Available online at www.sciencedirect.com
SCIENCE DIRECT®
Acta Tropica 86 (2003) 125–139
ACTA TROPICA
www.elsevier.com/locate/actatropica

Quantification of clinical morbidity associated with schistosome infection in sub-Saharan Africa

Marieke J. van der Werf [a,*], Sake J. de Vlas [a,b], Simon Brooker [c], Caspar W.N. Looman [a], Nico J.D. Nagelkerke [a], J. Dik F. Habbema [a], Dirk Engels [d]

[a] *Department of Public Health, Erasmus MC, University Medical Center Rotterdam, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands*

[b] *Prince Leopold Institute of Tropical Medicine, Nationalestraat 155, B-2000 Antwerp, Belgium*

[c] *Department of Infectious Disease Epidemiology, Imperial College School of Medicine, St Mary's Campus, Norfolk Place, London W2 1 PG, UK*

[d] *Parasitic Diseases and Vector Control, Communicable Diseases Control, Prevention and Eradication, World Health Organisation, Geneva, 20 Avenue Appia, CH-1211 Geneva 27, Switzerland*

Abstract

Health policy making in developing countries requires estimates of the (global) burden of disease. At present, most of the available data on schistosomiasis is limited to numbers of individuals harbouring the infection. We explored the relationship between the presence of schistosome infection and clinical morbidity, in order to estimate numbers of individuals with disease-specific morbidity for *Schistosoma haematobium* and *Schistosoma mansoni* infection in sub-Saharan Africa. We searched the literature for cross-sectional data from field studies reporting both schistosome infection and morbidity. This was used to derive a functional relationship between morbidity and infection. After standardisation for diagnostic method, the number of individuals with specific types of clinical morbidity or pathology was predicted. As only aggregated prevalences of infection were available for countries or areas, we adjusted for heterogeneity in infection levels within communities in those countries. In total, 70 million individuals out of 682 million (2000 estimate) in sub-Saharan Africa were estimated to experience haematuria in the last 2 weeks associated with *S. haematobium* infection, and 32 million dysuria. Ultrasound detected serious consequences of *S. haematobium*, major bladder wall pathology and major hydronephrosis, were predicted at 18 and 10 million, respectively. Infection with *S. mansoni* was estimated to cause diarrhoea in 0.78 million individuals, blood in stool in 4.4 million and hepatomegaly in 8.5 million. As the associations between prevalence of *S. mansoni* infection and prevalence of diarrhoea and blood in stool were not very clear, the resulting estimates may be underestimations. Using the very limited data available, we estimated the mortality rates due to non-functioning kidney (from *S. haematobium*) and haematemesis (from *S. mansoni*) at 150 000 and 130 000 per year. Given the overall high number of cases with schistosomiasis-related disease and associated death, we conclude that schistosomiasis remains an important public health problem in sub-Saharan Africa.

Keywords: *Schistosoma mansoni*; *Schistosoma haematobium*; Schistosomiasis; Morbidity; Pathology

* Corresponding author. Tel.: +31-10-408-7714; fax: +31-10-408-9449.
E-mail address: Vanderwerfm@kncvtbc.nl (M.J. van der Werf).

0001-706X/03/$ - see front matter © 2003 Elsevier Science B.V. All rights reserved.
doi:10.1016/S0001-706X(03)00029-9

1. Introduction

Health policy in developing countries is based on targeting diseases with high preventable burdens of disease. This requires estimates on the (global) burden of disease. Currently WHO estimates the burden of schistosomiasis on the basis of the number of individuals infected with *Schistosoma haematobium*, *Schistosoma mansoni* and *Schistosoma japonicum* (Murray and Lopez, 1996), with an associated low disability weight (0.005 compared with 0.172 for a malaria episode). However, not all infected individuals experience morbidity. Also, not all individuals with schistosomiasis-related disease are found positive at standard screening (De Vlas and Gryseels, 1992; Utzinger et al., 2001). Thus, estimates of the prevalence of morbidity are needed. Disability weights can then be assigned to symptoms to calculate the burden of disease, as is done for many other diseases in the burden of disease calculation (Murray and Lopez, 1997).

Often, epidemiological surveys only report the prevalence of schistosome infection (Brooker et al., 2000a; Chitsulo et al., 2000). Attempts to estimate the prevalence of specific symptoms from the prevalence of infection concluded that 20 million have serious clinical disease and 120 million are symptomatic, by using the well-known figure of 200 million infected individuals and assuming proportions of 10 and 60% for serious clinical disease and being symptomatic, respectively (WHO, 1993; Crompton, 1999; Savioli et al., 1997). Others assumed that intensity of infection is associated with morbidity and related the prevalence of morbidity in a population to intensity of infection (Chan et al., 1996; Gryseels and Polderman, 1991; Medley and Bundy, 1996). However, there is a dearth of data on intensity of infection, making it necessary to infer intensity from statistical associations between prevalence and intensity of infection (Guyatt and Bundy, 1991). Still others estimated morbidity due to helminth infection, by assuming a threshold value for the number of worms above which morbidity occurs (Chan et al., 1994; De Silva et al., 1997). These studies ignored that most symptoms and signs caused by helminth infection are non-specific (e.g. anaemia due to malaria infection and bloody diarrhoea due to amoebic dysentery).

This paper attempts to predict the number of individuals with morbidity associated with schistosome infection to serve as input for the Global Burden of schistosomiasis calculations. Since most accessible data are available for *S. haematobium* and *S. mansoni* infection and the majority of the individuals infected with schistosomes live in sub-Saharan Africa (165 vs. 28 million in the rest of the world, Chitsulo et al., 2000), we focussed on *S. haematobium* and *S. mansoni* infections in sub-Saharan Africa. We investigated the relationship between the presence of schistosome infection and clinical morbidity (or pathology) by using all published field studies. The parasitological data were standardised for differences in diagnostic sensitivity, we accounted for non-specific morbidity, and we adjusted our estimates for heterogeneity in infection.

2. Methods

In order to arrive at an estimate of the number of clinical cases from the prevalence of infection in a country, the following points were considered: (1) schistosomiasis causes many different signs and symptoms, out of which a selection had to be made; (2) morbidity is concentrated in individuals with current (or past) high intensity of infection; (3) most clinical morbidity associated with schistosomiasis is non specific; (4) prevalence of infection data were available on an aggregated level (country), but schistosomiasis occurs focally and, therefore, heterogeneity in the degree of endemicity among communities has to be accounted for; (5) the predictions are affected by uncertainty in assumptions and empirical data.

2.1. Identification of signs and symptoms of schistosome infection

A list of all signs and symptoms caused by infection with *S. haematobium* and *S. mansoni* was prepared from the literature (Chen and Mott, 1988, 1989; Jordan et al., 1993) and expert advice. Our analysis was restricted to signs and symptoms

for which information on both prevalence of infection and morbidity or pathology was available from field studies in populations unselected for infection status, disease or other criteria. The following signs and symptoms, probably related to infection with *S. haematobium* or *S. mansoni*, were excluded from analysis due to insufficient data. For both *S. haematobium* and *S. mansoni*: cercarial dermatitis, pneumonia at invasion stage, anaemia, and ectopic lesions. For *S. haematobium*: bladder cancer, genital lesions, and renal failure. For *S. mansoni*: Katayama fever, liver failure and cor pulmonale. For more subtle health effects evidence was conflicting: reduction of growth (Abdel-Salam and Abdel-Fattah, 1977; Ekanem et al., 1994; Forsyth and Bradley, 1964), impaired cognitive development (Kvalsvig, 1988; Nokes and Bundy, 1994) and reduced physical fitness (Kvalsvig, 1986; Stephenson et al., 1985).

