Epidemiol. Infect. (1992), **108**, 469–481
Printed in Great Britain

A new approach to morbidity risk assessment in hookworm endemic communities

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(*Accepted 24 January 1992*)

SUMMARY

The relationship between paired hookworm prevalence and mean intensity of infection data from geographically defined communities was examined. The results show that, in spite of major socio-economic and environmental differences between communities, the relationship is consistent and non-linear. A generalized value of k (the exponent of the negative binomial distribution) for hookworms was estimated to be 0·34, which is consonant with previous estimates from cross-sectional data. Maximum likelihood analysis indicates that the severity of hookworm aggregation in humans has an inverse relationship to mean worm burden which is less marked than for *Ascaris lumbricoides*. A simple model, based on published estimates of hookworm burdens associated with hookworm anaemia, was used to predict prevalence of morbidity from prevalence of infection data for Tanzania, Kenya and Zambia. Predictions correspond to the observation that hookworm anaemia is highly focal, and largely coastal, in distribution. These analyses suggest that locality-targeting of chemotherapy is particularly appropriate for the control of hookworm morbidity.

INTRODUCTION

Chronic blood loss and depletion of the body's iron stores in heavy hookworm infections often leads to iron-deficiency anaemia, a condition better known as hookworm anaemia. Layrisse and Roche [1] estimate one-third of all iron-deficiency anaemias to be of this type. In the severe form, hookworm anaemia is associated with mortality [2, 3]. Walsh and Warren [4] estimate the global occurrence of 900 million hookworm infections, of which 1·5 million develop hookworm anaemia resulting in 50000–60000 deaths each year. These figures emphasize the public health importance of hookworm infection as a cause of morbidity and mortality. According to Pawlowski [5] and WHO [6], the highest priority in hookworm control is the reduction of mortality and morbidity by community-based chemotherapy. Cheap, safe and efficacious broad spectrum anthelminthic drugs for community control of hookworms and other geohelminths now exist. However, formidable operational problems still remain, foremost being the identification of communities at high risk of disease where control efforts need to be focused in order to maximize their cost-effectiveness.

Efforts to circumvent this problem are now being made. Guyatt and colleagues

[7] determined the relationship between prevalence of *Ascaris lumbricoides* infection and mean intensity. Subsequently, Guyatt and Bundy [8] utilized the negative binomial probability distribution, a model of overdispersion of worms in host populations, to predict from prevalence data the proportion of the community at risk of morbidity due to heavy roundworm infection. Since it has been shown that the frequency distribution of hookworms in human populations is also highly overdispersed and that the negative binomial probability model provides an adequate description of empirical data [9], the methods used to predict morbidity due to *A. lumbricoides* may also be appropriate for similar analysis of hookworm infections.

The objectives of the present study are to use published data to: (1) determine the relationship between prevalence of hookworm infection and mean intensity; (2) investigate the effect of intensity of hookworm infection on haemoglobin levels in different communities; (3) determine the relationship between prevalence of hookworm infection and that of iron-deficiency anaemia; and (4) demonstrate how these relationships may be used to estimate the prevalence of morbidity due to hookworms from existing data on the prevalence of infection in Tanzania, Kenya and Zambia.

MATERIALS AND METHODS

The model

The model used in the present study has been described in detail for *A. lumbricoides* [7, 8]. Here we briefly describe its application to hookworms. Since the frequency distribution of hookworms in human populations is overdispersed relative to random (Poisson) and well described by the negative binomial probability model, the probability of not being infected, p, is given by the expression:

$$p = \left(1 + \frac{M}{k}\right)^{-k}, \tag{1}$$

where M is the mean intensity of infection, and k is the index of the degree of aggregation (overdispersion) of worms in human hosts. Equation (1) therefore allows k to be estimated from paired data of prevalance and mean intensity of infection in different communities. Observed data on hookworm prevalence and mean intensity were fitted with the negative binomial probability distribution using the maximum likelihood method, as in Guyatt and colleagues [7]. That is, the probability distribution of r uninfected individuals in a sample of N individuals is binomial, and therefore the likelihood L of observing r uninfected individuals is given by:

$$L = p^r(1-p)^{(N-r)}\{\text{terms not in } p\}, \tag{2}$$

where the terms not in p are the combinational factors concerning the order of observations. When equation (1) is substituted into equation (2) the likelihood function can be expressed as a function of k. If we ignore the terms not in p, then the log likelihood (l) function for $i = 1 \ldots n$ data sets, is:

$$\sum_{x=1}^{x=n}\left[(N_i - r_i)\ln\left(1-\left(1+\frac{M_i}{k}\right)^{-k}\right) - kr_i \ln\left(1+\frac{M_i}{k}\right)\right]. \tag{3}$$

https://doi.org/10.1017/S0950268800049980 Published online by Cambridge University Press

