Epidemiol. Infect. (1999), **123**, 487–497. Printed in the United Kingdom

Planning chemotherapy based schistosomiasis control: validation of a mathematical model using data on *Schistosoma haematobium* from Pemba, Tanzania

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(*Accepted 28 July 1999*)

SUMMARY

A mathematical model, based on a deterministic differential equation framework, has been developed to predict the impact of community chemotherapy programmes for human schistosomiasis. Here, this model is validated using data collected from a long-term control programme for urinary schistosomiasis on the island of Pemba, Zanzibar, United Republic of Tanzania, initiated in 1986 and still ongoing, in which schoolchildren were offered praziquantel chemotherapy every 6 months. Prevalence of infection and blood in urine were monitored in all the schools (total 26000 children from 60 schools) and more detailed data were collected in selected evaluation schools. Model predictions were run by using the initial prevalence as input. The predictions were very close to the observed decreases in prevalence and in prevalence of blood in urine. The correspondence improved further when the data were combined, going from single school level to district, and when the entire data set was combined. The accuracy of the predictions suggests that this model could be used as a tool to predict the consequences of chemotherapy control programmes. It is currently in press as a Windows software package under the name of 'EpiSchisto'.

INTRODUCTION

Among human parasitic diseases, schistosomiasis ranks second behind malaria in terms of socio-economic and public health importance in tropical and subtropical areas. Urinary schistosomiasis, caused by the species *Schistosoma haematobium*, is common in Africa and the Middle East. The main sign of infection is haematuria due to deposition of eggs by the adult female worms in the wall of the bladder and urinary tract [1]. The most effective form of treatment for the infected individual is the use of the drug praziquantel which kills the worms with high efficacy. Control programmes at community level often consist of mass chemotherapy possibly supplemented by snail (intermediate host) control. Since school-age children are the most heavily infected age group, suffer the most morbidity and are the major source of infection for the community, school targeted chemotherapy can be a cost effective approach to morbidity control [2, 3].

At present, the primary tool for planning schistosomiasis control programmes is experience of past programmes. Moreover, there is no quantitative method to predict the impact of a programme on the

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The model described in this paper is currently in press under the title 'EpiDynamics: Models of Helminth Epidemiology' to be published by the Wellcome Trust Centre for the Epidemiology of Infectious Disease. This CD-ROM will include the schistosomiasis programme 'EpiSchisto', the intestinal helminth programme 'EpiWorm' and the lymphatic filariasis programme 'EpiFil'. It has been developed for Windows 95/NT. Please direct enquiries about this software to M. S. Chan (man-suen.chan@ceid.ox.ac.uk).

numbers of cases of schistosomiasis infection or disease in future years. However, such projections would be useful, both for the initial planning and justification for the programme and also subsequently, for planning drug needs and monitoring the progress of the programme. Mathematical models have often been advocated as a means to fulfil this need [4, 5]. Although many models of helminth dynamics exist [4, 6], and in one case such a model has been used in the planning of a control programme for onchocerciasis [7], to date, no model has been routinely used in planning schistosomiasis control. Ideally, a model which is to be used in a control programme should be generally applicable, relatively simple to use, and perhaps most importantly, should offer convincing demonstration that the model predictions are correct. It is this validation, or comparing model predictions with observed data that permits a theoretical framework to become a valuable control tool.

A schistosomiasis model has been built which predicts the impact of chemotherapy programmes [8, 9] and will be shortly available as a software package for planning of control programmes. It is based on basic epidemiological theory and population dynamic models [10] and has been successfully validated against data for a *Schistosoma mansoni* control programme in Kenya [8, 11] and is currently also being tested for *S. haematobium* in Ghana [12]. A similar model for intestinal helminths also showed remarkable correspondence between model predictions and field data for *Ascaris lumbricoides* and *Trichuris trichiura* [13]. These models are predictive models in that only initial conditions are entered and a population dynamic model is used to predict the outcome of a treatment programme with no prior information as to what happens after the treatment programme.

In 1986, a control programme for urinary schistosomiasis was initiated on the island of Pemba, Zanzibar, United Republic of Tanzania [14, 15]. All schoolchildren on the island were targeted and offered treatment with praziquantel if found to be infected. Since diagnosis by parasitology requires skilled personnel and is time-consuming, other, more convenient methods of diagnosis were used, namely examination of urine for visible blood and if this is not present, use of reagent strips to detect traces of blood (microhaematuria). Calibration studies have confirmed that these indirect methods are extremely reliable [14–16].

