Modelling the Effects of Stigma on Leprosy

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Abstract The World Health Organization's leprosy-elimination campaign has significantly reduced global leprosy prevalence, but approximately 214,000 new cases of leprosy are reported each year. An ancient and neglected affliction, leprosy is also one of the most heavily stigmatised diseases of all time. We developed a mathematical model to examine the effects of stigma on sustaining disease transmission, using low and high degrees of stigma, as well as in its absence. Our results show that stigma does indeed play a central role in the long-term sustainability of leprosy. We also examined sensitivity of the outcome to all parameters and showed that the effects of stigma could increase the number of infected individuals by a factor of 80. Therefore both targeted education and shifts in cultural attitudes towards leprosy will be necessary for the eventual eradication of the disease.

Keywords Leprosy · Stigma · Mathematical model · Latin Hypercube Sampling · Partial rank correlation coefficients

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1 Introduction

Leprosy is a disease that has affected human beings for millennia; however, its causative agent, the bacteria *Mycobacterium Leprae*, was not identified until 1872 by Armauer Hansen. In the 1940s, a cure was developed with the drug dapsone; however, dapsone requires treatment for life. In the 1960s, drug resistance evolved due to widespread use of dapsone until the 1970s and 80s, when, upon recommendation from the World Health Organization (WHO), multi-drug therapy (MDT) was developed. Combining dapsone with the drugs clofazimine and rifampicin [17] resulted in a cure rate of 98% [4]. In addition to solving the drug-resistance problem, the MDT cocktail for leprosy also lessened the drug treatment timescale from life to a maximum of 24 months, depending on the type and severity of infection [18]. Thus, following the success of MDT for leprosy, the WHO launched a leprosy-elimination campaign in 1991 [10]. The target date of the 1991 WHO elimination campaign was the year 2000, for which elimination was defined in terms of a global prevalence threshold of less than 1 case in 10,000. In 1995, it was resolved that the MDT cocktail for leprosy would be provided to all patients worldwide for free [18]; in 2000, the WHO claimed to have achieved their elimination goal, citing a global prevalence of less than 600,000 cases. Yet, while all but six countries reported leprosy prevalences of less than 1 case in 10,000 in 2005 [17], approximately 214,000 new cases of leprosy are currently reported each year, with a global case-detection rate of 3.78 per 100,000 [4]. About 80% of all new cases come from India, Brazil and Indonesia [1, 4]. The WHO's original use of the term "elimination" has been criticised [10, 17] as an inhibiter to the progress of further leprosy reduction after 2000. The WHO later rebranded its leprosy efforts as an "Enhanced global strategy for further reducing the disease burden due to leprosy 2011–2015" [1].

Leprosy is a bacterial infection of the skin and is a leading infectious cause of disability [13, 18]. Yet, even among the neglected tropical diseases, it is one of the most overlooked [1]. This is in part because an effective treatment exists for the disease and in part because it is hard to quantify the cumulative socio-economic impact of the disease, as the disease is not fatal. Rather, leprosy infections lead to a plethora of secondary problems, such as infection of untreated wounds, debilitating ulcers on palms and soles, nerve-function impairment and damage, chronic disability, blindness and severe disfigurement [20].

The only known reservoirs of the *M. Leprae* bacteria are humans and South American armadillos [18]. However, *M. Leprae* can also survive outside the body for up to 45 days [10]. While the exact transmission mechanism is still unknown, most scholars agree that it involves direct contact with nasal fluids from the infected. Furthermore, it is thought that most people infected with *M leprae* do not develop clinical infections [18]. Two types of clinical infections may develop, either paucibacillary (PB) or multibacillary (MB) leprosy, with MB leprosy being the more severe. Of the two types of infections, MB leprosy is thought to be the only infectious type or at least the main source of *M. Leprae* [1, 18]. The type of infection that develops in an individual is thought to be largely mediated by the response of their immune

system [1]. In the case of MB leprosy, the bacteria spread systematically, and lesions tend to contain higher levels of bacilli. To simplify the diagnosis process in the field, an operational classification of leprosy has been developed by the WHO, in which patients are diagnosed simply by the number of skin lesions they have [4]. In cases where an infectee has five or more skin lesions, they are classified as having MB leprosy; otherwise, the classification is PB leprosy [18]. The incubation period from sub-clinical to clinical infections is extremely slow for leprosy, ranging from 2–12 years [18], and there is currently a lack of diagnostic tools for detecting early levels of *M. Leprae* [4]. While a vaccine specifically geared toward leprosy immunisation does not exist, the bacillus Calmette–Guérin (BCG) vaccine, originally developed for tuberculosis (TB), is known to provide variable protection against leprosy [13]. However, given that a new TB vaccine will likely supersede BCG in the future, the eventual consequences for leprosy control efforts remain unclear [13].

