1. Understanding non-compliance with WHO multi drug therapy among leprosy patients: Insights from a mathematical models

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Abstract. Leprosy, one of the neglected tropical diseases is a chronic, debilitating, disabling and disfiguring condition that occur most commonly in the setting of extreme poverty, especially among the rural poor and some disadvantaged urban populations. We formulate a deterministic mathematical model to investigate the impact of relapse cases and non-compliance with WHO multi drug therapy among leprosy patients. Qualitative analysis of the model reveals that the model has a disease-free equilibrium, which is globally asymptotically stable whenever the reproductive number is less than a unity. Centre Manifold theory is used to show that the endemic equilibrium is locally asymptotically stable when its corresponding reproduction number is greater than unity but close to one. Results obtained from the analysis of the basic reproduction number suggest that an increase in relapse and non-compliance cases to MDT increases the reproduction number leading
to an increase in Leprosy prevalence. Numerical simulations are provided to support the analytical results.

1. Introduction

Leprosy, also known as Hansen's disease, is a chronic infectious disease that primarily affects the skin, the peripheral nerves, the upper respiratory tract, and the eyes [36]. The causative agent is an acid-fast bacterium, *Mycobacterium leprae*, first identified in 1873 by the Norwegian physician, Gerhard Henrik Armauer Hansen. Leprosy was considered a divine curse for sin in the Old Testament and a karma in Buddhism. The term leprosy originates from the Latin word *lepros*, meaning defilement. The fact that leprosy has been deemed an incurable disease, causing severe deformities and disabilities, has resulted in severe stigmatization. This has resulted in double suffering by victims, both from the disease itself and from public discrimination. Although documented since antiquity, leprosy currently remains endemic in some developing parts of the world [23]. Leprosy is curable and treatment provided in the early stages averts disability. According to official reports received from 121 countries and territories, the global registered prevalence of leprosy at the beginning of 2009 stood at 213,036 cases, while the number of new cases during 2008 was 30,055 cases and 31,037 cases in 2007 [54, 51], for a disease which appeared to be vanishing in the 17th and 18th centuries [40]. In 1991, the World Health Organization (WHO) and its member states committed themselves to eliminate leprosy as a public health problem by the year 2000 [45]. Elimination was defined as a prevalence of less than 1 case per 10,000 persons. At the end of the year 2000, the deadline of the program, 597,232 leprosy cases were registered for treatment and 719,330 cases were newly detected in the world [52]. Despite these tremendous efforts by the World Health Organization to eradicate the leprosy pockets of high endemicity still remain in some developing countries, around the subtropical and tropical zone, where the social and economic resources have not been sufficient to support the living standards needed to limit the disease. Here, we list the highest registered prevalences as of 2008 Angola (1,184 cases), Brazil (39,914 cases), Democratic Republic of Congo (6,114 cases), Ethiopia (4,187 cases) India (134,184 cases), Madagascar (1,763 cases), Mozambique (1,313 cases), Nepal (4,708 cases), Sudan (1,901 cases), Nigeria (4,899 cases), Sri Lanka (1,979 cases) and the United Republic of Tanzania (3,276 cases) [54, 51].

The diagnosis of leprosy is mainly based on the clinical signs and the symptoms of the disease. Since 1995, multidrug therapy (MDT) treatment
has proved to provide a highly effective cure for all types of leprosy. The classification of leprosy is based upon two basic criteria that are, the clinical manifestations and the results of skin smears. In the classification based on skin smears, patients showing negative smears at all sites are grouped as paucibacillary leprosy (PB), while those showing positive smears at any site are grouped as having multibacillary leprosy (MB). However, skin smear services are not generally available. This made it more practical for most programs to use clinical criteria for classifying and determining the appropriate treatment regimen for individual patients. The clinical classification, for the purpose of treatment, uses the number of skin lesions and nerves involved as the basis for grouping leprosy patients into PB and MB leprosy. While classifying leprosy, care should be taken to ensure that patients with one form of the disease are not treated with the regimen of the other form. In case of diagnosis uncertainty, the MDT regimen is advisable.

Adhering to a treatment schedule and successfully completing it are crucial to the control of any disease [33, 48, 49]. Poor adherence to self administration of treatment is a common behavioural problem among patients suffering from chronic diseases [35, 17], including TB [10, 11, 12] and leprosy [9, 19, 20]. MDT has proven to be a powerful tool in the control of leprosy, especially when patients report early and start prompt treatment. Adherence to and its successful completion are equally important. Unfortunately, due to a number of personal, psychosocial, economic, medical and health services factors, a significant number of patients become irregular and default from MDT [39, 33]. Low treatment completion rates nullify the effects of MDT and jeopardize the control and eradication program [53, 25]. The World Health Organization defines a defaulter as a patient who has not collected MDT treatment for 12 consecutive months [49]. However, in common parlance, a defaulter is someone who does not complete the stipulated course of treatment. Other terms used synonymously are absentees, discontinuation, non-compliance, non-adherence etc, each having slightly different connotation. In a number of national programmes, as many as 40% of newly detected patients have been considered defaulters [33, 15, 5]. As long as defaulters continue to live in their place of residence and have yet to complete the full course of MDT treatment, they remain potential sources of infection, and the patients suffer from irreversible complications. For instance, more than 7,000 individuals in the U.S. were infected by leprosy between 2002 and 2005, when immigrants brought leprosy from India, Brazil, the Caribbean and Mexico [42], and this reminds us that besides the fact that the disease is one of the neglected tropical diseases confined to resource limited settings, it continues to slowly journey around the globe and
may show up or be imported anywhere with the current world movement of humans.