In this investigation, the schistosomiasis model is validated for *S. haematobium* control programmes using the Pemba data set. As well as being for a different species, the current analysis also differs from the analysis of the *S. mansoni* data set [8] in that it involves data from a large-scale control programme rather than an intervention study in single communities. This has the advantage that data are available from different geographical areas and from a relatively large population (26000 children). The situation in the Pemba data set therefore reflects the type of data that would be available in a typical control situation.

METHODS

Model development

The model used in this investigation has been fully described elsewhere [17] and will only be described in summary here. The model simulates the mean intensity of infection by age over the time of the repeated interventions. Chemotherapy is assumed to kill a proportion of the worms and hence the intensity of infection will drop instantaneously on treatment in the treated age groups. Prevalence of infection is predicted from the mean intensity by assuming a negative binomial distribution with a linear increase in the aggregation parameter with mean intensity, with a correction term to account for predicting egg prevalence from worm prevalence [8, 18, 19]. For this analysis, parameters suitable for *S. haematobium* were used [20].

The main assumptions are summarized below:

1. Infection intensity (mean worm burden) is modelled as a continuous function of age and time using a partial differential equation framework.

2. There is a density dependent reduction in the rate of infection with increasing worm burden (which has similar consequences to concomitant immunity). The rate of infection is modelled as a decreasing function of current worm burden. No other direct density dependent mechanisms (such as density dependent fecundity) are included.

3. Acquired protective immunity is modelled as a function of past experience of infection which decays with time and is therefore different from concomitant immunity which reflects only current worm burden. As acquired immunity is a function of past experience, it will tend to be higher in adults than children, resulting in lower infection rates in adults.

4. The rates at which individuals become infected and contaminate the environment with eggs are

functions of age that peak in the early teenage years. Therefore, the lower infection rates in adults are due to combination of exposure and immunity.

5. The number of individuals in each age class is modelled with simple mathematical functions (exponential or normal) and fitted to demographic data.

6. Data are input to and output from the model as arithmetic mean count (assuming a negative binomial distribution). The arithmetic mean is used as it is directly proportional to the mean worm burden which is the driving variable in the model.

7. Chemotherapy is modelled as an instantaneous reduction in mean worm burden determined by the coverage and drug efficacy and can be targeted at specific ages. It is assumed that acquired immunity is not directly affected by chemotherapy.

The control programme

In the Pemba Control Programme, treatment was initially offered to all schoolchildren at 6-monthly intervals. Control programme teams visited all the schools in Pemba and examined urine samples of all the children present at each school. The total number of children examined at baseline was 24462. The number of children examined at baseline in each of the four districts of Pemba were 3607 in Micheweni, 6912 in Wete, 7164 in Chake and 6779 in Mkoani. The exact numbers participating in subsequent interventions varied slightly. The average number of children per school was approx. 500 [15, 21].

At each survey/intervention time, children were classified as either with visual haematuria (blood in urine), with microhaematuria (by reagent strip) or negative. All children positive by any method were treated with a single dose of praziquantel 40 mg/kg body weight. Treatment occurred at approx. 6-monthly intervals except that one treatment was missed in 1989. The model was validated for the period 1986–91. For the modelling, it was assumed that children between the ages of 6 and 15 years were treated with treatment coverage 90% (estimated by the control team) and drug efficacy 95% (estimated from the literature). Both these values may be expected to influence the impact of treatment predicted by the model. In particular, coverage may vary between different treatment times.

Previous analyses have shown that the prevalence of microhaematuria is a very good predictor of infection both at population level (regression gave a result of $y = 1{\cdot}022x$ with $r^2 = 0{\cdot}9877$) and at individual level (sensitivity, 80%; specificity, 80%). Likewise, visual blood is a very good predictor of infections over an egg count of 50 eggs per 10 ml urine, both at a population (regression $y = 0{\cdot}909x$, $r^2 = 0{\cdot}93$) and at the individual (sensitivity, 40%; specificity, 95%) level [16]. Therefore, for the purposes of this analysis we have assumed that prevalence of microhaematuria is equivalent to the prevalence of infection and that prevalence of visual blood is equivalent to prevalence of heavy (> 50 eggs per 10 ml) infection.

In addition to the school surveys, three evaluation surveys (1986, 1987, 1988) in different schools were carried out. The number of schools examined differed in each survey but at least one school from each district was examined at each survey [15, 21]. These surveys were more detailed and included direct measurement of egg counts as recommended by WHO [22]. The evaluation survey data were used to verify the assumption of the negative binomial distribution of infection intensity in the model.