Stigma confers itself in several forms: exterior social forces, sometimes denoted "community stigma", and the emotional harm contained by an individual within themselves [23]. A further understanding has been reached concerning the layers of cognitive categories and the ways that they complement the predisposed beliefs of a particular disease. These include labelling, stereotyping, cognitive separation and emotional reactions [9]. Perception of stigma and experiences of discrimination cause people to feel ashamed and may cause them to isolate themselves from society [19], thus perpetuating the stereotype that leprosy is something shameful to be hidden away [23]. Alongside the emotional trauma is the added effect of prolonging individual instances of infection and increasing the chance of spread to others [7, 26]. The impact of knowing that one carries the disease and the anticipated stigma is in some instances as great or an even greater source of suffering than symptoms of the disease itself [22, 24], These factors play into the propensity to hide the ailment, which prolongs its affliction on the individuals involved and society as a whole [26]. Recently, there has been a substantial interest in understanding and diluting the overarching trend of stigma in many of today's diseases [24]. Several initiatives are being explored to address the prominence of stigma in sustaining the disease and the impact it has from the perspective of the individual [14]. These include alleviating health problems with improved social policies, unhinging the inclination to stigmatise on the part of perpetrators and better supporting those already affected by social neglect [24]. These all aspire to the same end goal, which is the transformation of stigma into social support rather than an increased burden [3].

The effects of leprosy stigma are widespread, negatively affecting employment, marriages and social activities of those infected, recovering or recovered [16]. Such aspects of disease-related stigma further deteriorate both the psychological and physiological states of individuals, promoting a feedback loop of negative overall health [24]. Furthermore, there is much ignorance regarding leprosy in countries where it persists. For example, stigmatisation of infected individuals is promoted through local legislation in some countries, while many believe the disease to be hereditary when it is not [21]. The reason for this misconception is that family members of those infected are disproportionately at higher risk of infection due to frequent close contact with infected individuals [1]. Leprosy also disproportionately affects poorer

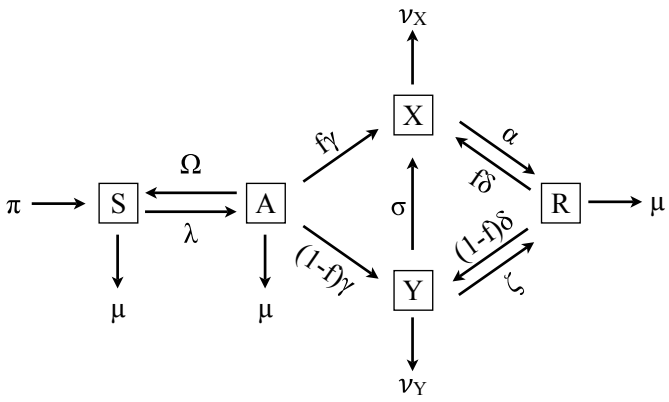
citizens who lack access to care, which further promotes unfounded stigma against the poor [11]. Hence recovered infectees face substantial risks to their overall health and well-being even after being released from MDT [23]. It is also known that stigma can lead to significant delays with respect to case detection and self-diagnosis [24]. However, it is when individuals first develop symptoms that they derive the most benefit from MDT. This is because, while MDT is an effective treatment at all stages, severe nerve damage or further complications arising from the disease grow with time and remain permanent after infections are cleared [21].

To date, only a handful of mathematical models have addressed leprosy [6]. Models have used compartments [8], been simulation based [12] or individual based [5] and have considered treatment and relapse [15]. However, to the best of our knowledge, there have been no attempts to model the effects of stigma in the transmission dynamics of leprosy. Therefore, we propose a simple model for the transmission dynamics of leprosy that can account for the effects of stigma. We address the following research questions: 1. What role does stigma play in the transmission dynamics of leprosy? 2. How sensitive is the outcome to variation in disease parameters, including stigma? 3. Can leprosy be eradicated if stigma is removed?

2 The Model

Our model consists of susceptible, exposed, infected and recovered individuals, with the productively infected compartment split in two. The model allows for otherwise healthy individuals to contract leprosy, clear asymptomatic infections, progress from asymptomatic to symptomatic infection states, recover through MDT or relapse to symptomatic infection. Specifically, the five classes under consideration are as follows: the susceptible class ‘S’, those with sub-clinical or asymptomatic infections ‘A’, those with symptomatic infections that they choose to disclose ‘X’, those with symptomatic infections that they choose to conceal ‘Y’, and those who have recovered from the disease ‘R’. By splitting the non-asymptomatic infection compartment into two discrete groups, the model mimics the choice, available to members of the population who develop symptomatic leprosy infections, to either conceal or disclose their infection. Likewise, the same choice is available to members of the population who relapse into symptomatic infections. Two further possibilities are accounted for by the model, in which members who originally concealed their symptomatic infection may later change their minds, disclosing their infection or are discovered. This is manifested as a path from ‘Y’ to ‘X’. Incorporating this split in the infection compartment is a simple way to explicitly account for the effects of stigma on the transmission of leprosy.

Fig. 1 Model flow diagram



The differential equations governing our model are as follows:

$$\begin{aligned} S' &= \pi + \Omega A - (\mu + \lambda)S \\ A' &= \lambda S - (\mu + \gamma + \Omega)A \\ X' &= f\gamma A + \sigma Y + f\delta R - (\nu_X + \alpha)X \\ Y' &= (1-f)\gamma A + (1-f)\delta R - (\nu_Y + \sigma + \zeta)Y \\ R' &= \alpha X + \zeta Y - (\mu + \delta)R, \end{aligned} \tag{1}$$

with the force of infection given by $\lambda = \beta_1(1-\eta)A + \beta_1 Y + (\beta_1 - \frac{\beta_2 X}{m+X})X$.

