CHAPTER THREE

Soil-Transmitted Helminths: Mathematical Models of Transmission, the Impact of Mass Drug Administration and Transmission Elimination Criteria

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Abstract

Infections caused by soil-transmitted helminthias (STHs) affect over a billion people worldwide, causing anaemia and having a large social and economic impact through poor educational outcomes. They are identified in the World Health Organization (WHO) 2020 goals for neglected tropical diseases as a target for renewed effort to ameliorate their global public health burden through mass drug administration (MDA) and water and hygiene improvement. In this chapter, we review the underlying biology and epidemiology of the three causative intestinal nematode species that are mostly considered under the STH umbrella term. We review efforts to model the transmission cycle of these helminths in populations and the effects of preventative chemotherapy on their control and elimination. Recent modelling shows that the different epidemiological characteristics of the parasitic nematode species that make up the STH group can lead to quite distinct responses to any given form of MDA. When connected with models of treatment cost-effectiveness, these models are potentially a powerful tool for informing public policy. A number of shortcomings are identified; lack of critical types of data and poor understanding of diagnostic sensitivities hamper efforts to test and hence improve models.

List of Abbreviations

DALY	disability-adjusted life year
epg	eggs per gram of faeces
MDA	mass drug administration
NTD	neglected tropical disease
PCR	polymerase chain reaction
pre-SAC	pre-school age children
qPCR	quantitative PCR
R_0	basic reproduction ratio or number
SAC	school age children
STH	soil-transmitted helminth
WASH	water, sanitation and hygiene
WHO	World Health Organization

1. INTRODUCTION

The most common neglected tropical diseases (NTDs) are the soil-transmitted helminthiases, which are caused by the intestinal parasitic nematodes *Ascaris lumbricoides*, *Trichuris trichiura* and the hookworm species, *Ancylostoma duodenale* and *Necator americanus*. (Within this chapter, *Ascaris* and

Trichuris will be taken to refer to the human species, *A. lumbricoides* and *T. trichiura*, respectively and hookworm will denote *Ancylostoma duodenale* and/or *N. americanus*, which are rarely distinguished in population-level studies.) It is estimated that 5.3 billion people worldwide, including one billion school-aged children (SAC), live in areas of endemic infection for at least one of these soil-transmitted helminth (STH) species (Pullan and Brooker, 2012). The impact of infection on the host is rarely acute and usually long term and cumulative in nature. STH infections rarely cause death, but chronic and intense infections can contribute to malnutrition, anaemia, and can also adversely affect physical and cognitive development in childhood (Brooker et al., 2010; World Bank, 2003; Albonico et al., 2008). As a consequence, measuring the burden of morbidity is difficult, and further complicated by the fact that the highest prevalences are in low-income countries (Brooker et al., 2006). Within these countries, spatial distribution of STH burden remains highly heterogeneous. This aspect is well illustrated by the maps to be found at the Global Atlas of Helminth Infections (http://www.thiswormyworld.org/). The Global Burden of Disease 2010 Study estimated that 5.19 million disability-adjusted life years (DALYs) are attributable to STH infections (Pullan et al., 2014b; Murray et al., 2012).

The World Health Organization's (WHO) policy for STH control focusses on mass drug administration (MDA) to control and ultimately eliminate STHs, although efforts are also being made to improve access to clean water and hygiene (Strunz et al., 2014). MDA strategies identify three groups, preschool-aged children (pre-SAC), SAC, and women of childbearing age, on the basis that heavy infection in these groups will have a detrimental impact on anaemia, child growth, and development. The current WHO guidelines focus on SAC, both for monitoring infection and as a target for treatment, although treatment of pre-SAC and women of childbearing age is also recommended where sustainable delivery mechanisms exist, especially in areas of intense transmission (WHO, 2012). The guidelines recommend treating SAC annually where any STH prevalence falls between 20% and 50% and twice a year where it exceeds 50% (WHO, 2006).

The long-term nature of STH-associated morbidity and the clustered nature of STH worm burden in hosts mean that measuring the impact of treatment is difficult. A recent systematic review found very few studies of the highest quality (randomized or controlled clinical trials) to demonstrate any cognitive or educational benefits of regular chemotherapy (Taylor-Robinson et al., 2015). A number of studies that fall outside this strict

selection criterion offer evidence of long-term educational and economic benefits due to deworming (Hicks et al., 2015; Ahuja et al., 2015). However, to date, there are insufficient high-quality studies to confirm a correlation.

In 2012, the WHO announced its intention of scaling up MDA for soil-transmitted helminthiases to treat 75% of the pre-SAC and SAC population in need by 2020 (WHO, 2012). This decision was further endorsed by the London Declaration on Neglected Tropical Diseases (Uniting to Combat NTDs, 2012). Progress has been good in some areas, but less so in others. In 2013, global therapeutic coverage of those in need was 39% for SAC and 49% for pre-SAC (World Health Organization, 2015). Data for more recent years are yet to be published by the WHO, but a huge gain in coverage is not expected. Recent research has suggested a change in policy for the control of STHs by MDA, to broaden coverage to include adults who often harbour significant reservoirs of infection especially in the case of hookworm (Anderson et al., 2015).

This chapter examines recent progress in the development and application of mathematical models in the study of the transmission dynamics and control by MDA of the STHs. Work in this area up to the 1990s is reviewed by Anderson and May (1992). More recent developments are described in Anderson et al. (2013) and Truscott et al. (2014b). Our focus in this paper is the development of probability models to relate STH worm burdens in hosts to egg counts in faeces, deterministic elimination criteria to break transmission and the associated coverage of MDA, and comparisons between the predictions of individual-based stochastic models of transmission with their deterministic counterparts.

1.1 Soil-transmitted helminth life cycles

Soil-transmitted helminths live in the intestine of their (human) hosts and their eggs are passed in the faeces of infected persons (Fig. 1). If an infected person defecates not using a toilet or latrine (near bushes, in a garden or field) or if the faeces of an infected person are used as fertilizer, eggs are deposited on soil. The STH parasites have a direct life cycle which requires no intermediate hosts or vectors, so it is also possible for eggs to be transmitted through direct contact or food preparation as a consequence of poor hygiene as well as within the household.

The STH species differ markedly in their behaviour outside the host. Eggs initially undergo a period of maturation for 2–3 weeks, after which they become infectious. *Ascaris* and *Trichuris* eggs can remain viable in the

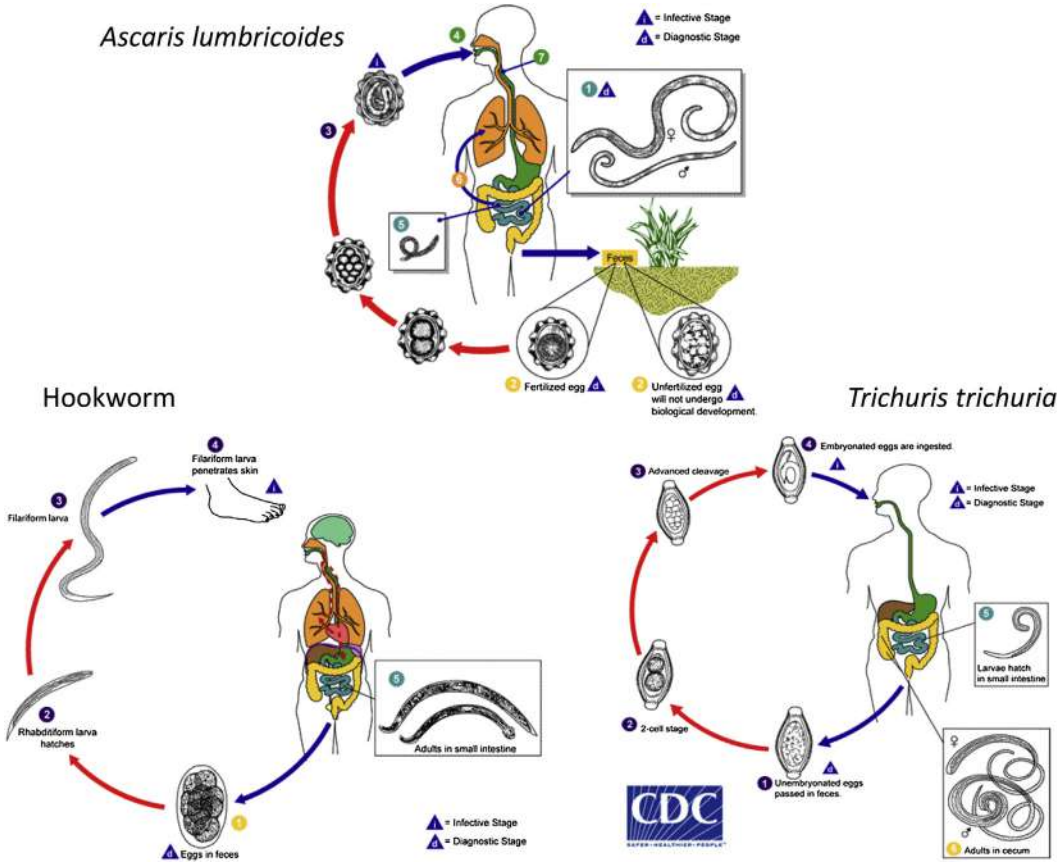

Figure 1 Diagrammatic representation of the life cycles of *Ascaris*, *Trichuris* and hookworm. *From CDC, Creative Commons (Center for Disease Control and Prevention, 2015. Parasites [Online]. Available at: http://www.cdc.gov/parasites/.).*

soil for several months. Hookworm eggs hatch into larvae which can survive for several weeks without finding a new host, depending on environmental conditions. To infect a new host (or reinfect the original host), *Ascaris* and *Trichuris* eggs need to be ingested. This can happen when hands or fingers that have contaminated dirt on them are put in the mouth or by consuming vegetables and fruits that have not been carefully cooked, washed or peeled. The larvae hatch in the intestine and penetrate the intestinal wall into the bloodstream (Jia et al., 2012). In the case of *Ascaris*, the larvae are carried via the portal and systemic circulation to the lungs, from which they ascend the bronchial tree, reach the throat, and are swallowed. Upon reaching the small intestine, they develop into adult worms (https://www.cdc.gov/parasites/ascariasis/biology.html). In the case of *Trichuris*, there is no pulmonary passage, but the larvae mature and establish themselves as adults in the colon (http://www.cdc.gov/parasites/whipworm/biology.html). Hookworm larvae must enter through the skin and infection is transmitted primarily by walking barefoot on contaminated soil (although *An. duodenale* can also be transmitted through the ingestion of larvae) (http://www.cdc.gov/parasites/hookworm/biology.html). Figure 1 illustrates the life cycle of the species considered under the STH term.

The species also show differing responses to environmental conditions. Humidity is an important factor for all species, with *Ascaris* and *Trichuris* eggs being unable to embryonate at less than 50% humidity. Maximum survival rates for hookworm larvae occur between 20°C and 30°C and development rates for eggs peak close to 30°C (Brooker et al., 2006). Since survival to infect a new host is an essential part of the transmission cycle, environmental conditions can be expected to have a strong impact on the components of the species' transmission cycles that take place outside the human host. Work examining the correlations between environmental conditions and infection prevalence indicates that hookworm is considerably more temperature tolerant than *Ascaris* or *Trichuris*. Prevalences for the latter fall off rapidly for mean land surface temperatures above 30°C, while hookworm maintains high prevalences up to about 45°C (Brooker et al., 2006). This hardiness can probably be ascribed to the ability of the larvae, being motile, to find protection from local extremes of temperature. This temperature sensitivity can be used to predict large-scale spatial distributions of infection from satellite-derived environmental data. Temperature and humidity in a given location can also vary strongly on an annual cycle. Helminth infection rates of domestic animals have been noted to increase markedly during rainy seasons

(Lima, 1998; Sissay et al., 2007; Nwosu et al., 2007). Although little corresponding work has so far been directed towards human hosts, there is some evidence that similar effects apply (Niangaly et al., 2012). This has clear implications for the timing of treatment and monitoring efforts in regions with strongly seasonal climates.

From ingestion to establishment and maturity takes 2–3 months in all species, although the details of the process vary between species (Bethony et al., 2006). Both hookworm and *Ascaris* reach the lungs via the bloodstream, before being swallowed and establishing themselves in the small intestine. *Trichuris* eggs are conveyed directly to the small intestine, where they hatch and then establish themselves in the colon (Knopp et al., 2012). All three species are dioecious with separate sexes and the production of fertilized eggs requires the presence of male and female worms within the same host. Eggs are expelled in the faeces to complete the infection cycle. Female *Ascaris* worms release eggs into the intestine whether they are fertilized or not, whereas *Trichuris* and hookworm are thought to only release fertilized eggs. This biological property is relevant to a number of issues including the assessment of the impact of control programmes on sustained transmission and the inference of worm load from egg counts in faeces.

The human host is also exploited by not only the species already mentioned, but also by others adapted to other hosts species, giving rise to the potential for animal reservoirs of infection. *Ascaris* also infects pigs, in the form of the species *Ascaris suum*. However, there is considerable uncertainty as to whether *A. suum* and *A. lumbricoides* qualify as truly different species. Cross-infection is known to be possible and the cross-infected parasites are capable of completing their life cycle (Nejsum et al., 2012). Hybridization has also been observed (Criscione et al., 2007). Given the close domestic proximity of pigs and humans, it has been argued that there is little justification in recognizing two distinct species (Leles et al., 2012). For *Trichuris*, the similarity between *T. trichiura* and *Trichuris suis* (infecting pigs) makes it difficult to identify cross-infection, but cases of patent infection of humans with *T. suis* have been recorded. Eggs of *Trichuris vulpis* have also been detected in human faeces, indicating a zoonosis in dogs. Several hookworm species can also infect humans. *Ancylostoma ceylanicum* (natural host: dogs and cats) can successfully complete its life cycle in humans. *Ancylostoma caninum* can also infect humans, but there is no evidence of egg production.

It is not known what contribution zoonosis makes to the overall transmission of STHs, but as the human transmission cycle is controlled by chemotherapy and improvements in hygiene, a zoonotic infection cycle

may allow the parasite to persist. This process is well illustrated by the impact of canine zoonosis on efforts to eradicate Guinea worm (*Dracunculus medinensis*) (Callaway, 2016).

1.2 Diagnosis of infection

Identification of infected persons is traditionally achieved by the examination of stool samples for the eggs of the three STH species. The most common method is the Kato-Katz technique, based on a faecal smear followed by microscopy examination. This was first developed in Japan in the 1950s (Holland and Kennedy, 2002) and is still by far the commonest diagnostic technique in use for population-scale studies (see Medley et al., 2016; this volume). Not coincidently, it is also the diagnostic technique recommended by the WHO for detection of STH infections (WHO, 2006). A range of other faecal egg count techniques exist, such as ether concentration (Garcia, 2007), FLOTAC (Cringoli, 2006), mini-FLOTAC (Barda et al., 2013), and while some have superior sensitivity, they generally require an additional overhead in terms of equipment and training over Kato-Katz variants. The sensitivity of the various tests is hard to assess in the absence of a 'gold standard' for the presence of infection or the concentration of eggs in the stool, and studies have used aggregate measures or latent class methods. Sensitivities for Kato-Katz are generally assessed to be in the range 50–90% for *Ascaris*, with lower values (20–40%) for *Trichuris* and hookworm. Sensitivity drops markedly at low intensity of infection and there is much variability between studies (Nikolay et al., 2014; Glinz et al., 2010; Tarafder et al., 2010). PCR and qPCR techniques are now becoming available and show much higher levels of sensitivity and specificity than microscopy techniques, pointing to their possible adoption as a gold standard (Becker et al., 2015; Easton et al., 2016).

