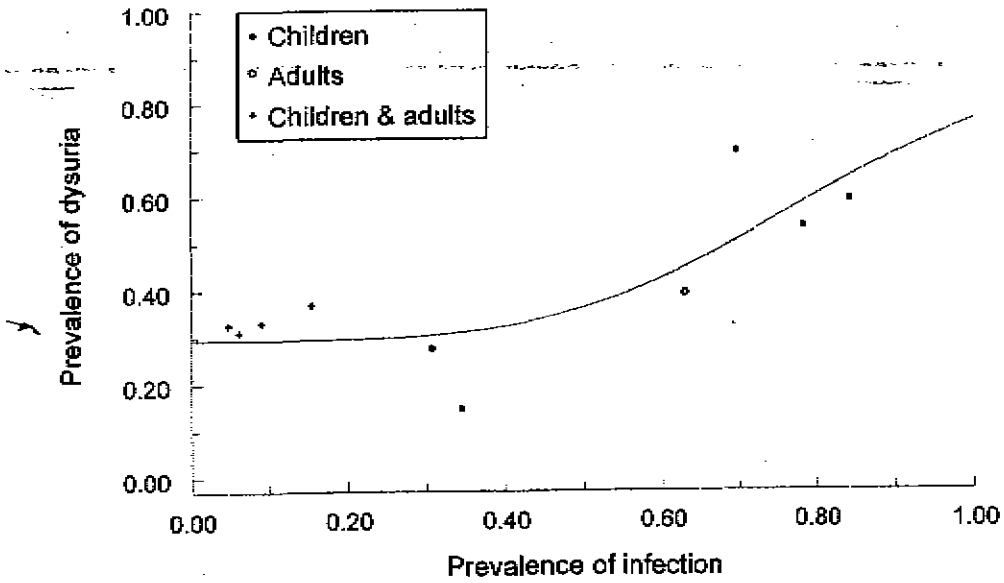

Figure 1.2.2: Prevalence of dysuria measured by questionnaire by prevalence of *S. haematobium* infection.

1.3 Urinary tract morbidity

S. haematobium infection can induce severe pathology in the urinary tract, which can be diagnosed by intravenous pyelography (IVP) or by ultrasound. The lesions are caused by granuloma formation around eggs in the tissues of the urinary tract. This produces two main kinds of pathology; 1) obstructive uropathy and 2) abnormalities in the bladder.
The pathology that develops due to obstruction depends on the location and the duration of the obstruction. Obstruction in the ureter close to the bladder will give hydro-ureter and in a later stage hydronephrosis, obstruction high in the ureter, close to the kidney will only induce hydronephrosis. Both types of obstructive uropathy can eventually give rise to non-functioning kidney.
The abnormalities diagnosed by IVP in the bladder are bladder calcification and bladder filling defects. By ultrasound, calcification, irregularities and thickening of the bladder wall and (pseudo) polyps can be visualised.
Bladder calcification is caused by calcification of *S. haematobium* eggs in the bladder submucosa. Bladder filling defects are mainly caused by the granulomas and by polypoid lesions.
The development of obstructive uropathy and bladder abnormalities can take several years. Therefore, we do not expect a direct relationship between intensity of infection of an individual patient and the presence and severity of the obstructive pathology and the bladder abnormalities.

1.3.1 IVP

In table 1.3.1, we try to summarise the studies that report on urinary tract morbidity visualised by IVP.

The effect of treatment on urinary tract morbidity is reported by two studies. Lucas *et al.* (1966) (Lucas *et al.*, 1966) treated 12 patients with gross abnormalities at the initial IVP. After treatment, 8 IVPs showed definite improvement. In the second study, the authors treated 10 farmers (Farid *et al.*, 1967). Two or 3 months after treatment, 7 of the 10 patients had remarkably improved pyelograms.

A number of the studies that contain information on urinary tract morbidity do not contain information on the selection of the investigated individuals, the infection status of the studied population or the infection status of the population from which the investigated individuals are selected (Forsyth & Bradley, 1964; Forsyth & MacDonald, 1965; Gelfand, 1965). This makes these studies unsuitable for calculating morbidity estimates.

Table 1.3.1: Summary of the literature on *S. haematobium* infection and urinary tract morbidity detected by IVP.

Author	Study group	Study group	No. of IVPs**	Bladder calcification	Bladder filling defects	Ureteral dilatation/ deformity	Bilateral obstructive uropathy	Hydro-ureter	Hydrone-phrosis	Non functioning kidney
Nabawy (1961)	positives	children	108	32	-	-	-	-	4	-
Forsyth (1965)	86% infected	children	358	25	-	-	-	-	29	-
Gilles (1965a)	91% infected	children	78	7	29	-	-	-	-	-
Gilles (1965b)	50% infected	adults	94	30	3	-	-	-	3	-
Forsyth (1966a)*	98% infected	children	106	21	-	45	-	-	20	0
Forsyth (1966a)*	30% infected	children	109	5	-	12	-	-	9	1
Forsyth (1966b)	42% infected	children & adults	751	34	-	-	-	28	25	5
Wolfe (1967)	positives	adults	22	3	-	3	-	-	4	-
Forsyth (1969)*	65% infected	children & adults	794	111	-	189	-	-	119	36
Lehman (1970)	positives or persons with typical IVP lesions	children & adults	75	31	32	23	35	44	41	6
Lehman (1973)	positives or persons with typical IVP lesions	children & adults	200	87	57	-	84	92	95	12
Pugh (1979)	positives selected on intensity of infection	children & adults	92	12	-	-	-	5	6	-
Rugemalila (1979)	positives	children & adults	100	52	-	-	-	33	22	-
Warren (1979)	positives selected on intensity of infection	children	17	3	-	-	-	6	6	-
El-Hawey (1981)	positives	adults	36	15	-	3	-	-	-	-
Moyou Somo (1987)*	positives	children & adults	129	51	-	-	81	-	-	-
Moyou Somo (1987)*	negatives	children & adults	19	1	-	-	0	-	-	-
Chugh (1986)	positives	adults	44	16	4	23	-		4	

* same study

** IVP= intravenous pyelogram

References: Chugh *et al.*, 1986; el-Hawey *et al.*, 1981; Forsyth, 1969; Forsyth & Bradley, 1966; Forsyth & MacDonald, 1965; Forsyth & MacDonald, 1966; Gilles *et al.*, 1965a; Gilles *et al.*, 1965b; Lehman *et al.*, 1970b; Lehman *et al.*, 1973; Moyou Somo *et al.*, 1987; Nabawy *et al.*, 1961; Pugh *et al.*, 1979; Rugemalila, 1979; Warren *et al.*, 1979; Wolfe, 1967

In most articles, the authors studied only individuals with *S. haematobium* eggs in the urine (Chugh *et al.*, 1986; Nabawy *et al.*, 1961; Pugh *et al.*, 1979; Rugemalila, 1979; Warren *et al.*, 1979; Wolfe, 1967) and sometimes combined with individuals showing clinical or radiological evidence of *S. haematobium* infection (el-Hawey *et al.*, 1981; Lehman *et al.*, 1970b; Lehman *et al.*, 1973). Other studies investigated the whole population (Forsyth, 1969; Forsyth & MacDonald, 1965; Forsyth & MacDonald, 1966; Gilles *et al.*, 1965a; Gilles *et al.*, 1965b). Without a control population from an area where *S. haematobium* infection is low or absent, the additional morbidity caused by *S. haematobium* infection can not be calculated. Forsyth *et al.* (1966) tried to include a control group (Forsyth & MacDonald, 1966). They investigated 2 groups of children from different areas, one with almost 100% prevalence of *S. haematobium* infection and the other with a prevalence of 30%, the control group. The group with the low prevalence of infection had less urinary tract morbidity compared to the population with the high prevalence of infection. However, the selection of the study

population makes it less useful for calculation of morbidity. The researchers investigated all boys in the study population but only the girls that were positive for *S. haematobium* eggs in the urine. In the results of the IVP they combined the outcomes of the girls and boys.
Another study that tried to solve the problem of the control group selected a group of 19 persons from a low endemic village in the same region (Moyou Somo *et al.*, 1987). Only 1 person in the control population had calcification of the bladder whereas only 13 from the 102 persons from the infected population had a normal IVP. This indicates that almost all lesions diagnosed in positive individuals are caused by *S. haematobium* infection.

The presented studies provided insufficient information for estimation of an association between prevalence of infection and prevalence of deformed ureter and hydronephrosis using our standard procedures (see Appendix A6). We have used data from ultrasound studies instead (see 1.3.2). For non functioning kidney an alternative approach using IVP data was applied, see below.

1.3.1.1 Non functioning kidney

For the calculation of the number of individuals with non functioning kidney we used the data provided by two community studies (Forsyth, 1969; Forsyth & Bradley, 1966). The number of individuals investigated was 751 and 794; the prevalence of infection was resp. 42% and 65%. Resp. 5 and 36 individuals had at least one non-functioning kidney.

We assumed that only individuals with high egg count (> 50 eggs/10 ml) are at risk. We calculated the number of individuals with egg counts > 10 eggs/10 ml and > 50 eggs/10 ml (see Appendix A8, figure 6).

For the first study an estimated 16% had over 50 eggs/10 ml (120 individuals). For the second study an estimated 51% had over 50 eggs/10 ml (405 individuals). We assume that non functioning kidney can only develop if there are individuals with > 50 eggs/10 ml in the population. Then resp. 5 / 120 = 0.0417 of the individuals with > 50 eggs/10 ml and 36 / 405 = 0.0889 of the individuals with > 50 eggs/10 ml will have non functioning kidney (mean 0.0653). The authors want to stress that this estimate is calculated from only 2 community studies and is therefore not very reliable. However, it is reassuring that both studies give an estimate of the same order of magnitude.
For the calculation of the estimated number of individuals with non functioning kidney we used the association between the prevalence of infection and the prevalence of > 50 eggs/10 ml as described in section A8.

Uni- or bilateral non-functioning kidney is related to a higher mortality of the affected individuals. This was investigated in two follow-up studies in Tanzania and Egypt. In one study the authors traced seven patients who were found to have a non-functioning kidney at the initial study (Forsyth *et al.*, 1970). Six years later, 3 of them had died. This is a high death rate, however all three patients were already "old" at the initial study.
In the other study 11 patients with one or two non-functioning kidney(s) (9 one kidney, 2 two kidneys) were followed after hospital investigation (Lehman *et al.*, 1970a). Five patients were dead when follow-up was obtained, 4 died within six months of discharge from the hospital and two of them were uraemic at the at the time of death. The age of these patients ranged from 16 up to 40 years.

Chance of dying u from non-functioning kidney in individuals with non-functioning kidney due to *S. haematobium* infection:

$u = -\ln(1-p)/t$

p = death rate
t = time in years

Study 1 (Forsyth *et al.*, 1970): $p = 0.09$ per year (community study)
Study 2 (Lehman *et al.*, 1970a): $p = 0.9$ per year (hospital patients)

Calculation of incidence and mortality of non functioning kidney

Assumptions:
- All non functioning kidney cases in endemic areas are due to *S. haematobium* infection.
- Non functioning kidney is irreversible.
- Death rate in endemic areas is 0.02 (crude estimate based on http://www.statistical-data.org/index.html [16 August 2001]).
- Death rate due to non functioning kidney is 0.09.

Incidence = Prevalence · (General death rate + death rate due to non functioning kidney)

Number of individuals with non functioning kidney (see Appendix C, table 4, 10 and 16) based on association between morbidity and prevalence of infection as stated above, only adults:
WHO Africa D Region: 1.0 million
WHO Africa E Region: 0.57 million
WHO EMR-D Region: 0.10 million

Incidence of non functioning kidney per WHO Region per year:
WHO Africa D Region: 1.0 million · (0.02 + 0.09) = 110,000
WHO Africa E Region: 0.57 million · (0.02 + 0.09) = 62,700
WHO EMR-D Region: 0.10 million · (0.02 + 0.09) = 11,000

Mortality of non functioning kidney per WHO Region per year:
WHO Africa D Region: 1.0 million · 0.09 = 90,000
WHO Africa E Region: 0.57 million · 0.09 = 51,300
WHO EMR-D Region: 0.10 million · 0.09 = 9,000

1.3.2 Ultrasound detected urinary tract pathology

Since the introduction of ultrasonography in the late 1970s it has been increasingly used for the study of urinary tract lesions caused by *S. haematobium* infection. Ultrasound can be easily performed in field studies to investigate large population samples because it is non-invasive, simple to perform, does not have the disadvantages of radiation and is comparatively cheap (Hatz *et al.*, 1990). This resulted in numerous field studies, which included ultrasound investigation of the study population. Studies with an unselected population including both individuals positive for *S. haematobium* infection and negative were used for the analysis.

1.3.2.1 Bladder pathology

Most studies report minor and major bladder pathology. Minor bladder pathology includes slightly irregular bladder wall and/or bladder wall thickness between 6 and 10 mm and/or single localised hypertrophy. Major bladder pathology is often classified as very irregular bladder wall and/or bladder wall thickness >10 mm and/or several localised hypertrophies and/or bladder calcification. Some studies report an intermediate group "moderate bladder pathology".

The fitted curve is represented by $a = 0.056$, $b = 2.368$ and $c = 1.734$ (figure 1.3.2.1.1).

The fitted curve for major bladder pathology had point of inflection at 0.73. The curve is represented by $a \approx 0$, $b = 0.286$ and $c = 1.447$ (figure 1.3.2.1.2).
The finding that $a \approx 0$ indicates that major bladder pathology very specifically caused by infection with *S. haematobium*.

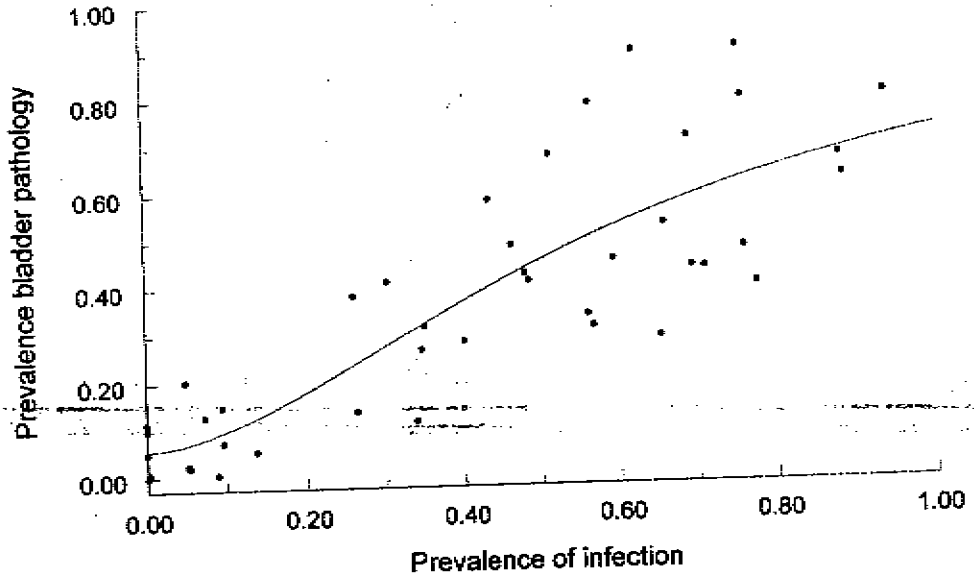

Figure 1.3.2.1.1: Prevalence of all bladder pathology measured by ultrasound by prevalence of *S. haematobium* infection.

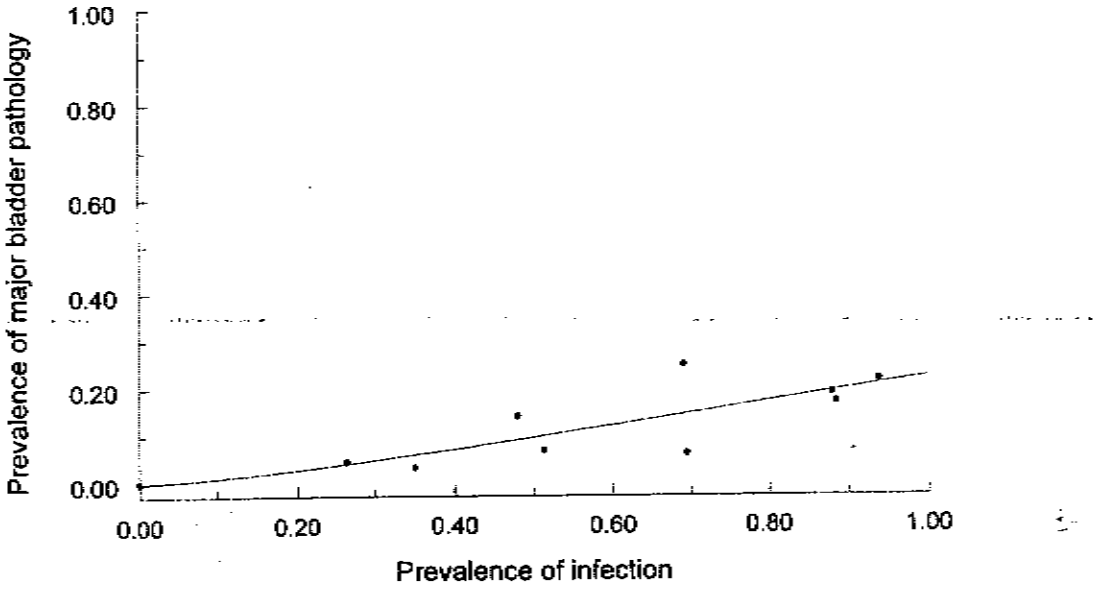

Figure 1.3.2.1.2: Prevalence of major bladder pathology measured by ultrasound by prevalence of *S. haematobium* infection.

1.3.2.2 Hydronephrosis

Studies reporting on hydronephrosis detected by ultrasound use different classifications. We tried to group the detected pathology in minor, moderate and major hydronephrosis. Minor hydronephrosis includes the initial stage of dilatation, mild dilatation of the renal pelvis and calices. Moderate hydronephrosis is characterised by marked renal pelvis and calices dilatation. If the functional kidney parenchyma is severely decreased, the patient is diagnosed as having major hydronephrosis.

If only studies including all three groups of hydronephrosis are used for analysis it is evident that minor hydronephrosis is not strongly associated with prevalence of *S. haematobium* infection. The weak association between prevalence of *S. haematobium* infection and prevalence of minor hydronephrosis is probably caused by something unrelated to infection such as poverty. Moderate and major hydronephrosis are more clearly associated with prevalence of *S. haematobium* infection (figure 1.3.2.2.1). Therefore, only studies reporting moderate and major hydronephroses were included in the analysis.

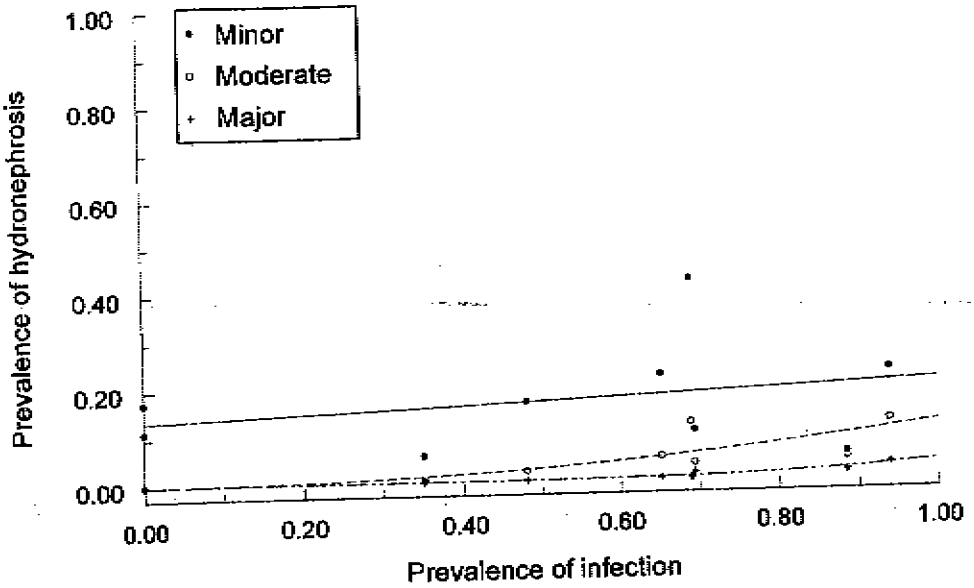

Figure 1.3.2.2.1: Prevalence of minor, moderate and major hydronephrosis measured by ultrasound by prevalence of *S. haematobium* infection. Data come from studies where all three categories have been measured.