In light of the above literature, together with the available disease statistics in human population [18, 34, 54], motivate this study, thus we wish to investigate the effects of non-compliance and relapse cases with WHO-multidrug therapy among leprosy patients. Evaluating the effectiveness of a chemotherapeutic regimen is essential to the leprosy-control program. One of the best methods of evaluation is the monitoring of relapse after the completion of a respected treatment protocol [6, 13, 14, 18, 24, 30, 37]. Data gathered by the Action Programme for the Elimination of Leprosy, WHO, from a number of control programs show that the relapse rate is 0.1% per year for PB and 0.06% per year for MB on average [13, 14, 18]. It is worth noting that when an individuals begin leprosy treatment in period of 3-4 weeks [43, 46, 47, 44, 50] he/she will be no longer infectious but for successful and effective treatment it is assumed that paucibacillary patients should be treated for 6 months while multibacillary patients should be treatment for 12-24 months, albeit it was discovered that most of the high bacteriological index patients will continue to improve after the completion of the 12-month regimen. Nevertheless, an additional 12 months of multidrug therapy (MDT) for MB leprosy is needed for patients showing evidence of deterioration. Thus, the length of the regimen may result in some individuals failing to complete treatment since in most cases, they will be no longer infectious and probably unwise self-examination that they no longer need treatment, through noticing signs of recovery which are easily noticed in a period of 3-4 weeks [43, 46, 47, 44, 50]. In this study, a defaulter is defined as a patient who has not collected the MDT for 3 consecutive months and has discontinued the treatment.

The paper is structured as follows. The model is formulated in Section 2 and comprehensively analyzed in Section 3. Expected population effects from improved public health practices are investigated in Section 4 through numerical simulations of the model using parameter values representative of the region. The last Section concludes the paper.

2. Model formulation

Based on epidemiological status, the population is subdivided into five classes namely: susceptibles (S), individuals who are not yet infected by the disease and can be infected by *Mycobacterium leprae* and join a latently infected class (E). Those who progress to active disease can do so in two different ways. They can develop localized, paucibacillary leprosy (P), with a strong cell-mediated response, which may resolve spontaneously, affects host
survival only minimally, and is much less transmissible [16, 40]. Alternatively, they can develop disseminated, multibacillary, disease (M), which will somewhat reduce average survival time and is more contagious. The pathway taken (paucibacillary (PB) or multibacillary (MB)) seems to be dependent not on the strain of organism but on the host response [16, 40]. Because borderline cases will often progress over time to either paucibacillary or multibacillary forms, for the purposes of simplifying our study, we have included only these two pathways. This division of the active states of leprosy into two discrete forms has been used in other studies [1, 29, 40]. Infectious individuals are assumed to be administered to treatment and join the recover class (R), at rates $\alpha_P$ and $\alpha_M$ for those infected with paucibacillary or multibacillary respectively. Thus, the total population ($N$) at a time $t$ is given by,

$$N = S + E + P + M + R.$$  

New recruits join the susceptible class at a constant rate $\Lambda$ through birth. Assuming homogeneous mixing of the population, the susceptible acquire leprosy infection at rates $\lambda_p = \frac{\beta_p P}{N}$ and $\lambda_M = \frac{\beta_M M}{N}$ following effective contact for disease transmission with paucibacillary infective or multibacillary infective, respectively. Latent individuals progress to active leprosy at rates $\gamma_F$ and $\gamma_M$ for PB and MB, respectively. To account for the level of non-compliance (defaulters), we assume that a fraction $f$ have not collected the MDT for 3 consecutive months and have discontinued the treatment, while the complementary fraction $(1 - f)$ will successful complete treatment. Some individuals in R class relapse back into infective state at rates $q_p$ and $q_M$ for PB and MB, respectively. Natural mortality occurs in all classes at a constant rate $\mu$ with infectious individuals suffering additional mortality rates $\nu_p$ and $\nu_M$, respectively, due to the disease.