2.2. Associating prevalence of infection and prevalence of morbidity/pathology

Pubmed (National Library of Medicine, United States) was searched for field studies in unselected study populations on *S. haematobium* and/or *S. mansoni* infection and morbidity. The references in collected articles were searched for additional articles and quantitative information was extracted. As prevalence data from each reported community or school were included as independent data points, one study could contribute several data points to the analysis.

In all identified field studies, the prevalence of *S. mansoni* infection was assessed by stool sample examination. Quantity of stool (number of stools × number of samples per stool × weight per sample) differed among studies (range 25–300 mg) and this affected the reported prevalence of infection. Using an existing egg count model (De Vlas et al., 1992), we standardised *S. mansoni* prevalences to those of a default diagnostic technique (i.e. a single 41.7 mg Kato-Katz faecal sample) to be able to compare prevalences obtained by the examination of different quantities of stool (van der Werf et al., 2002). *S. haematobium* prevalences were all determined by examining 10 ml urine samples with the standard filtration technique. Therefore, standardisation was not necessary.

Various methods have been used for measuring morbidity and pathology, e.g. questionnaire, inspection of urine or stool sample, haemasticks, clinical examination and ultrasound. We decided to use questionnaire data on haematuria and dysuria for *S. haematobium* infection, and questionnaire data on diarrhoea, blood in stool, abdominal pain and haematemesis for *S. mansoni* infection. If morbidity was reported for more than one recall period we used the recall period closest to 2 weeks. Data for hepatomegaly, splenomegaly and ascitis were obtained from studies that used clinical examination. For hepatomegaly we used data from studies reporting prevalence measured at mid-sternal level (MSL) as it is thought to be more related to infection with intestinal schistosomes than measurements at mid-clavicular level (MCL). Minor bladder wall pathology prevalences were included if the pathology had been detected by ultrasound and was defined as presence of at least 'irregular bladder wall', 'bladder wall thickness >5 mm', 'presence of masses', or 'presence of pseudopolyps' and major bladder wall pathology had to be defined as presence of at least 'bladder wall thickness >10 mm' or 'several localised hypertrophies'. Hydronephrosis data were included if detected by ultrasound and defined as marked pyelocalyceal dilatation (moderate hydronephrosis) or marked reduction of functional parenchym (major hydronephrosis).

From these data, we tried to determine the relation between community prevalences of infection and prevalences of each type of morbidity (or pathology), assuming a three parameter (a, b, and c) non-linear mathematical relationship (Appendix A). This equation allows for a baseline morbidity defined by parameter a (prevalence due to other diseases), has zero derivative at $x = 0$ and $y = a$ (i.e. no morbidity due to schistosome infection at very low prevalences) and asymptotically (but not necessarily) reaches a prevalence of morbidity of 100%. Due to the convex association between prevalence of infection and prevalence of morbidity, communities with relatively high infection prevalences contribute disproportionately to the burden of morbidity.

2.3. Predicting the number of individuals with morbidity

Using the above quantitative relationship, prevalence of morbidity can be calculated from available data on the prevalence of infection in areas of sub-Saharan Africa. Prevalences of infection data were provided by an international initiative launched by WHO and its partner at Imperial College, London, which attempted to collate the available schistosomiasis survey data from both published and unpublished sources (see Brooker et al., 2000a for inclusion criteria and further details). As most available data are on school-aged prevalence, prevalence of infection in pre-school children and adults was estimated from data on school children using species-specific regression models (Guyatt et al., 1999a), thereby providing a more reliable estimate of total numbers infected (Brooker et al., 2000b). In areas without comprehensive survey data, estimates of infection prevalence were made using models of the distribution of infection in relation to environmental variables (Brooker et al., 2002), and were counterchecked with other information (Doumenge et al., 1987) and expert opinion. This provided prevalence data of schistosomiasis in defined at risk populations in sub-Saharan Africa (Africa except Algeria, Egypt, Eritrea, Libya, Morocco, Tunisia and Western Sahara).

As prevalence data were not available on the community level, we had to estimate the geographical heterogeneity in the prevalence of infection for communities at a given mean prevalence of infection in an area/country. A normal distribution of logit transformed prevalence data appeared to provide an adequate description of this heterogeneity (Appendix B). The number of individuals with morbidity was calculated by multiplying the mean estimated prevalence of morbidity with the at risk population in a country/region. Estimates of morbidity and pathology (haematuria, dysuria, bladder pathology, hydronephrosis, diarrhoea, blood in stool, hepatomegaly and splenomegaly) were calculated as described above for pre-school children, schoolchildren and adults, separately. Estimates for major hydronephrosis were assumed to apply to schoolchildren and adults only; the possible cases among pre-school children were neglected. The number of individuals with moderate hydronephrosis was calculated by subtracting the number of individuals with major hydronephrosis from the number of individuals with both moderate and major hydronephrosis. Numbers of other chronic morbidity (ascitis and haematemesis) were attributed to adults only.

To estimate 90% confidence intervals for the number of individuals with morbidity in sub-Saharan Africa, we used bootstrapping (Efron and Tibshirani, 1993). This is a generally applicable way for constructing confidence intervals where in a series of replica data sets are created by drawing samples from the original set of data points. The new data sets have the same size as the original data set and are drawn with replacement. In this way the replication of the sampling procedure is mimicked and the distribution of the number of individuals as based on each replica represents what would have happened if we had reconducted the data sampling hundreds of times. This procedure gives confidence intervals in situations where analytical solutions are not possible, i.e. in this situation where we could not formulate the model as a generalised linear model. In our study, we generated 200 bootstrap samples for each type of schistosomiasis related morbidity. Then we calculated the parameters a, b and c for each bootstrap sample and predicted the number of individuals with morbidity as described in Appendix B. The 200 estimates of the number of individuals with morbidity were ranked and the 10th and 190th were selected to represent the 90% confidence interval. Intervals could be calculated for haematuria, dysuria, bladder pathology, diarrhoea and blood in stool. Calculation of intervals occasionally failed because the association between prevalence of infection and morbidity was not very distinct (e.g. hepatomegaly) or because of too few data points (e.g. haematemesis). The 90% confidence intervals only take into account the uncertainty in the curve parameters a, b and c.

The number of individuals with morbidity or pathology associated with *S. haematobium* and *S. mansoni* were estimated for Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Côte d'Ivoire, DR

Congo, Ethiopia, Gambia, Ghana, Guinea, Kenya, Liberia, Madagascar, Malawi, Mali, Mauritania, Mozambique, Namibia, Niger, Nigeria, Senegal, Sierra Leone, Somalia, South Africa, Sudan, Tanzania, Togo, Uganda, Zambia, Zimbabwe. No estimates of *S. mansoni* associated morbidity were provided for Congo, Equatorial Guinea, Eritrea, Gabon, Guinea-Bissau and Somalia, as this infection was non or very low endemic (prevalence ~ 0.0). Similarly, estimates of *S. haematobium* associated morbidity were not calculated for Burundi, Equatorial Guinea, Eritrea and Rwanda.

2.4. Mortality

Mortality caused by infection with *S. haematobium* will mainly be due to kidney failure and bladder cancer. Mortality due to *S. mansoni* infection will be caused by haematemesis or liver failure. As few studies report the prevalences of these conditions or their mortality rate, our estimates of incidence and mortality due to kidney failure and haematemesis are crude (Appendix C). Data on bladder cancer (squamous cell carcinoma) from *S. haematobium* infection are sufficient to suggest a causal relationship (Bedwani et al., 1998; Kitinya et al., 1986; Lucas, 1982; Mostafa et al., 1999; Thomas et al., 1990) but these data did not allow for estimating the prevalence, incidence or mortality rate. Estimates on incidence and mortality due to liver failure caused by *S. mansoni* infection were also not possible due to lack of data.