A schematic of the model is shown in Fig. 1, and the model parameters are described in Table 1.

In deriving this model of leprosy, we make the following assumptions:

1. The chance of infection depends upon interactions between S and classes A, X and Y, although the most prominent course of infection remains the interaction between S and Y (the stigma class); the β_1 term is thus the largest of the transmission terms.
2. Because it remains difficult to detect asymptomatic infections, members of the A class act as usual, interact with susceptibles as usual and die at the natural death rate.
3. The asymptomatic class, which carries the *M. Leprae* bacteria, has a naturally reduced transmission compared to the stigma class.
4. The effect of transmission from the X class is modified by a dampening term that reduces infectivity. This dampening term takes the form of a Holling Type II function with the property that the effect saturates at a level β_2 when there are large numbers of individuals in the disclosing class. This reflects the fact that susceptible individuals will likely attempt to reduce contact with individuals who openly display symptoms, but the effect of such avoidance is limited when numbers are large. As such, $\beta_1 > \beta_2$.
5. A large fraction Ω of members with asymptomatic leprosy infections clear such infections [18], after which they return to the susceptible class.

Table 1 Variables and parameters

Symbol	Description	Range	Units	Reference
S	Susceptible individuals	–	people	–
A	Asymptomatically infected individuals	–	people	–
X	Infected individuals with disclosed, symptomatic infections	–	people	–
Y	Infected individuals with undisclosed, symptomatic infections	–	people	–
R	Recovered individuals	–	people	–
π	Birth rate	10–30	$\frac{\text{people}}{\text{year}}$	[25]
λ	Force of infection	–	$\frac{1}{\text{year}}$	–
β_1	Transmissibility between susceptibles and non-disclosing infectees	0.001–0.01	$\frac{1}{\text{people} \cdot \text{year}}$	[4]
β_2	Dampened transmissibility between susceptibles and disclosing infectees	$\frac{\beta_1}{2}$	$\frac{1}{\text{people} \cdot \text{year}}$	Estimate
η	Coefficient of reduced infection between for asymptomatic infectees	0–1	–	–
m	Half-saturation constant	0–5	people	Estimate
Ω	Clearance rate of asymptomatic infection	0.5–1	–	[18]
μ	Natural death rate	0.01–0.03	$\frac{1}{\text{year}}$	(Lifespan of 33–100 years)
γ	Rate of developing symptoms	0–0.2	$\frac{1}{\text{year}}$	[18]
f	Fraction who disclose infection	0–1	–	–
σ	Rate of eventual disclosure of infection	0.5–1	$\frac{1}{\text{year}}$	[18]
ν_X	Disease death rate (unstigmatised)	0.03–0.09	$\frac{1}{\text{year}}$	Estimate
ν_Y	Disease death rate (stigmatised)	0.09–1	$\frac{1}{\text{year}}$	Estimate
α	Recovery rate without stigma	0.1–1	$\frac{1}{\text{year}}$	[18]
ζ	Recovery rate with stigma	0–0.1	$\frac{1}{\text{year}}$	Estimate
δ	Relapse rate	0–0.1	$\frac{1}{\text{year}}$	[4, 18]

6. A fraction f of individuals who develop symptomatic infections will disclose their infection and seek MDT; we assume this fraction is the same at the onset of initial infection as it is when immunity lapses.
7. Those who initially conceal their symptomatic infection are identified at rate σ, either by changing their minds or due to discovery.
8. Individuals who do not disclose their symptoms consequently do not seek MDT and do not recover.

9. In the absence of stigma, all members who progress to symptomatic infection have the opportunity to seek MDT, which is highly successful and freely available.
10. There is a small chance for symptomatic infection relapse (approximately 2–3%) [18].
11. Some stigmatised individuals may disclose only to their doctors and receive MDT; we assume this factor will be much smaller than stigmatised individuals who seek treatment.

In addition to these primary assumptions, we further assume constant birth and death rates and ignore vaccination.

Remark We note that, when $f = 1$, then $Y = 0, \sigma$ is not relevant, $\lambda = \beta_1(1-\eta)A + (\beta_1 - \frac{\beta_2 X}{m+X})X$, and our model collapses to the special case of leprosy without stigma, corresponding to assumption (9).

3 Analysis

3.1 Equilibria

The disease-free equilibrium (DFE) is given by $(\overline{S}, \overline{A}, \overline{X}, \overline{R}) = (\pi/\mu, 0, 0, 0)$.