Table 1. *Hookworm prevalence of infection, mean worm burdens and k-values determined from cross-sectional studies of different communities in the world*

Species*	Place	No. examined	Prevalence of infection (%)	MWB†	*k*-Value	Source
N. amer.	PNG‡	123	94	25·3	0·37	[14]
Mixed	India	325	43	5·1	0·24	[15]
N. amer.	Zimbabwe	131	54	5·9	0·35	[18]
Mixed	India			51	0·34	[19]

* Mixed, both *Ancylostoma duodenale* and *Necator americanus*; *N. amer.*, *N. americanus*.
† MWB, mean worm burden.
‡ PNG, Papua New Guinea.

Thus k can be estimated using standard iterative techniques to maximize equation (3) based on observed values of N_i, r_i and M_i. This means a k value can be estimated common to all hookworm endemic communities if the prevalence of infection, mean intensity and sample size are known.

The probability of being infected, P, can be obtained by subtracting equation (1) from unity thus:

$$P = 1 - \left(1 + \frac{M}{k}\right)^{-k}. \tag{4}$$

Given that the frequency distribution of parasites in a host population determines the form of relationship between prevalence of infection and mean intensity, equation (4) can also define the relationship between prevalence of infection P, and mean intensity M, where k is the index of the degree of aggregation.

Based on the assumption that a certain threshold number of hookworms induce iron-deficiency anaemia in the host, and using k as an index of overdispersion of infection, the relationship between prevalence of infection and that of hookworm anaemia can be investigated. Applying the negative binomial distribution, the probability $P_{(x)}$ of an individual having x number of hookworms at a given mean intensity of infection is:

$$P_{(x)} = \left(1 + \frac{M}{k}\right)^{-k} \left(\frac{\Gamma(k+x)}{x!\,\Gamma(k)}\right) \left(\frac{M}{M+k}\right)^{x}, \tag{5}$$

where $\Gamma(\cdot)$ represents the gamma function.

Equation (5) can be used to determine the probability of an individual having a certain worm burden and therefore the proportion of the community harbouring that particular number of worms. If D is the threshold number of hookworms assumed to cause iron-deficiency anaemia, then the proportion of the community at risk of developing hookworm anaemia (i.e. with D or more worms), is:

$$A = 1 - \sum_{x=0}^{D-1} P_{(x)}. \tag{6}$$

It follows that the proportion of the population harbouring D worms or more, the threshold for disease, is a function of prevalence of hookworm infection. Guyatt

and Bundy [8] in examining *A. lumbricoides* infection, showed that an increase in prevalence shifted the dispersion of infection so as to increase the proportion of people with heavy worm burdens at the tail of the distribution.

Data sources

Relationship between prevalence of infection and mean intensity

Data for this investigation were obtained from published hookworm (both *Necator americanus* and *Ancylostoma duodenale*) expulsion studies where both prevalence of infection and mean worm burdens were recorded. These included studies in Puerto Rico [10]; Australia [11]; Brazil [12, 13]; Papua New Guinea [14]; India [15, 16]; and Sri Lanka [17].

Relationship between k and mean intensity

Table 1 lists the sources of data of cross-sectional studies on hookworms where the prevalence of infection, mean intensity and k values were determined. The data were used to investigate the relationship between k and mean worm burden, by examining the statistical improvement to the fit of the data by assuming k to be a function of mean intensity.

Relationship between mean intensity of infection and hookworm anaemia

Data were obtained from studies which investigated the relationship between faecal egg count, as an indirect measure of hookworm worm load, and haemoglobin (Hb) concentration in blood in order to establish the threshold egg count for anaemia: Layrisse and Roche [1] in Venezuela, Udonsi [20] in Nigeria, Areekul [21] in Thailand and Crompton and Stephenson [22] in Kenya. These studies describe infection with *N. americanus* [1] or mixed hookworm infection in which *N. americanus* is the predominant species. The minimum EPG (eggs per gram) at which all the studies recorded a significant reduction in Hb was determined, as well as the EPG value associated with an Hb concentration equal to or lower than 11·0 g/100 ml of blood, the WHO [23] threshold for anaemia. The EPG values were converted to worm burdens using the relationship between faecal egg count and worm load in hookworm, described by Anderson and Schad [9]. The estimated worm loads were then used in the model (equations 5 and 6) to determine the relationship between prevalence of infection and that of hookworm anaemia in endemic communities.