Validation methodology

1. The schools were divided into prevalence classes according to their initial prevalence before treatment. Six classes of 20–29, 30–39, 40–49, 50–59, 60–69, $\geqslant 70$% were used.

2. Using the midpoint prevalence of each prevalence class, the mean egg count is estimated using the distribution assumed in the model. This is assumed to be the peak intensity by age as the actual age intensity distribution is unavailable.

3. The mean egg count in other age classes are estimated using age weights for intensity (if the intensity at ages 10–15 is given a weight of 1, the other age groups are given weights of: 0–5 (0·22), 5–10 (0·67), 15–25 (0·45), 25–35 (0·16) and 35–80 yr (0·13)) [10]. Peak shifts are not taken into account.

4. An age-dependent 'force of infection' curve is estimated from the age intensity curve.

5. The model is run, giving outputs of infection prevalence and visual prevalence (the prevalence of visible blood in the urine) in the treated age groups over time to allow direct comparison between the model and the data.

6. The above analyses are repeated using aggregate data for whole districts (four districts in total) and for the whole of Pemba.

7. The proportion of the variation explained by the model (the coefficient of determination, R^2) was

calculated for the district level and for the whole of Pemba using the following equation:

$$R^2 = 1 - \frac{\Sigma (p_i - \hat{p}_i)^2}{\Sigma (p_i - \bar{p})^2}, \quad (1)$$

where p_i is the prevalence observed at time point i, $\hat{p}_i$ is the model prevalence and $\bar{p}$ is the average prevalence between time points (unweighted by sample size).

A χ^2 test was also carried out using the likelihood of the data given the model. This was carried out using the numbers infected assuming a binomial distribution for being infected/not infected. The χ^2 statistic can be calculated as twice the difference in likelihood between the predicted model and the saturated likelihood which is the likelihood of the data itself.

RESULTS

Evaluation survey

The results of the evaluation survey were used to validate the assumptions about distribution of infection intensity in the population. For this purpose, the results of the three evaluation surveys (one pre-intervention, two post-intervention) were taken together. Direct egg counts were taken in these surveys but the eggs were counted only up to 50 eggs per 10 ml urine.

The graph of prevalence of infection against prevalence of heavy infection (Fig. 1) shows good correspondence between the data and the model. The model prediction is not obtained by fitting to the data but calculated using parameters derived from other sources. Hence this is a test of the model. Two measures of heavy infection are used, the prevalence of infections of more than 50 eggs/10 ml, and the indirect measure of prevalence of visual blood in urine, which is strongly correlated with prevalence of heavy infection [16]. The relationship between prevalence of heavy infection and prevalence of infection shows a non-linear relationship, with the prevalence of heavy infection being disproportionately high at high infection prevalence. This is due to the severe aggregation of infection intensity in the population. Both measures of heavy infection (egg count and visual blood) show a very close correspondence to the model. The value of R^2 was 0·59 and 0·74 respectively (Table 1) for visual prevalence and for prevalence of heavy infection, the value for heavy infection being higher as this is a more direct measure of intensity.

The above results allow the validation of the model to proceed with some confidence that the assumptions about the distribution of infection in the population are reasonable.

School level dynamics

The comparison between the model and data at the school level (average sample size approx. 500) is shown in Figures 2a–c. Only three prevalence classes are shown for illustrative purposes, similar patterns are seen in the other prevalence classes. There is some variability between the different schools in each prevalence class but the overall decrease in prevalence is fairly consistent between different schools for each prevalence class. The trends for the different schools in each prevalence class are not parallel, which reflects the fact that the differences amongst schools cannot be solely explained by differing initial prevalence, but also involve a combination of demographic stochasticity (random birth and death processes) and other potentially identifiable factors not taken into account in the model. The graphs show that for most schools there is an initial decrease in prevalence over the first 2 years of the programme to a low level which is maintained but does not necessarily decrease further. In some schools there is an increase in prevalence towards the end of the time series shown.

The model simulations (shown as heavy solid lines in the graphs) reflect the declining prevalence in each prevalence class and each school. The degree of correspondence depends upon the initial prevalence class. In the intermediate prevalence classes (40–50, 50–60, 60–70%, e.g. Fig. 2b) the model and data correspond well. However, in the lower prevalence classes (Fig. 2a), the model appears to overestimate the impact of treatment while in the highest prevalence class (Fig. 2c) the model tends to underestimate the impact of treatment, producing a possible systematic bias.