For the association between prevalence of *S. haematobium* infection and moderate + major hydronephrosis the point of inflection of the standard curve is too early to be biologically realistic. Therefore, we used the alternative curve with point of inflection at 1.0 to calculate the association. The fitted curve is represented by $a = 0.015$, $b_{1.0} = 0.271$ and $c = 1.742$ (figure 1.3.2.2.2).

For the association between prevalence of *S. haematobium* infection and major hydronephrosis the point of inflection of the standard curve is too early to be biologically realistic. Therefore, we used the alternative curve with point of inflection at 1.0 to calculate the association. The fitted curve is represented by $a = 0.010$, $b_{1.0} = 0.105$ and $c = 1.234$ (figure 1.3.2.2.3).

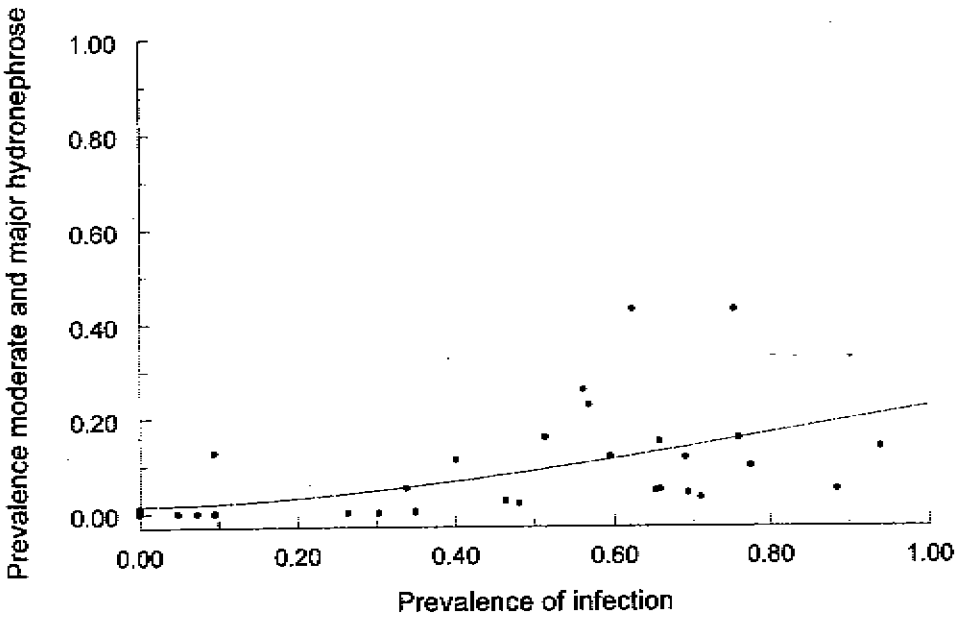

Figure 1.3.2.2.2: Prevalence of moderate + major hydronephrosis measured by ultrasound by prevalence of *S. haematobium* infection.

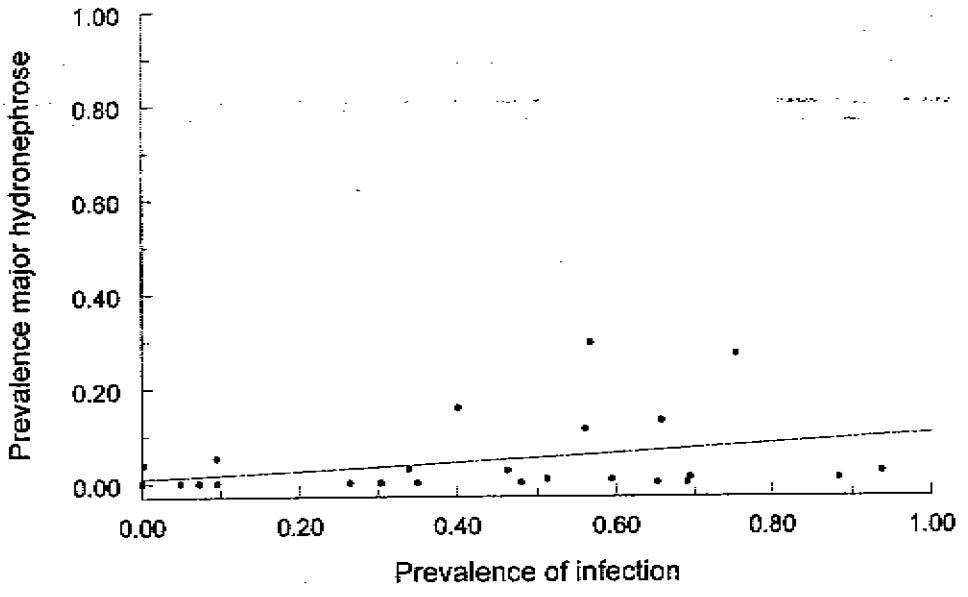

Figure 1.3.2.2.3: Prevalence of major hydronephrosis measured by ultrasound by prevalence of *S. haematobium* infection.

1.4 Bladder cancer

Since Ferguson (Ferguson, 1911) first mentioned the possible relationship between *S. haematobium* infection and bladder cancer in 1911, there has been increasing evidence which supports this theory. The evidence can be categorised into 5 groups.

First, bladder cancer is one of the leading malignant diseases in a number of countries with a high prevalence of *S. haematobium* infection (Al-Saleem *et al.*, 1990; Al-Shukri *et al.*, 1987; Elem & Purohit, 1983; Kahan *et al.*, 1997; Lucas, 1982b). In contrast, in schistosome free countries such as Germany, the United States, the United Kingdom and Turkey, bladder carcinoma ranks from the 5th to 7th most common cancer in men and from the 7th to 14th in women (Mostafa *et al.*, 1999).

Second, squamous cell carcinoma, a histological type of bladder cancer which is generally accepted to be related to schistosomiasis infection, occurs at a higher frequency compared to the other histological types in areas endemic for *S. haematobium* (table 1.4.1).

Third, the tissue of squamous cell carcinoma more often contains *S. haematobium* eggs than the tissue of the other histological types (table 1.4.2). In case-control studies, researchers report a higher prevalence of schistosomiasis in bladder cancer cases than in controls (Bedwani *et al.*, 1998; Vizcaino *et al.*, 1994).

Fourth, the age of onset of squamous cell carcinoma is often in the forth and fifth decade of life, while the other histological types occur at higher ages (Al Adnani & Saleh, 1983; Bowry, 1975; Elem & Purohit, 1983; Gelfand *et al.*, 1967; Lucas, 1982b; Malik, 1975). This might indicate a different pathological mechanism or a different cause for the development of squamous cell carcinoma.

Fifth, Mostafa *et al.* (Mostafa *et al.*, 1995) postulated a mechanism by which *S. haematobium* infection might induce bladder cancer. They report that the infection gives rise to elevated levels of nitrosamines, potent initiating carcinogens. They also discuss a specific kind of DNA damage in the tissue from schistosomiasis induced bladder cancer which is not present in other Egyptian cancer patients. The chronic irritation in bladders infected with schistosomiasis could also facilitate the development of cancer (Mostafa *et al.*, 1999). Other researcher were able to induce bladder cancer in laboratory animals by infection with schistosomes (Schwartz, 1981).

Table 1.4.1: Frequency of squamous carcinoma of the bladder in relation to other histological types in different countries. In countries endemic for *S. haematobium*, there is a higher percentage of the bladder cancers of the squamous cell type carcinoma than in non-endemic countries.

Country	Percentage squamous cell carcinoma
England (Payne, 1959)	1.6
USA (Kantor, 1988)	2.7
Scotland (Holland, 1952)	3.9
USA (Warren, 1951)	4.2
S. African whites (Oettle, 1955)	7.8
Saudi Arabia (Khurana, 1992)	20.0
South Africa (Groeneveld, 1996)	25.2
Sudan (Sharfi, 1992)	26.5
South Africa (Hinder, 1969)	27.8
Nigeria (Udeli et al., 1966)	38.7
Nigeria (Aghaji et al., 1989)	38.8
Sudan (Malik et al., 1975)	39.7
Uganda (Dodge, 1964)	40.0
Iraq (Al Adnani, 1983)	48.8
Kenya (Bowry, 1975)	50.0
Uganda (Anthony, 1974)	54.0
South Africa (Cooppan, 1984)	56.0
S. Africa Africans (Oettle, 1955)	57.1
Mozambique Africans (Prates and Gillman, 1959)	58.6
Rhodesia Africans (Gelfand et al., 1967)	61.7
Egypt (Hashem, 1961)	62.3
Zimbabwe (Houston, 1964)	63.0
Nigeria (Attah, 1976)	64.2
Tanzania (Kitinya, 1986)	66.0
Mozambique (Prates and Torres, 1965)	67.0
Zimbabwe (Thomas, 1990)	70.0
Zambia (Elem & Purohit, 1983)	72.0
Zambia (Bhagwandeen,1976)	75.1
Malawi (Lucas, 1982)	79.2

References: Malik *et al.*, 1975 + update Kantor *et al.*, 1988, Groeneveld *et al.*, 1996; Khurana *et al.*, 1992, Aghaji & Mbonu, 1989; Al Adnani & Saleh, 1983; Anthony, 1974; Attah & Nkposong, 1976; Bhagwandeen, 1976; Bowry, 1975; Cooppan *et al.*, 1984; Elem & Purohit, 1983; Hinder & Schmaman, 1969; Houston, 1964; Kitinya *et al.*, 1986; Lucas, 1982a; Prates & Torres, 1965; Sharfi *et al.*, 1992; Thomas *et al.*, 1990

Table 1.4.2: The percentage of squamous cell carcinomas and transitional cell carcinoma of the bladder with schistosome eggs in tumour tissue. Schistosome eggs are more frequently diagnosed in the tissue of squamous cell carcinoma than in tissue of transitional cell carcinoma.

Authors	Country	% with schistosome eggs in tumour tissue, squamous cell	% with schistosome eggs in tumour tissue, transitional cell
Hinder (1969)	South Africa	68	19
Bowry (1975)	Kenya	67	29
Malik (1975)	Sudan	65	5
Bhagwandeen (1976)	Zambia	60	52
Lucas (1982)	Malawi	70	39
Al Adani (1983)	Iraq	70	17
Cooppan (1984)	South Africa	61	13
Kitinya (1986)	Tanzania	47	3
Khurana (1992)	Saudi Arabia	67	0
Groeneveld (1996)	South Africa	85	10

References: (Al Adnani & Saleh, 1983; Bhagwandeen, 1976; Bowry, 1975; Cooppan *et al.*, 1984; Groeneveld *et al.*, 1996; Hinder & Schmaman, 1969; Khurana *et al.*, 1992; Kitinya *et al.*, 1986; Lucas, 1982a; Malik, 1975)

The correlation between squamous cell carcinoma and schistosomiasis infection, the development of bladder cancer at younger ages, the higher prevalences of squamous cell carcinoma in tropical countries and the evidence from laboratory studies all point at a causal relationship between squamous cell carcinoma and *S. haematobium* infection. However, there are no studies which provide data on the number of bladder cancer cases caused by schistosomiasis. The published literature on *S. haematobium* infection and bladder cancer mainly contains retrospective hospital based studies. Researchers collect specimens of the bladder that were obtained by cystectomy, cystoscopy or during a postmortem examination and perform a (re-)examination of the material with special attention for evidence of schistosoma ova in the tissue.

Due to the lack of studies which provide incidence or prevalence data of schistosomiasis related bladder cancer we calculated the mortality rate of bladder cancer by using an overall age-standardised mortality rate for bladder cancer provided by La Vecchia *et.al.*.(La Vecchia *et al.*, 1993). We calculated the risk of death from bladder cancer for patients infected with *S. haematobium* in Egypt.

Death rate from bladder cancer for patients infected with S. haematobium *in Egypt.*

Bladder cancer age-standardised mortality in Egypt: 10.8 per 100,000 for men and 2.3 per 100,000 for women in the 1950s (La Vecchia *et al.* 1993)

Assumption 1: Not all bladder cancer deaths are registered as bladder cancer deaths. Especially in tropical countries it is likely that there is an underestimation of the number of cancer death, due to lack of medical facilities for diagnosis and documentation. Therefore, we assume that 50% of the bladder cancer deaths are registered correctly.

Corrected age-standardised mortality:
men: $10.8 \cdot (1 / 0.5) = 21.6$ per 100,000 per year
women: $2.3 \cdot (1 / 0.5) = 4.6$ per 100,000 per year

Assumption 2: *S. haematobium* infection causes squamous cell type carcinoma, it does not cause other histological types of bladder carcinoma.

Assumption 3: The death rate of bladder cancer of the squamous cell type is comparable to the general death rate of bladder cancer.

A study from 1961 (Hashem, 1961) reports that in Egypt 62.3% of all bladder cancers are squamous cell type (table 1.4.1). We calculated the number of death due to squamous cell type bladder tumours in Egypt.
men: 21.6 per 100,000 · 0.623 = 13.5 per 100,000 per year due to squamous cell cancer
women: 4.6 per 100,000 · 0.623 = 2.87 per 100,000 per year due to squamous cell cancer

The prevalence of *S. haematobium* was 25.8% in the Nile delta area in 1962 (Farooq *et al.*, 1966). 16.4% is estimated to have a severe infection (> 50 eggs/10 ml, Epiworm). If we assume that bladder cancer only occurs in individuals with severe infection and that men and women are equally infected we can calculate that
men: 13.5 / 16,400 = 0.000823 severe infected individuals will die of bladder cancer due to *S. haematobium* infection
women: 2.87 / 16,400 = 0.000175 severe infected individuals will die of bladder cancer due to *S. haematobium* infection

For the calculation of the estimated number of individuals dying of bladder cancer due to *S. haematobium* infection we applied heterogeneity in prevalences of (severe) infection of the countries (see appendix A9).

B2 Intestinal schistosomiasis

2.1 (Bloody) diarrhoea and blood in stool

Diarrhoea, bloody diarrhoea and blood in stool are all reported in the literature on intestinal schistosomiasis and morbidity. The difference between the three symptoms is gradual and probably difficult to discern. Most studies that report prevalence of bloody diarrhoea do not report prevalence of blood in stool and vice versa.
For the calculations of the morbidity, therefore, we will concentrate on diarrhoea and blood in stool. These two symptoms are easy to distinguish, whereas there will be overlap between diarrhoea and bloody diarrhoea and blood in stool and bloody diarrhoea. We also chose for blood in stool because it is considered to be the most specific symptom related to intestinal schistosomiasis.
Data on *S. japonicum* infection and bloody diarrhoea were not available. Information on prevalence of blood in stool in relation to infection with *S. japonicum* was only provided by a few studies in the English literature. There were no studies that reported prevalence of blood in stool for different intensity of *S. japonicum* infection groups (i.e. no figure).
Due to lack of information we were not able to calculate the relation between prevalence of blood in stool and prevalence of *S. japonicum* infection. Therefore, we assumed that the shape of the curve for the relation between prevalence of blood in stool and prevalence of infection will be the same for *S. mansoni* and *S. japonicum*, only the start of the curve could be at a different level. So for calculating the estimated number of individuals with morbidity the same curve can be used.

S. mansoni

The prevalence of diarrhoea is measured by questionnaire. The time period used by the questionnaire method differs widely between the different field studies (one day to 8 weeks, often not specified). Some studies reported prevalence of diarrhoea for more than one time period. The results from the time period nearest to 2 weeks were used for the analysis.
Diarrhoea is an aspecific symptom that can be caused by several diseases; this can explain the considerable difference in baseline levels as shown in figure 2.1.1.
The association between prevalence of *S. mansoni* infection and prevalence of diarrhoea is represented by a curve with $a = 0.214$, $b = 0.287$ and $c = 8.659$ (figure 2.1.4). According to the figure only at high prevalences, *S. mansoni* infection contributes to diarrhoea.

Although figure 2.1.2 shows an association between intensity of infection and prevalence of bloody diarrhoea, we did not find the association between prevalence of infection and bloody diarrhoea, figure 2.1.5.

The prevalence of blood in stool is measured by questionnaire. The time period used by the questionnaire method differs widely between the different field studies (one day to one year, often not specified). Some studies reported prevalence of blood in stool for more than one time period. The results from the time period nearest to 2 weeks were used for the analysis.
Figure 2.1.3 show an association between intensity of infection and prevalence of blood in stool.
Two studies provided most data points, Utzinger *et al.* (2000) 60 data points and Lengeler *et al.* (2000) 54 data points. The shape of the individually fitted curves for the data points from Utzinger *et al.* and Lengeler *et al.* was comparable to the shape of the curve for the other data points. Therefore, a combined curve for all data points was fitted (standard curve). The curve is represented by $a = 0.186$, $b = 0.689$ and $c = 4.948$ (figure 2.1.6).

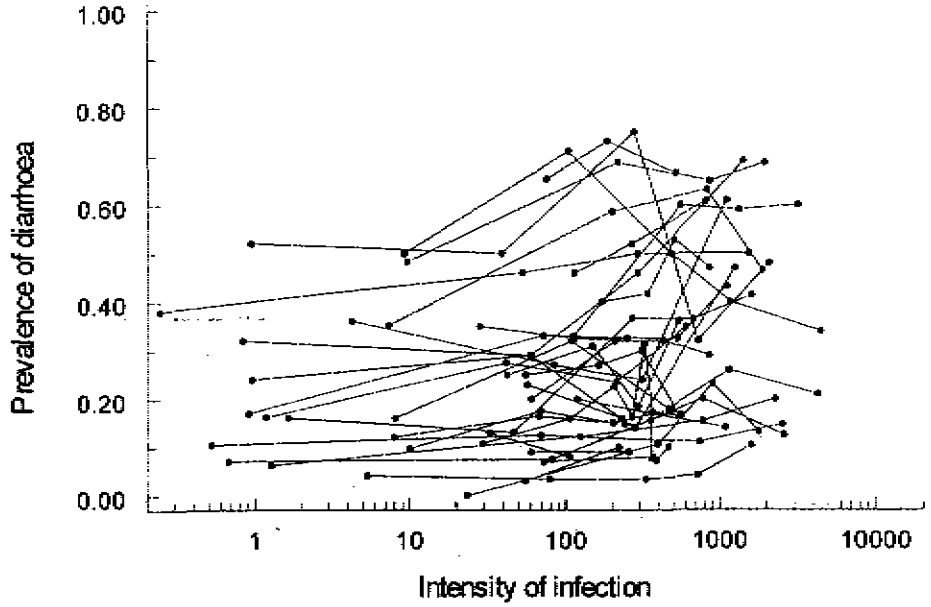

Figure 2.1.1: Prevalence of diarrhoea measured by questionnaire by intensity of *S. mansoni* infection. Points from the same study are connected.

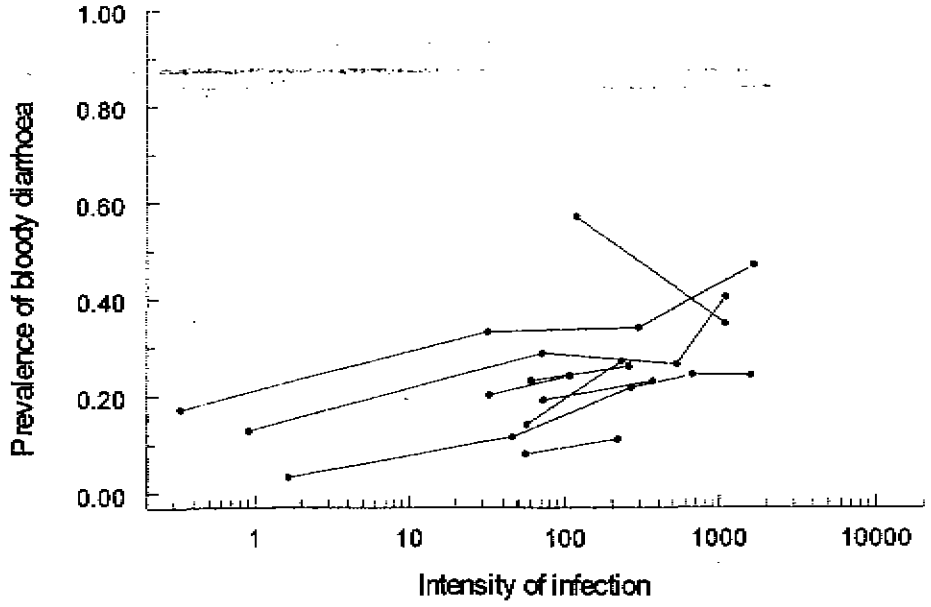

Figure 2.1.2: Prevalence of bloody diarrhoea measured by questionnaire by intensity of *S. mansoni* infection. Points from the same study are connected.

