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A comparison of two mathematical models of the impact of mass drug administration on the transmission and control of schistosomiasis

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ABSTRACT

The predictions of two mathematical models describing the transmission dynamics of schistosome infection and the impact of mass drug administration are compared. The models differ in their description of the dynamics of the parasites within the host population and in their representation of the stages of the parasite lifecycle outside of the host. Key parameters are estimated from data collected in northern Mozambique from 2011 to 2015. This type of data set is valuable for model validation as treatment prior to the study was minimal. Predictions from both models are compared with each other and with epidemiological observations. Both models have difficulty matching both the intensity and prevalence of disease in the datasets and are only partially successful at predicting the impact of treatment. The models also differ from each other in their predictions, both quantitatively and qualitatively, of the long-term impact of 10 years' school-based mass drug administration. We trace the dynamical differences back to basic assumptions about worm aggregation, force of infection and the dynamics of the parasite in the snail population in the two models and suggest data which could discriminate between them. We also discuss limitations with the datasets used and ways in which data collection could be improved.

1. Introduction

Mathematical and computational tools are essential for synthesizing information to understand epidemiological patterns, and for developing and weighing the evidence base for decision-making in public health policy. The field of mathematical model development for the study of infectious disease epidemiology and control has been recently reviewed by Heesterbeek and colleagues (Heesterbeek et al., 2015). They document many examples where models have been influential in the formulation of public health policy, especially for directly transmitted viruses such as influenza A.

In recent years, efforts have been made to compare the behaviour of independently developed models, parameterized with standardized data, in order to understand the sometimes substantial differences between their predictions. A prime example is the HIV modelling consortium, which has had considerable success in understanding the key features of HIV transmission and identifying important biases in existing models (Eaton et al., 2015). More formal, Bayesian methods are also being employed to create weighted model ensembles which can generate more robust predictions of epidemic progress (Lindström et al., 2015; Webb et al., 2017). The Bill and Melinda Gates Foundation (BMGF) recently funded a consortium of research groups to develop mathematical models of the transmission dynamics and impact of control measures of certain neglected tropical diseases (NTDs) (http://www.ntdmodelling.org). Two groups were funded to address each of the chosen infectious diseases to allow comparisons of the predictions of different mathematical models relating to how various control measures impact the prevalence and intensity of infection in defined settings (Anderson et al., 2015; Gurarie et al., 2015; Hollingsworth et al., 2015).

Studies of the transmission dynamics of the *Schistosoma* infections have a long history, dating back to the pioneering work of

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George Macdonald. His models were the first to use differential equations with mating probabilities to represent the dioecious nature of these parasites and the fact that they cannot leave the host in the adult worm state to find a mate (Macdonald, 1965). This is critical, as both female and male worms must be present in the same host to create viable eggs to continue the parasite life cycle. Prior to Macdonald's studies, Nelson Hairston had employed life table analyses from population ecology in an attempt to quantify reproduction and mortality throughout the two-host life cycle of these digenean parasites (Hairston, 1962, 1965). More recent work in this field has been reviewed by Anderson and colleagues (Anderson et al., 2016).

The present paper considers two mathematical models to describe the transmission dynamics and control of the schistosome parasites. One model is deterministic in structure, dividing the host population into classes harbouring different burdens of parasites (as originally described by Kostitzin, 1934) and includes greater detail on the parasite life cycle, including the dynamics of the intermediate snail host (Gurarie et al., 2015). The second model considers the dynamics of the adult worm in the human host, with a hybrid structure representing the probability distribution of parasites per host and the associated mating function (for a negative binomial distribution with fixed value k and monogamous mating) (Anderson et al., 2015). These two models have some similarities, however, there are significant differences in the structure and methods employed in parameter estimation. These differences are described in brief in the Methods section.

Model validation is based on a data set from a study of targeted mass-drug administration (MDA; targeted by age group) strategies performed in northern Mozambique from 2011 to 2015. This data set is particularly valuable for model validation as it was carried out in a population that had not previously been heavily treated. Formal quantitative comparisons are made on the impact of a defined MDA programme on infection prevalence and intensity over time.

