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Measuring and modelling the effects of systematic non-adherence to mass drug administration

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ABSTRACT

It is well understood that the success or failure of a mass drug administration campaign critically depends on the level of coverage achieved. To that end coverage levels are often closely scrutinised during campaigns and the response to underperforming campaigns is to attempt to improve coverage. Modelling work has indicated, however, that the quality of the coverage achieved may also have a significant impact on the outcome. If the coverage achieved is likely to miss similar people every round then this can have a serious detrimental effect on the campaign outcome. We begin by reviewing the current modelling descriptions of this effect and introduce a new modelling framework that can be used to simulate a given level of systematic non-adherence. We formalise the likelihood that people may miss several rounds of treatment using the correlation in the attendance of different rounds. Using two very simplified models of the infection of helminths and non-helminths, respectively, we demonstrate that the modelling description used and the correlation included between treatment rounds can have a profound effect on the time to elimination of disease in a population. It is therefore clear that more detailed coverage data is required to accurately predict the time to disease elimination. We review published coverage data in which individuals are asked how many previous rounds they have attended, and show how this information may be used to assess the level of systematic non-adherence. We note that while the coverages in the data found range from 40.5% to 95.5%, still the correlations found lie in a fairly narrow range (between 0.2806 and 0.5351). This indicates that the level of systematic non-adherence may be similar even in data from different years, countries, diseases and administered drugs.

1. Background

Mass drug administration (MDA) is the cornerstone of a number of control programs, particularly helminth control and trachoma programs, and also forms a part of the suite of interventions for diseases such as malaria and yaws (World Health Organization, 2013). These programs are based on the use of drugs with a good safety profile which can be distributed without close clinical supervision, and are usually prioritised because they are much more cost-effective than screening and treating only infected individuals due to the logistic costs involved (Brooker et al., 2008; Holland et al., 1996). For neglected tropical diseases (NTDs), billions of individuals have been treated in MDA programs. In some of these programmes key disease control goals have been met so that MDA could be stopped (e.g. MDA programmes for lymphatic filariasis in Egypt, Yemen, Sri Lanka, etc. World Health Organization, 2015). However, other programs are not achieving the expected goals, and so we are facing the question of why these "failures" are occurring and how better to measure the effectiveness of control programs.

Mathematical modelling plays an important role in the design of MDA programs—who to treat, when to treat (Anderson et al., 2012, 2015; Coffeng et al., 2014, 2015; Gambhir and Pinsent, 2015; Gurarie et al., 2015; Irvine et al., 2015; Jambulingam et al., 2016; Liu et al., 2015; Singh and Michael, 2015; Stolk et al., 2015; Truscott et al., 2015; Winnen et al., 2002)—and in setting the 'expected' prevalence after a certain number of rounds, particularly for onchocerciasis (Tekle et al., 2016). Modelling studies have highlighted the importance of coverage (the proportion of the target population who are treated), with high coverage leading to

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more rapid declines in prevalence and sustained high coverage leading to the possibility of elimination (Okell et al., 2011; Slater et al., 2014). Empirical studies (Krentel et al., 2013; Brieger et al., 2012; King et al., 2011; Boyd et al., 2010) have highlighted that some individuals do not receive treatment not through chance, but through a systematic lack of access to the treatments (such as workers who are away during the daytime treatments, Rock et al., 2015; Mpanya et al., 2012) or lack of acceptance of the treatment. These studies, among others, investigate how treatment campaigns and interventions are affected by the cultural and socio-economic contexts in which they occur (Krentel et al., 2016; Parker and Allen, 2013a, 2013b; Roy et al., 2013; Shuford et al., 2016). In addition, many investigations into treatment campaign coverage highlight the unreliability of reported coverage data, further complicating modelling efforts (Brieger et al., 2011; Cromwell et al., 2009).

Early modelling work for lymphatic filariasis highlighted how these types of systematic non-adherence to a program can undermine the success of that program and, depending on the size of the untreated group, act as an important reservoir for infection, leading to onward transmission to the rest of the population (Plaisier et al., 2000). The decision to proceed with post treatment surveillance may be based on the reported coverage levels combined with modelling predictions (for example in lymphatic filariasis, where achieving around 7 years of high coverage is seen as a trigger to begin transmission assessment surveys). It is important to measure and understand these effects to prevent the danger of stopping too soon or continuing costly interventions after they are no longer needed. If untreated individuals are geographically clustered, then this type of non-adherence, or lack of access, can lead to hotspots of ongoing transmission. A more recent study applied the method by Plaisier et al. (2000) (which was previously used in a deterministic setting) to study the effect of different models of systematic non-adherence in an individual-based model of helminth infections (Farrell et al., 2017).

