

ARTICLE TYPE

A qualitative analysis of a *Mycoplasma genitalium* epidemiological model[†]Ricardo Almeida^{*1} | M. Teresa T. Monteiro² | Ezio Venturino³ | Luís Machado⁴¹Center for Research and Development in Mathematics and Applications (CIDMA), Department of Mathematics, University of Aveiro, , 3810–193 Aveiro, Portugal²Algoritmi R&D Center, Department of Production and Systems, University of Minho, Campus de Gualtar, 4710–057 Braga, Portugal³Member of the INdAM research group GNCS, Dipartimento di Matematica “Giuseppe Peano”, Università di Torino, 10123 Torino, Italy⁴Institute of Systems and Robotics – Coimbra, 3030–290 Coimbra, Department of Mathematics, University of Trás-os-Montes e Alto Douro (UTAD), 5001–801 Vila Real, Portugal

Correspondence

^{*}Ricardo Almeida. Email: ricardo.almeida@ua.pt

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Summary

The objective of the paper is to present a qualitative analysis of a mathematical model for the spread of a sexually transmitted infection caused by *Mycoplasma genitalium*. Recent investigations revealed that this pathogen is becoming resistant to the use of macrolides and can turn into a superbug in the next few years.

We present an epidemiological model to describe the spread of the disease. The equilibrium points as computed, and local and global stability of them is studied.

In order to make the mathematical problem more realistic, we propose two different optimal control problems that establish a balance between the number of infected individuals and the use of macrolides. Several numerical illustrations regarding the solutions of the proposed problems will be provided.

KEYWORDS:

Mycoplasma genitalium; Epidemiological models; optimal control; stability

1 | INTRODUCTION

In July 2018, the British Association for Sexual Health and HIV came up with a concern that the little known but common sexually transmitted infection (STI) called *Mycoplasma genitalium* (*M. genitalium*) could become a “superbug” within ten years. In most part of the cases, infections caused by the pathogen *M. genitalium* have no symptoms and when they have, they can be mistaken with other STI, like chlamydia or gonorrhea. This in turn can lead to prescriptions of wrong antibiotics, inappropriate dose or inadequate time of treatment, which can result in an emerging increasing of antimicrobial resistance and, consequently, to a globally public health problem.

The first cases of *M. genitalium* have been identified in 1981 in two men with nongonococcal urethritis²³. During a long time it was not a cause of concern mainly because it was not associated with serious illness or sequelae. For a period, it was even discussed whether treatment would be necessary when this bacterium was found, since in the vast majority of cases it appeared as an asymptomatic infection¹⁸. However, in the last decade, several studies associated the infection by *M. genitalium* to acute and chronic urethritis in men and vaginal discharge, cervicitis and pelvic inflammatory disease in women. Additionally, it can cause serious risks of endometriosis, spontaneous abortion, premature birth and infertility. According to community based studies from the United States, United Kingdom, Australia and Scandinavia, the estimated prevalence of *M. genitalium* is in the range 1%–3% in men and women population (see²¹ and references therein).

M. genitalium is the smallest known bacterium that can replicate itself. In a laboratory setting, this fastidious bacterium is extremely slow growing and therefore culture is not appropriate for diagnosis⁷. Nucleic acid amplification tests (NAATs) are the only useful diagnostic method that detect

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M. genitalium DNA or RNA in clinical specimens²⁴. NAATs use polymerase chain reaction and can be performed on multiple sample types, including urethral, vaginal, and cervical swabs, first void urine, and endometrial biopsies. One of the main obstacles for diagnosing the *M. genitalium* is the lack of commercially available diagnostic tests. NAATs for diagnosing *M. genitalium* use assays that were developed for the research setting and, as a result, NAATs are only available in reference labs, usually at large university hospitals. Also these methods of diagnosis are extremely expensive. Nevertheless, it is also recommended that, where possible, all positive *M. genitalium* should be tested for macrolide resistance mediating mutations⁸.