The aforementioned assumptions and description above give rise to the following system of ordinary differential equations

\begin{align*}
S' &= \Lambda - (\lambda_p + \lambda_M + \mu)S, \\
E' &= (\lambda_p + \lambda_M)S + f\alpha_p P + f\alpha_M M - (\gamma_p + \gamma_M + \mu)E, \\
P' &= \gamma_p E + q_p R - (\alpha_p + \mu + \nu_p)P, \\
M' &= \gamma_M E + q_M R - (\alpha_M + \mu + \nu_M)M, \\
R' &= (1 - f)\alpha_p P + (1 - f)\alpha_M M - (q_p + q_M + \mu)R.
\end{align*}
(1)
2.1. Model basic properties

In this section, we study the basic results of solutions for model system (1), which are essential in the proofs of stability.

**Lemma 1.** *The equations preserve positivity of solutions.*

*Proof.* The vectorfield given by the right hand side of (1) points inward on the boundary of \( \{0\} \).

For example, if \( P = 0 \), then, \( P' = \gamma_p E + q_p R \geq 0 \). All the other components are similar.

**Lemma 2.** *Each non-negative solution is bounded in \( L^1 \)-norm max \{\(N(0)\), \(\Lambda/\mu\)\}.*

*Proof.* The \( L^1 \)-norm of each non-negative solution is \( N \) and it satisfies the inequality \( N' \leq \Lambda - \mu N \). Solutions to the equation \( M' = \Lambda - \mu M \) are monotone.

![Model flow diagram](image-url)
increasing and bounded by $\frac{\Lambda}{\mu}$ if $M(0) < \frac{\Lambda}{\mu}$. They are monotone decreasing and bounded above if $M(0) \geq \frac{\Lambda}{\mu}$. Since $N' \leq M'$, the claim follows.

**Corollary 1.** The region

$$\Phi = \left\{(S, E, P, M, R) \in \mathbb{R}_+^5 : N \leq \frac{\Lambda}{\mu}\right\}.$$  \hspace{1cm} (2)

is invariant and attracting for system (1).

**Theorem 1.** For every non-zero, non-negative initial value, solutions of model system (1) exist for all times

**Proof.** Local existence of solutions follows from standard arguments since the right hand side of (1) is locally Lipschitz. Global existence follows from the a-priori bounds.

3. Equilibrium states, reproductive number and stability

In this section, we derive the equilibrium states, disease-free (DFE) and endemic (EE), of the system (1) and investigate their stability using the reproductive number.

3.1. Disease-free equilibrium (DFE)

Model system (1) has a DFE given by

$$E^0 = \left(S^0, E^0, P^0, M^0, R^0 = \left(\frac{\Lambda}{\mu}, 0, 0, 0, 0\right). \right.$$  \hspace{1cm} (3)

Following van den Driessche and Watmough [41], and using the notation defined therein, the matrices $F$ and $V$, for the new infection terms and the remaining transfer terms are, respectively, given by

$$F = \begin{bmatrix} 0 & \beta_P & \beta_M & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix},$$

and,
It follows that the reproductive number of model system (1) is given by
\[
\mathcal{R}_{PM} = \frac{\beta_p [K_3 K_4 \gamma_p + \alpha_M (1 - f)(q_p \gamma_p - q_p \gamma_M)] + \beta_M [(1 - f)(q_M \gamma_M - q_M \gamma_p) \alpha_p - K_2 K_4 \gamma_M]}{K_1 [K_2 (K_3 K_4 + (1 - f)(\alpha_M q_M - K_4 \alpha_p q_p)) + K_4 (K_3 K_4 \gamma_M - K_2 \alpha_p \gamma_p)]}.
\]

The threshold quantity $\mathcal{R}_{PM}$, measures the average number of new secondary cases generated by a single infectious individual in a population where the aforementioned control measures are in place. An associated epidemiological threshold, the basic reproductive number $\mathcal{R}_0$, obtained using a similar technique of the next generation by considering model system (1) in the absence of leprosy treatment is given by
\[
\mathcal{R}_0 = \frac{\beta_p \gamma_p (\mu + \nu_M)}{(\mu + \gamma_p + \gamma_M) (\mu + \nu_p)}.
\]

The parameter $\mathcal{R}_0$ gives the average number of secondary cases produced by a typical infectious individual during his/her entire life in a population of mostly susceptibles. Using Theorem 2 in [41], the following result is established.

**Lemma 3.** The disease-free equilibrium $E^0$ of system (1) is locally asymptotically stable (LAS) if $\mathcal{R}_{PM} < 1$ and unstable if $\mathcal{R}_{PM} > 1$.