3. Results

Table 1 summarises the types of morbidity and pathology for which data were available, the method of measurement used in the different studies and the number of articles concerned.

Table 2 shows the estimated number of individuals with signs and symptoms due to infection with *S. haematobium* in sub-Saharan Africa. Haematuria (in the last 2 weeks) is predicted to occur in 70 (51–87) million individuals. Haematuria is generally thought to result from bladder pathology, therefore, it is reassuring that our calculations predicted a comparable number of individuals with ultrasound detected minor bladder wall pathology, 88 (67−102) million. More serious pathology, major bladder wall pathology and moderate and major hydronephrosis was estimated to occur in, respectively, 18, 9.3 and 9.6 million individuals. In most West African countries the percentage of the total population with haematuria associated with *S. haematobium* infection is $>15\%$, up to 24% in Gambia (Fig. 1). Other countries with a high burden (percentage cases with haematuria of the total population) are Angola (18%), Malawi (20%), Mozambique (24%), Tanzania (18%) and Zimbabwe (16%). Kenya, Ghana, Mozambique, Tanzania and Nigeria are predicted to account for more than 50% of the morbidity cases associated with *S. haematobium*, partly due to their large populations. Other countries with many cases (>2 million haema-

Table 1
Data used for the analysis: type of morbidity or pathology, method of measurement and number of articles identified

Type of morbidity or pathology	Measured by	Number of articles
S. haematobium		
Haematuria in last 2 weeks	Questionnaire	15
Dysuria in last 2 weeks	Questionnaire	10
Minor bladder pathology	Ultrasound	21
Major bladder pathology	Ultrasound	8
Moderate hydronephrosis	Ultrasound	17
Major hydronephrosis	Ultrasound	13
S. mansoni		
Diarrhoea in last 2 weeks	Questionnaire	15
Blood in stool in last 2 weeks	Questionnaire	21
Abdominal pain	Questionnaire	22
Hepatomegaly (MSL)	Clinical examination	30
Splenomegaly	Clinical examination	43
Ascitis	Clinical examination	9
Haematemesis ever	Questionnaire	11

Details are reported in van der Werf et al. (2002) and van der Werf et al., submitted and Fig. 3 (dysuria).

Table 2
Estimated number of individuals with morbidity or pathology due to *S. haematobium* infection by age group in sub-Saharan Africa in millions (90% confidence interval)

Category	Pre-school children	School children	Adults	Total
At risk of infection	71	168	196	436
Infected	14	56	43	112
Haematuria in last 2 weeks	9.5 (6.6–12)	33 (25–39)	28 (20–36)	70 (51–87)
Dysuria in last 2 weeks	3.6 (1.7–7.0)	17 (10–28)	11 (5.5–21)	32 (17–54)
Minor bladder wall pathology	12 (8.5–15)	41 (33–46)	35 (25–42)	88 (67–102)
Major bladder wall pathology	2.3 (0.5–3.5)	9.0 (3.0–13)	6.9 (1.6–10)	18 (5.1–27)
Moderate hydronephrosis	2.4	4.1	2.8	9.3
Major hydronephrosis	0	5.2	4.3	9.6

Intervals could be calculated for haematuria, dysuria and bladder pathology.

turia cases) are Angola, Burkina Faso, Côte d'Ivoire and Sudan.

The estimated number of cases due to infection with *S. mansoni* is shown in Table 3. Hepatomegaly at MSL is predicted to occur in most individuals (8.5 million). Diarrhoea was estimated to occur in only 0.78 million individuals in sub-Saharan Africa, but this prediction was subject to a lot of uncertainty. In East African countries the percentage of the population affected by *S. mansoni* infection was generally higher than in West Africa (see Fig. 2). More than 50% of the morbidity/pathology cases associated with *S. mansoni* infection can be found in Tanzania, DR Congo, Nigeria and Kenya. Sudan, Mozambique and Ethiopia also have a significant burden (>0.5 million hepatomegaly MSL cases).

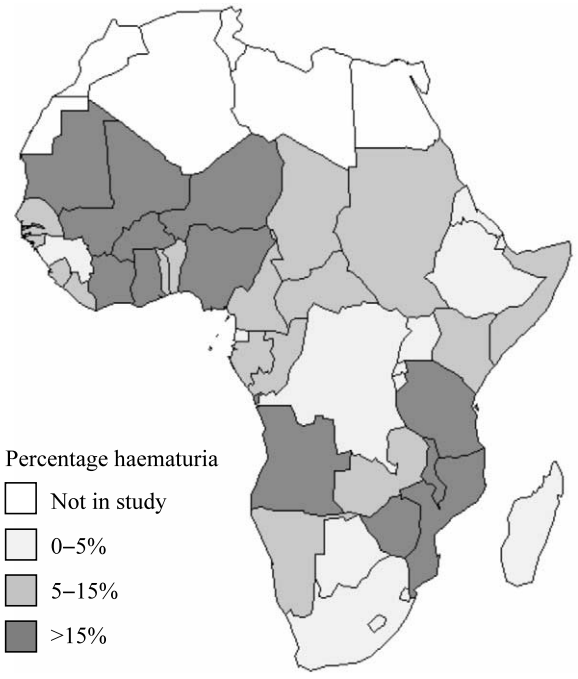

Fig. 1. Map of Africa indicating predicted proportion of the total population with haematuria from *S. haematobium* infection by country.

Infection with *S. haematobium* does not seem to give widespread morbidity in Ethiopia, Uganda and Madagascar (prevalence $\leq 1\%$). Burundi, Rwanda, Equatorial Guinea and Eritrea are neither very low endemic for *S. haematobium*. Countries with low morbidity associated with *S. mansoni* infection are Rwanda, Gambia, South Africa and Mauritania. Whereas, Congo, Equatorial Guinea, Eritrea, Gabon, Guinea Bissau and Somalia are non or very low endemic for *S. mansoni*.

The number of cases with haematemesis (ever) was estimated at 0.9 million. From the assumed disease specific death rate and overall mortality (Appendix C), we estimated the annual incidence and mortality due to haematemesis for sub-Saharan Africa to be, respectively, 150 000 and 130 000. Using the association between prevalence of (heavy) infection with *S. haematobium* and prevalence of non-functioning kidney (Appendix C), we estimated 1.7 million individuals with at least one non-functioning kidney in sub-Saharan Africa. This corresponds with a predicted incidence of 180 000 and a mortality of 150 000 due to this cause per year.

Table 3
Estimated number of individuals with morbidity or pathology due to *S. mansoni* infection by age group in sub-Saharan Africa in millions (90% confidence interval)

Category	Pre-school children	School children	Adults	Total
At risk of infection	65	152	177	393
Infected	4.7	25	23	54
Diarrhoea in last 2 weeks	0.034 (0.00–0.72)	0.42 (0.0–3.6)	0.32 (0.0–3.5)	0.78 (0.0–7.8)
Blood in stool in last 2 weeks	0.24 (0.16–0.69)	2.3 (1.6–4.1)	1.9 (1.3–3.7)	4.4 (3.0–8.3)
Hepatomegaly (MSL)	0.076	4.0	3.8	8.5
Splenomegaly	[0.61]	[2.9]	[2.8]	[6.3]
Ascitis	[0]	[0]	[0.29]	[0.29]
Haematemesis ever	[0]	[0]	[0.93]	[0.93]

[ ] use with caution, risk for confounding (splenomegaly) or estimations derived from limited literature data (ascitis and haematemesis). Intervals could be calculated for diarrhoea and blood in stool.