District level dynamics

The dynamics of prevalence of infection were also examined with the aggregate data for each district and compared with the simulations for the appropriate prevalence class (Fig. 3a–c). Examination of the data shows that, although the patterns of decrease in prevalence are similar to those found at the school level, there is considerably less variability and fluctuations. This is due both to a larger population and

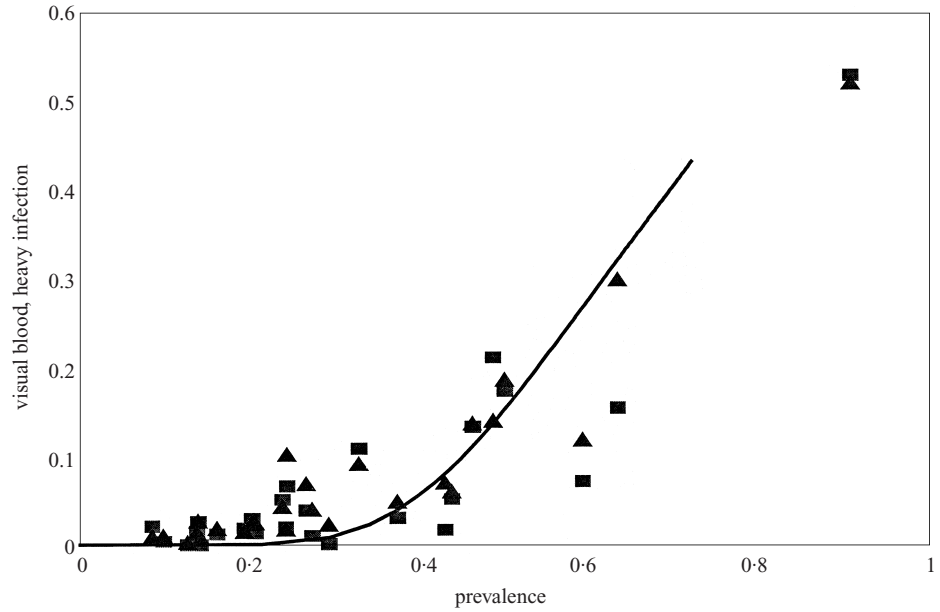

Fig. 1. Validation of the model with the evaluation surveys. Prevalence of visual blood (squares) and heavy infection (> 50 eggs per 10 ml, triangles) *vs*. infection prevalence. Each school is represented by one point at each survey. Model prediction is shown as solid line.

Table 1. *The proportion of the variation in prevalence or visual prevalence explained by the model* (R^2) *for the distributions in evaluation surveys and for the predictions of the model overall*

Model	Area	Data type	Variation explained (all data)	Variation explained (first six surveys)
Distribution	Evaluation survey	Visual prevalence	0·5911	n.a.
Distribution	Evaluation survey	Heavy infection	0·7449	n.a.
Model	District 1	Infection prevalence	0·6814	0·9905
Visual prevalence	District 1	Visual prevalence	0·9565	0·9859
Model – District 2	District 2	Infection prevalence	0·6123	0·9475
Visual prevalence	District 2	Visual prevalence	0·9433	0·9687
Model – District 3	District 3	Infection prevalence	0·6196	0·6251
Visual prevalence	District 3	Visual prevalence	0·4201	0·3927
Model – District 4	District 4	Infection prevalence	0·8144	0·9805
Visual prevalence	District 4	Visual prevalence	*	*
Model – Pemba	Pemba	Infection prevalence	0·8249	0·9794
Visual prevalence	Pemba	Visual prevalence	0·8729	0·8771

* In this case the model explained less of the variation than the mean.
n.a., not applicable.

possibly averaging of local variations. The graphs also show the decreasing trend in the prevalence and visual haematuria (at school level, this shows too much variability to be very informative). Visual haematuria is seen to decrease very rapidly to very low levels within the first year of control.

The results for District 1 (Micheweni) are shown in Figure 3a. There is a close correspondence between the data and the predicted prevalence of infection except in the latter stages of the programme where the prevalence increases in the data. Likewise, the model correctly predicts the initial prevalence of visual haematuria (which is not entered as an initial condition) and the decline of visual haematuria during the course of the programme.