2. Methods

2.1. Imperial college London (ICL) model

The model developed by the ICL team has an age structured deterministic partial differential framework with probability elements for the description of parasite natural history and transmission (Anderson et al., 2015). Partial differential equations representing changes over time and age are employed to describe the evolution of the mean worm burden (MWB) in an age-structured population and the dynamics of a single shared environmental reservoir of infection from the cercarial stage released by the snail intermediate host (See Supplementary Information 1). It assumes that the parasite is dioecious and monogamous, has density-dependent egg production and a degree of parasite aggregation across hosts defined by the negative binomial (NB) probability distribution with a fixed k value. A stochastic individual based analogue of this model has recently been described where the parasite distribution within the human host population is dynamic over time and age group, but the mean predictions of replicated runs of the stochastic model well match the deterministic predictions described in this paper (Farrell et al., 2017). In the model, it is assumed that the age-intensity profiles are generated by age-dependent exposure to the aquatic cercarial stages in the environment and not through acquired immunity. Though the model has a continuous age structure, the outputs can be grouped into programmatically meaningful categories (such as school-aged children; SAC 5–14 years of age and adults $\geq$15 years of age) which form the basis of the individuals to be targeted in a treatment programme.

2.2. Case western reserve university (CWRU) model

The CWRU model employs a stratified worm burden (SWB) approach based on the model originally developed by Kostitzin (1934) for age-structured host communities (Gurarie et al., 2010). In this approach, each community and population group is subdivided into worm burden strata with transitions among strata determined by the rate of worm accumulation, i.e. human force of infection (FOI, λ), and worm mortality (natural or drug-induced). The system accommodates essential features of in-host biology: worm mating, density-dependent reduction in fecundity, and irregular (over-dispersed) egg release from tissue into human urine or stool. The worm distribution within hosts is not constrained by any prescribed function, and the resulting patterns are typically Poisson-like. To account for overdispersed test results it is assumed that the egg output by fertilized female worms and individual hosts in the CWRU model follows a negative binomial distribution with small aggregation parameter k (see Gurarie et al., 2016; Hubbard et al., 2002).

Each demographic group has a specific set of parameters (FOI λ, maximal fecundity, density-dependent loss in fecundity and aggregation k). The model predicts egg release by individual hosts, their worm burden strata and aggregate host communities as functions of age-dependent FOIs and in-host (biological) parameters. The egg-release function serves a double role. It allows simulation of the outcome of a typical diagnostic test for sampled groups and communities, as is used in model calibration. It also gives estimates of the force of snail infection, and thereby gives transmission coefficients ("human-to-snail" and "snail-to-human") in coupled human-snail systems. The snail model utilizes a logistic model of population growth and SEI infection with susceptible [S], prepatent [exposed; E] and patent [infected; I] compartments, with known or calibrated local environmental carrying capacity, snail growth, death and proliferation, and estimated patency for transmission. An important novel feature of snail system is nonlinear(saturated) FOI as functions of human infectivity. The complete human-snail model is a deterministic system of differential equations, with the host population stratified according to age and burden, with a corresponding 3-compartment snail component.

For the modelled Mozambique communities, the demographic categorization consisted of 3 age groups: Pre-SAC 0–5 years of age, SAC 5–14 years of age, and adults >15 years of age, where each group was represented by its own SWB with age-specific parameters. A complete set of human-snail population/infection data across all demographics could allow for detailed local calibration based on algebraic relations between state variables and model parameters (for example, see Gurarie et al., 2010, 2016). In the case of incomplete data sets, one has to fill in missing demographic/snail inputs by comparison with other, better sampled communities. In the present analysis, the CWRU model employed such methodology for Mozambique communities using some biological parameters previously calibrated from data from another *S. haematobium* control study in Kenya (the Msambweni study, Gurarie et al., 2015). This aspect of the model is described in full in Supplementary Information 2.

2.3. Key model differences

Model development was conducted separately and based on the details of the *S. haematobium* life cycle and known population processes (Anderson and May, 1991). A summary of differences between the models is outlined in Table 1. Some parameter values were derived from the published literature, such as the adult worm life expectancy and the density-dependent relationship between worm burden and egg output, whilst others were derived through parameter estimation based on observed epidemiological pattern