**Sensitivity analysis of the reproductive number**

**Effects of non-compliance**

We now investigate the impact of non-compliance on the transmission dynamics of. Let
\[
\begin{align*}
\tilde{h}_1 &= K_4 K_4 \gamma_p, & \tilde{h}_2 &= \alpha_M (q_p \gamma_p - q_p \gamma_M), & \tilde{h}_3 &= \alpha_p (q_p \gamma_M - q_M \gamma_p), & \tilde{h}_4 &= K_2 K_4 \gamma_M, \\
\tilde{h}_5 &= K_2 K_4 K_4, & \tilde{h}_6 &= K_2 (\alpha_M q_M - K_3 \alpha_p q_p), & \tilde{h}_r &= K_4 (K_2 \alpha_M \gamma_M - K_4 \alpha_p \gamma_p),
\end{align*}
\]
so that

\[ R_{PM} = \frac{\beta_p [\bar{h}_1 + (1 - f)\bar{h}_2] + \beta_2 [1 - f - \bar{h}_2]}{K_1(\bar{h}_6 + (1 - f)\bar{h}_8) + f\bar{h}_7} \]

After some little arrangements, equation (7) can be written as

\[ R_{PM} = \frac{W_1 + (1 - f)W_2}{W_3 - fW_4}, \tag{8} \]

with \( W_1 = \beta_p \bar{h}_1 - \beta_{2d} \bar{h}_4, \ W_2 = \beta_p \bar{h}_2 + \beta_{5d}, \ W_3 = K_1(\bar{h}_6 + \bar{h}_8), \ W_4 = K_1 \bar{h}_7 - \bar{h}_7. \)

Taking the partial derivative of (8) with respect to \( f \) gives

\[ \frac{\partial R_{PM}}{\partial f} = \frac{W_1 W_4 + W_2 (W_4 - W_3)}{(W_3 - fW_4)^2} \tag{9} \]

If \( W_3 < W_4 \), then, equation (9) is positive (from the graphical representation below, it is evident that the inequality holds). Thus, non-compliance may increase leprosy prevalence in the community. The result is further supported graphically in Figure 2 below and parameter values used are in Table 1.

Clearly, results in Figure 2 suggests that an increase non-compliance rate to MDT leads to (almost a linear) increase in initial disease transmission.

**Effects of disease relapse when both strains co-exists**

In this Section, we investigate the effects of disease relapse on disease prevalence. For simplicity, let the progression rate for a non-symptomatic carriers (E) to either PB or MB be denoted by \( \gamma \), disease-induced mortality with respect to either PB or MB be \( \nu \) recovery rate for individuals on treatment be denoted by \( \alpha \), and relapse rate by \( q \), so that equation (5) reduces to

\[ R_{PM} = \frac{\gamma(\beta_{2d} + \beta_p)(2q + \mu)}{2f\alpha\mu(q - \gamma) + (2\gamma + \mu)(2q(\mu + \nu) + \mu(\alpha + \mu + \nu))}. \tag{10} \]

Taking the partial derivative of (10) with respect to relapse rate \( q \), we obtain

\[ \frac{\partial R_{PM}}{\partial q} = \frac{2(\beta_{2d} + \beta_p)(1 - f)[2\gamma + \mu]2q(\alpha + \mu + \nu)}{[2f\alpha\mu(q - \gamma) + (2\gamma + \mu)(2q(\mu + \nu) + \mu(\alpha + \mu + \nu))]^2} > 0. \tag{11} \]
Figure 2. Relationship between the reproductive number RPM and the proportion of leprosy patients who lose sight.

Table 1. Model parameters and their interpretations.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruitment rate for humans</td>
<td>( \Lambda )</td>
<td>100 000 yr(^{-1} )</td>
<td>[31]</td>
</tr>
<tr>
<td>Natural mortality rate for humans</td>
<td>( \mu )</td>
<td>0.02 yr(^{-1} )</td>
<td>[31]</td>
</tr>
<tr>
<td>Disease-induced mortality rate</td>
<td>( \nu_s, \nu_m )</td>
<td>(0.2, 0.25) yr(^{-1} )</td>
<td>Assumed</td>
</tr>
<tr>
<td>Effective contact rate</td>
<td>( \beta_p, \beta_m )</td>
<td>0.15, 0.30 (0.11-0.95)</td>
<td>[21]</td>
</tr>
<tr>
<td>Relapse rate</td>
<td>( q_p, q_m )</td>
<td>(0.1, 0.06) yr(^{-1} )</td>
<td>[22]</td>
</tr>
<tr>
<td>Recovery rate</td>
<td>( \alpha_p, \alpha_m )</td>
<td>(0.65, 0.63) yr(^{-1} )</td>
<td>Assumed</td>
</tr>
<tr>
<td>Rate of progression from latent to active stage</td>
<td>( \gamma_p, \gamma_m )</td>
<td>(0.14, 0.2) yr(^{-1} )</td>
<td>[51]</td>
</tr>
<tr>
<td>A fraction of individuals who lose sight</td>
<td>( f )</td>
<td>0.1</td>
<td>Assumed</td>
</tr>
</tbody>
</table>

Thus, an increase cases of leprosy relapse may have a negative impact on reducing public health burden caused by leprosy epidemic.

### 3.2. Global stability of the disease-free

We claim the following result.
Lemma 4. The disease-free equilibrium $\mathcal{E}^0$ of model system (1) is globally-asymptotically stable (GAS) if $R_{PM} < 1$ and unstable if $R_{PM} > 1$.