To find the endemic equilibrium, we start by setting the governing equations of our model to zero:

$$0 = \pi + \Omega A - \mu S - \beta_1(1-\eta)SA - \beta_1 SY - \left(\beta_1 - \frac{\beta_2 X}{m+X}\right)SX \tag{2}$$

$$0 = \beta_1(1-\eta)SA + \beta_1 SY + \left(\beta_1 - \frac{\beta_2 X}{m+X}\right)SX - (\mu+\gamma+\Omega)A \tag{3}$$

$$0 = f\gamma A + \sigma Y + f\delta R - (\nu_X + \alpha)X \tag{4}$$

$$0 = (1-f)\gamma A + (1-f)\delta R - (\nu_Y + \sigma + \zeta)Y \tag{5}$$

$$0 = \alpha X + \zeta Y - (\mu+\delta)R. \tag{6}$$

We rearrange Eq. (6) to obtain

$$R(X,Y) = \frac{\alpha}{\mu+\delta}X + \frac{\zeta}{\mu+\delta}Y. \tag{7}$$

Next, we substitute Eq. (7) into Eq. (5), giving

$$0 = (1-f)\gamma A + (1-f)\frac{\alpha\delta}{\mu+\delta}X + (1-f)\frac{\zeta\delta}{\mu+\delta}Y - (\nu_Y + \sigma + \zeta)Y, \tag{8}$$

which we then rearrange to get

$$A(X,Y) = \left((\nu_Y + \sigma + \zeta)Y - (1-f)\frac{\zeta\delta}{\mu+\delta}Y - \frac{(1-f)\alpha\delta}{\mu+\delta}X\right)\frac{1}{(1-f)\gamma}. \quad (9)$$

Next, substituting our expressions for $A(X,Y)$ and $R(X)$ into Eq. (4), we get

$$Y(X) = \frac{(\nu_X + \alpha)(1-f)}{f(\nu_Y + \sigma + \zeta) + \sigma(1-f)}X \equiv qX. \quad (10)$$

We re-express (9) as

$$A(X) = \left[(\nu_Y + \sigma + \zeta)q - \frac{(1-f)\zeta\delta}{\mu+\delta}q - \frac{(1-f)\alpha\delta}{\mu+\delta}\right]\frac{1}{(1-f)\gamma}X \equiv nX, \quad (11)$$

and it is easy to show that $n > 0$. We now substitute $A(X)$ and $Y(X)$ into Eq. (3) and use the fact that $X \neq 0$ to get

$$S(X) = \frac{n(\mu+\gamma+\Omega)}{n(1-\eta)\beta_1 + \beta_1 q + \left(\beta_1 - \frac{\beta_2 X}{m+X}\right)}. \quad (12)$$

Note that

$$\beta_1 - \frac{\beta_2 X}{m+X} > \beta_1 - \beta_2 > 0,$$

and hence $S(X) > 0$.

Finally, we substitute Eq. (12) into Eq. (2) along with the condensed forms of Eqs. (10) and (11) to find that

$$\begin{aligned}
0 &= X^2\left[\beta_1(1-\eta)n^2(\mu+\gamma) + \beta_1 qn(\mu+\gamma) + \beta_1 n(\mu+\gamma) - \beta_2 n(\mu+\gamma)\right] \\
&\quad + X\Big[\mu n(\mu+\gamma+\Omega) + \beta_1(1-\eta)n^2(\mu+\gamma)m + \beta_1 qn(\mu+\gamma)m + \beta_1 mn(\mu+\gamma) \\
&\qquad + \pi\beta_2 - \pi n(1-\eta)\beta_1 - \pi\beta_1 q - \pi\beta_1\Big] \\
&\quad + \mu n(\mu+\gamma+\Omega)m - \pi n(1-\eta)\beta_1 m - \pi\beta_1 qm - \pi\beta_1 m \\
&= a_1 X^2 + b_1 X + c_1.
\end{aligned}$$

Since $\beta_1 > \beta_2$, it follows that $a_1 > 0$, and hence this is an upward-facing parabola. Furthermore, since $S \leq \frac{\pi}{\mu}$ (the upper bound of the population), then, using Eq. (12), the constant term satisfies

$$\begin{aligned} c_1 &= \mu n(\mu+\gamma+\Omega)m - (\pi n(1-\eta)\beta_1 + \pi\beta_1 q + \pi\beta_1)m \\ &\leq \pi n(1-\eta)\beta_1 m + \pi\beta_1 qm + \pi\beta_1 m - \frac{\pi\beta_2 Xm}{m+X} - (\pi n(1-\eta)\beta_1 + \pi\beta_1 q + \pi\beta_1)m \\ &= -\frac{\pi\beta_2 Xm}{m+X} < 0 \end{aligned}$$

if $X > 0$. It follows that the parabola has a negative y-intercept. An upward-facing parabola with a negative y-intercept can only have a single positive x-intercept, regardless of the sign of b_1. It follows that there is a unique positive endemic equilibrium given by

$$\bar{X} = \frac{-b_1 + \sqrt{b_1^2 - 4a_1c_1}}{2a_1}. \tag{13}$$

If $X = 0$, we have $c_1 = 0$. Hence the endemic equilibrium collides with the DFE at this point.

