A quantitative framework for evaluating the effect of community treatment on the morbidity due to ascariasis

G. F. MEDLEY, H. L. GUYATT* *and* D. A. P. BUNDY

Wellcome Trust Centre for Research into Parasitic Infections, Imperial College of Science, Technology and Medicine, London SW7 2BB

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SUMMARY

There is growing emphasis on the use of community treatment to reduce the level of morbidity caused by helminth infection. The design of chemotherapy programmes, in terms of frequency of treatment and proportion of the community treated, would be assisted by a quantitative framework which enabled the morbidity reduction achieved by different approaches to be compared. The present study describes a model developed for this purpose which embodies two innovative features. First, a quantitative score of morbidity (the proportion of individuals harbouring an intense infection) is used to rate the success of a programme and, second, the distribution of helminths in the host population is generated by a mechanism that allows the distribution to change dynamically as a function of both treatment and reinfection. The model behaviour, using values typical of *Ascaris lumbricoides*, indicates that the benefit derived from community chemotherapy increases non-linearly with the coverage and efficacy of treatment.

Key words: geohelminths, epidemiology, mass chemotherapy, *Ascaris lumbricoides*, mathematical models.

INTRODUCTION

There has been recent concern over the health burden that the common geohelminths impose on the world's population, and the design of large-scale, community-based control programmes has received renewed attention. This concern has resulted in a number of new initiatives to control helminths by chemotherapy (Bundy, 1990; Warren *et al.* 1990). Experience has demonstrated that the eradication of helminthiases is not a feasible goal, but rather that programmes should be designed with the aim of reducing the morbidity associated with heavier infection. This implies that chemotherapy should be repeated at appropriate intervals to maintain the parasite burden at some level below that associated with disease. Repeated chemotherapy is required, as treated individuals reacquire parasites continuously and the parasite population will ultimately return to its equilibrium level in the absence of further treatment. The frequency with which chemotherapy should be given to a community is dependent on a number of variables which include: species of parasite (especially the average life-expectancy of adult parasites), the coverage of treatment (proportion of the community receiving treatment), the efficacy of the drug and local transmission conditions (Anderson & Medley, 1985).

The application of chemotherapy changes the rate of transmission of parasites within a community. Repeated chemotherapy increasingly complicates the changes in transmission rate, and hence reinfection, so that predicting the long-term impact of different chemotherapy programmes is increasingly difficult with more complex programmes. The process of designing chemotherapy programmes aims to maximize the impact on the parasite population within various specified financial and logistic constraints. Given the complexity of assessing the interaction between impact and cost, some quantitative framework is required. Dynamic, mathematical models offer a powerful analytical method to reproduce the changes in transmission (and hence reinfection) caused by perturbation due to chemotherapeutic interventions.

Existing models have been very influential in developing understanding of the ecology and population dynamics of parasite populations (for a review see Anderson & May, 1991). However, for practical applications, two important modifications must be included. The first is the inclusion of a distribution of parasite intensities which changes such that the effects of both chemotherapy and reinfection are incorporated realistically (Anderson & May, 1982). The second is the connexion between the distribution of worm burdens in a host population and the consequent pattern of morbidity.

The model described here attempts to reproduce the population dynamical and epidemiological consequences of a particular treatment programme for geohelminthiases, and to express the outcome in terms of the public health benefit. Parameter values appropriate to *Ascaris lumbricoides* infection are employed since the most detailed data are available for this species. The paper is divided into three

* Present address: Swiss Tropical Institute, Socinstrasse 57, CH-4002 Basel, Switzerland.

sections. The first provides narrative descriptions of the model and the way in which the assessment of the impact of chemotherapy is calculated. The second is a formal description of the model, and of the biological assumptions that it incorporates, giving emphasis initially to the generation of heterogeneity in parasite burdens in the absence of chemotherapy, before adding the complication of treatment. The third part of the paper examines the behaviour of the model, and assesses its relevance to practical applications.

NARRATIVE DESCRIPTION

The dynamic model is based on the evaluation of a simple differential equation which describes the changes in mean parasite burden over time from some starting value. The establishment of new parasites is assumed to be regulated by the overall density of parasites. The density-dependent function is in effect a weighted average parasite burden, such that those parasites in more intensely infected individuals contribute less to parasite establishment, and consequently have a lower weighting. The exact form of this function depends on both the strength of the density-dependent effects, and the distribution of parasites among hosts. Density dependence in human geohelminth infections is very difficult to quantify experimentally (Keymer & Slater, 1987; Quinnell, Medley & Keymer, 1989), and we have chosen a parsimonious formulation which agrees with current understanding. We assume that density of current parasite burdens acts to reduce the establishment of adult parasites, without adding any further biological interpretation.

The majority of previous quantitative work intended to guide the form of application of chemotherapy within human communities has considered the immediate 'cure rate', i.e. the proportion of individuals from whom infection is removed (Prescott, 1987; Weimer, 1987). However, chemotherapy has the additional effect of depressing the parasite population for some time after treatment until the endemic state (= equilibrium) is again attained. The use of a dynamic model allows this long-term impact also to be included. Fig. 1 shows a diagrammatic representation of a parasite population perturbed by two rounds of treatment at 0 and 2·5 years after the start of control. Rather than measure the impact of treatment as the immediate reduction in parasite population at the two treatment times, we consider the depression generated over time as indicated by the shaded area. Rosenfield, Smith & Wolman (1977) compared the time-dependent impact of different methods of control (chemotherapy and environmental changes) on infection prevalence, but did not consider the impact of different chemotherapy strategies on disease. Three different aspects of the parasite population are considered (i.e. three