The results for District 2 (Wete) and District 4 (Mkoani) are shown together in Figure 3b since they have similar initial prevalence. The trends in prevalence and visual haematuria for the districts are close when comparing the two districts which lends support to the hypothesis that local differences may be homogenized when the geographical area from which

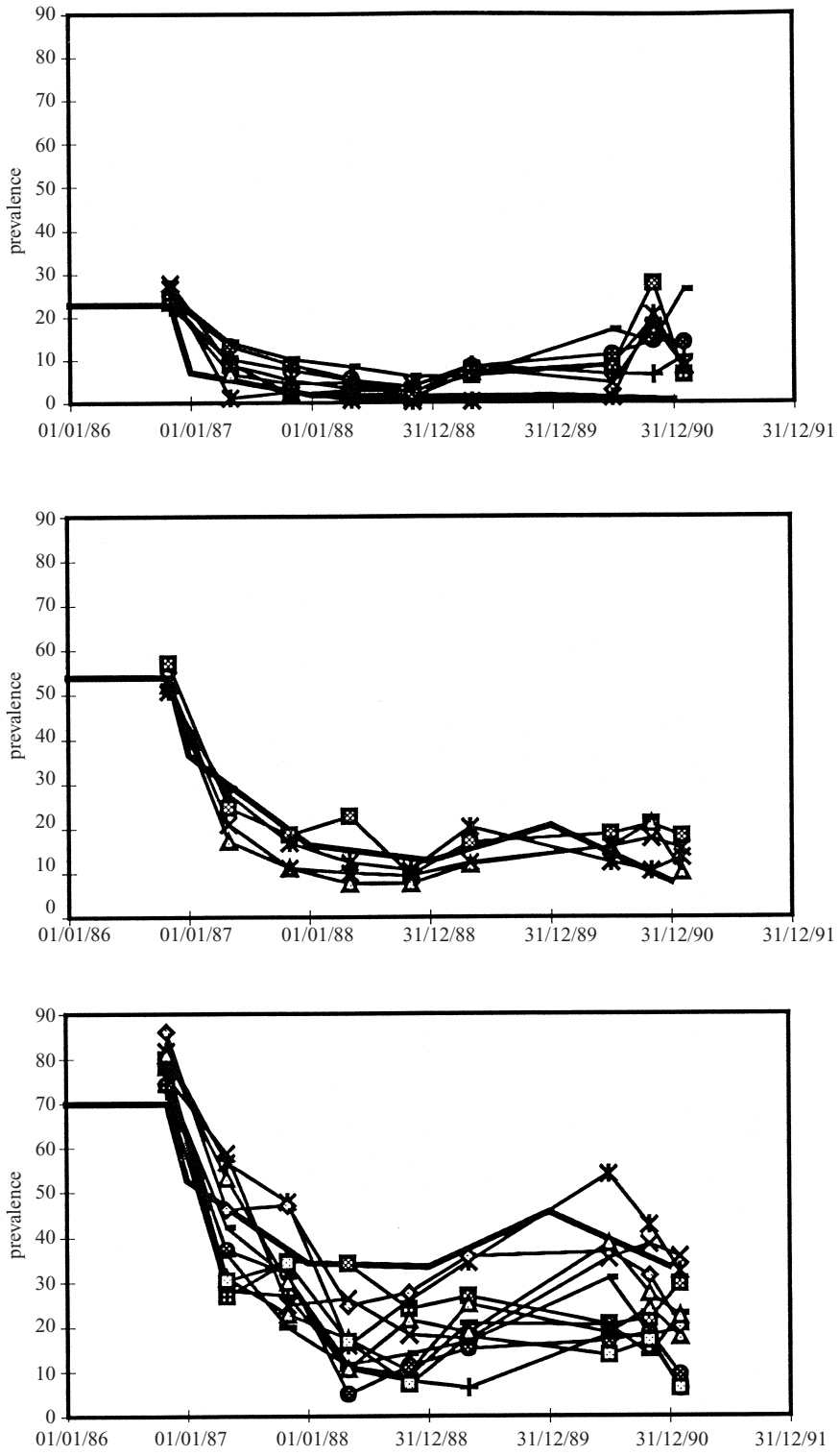

Fig. 2. Validation of school level dynamics. In each graph, the heavy solid line shows the model prediction of infection prevalence over time. The light lines each show actual data from different schools which started in the same prevalence class in 1986. The prevalence classes are 2a, 20–30%; 2b, 50–60%; 2c, $\geqslant$ 70%.

the data are taken is larger. Again the model predicts the trends in both prevalence and visual haematuria in both districts except for the initial visual haematuria in District 4 which is lower than the model prediction, and the higher than predicted prevalence towards the end of the programme.