Relationship between prevalence of hookworm infection and that of hookworm anaemia

Since the threshold worm burden for hookworm anaemia may not be identical in all endemic communities, the relationship between prevalence of infection and that of morbidity was investigated at different worm threshold levels using equations 4, 5 and 6.

Estimated prevalence of hookworm anaemia in Tanzania, Kenya and Zambia

Data on the prevalence of hookworm infection covering most of the administrative regions of Tanzania were obtained from Kihamia [24] and Tanner and colleagues [25], and on most provinces of Kenya from Stephenson, Latham

and Oduori [26]. Data for Zambia were obtained from Wenlock [27]. Applying the model (equations 4, 5 and 6) to the regional prevalence data allows the estimation of the proportion of the population with worm burdens above the threshold and hence the proportions of each community at risk of developing iron-deficiency anaemia attributable to hookworm infection.

RESULTS

Relationship between prevalence of infection and mean intensity

Since the two hookworm species cannot be easily distinguished in survey procedures, most studies do not provide separate estimates of mean intensity for each, and the data are considered to represent mixed infections. Fig. 1 illustrates the relationship between prevalence of hookworm infection and mean worm burdens for a range of geographical locations. The curve shows that up to a prevalence value of 70%, the mean worm burden varies linearly with the prevalence of infection. However, above this prevalence, the relationship becomes non-linear such that a small increase in prevalence results in a large increase in mean worm burden. Fitting the log-likelihood function to the data (equation 3) results in a maximum likelihood estimate of the negative binomial exponent k of 0·343, which closely resembles values estimated independently from cross-sectional studies (see Table 1).

Relationship between k and mean intensity

Maximum-likelihood estimation of the data in Fig. 1 indicates a significantly improved fit when k is linear function of mean intensity as judged from likelihood ratios (see legend for Fig. 1). Fig. 2 compares this predicted relationship between k and mean intensity with observed values obtained from cross-sectional data. The trend for k to increase (aggregation to decrease) with increasing mean worm burden is weak and only marginally different from independence of k from worm burden.

Relationship between mean intensity of infection and hookworm anaemia

The relationship between intensity of predominantly *N. americanus* infection and haemoglobin concentration (g/100 ml of blood), determined independently in four separate studies, is shown in Fig. 3. In all four studies, Hb was significantly reduced at an infection level of 2000 EPG, although it was still above 11·0 g/100 ml of blood, the WHO threshold for clinical anaemia [23, 5]. Hb fell below 11·0 g/100 ml of blood at different intensities in each study, ranging from 2500 to 8000 EPG. When these threshold egg counts are converted to worm burdens using the relationship already established [9], they correspond to 40 and 162 worms, respectively.

Relationship between prevalence of hookworm infection and that of hookworm anaemia

Fig. 4 shows the predicted relationship between the prevalence of infection and of hookworm anaemia for different worm burden thresholds for anaemia, assuming k to be independent of worm burden. The relationship is markedly non-linear, with

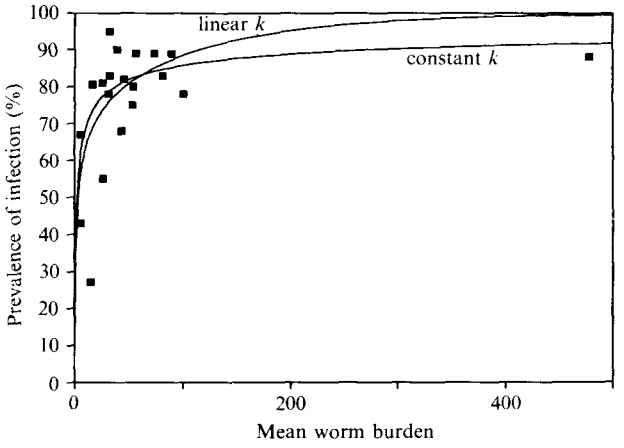

Fig. 1. Relationship between hookworm prevalence of infection and mean worm burden. The curves are the best maximum-likelihood fits for the negative binomial probability distribution with a constant k ($k = 0{\cdot}343$) and when k is a linear function of mean intensity ($k = a + bM$; $a = 0{\cdot}2686$; $b = 0{\cdot}0012$). Log-likelihood function (l) $= -4277{\cdot}9598$ for constant k and l $= -4256{\cdot}4384$ for linear k. Hookworm prevalence of infection and mean worm burden show a non-linear association which is adequately described by the negative binomial probability distribution. (Data sources given in the text.)

