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Probabilistic forecasts of trachoma transmission at the district level: A statistical model comparison

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ABSTRACT

The World Health Organization and its partners are aiming to eliminate trachoma as a public health problem by 2020. In this study, we compare forecasts of TF prevalence in 2011 for 7 different statistical and mechanistic models across 9 de-identified trachoma endemic districts, representing 4 unique trachoma endemic countries. We forecast TF prevalence between 1–6 years ahead in time and compare the 7 different models to the observed 2011 data using a log-likelihood score. An SIS model, including a district-specific random effect for the district-specific transmission coefficient, had the highest log-likelihood score across all 9 districts and was therefore the best performing model. While overall the deterministic transmission model was the least well performing model, although it did comparably well to the other models for 8 of 9 districts. We perform a statistically rigorous comparison of the forecasting ability of a range of mathematical and statistical models across multiple endemic districts between 1 and 6 years ahead of the last collected TF prevalence data point in 2011, assessing results against surveillance data. This study is a step towards making statements about likelihood and time to elimination with regard to the WHO GET2020 goals.

1. Introduction

Trachoma remains the world's leading infectious cause of blindness (Anon, 2012; Mariotti et al., 2009), and it is currently estimated that 200 million individuals are living at risk of blindness from trachoma (World Health Organization, 2016). WHO and its partners are aiming to eliminate trachoma as a public health concern by 2020. To help achieve this, WHO endorses the SAFE strategy. This four pronged approach includes: Surgery for trichiasis, Antibiotics, particularly mass treatment with azithromycin of all residents of endemic districts, Facial cleanliness, and Environmental improvement (Taylor et al., 2012).

Elimination of trachoma as a public health problem has a definition with two component goals. The first is to reduce the prevalence of trachomatous inflammation- follicular (TF) in children 1–9 years old to <5% at the district level by 2020. The second is to reduce the prevalence of trachomatous trichiasis cases to <1/1000 at the district level. In this article we focus on the achievement of the first goal outlined.

Mathematical and statistical modelling continues to be used for a wide range of infectious diseases, including trachoma (Gebre et al., 2012; Lietman et al., 2011; Liu et al., 2013; Gambhir et al., 2009; Blake et al., 2009; Pinsent et al., 2016a). Studies are conducted to help understand and quantify epidemiological outcomes following clinical trials, and to assess the impact of different treatment interventions. In trachoma, detailed randomised control trial (RCT) data have been analysed and modelled with statistical and dynamic models (Lietman et al., 2011; Liu et al., 2013; Liu et al., 2015a; Lietman et al., 1999; Liu et al., 2015b) to assess and predict the outcomes of given interventions. Such models can also be used to estimate the resource requirements to achieve certain goals, such as elimination or the achievement of specific disease

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prevalence/incidence thresholds (Hollingsworth et al., 2015; Stolk et al., 2015a; Wouters et al., 2014; Stolk et al., 2015b; Turner et al., 2016). While producing highly informative and accurate forecasts for an infectious disease is challenging, it is desirable from a public health perspective. This is because they enable high priority regions to be identified and help to develop an understanding of the resources required in different areas in order to achieve the proposed targets.

Mathematical and statistical models are used to make predictions about the future prevalence and incidence of infectious diseases. However, predictions from individual models are not commonly tested robustly against other potential forecasts, nor are they regularly validated against independent data. Nevertheless, robust statistical model comparison of outcomes from different models is essential, in order to understand the limitations and strengths of different mathematical and statistical modelling approaches. Most commonly in trachoma, the Susceptible, Infected, Susceptible (SIS) model structure has been used (Lietman et al., 2011; Liu et al., 2013; Gambhir et al., 2009; Liu et al., 2015a; Lietman et al., 1999; Liu et al., 2015b; Ray et al., 2007; Ray et al., 2009), though variants of this structure have also been proposed (Pinsent et al., 2016a; Liu et al., 2015b; Shattock et al., 2015). Liu et al. (Liu et al., 2015a) conducted a statistical model comparison assessing a variety of statistical and mechanistic models. Fitting each model to PCR data, the authors found that statistical regression models and SIS mechanistic models performed significantly better than expert opinion. This suggests that the use of mathematical and statistical modelling may be useful in projecting trachoma prevalence (Liu et al., 2015a).