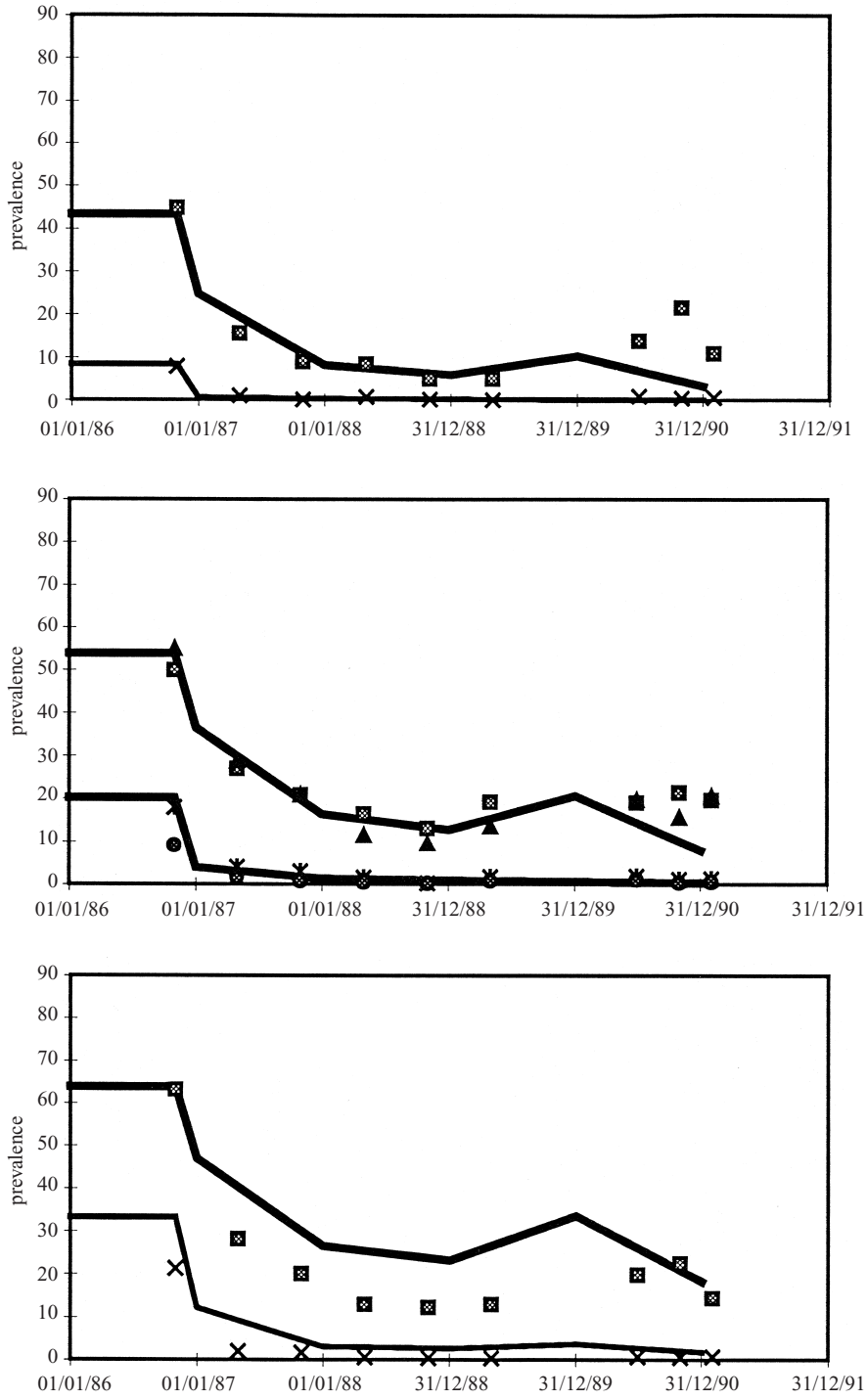

Fig. 3. Validation of district level dynamics. The top line shows the model prediction of decline in infection prevalence and the lower line the decline in visual prevalence. The associated symbols show the actual data. 3a. District 1 Micheweni. 3b. District 2 Wete and District 4 Mkoani. District 2, prevalence squares, visual asterisks. District 4 prevalence triangles, visual circles. 3c. District 3 Chake Chake.

District 3 (Chake Chake) is shown in Figure 3c. In this case, the model prediction underestimates the observed impact of the interventions. Note that the initial prevalence is higher than in the other districts, and that the predictions of the model at school level also tended to underestimate impact for areas of high initial prevalence.

Statistical analysis showed that the model explained most of the variability in the data (Table 1), especially for the first six surveys where over 90% of the

Table 2. *χ^2 values for the evaluation surveys and for the predictions of the model overall*

Data	χ^2 (all data)	χ^2 (first six surveys)
Evaluation – visual prevalence	2481·32	n.a.
Evaluation – heavy infection	2498·34	n.a.
Model – District 1 – prevalence	1936·44	47·16
Visual prevalence	2382·13	809·01
Model – District 2	2386·43	183·23
Visual prevalence	7250·16	143·07
Model – District 3	2542·96	2381·12
Visual prevalence	1984·41	1775·81
Model – District 4	1318·13	141·85
Visual prevalence	2738·74	902·76
Model – Pemba	5053·85	394·16
Visual prevalence	13442·10	674·96

n.a., not applicable.