Quantitative information on intensity of infection can also be recovered from microscopy techniques in the form of eggs per gram of faeces (epg). These show considerable variability across successive measurements (Anderson and Schad, 1985; Krauth et al., 2012; Sinniah, 1982; Croll et al., 1982). Intensity of infection can also be directly measured by counting worms expelled in the days after treatment (Bundy et al., 1987; Elkins et al., 1986; Bradley et al., 1992). Simple models are available to link an individual's worm burden with their egg output. A comparison of model fits indicates that there is considerable variability in egg output per worm as measured across different studies, possibly arising from lack of diagnostic rigour or poor standardization (Hall and Holland, 2000). These two sources

of uncertainty make inferring worm burden from egg output difficult. qPCR techniques have been shown to correlate well with egg output in some circumstances and so may become a useful indicator of individual worm burden (Easton et al., 2016).

2. KEY EPIDEMIOLOGICAL FEATURES AND PROCESSES

2.1 Age intensity profiles and mixing

Cross-sectional epidemiological profiles of infection prevalence and intensity (measured by eggs per gram of faeces or worm expulsion methods) with host age reveal different and characteristic patterns for the three major STH infections (Fig. 2). Age profiles in both infections with *Ascaris* and *Trichuris* exhibit convex curves, in which infection intensity peaks in children and declines in adults, usually more so in the case of *Trichuris*. In hookworm infection, the age-specific intensity trend is much more monotonic in structure, being generally low in children before plateauing or rising more slowly in adults. Assuming that worm life span is not significantly affected by the age of the host, these patterns must result from a combination of age-dependent force of infection or failure of worms to establish, due to acquired immunity. There is considerable uncertainty about the role played by immunity in the life cycle of STHs. All three species trigger a strong immune response in the host. However, there is no clear evidence that the responses generated offer any protection, as illustrated by the ability of hosts to become repeatedly infected throughout their lives (Lamberton and Jourdan, 2015; Loukas and Prociv, 2001; Barda et al., 2015). In the case of *Ascaris*, there is evidence that antibody levels track infection status rather than control it and that age-specific patterns reflect changes in risk behaviour with time (Bundy and Medley, 1992). This is in contrast to the case for *Schistosoma haematobium*, in which the protective nature of the immune response is reflected in a negative correlation between infection intensity and antibody status with age, indicating a protective aspect to immune response (Mutapi et al., 1998). In animal models, protective immunity has been observed for hookworm reinfection (Davey et al., 2013). Ultimately, the role played by immunity in the establishment and persistence of soil-transmitted helminthiases in humans is unclear. Detailed data linking infection intensity to immune status and the response of both to chemotherapy would greatly improve our current understanding.

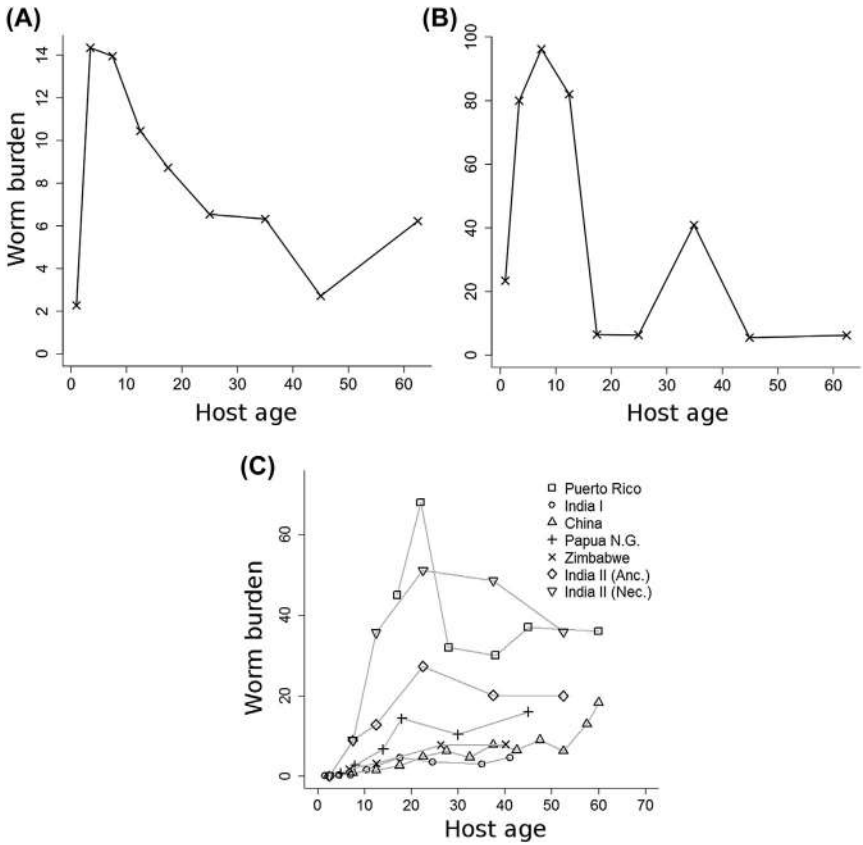

Figure 2 Typical age−intensity profiles for (A) *Ascaris*, (B) *Trichuris* and (C) hookworm in terms of worm burden. *Data sources: (A)* Ascaris *data from Pulicat, South India study (Elkins, D.B., Haswell-Elkins, M., Anderson, R.M., 1986. The epidemiology and control of intestinal helminths in the Pulicat Lake region of Southern India. I. Study design and pre- and post-treatment observations on* Ascaris lumbricoides *infection. Trans. R. Soc. Trop. Med. Hyg. 80, 774−792); (B)* Trichuris *data from St. Lucia Island study (Bundy, D.A., Thompson, D.E., Cooper, E.S., Golden, M.H., Anderson, R.M., 1985a. Population dynamics and chemotherapeutic control of* Trichuris trichiura *infection of children in Jamaica and St. Lucia. Trans. R. Soc. Trop. Med. Hyg. 79, 759−764); (C) Hookworm data sets collated by Brooker and co-workers (Brooker, S., Bethony, J., Hotez, P.J., 2004. Human hookworm infection in the 21st century. Adv. Parasitol. 58, 197−288), supplemented with data from West Bengal study (Nawalinski, T., Schad, G.A., Chowdhury, A.B., 1978. Population biology of hookworms in children in rural West Bengal. I. General parasitological observations. Am. J. Trop. Med. Hyg. 27, 1152−1161).*

The age profiles observed are therefore most likely the result of different levels of contact with the infectious material in the environment for hosts with respect to age class. Hence, the profiles reflect the social structure of the host community, where eggs are deposited and who comes in contact with them, as well as the details of the nature of the infectious material. It may be significant that hookworm, which has a fairly short-lived larval infectious stage, has a different profile to the parasites that are transmitted through longer-lived eggs.

The significance of the different infection age profiles of the STH species for the effectiveness of age-group targeted MDA was examined by Anderson et al. (2013). Intervention strategies are frequently targeted at SAC (5–15 years of age). Typically, only 30% or less of populations in STH-affected areas fall into this age category, rising to 50% if pre-SAC are included. Combining this with mean worm burdens by age group shows that the fraction of the worm population reachable by such strategies may be strongly dependent on species. Only 15% or less of hookworm burden will fall in the treated age group, while for *Ascaris*, this may reach 50%. Treatment coverage of SAC is usually achieved through the agency of local schools, but these routinely enrol only 40–90% of the target population (Anderson et al., 2013). As a result, it is clear that the impact of treatment targeted at SAC will vary widely across different causative species and, in the case of hookworm, potentially have a very limited impact (Anderson et al., 2015). Within models, age-dependent contact and parasite establishment rates are described by a composite parameter $\beta(a)$. Given an environmental intensity of infectious material $L(t)$, individuals at a given time (t) and age (a) experience a force of infection, $L(t)\beta(a)$. The worm burden of an individual of a given age is a result of the worms they have acquired up to that age, less those that have already died. Hence, the profile reflects both the age-specific contact rate and the worm life span.

2.2 Parasite aggregation within hosts

A common feature of a wide range of parasitic helminths is a pronounced aggregation of worms amongst hosts where the variance in the numbers per host greatly exceeds the mean value (that is, some hosts have far more worms than others). Some typical patterns based on worm expulsion studies are recorded in Fig. 3. Whereas for diseases like schistosomiasis and onchocerciasis, worm distributions are difficult to record, except via autopsy studies (Cheever et al., 1977) or nodulectomy studies (Duerr et al., 2001), respectively, worm expulsion techniques can be used for the intestinal

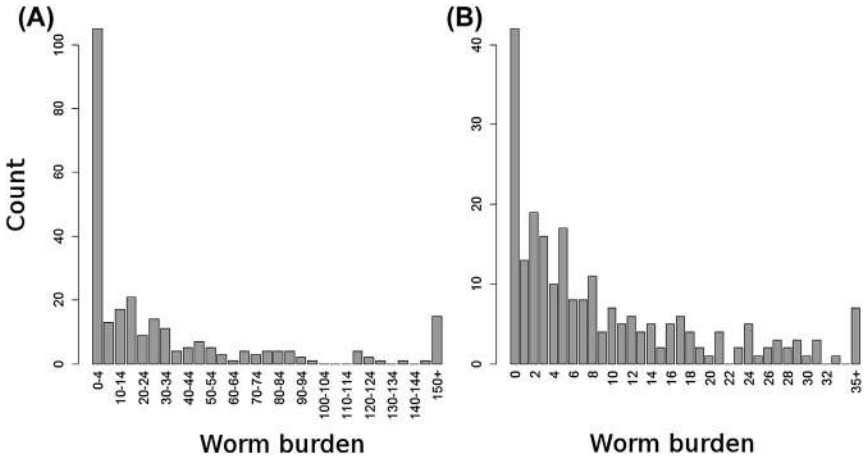

Figure 3 Frequency distributions of worm numbers per person. (A) Hookworm burdens from West Bengal study (Anderson and Schad, 1985); (B) *Ascaris* worm burdens from Pulicat Lake study (Elkins et al., 1986), both studies conducted in India.

helminths and the degree of aggregation measured directly. The process of expulsion is necessarily more involved and time-consuming than egg-counting techniques. Studies show that to achieve a high sensitivity for the test, it is necessary to collect all stool output from the subject over a number of days; estimates include from the second to the sixth day for 80% of the burden and up to the seventh day for 97% (Easton et al., 2016; Forrester and Scott, 1990). These factors are likely to depend also on the type and quantity of drug given and the species being collected (Williams-Blangero et al., 1999; Bundy et al., 1985a). Specificity of expulsion is likely to be very high. A further important point, particularly in the context of detailed studies, is that, unlike egg counting techniques, expulsion is both a measurement and a treatment and consequently destabilizes the parasite population being studied.

The distribution of worms amongst hosts is typically negative binomial in character. The shape parameter of the distribution, k, varies inversely with the degree of worm clumping (a value above 5 denotes a Poisson distribution). Fig. 3 shows worm count data for hookworm and *Ascaris*. Aggregation is also observed within individual age groups of the population, although with slightly varying degrees of aggregation across age groups (Anderson and May, 1985; Holland et al., 1989; Hall et al., 1999). Combining a number of individual studies, further details of worm aggregation emerge. The degree of aggregation appears to be a

function of the overall worm prevalence in the population. The higher the prevalence, the larger the value of k and the less aggregated the worm population is among hosts. This effect has been observed for both hookworm and *Ascaris* (Lwambo et al., 1992; Guyatt et al., 1990). As a result, as prevalence drops, worms appear to be increasingly concentrated in just a few individuals.

The main mechanisms proposed to account for aggregation are host predisposition to heavy or light infection and/or environmental heterogeneity (Anderson and Medley, 1985). The predisposition model assumes that individual hosts have a wide range of rates of parasite exposure/establishment, either as a result of genetic or immunological factors in the population, or through experiencing a different force of infection through different patterns of behaviour. If the rates of parasite establishment are gamma-distributed within the population and parasite death rates are constant with time, then a negative binomial distribution of parasites will arise across the host population. Environmental heterogeneity can assume that the variability lies in the clustering of infectious material, such that the number of worms established from an infection event is aggregated (Walker et al., 2010a,b). Other forms of environmental heterogeneity in exposure may arise, where, for example, people are exposed nonrandomly depending on spatial location and other behavioural factors, but in this case, it will typically manifest itself as predisposition to infection dependent on behaviour and spatial location. Theses generating processes have been investigated by Anderson and Medley using an individual-based stochastic model, where they recover the negative binomial distribution through a log-distribution of egg clumping (Anderson and Medley, 1985). A potentially important difference between the two approaches to aggregation is that an egg-clumping paradigm leads to significantly slower recovery of worm burden in the host community after treatment. In reality, however, both these mechanisms may be playing a role in any given community.

2.3 Density-dependent processes – fecundity

For STH species, it is believed that the main density-dependent process acts on the parasite's fecundity based on patterns observed in epidemiological studies involving faecal egg counts and worm expulsion. As the number of worms increases within a host, the rate at which each female worm produces eggs decreases. The overall egg output may continue to rise with female worm burden or may begin to fall, for some forms of density dependence. This negative density dependence is probably the main

mechanism that limits the overall worm burden in a community (Walker et al., 2009). A secondary effect is that the efficacy of chemotherapeutic interventions on transmission can be highly nonlinear, where, for example, decreasing the parasite load by 50%, will not decrease transmission by 50% due to the presence of density-dependent egg production. Consequently, the indirect benefits of treatment on the reduction in transmission will depend on the number and distribution of parasites between hosts (Anderson and May, 1992).

Data illustrating this process are recovered from individuals in a two-stage process, whereby an initial round of egg intensity measurements (typically using the Kato-Katz technique) is followed up with worm expulsion and counting. Fig. 4 shows such a data sets for hookworm and *Ascaris*. Averaged over discrete age groups, the downward trend in fecundity is clear for the *Ascaris* data. Looking at the raw data, as exemplified by the hookworm data in panel A, the large variability in egg output for a given worm burden is evident.

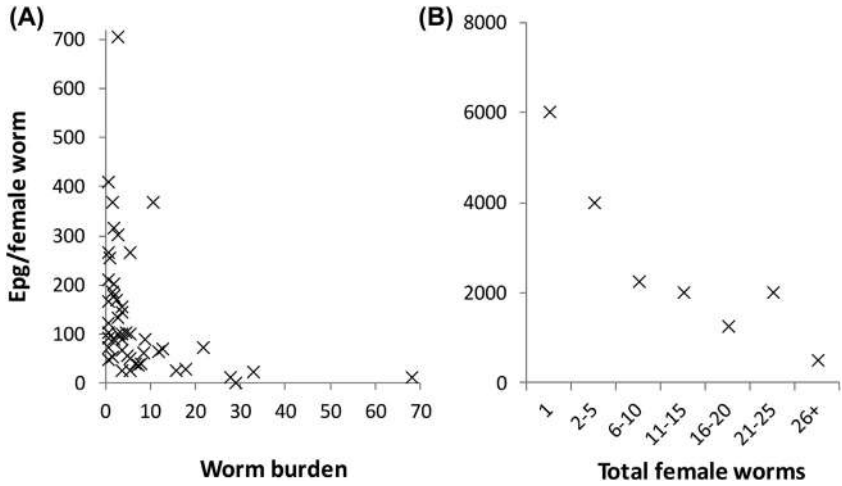

Figure 4 (A) Egg output (epg) per female hookworm plotted against total worm burden. (B) Egg output per female *Ascaris* worm plotted against total female worm population in a given host. *(A) Data from Zimbabwe study (Bradley, M., Chandiwana, S.K., Bundy, D.A., Medley, G.F., 1992. The epidemiology and population biology of Necator americanus infection in a rural community in Zimbabwe. Trans. R. Soc. Trop. Med. Hyg. 86, 73–76). (B) Data from Nigeria study (Holland, C.V., Asaolu, S.O., Crompton, D.W., Stoddart, R.C., Macdonald, R., Torimiro, S.E., 1989. The epidemiology of* Ascaris lumbricoides *and other soil-transmitted helminths in primary school children from Ile-Ife, Nigeria. Parasitology 99, 275–285).*

Within most of the models described here, an exponential description is used, such that the mean egg production from a single female worm among a population of n females is given by $\lambda e^{-\gamma n}$. Hence, the mean egg production from a host with n females would be $\lambda n e^{-\gamma n}$. Other models of fecundity have been used, such as a power law dependence on worm burden (egg production/female $= \lambda n^{-\gamma}$) and may in some instances fit the data slightly better (Croll et al., 1982). However, they are considerably more difficult to integrate into a simple closed-form model framework.