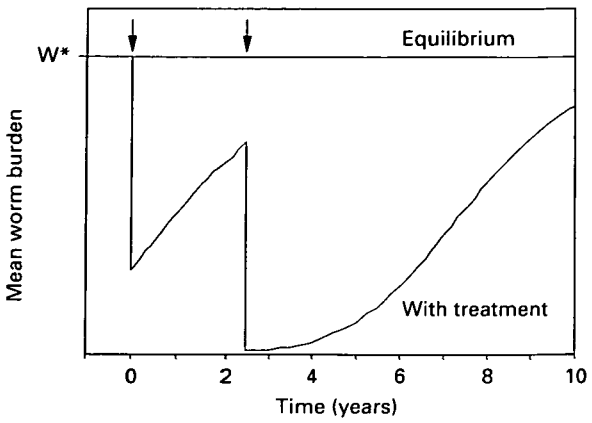

Fig. 1. Diagrammatic representation of the benefits induced by two chemotherapy programmes (shown by vertical arrows). The benefit achieved (in this case the reduction in mean worm burden) is the shaded area between the equilibrium level (which would have pertained if no chemotherapy had been used) and the level induced by chemotherapy. The benefits reported in the paper are the average levels per year.

different measures on the vertical axis in Fig. 1): mean parasite burden, prevalence of infection and prevalence of disease. Disease is measured as the proportion of the host population that harbours a worm burden equal to or greater than some threshold parasite burden associated with disease. The units of the benefits are measured, respectively, as the average reduction in parasite burden/person/year, the average infections prevented/person/year and the average disease cases prevented/person/year. Note that the benefit measures are all means since they involve the integral of the benefit over a specified time-period, in this case one year.

An innovative feature of the framework is that it incorporates a dynamic model of the processes which determine the distribution of parasites between hosts, thus allowing the effects of perturbation by treatment to be described dynamically. In practice, the distribution of parasites is generated by dividing the host population into a number of different 'types', with each type having a particular susceptibility to establishment of parasites. The susceptibility of the types is chosen so that at equilibrium the distribution of parasites follows a negative binomial distribution, as is observed empirically (Anderson & May, 1985). During reinfection (i.e. the return to equilibrium levels following chemotherapeutic intervention), the model reproduces the empirically observed phenomenon of predisposition, by which those individuals (= types) with relatively high infection levels prior to treatment display relatively high infection levels post-treatment (Keymer & Pagel, 1990; Bundy & Medley, 1992). The host types are simply mathematical constructs, and have no direct biological interpretation. The distribution of parasites during re-

infection is a combination of those parasites that survived the last treatment round (because treatment coverage is less than 100%, or drug efficacy is less than 100%, or both) and those parasites that have established since the last treatment.

FORMAL DESCRIPTION

Basic population dynamics

We model the basic epidemiology of geohelminths using the deterministic framework developed by Anderson (1980, 1982) and Anderson & May (1985, 1991). We briefly summarize the framework here, although further details and discussion are given in the referenced papers. Let W represent the mean parasite burden in a community, then the system describing the population dynamics of the parasites can be written as a differential equation:

$$\frac{dW}{dt} = \mu R_0 f(W) - \mu W, \tag{1}$$

where μ is the *per capita* death rate of the parasites and R_0 is the basic reproductive rate. The function $f(W)$ represents the density-dependent effects caused by crowding of parasites. When there is no density dependence operating then $f(W) = W$, the mean parasite burden. We assume that the form of density dependence is negative exponential with parameter γ, such that if there are n parasites in a host, their *per capita* reproductive capacity is reduced by exp $\{-\gamma n\}$. Let p_n be the probability that a host is harbouring n parasites, then:

$$f(W) = W \sum_{n=0} p_n e^{-\gamma n}. \tag{2}$$

Given a distribution for the p_n, it may then be possible to simplify the summation in this expression. If the distribution of parasites follows a negative binomial distribution with over-dispersion parameter, k, then the function may be written:

$$f_{NB}(W; k, \gamma) = W\left[1 + \frac{W}{k}(1 - e^{-\gamma})\right]^{-(k+1)} \tag{3}$$

and if Poisson distributed:

$$f_P(W; \gamma) = W e^{-W(1-e^{-\gamma})}. \tag{4}$$

In order to be able to solve equation (1) we require to know what the distribution of parasites is in a community, before and immediately after chemotherapy and during reinfection. Generally these will not follow any simple distribution.

A dynamic model of the distribution of parasites between hosts

In order to be able to model a distribution of parasites that does not follow any particular, theoretical distribution, we construct a method of developing the heterogeneity using an underlying mechanism described in the following sub-model. Consider that each host has some susceptibility to adult parasite establishment which is particular to that host and which does not change with time. The susceptibility factors are measures of a host's relative susceptibility to parasite establishment. We do not propose any biological assumptions regarding susceptibility, and it could equally be perceived as having its basis in differences in exposure or in immuno-regulation of immature parasite establishment or survival. Let the susceptibility factor for host i be denoted by h_i, and the mean establishment rate of parasites in the host community be $\Lambda(t)$, which is some function of the current parasite burden. Then the mean establishment rate for host i is $\Lambda(t)\, h_i$, as the h_i are chosen to have a mean of unity. The parasite burden in each host, M_i, is described by an 'immigration-death' process, and is altered by establishment and death occurring at rates $\Lambda(t)\, h_i$ and $\mu\, M_i$ respectively. This results in a Poisson distribution of parasites both between hosts with the same susceptibility factor and within the same host at different times.