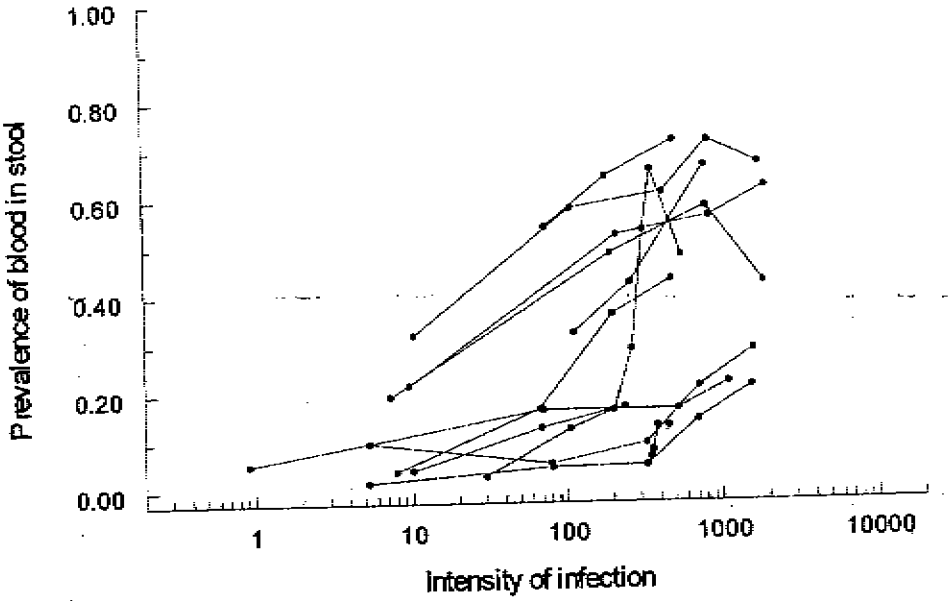

Figure 2.1.3: Prevalence of blood in stool measured by questionnaire by intensity of *S. mansoni* infection. Points from the same study are connected.

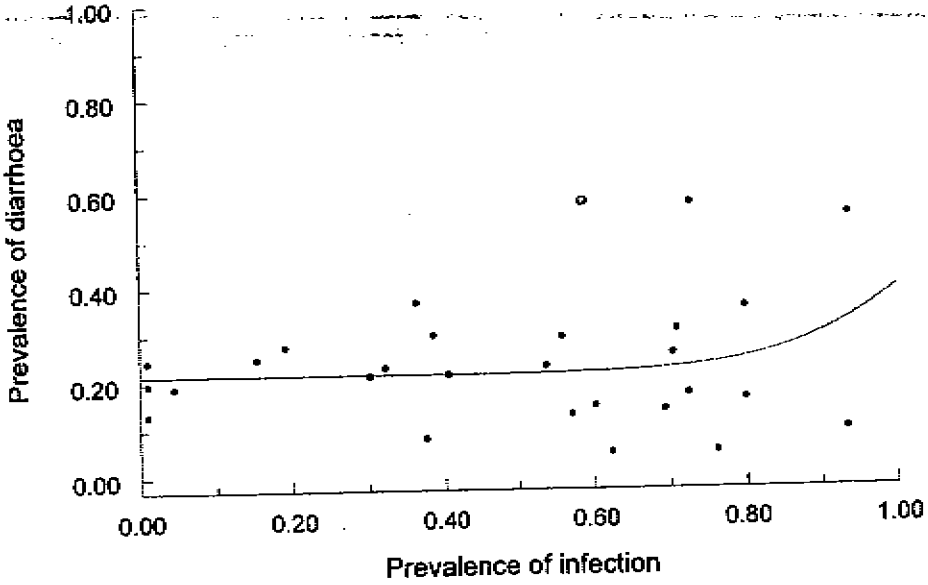

Figure 2.1.4: Prevalence of diarrhoea measured by questionnaire by prevalence of *S. mansoni* infection.

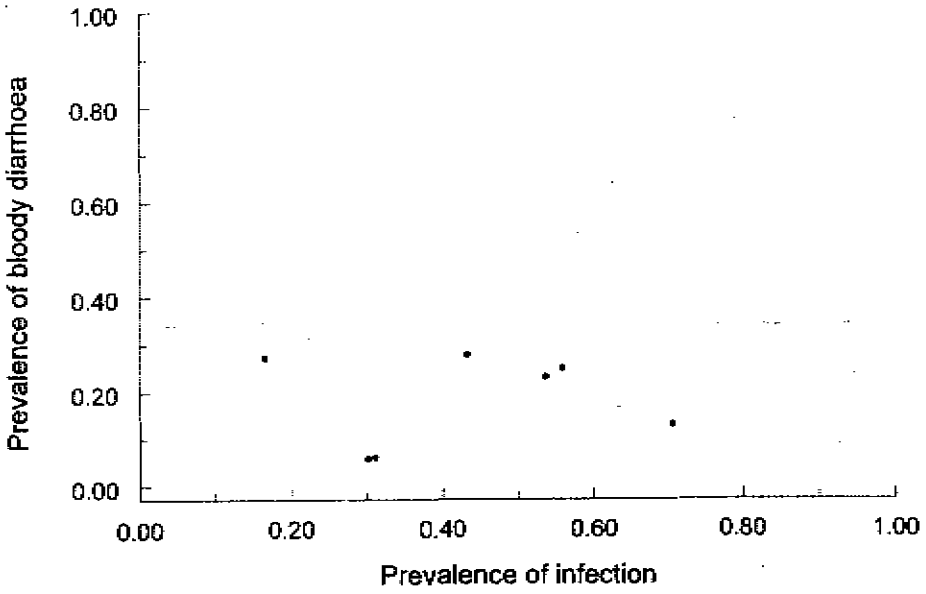

Figure 2.1.5: Prevalence of bloody diarrhoea measured by questionnaire by prevalence of *S. mansoni* infection.

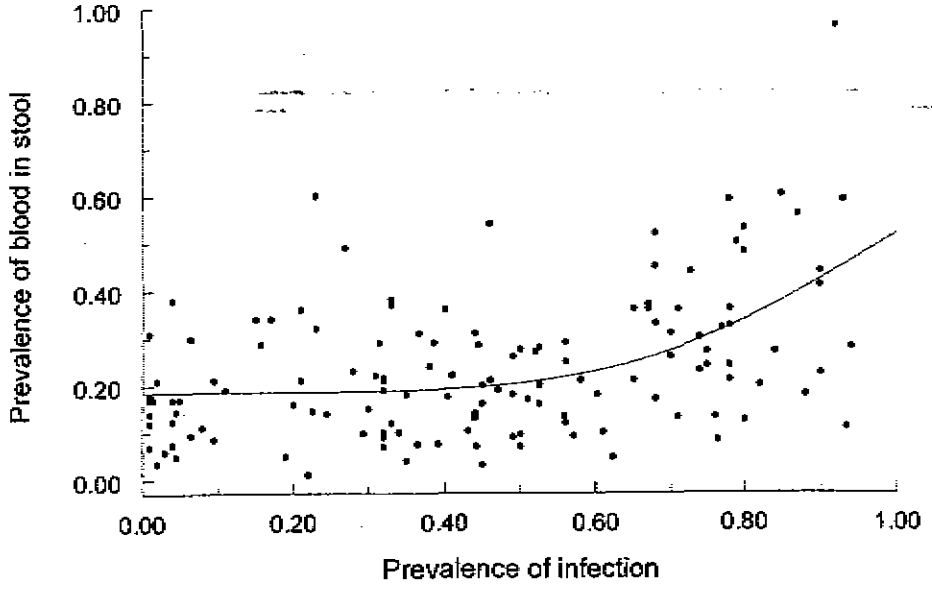

Figure 2.1.6: Prevalence of blood in stool measured by questionnaire by prevalence of *S. mansoni* infection.

S. japonicum

The prevalence of diarrhoea is measured by questionnaire. The time period used by the questionnaire method differs widely between the different field studies (one day to 2 weeks, often not specified). Some studies reported prevalence of diarrhoea for more than one time period. The results from the time period nearest to 2 weeks were used for the analysis.
There is a positive association between intensity of infection and prevalence of diarrhoea (figure 2.1.7)
There was only one study with a prevalence of infection above 50%. Therefore, we used the shape of the curve of the prevalence of diarrhoea and prevalence of *S. mansoni* infection (b = 0.287 and c = 8.659). The starting point a was fitted for the data from the *S. japonicum* studies, a = 0.117 (figure 2.1.8).

The base-line prevalence of diarrhoea is lower in areas endemic for *S. japonicum* compared to areas endemic for *S. mansoni*, resp. 0.117 and 0.214.

There are no field studies that reported prevalence of bloody diarrhoea in *S. japonicum* infected individuals.

Due to lack of data we were not able to calculate the relation between prevalence of blood in stool and prevalence of *S. japonicum* infection. Therefore, we assumed that the shape of the curve for the relation between prevalence of blood in stool and prevalence of infection will be the same for *S. mansoni* and *S. japonicum* (b = 0.689 and c = 4.948), only the start of the curve a was fitted from the data, a = 0.159 (figure 2.1.9).

The base-line level of the fitted curve was comparable to the base-line level for *S. mansoni*, resp. 0.159 and 0.186.

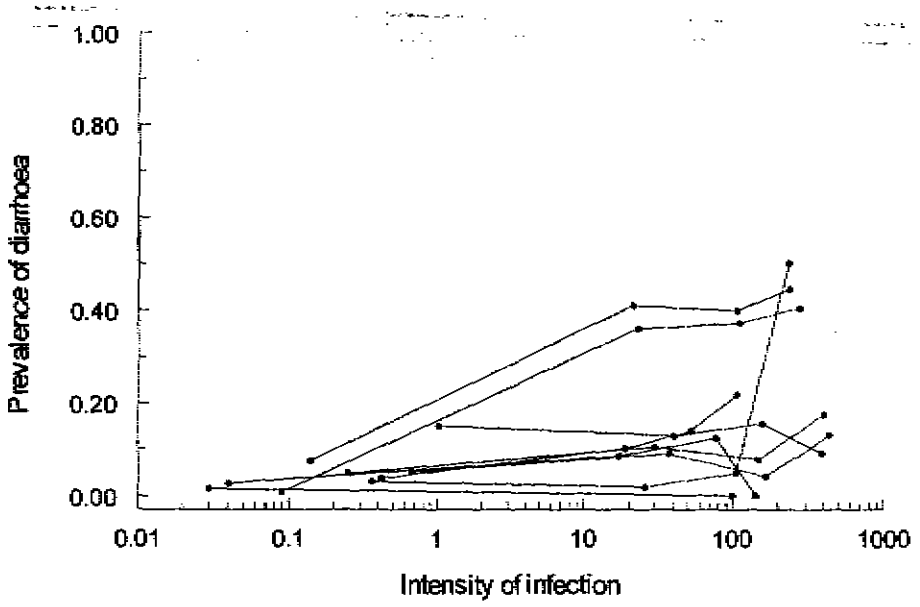

Figure 2.1.7: Prevalence of diarrhoea measured by questionnaire by intensity of *S. japonicum* infection. Points from the same study are connected.

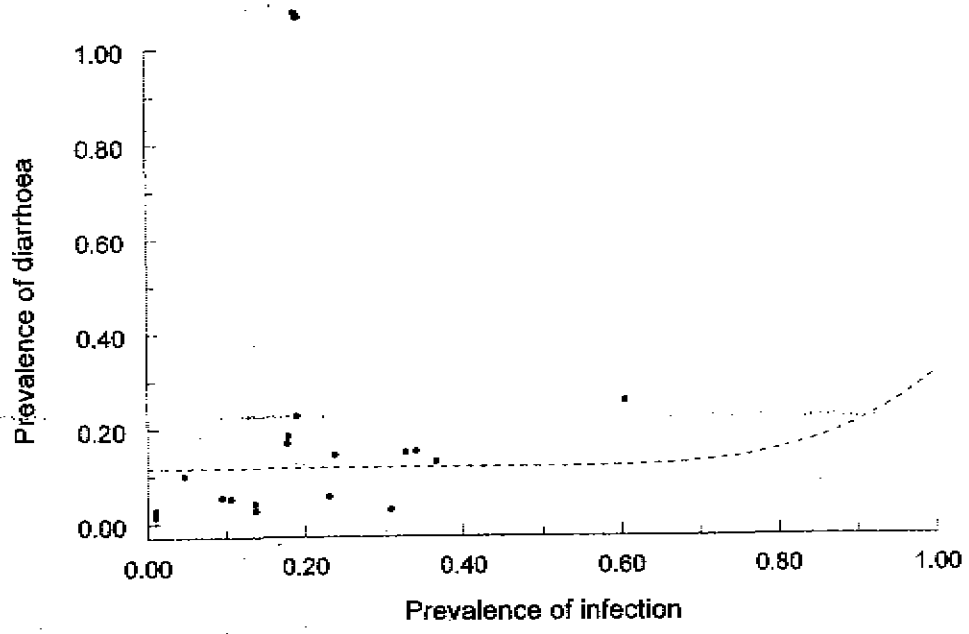

Figure 2.1.8: Prevalence of diarrhoea measured by questionnaire by prevalence of *S. japonicum* infection. Dotted line has the shape of the curve from relationship between prevalence of diarrhoea and prevalence of *S. mansoni* infection (figure 2.1.4) with a separately fitted starting point.

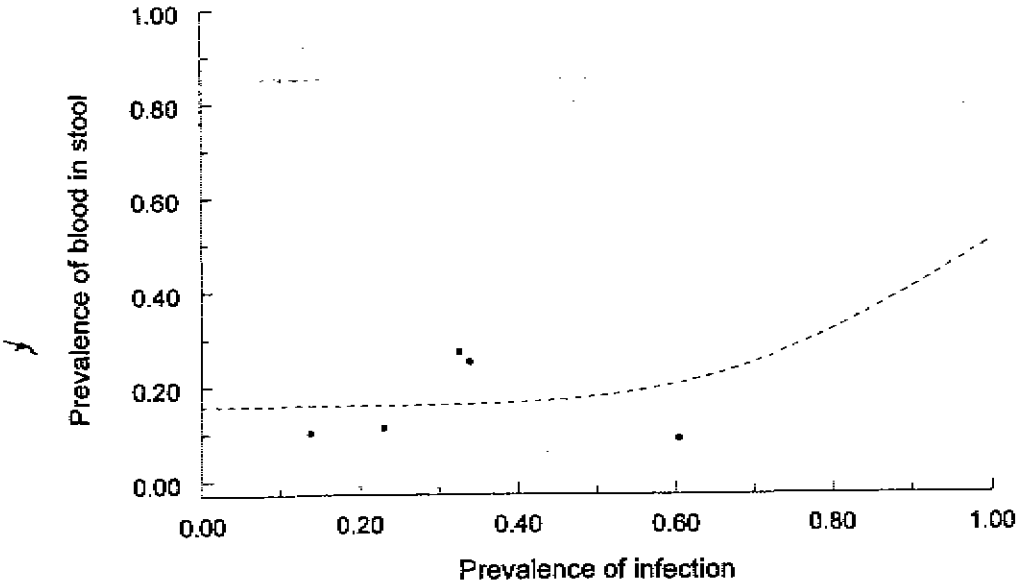

Figure 2.1.9: Prevalence of blood in stool measured by questionnaire by prevalence of *S. japonicum* infection. Dotted line has the shape of the curve from relationship between prevalence of blood in stool and prevalence of *S. mansoni* infection (figure 2.1.6) with a separately fitted starting point.

2.2 Abdominal pain

S. mansoni

The prevalence of abdominal pain is measured by questionnaire. The time period used by the questionnaire method differs widely between the different field studies (1 day to 8 weeks, often not specified). Some studies reported prevalence of abdominal pain for more than one time period. The results from the time period nearest to 2 weeks were used for the analysis.

There is no association between intensity of infection and prevalence of abdominal pain (figure 2.2.1).

Calculation of the relationship between prevalence of abdominal pain and prevalence of *S. mansoni* infection was non-conclusive (see figure 2.2.2).

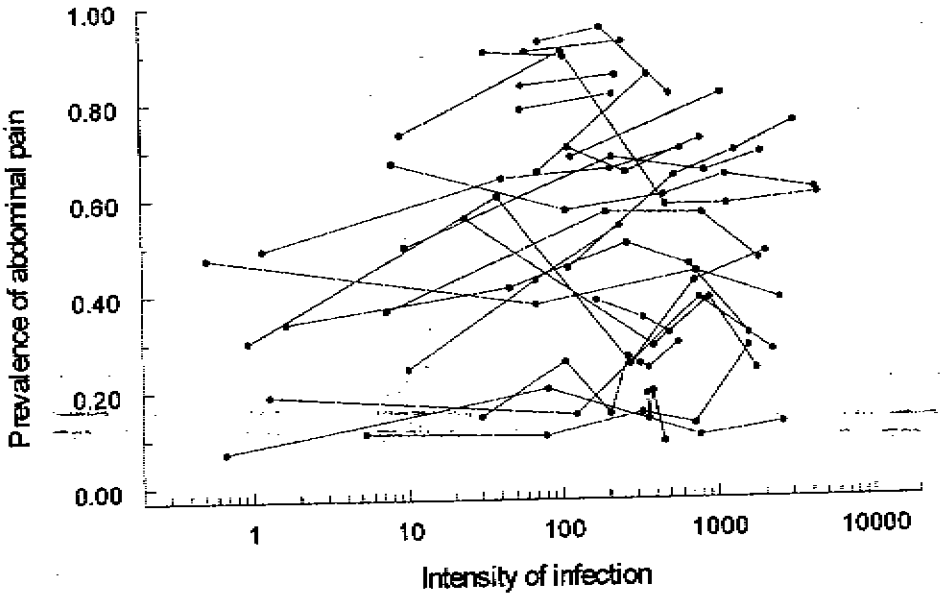

Figure 2.2.1: Prevalence of abdominal pain measured by questionnaire by intensity of *S. mansoni* infection. Points from the same study are connected.

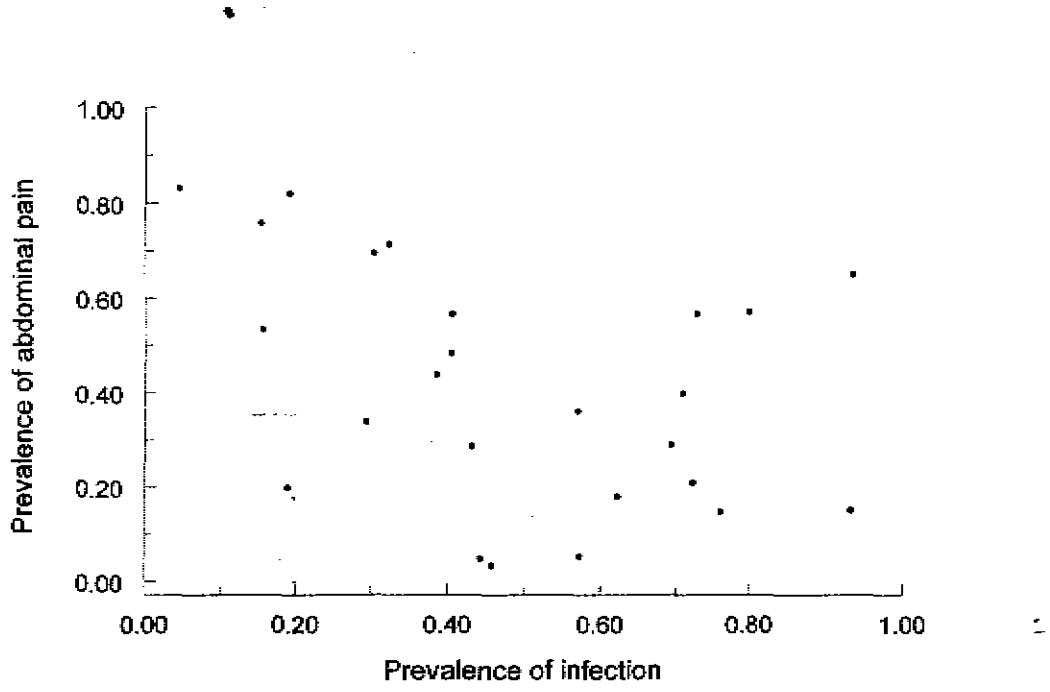

Figure 2.2.2: Prevalence of abdominal pain measured by questionnaire by prevalence of *S. mansoni* infection.