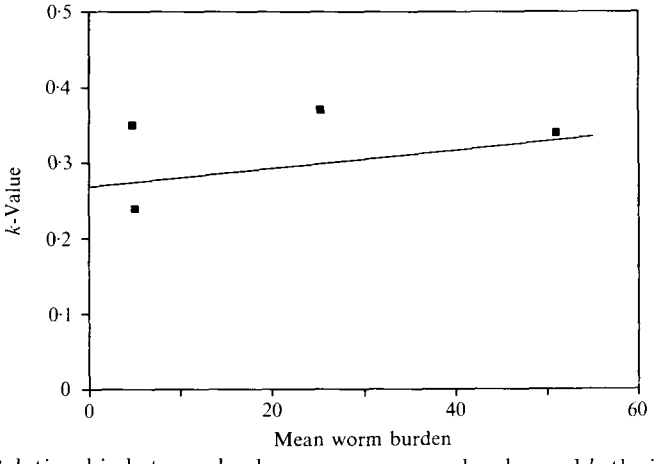

Fig. 2. Relationship between hookworm mean worm burden and k, the inverse measure of the degree of worm aggregation in host population. The line is the best maximum-likelihood fit to empirical paired data of prevalence of hookworm infection and mean worm burden (obtained from Fig. 1) when k is a linear function of mean intensity. The degree of worm aggregation within a community is inversely related to mean worm burden. (Data sources as in Table 1.)

predicted prevalence of anaemia increasing disproportionately at high values of prevalence of infection. The prevalence of disease at a certain prevalence of infection is dependent on the threshold intensity for hookworm anaemia. At large threshold worm burdens (> 80 worms), the curves in Fig. 4 come close together,

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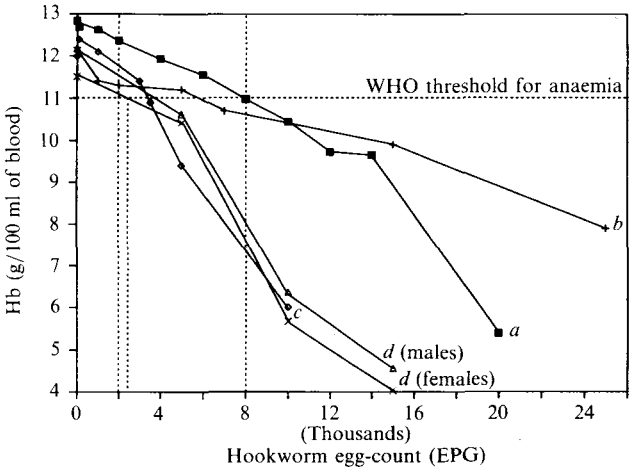

Fig. 3. Relationship between intensity of hookworm infection (EPG) and haemoglobin (Hb) concentration in blood. Data from published studies of geographically defined communities in different parts of the world: *a*, Thailand [21]; *b*, Kenya [22]; *c*, Venezuela [33]; *d*, Nigeria [20]. At 2000 EPG (shown by the first vertical dotted line), Hb was reported by all the studies to be significantly lower than at zero. At an EPG range of 2500–8000 (shown by second and third vertical dotted lines) the Hb in all studies fell below 11·0 g/dl of blood, the WHO [23] threshold for anaemia.