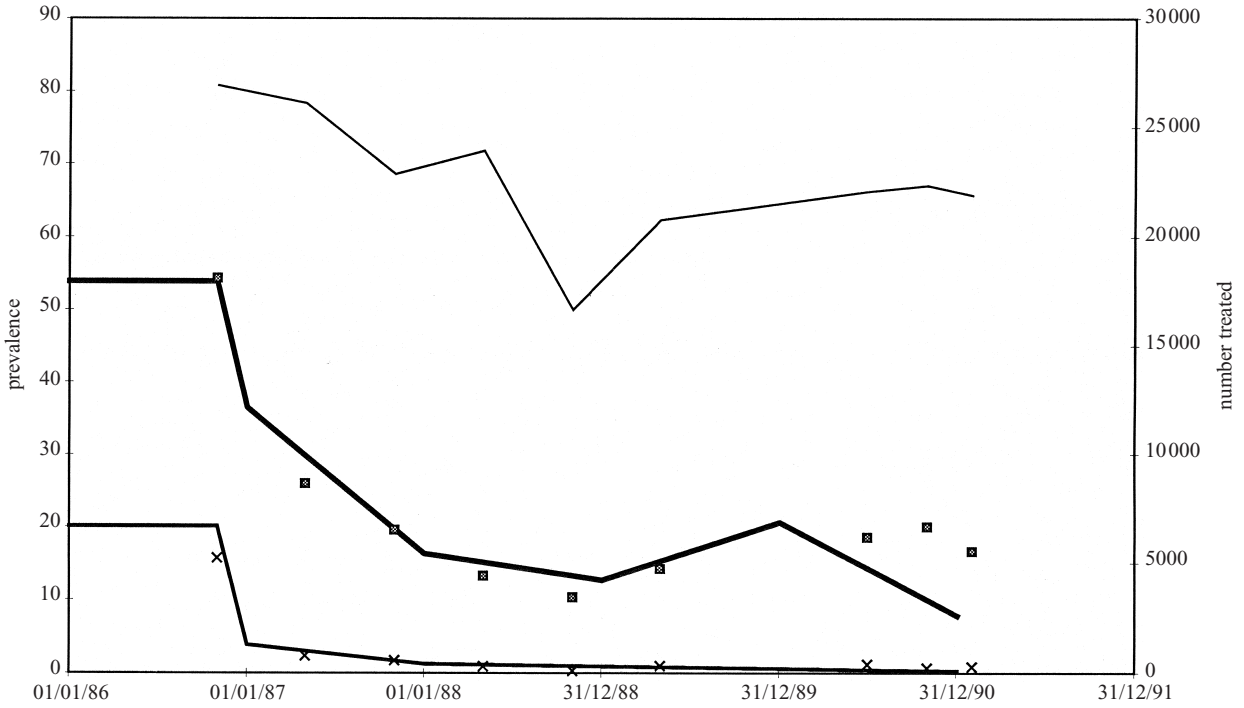

Fig. 4. Validation of Pemba level dynamics. The upper heavy solid line shows prediction of infection prevalence and the lower visual prevalence. The data are shown as squares (prevalence) and crosses (visual prevalence). The light solid line (refer to the secondary *y* axis) is the number of children treated at each round.

prevalence was explained by the model in all districts except District 3. However Table 2 shows high χ^2 values which indicate significant variation not explained by the model.

Total population dynamics

The comparison of the model simulation with the aggregate data for the whole of Pemba data set is shown in Figure 4. Close correspondence between the prevalence of infection predicted by the model and the observed data is seen during the first six surveys. Likewise, the prevalence of visual haematuria, before and also during the programme is predicted. The sample size for these data is approx. 26000 children. With this large population, the effects of both demographic stochasticity and local variability will be small and a better correspondence than at the lower

spatial levels would be expected. As observed in several of the other graphs, there is less correspondence towards the end of the programme, when the observed prevalence shows a slight increase. This increase is probably due to a decrease in coverage during the course of the actual programme, whereas the model assumes a constant coverage. Although coverage cannot be estimated directly (the total numbers of children are unknown), a plot of the number of children treated in each round of treatment (obtained from the same data set) does show a decrease over the course of the programme just before the prevalence starts to increase (Fig. 4). For all the surveys taken together 82% of the prevalence and 87% of the visual prevalence is explained by the model; when only the first six surveys are taken these figures increase to 98 and 88%, respectively (Table 1). Again the χ^2 values show that there are significant differences between the model and the data.