S. japonicum

The prevalence of abdominal pain is measured by questionnaire. The time period used by the questionnaire method differs widely between the different field studies (one day to 2 weeks, often not specified). Some studies reported prevalence of abdominal pain for more than one time period. The results from the time period nearest to 2 weeks were used for the analysis. There is no clear association between intensity of infection and prevalence of abdominal pain (figure 2.2.3)
The shape of the standard curve was unrealistic. Therefore, we used the alternative curve with point of inflection at 1.0 to calculate the association between *S. japonicum* infection and abdominal pain. This curve is represented with $a = 0.204$, $b_{1.0} = 0.252$ and $c = 1.673$ (figure 2.2.4). Note that the rising trend is mainly due to one data point. Also, figure 2.2.3 does not suggest a relation between intensity of infection and prevalence of morbidity.

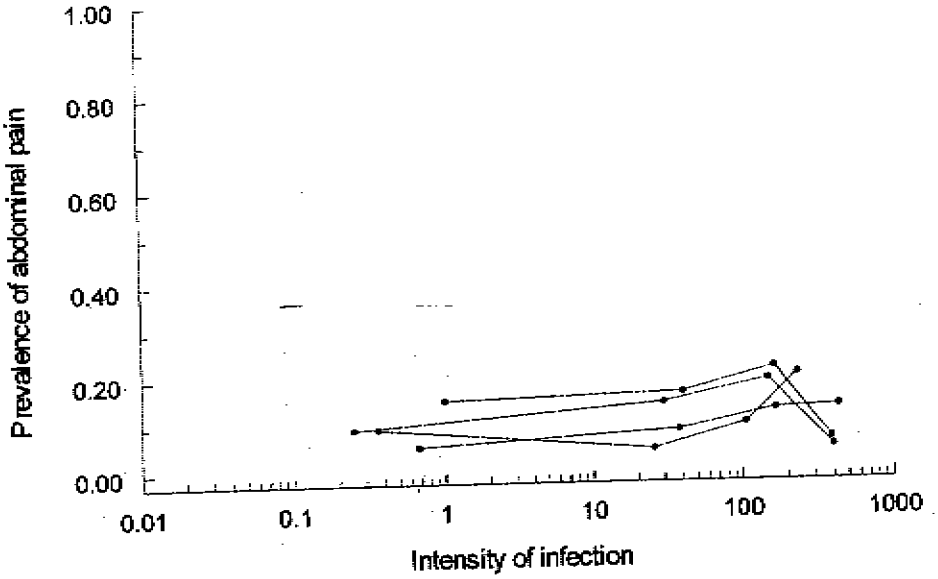

Figure 2.2.3: Prevalence of abdominal pain measured by questionnaire by intensity of *S. japonicum* infection. Points from the same study are connected.

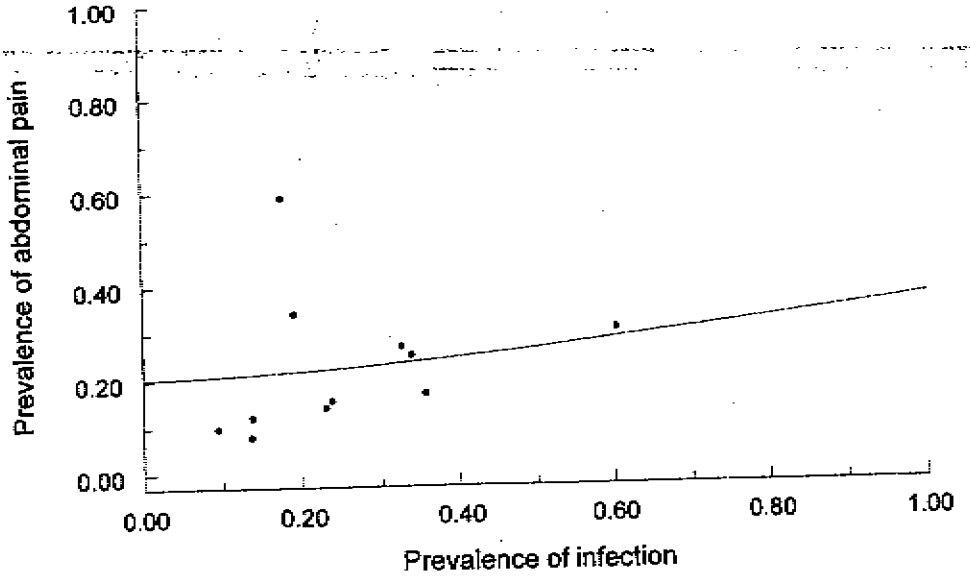

Figure 2.2.4: Prevalence of abdominal pain measured by questionnaire by prevalence of *S. japonicum* infection.

2.3 Hepatomegaly

The prevalence of hepatomegaly is measured by clinical examination or by ultrasound. For this analysis we only used the results of studies that reported hepatomegaly by clinical examination.
Hepatomegaly can be measured at mid-sternal level (MSL, enlargement is related to schistosomiasis infection) or mid-clavicular level (MCL). The cut-off points for defining hepatomegaly differed between the studies (MSL: from palpable to > 5cm, MCL: from palpable to > 4 cm). Some studies reported prevalence of hepatomegaly for more than one cut-off point. The results of the lowest cut-off point (i.e. palpable) at mid-sternal level were used for the analysis.

S. mansoni

Figure 2.3.1. represents the association between intensity of infection and prevalence of hepatomegaly (MCL).
The shape of the fitted standard curve for the association between *S. mansoni* infection and hepatomegaly (MCL) was unrealistic. Therefore, we used the alternative curve with point of inflection at 1.0 to calculate the association. The curve is represented by $a = 0.143$, $b_{1.0} = 0.165$ and $c = 1.395$ (figure 2.3.3).

Figure 2.3.2 represents the association between intensity of infection and prevalence of hepatomegaly (MSL).
The shape of the fitted standard curve for the association between *S. mansoni* infection and hepatomegaly (MSL) was unrealistic. Therefore, we used the alternative curve with point of inflection at 1.0 to calculate the association between *S. mansoni* infection and hepatomegaly (MSL). The curve is represented by $a = 0.183$, $b_{1.0} = 0.217$ and $c = 1.555$ (figure 2.3.4).

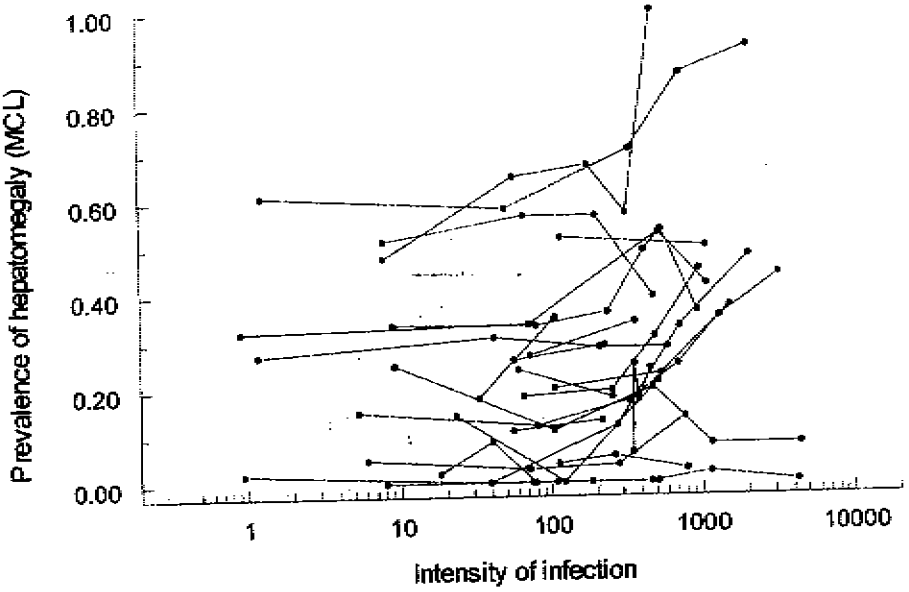

Figure 2.3.1: Prevalence of hepatomegaly (MCL) measured by clinical examination by intensity of *S. mansoni* infection. Points from the same study are connected.

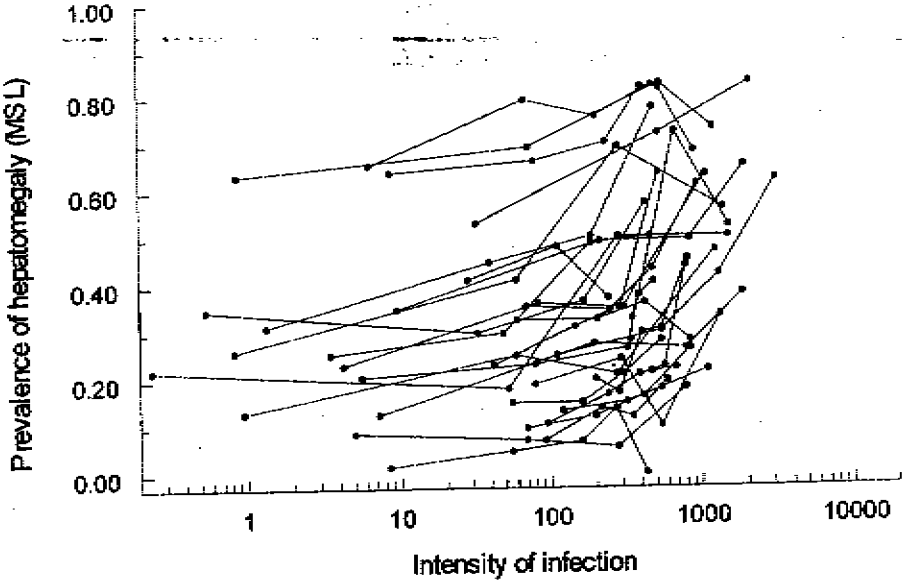

Figure 2.3.2: Prevalence of hepatomegaly (MSL) measured by clinical examination by intensity of *S. mansoni* infection. Points from the same study are connected.

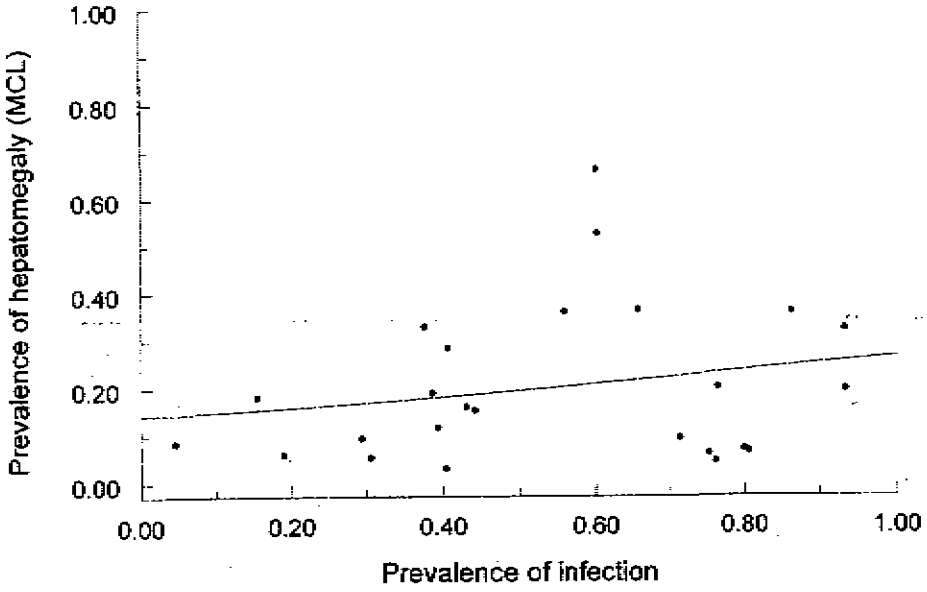

Figure 2.3.3: Prevalence of hepatomegaly (MCL) measured by clinical examination by prevalence of *S. mansoni* infection.

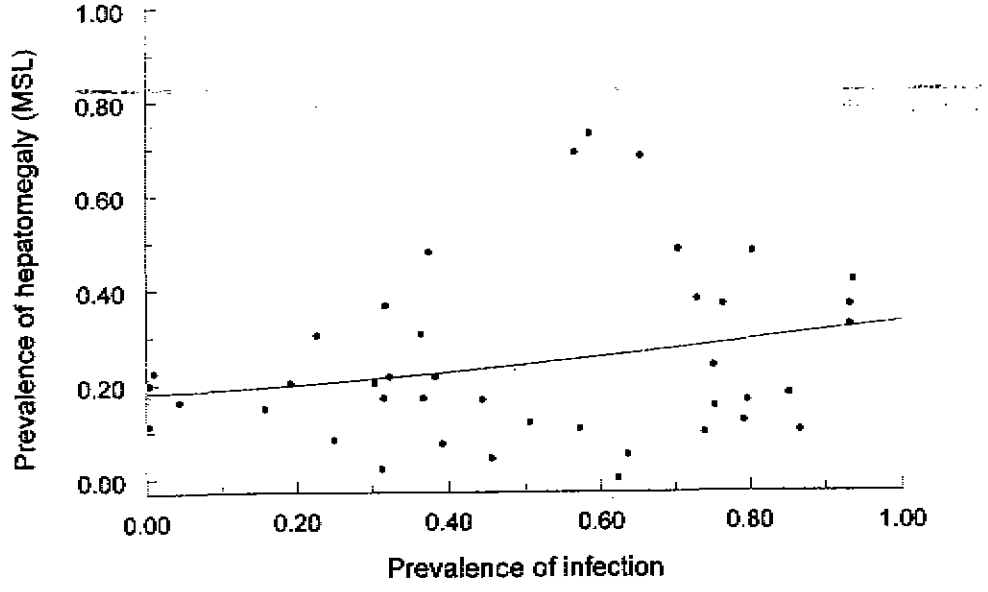

Figure 2.3.4: Prevalence of hepatomegaly (MSL) measured by clinical examination by prevalence of *S. mansoni* infection.

S. japonicum

All studies reported hepatomegaly (MCL) with a cut-off level of >2 cm below the subcostal margin.
Figure 2.3.5 represents the association between intensity of infection and prevalence of hepatomegaly (MCL).
For hepatomegaly (MCL) the standard curve was fitted. The curve is represented by $a = 0.041$, $b_{1.0} = 4.581$ and $c = 7.390$ (figure 2.3.7). Only one data point > 50% prevalence of infection was available. This mainly defines the shape of the curve.

Except for one study, all studies reported hepatomegaly at mid-sternal level with a cut-off level of > 3cm below the costal margin.
Figure 2.3.6 represents the association between intensity of infection and prevalence of hepatomegaly (MSL).
The shape of the fitted standard curve of the association between *S. japonicum* infection and hepatomegaly (MSL) was unrealistic. Therefore, we used the alternative curve with point of inflection at 1.0. The curve is represented by $a = 0.254$, $b_{1.0} = 0.294$ and $c = 1.834$ (figure 2.3.8).
The base-line level of hepatomegaly (MSL) is higher in areas endemic for *S. japonicum* compared to areas endemic for *S. mansoni*, resp. 0.208 and 0.165. The increase in morbidity by increasing prevalence of infection is faster for *S. japonicum*.

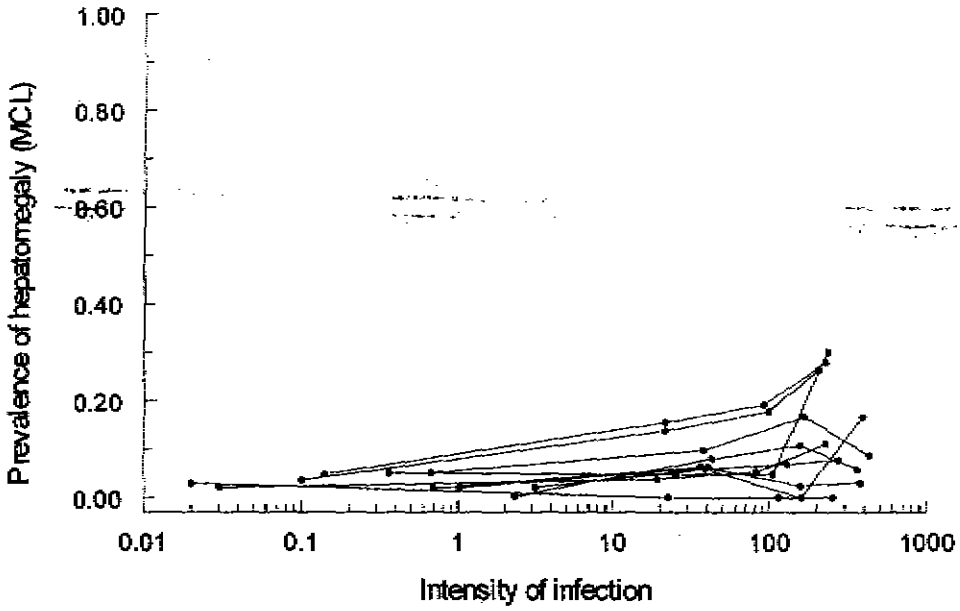

Figure 2.3.5: Prevalence of hepatomegaly (MCL) measured by clinical examination by intensity of *S. japonicum* infection. Points from the same study are connected.

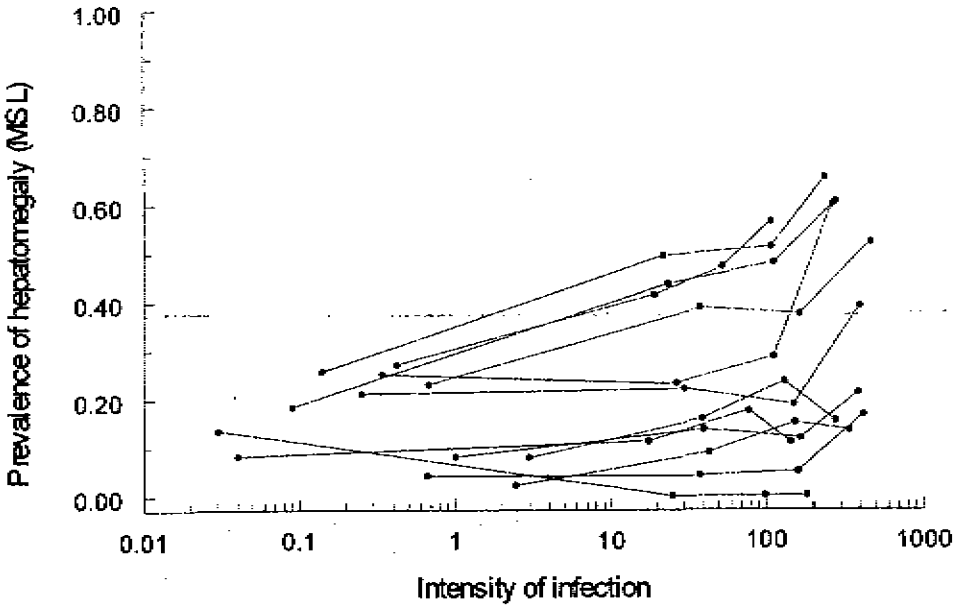

Figure 2.3.6: Prevalence of hepatomegaly (MSL) measured by clinical examination by intensity of *S. japonicum* infection. Points from the same study are connected.

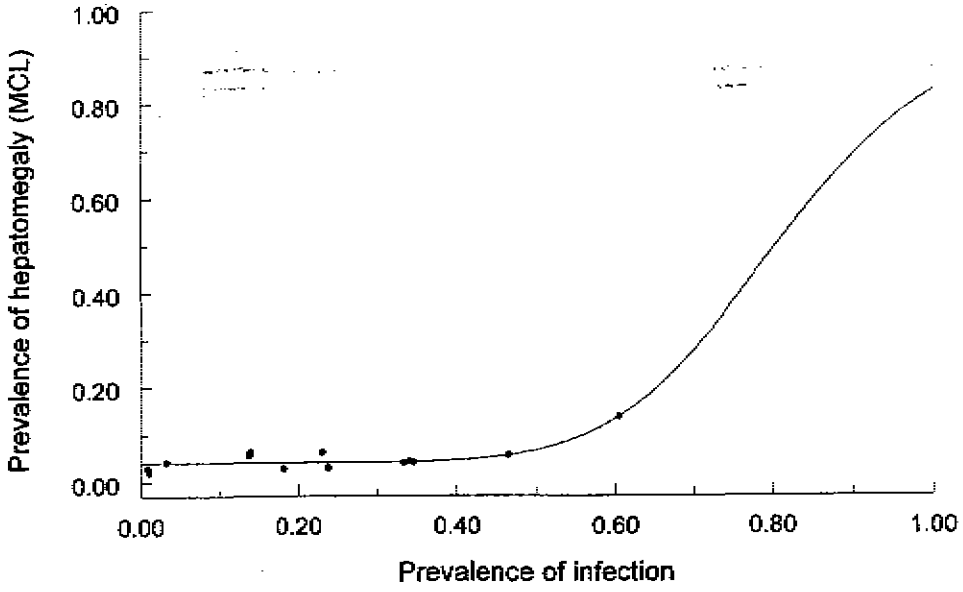

Figure 2.3.7: Prevalence of hepatomegaly (MCL) measured by clinical examination by prevalence of *S. japonicum* infection.