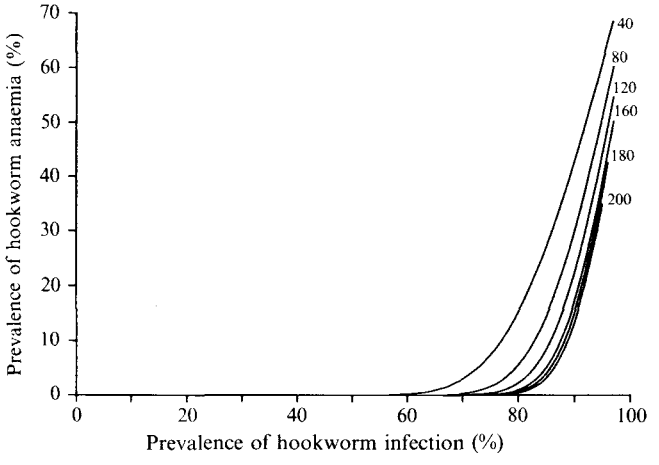

Fig. 4. Relationship between prevalence of hookworm infection and that of hookworm anaemia at different worm burden thresholds for morbidity. Above a threshold worm burden of 80 worms/host, the relationship between prevalence of infection and that of hookworm anaemia is not sensitive to differences in threshold worm burdens for morbidity between communities.

suggesting that the relationship between prevalence of infection and disease becomes less sensitive to the threshold value at high infection prevalences.

Estimated prevalence of hookworm anaemia in Tanzania, Kenya and Zambia

Since a mean worm burden range of 40–162 hookworms was shown to cause iron-deficiency anaemia in different communities (Fig. 3), these values were used

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Table 2. *Prevalence of morbidity (hookworm anaemia) according to the prevalence of hookworm infection in different provinces (or ecological zones) of Tanzania, Kenya and Zambia. Threshold worm burden for hookworm anaemia ranges from 40 to 162 worms/host*

Country/provinces	Prevalence of infection (%)	Prevalence (%) of hookworm anaemia at threshold worm burdens of	
		40 worms	162 worms
Tanzania			
Mwanza	82·0	33·132	8·679
Tanga	81·5	31·627	7·647
Morogoro	65·0	2·985	0·004
Iringa	64·9	0·269	0
Coast	55·5	0·230	0
Kagera	55·0	0	0
Dodoma	37·0	0	0
Kigoma	36·0	0	0
Dar es Salaam	30·0	0	0
Tabora	28·0	0	0
Mara	18·1	0	0
Mbeya	3·5	0	0
Kenya			
Coast	66·0	3·650	0·008
Nyanza	43·0	0·002	0
Western	34·0	0	0
Central	24·0	0	0
Nairobi	22·0	0	0
Eastern	19·0	0	0
Rift Valley	11·0	0	0
Zambia			
Lake Tanganyika basin	77·1	19·927	2·030
Zambezi River, West Prov.	76·0	17·469	1·364
Chambeshi River Valley	68·2	5·487	0·032
Lake Bangweulu Basin	59·1	0·753	0
Mongu Distr. West Prov.	58·6	0·659	0
Gwembe Valley, South Prov.	55·6	0·277	0
Northern Highland	44·5	0·007	0
Kaoma Distr. West Prov.	43·9	0·004	0
Kabompo River, Northwest	42·0	0·003	0
Plateau Area, South	41·4	0·001	0
Central Province East	41·2	0	0
Zambezi River, Northwest	40·4	0	0
Ndola Rural District	39·0	0	0
Central Province West	37·1	0	0
Eastern Province	11·6	0	0
Chizera Distr. Northwest	11·4	0	0

as thresholds in the application of the model to observed hookworm prevalence data. Table 2 shows the reported prevalence of hookworm infection and the estimated prevalence of hookworm anaemia in different regions of Tanzania, Kenya and Zambia. As illustrated in Fig. 5, the predicted geographical distribution of hookworm anaemia (prevalence $> 2\%$) in the three countries is highly focal. Apart from two isolated areas in Tanzania and Zambia, hookworm