Usually, the first line treatment is done with a single 1g oral dose of the macrolide azithromycin. However, mutations in region V of the 23S ribosomal RNA gene are becoming frequent, thus inducing a powerful strain of the bacterium resistant to macrolides¹⁶. Owing to emergence of resistance, the efficacy of azithromycin has drastically decreased during the past decade, thus requiring more aggressive treatments²⁴. This represents a big problem for health authorities, since this mutation can lead to a dominant strain of the bacterium resistant to antibiotics. This is where mathematical modeling comes into play.

Mathematical modeling is an essential tool in studying a diverse range of infectious diseases that have impact, not only in terms of physical or mental suffering, but also on a social and economic level. Main goals include the study of disease spread, the better understanding of transmission mechanisms and those properties who are most influential in that spread, and also in the practice of disease management and control¹⁵. In the latter, mathematical models play an important role in making public health decisions on the control of infectious diseases¹.

The importance of modeling infectious diseases dates back to 1760, when Daniel Bernoulli came up with a solution to his mathematical model on smallpox. However, only in the 20th century, mathematical methods have been recognized as fundamental tools in epidemiology². Since then, a huge variety of models have been formulated, mathematically analyzed and applied to infectious diseases, what can be checked in several reviews of the literature (see, for instance, ^{1,6,15}).

Following this reasoning, a mathematical model to investigate the contribution of the *de novo* macrolide resistance mutations to the spread of the antimicrobial resistant *M. genitalium* has been proposed in³. It consists on the SIS (Susceptible–Infectious–Susceptible) model, since an infection by *M. genitalium* does not confer immunity. Thus, susceptibles become infected and then become susceptible again upon recovery. The model have been fitted to data from France, Sweden and Denmark and the authors observed that the high probability of the *de novo* macrolide resistance mutations accelerates the spread of antimicrobial resistant *M. genitalium*.

In this paper, a qualitative analysis of the *M. genitalium* epidemiological model proposed in³ is presented. Namely, we study the existence and uniqueness of solutions of the proposed system of ordinary differential equations, determine the equilibrium points of the system and finally study their global stability. Moreover, two optimal control problems will be formulated in order to give strategies to control the spread of the *de novo* macrolide resistance mutations due to the emergence of azithromycin resistant *M. genitalium*.

The organization of the paper is the following. In Section 2, we recall the SIS mathematical model proposed in³, and prove the existence and uniqueness of solutions in Section 3. In Section 4, we determine the two equilibrium points of the system, namely the disease free equilibrium point and the endemic equilibrium point, and study their stability. In Section 5, we improve the mathematical model given in³ by allowing the treatment rate to vary along time, with the formulation of two different optimal control problems. Necessary optimality conditions are derived using the Pontryagin maximum principle. For these problems, a trade-off between the spread of the infectious individuals and the administration of macrolides is established. This in turn will be helpful for health organizations to make decisions regarding the control of the spread of resistant strains of *M. genitalium*. Several numerical illustrations will be provided in Section 6 for the two optimal control problems, in order to corroborate the theoretical issues derived along the sequel. Finally, using real data provided by the Public Health England, we estimate the transmission and treatment rates to study the spread of *M. genitalium* in England as a study case in Section 7. We finish the paper with some epidemiological implications.

2 | MYCOPLASMA GENITALIUM EPIDEMIOLOGICAL MODEL

In³, a mathematical model to describe the spread of the STI *M. genitalium* is presented. The population is divided in three disjoint compartments (see Figure 1) and it is assumed that NAATs have been performed to diagnose the presence of *M. genitalium*:

1. s , the susceptibles, that is, individuals that can become infected if exposed to the bacterium;
2. i_s , individuals infected with a drug-susceptible strain of the bacterium;
3. i_r , individuals infected with a drug-resistant strain of the bacterium.