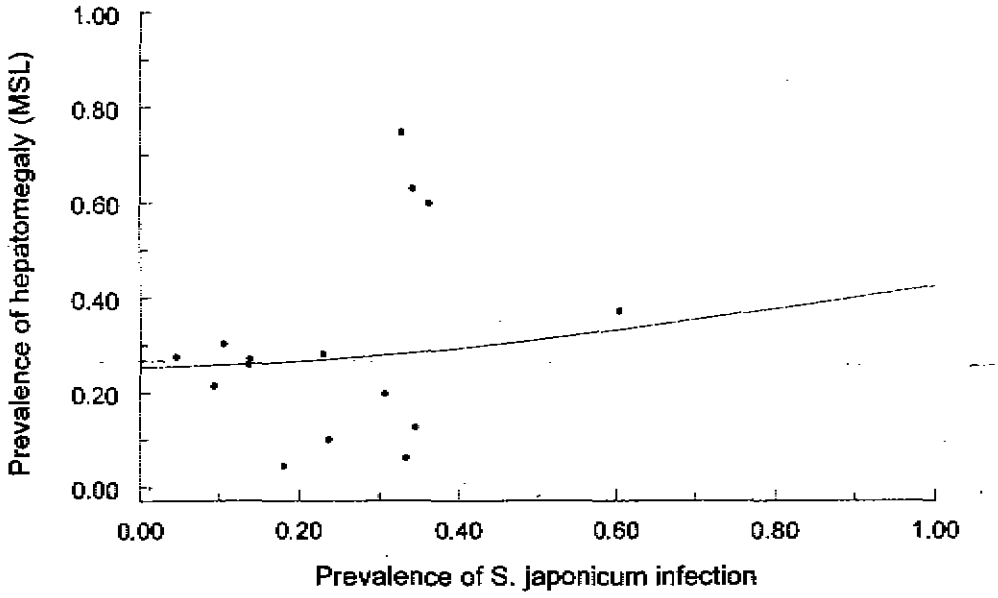

Figure 2.3.8: Prevalence of hepatomegaly (MSL) measured by clinical examination by prevalence of *S. japonicum* infection.

2.4 Splenomegaly

The prevalence of splenomegaly is measured by clinical examination or by ultrasound. For this analysis we only used the results of studies that reported splenomegaly by clinical examination.
The cut-off points for defining splenomegaly differed between the studies (Hackett grade 1 and 2 and comparable measures). Some studies reported prevalence of splenomegaly for more than one cut-off point. The results of the lowest cut-off point (i.e. palpable spleen) were used for the analysis.
It should be noted that areas with a high prevalence of *S. mansoni* may also have a relatively high prevalence of malaria. This will overestimate the association between prevalence of *S. mansoni* infection and splenomegaly.

S. mansoni

Figure 2.4.1 represents the association between intensity of infection and prevalence of splenomegaly.
The shape of the fitted standard curve was unrealistic. Therefore, we used the alternative curve with point of inflection at 1.0 to calculate the association between *S. mansoni* infection and splenomegaly. This curve is represented with $a = 0.094$, $b_{1.0} = 0.120$ and $c = 1.272$ (figure 2.4.2).

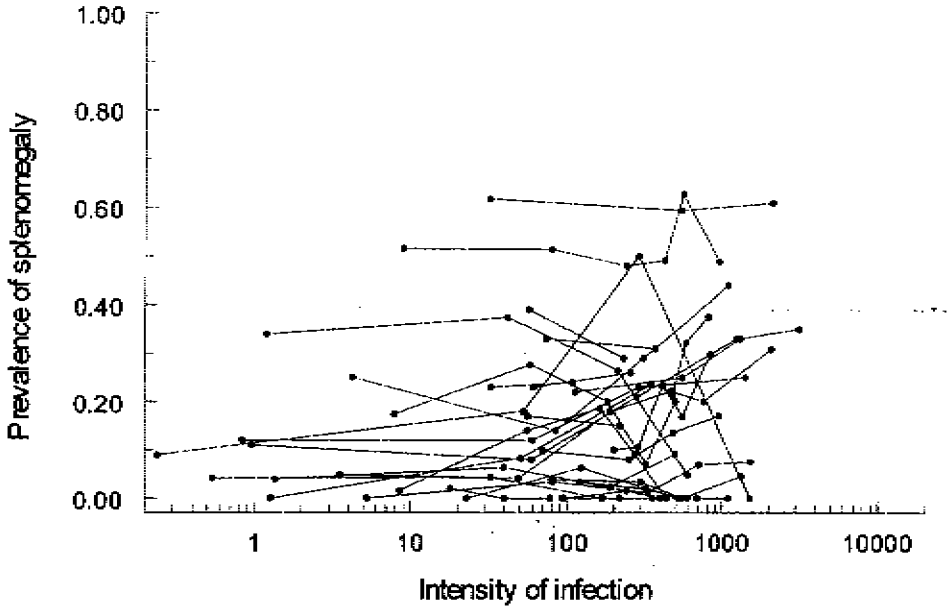

Figure 2.4.1: Prevalence of splenomegaly measured by clinical examination by intensity of *S. mansoni* infection. Points from the same study are connected.

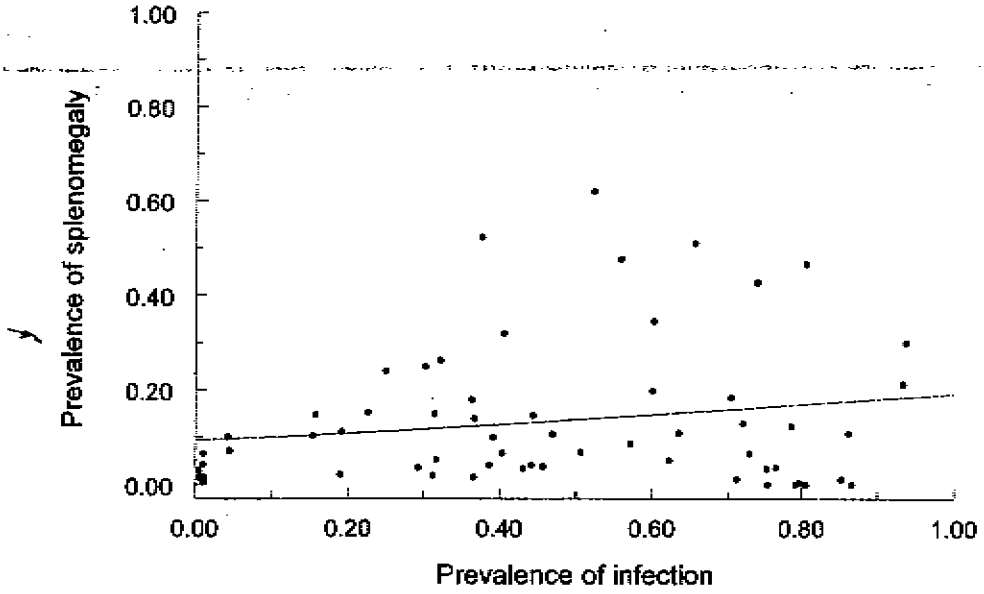

Figure 2.4.2: Prevalence of splenomegaly by clinical examination by prevalence of *S. mansoni* infection.

S. japonicum

Figure 2.4.3 represents the association between intensity of infection and prevalence of splenomegaly.
The point of inflection of the fitted standard curve was < 0.5. Therefore, we used the alternative curve with point of inflection at 1.0 to calculate the association between *S. japonicum* infection and splenomegaly. The curve is represented by $a = 0.018$, $b_{1.0} = 0.176$ and $c = 1.428$ (figure 2.4.4).

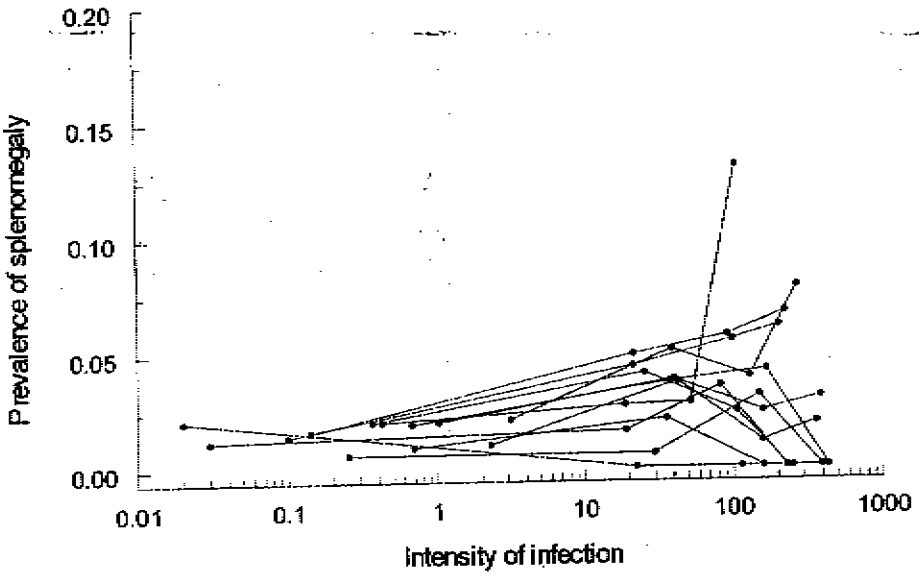

Figure 2.4.3: Prevalence of splenomegaly measured by clinical examination by intensity of *S. japonicum* infection. Points from the same study are connected.

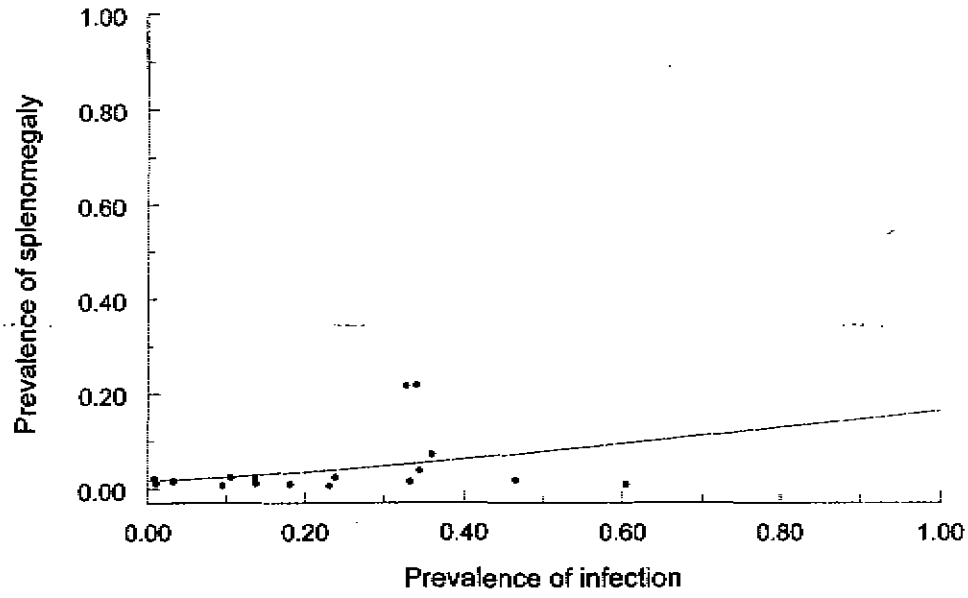

Figure 2.4.4: Prevalence of splenomegaly by clinical examination by prevalence of *S. japonicum* infection.

2.5 Hematemesis and ascitis

The literature on long-term morbidity caused by *S. mansoni* infection consists mainly of field studies. As part of these studies, individuals are interviewed and questioned if they have had hematemesis and they are clinically examined for ascitis. We were not able to identify field studies on *S. japonicum* infection and hematemesis or ascitis.
The long development time of oesophageal varices and ascitis and the high mortality make it difficult to calculate estimates of prevalence of this morbidity.

S. mansoni

It takes 10 to 15 years to develop severe morbidity, therefore the relationship between the current intensity of infection and the existence of long-term morbidity is not obvious. Also, individuals with hematemesis have a significant chance of dying from exsanguation, which reduces the number of individuals with a hematemesis history that can be identified in a cross-sectional community study.

We present the number of infected individuals in all studies with an unselected study population and the total number of individuals with hematemesis or ascitis (table 2.5.1 and 2.5.2).

Table 2.5.1: Summary of the literature on *S. mansoni* infection and hematemesis.

Author	Country	No. of individuals tested	No. of individuals positive (prevalence in %)	No. of individuals with hematemesis
Ongom (1972)	Uganda	231	206 (89.2)	12
Hiatt (1976)	Ethiopia	197	94 (47.7)	3
de Lima (1985)	Brazil	1106	806 (72.9)	1
Friis (1987)	Botswana	354	285 (80.5)	0
Gryseels (1987)	Zaire	531	510 (96.0)	0
Gryseels (1988)	Burundi	6203	2035 (32.8)	0
Gryseels (1990)	Burundi (area A)	547	216 (39.5)	0
Gryseels (1990)	Burundi (area B)	662	107 (16.2)	0
Gryseels (1990)	Burundi (area C)	365	19 (5.2)	0
Gaye (1991)	Senegal	1260	527 (41.8)	1
Boisier (1995)	Madagascar (Antanetibe)	48	12 (25.0)	0
Boisier (1995)	Madagascar (Belagera)	482	298 (61.8)	5
Homeida (1996)	Sudan (Elhusein)	2910	1368 (47.0)	35
Homeida (1996)	Sudan (Elnur)	901	378 (42.0)	18
Kardorff (1997)	Tanzania	1651	1426 (86.4)	1
Kabatereine (2000)	Uganda	890	763 (85.7)	0

References: Ongom & Bradley, 1972; Hiatt, 1976; de Lima e Costa *et al.*, 1985; Friis & Byskov, 1987; Gryseels & Polderman, 1987; Gryseels, 1988; Gryseels & Nkulikyinka, 1990; Gaye *et al.*, 1991; Boisier *et al.*, 1995; Homeida *et al.*, 1996; Kardorff *et al.*, 1997; Kabatereine, 2000

The relationship between prevalence of *S. mansoni* infection and prevalence of hematemesis is described by alternative curve with point of inflection at 1.0, $a \approx 0$, $b_{1.0} = 0.0133$ and $c = 1.027$ (figure 2.5.1). However, the shape of the curve is mainly determined by a few points. We also want to remark that the quality of the data points might be questionable. Determining the (life time) prevalence of hematemesis in fieldstudies might not be that accurate.

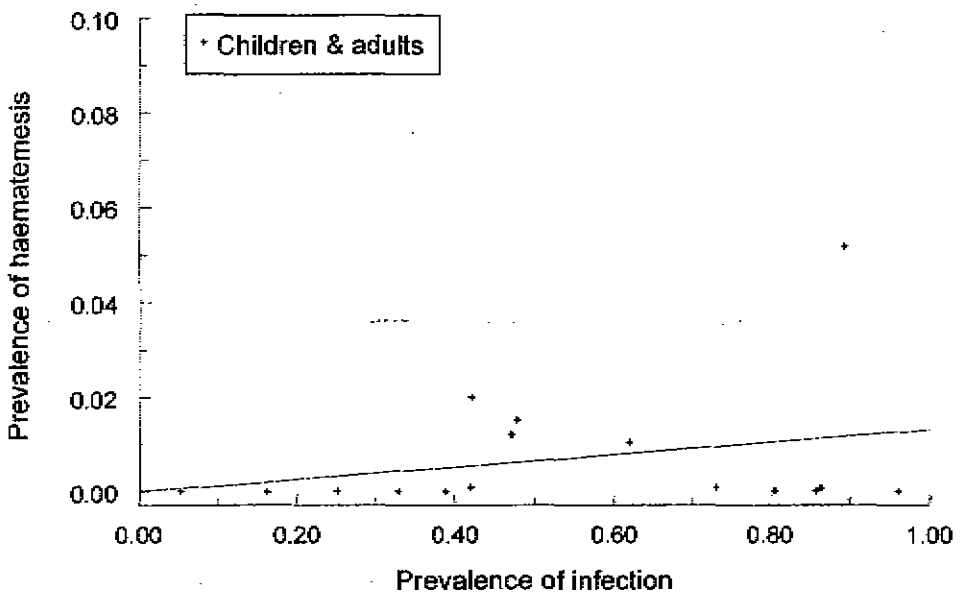

Figure 2.5.1: (Life time) prevalence of reported hematemesis by prevalence of *S. mansoni* infection.

Long-term morbidity can be studied by comparing high and low prevalence villages in the same area and with the same ethnic group. Boisier *et al.* (1995) compared two villages, one with a high prevalence of *S. mansoni* infection (482 individuals) and the other with a low prevalence (48 individuals). In the low prevalence population there was no person with long-term morbidity. This is in agreement with a baseline morbidity $a \approx 0$ (i.e. in areas endemic for *S. mansoni* infection almost all cases of hematemesis are due to infection with *S. mansoni*).

Kiire (1989) reported the chance of re-bleeding and death in patients with histologically proven non-cirrhotic portal fibrosis. Of the 25 patients, 20 rebled within one year and in total 5 died. In another study, 27 patients who attended hospital for hematemesis were followed for 28 months. Eight rebled within the follow-up period and four died of the rebleeding. Four others died of anemia, ascitis and hepatic failure (Richter *et al.*, 1998).

Rate of dying in individuals with hematemesis who visited a hospital:
Study 1 (Kiire, 1989): $p = 0.22$ per year
Study 2 (Richter *et al.*, 1998): $p = 0.069$ per year

Calculation of incidence of hematemesis

Assumptions:
- All hematemesis cases in endemic areas are due to *S. mansoni* infection.
- Hematemesis is irreversible.
- Death rate in endemic areas is 0.02 (crude estimate based on http://www.statistical-data.org/index.html [16 August 2001]).
- Death rate due to hematemesis is 0.14 (average of 0.22 and 0.069).

Incidence = Prevalence · (General death rate + death rate due to hematemesis)

Number of individuals with reported hematemesis (lifetime) (see Appendix C, table 5, 11 and 17) based on association between morbidity and prevalence of infection as stated above, only adults:
WHO Africa D Region: 0.14 million
WHO Africa E Region: 0.26 million
WHO EMR-D Region: 0.026 million

Incidence of hematemesis per WHO Region per year:
WHO Africa D Region: 0.14 million · (0.02 + 0.14) = 22,400
WHO Africa E Region: 0.26 million · (0.02 + 0.14) = 41,600
WHO EMR-D Region: 0.026 million · (0.02 +0.14) = 4,160

Mortality of hematemesis per WHO Region per year:
WHO Africa D Region: 0.14 million · 0.14 = 19,600
WHO Africa E Region: 0.26 million · 0.14 = 36,400
WHO EMR-D Region: 0.026 million · 0.14 = 3,640

Table 2.5.2: Summary of the literature on *S. mansoni* infection and ascitis.

Author	Country	No. of individuals tested	No. of individuals positive (prevalence in %)	No. of individuals with ascitis
de Lima (1985)	Brazil	1106	806 (72.9)	2
Gryseels (1987)	Zaire	531	510 (96.0)	0
Gryseels (1988)	Burundi	6203	2035 (32.8)	0
Gryseels (1990)	Burundi (area A)	547	216 (39.5)	0
Gryseels (1990)	Burundi (area B)	662	107 (16.2)	0
Gryseels (1990)	Burundi (area C)	365	19 (5.2)	0
Kongs (1996)	Senegal	245	183 (74.7)	0
Boisier (1998)	Madagascar	289	190 (65.7)	2

References: de Lima e Costa *et al.*, 1985; Gryseels & Polderman, 1987; Gryseels, 1988; Gryseels & Nkulikyinka, 1990; Kongs *et al.*, 1996; Boisier *et al.*, 1998

The relationship between prevalence of *S. mansoni* infection and prevalence of ascitis is described by alternative curve with point of inflection at 1.0, $a \approx 0$, $b_{1.0} = 0.00249$ and $c = 1.005$ (figure 2.5.2).