2.4 Density-dependent processes – sexual reproduction

The soil-transmitted helminth parasites exist as distinct sexes within the host, so it is necessary for a female worm to share a host with male worms in order for viable, fertilized eggs to be generated. As a result, the probability of being co-established with a male of the species can be very low when worm burdens are low in the population, giving a positive density dependence on mean worm burden for fertilized egg output. Fig. 5 illustrates the resulting relationship between worm burden and egg fertilization for *Ascaris* (from Seo et al. (1979)). The fraction of unfertilized egg passers drops rapidly to less than 10% for more than five detected worms. A consequence of this

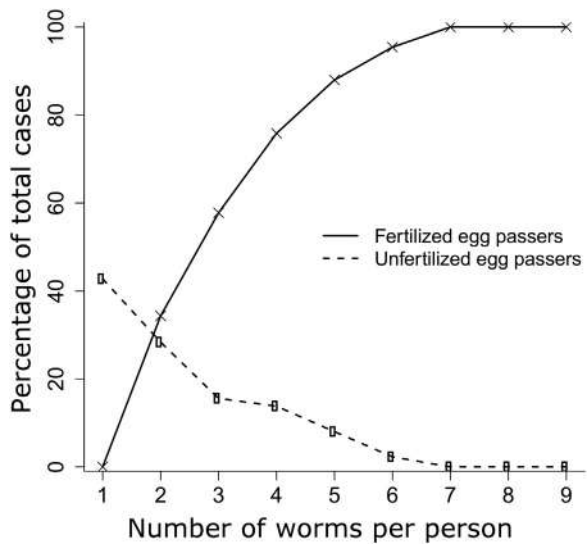

Figure 5 Fraction of people passing fertilized and unfertilized egg as a function of the measured worm burden of *Ascaris lumbricoides*. *Data taken from Seo, B.S., Cho, S.Y., Chai, J.Y., 1979. Egg discharging patterns of* Ascaris lumbricoides *in low worm burden cases. Korean J. Parasitol. 17, 98–104.*

dependency is the theoretical existence of a breakpoint for the parasite in a community such that for average worm burden below a critical level, there are insufficient fertilized female worms to support the parasite population and it will be eliminated from the host population in time (Anderson and May, 1992; Macdonald, 1965; May, 1977). The form of mating for STH parasites is generally assumed to be polygamous, since, unlike schistosomes, the parasites are not found as male–female pairs as established adults. However, the existence of a breakpoint is quite general across different forms of mating.

Mathematically, the dependence of fertile egg production on parasite aggregation and mode of reproduction has been analysed in detail, leading to a mating probability factor multiplying the total egg output from a given population, φ (May, 1977; Leyton, 1968); effectively, the fraction of egg output that is fertilized. For STHs, the reproductive strategy is usually assumed to be polygamous (see disease description section), where the presence of a single male allows the fertilization of all females present,

$$\varphi(M;z,k) = 1 - \left[\frac{1 + M(1-z)/k}{1 + M(2-z)/k}\right]^{k+1} \tag{1}$$

With the inclusion of sexual reproduction, it becomes important to be clearer about what the variable M represents. In the above and all equations within this chapter, M refers to the female worm burden, with the assumption that any given worm in a host has an equal probability of being male or female. Parameter z in Eqn (1) is defined in terms of density-dependent fecundity, as explained in the text following the expressions given in Eqn (7).

In general, given the aggregated nature of STH parasites, the mating probability term is close to 1 for all but the lowest worm burdens and is therefore often ignored. However, as we have recently shown, sexual reproduction can have a significant impact in the context of regular mass drug treatment and elimination (Anderson et al., 2013; Truscott et al., 2014a).

2.5 Parameter assignments for the key biological processes in transmission and treatment

In terms of structure, the mathematical models describing the transmission dynamics of these different STH species are identical due to the common direct life cycle structure. Differences in the mechanisms of worm establishment are not significant in the context of population-level descriptions

of changing parasite burden, although this might not be the case if immunity or some form of prophylactic treatment (immunization) were to have a significant effect on the parasite establishment process in the human host. In any event, it is notable that the time delay from infection to establishment in the intestine as an adult worm is similar in all three species and generally much shorter than the life span of the worm in the host and so would contribute little to differentiating the species (Anderson and May, 1985).

A key problem in estimating parameter values for STH parasites is the 'indirect' nature of the majority of the data. The central feature of any model is the worms; their acquisition, death and their production of new infectious material. The majority of data, however, concerns the detection of eggs in stool samples. Most frequently, epidemiological data are available only in the form of summary statistics, such as the prevalence (fraction infected) or the mean intensity in terms of egg counts within a population or age category. Such data are typically cross-sectional by age or age group. It is seldom longitudinal over time. More usefully, this kind of data is sometimes available in its raw form as readings or sets of readings from individuals of egg counts (usually only directly from the original authors). In the case of *Ascaris*, some of the available data can also distinguish between fertilized and unfertilized eggs. The paucity of quality data in this area of epidemiological study, especially raw data from each person sampled, highlights the need for international electronic registers of collected information as is often organized in other fields of epidemiological study.

Much more rarely, worm expulsions are carried out on a subset of the human population, subsequent to egg intensity measurements, providing worm counts for individuals. In some cases, these data can be further stratified by worm sex and weight. However, the time, expense and labour intensiveness of this process means that expulsions are rarely done as a matter of course in MDA impact monitoring programmes, but only within the context of specific research epidemiological studies. As a result, little of the available data are of great value in estimating key parameters that influence the impact of MDA programmes and define breakpoints in transmission or therapeutic coverage levels required to halt transmission.

Tables 1 and 2 document current estimates of the key population parameters that influence the transmission dynamics of STH species. Drug efficacy

Table 1 Population parameters, development rates and life expectancies of parasites and free-living infective stages

Parameter	*Ascaris lumbricoides*	*Trichuris trichiura*	Hookworm	Sources
Infective stage	Ova	Ova	Larvae	
Egg production (eggs/female worm/day)	10,000–200,000	2,000–20,000	3,000–20,000	Anderson and May (1982), Bundy and Cooper (1989) and Crompton (2001)
Life expectancy of free-living infective stages	28–84 days	10–30 days	3–10 days	Anderson and May (1982), Bundy and Cooper (1989) and Crompton (2001)
Adult life span	1–2 years	1–2 years	3–4 years	Anderson and May (1992)
Pre-patency (adult development to sexual maturity)	50–80 days	50–84 days	28–50 days	Anderson and May (1992)
Larval development time to infective stage	8–37 days	20–100 days	2–14 days	Smith and Schad (1989), Nwosu (1978) and Beer (1976)
Maximum temperature of viable development	35–39°C	37–39°C	40°C	Smith and Schad (1989), Nwosu (1978) and Beer (1976)
Basic reproduction number (R_0)	1–5	4–6	2–3	Anderson and May (1992)
Maximum mean no. eggs per gram of faeces per female worm, λ	650–9,900	370	200	Bradley et al. (1992), Bundy et al. (1985a), Croll et al. (1982), Holland et al. (1989) and Martin et al. (1983)
Density-dependent fecundity, γ (power law)	0.25–0.6	–	–	Hall and Holland (2000)

Table 1 Population parameters, development rates and life expectancies of parasites and free-living infective stages—cont'd

Parameter	*Ascaris lumbricoides*	*Trichuris trichiura*	Hookworm	Sources
Density-dependent fecundity, γ (exponential) [/female worm]	0.05—0.0035	0.01	0.03—0.08	Bradley et al. (1992), Bundy et al. (1985a), Elkins et al. (1986), Sinniah (1982) and Ye et al. (1994)
Negative binomial aggregation parameter, k	0.57—0.75	0.3—0.4	0.23—0.64	Anderson and Schad (1985), Bradley et al. (1992), Bundy et al. (1985b) and Ye et al. (1994)

Table 2 Reported cure rates (a measure of drug efficacy) of albendazole and mebendazole (Keiser and Utzinger, 2008)

	Cure rates (95% Confidence Interval)	
	Albendazole	**Mebendazole**
Ascaris lumbricoides	88% (79—93%)	95% (91—97%)
Hookworms	72% (59—81%)	15% (1—27%)
Trichuris trichiura	28% (13—39%)	36% (16—51%)

Cure rate: the percentage of individuals who became helminth egg negative following treatment with an anthelmintic drug. Values are taken from a meta-analysis performed by Keiser and Utzinger (2008).

figures are given in Table 2 for the three main species (Keiser and Utzinger, 2008).

2.6 Parameter estimation

Cross-sectional study data, in which individual data are supplemented with host age, is essential to parameterize the age-dependent aspects of a model. Within the model, age-related infection patterns arise from age-dependent contact of the host with infectious material in the environment and the

probability of parasite establishment upon contact, represented by the composite parameter, $\beta(a)$. In practice, a limited number of beta values are used, corresponding to critical age categories of the host population (infant, pre-SAC, SAC and adult), as dictated by the data. The role of $\beta(a)$ in the model is fully elaborated in Section 3.2. If the data can be considered to come from an undisturbed baseline, then parameters can be estimated using the equilibrium solution of the model. The generic baseline individual data set will comprise three possible types of age-specific data; worm counts $\{a_i,w_i\}$, egg intensities $\{a_i,E_i\}$ and paired egg and worm data $\{a_i,w_i,E_i\}$.

If we define $\mathbf{I}_w,\mathbf{I}_{wE},\mathbf{I}_E$ as the indices of individuals with worm counts, worm and egg counts and egg counts only, we can write an overall likelihood for the complete data set {D} given the theta parameters, as the product of three terms,

$$L(\{D\}|\boldsymbol{\theta}) = L_w(\{w\}|\boldsymbol{\theta}_\mathbf{w})L_{wE}(\{w,E\}|\boldsymbol{\theta}_\mathbf{E})L_E(\{E\}|\boldsymbol{\theta}_\mathbf{w},\boldsymbol{\theta}_\mathbf{E}) \tag{2}$$

where

$$L_w(\{w\}|\boldsymbol{\theta}) = \prod_{\mathbf{I_w}} L_w(w_i|M(a_i,\boldsymbol{\theta}_\mathbf{w}),k)$$

$$L_{wE}(\{w,E\}|\boldsymbol{\theta}) = \prod_{\mathbf{I_{wE}}} L_{E|w}(E_i|w_i,\boldsymbol{\theta}_E)$$

$$L_E(\{E\}|\boldsymbol{\theta}) = \prod_{\mathbf{I_E}} \sum_{X=0}^{X_{\max}} L_{E|w}(E_i|X,\boldsymbol{\theta}_E)L_w(X|M(a_i,\boldsymbol{\theta}_\mathbf{w}),k)$$

In the above equation, $\boldsymbol{\theta}_\mathbf{w} = \{R_0,\beta(a),\rho(a),\gamma,k,\sigma\}$, where $\rho(a)$ is the age-specific relative contribution of infectious stages to the environmental reservoir and sigma is the per capita mortality rate of adult worms, is the set of parameters that control the worm burden age profile for the endemic (= the equilibrium where parasites persist) state of the model, and $M(a_i,\boldsymbol{\theta}_\mathbf{w})$ is the model equilibrium worm burden at age a_i (see Eq. (11)). The grouping $\boldsymbol{\theta}_\mathbf{E} = \{\lambda,\gamma,k_E\}$ describes the relationship between egg output of an individual host and their worm burden. Of the three terms in the likelihood expression, only the worm burden term, L_w, directly relates worm burden data at a given age to the model worm burdens. The term L_E describes the likelihood of age-related egg output data in terms of the model worm burdens and the relationship of worm burden to egg output. Since the transmission model is formulated in terms of the mean worm burden by age, it is necessary to sum the weighted contributions from all possible worm burdens in an individual. The uncertainty in the number of female worms in the host reduces the

inferential power of egg count data. This effect is further compounded by the variance in the submodel that connects egg output to worm burden.

Given paired data, $\{E_i,w_i\}$ for individual i, the mean egg output is given by $\overline{E} = \lambda w \varphi'(w,\gamma)$, where $\varphi'(w,\gamma)$ is the reduction in fecundity due to worm burden. If $p(E;\overline{E},k_E)$ is the probability for a measurement E, where k_E parameterizes the variance of the distribution, we can write the likelihood as

$$L_{E|w}(E_i|w_i,\boldsymbol{\theta}_{\mathbf{E}}) = p(E_i;\overline{E}(w_i,\lambda,\gamma),k_E) \tag{3}$$

Previous studies of variability in egg output for individuals across multiple measurements show high variance to mean ratios, characteristic of negative binomial distributions (Anderson and Schad, 1985; Croll et al., 1982). Preliminary analysis of paired data from expulsion studies for the three STH species shows that this distribution also accounts well for the variability in egg output across the population. These high variance to mean ratios also contribute to the 'broadness' of the L_E likelihood term, further reducing its capacity to inform parameter values.

The likelihood term, L_w, which appears also in L_E, is not equally informative with regard to all parameters in $\boldsymbol{\theta}_{\mathbf{E}}$. In particular, it is particularly poor at independently specifying values for γ and the basic reproduction number, R_0. The reason for this can be seen in the simplest models for mean worm burden. Anderson and May (1992) quote the following for mean worm burden in a model without age structure (where z is a function of density-dependent worm fecundity as explained below),

$$\overline{M} = \frac{k\left(R_0^{1/(k+1)} - 1\right)}{1-z} \simeq \frac{k\left(R_0^{1/(k+1)} - 1\right)}{\gamma} \tag{4}$$

In practice, maximizing L_w with respect to $\boldsymbol{\theta}_{\mathbf{E}}$ is dominated by matching the mean worm burden of the observed data to that of the model. As a result, worm burden data can specify the value of the function of R_0, k and γ as shown in Eq. (4), but is very poor at inferring their individual values. For example, increasing both k and γ by 20% would leave $\overline{M}$ unchanged and have little effect on the quality of model fit. This effect can be seen clearly in three different fits to worm burden data from the baseline of the Pulicat Lake study (Elkins et al., 1986), shown in Table 3. The three columns give maximum likelihood estimators and 95% credible intervals for three different scenarios. In the first two columns, values for k and γ are taken from independent fits to egg output/worm data (from Pulicat Lake, India

Table 3 Maximum likelihood estimates (MLEs) of model parameters for fits to baseline data for *Ascaris lumbricoides* from the Pulicat data set from India (a), and the Ile-Ife dataset from Nigeria (b). The values in square brackets indicate the 95% Credible Intervals.

Parameter (units)	Fit to worm burden $\gamma = 0.04$[a]	Fit to worm burden $\gamma = 0.08$[b]	Fit to complete data set[c]
R_0	1.7 [1.57−2.28]	2.45 [2.17−4.09]	2.12 [1.68−3.22]
β_{0-1}	0.47 [0.28−1.31]	0.47 [0.29−1.31]	0.22 [0.13−0.55]
β_{2-4}	1.86 [1.21−4.4]	1.86 [1.18−5.4]	1.88 [1.07−3.19]
β_{15+}	0.56 [0.38−0.92]	0.56 [0.38−1.0]	0.53 [0.36−0.79]
γ	0.04	0.08	0.07 [0.048−0.098]
k	0.7	0.7	0.9 [0.76−1.12]
σ (/yr)	1	1	1
λ (epg/female worm)	NA	NA	3893 [3227−5146]
k_E	NA	NA	0.88 [0.73−1.0]

Age categories for the contact and contamination parameter β are 0−1, 2−4, 5−14, 15+ years with $\beta_{5-14} = 1$. Parameter γ estimated from (a) Pulicat study independently, (b) Nigeria study (Holland et al., 1989) and (c) Pulicat study, jointly with other parameters. Square brackets contain 95% credible intervals assuming uniform priors, where relevant.

and Ile-Ife, Nigeria, respectively), while in the third, all available data are included in Eq. (2). While the values for the age-specific contact parameters are largely preserved across different fits, a range of values for R_0 are recovered, dependent on which values of gamma and k are used. In all three cases, the value of $\overline{M}$ predicted by Eq. (4) is almost identical ($\overline{M} \simeq 6.4$). In general, an increase in the value of the fecundity parameter is matched by an increase in R_0 and/or k. Note also the (Bayesian-derived) credible intervals associated with these parameter estimates. Intervals tend to be wide, reflecting the high variance associated with the negative binomial distribution which underlies both the distribution of worms in hosts and also egg output from a single host. It also reflects the quantity of data points, with short age range β values for infants and pre-SAC being poorly specified. Estimates from fits to the full data set (column three) show tighter intervals in general.