If the susceptibility factors come from a gamma distribution then the distribution of parasites will be negative binomial. This relationship has been used many times in models of geohelminth epidemiology (Dietz, 1982; Hadeler & Dietz, 1983; Anderson & Medley, 1985; McCallum, 1990). The gamma distribution with mean unity and parameter k has the probability distribution function given by:

$$g(h; k) = \frac{k^k h^{k-1} e^{-kh}}{\Gamma(k)}, \tag{5}$$

where $\Gamma(.)$ represents the gamma function. The variance of this distribution is $1/k$.

The arguments for heterogeneity generation based on individual hosts apply equally to groups of hosts each with the same susceptibility. We now divide the host population into a discrete number of 'types', denoted by index $j (j = 1 \ldots \mathcal{J})$, each with a rate of establishment relative to the whole population, h_j, and proportional representation in the population, ω_j. These types are simply theoretical constructs to enable us to deal with the dimension of susceptibility in a discrete rather than continuous manner without considering individual hosts specifically.

In order to calculate the h_j and ω_j, the h dimension is divided into discrete intervals with upper limit for each interval H_j. The weighted average value of h within each interval, and the integral of $g(h; k)$ over the interval, are h_j and ω_j respectively. Let $P(x; k)$ be the incomplete gamma integral, where:

$$P(x; k) = \frac{1}{\Gamma(k)} \int_0^x \tau^{k-1} e^{-\tau} d\tau. \tag{6}$$

Then if host type j spans the h dimension from H_{j-1}

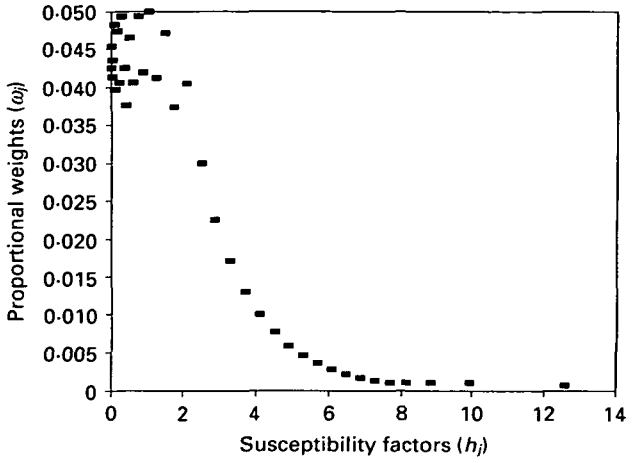

Fig. 2. The discrete distribution of susceptibility factors (h_j) and proportional weights (ω_j) used in the model. There are 38 points each of which represents one host type. The values of each point are calculated using equations (5)–(7). Note that the susceptibility factors are multiplicative so that the most susceptible host type has an equilibrium worm burden 12·6 ($= h_{38}$) times greater than the population mean. The erratic behaviour of ω_j for low susceptibility factors is a consequence of the algorithm that chooses H_j. The algorithm chooses a value for H_j 0·4 greater than H_{j-1}, and then increases or decreases it by a factor $\sqrt{2}$ until ω_j lies between 0·001 and 0·05. The numerical values were chosen by trial to give the best compromise between accuracy of simulation and number of host types.

to H_j (with $H_0 = 0$), the susceptibility factors and weighting for each host type are:

$$\omega_j = P(kH_j; k) - P(kH_{j-1}; k)$$
$$h_j = \frac{P(kH_j; k+1) - P(kH_{j-1}; k+1)}{\omega_j}. \quad (7)$$

Fig. 2 shows the discrete distribution of susceptibilities used throughout the paper with $k = 0{\cdot}543$ estimated for *Ascaris lumbricoides* by Guyatt *et al.* (1990) from data across many different communities.

The distribution of host types shown in Fig. 2 gives a distribution of parasites which is very close to negative binomial when combined across the whole population. The probability that a host of type j has n parasites, p_{nj}, follows a Poisson distribution with mean W_j. The distribution of parasites within the whole community can be found by combining the distributions of the individual types:

$$p_n = \sum_j p_{nj}\omega_j \quad (8)$$

where p_n is the probability that a host has n parasites. This distribution is close to negative binomial because the p_{nj} follow a Poisson distribution for each j, and the ω_j come from a gamma distribution. The maximum parasite burden considered is n_{max}, which is chosen to be large enough (300) to have only a very small probability of a host having that many parasites. Table 1 shows that the values of the variance and prevalence of parasite burdens (from the p_n) for different population mean burdens calculated from equation (8) closely approximates those predicted by a negative binomial distribution.

Table 1. Parasite distributions generated by the method of discrete host types and the negative binomial distribution

(The table shows the comparison between the variance and prevalence of worm burdens given as from the p_n calculated using the distribution of host susceptibilities in Fig. 2 and equation (8) with those expected from the negative binomial. The mean values are exactly equal in each case. The value of n_{max} was 300 (see text for discussion).)