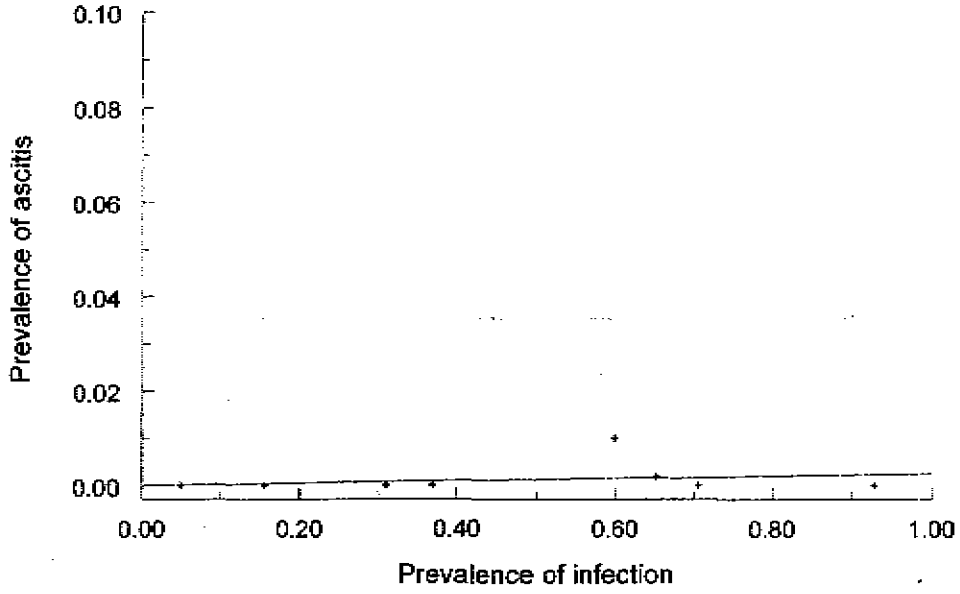

Figure 2.5.2: Prevalence of ascitis measured by clinical examination by prevalence of *S. mansoni* infection.

S. japonicum

There are no data from field studies on prevalence of hematemesis and prevalence of *S. japonicum* infection, therefore we were not able to estimate the relationship between prevalence of hematemesis and prevalence of *S. japonicum* infection.

There are no data from fieldstudies on prevalence of ascitis and prevalence of *S. japonicum* infection, therefore we were not able to estimate the relationship between prevalence of ascitis and prevalence of *S. japonicum* infection.

2.6 General mortality due to schistosomiasis

The course of a schistosome infection complicates the prediction of mortality figures. Often there is a long interval between infection and death, most patients that will die of schistosomiasis die more than 10 years after the initial infection. Only a few people will die during or just after the invasion stage of the infection (Katayama fever). Another complicating factor is that the direct cause of death is liver failure or hematemesis. These sequelae can also be induced by other causes, which are prevalent in countries endemic for schistosomiasis, such as hepatitis B infection or excessive alcohol use.
Both the long time span between initial infection and mortality and the aspecific direct cause of death complicate the predictions of mortality. We were able to identify a few studies, which present mortality data for intestinal schistosomiasis.

S. mansoni mortality

Mortality due to *S. mansoni* infection has been studied in a village in Sudan (total population 1135) from 1987 to 1994 (Kheir *et al.*, 1999). During this period 4 individuals died of schistosomiasis.
A review study from Brazil reports a prevalence of infection of 15.6% in 1950 and 9.5% in 1990 (Katz, 1998). The mortality rate due to schistosomiasis as reported by the National Health Foundation for 1993 was 0.30/100,000 inhabitants.
The data from these studies were insufficient to estimate general mortality due to *S. mansoni* infection. Mortality due to hematemesis is described in paragraph 2.5.

S. japonicum mortality

Blas *et al.* (1986) performed a follow-up study of 278 individuals who were found to be positive for *S. japonicum* eggs 12 years previously (population prevalence 48%). In total, 135 untreated cases could be located. Eight of them had died of schistosomiasis. Schistosomiasis specific death rate in infected individuals 4.94/1,000.
A study from Japan compared observed and expected standardised mortality ratios (SMR) from a population that was heavily infected with *S. japonicum* in 1957, prevalence >90%. From 1957 up to 1982, the observed number of deaths due to cirrhosis of the liver was 39 for men (SMR 4.05) and 28 for women (SMR 5.53), this was significantly increased compared to the expected number of deaths in this population.

B3 Hookworm anemia

Hookworm is a well-known cause of iron-deficiency anemia. Although the association has already been mentioned in 1880 (Perroncito, 1880), studies on the relationship of hookworm infection and anemia were performed much later. Now, there is a huge amount of evidence that hookworm is one of the main causes of iron deficiency anemia in tropical countries. The anemia is caused by the feeding activities of fourth stage larvae (L_4) and adult worms on the gastrointestinal mucosa and the subsequent bleeding from the wounds so produced (Pritchard *et al.*, 1990). By using radioactive tracers it was estimated that one *Necator americanus* worm causes 30 1 blood loss per day, and *Ancylostoma duodenale* 260 1 (Gilles *et al.*, 1964; Roche & Layrisse, 1966). As most hookworm infections are chronic and hookworms accumulate throughout a person's lifetime, this daily loss of blood will eventually cause iron deficiency anemia.

Studies investigating the relationship between hookworm infection and anemia report their results in two ways: 1) infection related to mean haemoglobin levels and 2) infection related to prevalence of anemia.
The results of the studies using mean haemoglobin levels are summarised in figure 3.1.1. We used the studies reporting prevalence of infection and percentage anemia for the calculations. These studies use different cut-off levels below which a person is diagnosed with anemia. The values of the cut-off levels range from 7 gr/dl haemoglobin to 14 gr/dl, sometimes one study uses different cut-off values for men, women and children. If a study reported prevalence of anemia for different cut-off levels than the results of the most conservative cut-off level were used for the calculations. We grouped the results in anemia (> 8 gr/dl up to 14 gr/dl) and severe anemia (≤ 8 gr/dl). Figure 3.1.2 summarises the prevalence of anemia in different intensity of infection groups and shows a clear increase of disease with intensity.

The base-line level of anemia is considerable (almost 25%) but dependent on only one low endemicity study. This might underestimate the impact of hookworm on anemia. The fitted curve is represented by $a = 0.238$, $b = 2.199$ and $c = 7.770$ (figure 3.1.3).

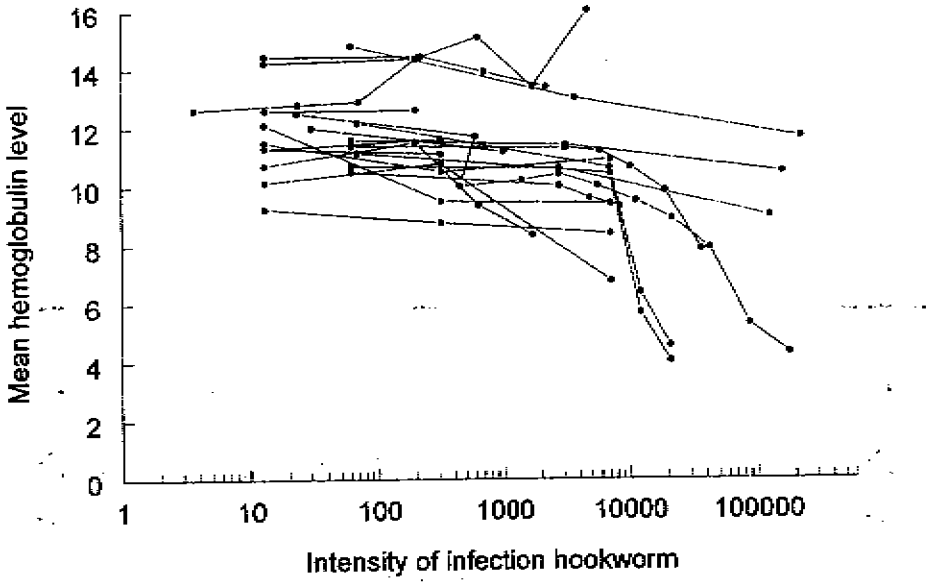

Figure 3.1.1: Mean haemoglobin concentration at different intensity of hookworm infection levels. Pionts from the same study are connected.

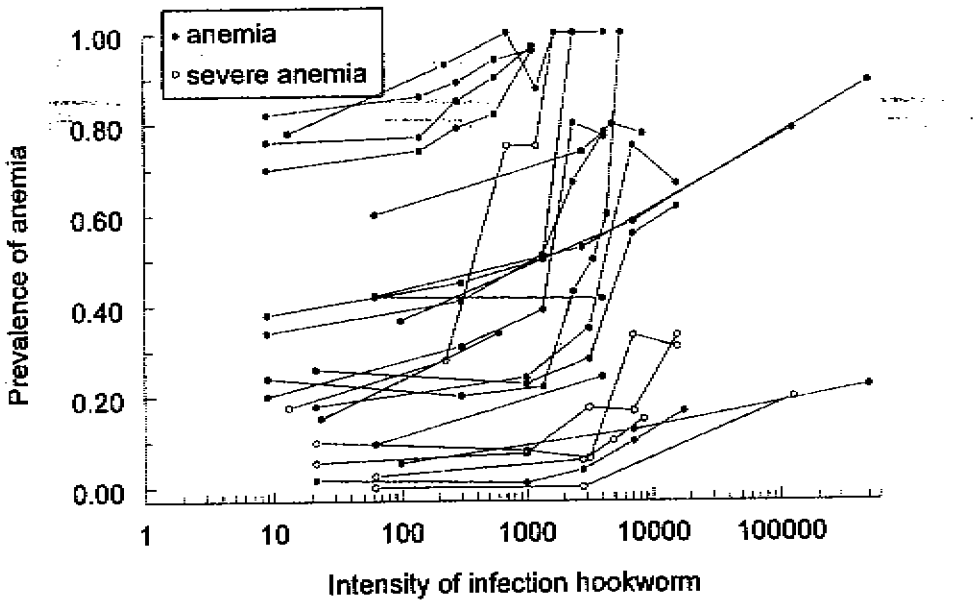

Figure 3.1.2: Percentage with anemia for different intensity of hookworm infection levels. Points from the same study are connected. (Severe anemia ≤ 8 gr/dl)

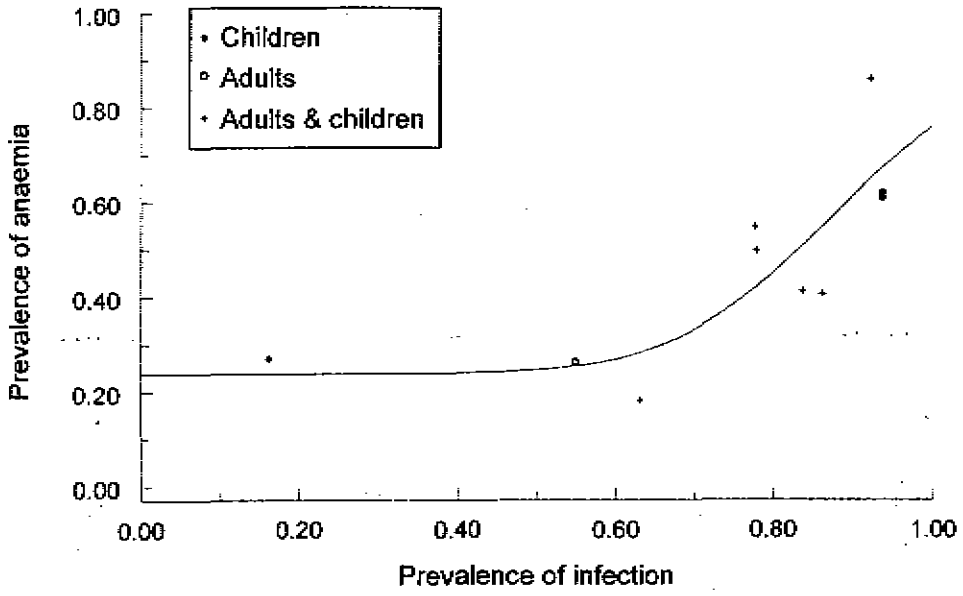

Figure 3.1.3: Prevalence of anemia by prevalence of hookworm infection.

B4 Ascariasis morbidity and mortality

Morbidity caused by *Ascaris lumbricoides* can be divided into two groups: 1) subtle morbidity, e.g. growth reduction, impaired cognitive development and reduced physical fitness and 2) clinically overt, acute disease mainly caused by a high number of worms (intestinal obstruction) or worms that migrated to the biliary or pancreatic duct or the appendix.

Recently, de Silva *et al.* (de Silva *et al.*, 1997a) published an article in which they describe a modification of the Chan model (Chan *et al.*, 1994). On the basis of an analysis of published data and results from their previous studies (de Silva *et al.*, 1997b), they modify a number of model parameters used by Chan *et al.*.

The model of Chan *et al.* estimates the morbidity caused by all soil-transmitted helminth infections, however, they do not estimate mortality caused by these infections. De Silva *et al.* calculate both morbidity and mortality figures for ascariasis. For the mortality figures they assume that all deaths occur in the group of patients with acute disease.

The estimates used for the case fatality rate are derived from an analysis of the literature on studies of a minimum of 100 patients hospitalised due to any acute complication of ascariasis. The calculated case fatality rate is 5%.

We analysed all published studies of patient series with intestinal obstruction due to ascaris (table 4.1). The calculated case fatality rate in this analysis was 3.7% for patients that presented to hospital with (sub) acute intestinal obstruction and 10.9% for patients that were operated to remove the obstruction.

Most likely, both the 5% and the 3.7% case fatality rate will be an underestimate. The studies used in the analysis were mainly performed in specialised children's hospitals or in the university clinics. The survival of the patients that do not reach these specialised clinics will probably be less favourable.

Table 4.1: Summary of the literature on intestinal obstruction due to *Ascaris lumbricoides*.

Author	Country	Period	Age of the study population in years	No. with intestinal obstructions due to ascariasis	No. of death (percentage)	No. of cases with intestinal obstructions in which surgery is performed	No. of death (percentage) in the individuals that were operated
Swarzwelder (1946)	USA	1940s	1-48	18	6 (33.3%)	?	?
Okumura (1974)	Brazil	1945-1970	1-11	455	39 (8.6)	130	34 (26.2%)
Jenkins (1954)	USA	1948-1952	1-9	31	2 (6.5%)	5	0 (0%)
Solanke (1968)	Nigeria	1957-1966	0-70	45	0 (0%)	40	0 (0%)
Louw (1966)	South Africa	1958-1962	1-12	100	3 (3.0%)	?	?
Dayalan (1976)	India	1965-1970	?	72	12 (16.7)	11	2 (18.2%)
Rao (1978)	India	1969-1977	1-15	10	2 (20%)	4	1 (25%)
Blumenthal (1975)	USA	1970-1973	0-15	21	0 (0%)	2	0 (0%)
Wambwa (1974)	Kenya	1971-1973	1-50	13	3 (23.1%)	?	?
Wynne (1983)	South Africa	1973-1977	children	73	0 (0%)	6	0 (0%)
Ochola-Abila (1982)	Kenya	1973-1979	all	50	2 (4.0%)	33	1 (3.0%)
Akamaguna (1985)	Nigeria	1974-1982	0-15	12	0 (0%)	?	?
Ihekwaba (1980)	Nigeria	1975-1977	0-46	46	3 (6.5%)	18	3 (16.7%)
Chrungoo (1992)	India	1980s	0-40	399	?	161	7 (4.3%)
Surendran (1988)	India	1980-1984	children	142	4 (2.8%)	22	4 (18.2%)
Thein-Hlaing (1987)	Burma	1981-1983	1-15	1109	?	79	4 (5.1%)
Archibong (1994)	Nigeria	1981-1990	children	74	2 (2.7%)	24	2 (8.3%)
Rahman (1992)	India	1983-1985	children	50	2 (4%)	15	2 (13.3%)
Carneiro (1987)	Tanzania	1984-1985	2-8	6	0 (0%)	0	0 (0%)
Thein-Hlaing (1990)	Burma	1984-1986	0-12	161	6 (3.7%)	12	2 (16.7%)
Wardhan (1989)	India	1984-1986	3-9	33	0 (0%)	15	0 (0%)
Villamizar (1996)	Colombia	1984-1994	1-14	87	0 (0%)	23	0 (0%)
Rode (1990)	South Africa	1985-1989	1-14	148	2 (1.4%)	17	2 (11.8%)
Mohta (1993)	India	1986-1990	3-8	74	1 (1.4%)	26	1 (3.8%)
Wasadikar (1997)	India	1989-1995	all	92	12 (13%)	19	7 (36.8%)
Pinus (1985)	Brazil	?		188	20 (10.6%)	?	?
Yu (1993)	China	?	all	2944	63 (2.1%)	?	?
TOTAL				4945	184 (3.7%)	662	72 (10.9)

? not reported in the article

References: Akamaguna & Odita, 1985; Archibong *et al.*, 1994; Blumenthal & Schultz, 1975; Carneiro, 1987; Chrungoo *et al.*, 1992; Dayalan & Ramakrishnan, 1976; Ihekwaba, 1980; Jenkins & Beach, 1954; Louw, 1966; Mohta *et al.*, 1993; Ochola-Abila & Barrack, 1982; Okumura *et al.*, 1974; Pinus, 1985; Rahman *et al.*, 1992; Rao *et al.*, 1978; Rode *et al.*, 1990; Solanke, 1968; Surendran & Paulose, 1988; Swartzwelder, 1946; Thein-Hlaing, 1987; Thein-Hlaing *et al.*, 1990; Villamizar *et al.*, 1996; Wambwa, 1974; Wardham *et al.*, 1989; Wasadikar & Kulkarni, 1997; Wynne & Ellman, 1983; Yu & Xu, 1993

De Silva *et al.* (1997) used their model to estimate the number of people in four morbidity groups.

A) Reversible faltering growth and/or reduced physical fitness, which lasts for the duration of the infection
B) Permanent growth retardation, which is al lifelong consequence of infection, occurring only in children
C) Clinically overt, acute illness (such as intermittent abdominal pain or discomfort, nausea, anorexia or diarrhoea)
D) Acute complications (intestinal obstruction, biliary or pancreatic disease, appendicitis, peritonitis, etc.).

Table 4.2: Estimates of the numbers infected with *A. lumbricoides* and at risk of morbidity and mortality by region (de Silva *et al.*, 1997).

Region*	Population in millions	Infections in millions (prevalence)	No. at risk of each type of morbidity (in thousands)**				No of deaths (in thousands)
			A	B	C	D	
SSA	510	105 (20.6)	3382	93	623	14	0.7
LAC	444	171 (38.5)	8783	230	1716	30	1.5
MEC	503	96 (19.1)	3228	87	622	13	0.6
IND	850	188 (22.1)	7218	190	1416	27	1.3
CHN	1134	410 (36.2)	18080	439	3537	71	3.5
OAI	683	303 (44.4)	18351	487	3609	55	2.8
Total	4120	1274	59043	1527	11523	209	10.5

* SSA, Sub-Saharian Africa; LAC, Latin America and the Caribbean; MEC, Middle Eastern Crescent; IND, India; CHN, China; OIA, Other Asia and Islands

** A) reversible faltering growth and/or reduced physical fitness, which lasts for the duration of the infection; B) permanent growth retardation, which is al lifelong consequence of infection, occurring only in children, C) clinically overt, acute illness, D) acute complications

B5 Helminth infection and growth and nutrition

Intuitively, intestinal parasites will have an effect on nutrition, first of all by using the food in the gut where they live to grow and reproduce. There is also evidence from laboratory studies in pigs that helminth infections influence the digestion and absorption of nutrients, induce a loss of macronutrients due to diarrhoea or vomiting or following a decreased appetite cause decreased consumption of nutrients. Furthermore, helminth infections might also increase the nutrient requirements of the body.

Another reason why it is important to consider the influence of helminth infections on nutrition for estimating morbidity, is that helminth infections are most prevalent in developing countries where various forms of malnutrition and other diseases are already common. The extra burden of helminth infection might be the trigger for inducing serious malnutrition. Moreover, the people with the highest intensities of infection are normally young children who are in maximum need of nutrients for their growth. Therefore, it is likely that the infected children in developing countries suffer from impaired growth and malnutrition at least partly due to the (soil-transmitted) helminth infections.

Until now, it has been difficult to study the influence of one helminth infection on nutrition. Soil-transmitted helminth infections are known to cluster, a child infected with one helminth species is more likely to be infected with another (Booth *et al.*, 1998). There are only few communities which are known to be predominantly infected with one parasite species and these might not be representative for the normal situation. Most communities harbour different worm species. Therefore, most research is conducted while taking into account the combined influence of different helminth infections.
Also, the helminths of one species are clustered, most individuals will have a few worms and a few individuals will have a large number of worms. It is unlikely that individuals, which harbour a few worms, will suffer from severe morbidity. In contrast, the individuals with the high wormloads are very likely to suffer from severe morbidity. This has been addressed in a number of studies (e.g. Latham *et al.*, 1990; Stephenson *et al.*, 1993a).