The corresponding fits to data, based on the maximum likelihood estimates (MLEs), can be judged in Fig. 6, which shows the model equilibrium worm burden from the model against the worm expulsion data, along with 5- and 95-percentiles for the underlying negative binomial distribution. The different fits are effectively identical and the predicted 5 and 95% intervals contain approximately 90% of the data points.

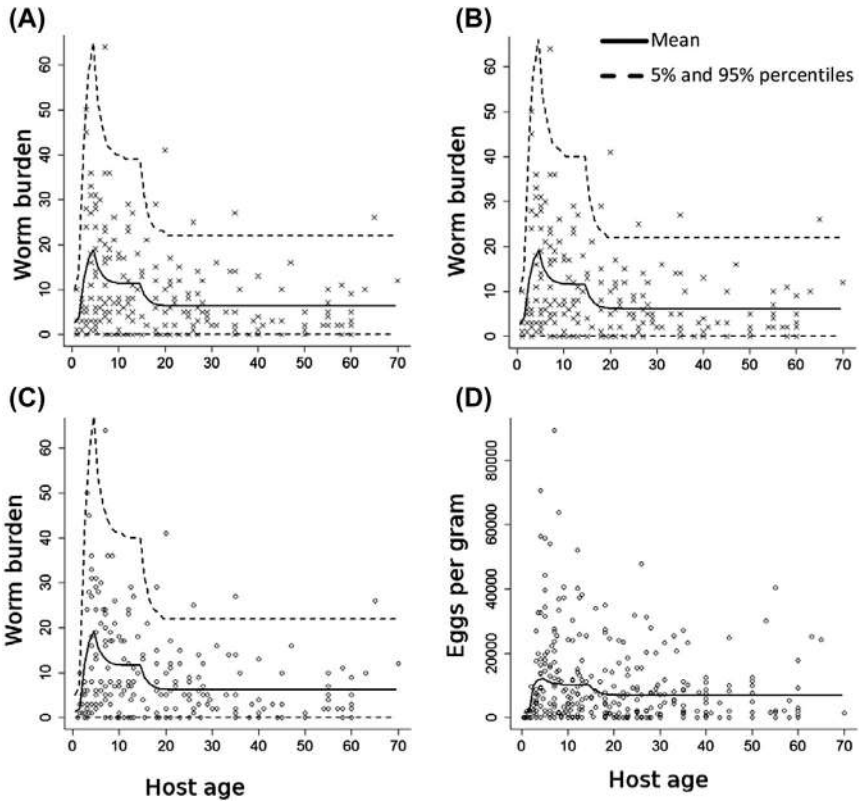

Figure 6 Equilibrium worm burden generated by the model for different fits to *Ascaris* data from the Pulicat study data. Parameters are taken from Table 3. (A) $\gamma = 0.04$, (B) $\gamma = 0.08$, (C and D) Worm burden and egg output fit respectively to full data set (Table 3 column 4).

Table 4 records the maximum likelihood parameter estimates for paired data sets for hookworm and *Trichuris*. The original data come from the epidemiological studies described in the publications of Bundy et al. (1985a) on *Trichuris* and Bradley et al. (1992) on hookworm. In the case of *Trichuris*, an individual-based expulsion data set has been used from a St. Lucia-based study, comprising 119 individual records (Bundy et al., 1985a). For hookworm, raw data from the original study (based in Zimbabwe) cannot be recovered and only age group averaged burdens are available. The lack of individual data means that the aggregation parameter, k, cannot be simultaneously calculated and the value is taken from a separate expulsion arm of the same study. Expulsion data are the source of the fecundity parameters used.

Table 4 MLE parameter values for fit of model equilibrium to worm burden data for hookworm (Bradley et al., 1992) and *Trichuris* (Bundy et al., 1985a)

Parameter (units)	Fit to hookworm worm data	Fit to *Trichuris* worm data
R_0	2.34	1.77 [1.44−2.5]
β_{inf}	0.03	0.3 [0.22−1.48]
$\beta_{\text{pre-SAC}}$	0.09	1.28 [1.09−5.9]
β_{adults}	2.5	0.17 [0.12−1.03]
k	0.35 (not fitted)	0.38 [0.3−0.48]
γ	0.08 (not fitted)	0.0035 (not fitted)
σ (/yr)	0.5 (not fitted)	1 (not fitted)

Different contact age groups are used for each species. For *Trichuris*, age breaks are 0, 2, 7, 12, 75; for hookworm, 0, 2, 5, 15, 75. Square brackets contain 95% credible intervals assuming uniform priors, where relevant. Intervals not given for hookworm due to poor data.

The quality of the fits for the two species is shown in Fig. 7. Note that the mean worm burdens across the three species vary by two orders of magnitude. Of the three parameters in Eq. (4) that govern the value of the mean worm burden, the bulk of the variation is found in estimates of the fecundity parameter.

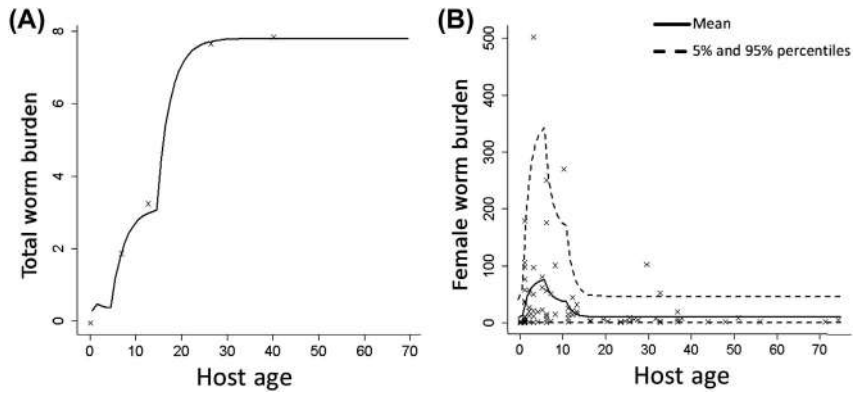

Figure 7 Equilibrium worm burden generated by model and fitted to data for (A) hookworm and (B) *Trichuris*. Parameters in Table 4. *Hookworm data are taken from Zimbabwe study and* Trichuris *data from St. Lucia study (Bradley, M., Chandiwana, S.K., Bundy, D.A., Medley, G.F., 1992. The epidemiology and population biology of* Necator americanus *infection in a rural community in Zimbabwe. Trans. R. Soc. Trop. Med. Hyg. 86, 73−76; Bundy, D.A., Thompson, D.E., Cooper, E.S., Golden, M.H., Anderson, R.M., 1985a. Population dynamics and chemotherapeutic control of* Trichuris trichiura *infection of children in Jamaica and St. Lucia. Trans. R. Soc. Trop. Med. Hyg. 79, 759−764).*

It is clear that age-stratified egg output or even worm output baseline data are insufficient to parameterize a transmission model. Different values of γ and k will lead to different fitted values of R_0 and these will, in turn, lead to different conclusions with regard to the resilience of the parasite in the presence of chemotherapy. Values of γ and λ, calculated from expulsion data, typically have quite a wide range of values, probably arising from differences in skill and practice in egg and worm counting (Hall and Holland, 2000). This is particularly true of λ, a further strike against the usefulness of egg output data. Hence, the best data sets to fit to are those that contain some worm expulsion data within them, ensuring more uniform diagnostic practices. Alternatively, high-quality reinfection studies should provide useful independent data to estimate R_0, although these are scarce.

2.7 Control policy for soil-transmitted helminth treatment by mass drug administration

The main control strategies for STH infections are regular periodic MDA targeting pre-SAC and SAC using anthelmintics (predominantly albendazole and mebendazole). Lymphatic filariasis control, where the whole community is treated with two drugs including albendazole, also impacts STH infections and contributes to their control (WHO, 2006; Keiser and Utzinger, 2008). STH control programmes, which originally used mobile teams to distribute the drugs, are now predominantly centred around school-based delivery systems (WHO, 2002; Hotez et al., 2006). This enables the programmes to be linked with the school educational system (WHO, 2002), which has been shown to be highly cost-effective (Hotez et al., 2006), and a practical method of reaching children in poor rural areas. In addition, SAC are believed to be most at risk for a large share of the overall morbidity and associated developmental consequences of STH infections (Brooker et al., 2010; World Bank, 2003). There has been a growing recognition of the disease burden in and potential benefit of treating pre-SAC (Albonico et al., 2008) and more broadly the whole community especially for the control of hookworm with its predominance in adult age groups (Anderson et al., 2015).

Although both albendazole and mebendazole have a good efficacy against *A. lumbricoides*, mebendazole fails to effectively clear hookworm infections, and neither drug has an adequate efficacy against *T. trichiura* (Keiser and Utzinger, 2008; Vercruysse et al., 2011) — with cure rates of 28 and 36%, respectively (see Table 2).

The recommendations for treatment of soil-transmitted helminthiases through MDA by the WHO are summarized in Table 5. Aside from SAC, WHO also recommends the treatment of pre-SAC, women of childbearing age, and adults in certain high-risk occupations (such as tea-pickers and miners) (WHO, 2006).

Many questions remain regarding how best to deliver STH treatment programmes to achieve the greatest impact; these include which age groups should be targeted, how often and how this should change in areas with different predominant STH species (Anderson et al., 2012). Mathematical models, along with epidemiological studies, provide a template to investigate optimal control programme design in defined settings.

3. MATHEMATICAL MODELS

The earliest work on the theory of helminth infection was published in the late 1960s by Tallis and Leyton through the development of stochastic models of transmission targeted to nematode parasites of sheep and cattle. These had little impact on practice due to an absence of connections to data or field epidemiological observations (Leyton, 1968; Tallis and Leyton, 1966, 1969). Using probability generating functions, they derived key parameters in the distribution of parasite numbers per host (e.g., mean, variance, skewness measures) and their output of infectious material. They included in their model stochastic descriptions of worm establishment

Table 5 WHO recommendations for the treatment of STHs with mass drug administration to SAC and pre-SAC age groups

Category	Prevalence of any STH infection at baseline	Control strategy	
		Preventive chemotherapy	Additional interventions
Schools in high-risk areas	≥50%	Treat all school-age children (enrolled and nonenrolled) twice a year[a]	Improve sanitation and water supply; provide health education
Schools in low-risk areas	≥20% and <50%	Treat all school-age children (enrolled and nonenrolled) once a year	Improve sanitation and water supply; provide health education

pre-SAC, preschool-aged children; *SAC*, school-aged children; *STH*, soil-transmitted helminth.
[a]If the resources are available and the prevalence is towards the higher end of the interval, a third drug distribution round might be added (in this case, the frequency will be every 4 months).

processes, mating dynamics and the acquisition of immunity by the host. While this approach is general, analytical results could not be obtained due to the highly nonlinear nature of the stochastic model excepting for some closed-form expressions for extinction. At about the same time, Macdonald identified that a consequence of sexually reproducing parasites distributed among individual hosts was an inability to generate fertile infectious material when prevalence is low (Macdonald, 1965). This phenomenon introduces the idea of two stable states, endemic infection and extinction separated by a breakpoint; namely, a level of infection intensity or prevalence below which insufficient fertile infectious material is generated by the parasites to maintain a viable transmission cycle.

Anderson and May introduced much more general descriptions of helminth population dynamics and melded into the model descriptions of host age, the distribution of worm numbers per host, density dependence in egg production and sexual mating functions dependent on worm distributions and mating habits (Anderson and May, 1982). The first adaptation of this helminth population dynamics model to soil-transmitted helminthiases was by Anderson in 1980 (Anderson, 1980). The widely observed negative binomial distribution of parasites per hosts can be dynamically generated by assuming a gamma-distributed distribution for host infectious contact rate. A simple exponential survival function for the parasites allows a simpler differential equation model for the evolution of the mean female worm burden, averaged across the population, $\overline{M}(t)$. The balance of parasite acquisition and loss within a host is described by

$$\frac{d\overline{M}}{dt} = \beta L - \sigma\overline{M} \tag{5}$$

where β is the mean infectious contact and parasite establishment rate across the population, σ is the reciprocal of the mean adult worm life span (A), and L represents the concentration of female eggs or larvae in the environment. The dynamics of the environmental stage of the parasite are represented by (where parameter psi represents the rate at which infectious stages enter the environmental reservoir),

$$\frac{dL}{dt} = \frac{\psi\lambda z\overline{M}}{\left[1 + (1-z)\overline{M}/k\right]^{(k+1)}} - \mu_2 L \tag{6}$$

A number of these parameters can be compressed into the basic reproduction number for macroparasites, R_0, describing transmission intensity

and being defined as the average number of female parasites produced by a female worm that themselves infect hosts and survive to reproductive maturity in a susceptible host population in the absence of density-dependent processes (e.g. sexual reproduction). The two equations are as follows,

$$\frac{d\overline{M}}{dt} = \sigma\overline{M}[R_0 f(\overline{M}, k, z) - 1],$$
$$f(\overline{M}, k, z) = [1 + (1 - z)\overline{M}/k]^{-(k+1)} \quad (7)$$
$$R_0 = \frac{\psi z \lambda \beta}{\sigma \mu_2}$$

where parameter psi is as defined above and $z = exp(-\gamma)$ represents the impact of density-dependent egg production, k is the aggregation parameter for the underlying negative binomial distribution, σ is the reciprocal $(1/A)$ of the mean life span of the adult worm in the human host, and μ_2 is the per capita mortality rate of the infective stages (eggs or larvae) in the environment. It is important that γ be in terms of the density of female worms in the host for the current formulation. If γ is in terms of total worm burden, it will need to be doubled to take account of the assumed one-to-one sex ratio in the host. The function f is derived from considering the mean egg output generated by a negatively binomially distributed worm burden with an exponential dependence of fecundity on host worm burden. This approach can be considered a pseudo-probabilistic model (a hybrid model), in that while the mean worm burden evolves deterministically, the model describes the distribution of worms in an individual at a given age.

The basic model shown above stands as a point of origin for most models of STH infection used to examine issues of control and elimination today and as such we examine in more detail the assumptions implicit within it.

3.1 Environmental contamination

The dynamics of infectious material in the environment are generally ignored. The timescale of external infectious stages is short compared to the life span of the parasite in the human host and is thus assumed to be in equilibrium. Additionally, current interventions for soil-transmitted helminthiases are predominantly chemotherapeutic and hence only target the adult worms in their parasitic stage. For strategies involving water, sanitation and hygiene (WASH), explicit modelling of an environmental reservoir may be necessary (Brooker et al., 2006; Cundill et al., 2011; Pullan and Brooker, 2012).

3.2 Age structure

The age profile of infection intensity in hosts is a fairly consistent distinguishing feature between the three main STH species and tells us about the varying rate of parasite acquisition with age (Fig. 2). Moreover, since chemotherapy is often targeted at particular age groups, modelling age structure is essential in analysing control and elimination. The model described above can be simply extended to a partial differential equation for changes over time and by age,

$$\frac{\partial M}{\partial t} + \frac{\partial M}{\partial a} = \Lambda(a) - \sigma M(a) \tag{8}$$

where $M(a,t)$ is the mean worm burden of individuals of age a and $\Lambda(a)$ is the age-dependent force of infection (Anderson and May, 1992). The presence of age structure requires us to consider how hosts of different ages contribute to and have contact with the infectious material in the environment. These interactions are described by a contribution function, $\rho(a)$, and a contact and establishment rate, $\beta(a)$. The parameter $\rho(a)$ can be thought of as a function describing the relative contribution with age since its magnitude is indistinguishable from the parameter ψ (the rate at which infectious stages enter the environmental reservoir) and the absolute quantity is embedded within the definition of R_0. The concentration of infectious material in the reservoir, L, is given by

$$\frac{dL}{dt} = \frac{\psi\lambda}{\overline{a}} \int_{a=0}^{\infty} M(a) f(M(a), z, k) \varphi(M(a), z, k) \rho(a) S(a) da - \mu_2 L \tag{9}$$

and $\Lambda(a) = L\beta(a)$; $S(a)$ is the probability of a host being alive at age a. The integral in this expression sums the contribution from hosts of each age to the total amount of infectious material entering the infectious reservoir. The function f, describing the output of eggs from a host aged a, is multiplied by the fraction of those eggs that are fertilized, φ. Contributions are further weighted according to the host survival curve, $S(a)$. The parameter $\overline{a}$ is the mean host age in the population.