The parameters of this model are displayed in Table 1. It is assumed that the size of population is constant, so that newborns or deaths will not be considered. Also, $\chi(1 - \mu)$ is less than γ (otherwise the treatment is useless). The transmission dynamics is described by a SIS model, ruled by

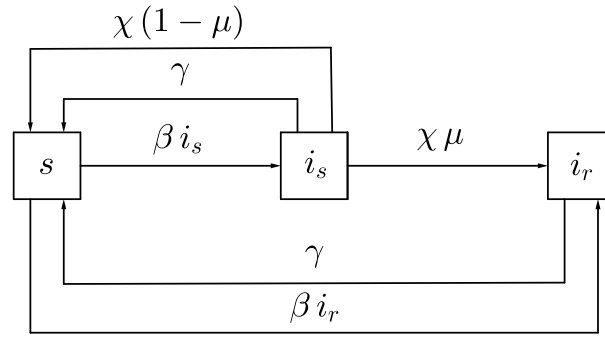


FIGURE 1 Disease transmission dynamics.

β	disease transmission rate
γ	natural rate of recovery from both infections (without treatment)
χ	rate of infected individuals who receive treatment
μ	probability of gene mutation causing resistance to the antibiotic during treatment

TABLE 1 Parameters of the model.

the following system of differential equations

$$\begin{cases} s'(t) = -\beta s(t)(i_s(t) + i_r(t)) + \gamma(i_s(t) + i_r(t)) + (1 - \mu)\chi i_s(t) \\ i_s'(t) = \beta s(t)i_s(t) - (\gamma + \chi)i_s(t) \\ i_r'(t) = \beta s(t)i_r(t) - \gamma i_r(t) + \chi\mu i_s(t), \end{cases} \quad (1)$$

with $t \in [0, T]$, ($T > 0$), subject to the initial conditions

$$s(0) = s_0, i_s(0) = i_{s0}, i_r(0) = i_{r0}, \quad (2)$$

where $s_0, i_{s0}, i_{r0} \in \mathbb{R}_0^+$. Observe that $(s(t) + i_s(t) + i_r(t))' = 0$, that is, the population size is constant along time.

3 | EXISTENCE OF NON-NEGATIVE SOLUTIONS

First, we prove that the problem is well-posed.

Theorem 1. For any initial condition $(s_0, i_{s0}, i_{r0}) \in (\mathbb{R}_0^+)^3$, problem (1)-(2) admits a unique solution.

Proof. System (1) can be written in the form $X'(t) = F(X(t))$, where for $t \in [0, T]$,

$$X = \begin{bmatrix} s \\ i_s \\ i_r \end{bmatrix} \quad \text{and} \quad F(X) = \begin{bmatrix} -\beta s(i_s + i_r) + \gamma(i_s + i_r) + (1 - \mu)\chi i_s \\ \beta s i_s - (\gamma + \chi)i_s \\ \beta s i_r - \gamma i_r + \chi\mu i_s \end{bmatrix}.$$

Since F is polynomial, F is locally Lipschitz continuous and thus problem (1)-(2) admits a unique solution X (Theorems 2.1 and 2.2 in⁹). $\square$

Now we prove the non-negativity of solution for system (1)-(2).

Theorem 2. The solution of system (1)-(2) is nonnegative.

Proof. Since

$$\begin{cases} s'|_{s=0} = \gamma(i_s + i_r) + (1 - \mu)\chi i_s \geq 0 \\ i_s'|_{i_s=0} = 0 \\ i_r'|_{i_r=0} = \chi\mu i_s \geq 0, \end{cases}$$

according to Lemma 2 of²⁵, we conclude that the solution of the system (1)-(2) is nonnegative. $\square$

4 | EQUILIBRIUM POINTS AND STABILITY

In this section, we study the stability of the equilibrium points for (1). To find the equilibrium points, we need to solve the algebraic system

$$s'(t) = 0; \quad i'_s(t) = 0; \quad i'_r(t) = 0. \quad (3)$$

In this way, we obtain two equilibrium points:

- a disease free equilibrium point $P_F = (1, 0, 0)$, and
- an endemic equilibrium point $P_E = (\gamma/\beta, 0, 1 - \gamma/\beta)$, if $\gamma/\beta \in [0, 1)$.