In general, there are two kinds of studies reporting on the relationship between helminth infection and growth/nutrition: 1) comparative studies, reporting the differences in nutritional parameters of infected and uninfected individuals and 2) intervention studies, reporting the different outcomes after treatment with an anti-helminthic and treatment with placebo.
It is difficult to interpret the results of the comparative studies due to clustering of helminth infections, low socio-economic status and other diseases (e.g. viral and bacterial origin). The interpretation of the results of the intervention studies is less difficult. If there is a significant difference between the outcomes of the treated and the placebo group after randomisation than it is very likely that this is caused by the removal of the worms by treatment. However, these studies do not allow us to come up with the burden that is caused by the infections because the permanent longterm effects of helminth infections on growht can not be extrapolated. Also, we were not able to come up with an association between prevalence of helminth infection and prevalence of growth inhibition.

We present the results of the literature search in table 5.1 and table 5.2.

Table 5.1: Summary of comparative studies on helminths and growth/nutrition

Author	Country	Species	Age in years	No. infected	No. not-infected	Weight difference sign.*	Height difference sign*
D. Forsyth (1964)	Tanzania	*S. haematobium*	10-16	168	55	p<0.05	p<0.05
O. Blumenthal (1976)	USA	Ascaris	2-10	30	30	n.s.	n.s.
E. Abdel-Salam (1977)	Egypt	*S. haematobium*	0-10	351	449	n.s.	n.s.
L. Stephenson (1980)	Kenya	Ascaris	1-6	61	125	n.s.	n.s.
D. Taren (1987)	Panama	Ascaris	3-6	77	107	n.s.	n.s.
L. Robertson (1992)	Panama	Ascaris	-	112	386	n.s.	n.s.
		Hookworm	-	18	386	n.s.	n.s.
		Trichuris	-	81	386	p=0.003	p=0.003
McGarvey (1992)	Philippines	*S. japonicum*	4-19.9	25	40	p<0.01	p<0.01
McGarvey (1993)	China	*S. japonicum*	12-17.9	38	15	p<0.005	p<0.03
E. Ekanem (1994)	Nigeria	*S. haematobium*	5-15	177	285	n.s.	n.s.

* n.s. = not significant

References: Abdel-Salam & Abdel-Fattah, 1977; Blumenthal & Schultz, 1976; Ekanem *et al.*, 1994; Forsyth & Bradley, 1964; McGarvey *et al.*, 1992; McGarvey *et al.*, 1993; Robertson *et al.*, 1992; Stephenson *et al.*, 1980; Taren *et al.*, 1987

Table 5.2: Summary of intervention studies on helminths and growth/nutrition.

Author	Country	Age in years	Follow-up time in months	No. treated	No. placebo or not treated	Weight difference sign.*	Weight difference in kg	Height difference sign.*	Height difference in cm
P. Shah (1975)	India	0-5	3	165	160	p=0.95	-	-	-
M. Gupta (1977)	India	0.5-4	8	60	73	p<0.01	-	-	-
W. Willet (1979)	Tanzania	0.5-7.5	12	39	39	p=0.03	0.26	n.s.	-0.14
B. Greenberg (1981)	Bangladesh	1.5-8	10	51	50	n.s.	-	-	-
K. Kloetzel (1982)	Brazil	1-8	10	165	172	n.s.	-	-	-
M. Gupta (1982)	Guatemala	2-5	12	81	78	p=0.0196	0.27	p=0.0087	1.06
M. Yokogawa (1983)	Thailand	9-16	10	187	265	n.s.	-	n.s.	-
L. Stephenson (1985)	Kenya	6-16	6	201	198	p=0.001	0.8	n.s.	0.1
L. Stephenson (1989a)	Kenya	6-16	6	78	72	p=0.0002	1.3	p=0.0092	0.6
L. Stephenson (1989b)	Kenya	6-16	8	208	104	p=0.0001	1.3	n.s.	0.2
M. Latham (1990)	Kenya	7-15	1.25	32	16	n.s.	0.2	n.s.	0.2
Thein-Hlaing (1991)	Burma	2-12	12	594	811	p=0.01	-	p=0.001	-
L. Stephenson (1993a)	Kenya	7-14	8.2	191	93	p=0.0001	1.0	n.s.	0.1
L. Stephenson (1993b)	Kenya	7-13	4	27	26	p=0.0002	1.0	p=0.003	0.6
D. Simeon (1995)	Jamaica	8	6	206	201	n.s.	-	n.s.	-
W. Watkins (1996)	Guatemala	6-12	6	116	110	n.s.	-0.13	n.s.	-0.06
V. Hadju (1997)	Indonesia	6-11	12	256	74	n.s.	-	n.s.	-
R. Stoltzfus (1997)	Tanzania	<10	12	2009	1054	n.s.	0.12	n.s.	0.19
Ph. Donnen (1998)	Zaire	0-4	12	123	117	n.s.	-0.55	n.s.	-1.24

* n.s. = not significant

References: Donnen *et al.*, 1998; Greenberg *et al.*, 1981; Gupta *et al.*, 1977; Gupta & Urrutia, 1982; Hadju *et al.*, 1997; Kloetzel *et al.*, 1982; Latham *et al.*, 1990; Shah *et al.*, 1975; Simeon *et al.*, 1995; Stephenson *et al.*, 1993a; Stephenson *et al.*, 1993b; Stephenson *et al.*, 1989a; Stephenson *et al.*, 1989b; Stephenson *et al.*, 1985; Stoltzfus *et al.*, 1997; Thein-Hlaing *et al.*, 1991; Watkins & Pollitt, 1996; Willett *et al.*, 1979; Yokogawa *et al.*, 1983

The average weight gain difference per was 1.12 kg per year and the average height gain difference per year was 0.48 cm per year for all studies.

B6 Summary of parameters

Table 6.1: Summary of the formulas predicting the prevalence (or incidence) of morbidity (and mortality) for a given prevalence of infection in a community.
b and c represent the estimated parameter values of the standard mathematical expression $P_{morb} = (b \cdot P_{inf}{}^{c}) / (1 + b \cdot P_{inf}{}^{c})$, where P_{morb} and P_{inf} denote resp. the prevalence of morbidity and infection. In some cases, the point of inflection was set at 1.0 and b represented by $b_{1.0}$.

Morbidity	Prevalence/ mortality	Paragraph	Association
S. haematobium:			
Haematuria	Prevalence	1.1	$b = 1.039$; $c = 1.400$
Dysuria	Prevalence	1.2	$b = 1.944$; $c = 4.225$
Bladder pathology, US	Prevalence	1.3.2.1	$b = 2.368$; $c = 1.734$
Major bladder pathology, US	Prevalence	1.3.2.1	$b = 0.286$; $c = 1.447$
Moderate and major hydronephrosis, US	Prevalence	1.3.2.2	$b_{1.0} = 0.271$; $c = 1.742$
Major hydronephrosis, US	Prevalence	1.3.2.2	$b_{1.0} = 0.105$; $c = 1.234$
Non-functioning kidney*	Prevalence	1.3.1.1	$0.0653 \cdot Prev_{>50\ eggs/10\ ml}$
Non-functioning kidney*	Deaths/year	1.3.1.1	$0.009 \cdot Prev_{non\ functioning\ kidney}$
Bladder cancer, males*	Deaths/year	1.4	$0.000823 \cdot Prev_{>50\ eggs/10\ ml}$
Bladder cancer, females*	Deaths/year	1.4	$0.000175 \cdot Prev_{>50\ eggs/10\ ml}$
S. mansoni:			
Diarrhoea	Prevalence	2.1	$b = 0.287$; $c = 8.659$
Blood in stool	Prevalence	2.1	$b = 0.689$; $c = 4.948$
Abdominal pain	Prevalence	2.2	Non-conclusive
Hepatomegaly (MSL)	Prevalence	2.3	$b_{1.0} = 0.217$; $c = 1.555$
Splenomegaly*	Prevalence	2.4	$b_{1.0} = 0.120$; $c = 1.272$
Ascitis*	Prevalence	2.5	$b_{1.0} = 0.00249$; $c = 1.005$
Hematemesis ever*	Prevalence	2.5	$b_{1.0} = 0.0133$; $c = 1.027$
Hematemesis*	Deaths/year	2.5	$0.14 \cdot Prev_{hematemesis}$
S. japonicum:			
Diarrhoea	Prevalence	2.1	$b = 0.287$; $c = 8.659$
Blood in stool	Prevalence	2.1	$b = 0.689$; $c = 4.948$
Abdominal pain	Prevalence	2.2	$b_{1.0} = 0.252$; $c = 1.673$
Hepatomegaly (MSL)	Prevalence	2.3	$b_{1.0} = 0.294$; $c = 1.834$
Splenomegaly*	Prevalence	2.4	$b_{1.0} = 0.176$; $c = 1.428$
Ascitis*	Prevalence	2.5	No data
Hematemesis ever*	Prevalence	2.5	No data
Hematemesis*	Deaths/year	2.5	No data
Hookworm:			
Anemia	Prevalence	3.1	$b = 2.199$; $c = 7.770$

US = Pathology measured by ultrasound
* Use with caution, see remarks Appendix B

Appendix C: Morbidity estimates

WHO Africa D region

Input for calculations

Table 1a: Number of individuals at risk of *S. haematobium* infection and prevalence of *S. haematobium* infection in the WHO Africa D region (data provided by D. Engels and S. Brooker).

Country	Number of pre-school children at risk	Overall prevalence of infection in pre-school children	Number of school children at risk	Overall prevalence of infection in school children	Number of adults at risk	Overall prevalence of infection in adults
Angola	1866752	0.258	4433536	0.426	5366912	0.278
Benin	982384	0.133	2333162	0.221	2824354	0.144
Burkina Faso	1828021	0.271	4341550	0.450	5255560	0.293
Cameroon	2393382	0.061	5684283	0.100	6880974	0.066
Chad	1212132	0.165	2878813	0.273	3484879	0.178
Equatorial Guinea	0	0	0	0	0	0
Gabon	130106	0.156	309002	0.258	374055	0.169
Gambia	166841	0.454	396248	0.753	479669	0.490
Ghana	2920532	0.250	6936265	0.415	8396531	0.270
Guinea	1026294	0.038	2437448	0.063	2950595	0.041
Guinea-Bissau	118775	0.175	282090	0.430	341477	0.235
Liberia	594844	0.188	1412753	0.312	1710175	0.203
Madagascar	1240000	0.088	2945000	0.144	3565000	0.095
Mali	1684217	0.198	4000015	0.328	4842124	0.213
Mauritania	443516	0.179	1053351	0.297	1275109	0.193
Niger	1616786	0.198	3839866	0.329	4648259	0.214
Nigeria	19302859	0.240	45844291	0.398	55495720	0.259
Senegal	1616618	0.081	3839467	0.131	4647776	0.087
Sierra Leone	606977	0.213	1441571	0.352	1745059	0.229
Togo	742572	0.134	1763609	0.221	2134895	0.145

Table 1b: Summary of the total numbers at risk and infected with *S. haematobium* in millions in the WHO Africa D region.

	At risk of infection	Infected
Pre-school children	40	8.3
School children	96	33
Adults	116	26
All	253	67

Table 2a: Number of individuals at risk of *S. mansoni* infection and prevalence of *S. mansoni* infection in the WHO Africa D region (data provided by D. Engels and S. Brooker).

Country	Number of pre-school children at risk	Overall prevalence of infection in pre-school children	Number of school children at risk	Overall prevalence of infection in school children	Number of adults at risk	Overall prevalence of infection in adults
Angola	528151	0.020	1254368	0.060	1518433	0.030
Benin	441712	0.037	1049067	0.101	1646755	0.053
Burkina Faso	548406	0.100	1302465	0.228	1576668	0.190
Cameroon	2393382	0.030	5684283	0.060	6880974	0.053
Chad	969705	0.040	2303050	0.084	2787903	0.072
Equatorial Guinea	0	0	0	0	0	0
Gabon	0	0	0	0	0	0
Gambia	45994	0.015	109236	0.015	132233	0.015
Ghana	282241	0.189	670323	0.441	811444	0.373
Guinea	1026294	0.066	2437448	0.155	2950595	0.131
Guinea-Bissau	0	0	0	0	0	0
Liberia	594844	0.024	1412753	0.043	1710175	0.044
Madagascar	1240000	0.055	2945000	0.126	3565000	0.106
Mali	1684217	0.048	4000015	0.086	4842124	0.052
Mauritania	24000	0.036	57000	0.084	69000	0.071
Niger	184000	0.137	437000	0.320	529000	0.271
Nigeria	15318264	0.041	36380878	0.096	44040010	0.082
Senegal	66504	0.157	157948	0.364	191200	0.308
Sierra Leone	606977	0.072	1441571	0.167	1745059	0.142
Togo	446102	0.088	1059493	0.202	1282544	0.172

Table 2b: Summary of the total numbers at risk and infected with *S. mansoni* in millions in the WHO Africa D region.

	At risk of infection	Infected
Pre-school children	26	1.2
School children	63	6.6
Adults	76	6.7
All	165	15

Table 3a: Number of individuals at risk of hookworm infection and prevalence of hookworm infection in the WHO Africa D region (data provided by D. Engels and S. Brooker)..

Country	Number of pre-school children at risk	Overall prevalence of infection in pre-school children	Number of school children at risk	Overall prevalence of infection in school children	Number of adults at risk	Overall prevalence of infection in adults
Angola	2011945	0.528	4778370	0.990	5784343	0.990
Benin	982384	0.060	2333162	0.120	2824354	0.150
Burkina Faso	1828021	0.108	4341550	0.203	5255560	0.235
Cameroon	2393382	0.080	5684283	0.150	6880974	0.172
Chad	1212132	0.029	2878813	0.054	3484879	0.073
Equatorial Guinea	107333	0.203	254917	0.380	308584	0.363
Gabon	181855	0.142	431905	0.267	522832	0.296
Gambia	208552	0.203	495310	0.381	599586	0.406
Ghana	2920532	0.151	6936265	0.284	8396531	0.313
Guinea	1026294	0.141	2437448	0.264	2950595	0.149
Guinea-Bissau	198850	0.115	472268	0.217	571693	0.248
Liberia	743554	0.439	1765942	0.826	2137719	0.833
Madagascar	2480000	0.035	5890000	0.051	7130000	0.064
Mali	1684217	0.037	4000015	0.071	4842124	0.103
Mauritania	443516	0.016	1053351	0.016	1275109	0.016
Niger	1616786	0.050	3839866	0.094	4648259	0.130
Nigeria	19302859	0.155	45844291	0.293	55495720	0.320
Senegal	1616618	0.021	3839467	0.021	4647776	0.021
Sierra Leone	720908	0.149	1712155	0.280	2072609	0.309
Togo	742572	0.061	1763609	0.114	2134895	0.150

Table 3b: Summary of the total numbers at risk and infected with hookworm in millions in the WHO Africa D region.

	At risk of infection	Infected
Pre-school children	42	6.0
School children	101	27
Adults	122	35
All	265	67

Results from calculations:

Table 4: Estimated number of individuals with morbidity due to *S. haematobium* infection in WHO Africa D region (in millions).

Morbidity	Number of pre-school children	Number of school children	Number of adults	Total number (5%-95%)
Haematuria in last 2 weeks	5.6	19	17	42 (31-52)
Dysuria in last 2 weeks	1.5	7.3	4.8	14 (10-33)
Minor bladder morbidity (US)	6.0	20	18	45 (40-54)
Major bladder morbidity (US)	1.8	6.7	5.6	14 (9.1-18)
Moderate hydronephrosis (US)	1.4	2.5	1.8	5.4
Major hydronephrosis (US)	-	3.0	2.6	5.6
Non-functioning kidney	-	-	[1.0]	[1.0]
Non-functioning kidney (deaths/year)	-	-	[0.090]	[0.090]
Bladder cancer, males (deaths/year)	-	-	[0.0067]	[0.0067]
Bladder cancer, females (deaths/year)	-	-	[0.0014]	[0.0014]

US = measured by ultrasound

[ ] use with caution, see remarks in Appendix B

Table 5: Estimated number of individuals with morbidity due to *S. mansoni* infection in WHO Africa D region (in millions).

Morbidity	Number of pre-school children	Number of school children	Number of adults	Total number (5%-95%)
Diarrhoea in last 2 weeks	0.0046	0.063	0.053	0.12 (0.0-2.2)
Blood in stool in last 2 weeks	0.040	0.41	0.36	0.81 (0.53-2.2)
Hepatomegaly (MSL)	0.20	1.1	1.1	2.4
Splenomegaly	[0.17]	[0.84]	[0.86]	[1.9]
Ascitis	-	-	[0.026]	[0.026]
Hematemesis ever	-	-	[0.14]	[0.14]
Hematemesis (deaths/year)	-	-	[0.020]	[0.020]

[ ] use with caution, see remarks in Appendix B

Table 6: Estimated number of individuals with morbidity due to hookworm infection in WHO Africa D region (in millions).

Morbidity	Number of pre-school children	Number of school children	Number of adults	Total number (5%-95%)
Anemia	1.3	8.3	11	20 (11-25)

WHO Africa E region

Input for calculations

Table 7a: Number of individuals at risk of *S. haematobium* infection and prevalence of *S. haematobium* infection in the WHO Africa E region (data provided by D. Engels and S. Brooker).

Country	Number of pre-school children at risk	Overall prevalence of infection in pre-school children	Number of school children at risk	Overall prevalence of infection in school children	Number of adults at risk	Overall prevalence of infection in adults
Botswana	236600	0.045	542789	0.075	612377	0.049
Burundi	0	0	0	0	0	0
Central African Republic	162049	0.247	371759	0.410	419420	0.267
Congo	479945	0.088	1101051	0.151	1242211	0.099
Côte d'Ivoire	2558067	0.197	5868506	0.326	6620878	0.213
DR Congo	2237861	0.160	5133917	0.265	5792111	0.173
Ethiopia	447723	0.123	1027129	0.205	1158812	0.134
Kenya	4670643	0.118	10715005	0.196	12088723	0.128
Malawi	1686350	0.260	3868685	0.440	4364671	0.280
Mozambique	3270767	0.339	7503524	0.561	8465515	0.365
Namibia	168586	0.326	386757	0.539	436341	0.351
Rwanda	0	0	0	0	0	0
South Africa	3469340	0	7959073	0	8979467	0
Uganda	341485	0.088	783407	0.146	883844	0.095
Tanzania	5579947	0.231	12801056	0.382	14442217	0.249
Zambia	1616934	0.140	3709436	0.232	4185005	0.151
Zimbabwe	1836935	0.199	4214145	0.330	4754420	0.211

Table 7b: Summary of the total numbers at risk and infected with *S. haematobium* in millions in the WHO Africa E region.

	At risk of infection	Infected
Pre-school children	29	5.1
School children	66	19
Adults	74	14
All	169	38

Table 8a: Number of individuals at risk of *S. mansoni* infection and prevalence of *S. mansoni* infection in the WHO Africa E region (data provided by D. Engels and S. Brooker).

Country	Number of pre-school children at risk	Overall prevalence of infection in pre-school children	Number of school children at risk	Overall prevalence of infection in school children	Number of adults at risk	Overall prevalence of infection in adults
Botswana	21306	0.196	48878	0.456	55144	0.387
Burundi	102217	0.099	234499	0.230	264563	0.195
Central African Republic	515975	0.066	1183707	0.154	1335464	0.131
Congo	0	0	0	0	0	0
Côte d'Ivoire	2558067	0.026	5868506	0.047	6620878	0.042
DR Congo	5314901	0.142	12193009	0.330	13756215	0.280
Ethiopia	5610758	0.052	12871740	0.121	14521963	0.103
Kenya	4395741	0.193	10084347	0.450	11377212	0.382
Malawi	1686350	0.080	3868685	0.180	4364671	0.150
Mozambique	2895046	0.120	6641576	0.310	7493060	0.135
Namibia	42311	0.134	97066	0.312	109510	0.134
Rwanda	7650	0.047	17550	0.049	19800	0.049
South Africa	2878814	0	6604337	0	7451047	0
Uganda	3711796	0.040	8515297	0.092	9607002	0.078
Tanzania	5579947	0.083	12801056	0.193	14442217	0.163
Zambia	1247275	0.031	2861396	0.072	3228242	0.062
Zimbabwe	1836935	0.019	4214145	0.045	4754420	0.038

Table 8b: Summary of the total numbers at risk and infected with *S. mansoni* in millions in the WHO Africa E region.

