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Forecasting the new case detection rate of leprosy in four states of Brazil: A comparison of modelling approaches

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ABSTRACT

Background: Brazil has the second highest annual number of new leprosy cases. The aim of this study is to formally compare predictions of future new case detection rate (NCDR) trends and the annual probability of NCDR falling below 10/100,000 of four different modelling approaches in four states of Brazil: Rio Grande do Norte, Amazonas, Ceará, Tocantins.

Methods: A linear mixed model, a back-calculation approach, a deterministic compartmental model and an individual-based model were used. All models were fitted to leprosy data obtained from the Brazilian national database (SINAN). First, models were fitted to the data up to 2011, and predictions were made for NCDR for 2012–2014. Second, data up to 2014 were considered and forecasts of NCDR were generated for each year from 2015 to 2040. The resulting distributions of NCDR and the probability of NCDR being below 10/100,000 of the population for each year were then compared between approaches.

Results: Each model performed well in model fitting and the short-term forecasting of future NCDR. Long-term forecasting of NCDR and the probability of NCDR falling below 10/100,000 differed between models. All agree that the trend of NCDR will continue to decrease in all states until 2040. Reaching a NCDR of less than 10/100,000 by 2020 was only likely in Rio Grande do Norte. Prediction until 2040 showed that the target was also achieved in Amazonas, while in Ceará and Tocantins the NCDR most likely remain (far) above 10/100,000.

Conclusions: All models agree that, while incidence is likely to decline, achieving a NCDR below 10/100,000 by 2020 is unlikely in some states. Long-term prediction showed a downward trend with more variation between models, but highlights the need for further control measures to reduce the incidence of new infections if leprosy is to be eliminated.

1. Introduction

Leprosy, or Hansen's disease, is an infectious disease caused primarily by *Mycobacterium leprae*. It affects the skin, peripheral nerves, the mucosa of the upper respiratory tract and the eyes (Leprosy, 1982). Most people are able to clear the bacterium before disease occurs, or are resistant to the leprosy infection. The most likely route of transmission of leprosy is through aerosols (Hatta et al., 1995), with contacts closest to a patient with leprosy, in particular within household contacts, having the highest risk of acquiring the infection (Fine et al., 1997; Moet et al., 2006). Detection of leprosy is based on clinical signs and classified into paucibacillary (PB; ≤5 skin lesions) and multibacillary (MB; >5 skin lesions) leprosy. Currently, the main strategies to control leprosy are early detection of cases, and treatment with multidrug therapy (Global leprosy update, 2015). Chemoprophylaxis and immune-prophylaxis are both potential interventions but are not yet routinely available.

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Global elimination of leprosy has been a target for many years. In 1991, the World Health Assembly set a goal for "elimination of leprosy as a public health problem", defined as a prevalence of less than 1 per 10,000, by the year 2000 (WHO, 1991). More recently, the World Health Organization (WHO) has formulated new targets for leprosy, which include global interruption of transmission or elimination by 2020, and reduction of grade-2 disabilities in newly detected cases to below 1 per million population at global level by 2020 (WHO, 2012). Currently, worldwide, more than 200,000 new cases of leprosy are detected annually, with India, Brazil and Indonesia accounting for around 80% of all new cases (Global leprosy update, 2015). This incidence has remained fairly stable over the past decade. Brazil has the second highest annual incidence with approximately 31,000 new cases and annual new case detection rate (NCDR) of 15.32 per 100,000 population in 2014 (Ministry of health, 2015). Brazil was one of the countries that did not achieve elimination by 2000 (Castro et al., 2016). In 2011, the Ministry of Health defined an integrated action plan to reduce the burden of leprosy and to eliminate leprosy as a public health problem by 2015. This plan includes active case finding and timely provision of treatment in prioritized municipalities, primarily located in the Amazon region (Ministry of Health, 2012).

The spatial distribution of leprosy in Brazil is known to be heterogeneous with the highest number of cases in the Northern, North-Eastern and Central-Western regions. Most high-risk states or districts are part of the Brazilian Amazon (Penna et al., 2009; Penna et al., 2013). In 2014, ten states (37%) had a NCDR of more than 20 per 100,000, eight states (30%) a NCDR between 10 and 20 per 100,000, and nine states (33%) with a NCDR of less than 10 per 100,000 (Ministry of health, 2015). The highest rates can be found in the hyperendemic states of Mato Grosso and Tocantins with NCDR of 82.03 and 69.88 per 100,000, respectively. Also, within each state, leprosy is known to be unevenly distributed (Alencar et al., 2012; Kerr-Pontes et al., 2004). Although recent numbers show a slight declining trend in most states, more than two thirds of the states in Brazil can be regarded as highly endemic.