For the age-structured model, the basic reproduction number is given by

$$R_0 = \frac{z\lambda\psi}{\mu_2 \overline{a}} \int_{a=0}^{\infty} \rho(a) S(a) \int_{x=0}^{a} \beta(x) e^{-\sigma(a-x)} dx da \tag{10}$$

The stable endemic solution for mean worm burden with age is given by

$$M^*(a) = L^* \int_{a'=0}^{a} \beta(a') e^{-\sigma(a-a')} da' = L^* Q(a) \tag{11}$$

Note that the infection age profile shape is determined only by the infection contact parameter and the worm death rate. The equilibrium reservoir state, L^*, is a solution of

$$\frac{\psi\lambda}{\overline{a}\mu_2} \int_{a=0}^{\infty} L^* Q(a) f(L^* Q(a), z, k) \varphi(L^* Q(a), z, k) \rho(a) S(a) da = L^* \tag{12}$$

There are either three solutions for the above (disease-free, breakpoint and endemic equilibrium) or one (disease-free) for low R_0 values.

The relationship between the age-structured model (9) and the basic model (6) can be seen by multiplying the age-structured model by $S(a)/\overline{a}$ and integrating out age. If $S(a) = exp(-\mu a)$, then

$$\frac{d\overline{M}}{dt} = \frac{L}{\overline{a}} \int_{a=0}^{\infty} \beta(a) S(a) da - (\sigma + \mu)\overline{M} = L\overline{\beta} - (\sigma + \mu)\overline{M} \tag{13}$$

where $\overline{\beta}$ is the mean contact and establishment rate over all ages, and where $\overline{M}(t) = \int_{a=0}^{\infty} M(a,t) \frac{S(a)}{\overline{a}} da$. It is clear that the term arising from the host death rate has been omitted from the original formulation, but since this is a small fraction of the worm death rate for STHs, the effect is negligible.

3.3 Models of drug treatment at a population level

Anderson and May (1992) use the model described by Eq. (7) to examine the impact of treatment on prevalence and intensity of infection and average egg output of the population. The authors develop a continuous model for the impact of a long sequence of regular treatment cycles. The impact is analogous to an additional death rate for the parasite population, c, where

$$c = -\ln(1 - gh)/\tau \tag{14}$$

Here g is the proportion treated per round, h is the efficacy of the drug and τ is the interval between treatments. This formulation assumes that those treated are randomly chosen from the population and that transient

disturbances in the parasite population following rounds of treatment have no long-term effects. Note that the term *gh* is the effective coverage.

Anderson (1980) and Anderson and May (1982) were the first studies to use models to address the impact of control programmes of drug treatment based on an individual's parasite burden and infection prevalence. The model used is deterministic and not specific to a particular helminth species. Results show that selective treatment [based on epidemiological evidence of predisposition to heavy or light infection (see Schad and Anderson, 1985)] can be effective in terms of reducing worm burdens per unit of drug supplied, particularly if the aggregation within hosts is high and the effect is not particularly sensitive to the selection threshold used. However, this analysis needs to be extended to take account of the additional cost of screening implicit in implementing a selective treatment programme. The detection of people with high worm burdens may also be problematic. High worm burden is assessed through correspondingly high egg output detected by diagnostic techniques such as Kato-Katz. Since egg output is highly variable within a stool sample, and from day-to-day in the same patient (see Anderson and Schad, 1985), and since Kato-Katz has poor sensitivity, the ability to select suitable candidates for treatment may be subject to error. In general, however, individual-based models are more appropriate for simulating selective treatment schemes and these are discussed later.

A range of models and concomitant numerical analyses were published in the 1990s by Chan, Guyatt and colleagues which are extensions of the models of the Anderson and May framework. Medley et al. (1993) constructed a model that allows host worm burden to adapt dynamically to treatment and reinfection processes. This also has the advantage of being able to distinguish between treated and untreated individuals and hence between treatment coverage and drug efficacy. The model does not include sexual reproduction dynamics or age structure. In Chan et al. (1994a), the authors added a simple age structure to the basic model with compartments representing worm burden in children and adults, respectively. This structure is later further refined to include a preschool-age group as well (Chan, 1997). Such a structure allows for the different worm burdens in children and adults, characteristic of STHs, by letting the two groups acquire worms from and discharge infectious material to the environment at different rates. This approach also facilitates the modelling of both MDA and treatment aimed at children only.

Medley et al. (1993) implemented the concept of a worm burden threshold as a measure of disease prevalence in a population. This metric

can then be used as a measure of effective control and hence to assess the success of an intervention within a model framework. The concept is originally introduced in Guyatt and colleagues and then further elaborated into a set of age-specific worm thresholds for each of the three STH species (Guyatt and Bundy, 1991; Chan et al., 1994b). Data exist relating morbidity measures such as growth stunting (*Ascaris*, *Trichuris*) and anaemia (hookworm) to epg output, and these can be back-calculated through estimated egg output per female worm to give a worm burden threshold. The considerable uncertainties in each stage of this process make the resultant thresholds approximate. This model is further employed to examine the cost-effectiveness of repeated rounds of treatment for *Ascaris* over a 5-year period and an equal period after treatment ends (Guyatt et al., 1993). The effects of a range of treatment frequencies on metrics of worm burden, infection and disease prevalence are examined using cost data from an actual chemotherapeutic control programme. The authors find that it is more cost-effective to intervene in high transmission areas than low, and that for low transmission areas, lower treatment frequencies are more cost-effective. This is a result of the slower bounce back time from treatment under lower transmission resulting in rapid follow-up finding few worms to treat.

Chan et al. (1994a) extended the use of disease burden as a metric by using a two-age group model (adults and children) to study the impact of targeted deworming. The authors validate their model against longitudinal treatment data from both *Ascaris* and *Trichuris* studies. The model demonstrates the interdependence of different age groups through the shared reservoir of infectious material, with treatment in one age group reducing worm burden and disease prevalence in another. In particular, they demonstrate that, over 5 years of treatment, annual treatment of children with a single initial round for adults is more beneficial than biannual treatment of children for the same period. This is the first demonstration that direct treatment of the risk population may not be the most effective mode of intervention for the whole community or the risk population in question. Guyatt et al. (1995) extend the investigation to these different forms of treatment considering their cost-effectiveness, using the same costing data. They found that, while treatment of the whole population is more effective by all metrics, interventions targeted at children are more cost-effective, due to the concentration of parasites in this subpopulation in the case of *Ascaris*. To some extent, the cost-effectiveness of an intervention was dependent on the metric applied. When an infection prevalence metric was used the result

indicated that annual treatment was optimal, whereas a high worm burden 'disease' metric suggested an interval of 2 years. Given that opinions may differ as to the goals of treatment (e.g., elimination of disease vs reduction in morbidity in children), the metric chosen can change the predicted optimal strategy. Chan (1997) extended the analysis of morbidity by using a three-age group model to assess the impact of SAC-targeted annual treatment on morbidity measured in DALYs. A recent study has used similar models to look at integrated cost-effectiveness across all three STH species and schistosomiasis (Lo et al., 2015).

The models discussed up to this point have all represented infectious material in the environment, be it eggs or larvae, as a single reservoir of material which decays exponentially. Chan et al. (1997) further extended the two-age group model by introducing more heterogeneous infectious contact structure. The environmental reservoir is divided into two independent parts and different contact patterns between age groups and reservoirs are explored. The different models are fitted to longitudinal hookworm data under treatment and show that for the given data, the standard assumption of a common reservoir is optimal over more complex structures.

3.4 Acquired immunity

Anderson and May (1992) also developed a partial differential equation for the acquisition of immunity, represented as an integral over past experience of infection or exposure to infection. At equilibrium, this model facilitated some analytical exploration for the age distribution of infection and how the convexity of the profile changes under different rates of acquiring immunity (Anderson and Medley, 1985).

As mentioned earlier, however, the evidence for immunity playing an important role in STH infection is limited despite evidence of immunological markers. Reinfection studies show that all age groups reacquire parasites despite long past exposure. As such, in this paper we focus on age-related exposure as opposed to acquired immunity, being the dominant factor in shaping age—intensity profiles.

3.5 Stochastic models

Anderson and Medley (1985) extended the basic principles described above to a stochastic individual-based model. The births and deaths of individual hosts are governed by a realistic age distribution for a typical low-income country. For each host, the processes of acquisition, maturation and death

of the individual's worms are modelled. The negative binomial aggregation of parasites in hosts is generated through the statistics of acquisition. Two models of acquisition were investigated: predisposition, in which an individuals' rate of parasite acquisition is particular to them and drawn from a gamma distribution, and environmental in which eggs/larvae are clumped in the environment (described by a log-normal distribution), but individuals have no predisposition. Hosts have an underlying age-dependent contact rate, allowing the model to match the characteristic age–intensity profiles observed in cross-sectional studies (as described in the Section 2.6). Egg production in hosts was modelled by an exponential model of density-dependent fecundity, as described above. However, the dynamics of sexual reproduction were omitted.

The individual-based nature of the model allows a much more precise description of treatment than the continuous approximation described by the earlier Anderson and May (1982) model. Each round of chemotherapy is treated as a discrete event and the choice of individuals to be treated can be a function of age, treatment compliance and past or current infection status. The drug efficacy is used as a treatment survival probability for individual worms in a treated host.

Anderson and Medley (1985) use their detailed individual-based stochastic model to examine the impact of different generators of parasite aggregation under treatment and the impact of different forms of selective treatment. Results show that recovery posttreatment is significantly faster with predisposition than with environmentally generated heterogeneity, driven by the rapid recovery of hosts with a strong predisposition and that selective treatment is improved if the most heavily infected people are repeatedly identified rather than identified only once. Such an approach is clearly much more laborious and expensive, even before considering how the wormiest people can be reliably identified.

While considerably more computationally intensive, this approach includes much more of the natural heterogeneity inherent in demography, human behaviour, environmental factors and parasite population processes. Output from the model is probabilistic in nature, so variability in results can be directly examined and compared with observed patterns of the distribution of parasite numbers per host. It also facilitates a much more detailed view of the population in which individuals can also be followed to look at details of reinfection and also compliance to treatment.

3.6 Model predictions on the control of disease and the likelihood that mass drug administration alone can break transmission for different soil-transmitted helminth species

We employ two examples (see Figs. 8 and 9) illustrating the differences between *Ascaris* and hookworm in the effect of control on heavy worm burden under different treatment regimes. The baseline age distributions for these both diseases are fitted to data (see Section 2.6 for the details) and have similar transmission intensities, as indicated by the value of the basic reproduction number, R_0. They also have similar patterns of density dependence in fecundity. As is clear from Figs. 2 and 3, their baseline age profiles and degrees of underlying parasite aggregation are quite different from each other. The threshold for high worm burden in each species is the lower of the two defined in the literature. We compare three different patterns of treatment: annual and biannual treatment of both pre-SAC and SAC, and annual mass treatment of all individuals. Effective coverage is 75%, reflecting a 95% drug efficacy and approximately 80% coverage. Results are generated by the age-structured model described in Truscott et al. (2014b) and averaged across age categories. At present, the primary goal of treatment is controlling morbidity in children, and all regimes examined are effective at this, although less so for *Ascaris* due to the greater prevalence of high worm burdens in that age group at baseline. For hookworm, model simulations suggest that annual mass treatment is preferable to biannual treatment of children. Treatment targeted at children has a direct impact on their morbidity whereas mass treatment has both a direct effect of child morbidity and an indirect effect on

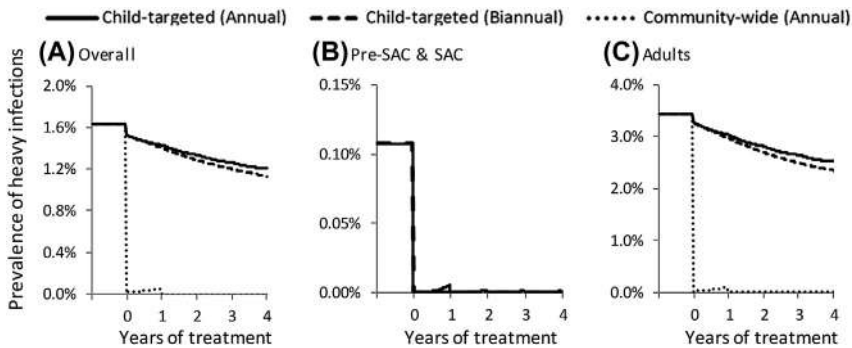

Figure 8 The effect of three different regimes of coverage on heavy worm burdens of hookworm. Mean prevalence of heavy worm burdens across (A) whole host population, (B) pre-SAC and SAC and (C) adult age groups. Parameters as in Table 4.

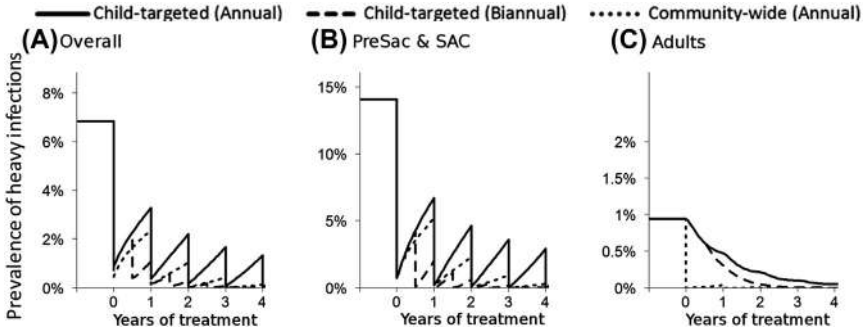

Figure 9 The effect of three different regimes of coverage on heavy worm burdens of *Ascaris*. Mean prevalence of heavy worm burdens across (A) whole host population, (B) pre-SAC and SAC and (C) adult age groups. Parameters taken from Table 3 (column 4).

the underlying force of infection. The age-intensity profile indicates that the majority of the worms are in adults, and treatment of the whole population also serves to reduce the force of infection on children, reducing their morbidity as well as that experienced by adults. For *Ascaris*, the highest infection intensity is in the SAC and pre-SAC age groups, and hence focussing on treatment of children targets the majority of the worms. As a result, morbidity in children is rapidly reduced along with the overall force of infection, benefitting adults as well without directly targeting them. The importance of the direct and indirect impact of interventions on the morbidity risk group (usually children) is a common consideration in microparasitic disease control (e.g., vaccination against childhood diseases) but is rarely discussed in the context of helminthiases (Medley et al., 1993).

Discussion of the possibility of the elimination of transmission occurs in some of the earliest work on helminth transmission models. It is first identified by Macdonald in the context of such models having an endemic and a worm-free equilibrium simultaneously, separated by an unstable breakpoint (Macdonald, 1965). Anderson and May (1982) point out that the aggregated nature of worms amongst hosts means that the breakpoint will occur at very low mean worm burdens and will therefore not play an important role in parasite dynamics. Anderson and May discuss a second, dynamic, form of elimination arising as the product of a treatment programme and which can be achieved without the effect of sexual reproduction based on reducing the basic reproduction number below unity in value. Using their continuous definition of regular chemotherapeutic treatment, they identify a critical proportion (chosen at random at each round of treatment) who must be treated per unit time, $\widehat{g}$, that will reduce the mean worm burden in the

host population to zero, where tau is the interval between treatments and A is the life expectancy of adult worms, 1 over sigma,

$$\widehat{g} = [1 - \exp((1 - R_0)\tau/A)]/h \tag{15}$$

Here h denotes drug efficacy. This formulation is derived on the assumption that the influence of sexual reproduction is negligible. Based on similar reasoning, they also develop an expression for a critical level of vaccine coverage $\overline{p}$ to achieve elimination $\overline{p} = [1 - 1/R_0]/\nu$, where ν is the average duration of vaccine protection for a vaccinated person. It should be noted that this type of elimination is only stable if treatment continues indefinitely unless sexual reproduction is present in the model.