	At risk of infection	Infected
Pre-school children	38	3.2
School children	88	17
Adults	99	15
All	226	36

Table 9a: Number of individuals at risk of hookworm infection and prevalence of hookworm infection in the WHO Africa E region (data provided by D. Engels and S. Brooker).

Country	Number of pre-school children at risk	Overall prevalence of infection in pre-school children	Number of school children at risk	Overall prevalence of infection in school children	Number of adults at risk	Overall prevalence of infection in adults
Botswana	261604	0.132	600151	0.233	677093	0.240
Burundi	1043035	0.229	2392845	0.430	2699620	0.453
Central African Republic	515975	0.221	1183707	0.416	1335464	0.440
Congo	479945	0.136	1101051	0.254	1242211	0.284
Côte d'Ivoire	2558067	0.337	5868506	0.635	6620878	0.649
DR Congo	8750175	0.226	20073932	0.425	22647513	0.449
Ethiopia	10586337	0.078	24286302	0.144	27399930	0.123
Kenya	4774042	0.169	10952214	0.318	12356344	0.346
Malawi	1686350	0.136	3868685	0.256	4364671	0.267
Mozambique	3270767	0.140	7503524	0.280	8465515	0.312
Namibia	287579	0.087	659739	0.164	744321	0.198
Rwanda	1117509	0.154	2563696	0.290	2892375	0.318
South Africa	7381574	0.000	16934198	0.000	19105249	0.000
Uganda	3711796	0.208	8515297	0.391	9607002	0.415
Tanzania	5579947	0.200	12801056	0.377	14442217	0.402
Zambia	1616934	0.075	3709436	0.140	4185005	0.175
Zimbabwe	1836935	0.327	4214145	0.614	4754420	0.629

Table 9b: Summary of the total numbers at risk and infected with hookworm in millions in the WHO Africa E region.

	At risk of infection	Infected
Pre-school children	55	8.4
School children	127	36
Adults	144	43
All	326	88

Results from calculations:

Table 10: Estimated number of individuals with morbidity due to *S. haematobium* infection in WHO Africa E region (in millions).

Morbidity	Number of pre-school children	Number of school children	Number of adults	Total number (5%-95%)
Haematuria in last 2 weeks	3.4	12	9.4	24 (18-24)
Dysuria in last 2 weeks	0.91	4.3	2.6	7.8 (5.9-19)
Minor bladder morbidity (US)	3.7	12	10	26 (23-32)
Major bladder morbidity (US)	1.1	4.0	3.1	8.2 (5.2-10)
Moderate hydronephrosis (US)	0.86	1.4	0.9	3.2
Major hydronephrosis (US)	-	1.8	1.5	3.3
Non-functioning kidney	-	-	[0.57]	[0.57]
Non-functioning kidney (deaths/year)	-	-	[0.051]	[0.051]
Bladder cancer, males (deaths/year)	-	-	[0.0036]	[0.0036]
Bladder cancer, females (deaths/year)	-	-	[0.00077]	[0.00077]

US = measured by ultrasound
[ ] use with caution, see remarks in Appendix B

Table 11: Estimated number of individuals with morbidity due to *S. mansoni* infection in WHO Africa E region (in millions).

Morbidity	Number of pre-school children	Number of school children	Number of adults	Total number (5%-95%)
Diarrhoea in last 2 weeks	0.028	0.36	0.26	0.65 (0.0-5.1)
Blood in stool in last 2 weeks	0.19	1.7	1.4	3.3 (2.3-5.8)
Hepatomegaly (MSL)	0.52	2.7	2.4	5.6
Splenomegaly	[0.40]	[1.9]	[1.8]	[4.1]
Ascitis	-	-	[0.050]	[0.050]
Hematemesis ever	-	-	[0.26]	[0.26]
Haematemsis (deaths/year)	-	-	[0.036]	[0.036]

[ ] use with caution, see remarks in Appendix B

Table 12: Estimated number of individuals with morbidity due to hookworm infection in WHO Africa E region (in millions).

Morbidity	Number of pre-school children	Number of school children	Number of adults	Total number (5%-95%)
Anemia	1.9	9.4	11	23 (7.4-31)

WHO EMR-D Region

Input for calculations

Table 13a: Number of individuals at risk of *S. haematobium* infection and prevalence of *S. haematobium* infection in the WHO EMR-D region (data provided by D. Engels and S. Brooker).

Country	Number of pre-school children at risk	Overall prevalence of infection in pre-school children	Number of school children at risk	Overall prevalence of infection in school children	Number of adults at risk	Overall prevalence of infection in adults
Sudan	3848268	0.139	9139636	0.230	11063770	0.150
Somalia	877918	0.301	2085057	0.499	2524016	0.325

Table 13b: Summary of the total numbers at risk and infected with *S. haematobium* in millions in the WHO EMR-D region.

	At risk of infection	Infected
Pre-school children	4.7	0.80
School children	11	3.1
Adults	14	2.5
All	30	6.4

Table 14a: Number of individuals at risk of *S. mansoni* infection and prevalence of *S. mansoni* infection in the WHO EMR-D region (data provided by D. Engels and S. Brooker).

Country	Number of pre-school children at risk	Overall prevalence of infection in pre-school children	Number of school children at risk	Overall prevalence of infection in school children	Number of adults at risk	Overall prevalence of infection in adults
Sudan	3015469	0.086	7161739	0.199	8669474	0.169

Table 14b: Summary of the total numbers at risk and infected with *S. mansoni* in millions in the WHO EMR-D region.

	At risk of infection	Infected
Pre-school children	3.0	0.26
School children	7.2	1.4
Adults	8.7	1.5
All	18	3.2

Table 15a: Number of individuals at risk of hookworm infection and prevalence of hookworm infection in the WHO EMR-D region (data provided by D. Engels and S. Brooker).

Country	Number of pre-school children at risk	Overall prevalence of infection in pre-school children	Number of school children at risk	Overall prevalence of infection in school children	Number of adults at risk	Overall prevalence of infection in adults
Sudan	5014481	0.068	11909392	0.127	14416633	0.162
Somalia	1527452	0.218	3627699	0.411	4391425	0.434

Table 15b: Summary of the total numbers at risk and infected with hookworm in millions in the WHO EMR-D region.

	At risk of infection	Infected
Pre-school children	6.5	0.67
School children	16	3.0
Adults	19	4.2
All	41	7.9

Results from calculations:

Table 16: Estimated number of individuals with morbidity due to *S. haematobium* infection in WHO EMR-D region (in millions).

Morbidity	Number of pre-school children	Number of school children	Number of adults	Total number (5%-95%)
Haematuria in last 2 weeks	0.56	2.0	1.7	4.2 (3.1-5.5)
Dysuria in last 2 weeks	0.19	0.92	0.61	1.7 (0.87-3.1)
Minor bladder morbidity (US)	0.60	2.1	1.8	4.5 (3.8-5.6)
Major bladder morbidity (US)	0.18	0.67	0.56	1.4 (0.86-1.8)
Moderate hydronephrosis (US)	0.14	0.22	0.16	0.53
Major hydronephrosis (US)	-	0.31	0.26	0.57
Non-functioning kidney	-	-	[0.10]	[0.10]
Non-functioning kidney (deaths/year)	-	-	[0.0090]	[0.0090]
Bladder cancer, males (deaths/year)	-	-	[0.00061]	[0.00061]
Bladder cancer, females (deaths/year)	-	-	[0.00013]	[0.00013]

US = measured by ultrasound.
[ ] use with caution, see remarks in Appendix B

Table 17: Estimated number of individuals with morbidity due to *S. mansoni* infection in WHO EMR-D region (in millions).

Morbidity	Number of pre-school children	Number of school children	Number of adults	Total number (5%-95%)
Diarrhoea in last 2 weeks	0.0016	0.021	0.018	0.040 (0.0-0.47)
Blood in stool in last 2 weeks	0.012	0.12	0.11	0.25 (0.16-0.50)
Hepatomegaly (MSL)	0.043	0.23	0.24	0.51
Splenomegaly	[0.034]	[0.17]	[0.18]	[0.38]
Ascitis	-	-	[0.0050]	[0.0050]
Hematemesis ever	-	-	[0.026]	[0.026]
Hematemesis (deaths/year)	-	-	[0.0036]	[0.0036]

[ ] use with caution, see remarks in Appendix B

Table 18: Estimated number of individuals with morbidity due to hookworm infection in WHO EMR-D region (in millions).

Morbidity	Number of pre-school children	Number of school children	Number of adults	Total number (5%-95%)
Anemia	0.13	0.70	1.0	1.8 (0.43-2.4)

Appendix D: Other topics

D1 Morbidity code list

morb-general.xls
morb-haematuria.xls
morb-anemia.xls

In all Excel files

ART_NR	Year of publication + number, e.g. 80001 (1980 + number 001)
STUDY_NR	Number of the study
COM_NR	Community number (every village has his own number)
GROUP_NR	Group number (e.g. males vs. females or different age groups)
SUBGR_NR	Subgroup number (e.g. different intensity of infection groups)
TREAT	Treatment of study population -1= no treatment 1= before treatment 2= after treatment
SAME_GR	Morbidity measured with different methods in same population -1= no 1= two different methods 2= three different methods
COUNTRY	Country where study is executed
C_CODE	Code of the country (according to alphabetical list of WHO how to … refer to WHO member states, 1st of May 1999)
TYPE_ST	-1= n.a. 1= community survey 2= school survey 3= hospital 4= case control 8= other 9= unknown
MIN_AGE	lower age limit -1= n.a. 99=unknown
MAX_AGE	upper age limit -1= n.a. 88= upper limit not specified 99= unknown
MEAN_AGE	mean age of the group in years -1= n.a.
SEX	-1= n.a. 1= man 2= woman
METH_UR	-1= n.a. 1= urine filtration 2= urine centrifugation 3= urine sedimentation 4= Bradley's technique 5= Bell's technique 6= Oliver (1973)
	99= unknown
NR_URINE	Number of urine samples examined -1= n.a. 9= unknown
NR_UR_EX	Number of examinations per urine sample -1= n.a. 9= unknown
QUANT_UR	Quantity of urine examined per examination in ml -1= n.a. 77= 1 total urine 88= 24 hour urine 99= unknown
TIME_UR	time of the day that urine was collected -1= n.a. 1= 10.00-14.00 h. 2= 12.00-14.00 h. 3= 0.00-24.00 h. 4= 10.00-12.00 h. 5= 12.00 h. 6= 9.00-12.00 h. 9= unknown
SH_MIN	lower limit eggs per 10 ml -1= n.a. 9999= unknown
SH_MAX	upper limit eggs per 10 ml -1= n.a. 8888= upper limit not specified 9999=unknown
GM_SH	mean egg count -1= n.a. 9999= unknown
GM_SH_M	method of calculation mean egg count, *S. haematobium* -1= n.a. 1= geometric mean not including 0 2= geometric mean including 0 3= arithmetic mean 4= geometric mean (unknown if 0 is included) 5= logarithmic transformed mean egg excretion 6= eggs per 10 cc 9= unknown
NR_SHTES	number of individuals tested for *S. haematobium* 0= n.a.
NR_SHPOS	Number of individuals positive for *S. haematobium* -1= n.a.
SH_PREV	Prevalence *S. haematobium* infection -1= n.a.

METH_ST	-1= n.a. 1= Kato-Katz 2= Teesdale 3= Direct smear 4= Ritchie 5= Formol ether centrifugation 6= MIFC 7= Beaver's technique 8= Bell Technique 9= modified Stoll technique 10= Bradley 11= filtration staining technique 12= Brine flotation method 13= Gordon and Whitlock technique 14= formol ethyl acetate concentration method 15= Macmaster egg counting chamber and concentrated saline dilution 16= technique of Ridley 17= $ZnSO_4$ concentration 18= Lane's method 19= sedimentation technique (Faust et al, 1970) 20= Caldwell and Caldwell method (1926) 99= unknown
NR_STOOL	Number of stool samples examined -1= n.a. 9= unknown
NR_ST_EX	Number of examinations per stool sample -1= n.a. 9= unknown
QUANT_ST	Quantity of stool examined per examination in mg -1= n.a. 99= unknown
SM_MIN	Lower limit eggs per gram stool -1= n.a. 9999= unknown
SM_MAX	Upper limit eggs per gram stool -1= n.a. 8888= upper limit not specified 9999=unknown
GM_SM	Mean egg count -1= n.a. 9999= unknown
GM_SM_M	Method of calculation mean egg count, *S. mansoni* -1= n.a. 1= geometric mean not including 0 2= geometric mean including 0 3= arithmetic mean 4= geometric mean (unknown if 0 is included) 5= mean epg 9= unknown

NR_SMTES	Number of individuals tested for *S. mansoni* 0= n.a.
NR_SMPOS	Number of individuals positive for *S. mansoni* -1= n.a.
SM-PREV	Prevalence *S. mansoni* infection -1= n.a.
SJ_MIN	Lower limit eggs per gram stool -1= n.a. 9999= unknown
SJ_MAX	Upper limit eggs per gram stool -1= n.a. 8888= upper limit not specified 9999= unknown
GM_SJ	Mean egg count -1= n.a. 9999= unknown
GM_SJ_M	Method of calculation mean egg count, *S. japonicum* -1= n.a. 1= geometric mean not including 0 2= geometric mean including 0 3= arithmetic mean 4= geometric mean (unknown if 0 is included) 5= mean epg 9= unknown
NR_SJTES	Number of individuals tested for *S. japonicum* 0= n.a.
NR_SJPOS	Number of individuals positive for *S. japonicum* -1= n.a.
SJ-PREV	Prevalence *S. japonicum* infection -1= n.a.
HK_MIN	Lower limit eggs per gram stool -1= n.a. 9999= unknown
HK_MAX	Upper limit eggs per gram stool -1= n.a. 8888= upper limit not specified 9999= unknown
GM_HK	Mean egg count -1= n.a.
GM_HK_M	Method of calculation mean egg count, hookworm -1= n.a. 1= geometric mean not including 0 2= geometric mean including 0 3= arithmetic mean 4= geometric mean (unknown if 0 is included) 5= mean epg 9= unknown
NR_HKTES	Number of individuals tested for hookworm 0= n.a.

NR_HKPOS	Number of individuals positive for hookworm -1= n.a.
HK-PREV	Prevalence hookworm infection -1= n.a.
AS_MIN	Lower limit eggs per gram stool -1= n.a. 9999= unknown
AS_MAX	Upper limit eggs per gram stool -1= n.a. 8888= upper limit not specified 9999= unknown
GM_AS	Mean egg count -1= n.a.
GM_AS_M	Method of calculation mean egg count, ascaris -1= n.a. 1= geometric mean not including 0 2= geometric mean including 0 3= arithmetic mean 4= geometric mean (unknown if 0 is included) 5= mean epg 9= unknown
NR_ASTES	Number of individuals tested for ascaris 0= n.a.
NR_ASPOS	Number of individuals positive for ascaris -1= n.a.
AS_PREV	Prevalence ascaris infection -1= n.a.
TR_MIN	Lower limit eggs per gram stool -1= n.a. 9999= unknown
TR_MAX	Upper limit eggs per gram stool -1= n.a. 8888= upper limit not specified 9999= unknown
GM_TR	Mean egg count -1= n.a.
GM_TR_M	Method of calculation mean egg count, trichuris -1= n.a. 1= geometric mean not including 0 2= geometric mean including 0 3= arithmetic mean 4= geometric mean (unknown if 0 is included) 5= mean epg 9= unknown
NR_TRTES	Number of individuals tested for trichuris 0= n.a.
NR_TRPOS	Number of individuals positive for trichuris -1= n.a.
TR_PREV	Prevalence trichuris infection -1= n.a.

In morb-anemia.xls

HB-MEAN	Mean Hb in gr per dl -1= n.a.
HB_GRPER	Mean Hb in gr%
M_CUTOFF	Male: anemia below cut-off -1= n.a. 99= unknown
F_CUTOFF	Female: anemia below cut-off -1= n.a. 99= unknown
AN_TES	Number of persons tested for Hb/anemia 0= n.a.
AN_POS	Number of persons with anemia -1= n.a.
ANPREV	Prevalence of anemia -1= n.a.

In morb-hematuria.xls

M_HAEM	Method used to study haematuria -1= n.a. 1= questionnaire 2= inspection 3= raising hands 9= unknown
TIMEHAEM	Time period for which M_HAEM was asked in weeks -1= n.a. 0= now 88= ever 99= unknown
NR_HTEST	Number of individuals tested for macroscopic haematuria -1= n.a.
NO_HAEM	Number of individuals without macroscopic haematuria -1= n.a.
MOD_HAEM	Number of individuals with brown urine -1= n.a.
HV_HAEM	Number of individuals with red urine -1= n.a.
PREVHAEM	Percentage with macroscopic haematuria
M_DYS	Method used to study dysuria -1= n.a. 1= questionnaire 2= observation 3= raising hands 9= unknown
TIMEDYS	Time period for which M_DYS was asked in weeks -1= n.a. 0= now 88= ever 99= unknown
NR_DTEST	Number of individuals tested for dysuria -1= n.a.

DYS_POS	Number of individuals with dysuria -1= n.a.
PREVDYS	Prevalence of dysuria -1= n.a.

In morb-general.xls

M_DIAR	Method used to study diarrhoea -1= n.a. 1= questionnaire 2= observation 3= raising hands 9= unknown
TIMEDIAR	Time period for which M_DIAR was asked in weeks -1= n.a. 0= now 88= ever 99= unknown
DIAR_TES	Number of individuals tested for diarrhoea 0= n.a.
DIARPOS	Number of individuals with diarrhoea -1= n.a.
PREVDIAR	Prevalence diarrhoea -1= n.a.
M_BLD	Method used to study bloody diarrhoea -1= n.a. 1= questionnaire 2= observation 3= raising hands 9= unknown
TIMEBLD	Time period for which M_BLD was asked in weeks -1= n.a. 0= now 88= ever 99= unknown
BLD_TES	Number of individuals tested for bloody diarrhoea 0= n.a.
BLDPOS	Number of individuals with bloody diarrhoea -1= n.a.
PREVBLD	Prevalence bloody diarrhoea -1= n.a.
M_BLST	Method used to study blood in stool -1= n.a. 1= questionnaire 2= observation 3= raising hands 9= unknown
TIMEBLST	Time period for which M_BLST was asked in weeks -1= n.a. 88= ever 99= unknown
BLST_TES	Number of individuals tested for blood in stool 0= n.a.
BLSTPOS	Number of individuals with blood in stool -1= n.a.
PREVBLST	Prevalence blood in stool -1= n.a.
M_ABD	Method used to study abdominal pain -1= n.a. 1= questionnaire 2= observation 3= raising hands 9= unknown
TIMEABD	Time period for which M_ABD was asked in weeks -1= n.a. 0= now 88= ever 99= unknown
ABD_TES	Number of individuals tested for abdominal pain 0= n.a.
ABDPOS	Number of individuals with abdominal pain -1= n.a.
PREVABD	Prevalence abdominal pain -1= n.a.
M_SPL	-1= n.a. 1= clinical examination 2= ultrasound 9= unknown
CUT_SPL	Cut-off value for splenomegaly -1= n.a. 1= Hackett's grade 1 2= Hackett's grade 2 3= > 1 cm 4= palpable in supine position 5= > 2 cm 6= below left midclavicular line 7= >= Hackett 3 8= ultrasound: longitudinal length> 9 cm 99= unknown
SPL_TES	Number of individuals tested for splenomegaly 0= n.a.
SPL-POS	Number of individuals with splenomegaly -1= n.a.
PREVSPL	Prevalence splenomegaly -1= n.a.
M_HEP	-1= n.a. 1= clinical examination 2= ultrasound 9= unknown

CUT_HEP	Cut-off value for hepatomegaly -1= n.a. 1= > 2 cm below the subcostal region in the mid-clavicular line 2= > 15 cm size 3= > 1 cm MCL 4= > 3 cm MCL 5= palpable in midline 6= > 0.5 cm below costal margin in MCL 7= > 4 cm MCL 8= MCL palpable 9= MSL palpable 10= > 2 cm MCL 11= > 3 cm MSL 12= > 6 cm MSL 13= > 1 cm MSL 14= > 2 cm MSL 15= > 5 cm MSL 16= palpable 17= > 2 cm below the anterior axillary line (right lobe) 18= ultrasound: span > 12 cm 99= unknown
HEP_TES	Number of individuals tested for abdominal pain 0= n.a.
HEPPOS	Number of individuals with abdominal pain -1= n.a.
PREVHEP	Prevalence abdominal pain -1= n.a.

n.a. = not applicable

D2 References

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