Mean	Expected variance	Variance	Expected prevalence (%)	Prevalence (%)
5	51·04	50·90	71·68	71·72
10	194·16	193·58	80·02	80·09
15	429·36	428·06	83·82	83·90
20	756·65	754·32	86·09	86·18

Density dependence of parasite establishment

The effect of density dependence is calculated by noting that the distribution of parasites within each host type is Poisson, and therefore the effect of density dependence within each type is given by $f_p(W_j; \gamma)$ in equation (4). As the mean parasite burden in each host type is the product of the susceptibility factor for that type and total mean parasite burden, the total effect of density dependence is given by:

$$f(W; k, \gamma) = W\sum_j h_j\omega_j e^{-Wh_j(1-e^{-\gamma})}, \quad (9)$$

where $f(.)$ is now dependent on k to define the host types. The value of γ for a given mean parasite burden, basic reproductive rate and host type distribution is the value which satisfies the following equation:

$$\sum_j \omega_j h_j \exp\{-Wh_j(1-e^{-\gamma})\} - \frac{1}{R_o} = 0. \quad (10)$$

This condition is used to derive numerically the value of γ for a given mean parasite burden and basic reproductive rate by varying the value of γ until equation (10) is satisfied. Equation (10) is derived as follows. The model defined in equation (1) has two equilibrium points. The first with no parasites, $W^* = 0$, and the second with a parasite population given implicitly by $W^* = R_o f(W^*)$. The first point is stable for $R_o < 1$, but if $R_o > 1$ then the parasite population will attain the second equilibrium point, which is stable for $R_o > 1$ and unstable for $R_o < 1$. At the non-zero equilibrium

$$f(W^*; \gamma) = \frac{W^*}{R_o}. \quad (11)$$

Table 2. Comparison between the model and the negative binomial probability distribution

(Comparison between the model and negative binomial results for a solution starting with a mean worm burden of 0·01 at time 0 (* denotes the equilibrium value). The table shows the mean and variance in parasite burden and the prevalence of infection and disease for the results of the model (equations (1) and (9)) and the negative binomial (equations (1) and (3)). The parameter values used are $k = 0{\cdot}543$ (Fig. 2 and for the negative binomial), $\mu = 1{\cdot}0$, $R_0 = 2$ and $T = 15$, and the value of γ calculated to give a mean burden of 10 parasites per host.)

	Model				Negative binomial			
Time	Mean	Variance	Prevalence	Disease	Mean	Variance	Prevalence	Disease
*	10	193·582	0·801	0·233	10	194·162	0·800	0·232
0	0·010	0·010	0·010	0	0·010	0·010	0·010	0
1	0·027	0·028	0·026	0	0·027	0·028	0·026	0
2	0·073	0·083	0·066	0	0·073	0·083	0·066	0
3	0·194	0·264	0·153	0	0·194	0·264	0·153	0
4	0·500	0·959	0·299	0	0·500	0·960	0·298	0
5	1·191	3·793	0·468	0·001	1·191	3·801	0·468	0·001
6	2·461	13·582	0·605	0·017	2·461	13·613	0·605	0·017
7	4·205	36·665	0·692	0·065	4·204	36·756	0·692	0·066
8	5·979	71·607	0·741	0·122	5·978	71·797	0·741	0·122
9	7·413	108·306	0·768	0·165	7·413	108·607	0·767	0·165
10	8·415	138·403	0·782	0·192	8·414	138·8	0·782	0·192

Substituting equation (9) into equation (11) and rearranging gives equation (10).

Estimating the proportion of the population with disease

This estimation is based on the assumption that disease is associated with worm burdens which exceed some threshold size (for discussion of this issue see Guyatt & Bundy (1991) and Lwambo, Bundy & Medley (1992)). Given the distribution of parasites throughout the host population it is possible to define the proportion of the population with disease, $D(t)$ as the proportion with a parasite burden equal to or greater than some threshold value, T,

$$D(t) = \sum_{i=T}^{n_{max}} p_i(t). \tag{12}$$

The helminth population dynamics within the whole host population are defined by the differential equation (1) with $f(W;k,\gamma)$ given by equation (9). Solution of this differential equation gives an overall mean parasite burden $W(t)$ with respect to time. The total distribution of parasites within the host population is approximately negative binomially distributed. Consequently, the system defined by equations (1) and (9) should be a close approximation to the system defined by equation (1) with $f(W)$ replaced by $f_{NB}(W;k,\gamma)$ in equation (3). Table 2 compares the results obtained from the two formulations starting from an essentially zero population of parasites, and shows that the approximation is strikingly similar for those variables required in the calculation of benefits (mean intensity, prevalence of infection and prevalence of disease), although marginally less good for the variance in intensity. The variance calculated in the model is sensitive to n_{max}, and the approximation can be improved by increasing this parameter.

Modelling the effect of treatment on the population dynamics

When considering the response of the parasite population to the application of chemotherapy in the community we divide the parasite population into two: those worms that survived the last round of chemotherapy and those that have infected hosts since the last treatment. Let S represent the mean burden of surviving worms and M the mean burden of worms established since treatment, where the total mean parasite burden is $W = M + S$. Then the differential equations for these populations may be written:

$$\begin{aligned} \frac{dS}{dt} &= -\mu S \\ \frac{dM}{dt} &= \mu R_0 f(W;k,\gamma) - \mu M \\ \frac{dW}{dt} &= \mu R_0 f(W;k,\gamma) - \mu W. \end{aligned} \tag{13}$$

Note that density-dependent reproduction, denoted $f(W;k,\gamma)$, is now a function of the total distribution of both parasite populations. The non-trivial equilibrium state (i.e. that with helminths present) is given as $S^* = 0$, $W^* = M^*$, where the actual value of W^* and the distribution of helminths is as given in the previous sections.

Modelling the effect of treatment on the distribution of parasites

The total distribution of parasites in the host community is dependent on the distributions of both surviving and newly established parasites. Parasites becoming established since the last treatment will follow the distribution described above: they will be Poisson distributed within each host type and approximately negative binomially distributed across the whole host population. The distribution of surviving parasites is more complicated, and will be determined by the distribution before treatment (which will be influenced by previous treatments) and the pattern of treatment itself.