3.2 Basic Reproduction Number

Using the next-generation method, R_0 is defined to be the largest eigenvalue of the matrix FV^{-1}, with F representing newly arising infections in the system and V the balance of transfers of existing infections between the classes. Thus

$$F = \begin{bmatrix} \beta_1(1-\eta)\frac{\pi}{\mu} & \beta_1\frac{\pi}{\mu} & \beta_1\frac{\pi}{\mu} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \text{ and } V = \begin{bmatrix} (\mu+\gamma+\Omega) & 0 & 0 \\ -f\gamma & (\nu_X+\alpha) & -\sigma \\ -(1-f)\gamma & 0 & (\nu_Y+\sigma+\zeta) \end{bmatrix}.$$

We find the reproduction number for leprosy with stigma to be:

$$\begin{aligned} R_0 = \beta_1\frac{\pi}{\mu}\frac{(1-\eta)}{(\mu+\gamma+\Omega)} &+ \beta_1\frac{\pi}{\mu}\frac{\sigma(1-f)\gamma + f\gamma(\nu_Y+\sigma+\zeta)}{(\mu+\gamma+\Omega)(\nu_X+\alpha)(\nu_Y+\sigma+\zeta)} \\ &+ \beta_1\frac{\pi}{\mu}\frac{(1-f)\gamma}{(\mu+\gamma+\Omega)(\nu_Y+\sigma+\zeta)}. \end{aligned}$$

These three terms represent the contributions from asymptomatic, unstigmatised and stigmatised individuals, respectively.

4 Numerical Simulations

To assess the effects of stigma, we considered three regimes: (a) moderate stigma, (b) high stigma, and (c) no stigma. We used sample values chosen within the ranges from the table and varied the effect of stigma using the disclosure rate σ to assess moderate versus high stigma regimes and turned off the proportion of individuals entering the stigma compartment for the no-stigma case.

Using recent leprosy-prevalence statistics [4], we conduct approximate order-of-magnitude estimates of our infection coefficients. Roughly 214,000 cases of leprosy were reported in 2014, with approximately 81% of those cases coming from Brazil, India and Indonesia. Approximating the populations of these nations by 200 million, 1.25 billion and 250 million, respectively, we estimate the coefficient of infection to be

$$\beta_1 = \frac{0.81 \times 214000}{1700000000} = 0.000101965 \approx 0.0001. \tag{14}$$

We considered a small village of 1000 individuals. Initial conditions were chosen so that there were 1000 susceptibles and a single infected non-stigmatised individual. Figure 2 illustrates the case of moderate stigma, showing an infection wave and a substantial number of uninfected individuals ($S + R = 636$ at the end of this simulation).

Next, we used the same parameters and initial conditions as in Fig. 2 except that we changed the rate of disclosure from $\sigma = 1$ to $\sigma = 0.1$. This reflects the

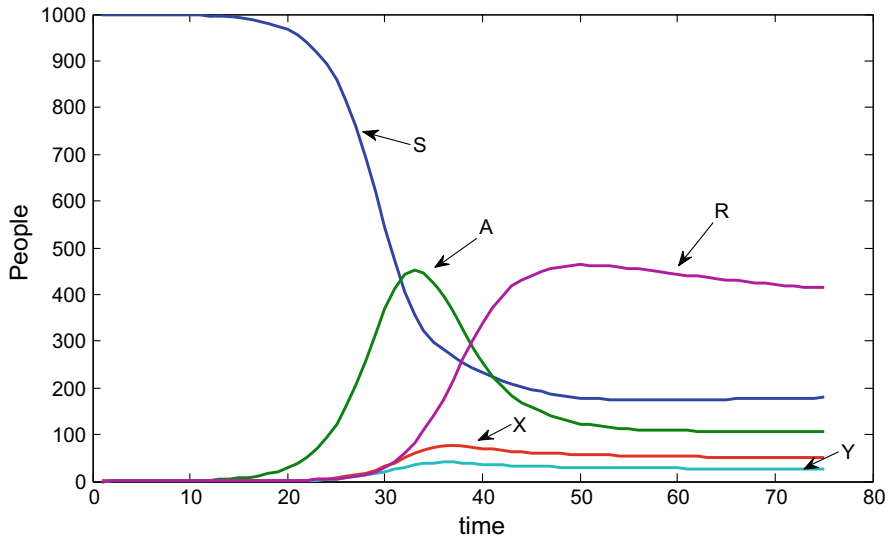


Fig. 2 Leprosy modelled in a moderate stigma regime. There is an infection wave, with an endemic disease outcome but a substantial number of recovered individuals. Parameters used were $\alpha = 1$; $\zeta = 0.1$; $\beta_1 = 0.01$; $\beta_2 = \beta_1/2$; $\gamma = 0.2$; $\delta = 0.1$; $\mu = 0.03$; $\nu = 0.09$; $\pi = 30$; $\sigma = 1$; $\Omega = 1$; $f = 0.5$; $m = 0.5$; $\eta = 0.8$. Note in particular that stigmatised individuals remain so for $\frac{1}{\sigma} = 1$ year