Different modelling groups have approached modelling systematic non-adherence (which we shall use as a catch-all term for the situation when some parts of the population repeatedly do not receive treatments) in different ways, but these different methods have never been explicitly compared with respect to the resulting simulated coverage patterns or the resulting predicted trends in infection. Here we aim to formalise a new model for this behaviour which is flexible enough to capture the different methodologies and allow more direct comparison with empirical data. We investigate the impact of different assumptions for systematic non-adherence using a simple susceptible-infected-susceptible (SIS) model and a helminth model. We use examples from the small number of published empirical studies which measure these phenomena to evaluate the size of the effect, and discuss the value of further surveys to inform future modelling work. We note that our work is an attempt to capture effects that may be general across multiple different diseases and to apply this to any particular disease or country would require more in-depth study of the specific situation.

2. Overview

We will begin by reviewing how various models include systematic non-adherence and introducing a new way of modelling treatment that allows the user to specify the level of systematic non-adherence in addition to the coverage (Section 3). Then we will consider the consequences of systematic non-adherence in MDA campaigns by implementing the various schemes into a (very simplified) model of SIS dynamics and one for helminth infections, demonstrating that the level of systematic non-adherence has a significant impact on the outcome of interventions (Section 4). Finally, we will consider what data is required (and how to analyse it) to assess the level of systematic non-adherence and will show that for the limited data in the literature the correlation between rounds of treatment lies in a narrow range of values (Section 5).

3. Modelling descriptions of systematic non-adherence

Many modelling descriptions of systematic non-adherence have been used in a variety of models of different diseases. Here we review and compare the different schemes and propose a new method.

3.1. List of schemes

1. Random – each round a randomly selected group of individuals are treated. (1 parameter – coverage)
2. Population partitioning:
   (a) Fully systematic – two groups that are treated: every round; or never treated (1 parameter – coverage)
   (b) Deterministic approximation to a semi-systematic scheme (number of parameters depends on the scheme)
3. Semi-systematic – each individual has a probability p_i (the same for every round) of being treated in each round. (1 parameter – coverage)
4. Variable correlation scheme – treated individuals are distributed with a given expectation while correlation is controlled by a given parameter. (2 parameters – coverage and correlation)
   (a) Scheme by Griffin et al. (2010) and Irvine et al. (2015)
   (b) Controlled correlation scheme introduced in this paper

We discuss each scheme in detail below.

3.1.1. Random

The majority of modelling predictions for the outcome of mass drug administration campaigns assume random coverage (Truscott et al., 2015; Gambhir and Pinsent, 2015; Liu et al., 2015; Blok et al., 2015; Pandey et al., 2015; Singh and Michael, 2015; Gurarie et al., 2015; Anderson et al., 2015). In this scheme, each individual in each round has the same probability, c, of receiving treatment, where c is the coverage achieved by the campaign. If the campaign continues running for enough rounds then eventually all individuals will have received at least one treatment. Since each individual has the same probability of being treated in each round, the proportion of the population that is never treated drops off very quickly as the number of rounds increases. To ensure a probability of at most T that a randomly selected individual has never received treatment, at a given coverage c, requires greater than $\log(T)/\log(1-c)$ rounds of MDA. The distribution of number of rounds attended in the population after 10 rounds at 70% coverage is shown in Fig. 2(a), demonstrating that the proportion of the population that have never attended a round is very small. The distribution is clustered around 7 rounds attended, since this would be the mean number of rounds attended after 10 rounds at 70% coverage under this scheme.

3.1.2. Population partitioning

A simple way of incorporating systematic non-adherence into any model (deterministic or individual-based) is to partition the population into subpopulations that receive different treatment regimes.

The most extreme version is a fully systematic scheme, where every individual either attends every round, or never attends any rounds. This scheme only requires knowledge of the coverage, which gives the proportion of the population that attends every round. This scheme is most useful as a 'worst case scenario'. This scheme is implemented as one of multiple schemes in a model for lymphatic filariasis (LYMFASIM: Stolk et al., 2008,