Proof. The proof is based on using a Comparison Theorem [28]. Note that the equations of the infected components in system (1) can be written as

$$
\begin{bmatrix}
E' \\
P' \\
M' \\
R'
\end{bmatrix} = [F - V] \begin{bmatrix}
E \\
P \\
M \\
R
\end{bmatrix} - \begin{bmatrix}
1 - \frac{S}{N}
\end{bmatrix} \begin{bmatrix}
0 & \beta_P & \beta_M & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0
\end{bmatrix} \begin{bmatrix}
E \\
P \\
M \\
R
\end{bmatrix}
$$

where $F; V, K_1, K_2, K_3, K_4$ are as defined earlier in Sec. 3.1 (Case 3). Since $S \leq N$, (for all $t \geq 0$) in $\Phi$, it follows that

$$
\begin{bmatrix}
E' \\
P' \\
M' \\
R'
\end{bmatrix} \leq [F - V] \begin{bmatrix}
E \\
P \\
M \\
R
\end{bmatrix}
$$

Using the fact that the eigenvalues of the matrix $F - V$ all have negative real parts, it follows that the linearized differential inequality system (12) is stable whenever $R_{PM} < 1$: Consequently, $(E, P, M, R) \rightarrow (0, 0, 0, 0)$ as $t \rightarrow \infty$. Thus, by Comparison Theorem [28] $(E, P, M, R) \rightarrow (0, 0, 0, 0)$ as $t \rightarrow \infty$ and evaluating system (1) at, $E = P = M = R = 0$ gives, $S \rightarrow S^0$ for $R_{PM} < 1$: Hence, the DFE $\mathcal{E}^0$ is GAS for $R_{PM} < 1$.

3.3. Endemic equilibrium and stability analysis

The endemic equilibrium point is given by $\mathcal{E}^* = (S^*, E^*, P^*, M^*, R^*)$, and it worth noting that permanence of the disease destabilizes the disease-free equilibrium $\mathcal{E}^0$ since $R_{PM} > 1$, thus the endemic equilibrium $\mathcal{E}^*$ exists.

Lemma 5. Model system (1) is uniformly persistent on $\Phi$.

Proof. Since this is not the primary focus of the study, we provide only a sketch of the proof. Uniform persistence system of (1) implies there exists a constant $\zeta > 0$ such that any solution of (1) which starts in

$$(S, E, P, M, R) \in \Phi,$$

satisfies,
\[ \zeta \leq \liminf_{t \to \infty} S(t), \quad \zeta \leq \liminf_{t \to \infty} E(t), \quad \zeta \leq \liminf_{t \to \infty} P(t), \quad \zeta \leq \liminf_{t \to \infty} M(t), \quad \zeta \leq \liminf_{t \to \infty} R(t). \]  

\( \limsup_{t \to \infty} S(t) \leq \frac{\Lambda}{\mu} \) and due to positivity of all model variables, \( \liminf_{t \to \infty} S(t) \geq 0 \), that is \( \zeta = 0 \), and hence the uniformity. Next, define the following Korobeinikov-Maini [26] type Lyapunov functional

\[ V(S, E, P, M, R) = (S - S^*) \ln S + (E - E^*) \ln E + (P - P^*) \ln P + (M - M^*) \ln M + (R - R^*) \ln R. \]  

which is continuous for all \((S, E, P, M, R) > 0\) and satisfies

\[ \frac{\partial V}{\partial S^*} = (1 - \frac{S^*}{S}), \ldots, \frac{\partial V}{\partial M^*} = (1 - \frac{M^*}{R}). \]  

Consequently, the endemic equilibrium \( E^* \) is the only extremum and the global minimum of the function \( V \in \mathbb{R}^5 \). Also, \( V(S, E, P, M, R) > 0 \) and \( V'(S, E, P, M, R) = 0 \) only at \( E^* \). Thus, \( V(S, E; P, M, R) \) is a Lyapunov function. At equilibrium, \( \Lambda = (\lambda^*_p + \lambda^*_M + \mu)S^* \), substituting this into the time derivative of \( V \) along the solution path of the model system (1), we have

\[ V'(S, E, P, M, R) = \left( S - S^* \right) \frac{S'}{S} + \left( E - E^* \right) \frac{E'}{E} + \left( P - P^* \right) \frac{P'}{P} + \left( M - M^* \right) \frac{M'}{M} \]

\[ + \left( R - R^* \right) \frac{R'}{R} \]

\[ \leq -\mu \frac{(S - S^*)^2}{S} + g(S, E, P, M, R). \]

The function \( g \), can be shown to be non-positive using Barbalat Lemma [2] or by the approach in McCuskey [32]. Hence, \( V'(S, E, P, M, R) \leq 0 \) with equality only at \( E^* \). The only invariant set in \( \Phi_1 \), the only interior of \( \Phi_1 \) is the set consisting of the endemic equilibrium \( E^* \). Thus, all solutions of model system (1) which intersect \( \Phi_1 \) limit to and invariant set, the singleton \( \{E^*\} \). Therefore, from the Lyapunov-Lasalle invariance principle, model system (1) is uniformly persistent.