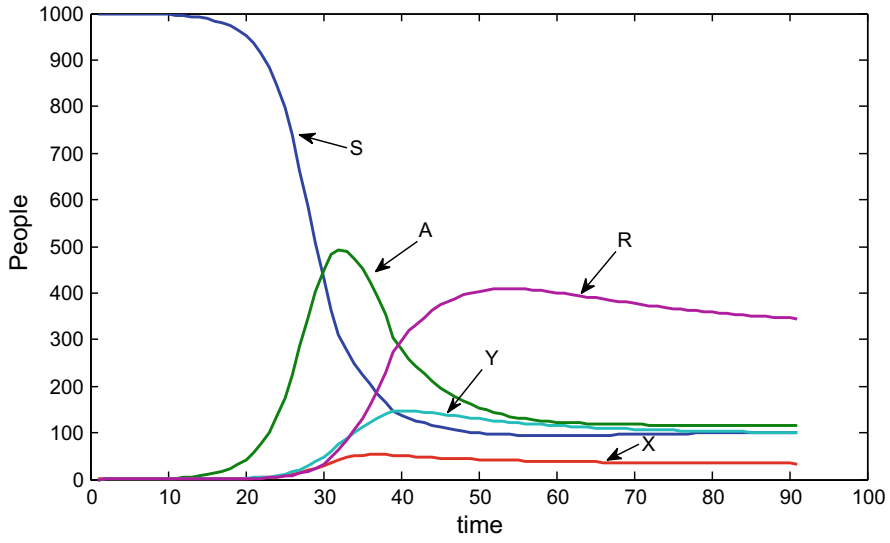


Fig. 3 Leprosy modelled in a high stigma regime. Parameters were as in Fig. 2 except that $\sigma = 0.1$ (i.e., stigmatised individuals remain so for an average of ten years). The number of recovered individuals is low, while stigmatised individuals persist. Note the re-ordering of the final outcome, compared to Fig. 2

case where individuals remain stigmatised for ten years (since the length of time remaining in a compartment is inversely proportional to the rate of leaving it). In this case, the number of stigmatised individuals exceeds the number of non-stigmatised or asymptomatic individuals, sustaining a high level of infected individuals. The number of uninfected individuals was significantly lower than in Fig. 2 ($S + R = 376$ in this simulation).

Finally, we modelled the case of no stigma. Parameters were as in Fig. 2 except that $f = 1$ to ensure that no individuals entered the stigma compartment. The outcome is similar to Fig. 2 except that there are slightly more uninfected individuals ($S + R = 729$ at the end of this simulation).

Additionally, we numerically explored the dependency of the results on the parameters β_2 and m. However, although these had an effect on the shape of the curves, they did not produce outcomes significantly different to Figs. 2, 3 and 4. (Results not shown.)

We also performed a sensitivity analysis on the reproduction number using Latin Hypercube Sampling (LHS) and Partial Rank Correlation Coefficients (PRCCs). Latin Hypercube Sampling is a statistical sampling method that evaluates sensitivity of an outcome variable to all input variables. PRCCs measure the relative degree of sensitivity to each parameter, regardless of whether the parameter has a positive or negative influence on the outcome variable [2].

PRCCs were calculated for the model and are displayed in Fig. 5 using the ranges from the table but with the range for β_1 extended to $0 \leq \beta_1 \leq 0.005$ to illustrate a wider outcome. This analysis provides a way to measure the sensitivity of a model to each parameter it contains. Figure 5 shows that β_1 and η are the most sensitive

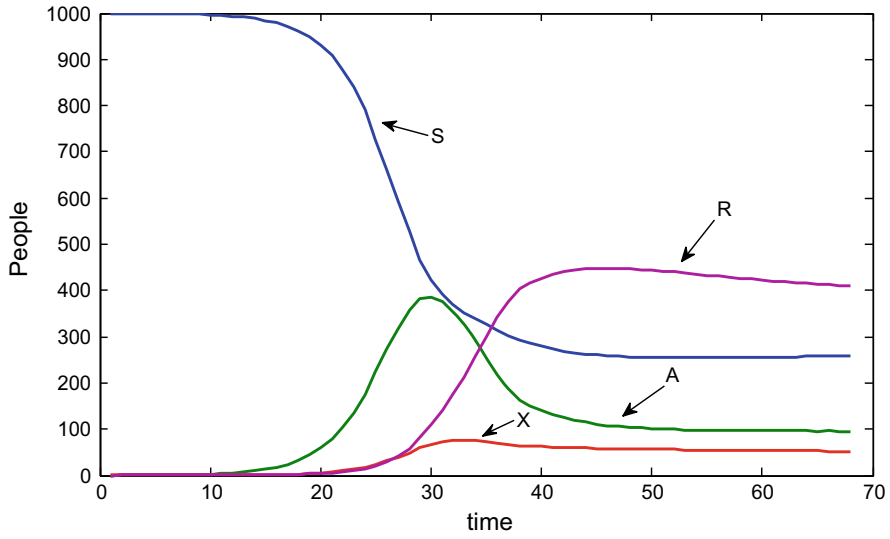


Fig. 4 Leprosy modelled in a stigma-free regime. Parameters were as in Fig. 2 except that $f = 1$ so that there were no stigmatised individuals. The number of infected cases is low, and the number of recovered individuals is high