4. Discussion

We attempted to estimate the numbers of individuals with morbidity or pathology due to schistosome infection by using all published data from field studies and taking into account 'confounding' factors. The quality of our estimates depends on the accuracy of the associations between prevalence of infection and morbidity, the quality of the available prevalence of infection data and the chosen degree of heterogeneity in prevalence of infection.

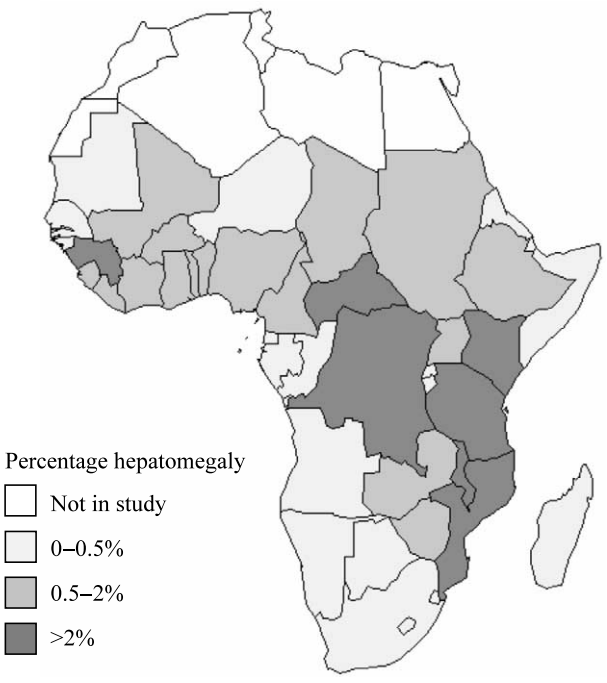

Fig. 2. Map of Africa indicating predicted proportion of the total population with hepatomegaly (MSL) from *S. mansoni* infection by country.

For some types of morbidity (major bladder wall pathology, haematemesis and ascitis) data were scarce resulting in predictions with wide uncertainty margins. The quality of the prevalence of infection and morbidity data differed among studies depending on the methods used and sample size. By aggregating all data we aimed to arrive at a grand average covering all endemicity levels and geographical areas. For most morbidity types and mortality, data were insufficient for estimating age-specific associations between prevalence of infection and prevalence of morbidity. Where data were available the association for children and adults appeared to be similar (van der Werf et al., 2002). For several signs and symptoms related to schistosomiasis, data were insufficient for estimating an association between prevalence of infection and morbidity/pathology (*S. haematobium* and *S. mansoni*: cercarial dermatitis, pneumonia at invasion stage, anaemia, and ectopic lesions; *S. haematobium*: bladder cancer, genital lesions, and renal failure; *S. mansoni*: Katayama fever, liver failure and cor pulmonale). For more subtle consequences (reduction of growth, impaired cognitive development and reduced physical fitness) evidence was conflicting. Therefore, these morbidity types could not be included in the calculations. As a consequence, the burden caused

by these signs and symptoms could not be included in the calculations of the total burden of schistosomiasis. Notably, this will result in an underestimation. The prevalence of infection data were derived from survey data (Brooker et al., 2000a) and additional country information. These data also vary in quantity and quality.

The number of *S. haematobium* and *S. mansoni* infected individuals in sub-Saharan Africa used for the calculations was estimated to be 112 and 54 million, respectively. It is difficult to compare these estimates with other estimates as some individuals may harbour both infections. Nevertheless, our values are comparable to those from other studies, e.g. 164 million schistosome infections in sub-Saharan Africa (Chitsulo et al., 2000; Iarotski and Davis, 1981) and 200 million in the world (WHO, 1993).

As prevalences of infection data range between 0.0 and 1.0, a normal distribution of logit transformed data was used to account for heterogeneity. Our estimate of the general degree of heterogeneity (standard deviation, $\sigma = 0.6$) cannot be directly compared with the results of others (Chan et al., 1994), as they did not use a logit transformation. However, the degree of heterogeneity from the non-transformed prevalence data in our study (σ^* ranging from 0.11 to 0.27) was comparable with that for *Ascaris lumbricoides*, *Trichuris trichiura* and hookworm (σ^* ranging from 0.13–0.32, 0.12–0.37 and 0.12–0.35, respectively, Chan et al., 1994). We did not find a relationship between mean and standard deviation as was found for Ascaris and Trichuris. To illustrate the importance of the degree of heterogeneity, we calculated the number of haematuria cases for different standard deviations. A $\sigma = 0.2$ results in 60 million haematuria cases, compared with 70 million for the chosen $\sigma = 0.6$. A higher standard deviation ($\sigma = 0.8$) predicted 75 million haematuria cases. Future work needs to focus on this heterogeneity and processes generating it. This will improve understanding of the spatial structure of schistosomiasis within endemic regions, and lead to a more precise mapping of distribution and more reliable estimates of disease burden.

We estimated that 6.4 million individuals have splenomegaly due to infection with *S. mansoni*. This figure should be used with much caution, as splenomegaly can also be the result of infection with *Plasmodium* species and these causes may concur as populations with a high prevalence of *S. mansoni* infection may have a high prevalence of malaria (mosquito breeding places in the irrigation canals where also the intermediate hosts of schistosomes could live) and, if so, effects of *S. mansoni* infection might be overestimated. Also, parasitic infections tend to cluster in poor populations (Booth et al., 1998a).

Using our estimations, it can be inferred that for *S. haematobium* 63% of the infected individuals had haematuria in the last 2 weeks due to their infection, 28% dysuria and 8.5% major hydronephrosis. This agrees with the previously used simplistic assumption of 60% of the infected individuals being symptomatic and 10% having serious clinical morbidity (WHO, 1993). For *S. mansoni* the proportions with morbidity and/or pathology were much lower: 1.5% for diarrhoea, 8% for blood in stool and 16% for hepatomegaly (MSL). The association between *S. mansoni* prevalence and diarrhoea is not very distinct. This may account for our low estimate and wide 90% confidence interval. The real number of morbidity cases could be much higher. Others have reported on the varying relation between morbidity and prevalence of *S. mansoni* infection, i.e. areas with high prevalence of infection and low prevalence of morbidity and vice versa (Gryseels, 1989, 1992). The association between *S. haematobium* infection and morbidity seems to be more straightforward (Booth et al., 1998b; Guyatt et al., 1999b; Lengeler et al., 1991, 2000). It must be noted that our 90% confidence intervals ignore uncertainty in the original measurements of prevalences and uncertainty in prevalence of infection in countries is also not taken account of.

Our estimate of the number of deaths in sub-Saharan Africa attributed to schistosomiasis (150 000 by non functioning kidney and 130 000 by haematemesis) is much higher than the estimate from the Global Burden of Disease Initiative (4000 deaths) (Murray and Lopez, 1996). The mortality estimates in this initiative have been based on models that use the relationship between general mortality and broad cause group mortality to

estimate cause specific mortality in areas such as sub-Saharan Africa which do not have fully functioning vital registration systems. We believe that the new estimates presented in this paper will greatly facilitate the process of updating WHO figures for deaths due to schistosomiasis.