From the epidemiological point of view, this result means that the disease persists at endemic state, which is of concern to the public health sector. We now analyze the stability of the endemic equilibrium \( E^* \), but before starting our main results, we give the following Theorem which will be useful in subsequent section.

**Theorem 2.** (See [4]) Consider the following general system of ordinary differential equations with a parameter \( \phi \),

\[ \frac{dx}{dt} = f(x, \phi), f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}^n \text{ and } f \in C^2(\mathbb{R}^n \times \mathbb{R}). \]  

\[ \zeta \leq \liminf_{t \to \infty} S(t), \quad \zeta \leq \liminf_{t \to \infty} E(t), \quad \zeta \leq \liminf_{t \to \infty} P(t), \quad \zeta \leq \liminf_{t \to \infty} M(t), \quad \zeta \leq \liminf_{t \to \infty} R(t). \]
Without loss of generality, it is assumed that 0 is an equilibrium for System (16) for all values of the parameter \( \phi \) that is \( f(0, \phi) = 0 \) for all \( \phi \) and assume
\[
A1: \quad A = D_x f(0, 0) = (\frac{\partial f_j}{\partial x_j}(0, 0)) \quad \text{is the linearisation of system (16) around the equilibrium 0 with } \dot{\phi} \text{ evaluated at 0. Zero is a simple eigenvalue of } A \text{ and other eigenvalues of } A \text{ have negative real parts;}
\]
\[
A2: \quad \text{Matrix } A \text{ has a right eigenvector } w \text{ and a left eigenvector } v \text{ corresponding to the zero eigenvalue.}
\]

Let \( f_k \) be the \( K^{th} \) component of \( f \) and
\[
a = \sum_{k, i, j = 1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0, 0),
\]
\[
b = \sum_{k, i = 1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0, 0). \tag{17}
\]
The local dynamics of (16) around 0 are totally governed by \( a \) and \( b \).

i. \( a > 0, \ b > 0 \). When \( \phi < 0 \) with \( |\phi| \ll 1 \), 0 is locally asymptotically stable, and there exists a positive unstable equilibrium; when \( 0 < \phi \ll 1 \), 0 is unstable and there exists a negative and locally asymptotically stable equilibrium;

ii. \( a < 0; \ b < 0 \). When \( \phi < 0 \) with \( |\phi| \ll 1 \), 0 is unstable; when \( 0 < \phi \ll 1 \), asymptotically stable, and there exists a positive unstable equilibrium;

iii. \( a > 0; \ b < 0 \). When \( \phi < 0 \) with \( |\phi| \ll 1 \), 0 is unstable, and there exists a locally asymptotically stable negative equilibrium; when \( 0 < \phi \ll 1 \); 0 is stable, and a positive unstable equilibrium appears;

iv. \( a < 0; \ b > 0 \). When \( \phi \) changes from negative to positive, 0 changes its stability from stable to unstable. Correspondingly, a negative equilibrium becomes positive and locally asymptotically stable.

To analyze the stability of this equilibrium point (\( \mathcal{E}^* \)) we make use of the Centre Manifold theory [3] as described in Theorem 4.1 of Castillo-Chavez and Song (2004) [4], to establish the local asymptotically, we define \( S = x_1, \ E = x_2, \ P = x_3, \ M = x_4, \ R = x_5 \), that \( N = x_1 + x_2 + x_3 + x_4 + x_5 \).Using
the vector notation $X = (x_1, x_2, x_3, x_4, x_5)^T$, model system (1) under these condition can be written in the form $\frac{dX}{dt} = F = (f_1, f_2, f_3, f_4, f_5)^T$, such that

\begin{align*}
x_1' &= f_1 = \Lambda - \frac{(\beta_p x_3 + \beta_M x_4)x_1}{x_1 + x_2 + x_3 + x_4 + x_5} - \mu x_1, \\
x_2' &= f_2 = \frac{(\beta_p x_3 + \beta_M x_4)x_1}{x_1 + x_2 + x_3 + x_4 + x_5} + f \alpha_p x_3 + f \alpha_M x_4 - (\gamma_p + \gamma_M + \mu)x_2, \\
x_3' &= f_3 = \gamma_p x_2 + q_p x_5 - (\alpha_p + \mu + \nu_p)x_3, \\
x_4' &= f_4 = \gamma_M x_2 + q_M x_5 - (\alpha_M + \mu + \nu_M)x_4, \\
x_5' &= f_5 = (1 - f)\alpha_p x_3 + (1 - f)\alpha_M x_4 - (q_p + q_M + \mu)x_5. \\
\end{align*}

(18)

The method entails evaluating the Jacobian of the system (18) at the disease-free ($E^0$) denoted by $J(E^0)$: This gives

\[ J(E^0) = \begin{bmatrix} -\mu & 0 & -\beta_p & -\beta_M & 0 \\ 0 & -\mu - \gamma_p - \gamma_M & f \alpha_p + \beta_p & f \alpha_M + \beta_M & 0 \\ 0 & \gamma_p & -\mu - \alpha_p - \nu_p & 0 & q_p \\ 0 & \gamma_M & 0 & -(1 - f)\alpha_p & q_M \\ 0 & 0 & (1 - f)\alpha_p & (1 - f)\alpha_M & -\mu - q_p - q_M \end{bmatrix} \]  \hspace{1cm} (19)