In this study we compare the probabilistic forecasts of TF prevalence generated by statistical (without trachoma-specific assumptions), mechanistic (SIS and partially acquired immunity) and mixed (SIS plus a random effect) models to TF prevalence estimates determined empirically in field based surveys, for 9 de-identified trachoma endemic districts. Probabilistic prevalence forecasts are scored as the log-likelihood of the observed 2011 data for each district given the model, allowing us to ascertain the strengths and weaknesses of different modelling approaches to make forecasts of TF prevalence.

2. Methods

2.1. Data

We used de-identified district level TF prevalence data collected and shared by the International Trachoma Initiative (ITI). These data contained district level TF prevalence at 1 or more time points, collected between the years 1995–2010. Data after 2010 were available; however, all forecasters were masked to it. Within this dataset, information regarding the number of rounds of MDA provided and the years in which they were administered were also provided for each district. Three of the 4 models we evaluated used country-level parameters or random effects. These parameters were estimated from the ITI data collected between 2001 and 2010. These were data from 43 countries which included 1037 unique districts, of which: 953 had a single survey, 82 had 2 surveys, 1 had 3 surveys, and 1 had 4 surveys.

To estimate the district-level random effects for the SIS and statistical regression models all district-level data in the ITI database collected between 1995 and 2010 was used. This included data on 1107 unique districts, of which: 918 had a single survey, 171 had 2 surveys, 17 had 3 surveys, and 1 had 4 surveys; 189 unique districts with at least 2 surveys were used to estimate the district-level random effects.

The district-level transmission coefficients for the deterministic transmission model used a total of 9 districts for which TF prevalence data were present for at least two time points between 1995 and 2010, and for which a TF prevalence data point was also available for 2011. As the data were de-identified by country and district it was not possible to know the population size of the district at each sampling time point. For each of the 9 districts we then forecast the distribution of TF prevalence in 2011. Trends in prevalence over time for each district are presented in Fig. 1, where each line represents a separate district. Across 8/9 districts we observed a gradual decline in TF prevalence following initiation of antibiotic treatment. We note, that for all districts follow-up was infrequent and hence we have used a much smaller subset of the data to fit the models. Data on TF prevalence and years they are reported for is presented in Table 1.

2.2. Mathematical models

2.2.1. Model 1: deterministic transmission model

The first type of model evaluated was an age-structured deterministic ordinary differential equation (ODE) transmission model. We used a model structure that has been statistically chosen (Pinsent and Gambhir, 2017) as the most appropriate and parsimonious when fitting to cross-sectional PCR and TF prevalence data (West et al., 2005). We consider individuals as susceptible to infection (S), exposed and incubating (E), infected and infectious with detectable TF (AI) and those who remain diseased but no longer infectious to others (D), individuals in the D state are susceptible to re-infection with a reduced probability. Those who were re-infected then returned to the AI state. We hereafter refer to this model as Model 1. A schematic diagram of this model structure is presented in Fig. S1.

The model followed a previously-detailed 'ladder of infection' structure (Gambhir et al., 2009; Pinsent et al., 2016a; Pinsent et al., 2016c), which accounted for the development of immunity to infection through successive infections (immunity here was represented as a reduction in an individual's infectivity and a faster rate of recovery from infection and disease with each successive infection). We assumed that both the infectivity and that the duration of infection and disease decreased exponentially with each successive infection. Further detail on the model structure and parameters used are provided in the supplementary information and Table S1.

For each of the 9 districts we performed a Markov Chain Monte Carlo (MCMC) search of the 2D parameter space to estimate and explore the uncertainty in both estimated parameters (MDA coverage and β). We then sampled 100 pairs of values from the posterior distribution to explore the inherent uncertainty in the 2011 forecast generated. Additionally, we also took 100 sets of samples from the posterior distributions when our model was fitted to cross-sectional PCR and TF data (West et al., 2005) which estimated the minimum rate of recovery from an individual's first infection and disease episode. Forecasts of the 2011 prevalence were thus generated incorporating uncertainty in the minimum rate of recovery from infection and disease as well as variation in the estimated value of β and coverage. This was done to ensure that we explored the uncertainty in the natural history parameters and how these uncertainties may impact the 2011 forecast. All calculations were performed in the R 3.2.1 (R Core Team, 2015), the package deSolve was used to solve the differential equation model (Soetaert et al., 2010).

2.2.2. Model 2: mixed mechanistic and statistical model

We also assessed a mixed-effect SIS model, of which there were three different types, hereafter referred to as Models 2.1, 2.2 and 2.3 respectively. 2.1) a model with country-district-level random effect given all-district data, 2.2) a model with country-district-