Apart from the timing of treatment, each round of chemotherapy considered here is defined by two parameters: the coverage (the proportion of people taking the drug) and the efficacy (the proportion of parasites killed by the drug). The distribution of parasites following a treatment round will be a mixture of the existing distribution in those individuals that were not treated, and the distribution induced in those that received treatment. Let p_{nj} be the existing (pre-treatment) parasite distribution in host type j, and let s_{nj} be the post-treatment distribution of parasites. We suppose that the effect of a drug with efficacy α on a population burden of r parasites is to produce a binomial distribution with individual terms:

$$B(n;r,\alpha)=\binom{r}{n}\alpha^n(1-\alpha)^{r-n},\quad n=0,\dots r \tag{14}$$

which are the probabilities of having n parasites when r parasites are treated. Note that we are ignoring any possibility of density-dependent effects on drug efficacy. Let c be the proportion of hosts treated, then

$$s_{nj}=(1-c)\,p_{nj}+c\sum_{r=n}^{n_{max}}B(n;r,\alpha)\,p_{rj}. \tag{15}$$

The summation in the second part runs over all possible pre-treatment parasite burdens that could contribute to a post-treatment burden of n parasites, and is the sum of probabilities of obtaining n parasites from each contributing pre-treatment burden weighted by the proportional size of the contribution.

It is assumed that the surviving parasite population suffers mortality at a constant rate (and no other population process). The death process starting with N individuals produces a binomial distribution at time t with mean $N\exp\{-\mu t\}$ (Bailey, 1964). This is essentially the same stochastic process as the effect of treatment considered above, but here natural mortality substitutes for the anthelmintic. Let $s_{nj}(t)$ be the probability that a host of type j has n surviving parasites at time t after the previous treatment round, then the $s_{nj}(0)\,(n=0\dots n_{max})$ describe the distribution of surviving parasites immediately after treatment, as given in equation (15). The distribution of these parasites is given as the sum of terms from a series of binomial distributions, one for each initial condition:

$$s_{nj}(t)=\sum_{r=n}^{n_{max}}s_{rj}(0)\,B(n;r,e^{-\mu t}). \tag{16}$$

The probability distribution of all parasites, whether those surviving treatment or those arising as a result of reinfection within each host type is denoted $p_{nj}(t)$ at a time t after treatment:

$$\begin{aligned}p_{nj}(t)&=\sum_{r=0}^{n}q_{rj}(t)\,s_{n-r,j}(t)\quad n=0-n_{max}\dots 1\\ p_{n_{max}j}(t)&=1-\sum_{n=0}^{n_{max}-1}p_{nj}(t).\end{aligned} \tag{17}$$

This is a convolution of the surviving parasite distribution, $s_{nj}(t)$, and the reinfection parasite distribution $q_{nj}(t)$. The $q_{nj}(t)$ are Poisson distributions for each j with mean $h_jM(t)$, where the value of $M(t)$ is given by the differential equation system (13). The distribution across all host types is the weighted average from each type as in equation (8). All that remains to complete the model is to calculate the effect of density dependence on the total parasite population:

$$f(W;k,\gamma)=\sum_j\omega_j W_j\sum_{n=0}^{n_{max}}p_{nj}(t)\,e^{-\gamma n}. \tag{18}$$

The three benefit measures (in terms of reduction of mean parasite burden, prevalence of infection and prevalence of disease) are denoted $B_W(.)$, $B_p(.)$ and $B_D(.)$ respectively as functions of the time-interval over which they are averaged. They are calculated as:

$$\begin{aligned}B_W(x)&=W^*-\int_{x-1}^{x}W(t)\,dt\\ B_p(x)&=(1-p_o^*)-\int_{x-1}^{x}(1-p_o(t))\,dt\\ B_D(x)&=D^*-\int_{x-1}^{x}D(t)\,dt,\end{aligned} \tag{19}$$

where x is the year of the model solution (i.e. for the first year, $x=1$, and the integrals run from 0 to 1). Generally, the benefits are the difference between the equilibrium values and those of the model solution with treatment. The integrals are calculated numerically from the model solution using appropriate time intervals.

A computer program to solve the model proceeds as shown in the flow diagram in Fig. 3. The parameters required for the model are the equilibrium mean parasite burden (W^*), the overdispersion parameter for the negative binomial (k),

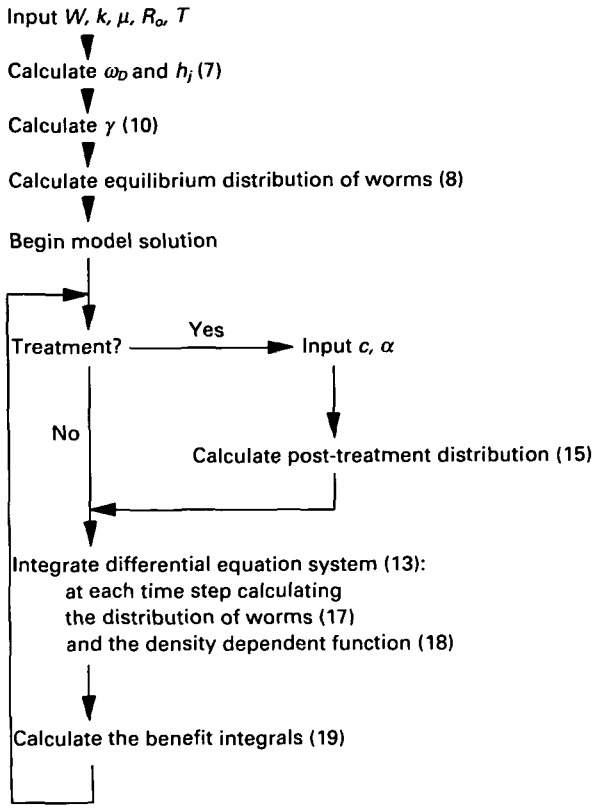

Fig. 3. Flow diagram showing the steps involved in the solution of the model to provide the output required. The numbers beside the steps refer to equations in the text defining mathematically what is done at each point. The symbols are defined in the text.