To study their stability, in order to simplify system (1), we consider the relation $s = 1 - i_s - i_r$, and thus system (1) becomes

$$\begin{cases} i'_s(t) = \beta(1 - i_s(t) - i_r(t))i_s(t) - (\gamma + \chi)i_s(t) \\ i'_r(t) = \beta(1 - i_s(t) - i_r(t))i_r(t) - \gamma i_r(t) + \chi\mu i_s(t). \end{cases} \quad (4)$$

The Jacobian matrix associated to system (4) is the following

$$J(P) = \begin{bmatrix} -\beta i_s + \beta(1 - i_s - i_r) - (\gamma + \chi) & -\beta i_s \\ -\beta i_r + \chi\mu & -\beta i_r + \beta(1 - i_s - i_r) - \gamma \end{bmatrix}. \quad (5)$$

Theorem 3. The disease free equilibrium point $P_F = (1, 0, 0)$ is

1. locally asymptotically stable if $\beta/\gamma < 1$;
2. unstable if $\beta/\gamma > 1$;

If $\beta/\gamma = 1$, then a critical case occurs.

Proof. The Jacobian matrix (5), evaluated at the disease free equilibrium point, is the following:

$$J(P_F) = \begin{bmatrix} \beta - \gamma - \chi & 0 \\ \chi\mu & \beta - \gamma \end{bmatrix}. \quad (6)$$

Since the spectrum of matrix (6) is

$$\sigma(J(P_F)) = \{\beta - \gamma, \beta - \gamma - \chi\},$$

we notice that if $\beta - \gamma < 0$, then all eigenvalues are reals and negative, and so system (4) is locally asymptotically stable, which ends the proof. $\square$

The condition $\beta - \gamma < 0$ is equivalent to $\beta/\gamma < 1$. The number

$$R_0 = \frac{\beta}{\gamma}$$

is known as the basic reproduction number. It plays an important role in epidemiology modeling since it is often used as the threshold quantity which determines a borderline between a persistence or a disease death.

Theorem 4. If $R_0 > 1$, then model (1) has an endemic equilibrium point given by $P_E = (1/R_0, 0, 1 - 1/R_0)$, and is locally asymptotically stable.

Proof. In this case, the Jacobian matrix is given by

$$J(P_E) = \begin{bmatrix} -\chi & 0 \\ -\beta + \gamma + \chi\mu & -\beta + \gamma \end{bmatrix},$$

and its eigenvalues are

$$\lambda = -\chi \vee \lambda = -\beta + \gamma.$$

So, the eigenvalues are reals and negative under the assumption $R_0 > 1$. $\square$

In the field of epidemic models, one of the most challenging questions is the stability analysis^{12,13,14,19,20,26}.

Theorem 5. If $R_0 < 1$, then the disease free equilibrium point $P_F = (1, 0, 0)$ of model (1) is globally asymptotically stable.

Proof. Consider the following Lyapunov function $V(i_s, i_r) = 2\mu i_s + i_r$. Differentiating V with respect to time gives

$$\dot{V} = \frac{\partial V}{\partial i_s} i'_s + \frac{\partial V}{\partial i_r} i'_r = 2\mu i'_s + i'_r.$$

Replacing the expressions for the derivatives in $\dot{V}$, and using the relation $\beta < \gamma$, it follows from (4) that

$$\begin{aligned}\dot{V} &= 2\mu[\beta(1 - i_s - i_r)i_s - (\gamma + \chi)i_s] + \beta(1 - i_s - i_r)i_r - \gamma i_r + \chi\mu i_s \\ &\leq -\gamma(i_s + i_r)(2\mu i_s + i_r) - \mu\chi i_s.\end{aligned}$$

Thus, $\dot{V} \leq 0$ for all $s, i_s, i_r \geq 0$. Moreover, $\dot{V} = 0$ if and only if $(s, i_s, i_r) = P_F$. Consequently, by LaSalle's Invariance Principle¹⁰, the disease free equilibrium point P_F is globally asymptotically stable. $\square$

Theorem 6. Let $R_0 > 1$. Then, the endemic equilibrium point $P_E = (s^*, i_s^*, i_r^*)$ of model (1) is globally asymptotically stable.