The possibility of elimination is not considered in the work by Medley, Bundy, Guyatt and colleagues from the 1990s, as it was seen as not feasible, given the resources available to provide drugs at the time (Medley et al., 1993). Additionally, the models employed lacked treatment of sexual reproduction and hence would be unable to generate unstable elimination equilibria over finite periods of treatment.

Truscott et al. (2014a) extend the analytical approach to parasite elimination introduced by Anderson and May (1982). In the context of simple age-structured models, they find five key dimensionless parameter groupings that control whether elimination by repeated SAC-targeted chemotherapy can be achieved. These include the following:

- R_0, the basic reproduction number for the parasite in the population as a whole;
- r_c, the fraction of the transmission cycle attributable to SAC;
- t_l, the effective treatment interval, defined as the interval between regular rounds of treatment as a fraction of the mean worm life span;
- gh, the effective treatment coverage for the population, the product of the therapeutic coverage and drug efficacy; and
- ε, the life span of infectious material in the environment as a fraction of the mean worm life span.

The parameter grouping r_c encapsulates the social structure within the model in that it contains all the information on the age-specific contact and deposition rates. As such, it is one of the main discriminants between different species. For both *Ascaris* and *Trichuris* $r_c \geq 0.65$, whereas for hookworm, its value will be significantly less than 0.2.

Fig. 10(A) shows the impact on parasite population growth rate at low parasite populations of effective coverage and the contribution of school children to transmission, r_c. The growth rate can be seen as a proxy for

the resilience of the parasite population to treatment. It is clear that for high values of r_c, at a given level of treatment, the parasite is much less resilient than at low levels, illustrating that elimination through school-based deworming will be much easier for *Ascaris* and *Trichuris* than for hookworm for a given level of effective coverage. Fig. 10(B) shows critical values of R_0 and effective coverage at which elimination occurs and illustrates how the dynamics of the infectious reservoir can impact elimination. The parameter ε represents the timescale for the turnover of infectious material in the reservoir. The $\varepsilon = 0$ curve corresponds to the standard assumption of a reservoir at equilibrium (Anderson and May, 1982). The more realistic value of 0.2 (for *Ascaris*) gives significantly more resilience to the parasite, arising from the fact that infectious material is able to 'shelter' in the environment, where treatment cannot reach it, and reinfect hosts later.

As the impact of mating among parasites is most marked at low worm prevalences, it is not surprising that sexual reproduction should have an impact on elimination. The inclusion of sexual reproduction makes the elimination at a given coverage level possible at a much higher R_0 value (see Anderson and May, 1992). The mechanism by which this happens can be seen in Fig. 11, which contrasts the time series of child mean worm burden under annual treatment with and without parasite sexual reproduction in place (Truscott et al., 2014a). Sexual reproduction acts to reduce the output of fertile infectious material even considerably above the point at which the 'breakpoint' burden occurs. The effect is that with

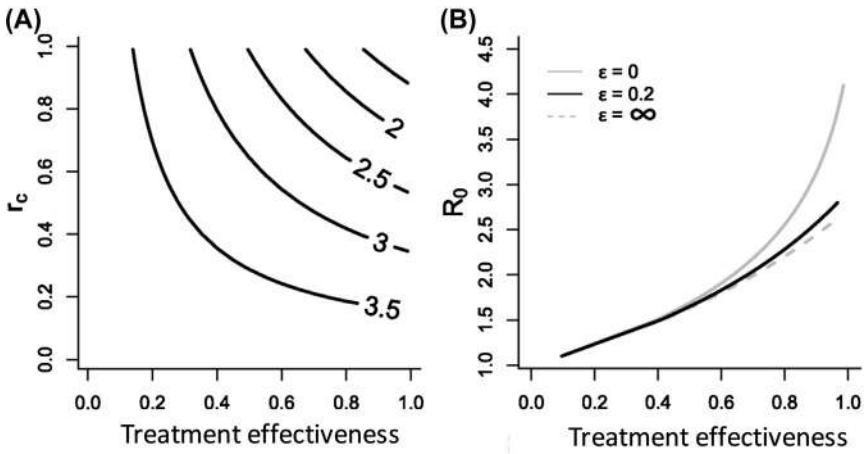

Figure 10 (A) The effects of the contribution of children to transmission, r_c, on resilience to the impact of treatment and (B) the effect of reservoir timescale, ε, on the possibility of elimination. Treatment of children is annual.

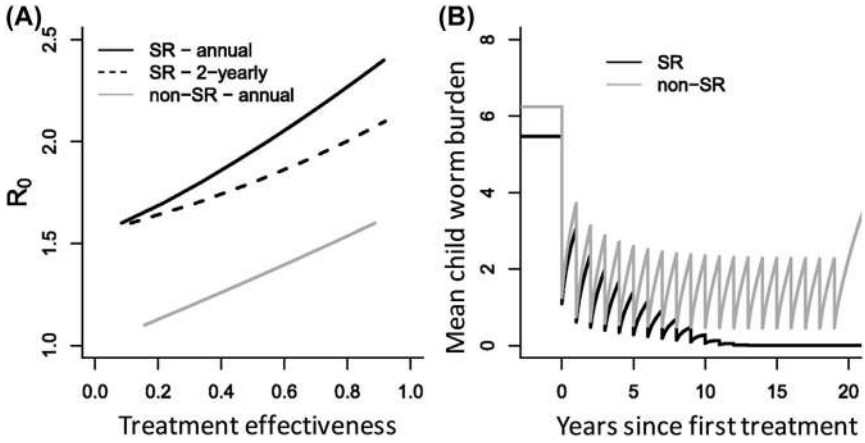

Figure 11 (A) Critical treatment effectiveness (coverage x efficacy) to reach elimination for STH sexual reproduction and nonsexual reproduction dynamics and different treatment intervals (annual vs. biennial) (annual vs. biennial). (B) Evolution of worm burden in children under annual treatment with and without sexual reproduction dynamics (Truscott et al., 2014a). *SR*, sexual reproduction.

sexual reproduction, the parasite population's recovery is always reduced with respect to that without sexual reproduction, and over many rounds of treatment this accumulated reduction finally leads to elimination.

The impact of low worm burden on parasite fertility also has consequences for how a given quantity of drugs should be administered in a community. Fig. 12(A) shows the mean worm burden in children over time under three different scenarios, all of which deliver the same quantity of drugs per unit time. Delivery with four or six monthly intervals, leads to elimination at approximately the same time, whereas annual treatment is significantly faster. The larger instantaneous delivery of drugs forces the parasite population temporarily into the regime of limited fecundity, hampering its bounce back and allowing the effect to accumulate over time. The continuous description originally devised by Anderson and May is formally the limit of shorter and shorter treatment intervals as depicted in Fig. 12(A), and as such its continuous nature represents an inefficient delivery method of a defined quantity of drug (Anderson and May, 1982). It is always better to give all at once rather than spreading it over time. In the absence of sexual reproduction, all treatment intervals will average the same over time. Fig. 12(B) shows the minimum number of rounds to achieve elimination at different treatment frequencies (effective coverage 80%). The optimal number of rounds varies between treatment

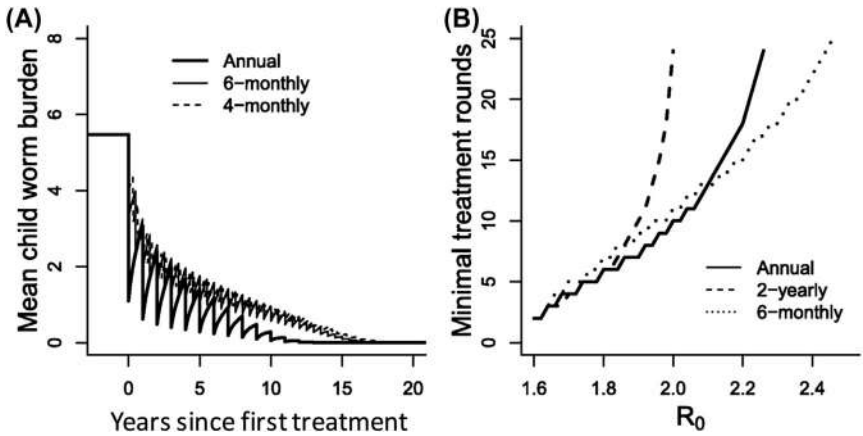

Figure 12 (A) Time series showing the effect of different intervention frequencies with same annual treatment rate. (B) Minimum number of treatment rounds necessary to achieve elimination (with sexual reproduction) as a function of R_0 and the interval between treatments (Truscott et al., 2014a).

frequencies as R_0 representing transmission intensity is varied (Truscott et al., 2014a). The implication is that the optimal number of rounds is found at different treatment intervals for different transmission intensities. Since the number of rounds is a strong indicator of the cost of a programme, the cost-effectiveness of elimination programs may be improved by careful choice of the treatment interval and measurement of the intrinsic transmission intensity (R_0) in a defined setting. Ideally, the latter should be measured prior to the initiation of MDA.

We can illustrate the dependence of elimination on effective coverage levels in different age groups for the population by mapping out the surface of critical levels of coverage that lead to elimination, within a given number of rounds (Anderson et al., 2014; Truscott et al., 2014b). Fig. 13 shows surfaces of the minimum coverage levels for annual treatment of pre-SAC, SAC and adults to achieve elimination of *Ascaris* within 25 years for estimated R_0 values between 1.7 and 2.5 as in Table 3. The number of rounds to elimination is defined as the least number of rounds of treatment from which the parasite population will not recover. The four panels represent different parameterizations of the model to the same data set (the Pulicat Lake study) as described in the earlier Section 2.6. Fig. 13A and B, are derived based on fits to the worm burden age profile (see Table 3) with $\gamma = 0.04$ and 0.08, respectively. Panel C shows the parameterization for panel B, but with $\gamma = 0.04$, while panel D is parameterized using both egg and worm burden profile data simultaneously.

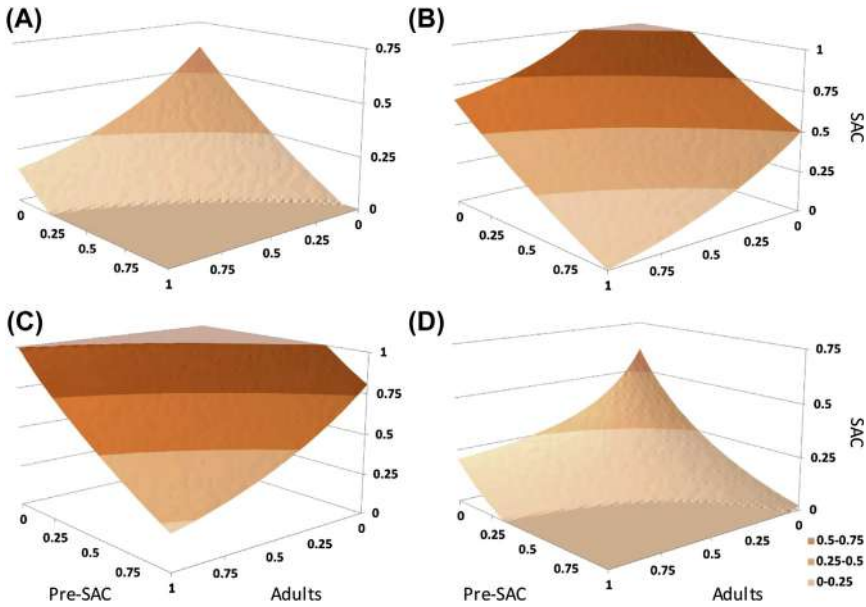

Figure 13 Elimination surfaces for *Ascaris*. The surface shows the minimum levels of effective coverage needed to effect elimination within 25 years. Values above the surface are predicted to always achieve elimination on the basis of the predictions of the deterministic models. Parameter values are derived from fits to baseline data from Table 3. (A) Fecundity parameter $\gamma = 0.04$ (Table 3, column 2), (B) $\gamma = 0.08$ (Table 3, column 3), (C) all parameters fitted together (Table 3, column 4), (D) parameters as for B, but with $\gamma = 0.04$. Model as described in Truscott et al. (2015).

All four panels show surfaces that are at approximately the same angle to the axes, indicating that the incremental effects of changing coverage in any of the age groups are approximately the same across them all. The impact of treatment of pre-SAC and adults is comparable, while treatment of SAC is approximately twice as effective. This reflects the lack of variability in the infectious contact parameters across the different fits to the baseline data. The position of the surface changes markedly between different parameterizations. The natural correlation between γ and R_0, discussed earlier, means that Fig. 13B has a higher R_0 value (2.46) than Fig. 13A (1.7). As a result, the parasite is significantly more resilient to elimination with the higher R_0 value. However, elimination is also very sensitive to the value of the fecundity parameter, γ. Fig. 13C has the same parameter values as Fig. 13B, but γ is reduced to 0.04. Although transmission intensity is the same, the parasite population is considerably more resilient. A possible explanation for this

effect is that the lower severity of density dependence allows larger mean worm burdens in the population. The effect of treatment on the worm population is proportional, so the impact of a given round should not be affected significantly. However, the breakpoint below which the parasite population can no longer support itself is largely unchanged and hence requires greater effective coverage and/or more rounds of treatment to achieve. For the fit to both egg and worm data, the value of R_0 (2.1) is higher than in panel A, but the higher value of γ reduces the resilience to give a similar elimination response.

The differences in response to treatment among the three STH species can be clearly seen by comparing the elimination surfaces for *Ascaris* in Fig. 13 with those for hookworm and *Trichuris* in Fig. 14. Parameters for the latter two diseases are defined in Table 4, generated from fitting to baseline worm burden data sets described in the earlier Section 2.6. The surfaces illustrate the strong differences between the three species in terms of their response to regular treatment. Hookworm distribution among hosts is dominated by the worm burden in adults. As a result, elimination is most sensitive to changes in coverage of the adult population (Fig. 14A). The low worm burdens in pre-SAC and SAC mean that treatment of these age groups has little effect on transmission in the community as a whole, although it may have a large effect on the morbidity of the groups treated.

For *Trichuris* (Fig. 14B), the low worm burden in adults as compared to the other two species means that treatment of adults is not very effective. Elimination of *Trichuris* is best achieved by a combination of coverage of pre-SAC and SAC age groups. Note also that although *Trichuris* has a lower R_0 in this example than hookworm, it is much more resilient to elimination. This is a consequence of the comparatively low density-dependent

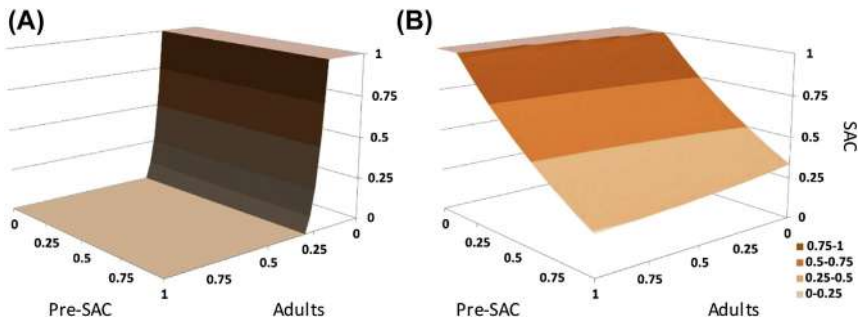

Figure 14 Elimination surfaces for hookworm (A) and *Trichuris* (B). Parameters are taken from Table 4. Model as described in Truscott et al. (2015).

fecundity for *Trichuris* (0.0035/female worm) with respect to hookworm (0.08/per female worm). This accounts for the relatively high mean worm burden and the difficulty in achieving elimination, which is the same effect observed for *Ascaris* above. Given the low drug efficacies of albendazole and mebendazole monotherapy for *Trichuris* (Table 2), this suggests that elimination will prove particularly difficult to achieve.