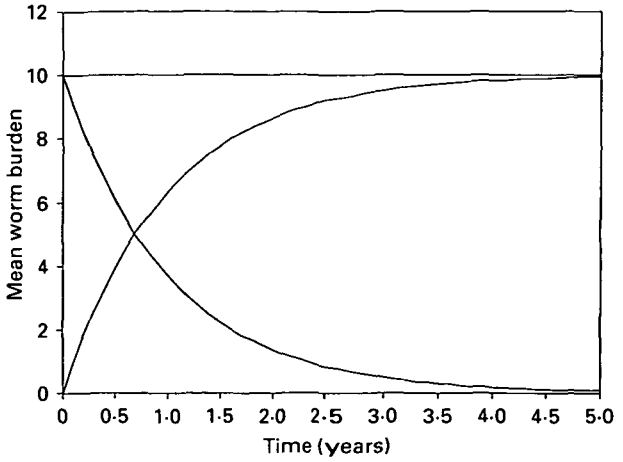

Fig. 4. Changes in the mean worm burdens over time derived from the model. There is a dummy treatment (i.e. zero coverage and zero efficacy) at time 0, so that the equilibrium worm burden at time 0 is considered as the surviving population. The mean burden of surviving worms drops from the equilibrium value of 10, the mean burden of reinfecting worms increases from 0 to 10, and the mean total worm burden (surviving and reinfecting combined) remains constant at 10 worms. The surviving worm population mean is very close to the theoretical value given by $W^* \exp\{-\mu t\}$. The parameter values used were $\mu = 1{\cdot}0$, $k = 0{\cdot}543$ (see Fig. 2), $R_0 = 2$ and $W^* = 10{\cdot}0$.

the basic reproductive rate (R_0), the *per capita* death rate of adult parasites (μ) and the disease threshold (T). The discrete version of the susceptibility factors (h_j and ω_j) are calculated, and the equilibrium distributions of parasites among the host types determined, and the value of the density-dependent parameter (γ) is determined. The population dynamics are calculated by integrating the differential equations (13) using a standard Runge-Kutta algorithm (NAG, 1990), using the value of $f(W; k, \gamma)$ given by equation (18), and using the parasite distribution given by equation (17). At each treatment, the distribution of surviving worms is calculated from equation (15).

Validation of the model and its computer implementation can be achieved by its comparison with exact results for particular circumstances. Table 2 shows that the discrete distribution of host types provides a good approximation to the exact negative binomial result for reinfection parasites. Fig. 4 shows the model result starting at equilibrium parasite distribution.

The model presented above is approximate in that it relies on the discretization of the skewed distribution of host susceptibilities, and the approximation improves as more, smaller intervals are taken on the susceptibility dimension, although at an increased computing cost. Our experience indicates that the mean and variance of a given negative binomial distribution can be fairly easily reconstructed in this way, although the prevalence is more sensitive to the number and size of intervals at low values of susceptibility. The scale of discretization used here (Fig. 2) is a compromise between accuracy (as judged from Table 2 and Fig. 4) and computing cost. An additional compromise must be made in the choice of the maximum parasite burden, n_{max}. The programme is written in FORTRAN 77, making extensive use of standard numerical routines (NAG, 1990). Running on a SUN Sparc-1 computer (rated at 13mips), Fig. 4 takes approximately 250 min to reproduce.

RESULTS

In this section we outline some of the properties of the model when the effects of single treatment applications are simulated. Examination of the model behaviour as it relates to the parameter values (sensitivity analysis) shows that following perturbation by treatment the rate of reinfection is increased by increasing the basic reproductive rate, R_0, and the parasite death rate. However, the velocity of reinfection is non-linearly related to the value of the basic reproductive rate, such that changes in R_0 have a smaller influence at high values (Fig. 5). The effect of R_0 and the parasite death rate, μ, on the form

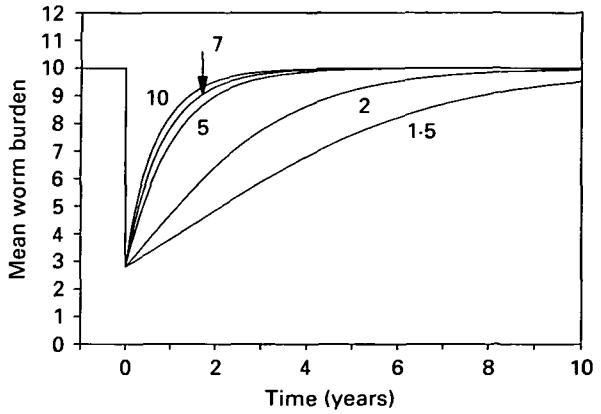

Fig. 5. The effect of varying the basic reproductive rate, R_0, on the reinfection curve of mean intensity following a single chemotherapy application. The values of R_0 used are shown on the figure. The parameter values used were $\mu = 1$, $k = 0{\cdot}543$, $W^* = 10$, $c = 0{\cdot}8$ and $\alpha = 0{\cdot}9$.