From (19) it follows that the reproductive number is given by

\[ R_{PM} = \frac{\beta_p [K_3 K_4 \gamma_p + \alpha_M (1 - f) (q_p \gamma_M - q_p \gamma_M)] + \beta_M [K_3 (1 - f) (q_p \gamma_M - q_p \gamma_M) + K_3 f] [K_2 K_4 \gamma_M + K_3 (1 - f) \alpha_p q_p] + K_3 f [K_2 \alpha_M \gamma_M + K_3 \alpha_p \gamma_M]}{K_1 [K_2 (K_3 K_4 + (1 - f) \alpha_M q_M - K_3 (1 - f) \alpha_p q_p) + K_3 f [K_2 \alpha_M \gamma_M - K_3 \alpha_p \gamma_M]].} \hspace{1cm} (20)\]

Since PB is less transmissible in comparison to MB [40], we assume that $\beta_p < \beta_M$, so that $\beta_M = \theta \beta_p$, where $\theta > 1$, is the modification parameter which captures the assumed increased transmissibility with MB strain. Let $\beta_p = \beta$, thus, equation (20) can be rewritten as

\[ R_{PM} = \frac{\beta [(K_3 K_4 \gamma_p + \alpha_M (1 - f) (q_p \gamma_M - q_p \gamma_M)] + \theta [(1 - f) (q_p \gamma_M - q_p \gamma_M) \alpha_p - K_3 K_4 \gamma_M]}{K_1 [K_2 (K_3 K_4 + (1 - f) \alpha_M q_M - K_3 (1 - f) \alpha_p q_p) + K_3 f [K_2 \alpha_M \gamma_M - K_3 \alpha_p \gamma_M]].}, \hspace{1cm} (21)\]

If $\beta$ is taken as the bifurcation parameter, solving for $\beta = \beta_*$ when $R_{PM} = 1$, we obtain
Thus, the linearized system of the transformed system (18) with \( \beta = \beta_s \) chosen as a bifurcation parameter has a simple zero eigenvalue, hence it can be shown that the Jacobian (19) at \( \beta = \beta_s \) has a right and left eigenvector given below.

**Eigenvectors of \( J(\mathcal{E}^0) \)**

It can be shown that the Jacobian \( J(\mathcal{E}^0) \) of system (18) at \( \beta = \beta_s \) has a right eigenvector (corresponding to the zero eigenvalue) given by \( \mathbf{w} = (w_1 \ w_2 \ w_3 \ w_4 \ w_5)^T \), where

\[
\begin{align*}
    w_1 &= -\frac{\beta_s (\alpha_p + \eta \gamma_p)}{\mu} w_2, \quad w_2 > 0, \\
    w_3 &= \frac{\gamma_p (w_2 + q_p \ w_6)}{\mu + \alpha_p + \nu_p}, \\
    w_4 &= \frac{\gamma_M (w_2 + q_M \ w_6)}{\mu + \alpha_M + \nu_M}, \\
    w_6 &= \frac{(1 - f)(\alpha_p \ w_2 + \alpha_M \ w_4)}{\mu + q_p + q_M}.
\end{align*}
\]

Further, the Jacobian \( J(\mathcal{E}^0) \) has a left eigenvector (associated with the zero eigenvalue) given by \( \mathbf{v} = (v_1 \ v_2 \ v_3 \ v_4 \ v_5)^T \), where

\[
\begin{align*}
    v_1 &= 0, \quad v_2 > 0, \\
    v_3 &= \frac{(f \alpha_p + \beta_s) \ v_3 + (1 - f) \alpha_p \ v_5}{\mu + \alpha_p + \nu_p}, \\
    v_4 &= \frac{(f \alpha_M + \theta \beta_s) \ v_3 + (1 - f) \alpha_M \ v_5}{\mu + \alpha_M + \nu_M}, \\
    v_5 &= \frac{q_p \ v_3 + q_M \ v_4}{\mu + q_p + q_M}.
\end{align*}
\]

**Computations of the bifurcation coefficients \( a \) and \( b \)**

For the system (18), the associated non-zero partial derivatives of \( F \) at \( \mathcal{E}^0 \) are given by

\[
\begin{align*}
    \frac{\partial^2 f_2}{\partial x_2 \partial x_3} &= \frac{\partial^2 f_2}{\partial x_3^2} = \frac{\partial^2 f_2}{\partial x_3 \partial x_5} = -\frac{2 \beta_s \mu}{\Lambda}, \\
    \frac{\partial^2 f_2}{\partial x_2 \partial x_4} &= \frac{\partial^2 f_2}{\partial x_4^2} = \frac{\partial^2 f_2}{\partial x_4 \partial x_5} = -\frac{2 \beta_s \mu}{\Lambda}, \\
    \frac{\partial^2 f_2}{\partial x_3 \partial x_4} &= -\frac{2(1 + \theta) \beta_s \mu}{\Lambda}.
\end{align*}
\]