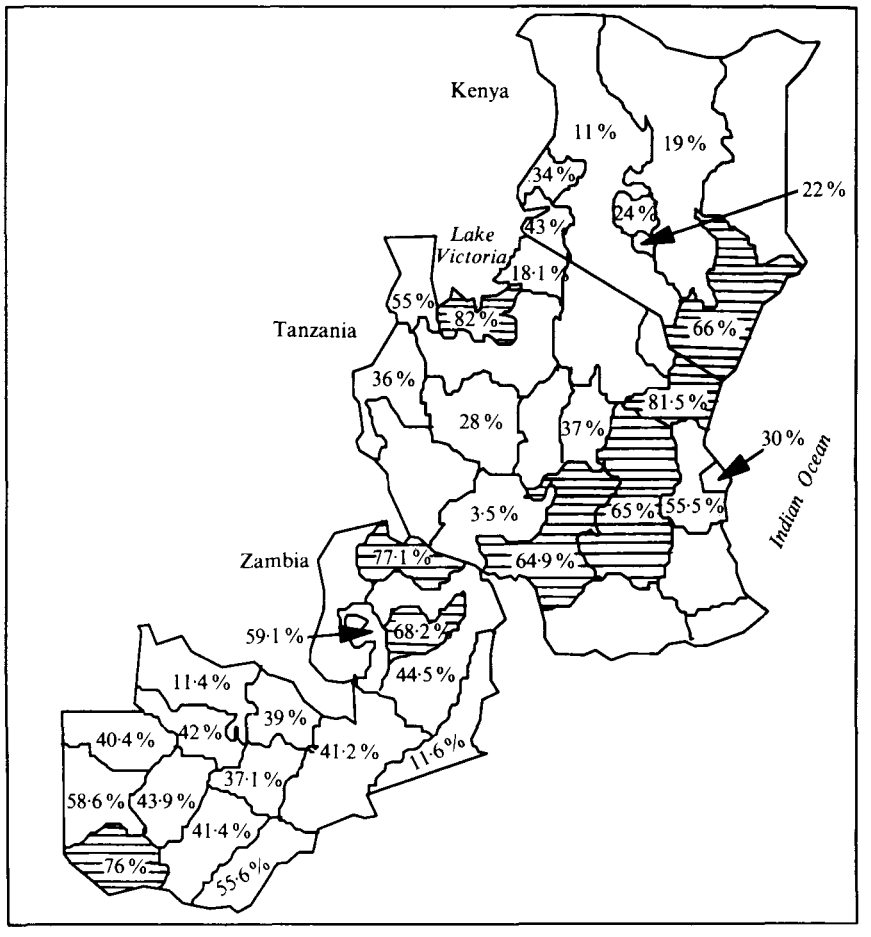

Fig. 5. Map of Tanzania, Kenya and Zambia showing the prevalence of hookworm infection in different administrative regions (provinces) of each country and areas of high risk (> 2·0%, ▤) of hookworm anaemia. The risk of hookworm anaemia is focal in distribution.

anaemia at greater than 2% is estimated to occur in a single narrow strip stretching from the Coastal Province of Kenya across Eastern Tanzania to North East Zambia. Translating these estimates of prevalence into risk of anaemia will depend on a range of factors which include special scale and local level of iron balance.

DISCUSSION

Guyatt and colleagues [7] demonstrated that in spite of differences between endemic communities in terms of geography, environment, race, socio-economic and cultural practices, and intensity of *A. lumbricoides* transmission, the relationship between the prevalence of roundworm infection and mean intensity was remarkably consistent and non-linear. The findings of the present investigation on hookworms are in agreement with this. The relationship is consistent in the

https://doi.org/10.1017/S0950268800049980 Published online by Cambridge University Press

present analysis despite the fact that the data describe mixed infection involving two hookworm species. This accords with observations from cross-sectional data which indicate a similar degree of aggregation for both mixed infections and those involving *N. americanus* alone (Table 1). Hookworm prevalences of up to 70% are linearly related to mean intensity, but at higher prevalences the relationship becomes markedly non-linear. Within the prevalence range 0–70%, infection prevalence appears to be a good indicator of hookworm mean intensity in a community, and indicates a mean worm burden of less than 10 worms/host (see Fig. 1).

The generalized value of k estimated for hookworms is 0·343 which compares with 0·543 for *A. lumbricoides* [7], an indication that hookworms are more highly aggregated than roundworms. The parameter k, for both hookworm and roundworm infections, is positively and linearly related to mean worm burden, implying that there is a decline in worm aggregation with increasing intensity for both helminth species. In hookworms, however, the slope of the curve relating k to mean intensity (Fig. 2), is an order of magnitude less than for *A. lumbricoides* [7]. This indicates that the decrease in the degree of worm aggregation as a function of mean intensity is much more severe in *A. lumbricoides* than in hookworm infections. This may relate to the difference in size between the two parasite species, perhaps indicating that the carrying capacity of the gut, in terms of space or resources, becomes limiting at relatively lower worm burdens for the larger *A. lumbricoides* than for the smaller hookworms. Thus density-dependent reduction of worm survival or establishment at high worm burdens [28–30] may occur, at relatively lower intensities in roundworms than in hookworms, as a result of intra-specific competition. This might suggest that fewer worms would be required to evoke disease in *A. lumbricoides* infections than in hookworms. This is in agreement with the estimated threshold intensity of 20 worms for 'clinical ascariasis' [8] against 40–162 worms for hookworm anaemia.