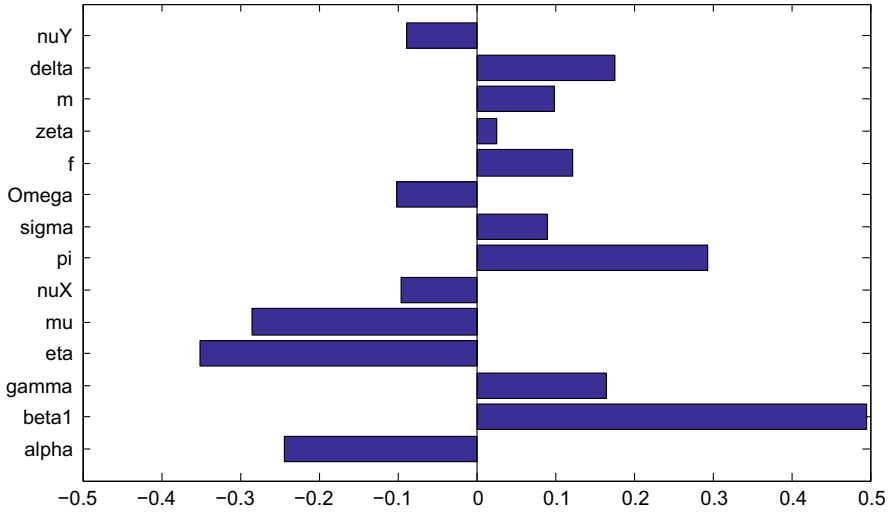


Fig. 5 Partial rank correlation coefficients for the model

parameters in the model. Note that the stigma parameters β_2 and m do not affect R_0, which is a measure of initial disease invasion.

In Fig. 6, we plot the individual Monte Carlo simulations of the two most sensitive model parameters. For $0 \leq \beta_1 \leq 0.5 \times 10^{-3}$, eradication will result, regardless of the values of the other parameters (i.e., if the disease transmission is extremely low). However, there is no value of η that can guarantee eradication; even if $\eta = 1$, fluctuations in the other parameters could still maintain the epidemic. Note that the threshold value of β_1 is larger than the value found in the literature using (14). This

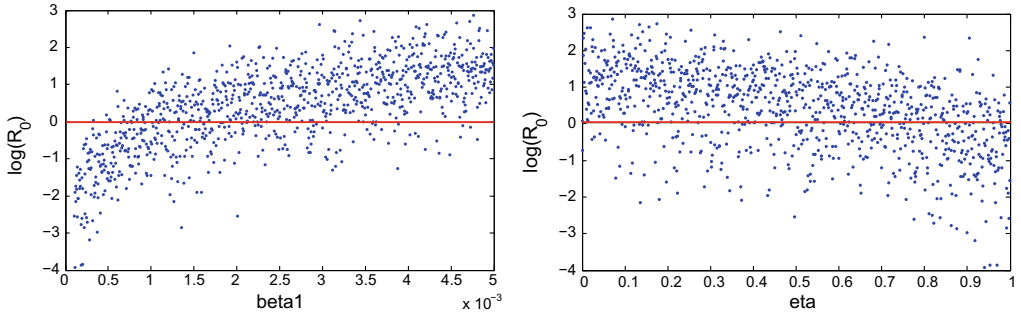


Fig. 6 Monte Carlo simulations for the two most sensitive model parameters, β_1 and η. The $R_0 = 1$ threshold is indicated by the horizontal line. Eradication can be achieved if β_1 is reduced below 0.0005. However, no value of η can guarantee eradication

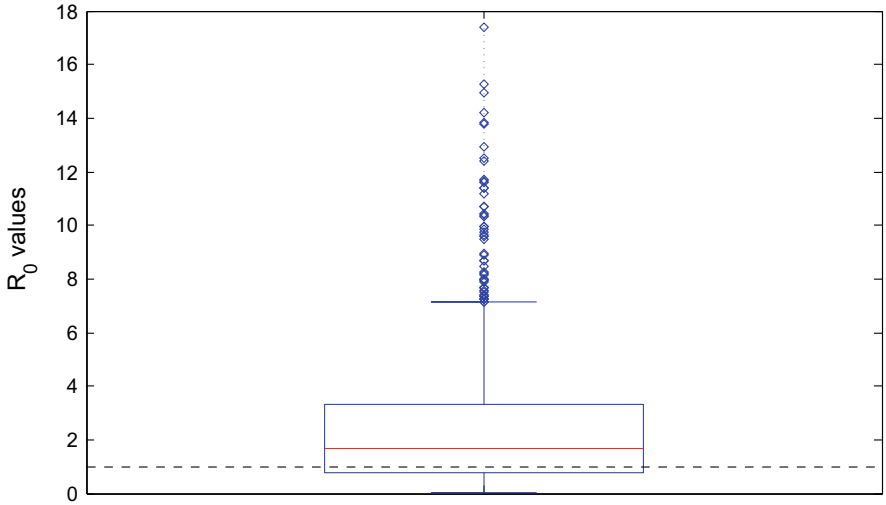


Fig. 7 Box plot of the range of R_0 values from Monte Carlo simulations

suggests that eradication is theoretically possible, but fluctuations in the parameters could have a significant effect on the outcome.

Figure 7 shows the complete range of R_0 values for all simulations. While the interquartile range crosses the $R_0 = 1$ threshold, suggesting that eradication is theoretically possible, the outlier values are quite extreme, suggesting that fluctuations in the parameter values could lead to significant epidemics. Note that this figure uses the extended range $0 \leq \beta_1 \leq 0.005$.