Proof. Consider the following Lyapunov function

$$V(i_s, i_r) = i_s + \left(i_r - i_r^* - i_r^* \ln \frac{i_r}{i_r^*} \right).$$

Differentiating V , we obtain

$$\dot{V} = i_s' + \left(1 - \frac{i_r^*}{i_r} \right) i_r',$$

and replacing the derivatives as given in (4), we obtain

$$\dot{V} = \beta(1 - i_s - i_r)i_s - (\gamma + \chi)i_s + \frac{i_r - i_r^*}{i_r} [\beta(1 - i_s - i_r)i_r - \gamma i_r + \chi\mu i_s].$$

Using the relation $\gamma = \beta - \beta i_r^*$, we deduce the following:

$$\begin{aligned}\dot{V} &= \beta i_s(i_r^* - i_s - i_r) - \chi i_s + \beta(i_r - i_r^*)(i_r^* - i_s - i_r) + \chi\mu i_s \frac{i_r - i_r^*}{i_r} \\ &= -\beta(i_r^* - i_s - i_r)^2 - \chi i_s \left[1 - \mu \frac{i_r - i_r^*}{i_r} \right].\end{aligned}$$

Observe that, for all $t \in [0, T]$, $1 - \mu(i_r - i_r^*)/i_r > 0$. In fact, if $(i_r - i_r^*)/i_r > 0$, and since $\mu \in (0, 1)$, we get that

$$0 < \frac{i_r^*}{i_r} < 1 - \mu \frac{i_r - i_r^*}{i_r} < 1.$$

The other case $(i_r - i_r^*)/i_r \leq 0$ is obvious. Therefore, $\dot{V} \leq 0$ for all $s, i_s, i_r \geq 0$. Also, $\dot{V} = 0$ if and only if $i_s = 0$ and $i_r = i_r^*$. Again, by LaSalle's Invariance Principle, the endemic free equilibrium point P_E is globally asymptotically stable. $\square$

In Figure 2, the results about stability of the model (1)-(2) are exemplified. For the numerical simulations three different values for β are considered: $\beta = 0.7 \text{ person}^{-1} \text{y}^{-1}$; $\beta = 0.9 \text{ person}^{-1} \text{y}^{-1}$ and $\beta = 2 \text{ person}^{-1} \text{y}^{-1}$. For the remaining parameters we took the ones given in³ for Denmark: $\gamma = 0.8 \text{ y}^{-1}$; $\chi = 0.13 \text{ y}^{-1}$ and $\mu = 12\%$. Moreover, according to^{21,22}, the estimated prevalence of *M. genitalium* infection is in between the range 1%–3% in men and women population. In the particular case of Denmark, according to a study report from 2006 to 2010, 27% to 42% of the specimens contained macrolide resistance mutation¹⁷. So, we also consider $(s_0, i_{s0}, i_{r0}) = (0.98, 0.013, 0.007)$ as initial conditions. Observe that, when

1. $\beta = 0.7 \text{ person}^{-1} \text{y}^{-1}$, the basic reproduction number is $R_0 = 0.875 < 1$ and so the disease free equilibrium point $P_F = (1, 0, 0)$ is globally asymptotically stable;
2. $\beta = 0.9 \text{ person}^{-1} \text{y}^{-1}$, $R_0 = 1.125 > 1$ and so the endemic equilibrium point $P_E = (0.889, 0, 0.111)$ is globally asymptotically stable;
3. $\beta = 2 \text{ person}^{-1} \text{y}^{-1}$, $R_0 = 2.5 > 1$ and so the endemic equilibrium point $P_E = (0.4, 0, 0.6)$ is globally asymptotically stable.