Our estimations have also to be treated with caution. The number of cases with haematemesis was derived from field studies, which could be biased due to the long recall period used in the questionnaires. Furthermore, haematemesis has a high mortality and individuals whom died of exsanguination are not identified in a cross-sectional population study. Similarly, our estimate for non-functioning kidney is not very reliable. On the other hand, bladder cancer (*S. haematobium*) and liver failure (*S. mansoni*) will also be responsible for a certain number of deaths, but currently no data are available to provide even the weakest estimates. Few other studies described death due to schistosomiasis. Kheir et al. (1999) reported mortality due to schistosomiasis in a highly endemic village in Sudan (four individuals died from haematemesis in 7 years (population size 1080)). And a study in Brazil reports a mortality rate due to schistosomiasis of 0.30/100 000. These studies did not allow for predicting a general mortality rate for *S. mansoni* infection.

Given the quality of the data available, we conclude that most of our morbidity estimates are at least a reasonable starting point to be used in (global) burden of disease calculations. Our study certainly provides the best attempt thus far to arrive at estimates using all information available. We have clearly demonstrated that number of cases with schistosomiasis-related signs and symptoms are high and easily concern millions. Moreover, we did not even include potentially important non-clinical morbidity, such as growth retardation. Our estimates of morbidity and pathology (and also death) associated with schistosomiasis underline that this classical tropical disease remains an important public health problem in sub-Saharan Africa. The global importance of schistosomiasis will further increase by including some endemic countries outside sub-Saharan Africa, such as Egypt (*S. haematobium* and *S. mansoni*), Brazil (*S. mansoni*) and China (*S. japonicum*).

Acknowledgements

The authors acknowledge the co-operation of H. Feldmeier, C.F. Hatz, J.R. Lambertucci, R. Olds, J. Richter. We thank J. Utzinger for providing data for the heterogeneity analysis. This study was performed within the WOTRO/NWO funded multidisciplinary programme 'Model-based decision support for schistosomiasis control in Ghana, Mali, Niger and Senegal' and was also funded by the department of Communicable Diseases Control, Prevention and Eradication, World Health Organisation, Geneva, Switzerland and the Wellcome Trust (in the form of a Wellcome Trust Prize Fellowship to SB (No. 062962).

Appendix A: Associating morbidity to infection

We related prevalence of morbidity (y-axis) to prevalence of infection (x-axis) on community level by using an expression related to the logistic regression curve (van der Werf et al., 2002):

$$y = (a + bx^c)/(1 + bx^c) \quad (1)$$

This equation allows for baseline morbidity defined by parameter a (prevalence due to other diseases) and the degree of association is described by b and c. The derivative at $x = 0$ and $y = a$ equals zero, which means that no morbidity is due to schistosome infection at very low prevalences. It asymptotically (but not necessarily) reaches a prevalence of morbidity of 100%. To estimate the values of parameters a, b and c we used a SYSTAT program (version 3.0, 1986) and fitted Eq. (1) to all n data points. The fit was determined by assuming a binomial distribution for each data point i ($i = 1, \ldots, n$) and without assigning weight according to size of the population. As an example, Fig. 3 shows the curve that was fitted for the association between prevalence of *S. haematobium* infection and dysuria. It shows a baseline prevalence of non-specific dysuria (i.e. dysuria due to other causes) of

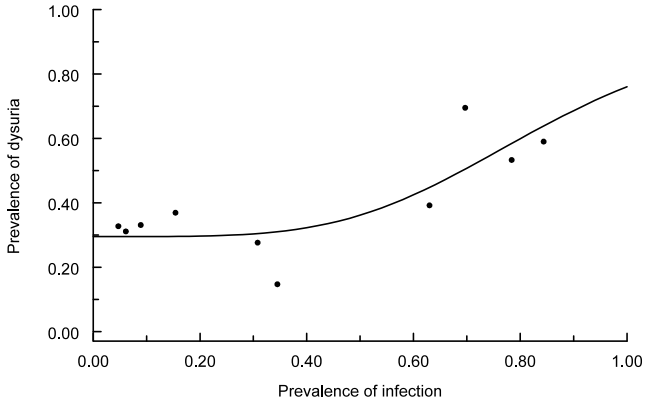

Fig. 3. Association between prevalence of *S. haematobium* infection and prevalence of dysuria in last 2 weeks (measured by questionnaire). The association is described by Eq. (1) with $a = 0.30$, $b = 1.94$ and $c = 4.23$. The data were derived from (Abdel-Wahab et al., 1992, 2000; Gabr et al., 2000; Hammam et al., 2000a,b; King et al., 1988; Masaba et al., 1983; Mungomba and Kalumba, 1995; Traquinho et al., 1998; Warren et al., 1979).

$a = 0.30$, and at around 0.25 prevalence of infection the prevalence of dysuria increases to 0.76.

For hydronephrosis, hepatomegaly (MSL) and splenomegaly, fitting Eq. (1) yielded biologically unrealistic curves (i.e. a sharp increase of pathology at low prevalence of infection) due to sparse data. For these types of pathology we reduced the number of parameters by pre-setting the point of inflection at 1.0, hence $b = (c-1)/(c+1)$. Entering $b = (c-1)/(c+1)$ in Eq. (1) results in:

$$y = \frac{a + ((c-1)/(c+1))x^c}{1 + ((c-1)/(c+1))x^c} \quad (2)$$

From the fitted expression, the curve with $a = 0$ (no baseline)

$$y = bx^c/(1 + bx^c), \quad (3)$$

or its alternative with $b = (c-1)/(c+1)$, can be used to make predictions for a community on the morbidity potentially due to infection with schistosomes. For further details see van der Werf (2002).

Data sources, graphical plots, data points and parameters b and c of the equations that are used for predicting the prevalence of morbidity in a community are described van der Werf (2002); van der Werf et al. (submitted) and in the report *Morbidity and infection with schistosomes or soil-transmitted helminths* by Marieke J. van der Werf and Sake J. de Vlas (at the request of WHO/PVC/CPE). Parameters for morbidity and pathology due to infection with *S. haematobium* are $b = 1.04$, $c = 1.41$ for haematuria, $b = 1.94$, $c = 4.23$ for dysuria, $b = 2.45$, $c = 1.66$ for minor bladder pathology, $b = 0.26$, $c = 1.75$ for major bladder pathology, $b = 0.27$, $c = 1.74$ for moderate and major hydronephrosis and $b = 0.11$, $c = 1.23$ for major hydronephrosis. For predicting morbidity due to *S. mansoni* infection, the parameters of the equation are $b = 0.27$, $c = 7.70$ for diarrhoea, $b = 0.69$, $c = 4.95$ for blood in stool, $b = 0.22$, $c = 1.56$ for hepatomegaly (MSL), $b = 0.12$, $c = 1.27$ for splenomegaly, $b = 0.029$, $c = 3.83$ for ascitis and $b = 0.024$, $c = 1.63$ for haematemesis. The association between *S. mansoni* infection and abdominal pain was non-conclusive. For haematemesis and ascitis we assumed all morbidity cases to be in the adult group and the reported prevalence of infection to reflect the total population.

Appendix B: Estimating the prevalence of morbidity in a country

The equations described in Appendix A allow for the estimation of morbidity in individual communities (mostly villages) but cannot be used to predict prevalences of morbidity on an aggre-

gated (e.g. country) level. Most morbidity will occur in villages with the highest prevalence of infection. However, even countries with a low mean prevalence will have some villages with relatively high prevalences of infection. Therefore, morbidity would be underestimated if the mean country prevalence of infection were used for the calculation. This is due to convexity of the relationship between community prevalence of infection and morbidity. Thus, we have to take into account the distribution of prevalences of infection in a country (Chan et al., 1994). Subsequently using Eq. (3), the prevalence of morbidity y in a country with mean prevalence of infection μ is predicted by:

$$y = \int_0^1 \frac{bx^c}{1 + bx^c} \Pr(x \_\text{sfnc}; \mu) \quad (4)$$

where $\Pr(x \mid \mu)$ denotes the probability of a community having prevalence of infection x given a country with mean μ.