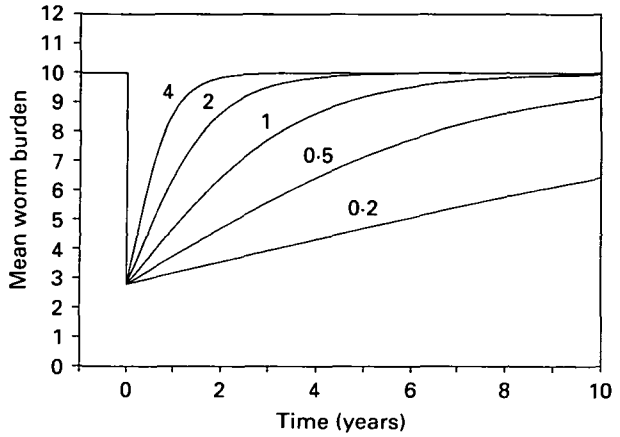

Fig. 6. The effect of varying the *per capita* mortality rate, μ, on the reinfection curve of mean intensity following a single chemotherapy application. The values of μ used were 0·2, 0·5, 1, 2 and 4 (corresponding to average life-expectancies of 5, 2, 1, 0·5 and 0·25 years respectively). The other parameters are as in Fig. 5 with $R_0 = 2$.

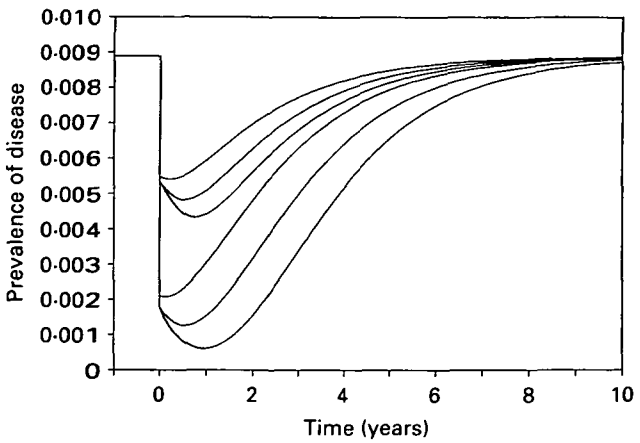

Fig. 7. The proportion of individuals with disease over time following a single chemotherapy application. Two coverage levels are considered: 0·4 and 0·8 (upper group and lower group of three respectively), with drug efficacy 0·5, 0·7 and 0·9 from top to bottom in each group. The parameter values used are $R_0 = 2$, $\mu = 1$, $k = 0{\cdot}543$, $W^* = 2$ and $T = 15$.

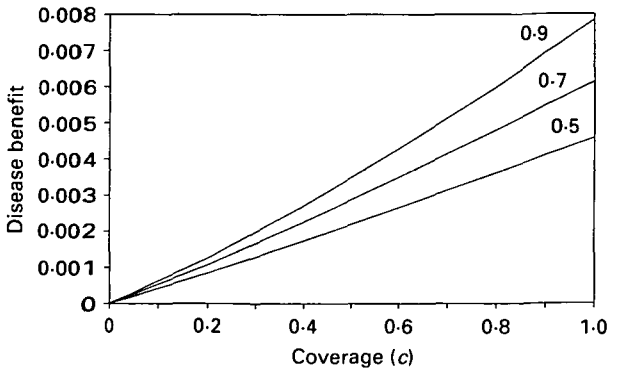

Fig. 8. The disease prevented by a single treatment. The benefits are the simple averages (i.e. not discounted) over 5 years following the treatment. Three different drug efficacies are considered (0·5, 0·7 and 0·9) for different coverage levels. The non-linearity of the lines is increased by considering short time-periods following disease. The parameters used are as for Fig. 7.

of the reinfection curve are inter-related such that the same result can be generated for different combinations of R_0 and μ. There is also a non-linear relationship between μ and the reinfection curve (Fig. 6), as has been noted previously for simpler models (Anderson & Medley, 1985).

Fig. 7 shows the changes in proportion of the host population with disease (i.e. those individuals with worm burdens exceeding the threshold) following chemotherapy regimes with different coverages and drug efficacies. Note that after the initial reduction due to chemotherapy, the proportion with disease continues to fall. The individuals with disease after treatment are those who retain heavy worm burdens. In the present model this is largely due to non-compliance with treatment. Their number declines during the early phase of reinfection because the total parasite population after treatment does not provide a large enough output of infective stages, and natural parasite mortality is greater than establishment in those heavily infected individuals. This effect is enhanced by increased drug efficacy and increased coverage. The greater the proportion of parasites removed within treated individuals and the greater the number of individuals treated, the better for those individuals that were untreated. Fig. 8 shows how the community benefit of chemotherapy is enhanced by this effect. Increasing the disease threshold, T, increases this effect.

DISCUSSION

The model described here is biologically very simple. The two primary biological features included are

heterogeneity in infection and density-dependent reproduction/establishment of parasites. One of the ubiquitous features of helminth population biology is the pattern of over-dispersion observed in the number of worms per host. The explanation of the processes that generate this pattern remains central to epidemiological research into geohelminths. In the construction of this model we required assumptions which were general and which conformed with empirical observation. There are only two empirical observations pertaining to the distribution of worms between hosts: the form of the distribution itself, and the phenomenon of predisposition. The negative binomial distribution has been shown to be a good empirical descriptor of the distribution of worms (Anderson & May, 1985; Guyatt *et al.* 1990). The concept of predisposition arises from the observation that when a community is treated with anthelmintics, the ranked intensities of individual hosts before and after treatment show non-random, positive assortment (Schad & Anderson, 1985; Bundy *et al.* 1987; Haswell-Elkins, Elkins & Anderson, 1987; Keymer & Pagel, 1990; Bundy & Medley, 1992). It has been suggested that both long- and short-term factors contribute to predisposition (McCallum, 1990). In this model, over-dispersion is generated by long-term factors alone. No assumption is made as to the biological causes of predisposition.