The parameters that determine the predictions of the model's response to regular treatment are γ, R_0, the life span of the parasite and the age-specific contact rates that control the force of infection and generate the characteristic age intensity profile observed in epidemiological studies (see Fig. 2). Of these, contact rates and γ are possibly the most variable between species, and between studies within a given species.

Predictions about elimination by MDA can be extended to derive the predicted number of rounds of treatment at a defined coverage level, for defined age groups and for a given frequency of treatment (e.g., annual or twice a year). Some sample calculations are shown in the tables displayed in Fig. 15 for *Ascaris* and *Trichuris* and for hookworm in Fig. 16. Each table in these two figures shows the minimum number of rounds of treatment necessary to eliminate the parasite as a function of the effective coverage (therapeutic coverage times drug efficacy) in adults, and SAC and pre-SAC jointly. The scan is effectively a cross-sectional slice through the equivalent surfaces in Figs. 13 and 14 in which SAC and pre-SAC coverage are equal to each other. The basic structure of these tables reflects that of the equivalent elimination surfaces. Note that close to the elimination threshold

(A)

Adults

SAC & Pre-SAC	0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.2	NA	NA	NA	NA	NA	NA	25	23	21	20	19
0.3	NA	NA	22	18	16	14	13	13	12	12	11
0.4	23	17	14	12	11	10	9	9	8	8	8
0.5	15	12	10	9	8	7	7	7	6	6	6
0.6	11	9	8	7	6	6	6	5	5	5	5
0.7	9	7	6	6	5	5	5	4	4	4	4
0.8	8	6	6	5	4	4	4	4	3	3	3
0.9	7	6	5	4	4	4	3	3	3	3	3
1	6	5	4	4	3	3	3	3	3	2	2

(B)

Adults

	0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.5	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.6	NA	NA	NA	25	23	22	22	21	20	20	20
0.7	16	15	15	14	14	13	13	13	13	12	12
0.8	11	11	10	10	10	9	9	9	9	9	9
0.9	8	8	8	7	7	7	7	7	7	7	6
1	7	6	6	6	6	5	5	5	5	5	5

Figure 15 Annual rounds of treatment predicted to lead to the elimination of transmission for (A) *Ascaris* and (B) *Trichuris*. Parameters as defined for Figs. 13 and 14. NA indicates more than 25 rounds of annual treatment required. Model as described in Truscott et al. (2015). *pre-SAC*, preschool-aged children; *SAC*, school-aged children.

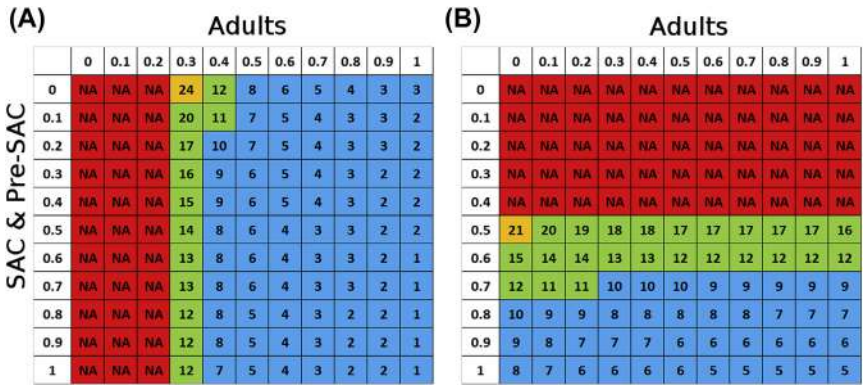

Figure 16 (A) Annual treatment rounds to elimination of hookworm and (B) 6-monthly rounds of treatment predicted to be required for the elimination of *Trichuris*. Model as described in Truscott et al. (2015). *pre-SAC*, preschool-aged children; *SAC*, school-aged children.

(breakpoint) it can take a long time to achieve a break in transmission. The models predict that it needs high levels of coverage to achieve elimination in the short term defined as between 5 and 10 years.

The predicted elimination surfaces and the predicted number of rounds required to achieve elimination are subject to a number of sources of variability. The parameter values used here are the maximum likelihood estimators derived from fitting to specific epidemiological data sets. It is clear that inferred values for a given species of STH vary considerably between studies. For example, hookworm worm burdens across a range of studies show large variations in magnitude, indicating matching variations in γ and/or R_0, if not in the age-dependent contact rates (Fig. 2). This suggests variation not only in transmission intensity but also in the hosts' response to the parasite. For a given data set, there will be uncertainty in the parameter values as a function of the quality and the quantity of data collected. A fully Bayesian approach will yield a posterior distribution of parameter values which will necessarily blur the surfaces represented by the MLE values. This approach will be addressed in future work.

A further source of variation is the underlying randomness of host demography and worm acquisition and death, as discussed in the following section on the formulation of a stochastic model. This is partially addressed by the negative binomial distribution of worm burdens, but the impact will be particularly important when addressing elimination effects. Under regular treatment, the infection state of individuals in the population will determine whether the disease is able to recover in the population or not. To

investigate the influence of demographic variability, we compare the behaviour of the deterministic model with a fully stochastic version.

3.6.1 Formulation of a stochastic model

Our stochastic model is an individual-based simulation operating at the level of individual worms within hosts and is closely based on the one developed by Anderson and Medley (1985). (Note that all the worms harboured by an individual host are identical yet their number is tracked within their hosts.) Table 6 lists the stochastic events involved and their associated rates. The events refer to an individual with index i, out of a population of H hosts, and age a_i with N_i worms in total, n_i of which are female. Each individual i has a predisposition to infection drawn from a gamma distribution with shape parameter k and mean 1.

$$\lambda_i \sim \Gamma(k, 1) \tag{16}$$

Treatment events are predetermined, occurring at times, t_j, where $j = 1 \ldots N_T$, where N_T is the number of treatments, but are still stochastic in their effect on a host and its worm burden. The dynamics of infectious material is governed by a deterministic formulation. Total rate of production of new infectious material, E_T, from the population is

$$E_T = \psi\lambda \sum_{i=1}^{H} n_i e^{-\gamma n_i} \mathbf{1}(N_i \neq n_i) \tag{17}$$

Table 6 Table of events for the stochastic model, giving the event type, its rate per individual and its effect on the state of the model

Event	Rate	Effect
Worm acquisition by host i, aged a	$\beta(a_i)\lambda_i L$	$N_i \to N_i + 1$; $n_i \to n_i + \mathrm{Ber}(0.5)$
Worm death in host i	σ/Worm	$N_i \to N_i - 1$; $n_i \to n_i - \mathrm{Ber}(0.5)$; $n_i \geq 0$
Host birth/death for host aged a	$\mu(a_i)$	Host age $a_i = 0$ $N_i = n_i = 0$
Treatment of host i, aged a	$\delta(t - t_j)g(a_i)$	Individual i is treated
Effect of treatment on worms in host, i	—	$n_i \to n_i' \sim B(n_i; 1 - h)$ $N_i \to n_i' + B(N_i - n_i'; 1 - h)$

Ber( ) represents a Bernoulli distributed random variable. The function $\delta(.)$ represents a delta function.

Here, **1**(.) is the index function evaluating to 0 or 1 depending on the argument, ensuring that infectious material is only generated by individuals with both male and female worms. The dynamics of the material in the reservoir is then described by

$$\frac{dL}{dt} = E_T - \mu_2 L \tag{18}$$

A degree of variability within the model is lost at this stage, since E_T is a sum of means and does not include the additional variability in egg output around the mean. However, for a host population of several hundred, it is assumed that the variability will be small in comparison to the mean.

The definition of elimination used for the deterministic model can be carried over in probabilistic terms to the stochastic model environment. In the deterministic case, if the numbers of rounds of treatment are less than the critical number, the probability of elimination is one. For rounds equal to or greater than the critical value, the parasite is eliminated and the probability is zero. In the latter case, there is a finite probability of elimination at any given number of treatment rounds. Fig. 17A shows the probability of elimination as a function of the number of rounds of annual treatment. The parameters used are the MLE values from fitting to the Pulicat data set (Table 3, column 4). Treatment coverage is 75% of SAC and pre-SAC with a drug efficacy of 99%, giving an effective coverage of just under 75%. In this scenario, the deterministic model achieves elimination after nine rounds. In the stochastic model, this corresponds to a probability of about 75% of elimination. To achieve a 95% probability of elimination, about 12 rounds are necessary. The relative ease of elimination between the deterministic and stochastic models can be understood by considering the variability in the infectious reservoir. In the deterministic model, if the amount of infectious material in the reservoir falls below the critical breakpoint value, elimination will occur and not otherwise. In the stochastic case, levels of infectious material vary around the deterministic mean. Hence, there is an additional mechanism by which the parasite population can cross the breakpoint and be eliminated. As a result, elimination within a stochastic paradigm is easier to achieve than within a deterministic description.

Fig. 17B shows a representative sample of 10 stochastic realizations as a time series. For populations that recover, the process takes approximately 10 years. The location of the breakpoint is clear at approximately one worm per individual on average. The large variation in recovery time

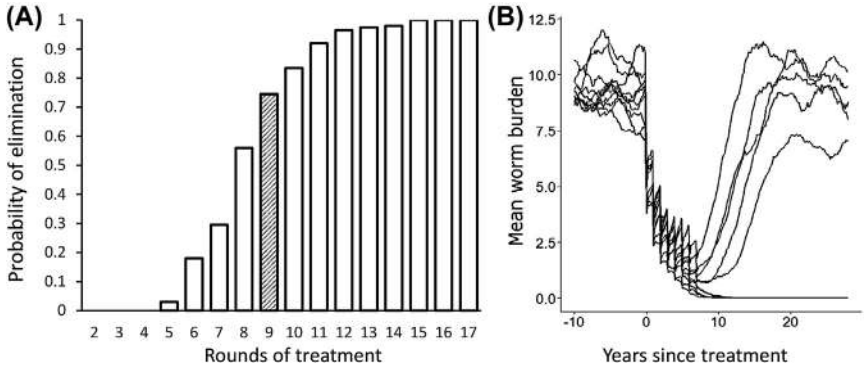

Figure 17 (A) Probability of elimination as a function of the number of annual rounds of treatment. Vertical *dashed shaded bar* indicates the minimum number of rounds to achieve elimination according to the equivalent deterministic model. (B) Time series showing total worm burden, averaged across the population, from a representative sample of stochastic runs used to calculate the probability of elimination for eight rounds of treatment delivered annually. Note that in some simulations elimination is not achieved.

reflects not only the randomness of worm establishment but also the variability in the proportion of the population in high infection exposure (a high force of infection) age categories.

A much fuller set of analyses based on the stochastic model will be given in a future publication, but a few key points are worth noting aside from the distribution of treatment rounds required to cross the transmission breakpoint. Figure 18 shows clearly the variation in worm load person by person and within an individual over time. We can also see the footprint of a changing rate of exposure to infection as an individual ages and moves from one age grouping to the next. It is also possible to observe from Fig. 18 the patchiness of treatment coverage due to the assumption of random selection of individuals at each round of treatment to meet a defined coverage level. Given enough repeat simulations, the mean worm burdens in each age group over time approach the deterministic predictions as is expected in models of this character where the existence of two stable equilibria and one unstable boundary is set deterministically by the biology of parasite reproduction. Future studies using the stochastic version of the age-structured deterministic model will examine other sources of variation including predisposition to infection, nonrandom compliance to treatment, immigration and emigration of people from communities and spatial structure in host population distribution and movement.

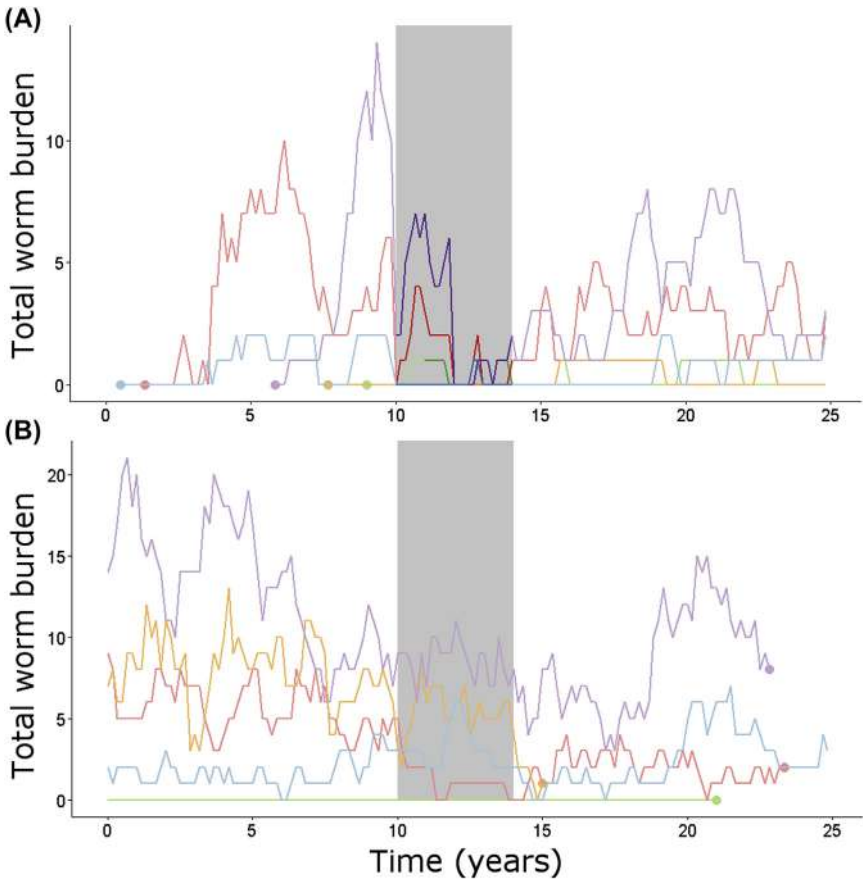

Figure 18 Five individual host worm burdens generated by a stochastic model during a 4-year annual treatment programme in which coverage is 75% for SAC and pre-SAC. (A) For five hosts eligible for treatment during the program and (B) five adults not eligible for treatment. *Large dots* represent birth (A) or death (B) of individuals in the community. The *grey* region indicates the time period during which treatment occurs, for comparison. *pre-SAC*, preschool-aged children; *SAC*, school-aged children.

3.7 Health economics

Mathematical models can be particularly useful tools for investigating the cost-effectiveness of interventions (a summary of the economic evaluations for soil-transmitted helminthiases using models is presented in Table 7 (Turner et al., 2015)). This is because models can be used to make projections over long time horizons and can, therefore, capture the long-term benefits of interventions — empirical approaches using primary data from the field (due to practical and time constraints) often have a limited time horizon

of a few years. Furthermore, models can be used to quantify the impact of different epidemiological and programmatic settings on the generalizability of the results. This is particularly important when investigating the cost-effectiveness of alternative interventions.