The distribution of prevalences within a country, can be gleaned from two data sets for *S. haematobium* (kindly provided by Guyatt et al., 1999a,b; Lengeler et al., 1991) and four data sets for *S. mansoni* (kindly provided by Barakat et al., 1995; Gryseels and Nkulikyinka, 1988; Lengeler et al., 2000; Utzinger et al., 2000). To allow for prevalences varying between at least 0.0 and at most 1.0, we have fitted a normal distribution to the logit transformed $^{10}\log(P_i/(1-P_i))$ prevalences P_i $(i = 1, \ldots, N)$ and estimated the standard deviation σ for each data set.

Fig. 4 shows an adequate fit for all data sets, but the standard deviations of the distributions ranged from $\sigma = 0.20$ to 0.87. Most data concerned prevalences in a district. Therefore, we assumed that the standard deviation for a country will be relatively high but not necessarily equal to the district with the largest heterogeneity. For both *S. haematobium* and *S. mansoni*, we chose a standard deviation of $\sigma = 0.6$ (comparable with Côte d'Ivoire) for country/region prevalence of infection to calculate the mean prevalence of morbidity in a country.

Appendix C: Estimating mortality due to non-functioning kidney and haematemesis

Incidence of mortality was estimated from the (estimated) number of cases with life-threatening morbidity, here non-functioning kidney due to *S. haematobium* and haematemesis due to *S. mansoni*. By assuming an exponential distribution, the disease specific annual death rate u can be obtained from follow-up studies by

$$u = -\ln(1-p)/t \quad (5)$$

in which p is the proportion dead within a period t in years. Given a number of cases with morbidity c, and assuming no time-trends, the incidence i is approximated by:

$$i = c(m + u) \quad (6)$$

in which m is the general mortality rate in the population. The number of disease specific deaths d per year can be calculated from:

$$d = iu/(m + u) = cu \quad (7)$$

To the best of our knowledge, only one published study provided data to infer a death rate of individuals with non functioning kidney and only two studies for haematemesis. Out of seven individuals with non-functioning kidney, three died within 6 year (Forsyth et al., 1970), leading to $u = 0.09$ per year for non-functioning kidney (Eq. (5). For haematemisis, 5 out of 25 patients died within 1 year (Kiire, 1989) and 4 out of 27 died within 28 months (Richter et al., 1998). This associates with an average of $u = 0.14$ per year. The general mortality rate ($m = 0.02$ per year) was obtained from http://www.statistical-data.org/index.html (16 August 2001).

The number of cases with haematemesis (ever) at cross-section could be obtained from our estimates using the prevalence of infection (see Appendix B). For non-functioning kidney (detected by intravenous pyelogram), only two studies were available to arrive at an association between infection and morbidity (Forsyth, 1969; Forsyth and Bradley, 1966). As this was not sufficient to fit Eq. (1) or Eq. (2), we chose a different procedure. First, we assumed that non-functioning kidney shows a linear association with the number of

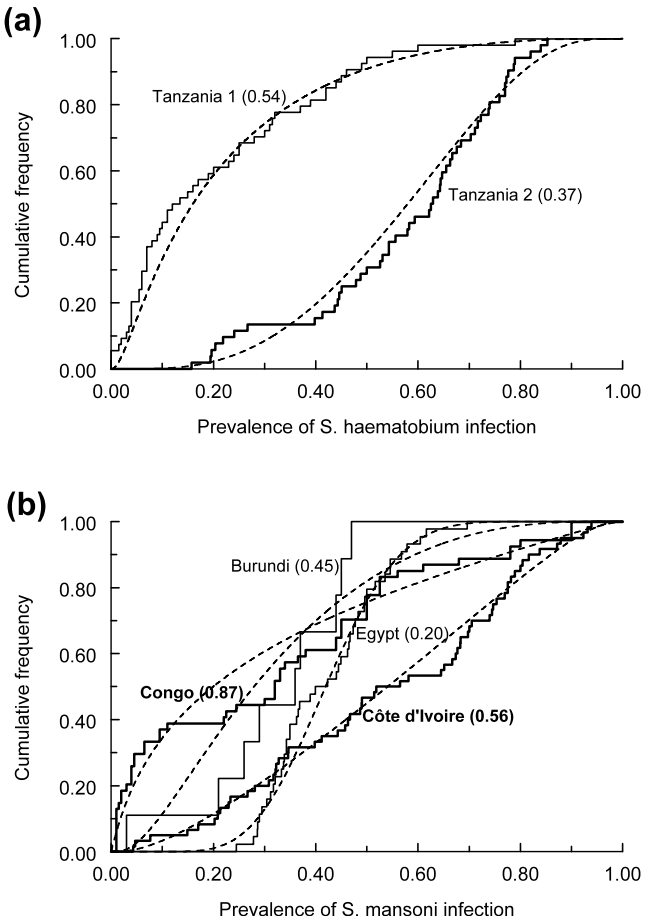

Fig. 4. Cumulative distribution of (a) *S. haematobium* prevalences in Kilombero district of Morogoro Region, Tanzania [Tanzania 1], N (number of schools or communities) = 54, mean = 0.16 ('anti-logit' of the mean of logit transformed data) and $\sigma = 0.54$ (Lengeler et al., 1991) and Magu district of Mwanza Region, Tanzania [Tanzania 2], $N = 52$, mean = 0.58 and $\sigma = 0.37$ (Guyatt et al., 1999b). And, (b) *S. mansoni* prevalences, of the Rusizi Plain, Burundi, $N = 9$, mean = 0.28 and $\sigma = 0.45$ (Gryseels and Nkulikyinka, 1988), the region of Kafr El Sheikh governorate, Egypt, $N = 44$, mean = 0.42 and $\sigma = 0.20$ (Barakat et al., 1995), the town of Matadi and the administrative zone of Songololo, Congo, $N = 54$, mean = 0.20 and $\sigma = 0.87$ (Lengeler et al., 2000), and the region of Man, western Côte d'Ivoire, $N = 60$, mean = 0.54 and $\sigma = 0.56$ (Utzinger et al., 2000) (data were kindly provided by the authors). The value between brackets is standard deviation σ of logit transformed prevalences. The steeper the line around 50% cumulative frequency, the lower the value of σ. The dashed lines represent the fitted distributions.

individuals with heavy infections (> 50 eggs per 10 ml); an estimate of this number for a given community prevalence of infection was obtained from an existing egg count model (De Vlas et al., 1992). Second, we assumed that all non functioning kidney cases in *S. haematobium* endemic areas are caused by the infection. Forsyth and Bradley (1966) investigated 794 *S. haematobium* infected individuals in a population with prevalence 65% (i.e. about 405 individuals > 50 eggs per 10 ml) by intravenous pyelogram and detected 36 with at least one non functioning kidney. Forsyth (1969) found among 751 infected individuals in a population with prevalence 42% (i.e. about 120 individuals > 50 eggs per 10 ml), five cases with at least one non functioning kidney. This means that on average 0.064 × the prevalence of individuals with heavy infection in a community will have at least one non functioning kidney.