Density-dependence in human helminth infection is difficult to demonstrate experimentally. With the current available techniques, fecundity is the only process in which density dependence can be empirically demonstrated and quantified (Elkins, Haswell-Elkins & Anderson, 1986; Bundy *et al.* 1987), although there are many problems associated with this area of research (Keymer & Slater, 1987). The model assumes that the density of current worm burdens acts to reduce the establishment of adult worms through reduced reproductive capacity of the worm population within individual hosts, without adding further biological interpretation. The point within the parasite life-cycle at which density dependence operates, and its interaction with the source of heterogeneity in parasite burdens has, however, been shown theoretically to have an important influence on the recovery rate of parasite populations (Quinnell *et al.* 1990).

Any set of assumptions is open to criticism. The important feature of the present framework is that the distribution of parasites during reinfection accurately mirrors that observed in the field, rather than the mechanisms, that creates it be biologically exact. Unfortunately, the distribution of worms in host populations through time following intervention is not known, and may not be possible to determine. Any quantitative approach to a practical problem requires empirical data for its validation. There have been few published studies which quantitatively describe the changes in geohelminth infection following chemotherapy with empirical field-based studies. As parasite expulsion is the most accurate measure of parasite infection level, only one point can be found on the reinfection curve post-treatment in field situations. However, intensity as measured by egg output and prevalence of infection are both available, and they show the same pattern during reinfection as those reproduced by the model (for examples see references below and Anderson & May, 1985).

The framework presented here is not truly stochastic, but rather hybrid in structure. The establishment of parasites is modelled as a time-dependent Poisson process rather than a birth process. This allows us to assume that the distribution of parasites within each host type is Poisson, and so calculate the total parasite distribution, density dependence and establishment rate. The parasite population dynamics, parasite distribution and consequently benefit values calculated should be regarded as 'average' values which would be expected in the field. For example, the model may predict the benefit of a certain treatment programme, but no variability (e.g. confidence interval) is given for that result. This simple model could be verified and variability for the benefit calculations derived from considering a completely stochastic model, such as a Monte Carlo simulation. Dietz (1982) and Hadeler & Dietz (1983) have developed a complex system of partial differential equations which describe the distribution of parasites with respect to both time and host age. To some extent, the model shown here is a realization of a reduced form of their model.

The model requires estimates of the basic reproductive rate and the parasite death rate. The basic reproductive rate, R_0, measures the transmission potential of the parasite (Anderson & May, 1985). The value of R_0 is determined by many individual components of the parasite life-cycle, including reproduction, death and transmission rates. The majority of published estimates of R_0 for *A. lumbricoides* lie in the range 1–1·8 (Martin *et al.* 1983; Thein-Hlaing *et al.* 1984; Chai *et al.* 1985; Bundy *et al.* 1987; Thein-Hlaing, Than-Saw & Myint-Lay-Kyin, 1991), with one estimate of 4·3 (Croll *et al.* 1982). The lower values of R_0 coincide with mean worm intensities of about 2, and the higher value with a mean intensity of about 20 worms per person. The adult worm life-expectancy ($1/\mu$) for *A. lumbricoides* is commonly considered to be about 1 year, although there is no direct method of confirming this (Croll *et al.* 1982). An alternative method of obtaining estimates of appropriate parameters is to fit the model output to a particular epidemiological situation (Rosenfield *et al.* 1977). However, in this case, care must be taken when using the model in different localities as some of the parameter values may be locale specific.

The model developed here is intended to initiate a new area of biological research: quantitative study of the dynamic relationships between parasite burden, development of disease and chemotherapy application. The important features of the framework for chemotherapy program design are that it allows the distribution of parasites to vary dynamically as a consequence of both reinfection and the perturbations induced by application of anthelmintics, and that the impact of chemotherapeutic intervention is measured in terms of disease prevention over time since the start of the program. This research will hopefully stimulate more detailed study of the population dynamics of parasites in the field. Figs 5 and 6 show the importance of obtaining reasonably accurate estimates of appropriate parameters for a particular parasite population if such an approach as this is to be applicable. Partly due to the uncertainty in parameter values, theoretical tools such as those developed here can be used to point out the programme most likely to achieve the desired result, but only carefully designed, long-term, large-scale intervention programmes will confirm how such programmes operate in the field.

The most important result from the preliminary study of this model is the effect that reduced transmission has on prevalence of disease as demonstrated in Figs 7 and 8. The more people who are treated and the more effective the treatment, the greater the benefit to those who were not treated. This result is somewhat analogous to the idea of herd immunity in viral and bacterial infections (Anderson & May, 1991). To our knowledge, this non-linear effect has not been quantified previously.

Although the present analysis focuses on *A. lumbricoides*, this approach may also be appropriate to other helminth parasites of humans. The framework encompasses the ability to model repeated chemotherapy, and could readily be extended to include a range of chemotherapy regimes, such as selective and targeted treatment. A full analysis of the benefits of chemotherapy programmes (including multiple treatments) combined with appropriate cost information is continuing.

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