In a recent systematic review on this area (Turner et al., 2015), only two studies (Guyatt et al., 1993, 1995) were identified that investigated the cost-effectiveness of alternative STH treatment strategies using a dynamic model. This is important as dynamic transmission models couple the rate of infection and the population abundance of infection by explicitly modelling the transmission cycle of the disease (Turner et al., 2014b; Brennan et al., 2006; Kim and Goldie, 2008; Edmunds et al., 1999). Consequently, these models can capture the so-called 'herd effect' or indirect effects of interventions, whereby individuals can benefit from an intervention even if they are not directly targeted. Fig. 19 illustrates this concept by showing that a school-based MDA programme treating children for *Ascaris* can also have a notable indirect benefit for the adults (whose worm burden is also reduced over time due to the reductions in transmission — even though they are not treated) (Turner et al., 2014b; Medley et al., 1993). Accounting for these herd/indirect effects of interventions can be crucial to the validity of the conclusions drawn from cost-effectiveness evaluations of interventions against infectious diseases (Brennan et al., 2006; Kim and Goldie, 2008; Edmunds et al., 1999). A further advantage of dynamic models is that they can be used to evaluate the possibility of breaking transmission. This is important given the recent interest in breaking transmission for STHs (Bill & Melinda Gates Foundation, 2014; Brooker et al., 2015b) and that potentially, new but more expensive interventions may be cost-saving/cost-effective in the long term, only because they enable achieving elimination faster (Geoffard and Philipson, 1997; Turner et al., 2014a,b). Despite this, static models (such as decision trees) are more widely used for economic evaluations (Lugner et al., 2010; Sonnenberg and Beck, 1993; Briggs and Sculpher, 1998; Bala and Mauskopf, 2006) — though this does not just apply for NTDs (Turner et al., 2014b). In these models, individual hosts acquire infection at a rate (i.e., the force of infection) which is not linked to the abundance of infection in the population as a whole). Consequently, they often assume that an individual's probability of being exposed to an infection is unaffected by an intervention (Lugner et al., 2010). This is often unrealistic for infectious diseases, where an individual's probability of being exposed to an infection can change over the course of an intervention (as it is dependent on the amount of infection in the population).

Table 7 Summary of the identified cost-effectiveness studies

Study	Question	Target of intervention	Effects	Primary conclusions	Source of the costs
Chan (1997)	Cost-effectiveness of school-based *Ascaris* control (***dynamic model***).	*Ascaris*	• DALY	The analysis indicates that treating SAC is highly cost-effective; US$8 per DALY averted (for a high prevalence community).	Unpublished data
Guyatt et al. (1993)	Cost-effectiveness analysis of mass anthelmintic treatment: Effects of treatment frequency on *Ascaris* infection (***dynamic model***).	*Ascaris*	• Unit reductions in mean worm burden • Infection cases averted • Disease cases averted	If the aim of an intervention is to reduce *Ascaris*-related morbidity using mass treatment, then it is more cost-effective to intervene in higher transmission areas. Furthermore, relatively long intervals between treatments offer the most cost-effective strategy.	Unpublished data
Guyatt et al. (1995)	Options for the chemotherapeutic control of *Ascaris* (***dynamic model***).	*Ascaris*	• Infection cases averted • Disease cases averted	Child-targeted treatment can be more cost-effective than mass treatment in reducing the number of disease cases. The results also imply that (with the assumed circumstances) enhancing coverage is more cost-effective than increasing frequency of treatment.	Guyatt et al. (1993) – Which was based on unpublished data

Hall et al. (2009)	The cost-effectiveness of using different thresholds for determining the treatment frequency (***static distribution model***).	STH	• Cost per infected person treated • Cost per moderately/heavily infected person treated • Cost per diseased person treated	This analysis suggests that a new three-tier treatment for deciding initial treatment frequency (if the combined prevalence is above 40%, treat all children once a year; above 60% treat twice a year; and above 80% treat three times a year), would be more cost-effective than the current WHO recommended thresholds.	PCD (1998), PCD (1999), Brooker et al. (2008) and Fiedler and Chuko (2008)
Lee et al. (2011)	The potential cost-effectiveness of a hookworm vaccine (***static model***).	Hookworm	• DALY	A hookworm vaccine may provide not only cost savings but potential health benefits to both SAC and non-pregnant women of childbearing age. The most cost-effective strategy may be to combine vaccination with the current drug treatment.	Hotez et al. (2006), Guyatt (2003) and Brooker et al. (2006)

DALY, disability-adjusted life years; *SAC*, school-aged children; *STH*, soil-transmitted helminths.
Adapted from Turner, H.C., Truscott, J.E., Hollingsworth, T.D., Bettis, A.A., Brooker, S.J., Anderson, R.M., 2015. Cost and cost-effectiveness of soil-transmitted helminth treatment programmes: systematic review and research needs. Parasit. Vectors 8, 355.

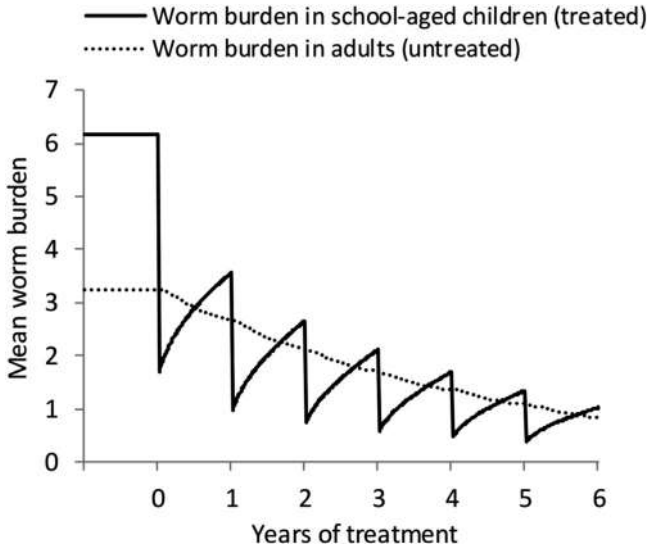

Figure 19 The model-projected indirect benefit of treating children (2–15 year olds) for *Ascaris lumbricoides* on the untreated adults (≥15 year olds). The results were obtained using a fully aged structured deterministic dynamic transmission model, described in more detail in Truscott et al. (2014b) and Anderson et al. (2014). Results assume a low transmission setting ($R_0 = 2$) and a high coverage (80%). *Figure adapted from Turner, H.C., Walker, M., French, M.D., Blake, I.M., Churcher, T.S., Basáñez, M.G., 2014b. Neglected tools for neglected diseases: mathematical models in economic evaluations. Trends Parasitol. 30, 562–570.*

Published studies examining the cost-effectiveness of alternative STH treatment strategies use a dynamic model focussing on *Ascaris* control and assume a mobile team distributed the drugs (the main delivery method at the time of the studies) (Guyatt et al., 1993, 1995). Consequently, the potential influence of the other STHs and the current school-/community-based delivery systems on the cost-effectiveness of different strategies has not been explored. This is particularly important for hookworm, which has a different age-profile of infection than *Ascaris* and *Trichuris*, with the adults usually having a larger proportion of the overall worm burden (Fig. 2). Consequently, ignoring this feature will significantly underestimate the cost-effectiveness of expanding MDA programmes to the whole community. Furthermore, the current treatments for STH have a much lower efficacy against *Trichuris* (Table 2). Models can be used to investigating the potential cost-effectiveness of alternative treatment regimens.

3.8 Cost data

Currently, the overwhelming majority of STH treatment cost data pertains to programmes targeting SAC once a year (Turner et al., 2015) (despite the current goals focussing on scaling up treatment for both pre-SAC and SAC). The absence of cost data for other age-groups (pre-SAC and adults) is a major barrier for further research regarding how best to optimize STH control, and there is an urgent need for further studies to investigate the costs for targeting different combinations of age groups at different treatment frequencies (Turner et al., 2015; Lee et al., 2015) It will be important, that these studies consider possible economies of scale (and scope), particularly when comparing the costs of different strategies and between different studies/settings (Mansley et al., 2002; Turner et al., 2015). Such economies of scale have been found to have significant implications when investigating the cost-effectiveness of STH control (Turner et al., 2016a; Brooker et al., 2008).

3.9 Effectiveness metrics

Due to the difficulties in developing statistical models that link the different clinical disease measures of the impact of STH infection to their population dynamics, most of the published modelling studies use infection-based effectiveness metrics (Table 7) (Turner et al., 2015). These studies defined disease as having a modelled worm burden above age and STH species-specific thresholds (Chan et al., 1994b; Medley et al., 1993; Turner et al., 2016a; Guyatt et al., 1993, 1995). It should be acknowledged that these intensity thresholds are uncertain and would be influenced by several host-specific factors such as nutritional status (Mascarini-Serra, 2011), history of infection, and for anaemia the initial iron balance (Gilles et al., 1964). Furthermore, the thresholds for hookworm were informed by a study in which *N. americanus* was the predominant species (Lwambo et al., 1992). Consequently, they may not be accurate for *An. duodenale* (which is associated with higher rates of blood loss) (Lwambo et al., 1992). Only two modelling studies (Lee et al., 2011; Chan, 1997) were found that used DALYs as the effectiveness measure. Though it should be acknowledged that the methodology and key assumptions surrounding DALY calculations are often unclear, and surrounded by notable uncertainty (GiveWell, 2010, 2011).

3.10 Interventions to add to community-based drug treatment

Models show that elimination by MDA alone is not possible in some settings. It is, therefore, necessary to consider other complementary control

interventions such as WASH (Pullan et al., 2014a) and improvements and health education. In addition in the future, there may be the possibility of a vaccine (perhaps partially efficacious). Models can be useful tools in informing how such interventions could impact transmission with and without MDA.

Mathematical models can also be useful in investigating potential alternative treatment regimens against *T. trichiura* (such as ivermectin coadministration (Turner et al., 2016b) triple dosing with standalone with the current monotherapy's, papaya cysteine proteinases (Levecke et al., 2014), oxantel pamoate-albendazole (Keiser et al., 2014; Speich et al., 2015) and pyrantel-oxantel (Albonico et al., 2002)). Previous analysis indicates it would be highly advantageous for pre-SAC to be eligible for any treatment combination against *T. trichiura* — particularly if policy goals for MDA shift to trying to break transmission (Turner et al., 2016b; Anderson et al., 2015).

4. CONCLUSIONS

Current demands from control implementers for the development of mathematical models of STH control by MDA centre on providing predictions to guide policy formulation on who to treat, how often to treat and for how long, in various transmission settings. The focus has recently shifted from the need for broad qualitative predictions on what age groups to treat (treating SAC will rarely interrupt transmission, except in low exposure settings, and never for hookworm with significant burdens in adults), to a number of more specific questions.

The first is that of model validation via field epidemiological studies to test prediction against observed outcomes. The conceptual challenge is obvious and important but the practice is more challenging. If models predict how many to treat, in which age classes and for how long, longitudinal epidemiological studies must be conducted with a variety of arms representing, for example, treating SAC only, treating pre-SAC and SAC, and treating the whole community, in three different transmission settings (low, medium and high). On top of this, randomization between and within arms must take place to manage heterogeneities such as social, cultural or environmental differences between different villages in the trial. Furthermore, given current predictions, such studies will have to be conducted over a 5- to 10-year horizons under high coverage levels to test if transmission is interrupted. One such trial has started in early 2015 in villages in a coastal region south of

Mombasa in Kenya. The trial is called TUMIKIA (Interrupting transmission of soil-transmitted helminths: a study protocol for cluster-randomized trials evaluating alternative treatment strategies and delivery systems in Kenya) and is in its early stages to test SAC treatment versus whole community treatment. An initial baseline survey of 20,104 individuals (of all ages) has been completed and involves 110 field officers and 40 laboratory technicians. The study will run over a 5-year period on a similar scale with components of the epidemiological study focussing on epidemiological parameter estimation, gathering cost data and recording compliance (Brooker et al., 2015a).

Published modelling work has thus far largely ignored the impact of uncertainty in model behaviour. There are two main sources; stochastic uncertainty which arises from the fundamentally random processes of worm acquisition, death and host demographic processes, and uncertainty in the parameter values that underpin the models. As is shown in the stochastic model section, the probabilistic nature of the results of stochastic simulations leads to a different interpretation of results, with firm boundaries for types of behaviour replaced with probability distributions and risks for given outcomes. These distributions could be expanded to include parameter uncertainty by drawing parameters values for individual stochastic runs from the appropriate posterior distributions arising from Bayesian parameter estimation.

Certain features are not dealt with in detail by the models described in this chapter. While seasonality of the environmental phase of STH species is sensitive to seasonal changes in temperature and humidity, we have not discussed seasonal movements of the hosts. Many communities experience seasonal patterns of migration to find work. These movements can be the source of parasite transmission over long distances and also lead to biases in disease monitoring, due to parts of the population being excluded from monitoring.

The details of the person-to-person transmission network are not included, as they are not currently known. An understanding of these processes would probably also lead to an understanding of the characteristic aggregation of parasites within hosts. Genetic data from studies of individuals within a community (Criscione et al., 2010) could possibly be used to develop an understanding of transmission dynamics in a similar fashion to the use of phylogenetic trees to understand outbreak dynamics for microparasites (e.g., Colijn and Gardy, 2014).

Insights from modelling also need to play a part in the design of monitoring and evaluation programmes. It is common in school-based deworming studies for follow-up monitoring to be confined to the age groups that

have been treated, largely to assess the direct impact of treatment. However, as is clear from modelling or just from looking at the infection age profiles for different species, these data do not give a clear impression of the infection status of the community as a whole. To gauge the optimal distribution of treatment in the population, particularly as elimination becomes a possible target, better quality and more comprehensive data are needed.

A further key issue is the currently poor understanding of the relationship between individual worm burden and the outcome of diagnostic tests. Egg counting and PCR methods are indirect and hence require additional models that will connect the transmission model (in terms of worms) to the observed data. Measures of prevalence using Kato-Katz are known to have often poor sensitivities that depend on the species being detected and its prevalence. PCR techniques appear to have much higher sensitivities, although these have not been characterized yet. Robust probabilistic models are needed to describe the relationship between 'true' prevalence and that measured by PCR and Kato-Katz that will function at the low prevalences that will be encountered as elimination is approached (see Medley et al., 2016; this volume). Infection intensity data from egg count and qPCR has the possibility of providing a better picture of the underlying force of infection which governs the elimination process. Data connecting qPCR and epg is now becoming available, and models of epg output as a function of worm burden exist but are insufficiently developed at present. The high degree of biological variability in egg output among worms and the range of parameter values across studies mean that it is unclear what the inferential value of intensity data will be. There is a lot of work to be done developing and testing probabilistic models for diagnostic tests and then evaluating which should be used and how to optimize the power of the study. A further dimension to consider is how these decisions would be affected by economic constraints.

The understanding that comes from epidemiological models needs to be extended by grafting on a layer of heath economics. Cost functions can be added to encompass the costs of treating under different strategies (such as age targeted vs mass preventive chemotherapy) while accounting of economies of scale (Turner et al., 2016a). Models are being developed as described in this paper, but the limiting factor is good cost data for the different potential strategies.

The final area is that of the impact on community-wide MDA on the likelihood of the emergence of drug-resistant strains of the parasites and their spread in the human population. Little is known about the genetic

determinants of resistance although in the veterinary field it is known that wide scale use of anthelmintics can induce resistance in nematode parasites (McManus et al., 2014). Some work has been done to use models to assess the implications of spread and how best to slow the spread of resistant genes (Churcher and Basáñez, 2008), but much remains to be done in the STH field. One impediment to progress at present is the absence of data on the parasite genes that are important and the identification of markers (but see Diawara et al., 2013). There is no great difficult in grafting on population genetic terms for a diploid organism on to the population dynamic framework (Anderson and May, 1992), but in the absence of both biological and epidemiological data, model predictions cannot be tested. One argument against community-wide treatment is that unlike SAC-targeted treatment it leaves no reservoir of parasites not exposed to the drug. So far, however, the experience in LF community-based treatment programmes is encouraging. As far as can be assessed these programmes have not induced the rapid rise of resistant parasite variants. The need is for careful monitoring of drug efficacy as the scale of treatment coverage rises.

All these questions are now a focus of modelling efforts and the coming year should see new insights and new models created by current research funded under the Gates Foundation NTD Modelling Consortium. The most important immediate task is the one of validation, namely testing model predictions in various field settings with different treatment strategies. Longitudinal community-based studies, if well designed, will be able to determine what else must be addressed in model formulation to take account of the many heterogeneities present in communities within given country settings. They will also help to improve parameter estimates of the key variables, determine what needs to be better measured to help policy formulation (e.g., cost and compliance data) evaluate what are the costs of different control options and how best to monitor and evaluate the impact of current control efforts based on MDA.

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