References

Abdel-Salam, E., Abdel-Fattah, M., 1977. Prevalence and morbidity of *Schistosoma haematobium* in Egyptian children. Am. J. Trop. Med. Hyg. 26, 463–469.

Abdel-Wahab, M.F., Esmat, G., Ramzy, I., Fouad, R., Abdel-Rahman, M., Yosery, A., Narooz, S., Strickland, G.T., 1992. *Schistosoma haematobium* infection in Egyptian schoolchildren: demonstration of both hepatic and urinary tract morbidity by ultrasonography. Trans. R. Soc. Trop. Med. Hyg. 86, 406–409.

Abdel-Wahab, M.F., Esmat, G., Ramzy, I., Narooz, S., Medhat, E., Ibrahim, M., El-Boraey, Y., Strickland, G.T., 2000. The epidemiology of schistosomiasis in Egypt: Fayoum Governorate. Am. J. Trop. Med. Hyg. 62, 55–64.

Barakat, R., Farghaly, A., el Masry, A.G., el Sayed, M.K., Husein, M.H., Miller, F.D., 1995. *Schistosoma mansoni* in the Nile Delta, Egypt. A large scale epidemiological study in Kafr El Sheikh Governorate. Trop. Geogr. Med. 47, 259–265.

Bedwani, R., Renganathan, E., El Kwhsky, F., Braga, C., Abu Seif, H.H., Abul Azm, T., Zaki, A., Franceschi, S., Boffetta, P., La Vecchia, C., 1998. Schistosomiasis and the risk of bladder cancer in Alexandria, Egypt. Br. J. Cancer 77, 1186–1189.

Booth, M., Bundy, D.A., Albonico, M., Chwaya, H.M., Alawi, K.S., Savioli, L., 1998a. Associations among multiple geohelminth species infections in schoolchildren from Pemba Island. Parasitology 116, 85–93.

Booth, M., Mayombana, C., Machibya, H., Masanja, H., Odermatt, P., Utzinger, J., Kilima, P., 1998b. The use of morbidity questionnaires to identify communities with high prevalences of schistosome or geohelminth infections in Tanzania. Trans. R. Soc. Trop. Med. Hyg. 92, 484–490.

Brooker, S., Rowlands, M., Haller, L., Savioli, L., Bundy, D.A.P., 2000a. Towards an atlas of human helminth infection in sub-Saharan Africa: the use of geographical information systems (GIS). Parasitol. Today 16, 303–307.

Brooker, S., Donnelly, C.A., Guyatt, H.L., 2000b. Estimating the number of helminthic infections in the Republic of Cameroon from data on infection prevalence in schoolchildren. Bull. WHO 78, 1456–1465.

Brooker, S., Hay, S.I., Bundy, D.A.P., 2002. Tools from ecology: useful for evaluating infection risk models. Trends Parasitol. 18, 70–74.

Chen, M.G., Mott, K.E., 1988. Progress in assessment of morbidity due to *Schistosoma mansoni*: a review of recent literature. Trop. Dis. Bull. 85, R1–R56.

Chen, M.G., Mott, K.E., 1989. Progress in assessment of morbidity due to *Schistosoma haematobium*: a review of recent literature. Trop. Dis. Bull. 86, R1–R36.

Chan, M.S., Medley, G.F., Jamison, D., Bundy, D.A.P., 1994. The evaluation of potential global morbidity attributable to intestinal nematode infections. Parasitology 109, 373–387.

Chan, M.S., Guyatt, H.L., Bundy, D.A.P., Medley, G.F., 1996. Dynamic models of schistosomiasis morbidity. Am. J. Trop. Med. Hyg. 55, 52–62.

Chitsulo, L., Engels, D., Montressor, A., Savioli, L., 2000. The global status of schistosomiasis and its control. Acta Trop. 77, 41–51.

Crompton, D.W., 1999. How much human helminthiasis is there in the world. J. Parasitol. 85, 397–403.

De Silva, N.R., Chan, M.S., Bundy, D.A., 1997. Morbidity and mortality due to ascariasis: re-estimation and sensitivity analysis of global numbers at risk. Trop. Med. Int. Health 2, 519–528.

De Vlas, S.J., Gryseels, B., 1992. Underestimation of *Schistosoma mansoni* prevalences. Parasitol. Today 8, 274–277.

De Vlas, S.J., Gryseels, B., Van Oortmarssen, G.J., Polderman, A.M., Habbema, J.D.F., 1992. A model for variations in single and repeated egg counts in *Schistosoma mansoni* infections. Parasitology 104, 451–460.

Doumenge, J.P., Mott, K.E., Cheung, C., Villenave, D., Chapuis, O., Perrin, M.F., Reaud-Thomas, G., 1987. Atlas of the Global Distribution of Schistosomiasis, Univeriste de Bordeaux Bordeaux, p. 400.

Efron, B., Tibshirani, R.J., 1993. An Introduction to the Bootstrap. Chapman and Hall, International Thomson Publishing, New York, p. 412.

Ekanem, E.E., Asindi, A.A., Ejezie, G.C., Antia-Obong, O.E., 1994. Effect of *Schistosoma haematobium* infection on the physical growth and school performance of Nigerian children. Central Afr. J. Med. 40, 38–44.

Forsyth, D.M., 1969. A longitudinal study of endemic urinary schistosomiasis in a small East African community. Bull. WHO 40, 771–783.

Forsyth, D.M., Bradley, D.J., 1964. Irreversible damage by *Schistosoma haematobium* in schoolchildren. Lancet 169–171.

Forsyth, D.M., Bradley, D.J., 1966. The consequences of bilharziasis: medical and public health importance in North–West Tanzania. Bull. WHO 34, 715–735.

Forsyth, D.M., Bradley, D.J., McMahon, J., 1970. Death attributed to kidney failure in communities with endemic urinary schistosomiasis. Lancet 2, 472–473.

Gabr, N.S., Hammad, T.A., Orieby, A., Shawky, E., Khattab, M.A., Strickland, G.T., 2000. The epidemiology of schistosomiasis in Egypt: Minya Governorate. Am. J. Trop. Med. Hyg. 62, 65–72.

Gryseels, B., 1989. The relevance of schistosomiasis for public health. Trop. Med. Parasitol. 40, 134–142.

Gryseels, B., 1992. Morbidity due to infection with *Schistosoma mansoni*: an update. Trop. Geogr. Med. 44, 189–200.

Gryseels, B., Nkulikyinka, L., 1988. The distribution of *Schistosoma mansoni* in the Rusizi plain (Burundi). Ann. Trop. Med. Parasitol. 82, 581–590.

Gryseels, B., Polderman, A.M., 1991. Morbidity, due to *Schistosomiasis mansoni*, and its control in Subsaharian Africa. Parasitol. Today 7, 244–248.

Guyatt, H.L., Bundy, D.A.P., 1991. Estimating prevalence of community morbidity due to intestinal helminths: prevalence of infection as indicator of the prevalence of disease. Trans. R. Soc. Trop. Med. Hyg. 85, 778–782.

Guyatt, H.L., Brooker, S., Donnelly, C.A., 1999a. Can prevalence of infection in school-aged children be used as an index for assessing community prevalence. Parasitology 118, 257–268.

Guyatt, H., Brooker, S., Lwambo, N.J., Siza, J.E., Bundy, D.A.P., 1999b. The performance of school-based questionnaires of reported blood in urine in diagnosing *Schistosoma haematobium* infection: patterns by age and sex. Trop. Med. Int. Health 4, 751–757.