Although the WHO target is the interruption of leprosy transmission globally by 2020, it is clear that this will not be feasible due, for example, to the long incubation time of leprosy. We therefore focus on the feasibility of reducing the NCDR to low levels, which is likely to result in a reduced transmission. The aim of this study is to compare four modelling approaches being applied to leprosy in the context of assessing whether a NCDR of less than 10 per 100,000 can be met by 2020 and predicting the annual probability of NCDR being below 10 per 100,000 in four states of Brazil: Rio Grande Do Norte (low endemic), Amazonas (medium-high endemic), Ceará (high endemic), and Tocantins (hyper endemic state). These states were purposively selected based on differences in levels of endemicity and historic patterns of leprosy NCDR.

Prediction of infectious disease patterns is complicated by the intrinsic non-linearity in the transmission process: more transmission leads to more infection which leads to more disease which leads to more transmission. Models are, by definition, abstract simplifications of reality, and in order to have confidence in their results, need to be challenged and validated. The best way to develop consensus advice is through comparison of outputs of different models. Consequently, we applied two statistical models and two mathematical transmission models to estimate future NCDR of leprosy from the same data, including: a linear mixed model, a Bayesian back-calculation approach, a deterministic compartmental model and the individual-based stochastic model SIMCOLEP. Back-calculation has shown potential to estimate numbers of newly infected individuals in Thailand (Crump and Medley, 2015). SIMCOLEP, which models the transmission and control of leprosy in a population structured by households, has been used to estimate future NCDR trends in Bangladesh, India, Brazil, and Indonesia, and to explore the potential impact of various interventions targeting household contacts (Blok et al., 2015a; de Matos et al., 2016; Fischer et al., 2011). In this study, we will explore the levels of agreement between these methods on future projections of the NCDR in the four chosen states. Model results are discussed to understand factors contributing to similarities and differences between methods.

2. Materials and methods

2.1. Data

Annual summary data by state were extracted via the SINAN database's web interface (SINAN, 2016) for the years 1990–2012. The SINAN database is the Brazilian government's repository for information on communicable diseases. The data retained for use in this study consisted of the annual number of new cases diagnosed (NC) and the annual new case discovery rate (NCDR) for MB and PB diagnoses combined, for 1990–2012, and for MB cases separately, from 2000 to 2012, along with the population size. Equivalent data for 2013 and 2014 were retrieved from documents on the Brazilian government's health portal (Ministry of health, 2015; Ministry of health, 2014). Population size and NCDR for MB diagnoses were not reported in the 2013 and 2014 data tables. However, the NCDR for total diagnoses and the number of total diagnoses and MB diagnoses were still included. Using the NCDR for total diagnoses and the number of total diagnoses, we calculated the population size and finally generated the NCDR for MB diagnoses for 2013 and 2014. Four states were chosen for inclusion in the study using NCDR to indicate the level of endemicity in the state. The states selected were Tocantins (NCDR in 2014 69.9 per 100,000), Ceará (22.9), Amazonas (14.6) and Rio Grande do Norte (8.0) (Ministry of health, 2015). The data for the four states are presented in Fig. 1.

2.2. Estimation approaches

The fundamental purpose is to compare four different methods for probabilistic forecasting of leprosy. Each method (whether Bayesian or frequentist) yields the probability distribution of future outcomes, i.e. results not used for training the model. Four approaches were used: a linear mixed model, a Bayesian back-calculation approach, a deterministic compartmental model, and the individual-based stochastic model SIMCOLEP. In no case did we use data used for fitting or training as part of the test or evaluation set. By bringing these models together, we can evaluate to what extent predictions of NCDR are similar or different in order to validate and to improve predictive quality. The next sections provide a brief description of each approach with further details provided in the supplementary materials S1–S3. The model code of the linear mixed model, back-calculation approach and deterministic compartmental model are provided in supplementary material S5. The model code of the individual-based model SIMCOLEP can be found in Blok et al. (Blok et al., 2015a).

2.3. Linear mixed models

A standard linear mixed effects regression was fitted to the data, as in Brook et al. (Brook et al., 2015). Specifically, we modelled the log of the annual new case detection rate as a linear function of time, with a random slope and intercept. We used only years 2001–2011 for the fitting. To model the uncertainty, we used the Metropolis algorithm (a Markov chain Monte Carlo (MCMC) procedure) to estimate the posterior joint distribution of the fixed effect estimates (overall slope and intercept), the variance of the random intercept and slope, and the residual error. Our method corresponds to a Bayesian analysis with noninformative priors; the