DISCUSSION

The results of this investigation generally show a good correspondence between the model predictions and the historical data collected during 6 years of control activities. The model predicts the decrease in infection prevalence adequately for most practical purposes; in the majority of simulations more than 90% of the variation was explained by the model. Where there are discrepancies, the absolute error is less than 10% prevalence. The existence of a small systematic bias in the discrepancies with respect to initial prevalence suggests that the aggregation parameters ($k = \text{mean}^2/(\text{variance} - \text{mean})$) of the parasite distributions may differ slightly in this data set from that estimated previously from global data [20]. The model also gives a good prediction of initial visual haematuria from the infection prevalence, both with the school survey and evaluation survey results. Furthermore the decreasing trend in visual haematuria was well predicted by the model at district and island-wide levels in spite of very low prevalences (of visual haematuria).

Before discussing the implications of the results, it is important to discuss areas where the model performed less well. Firstly, the statistical analysis does show highly significant differences between the model and the data. This would be expected in data sets of the size used here. We feel that the utility of the model should be assessed by whether the proportion of the variation explained is of practical significance. Clearly, a model which explains 90% of the variation would be useful, even if there are significant differences between the model and the data. Due to the bias in the results observed, the model may be less useful at high prevalence. However, it should be noted that at high prevalence the model gives a conservative estimate of the impact of the chemotherapy programme, which would be less problematic than an optimistic estimate.

There are several important implications from the observation that the model performs well. Firstly, it lends support to the utility of deterministic frameworks of intermediate complexity for modelling macroparasite population dynamics. If a sufficiently large population is considered (probably district level in this study), the effects of host demographic stochasticity and local heterogeneities, as well as individual host infection exposure patterns, need not be considered explicitly and can instead be approximated by a homogeneous mass action model, which only considers the dynamics at a population level. Although this is commonly accepted for microparasite models, particularly models of childhood infections [23], the utility of deterministic models for control of helminth infections has only rarely been demonstrated [13]. This is very encouraging for the future use of such models in the planning of helminth control programmes.

Secondly, a central assumption of the modelling framework is that after intervention, the distribution of intensity of infection can still be modelled as a negative binomial distribution [4, 8]. This has been demonstrated to work in the current data both through the analysis of the evaluation survey (Fig. 1) and, implicitly, because the prevalence of visual haematuria was well predicted. Although it is likely that intervention will change the distribution of worms in the community, the results suggest that this does not greatly affect the population level attributes of infection prevalence and prevalence of heavy infection. The implication that it is not therefore necessary to simulate heterogeneity at the individual level in order to predict population level characteristics is of practical importance since the population model used here is computationally much less demanding and requires less data collection than more complex models that seek to capture individual characteristics [7].

The third important implication of the results is that the model works with aggregate data at the district or even island-wide level. Conventional

wisdom in helminth epidemiology might suggest that the appropriate geographical unit to model would be rather small, such as one village, since this would be a single transmission system. However, the results of the present analysis suggest that the dynamics on a much larger scale are closer to the deterministic model. This does not necessarily imply that the whole of Pemba is a homogeneous transmission system, but suggests that the deterministic model is a good caricature of the system if it is used to predict the dynamics of population attributes such as infection prevalence. The prediction of reduction in prevalence in an island-wide control programme has also been convincingly demonstrated using a deterministic model for *Trichuris trichiura* in Montserrat [13].

On the practical front, the results of this investigation give a very positive outlook for the use of models for predicting the impact of schistosomiasis programmes during the intervention phase and in the first few years of reinfection. In particular, there are some points which would recommend this approach. Firstly the model is very simple in concept and does not require the measurement of many local parameters. Secondly, the possibility to use aggregate data over a large geographical scale (e.g. district) makes this model very convenient for programme managers. Last, and by no means least, this investigation has clearly shown that the model can reliably predict the impact of control programmes.

ACKNOWLEDGEMENTS

We wish to thank the following individuals for helpful discussions: Marco Albonico, Roy Anderson and Kenneth Mott. We thank Christl Donnelly for advice on statistics. This model was developed with the support of the Edna McConnell Clark Foundation. DAPB and MSC also acknowledge the support of the Wellcome Trust. The Direzione Generale per la Cooperazione allo Sviluppo of Italy is acknowledged for financial support of the Pemba Control Programme.

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