Hammam, H.M., Allam, F.A., Moftah, F.M., Abdel-Aty, M.A., Hany, A.H., Abd-El-Motagaly, K.F., Nafeh, M.A., Khalifa, R., Mikhail, N.N., Talaat, M., Hussein, M.H., Strickland, G.T., 2000a. The epidemiology of schistosomiasis in Egypt: Assiut governorate. Am. J. Trop. Med. Hyg. 62, 73–79.

Hammam, H.M., Zarzour, A.H., Moftah, F.M., Abdel-Aty, M.A., Hany, A.H., El-Kady, A.Y., Nasr, A.M., Abd-El-Samie, A., Qayed, M.H., Mikhail, N.N., Talaat, M., Hussein, M.H., 2000b. The epidemiology of schistosomiasis in Egypt: Qena governorate. Am. J. Trop. Med. Hyg. 62, 80–87.

Iarotski, L.S., Davis, A., 1981. The schistosomiasis problem in the world: results of a WHO questionnaire survey. Bull. WHO 59, 115–127.

Jordan, P., Webbe, G., Sturrock, R.F., 1993. Human Schistosomiasis. CAB International, Cambridge, London, p. 442.

Kheir, M.M., Eltoum, I.A., Saad, A.M., Ali, M.M., Baraka, O.Z., Homeida, M.M.A., 1999. Mortality due to *Schistosomiasis mansoni*: a field study in Sudan. Am. J. Trop. Med. Hyg. 60, 307–310.

Kiire, C.F., 1989. Controlled trial of propranolol to prevent recurrent variceal bleeding in patients with non-cirrhotic portal fibrosis, Lancet, July:. Br. Med. J. 298, 1363–1365.

King, C.H., Keating, C.E., Muruka, J.F., Ouma, J.H., Houser, H., Siongok, T.K., Mahmoud, A.A., 1988. Urinary tract morbidity in *Schistosomiasis haematobia*: associations with age and intensity of infection in an endemic area of Coast Province, Kenya. Am. J. Trop. Med. Hyg. 39, 361–368.

Kitinya, J.N., Lauren, P.A., Eshleman, L.J., Paljarvi, L., Tanaka, K., 1986. The incidence of squamous and transitional cell carcinomas of the urinary bladder in northern Tanzania in areas of high and low levels of endemic *Schistosoma haematobium* infection. Trans. R. Soc. Trop. Med. Hyg. 80, 935–939.

Kvalsvig, J.D., 1986. The effects of *Schistosomiasis haematobium* on the activity of school children. J. Trop. Med. Hyg. 89, 85–90.

Kvalsvig, J.D., 1988. The effects of parasitic infection on cognitive performance. Parasitol. Today 4, 206–208.

Lengeler, C., de Savigny, D., Mshinda, H., Mayombana, C., Tayari, S., Hatz, C., Degremont, A., Tanner, M., 1991. Community-based questionnaires and health statistics as tools for the cost-efficient identification of communities at risk of urinary schistosomiasis. Int. J. Epidemiol. 20, 796–807.

Lengeler, C., Makwala, J., Ngimbi, D., Utzinger, J., 2000. Simple school questionnaires can map both *Schistosoma mansoni* and *Schistosoma haematobium* in the Democratic Republic of Congo. Acta Trop. 74, 77–87.

Lucas, S.B., 1982. Squamous cell carcinoma of the bladder and schistosomiasis. East Afr. Med. J. 59, 345–351.

Masaba, S.C., Awiti, I.E., Muruka, J.F., 1983. Morbidity in urinary schistosomiasis in relation to the intensity of infection in Kisumu, Kenya. J. Trop. Med. Hyg. 86, 65–66.

Medley, G.F., Bundy, D.A.P., 1996. Dynamic modeling of epidemiologic patterns of schistosomiasis morbidity. Am. J. Trop. Med. Hyg. 55, 149–158.

Mostafa, M.H., Sheweita, S.A., O'Connor, P.J., 1999. Relationship between schistosomiasis and bladder cancer. Clin. Microbiol. Rev. 12, 97–111.

Mungomba, L.M., Kalumba, K., 1995. Validation of schistosomiasis morbidity symptoms in schoolchildren of Siavonga, Lake Kariba, Zambia. Ann. Trop. Med. Parasitol. 89, 439–442.

Murray, C.J.L., Lopez, A.D., 1996. The Global Burden of Disease. Harvard University Press, p. 990.

Murray, C.J.L., Lopez, A.D., 1997. Mortality by cause for eight regions of the world: Global Burden of Disease Study. Lancet 349, 1269–1276.

Nokes, C., Bundy, D.A.P., 1994. Does helminth infection affect mental processing and educational achievement. Parasitol. Today 10, 14–18.

Richter, J., Correia Dacal, A.R., Vergetti Siqueira, J.G., Poggensee, G., Mannsmann, U., Deelder, A., Feldmeier, H., 1998. Sonographic prediction of variceal bleeding in patients with liver fibrosis due to *Schistosoma mansoni*. Trop. Med. Int. Health 3, 728–735.

Savioli, L., Renganathan, E., Montresor, A., Davis, A., Behbehani, K., 1997. Control of schistosomiasis—a global picture. Parasitol. Today 13, 444–448.

Stephenson, L.S., Latham, M.C., Kurz, K.M., Miller, D., Kinoti, S.N., Oduori, M.L., 1985. Urinary iron loss and physical fitness of Kenyan children with urinary schistosomiasis. Am. J. Trop. Med. Hyg. 34, 322–330.

Thomas, J.E., Bassett, M.T., Sigola, L.B., Taylor, P., 1990. Relationship between bladder cancer incidence, *Schistosoma haematobium* infection, and geographical region in Zimbabwe. Trans. R. Soc. Trop. Med. Hyg. 84, 551–553.

Traquinho, G.A., Quinto, L., Nala, R.M., Gama Vaz, R., Corachan, M., 1998. Schistosomiasis in Northern Mozambique. Trans. R. Soc. Trop. Med. Hyg. 92, 279–281.

Utzinger, J., N'Goran, E.K., Ossey, Y.A., Booth, M., Traore, M., Lohourignon, K.L., Allangba, A., Ahiba, L.A., Tanner, M., Lengeler, C., 2000. Rapid screening for *Schistosoma mansoni* in western Cote d'Ivoire using a simple school questionnaire. Bull. WHO 78, 389–398.

Utzinger, J., Booth, M., N'Goran, E.K., Muller, I., Tanner, M., Lengeler, C., 2001. Relative contribution of day-to-day and intra-specimen variation in faecal egg counts of *Schistosoma mansoni* before and after treatment with praziquantel. Parasitology 122, 537–544.

van der Werf, M.J., De Vlas, S.J., Looman, C.W.N., Nagelkerke, N.J.D., Habbema, J.D.F., Engels, D., 2002. Associating community prevalence of *Schistosoma mansoni* infection

with prevalence of signs and symptoms. Acta Trop. 82, 127–137.

van der Werf, M.J., De Vlas, S.J., Looman, C.W.N., Engels, D., Habbema, J.D.F. Diagnosis of early clinical consequnces of *Schistosoma haematobiun* infection: a novel approach to compare the performance of ultrasound and three methods for haematuria detection. Submitted.

Warren, K.S., Mahmoud, A.A., Muruka, J.F., Whittaker, L.R., Ouma, J.H., Arap Siongok, T.K., 1979. *Schistosomiasis haematobia* in coast province Kenya. Relationship between egg output and morbidity. Am. J. Trop. Med. Hyg. 28, 864–870.

WHO (World Health Organization), 1993. The control of schistosomiasis. Technical report series No. 830, Geneva, p. 86.