It follows from (23) that,

\[
\begin{align*}
    a &= \frac{\alpha_2 \sum_{i,j=1}^{5} w_i w_j \partial^2 f_2}{\partial x_i \partial x_j} \frac{\partial^2 f_2}{\partial x_2 \partial x_3} = -\frac{2 \beta_s \mu (w_2 + w_3 + w_4 + w_6) (w_3 + \theta \ w_4)}{\Lambda} < 0.
\end{align*}
\]
For the sign of $b$, it can be shown that the associated non-vanishing partial derivatives of $F$ are

$$\frac{\partial^2 f_2}{\partial x_3 \partial \beta_*} = 1, \quad \frac{\partial^2 f_2}{\partial x_4 \partial \beta_*} = \theta.$$  \hspace{1cm} (25)

Thus,

$$b = (w_3 + \theta w_4)v_2 > 0,$$ \hspace{1cm} (26)

we summarise the result in Lemma 6 below.

**Lemma 6.** Whenever $R_{PM} > 1$, the endemic equilibrium ($\mathcal{E}^*$) for model system (1) exists and is locally asymptotically stable as guaranteed by Theorem 4.1 [4].

From Figure 3, it is evident that $\mathcal{E}^*$ is unique and model system (1) does not undergo the phenomenon of backward bifurcation.

![Figure 3](image-url)

**Figure 3.** Illustrates the resulting bifurcation (forward bifurcation) for $R_{PM}$. 

4. Population-level effects

In order to illustrate the results of the foregoing analysis, we have simulated model system (1) using the baseline parameters values summarized in Table 1.

The set of simulations (Figure 4) depicts the effects of an increase in the proportion of defaulters on the transmission dynamics of leprosy over a period of 100 years. Simulations suggests that when non compliance rate increases, then the size of each infected and latent populations increases too.

These numerical results are in agreement with analytical results given by equation (9) and the graphical representation in Figure 2.

The set of simulations (Figure 5) presents the dynamics of leprosy for different levels of disease relapse. It clearly shows that when disease relapse cases increase, the size of infected subpopulation ($PB$ and $MB$) increases, and

![Figure 4. Simulations of model system (1) showing the effects of non-compliance to MDT (modeled by the parameter $f$) on the dynamics of a) latent leprosy carriers (E), b) PB individuals (P), c) MB individuals (M) and d) recovery individuals (R) over a period of 100 years. The rest of parameters are fixed on their baseline values from Table 1.](image-url)
Figure 5. Simulations of model system (1) showing the effects of disease relapse on the dynamics of a) latent leprosy carriers (E), b) PB individuals (P), c) MB individuals (M) and d) recovery individuals (R) over a period of 100 years. We set $q = q_1 = q_2$, and the rest of parameters are fixed on their baseline values from Table 1.

this leads to an increase on the subpopulation of latent carriers due to an increase on the risk of exposure to leprosy. The numerical results suggest that an increase in disease relapse makes the eradication of leprosy difficult.

The final set of simulations (Figure 5) depicts the dynamics of the cumulative new infections and leprosy related deaths for different non-compliance and disease relapse rates. It confirms the observations from the previous set of graphical representations that an increase on either of the single factors under study (non-compliance or disease relapse) or both may lead to an increase in leprosy epidemic in the community. The simulation of the baseline scenario ($f = q = 0.95$) predicts an average of more than 21000 cumulative leprosy cases and about 1300 leprosy related deaths over a period of 25 years. In a nutshell, numerical results in this study show that an increase of either one factor in this study (non-compliance or disease relapse) or both may result in an increase in leprosy epidemic, and might make the target of eliminating leprosy difficult to attain.
5. Conclusion

A mathematical model focusing on the transmission dynamics of leprosy in the context of non-compliance and relapse cases with MDT is formulated and its mathematical properties are investigated in order gain insights on the dynamics of the disease. Stability of the equilibrium points have been rigorously analyzed. Analytic and numerical results from the study suggests that non-compliance and relapse of MDT may have a negative impact on leprosy eradication, for instance simulation in Figure 6 clearly shows that with increasing rates of defaulters and relapses cases, the cumulative leprosy cases and leprosy related deaths over a period of 25 years increase. In conclusion, the study highlights that non-compliance and relapse may result in leprosy prevalence increase and should be given prominence in leprosy eradication control strategy.

Figure 6. Simulations of model system (1) showing the effects of increase on non-compliance and disease relapse on the cumulative new infections and leprosy related over a period of 25 years. The rest of parameters are fixed on their baseline values from Table 1.
References


45. World Health Organization. 1991. World Health Assembly - Resolution WHA44.9. WHO.