Since the endemic equilibrium can be uniquely determined from (13), we used the LHS method to determine the effects of stigma on the outcome. We ran Monte Carlo simulations on the endemic equilibrium $\bar{X}$ and then applied the ratio of stigma to non-stigma cases using (10). The outcome is illustrated in the ordered scatterplot in Fig. 8. The blue dots (lower half of graph) illustrate the number of simulations where there were fewer stigma cases, while the red circles (upper half of graph) illustrate the number of simulations where there were more stigma cases. In this example,

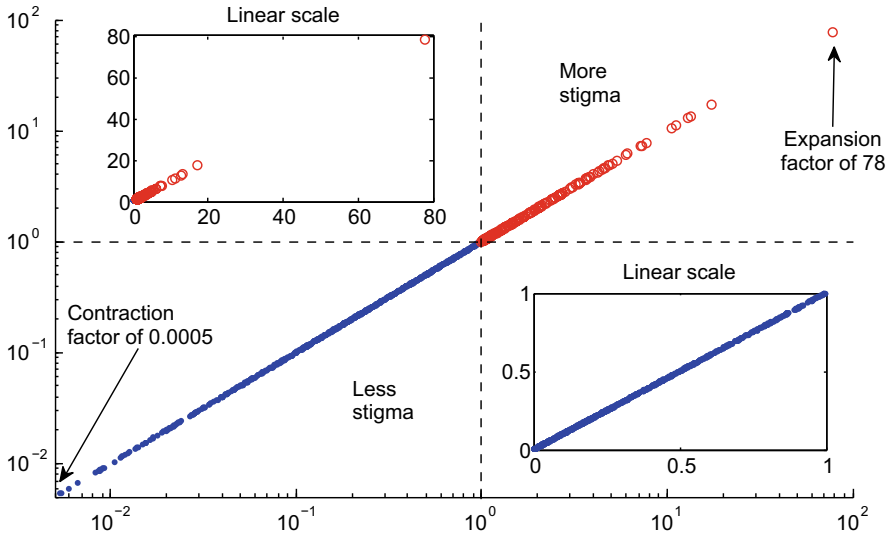


Fig. 8 Ordered scatterplot of the ratio of more-stigma versus less-stigma cases using LHS on the endemic equilibrium values on a log-log scale using ranges from the table. The red circles (upper right) are the Monte Carlo simulations where there are more stigma cases at equilibrium. The blue dots (lower left) are the simulations where there is less stigma at equilibrium. The inset graphs illustrate the two cases in a linear scale. Note that, at the extreme, there are 78 times as many stigma cases as non-stigma cases

there were 796/1000 cases where less stigma occurred and 204/1000 cases where more stigma occurred. However, although there were more cases where stigma was reduced, the degree of stigma expansion in the more-stigma case was extensive. At the extremes, the ratio of less-stigma to more-stigma cases ranged from a factor of 0.000545 to a factor of 78.

5 Discussion

We examined the effects of stigma on leprosy, both in the short term of initial disease outbreak (Figs. 5 and 6) and in the long term (Figs. 2, 3 and 4). Although stigma had no effect on initial disease invasion or eradication, differences in stigma levels had the potential to substantially alter the overall prognosis of leprosy in the population. To the best of our knowledge, this is the first mathematical model of leprosy to incorporate stigma.

Additionally, we used an ordered scatterplot to examine the ratio of increased stigma to decreased stigma across a range of parameter values. Although there were more cases where the amount of stigma was reduced, in the cases where it was increased, the result could be as much as an 80-fold increase in the number of stigmatised individuals. It follows that stigma is an important factor in the spread of leprosy.

Our model has some limitations, which should be acknowledged. We conflated "disclosure" and "stigma", whereas in practice the social phenomenon of leprosy-related stigma is more complex. We represent stigma by way of parameter choices, which is a simplification. Leprosy is an extremely heterogeneous disease in at least two major senses: it is heterogeneous with respect to those at risk of exposure to the *M. Leprae* bacteria and with respect to the spatial distribution of the disease. Therefore, given this heterogeneity, mass-action disease transmission may not be suitable for modelling this disease. We have also assumed constant birth and death rates, but, for any long-term disease, modelling time-varying birth and death rates may be more appropriate. Likewise, a further refinement would be to model the stigma parameters as randomly time-varying functions. Future work will examine the effect of TB vaccines against leprosy, which have been shown to be efficacious [18].

We thus see that stigma, whether moderate or high, plays a significant role in sustaining leprosy. Our sensitivity analysis showed that R_0 tends to range from 1 to 18 for typical model parameter ranges (Fig. 7). In practice, we may never have direct control over the transmission rate β_1, yet we may be able to influence σ, the rate at which non-disclosing symptomatic infectees either change their minds and disclose their infection or are discovered. Figure 3 shows that reducing this rate is critical.

In practice, leprosy-eradication strategies should focus on the reduction of leprosy-related stigma through a combination of targeted education about the disease and shifts in cultural attitudes towards leprosy. However, since the measure of stigma estimated in this model may conflate actual disease-related stigma with other important factors, such as knowledge or access to care, this model also highlights the importance of continuing to make leprosy MDT accessible while simultaneously educating at-risk populations about the possibility of such care. Finally, depending on how likely it is that asymptomatic infections can in turn generate new infections, such strategies may need to be supplemented by continued efforts to detect sub-clinical infections, which has been emphasised in the literature [17]. The persistence of leprosy is a complex problem; therefore a simple solution for its eradication is likely not possible; however, any approach incorporating the reduction of leprosy-related stigma will likely go a long way towards true leprosy eradication.

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