Iron-deficiency anaemia, the major clinical effect of hookworm infection, is associated with the intensity of the infection [1, 31, 22]. Fig. 3 summarizes the findings of four studies which show an inverse relationship between intensity of hookworm infection, as measured by faecal egg count, and haemoglobin concentration in blood. Since iron-deficiency anaemia is associated with intensity of hookworm infection, and the latter is non-linearly related to prevalence of infection, it follows that prevalence of infection has a non-linear relationship with iron-deficiency anaemia, as shown in Fig. 4. This relationship has obvious practical implications for communities in which infection prevalence is high since even minor increases in prevalence may result in a significant increase in disease, and vice versa. Thus control efforts which achieve even a small decrease in high infection prevalence may substantially ameliorate disease in hyperendemic communities.

It is apparent from the present model that the severity of the relationship between helminth infection and disease is related to the frequency distribution of infection and the threshold intensity at which morbidity occurs. Fig. 3 suggests that no single threshold hookworm burden for iron-deficiency anaemia for all endemic communities exists. Gilles and colleagues [32] have attributed the existence of different worm burden thresholds to differences in initial iron balance

status. In a community in which individuals have small reserves of iron and a marginal dietary intake of utilizable iron, even a small hookworm load may be enough to cause anaemia [31]. On the other hand, individuals may harbour relatively larger worm burdens for a prolonged period of time before becoming anaemic if their initial iron stores and dietary intake of utilizable iron were high. The present results indicate, however, that the relationship between prevalence of infection and that of hookworm anaemia is not particularly sensitive to the threshold worm burden, provided this is high (> 80 worms). A similar observation has been made for *A. lumbricoides* infection [8], although in the case of this large roundworm much smaller burdens (> 20 worms) were estimated to be associated with disease.

The present estimates of morbidity threshold are based on studies of infections in which *N. americanus* was the predominant species present (Fig. 3). Since *A. duodenale* infection is associated with higher rates of blood loss per worm [33], these are likely to be overestimates for areas in which *A. duodenale* is the predominant parasite. In such areas, the risk of morbidity will be enhanced at lower prevalences of infection.

The predicted focal, and largely coastal, distribution of hookworm anaemia in East Africa (Fig. 5) appears to correspond to observed patterns of hookworm disease in this area [34]. In a series of studies in Kenya, Latham and colleagues [35–38] showed that iron deficiency anaemia was not only highly prevalent in the Coastal Province but was also correlated with hookworm infection. This suggests that the model has practical predictive value. It should be recognized, however, that the predictions are at the regional level, and that there is likely to be considerable variation between individual communities within a region.

Chemotherapy targeted at school-age children, and delivered through schools, appears to offer the most cost-effective means of controlling morbidity due to *A. lumbricoides* and *Trichuris trichiura* [39, 40]. The argument behind this strategy is that the school age group bears the highest prevalence and intensity of infection with these species and is therefore both at greatest risk of morbidity and also the major source of infective stages. These considerations may not, however, apply to hookworm infection since both the prevalence and intensity of infection appear to increase with age well into adulthood [41]. School delivery of treatment for hookworm infection may offer cost advantages, but is unlikely to be advantageous in terms of effectiveness. The present results indicate, however, that unlike *A. lumbricoides* and *T. trichiura* infections, which tend to be generally distributed, clinically significant hookworm infection is markedly focal in distribution. This may indicate that locality-targeting, rather than age-targeting, is the more cost-effective approach to the control of hookworm anaemia.

The present model may be of relevance to community health planners because it enables objective decisions on resource allocation for hookworm disease control to be made. Guyatt and Bundy [8] demonstrated that the estimated cost of controlling ascariasis in children in Brazil was dependent on the degree of morbidity reduction required. The present model would enable community health planners to make similar predictions on communities at risk of hookworm morbidity, based on easily obtainable prevalence of infection data, and target control interventions in accordance with the resources available.

ACKNOWLEDGEMENTS

This study was conducted while N.J.S.L. was in receipt of a WHO Research Training Grant. D.A.P.B. gratefully acknowledges the support of the Wellcome Trust. G.F.H.M. is a Royal Society University Research Fellow.

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