In Figure 3 we present the evolution of the bacterium propagation, taking into consideration different values of the total number of infected individuals I_0 at the initial time, as well as different values of transmission rate β .

Note that all the sensitivity surfaces are drawn at time $t = 10$ years, at which none of the populations has reached a steady state, the dynamics is still changing in time. But they are comparable, as all of them are drawn at this time.

All the figures show that the influence of the initial condition on the total number of infected I_0 does not influence the outcome as is expected, due to the global stability of the equilibrium points..

Instead, the contact rate β has a relevant role in the disease propagation. A steady increase of the infected is observed with an increasing value of this rate. In each country, the attained size of the infected individuals, for the maximum explored value of the transmission rate, $\beta = 3$ differs. For France, the fraction of infected with a drug-susceptible strain of the bacterium lies between 0.30 and 0.35, probably attaining the value 0.32 while the corresponding fraction of infected with a drug-resistant strain attains the value 0.4. In Sweden, the former is only 0.2 while the drug-resistants are a half of the total population, thereby the situation would be worse than in France. The situation in Denmark appears to be a little better than in Sweden, as the drug-susceptibles are slightly above the value 0.2, maybe around 0.22, at the expense of the drug-resistants that fall slightly below 0.5.

The bottom line is that the drug-resistants in all cases are bound to increase to an alarming percentage of the population under scrutiny.

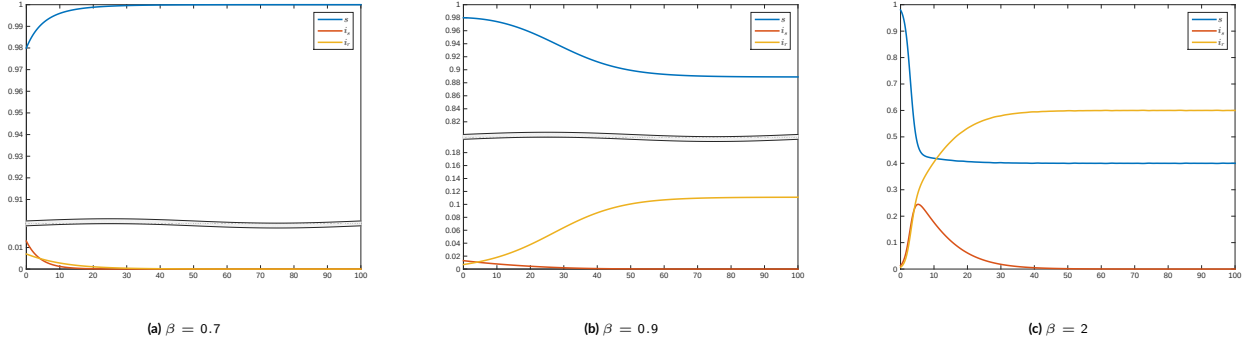


FIGURE 2 Dynamics of susceptible and infected population.

5 | AN OPTIMAL CONTROL APPROACH

So far, we considered the rate of infected individuals that will receive treatment constant during the process, $\chi \in \mathbb{R}_0^+$. Since treatment involves costs, and in any situation, health organizations have to find a balance between financial issues and diseases control, in this section we consider a treatment rate depending on time, $\chi : [0, T] \rightarrow \Omega$, which will be the control. We assume that the control is bounded, $\Omega = [0, \chi_{\max}]$, in order to deal with a more realistic model and two distinct optimal control problems will be proposed.

The first optimal control problem ($\mathcal{P}_1$) is stated as follows:

$$\min_{\chi \in \Omega} \mathcal{J}_1 = \int_0^T \left(\omega_s i_s(t) + \omega_r i_r(t) + \frac{\omega_\chi}{2} \chi^2(t) \right) dt \quad (7)$$

subject to the system

$$\begin{cases} i'_s(t) = \beta(1 - i_s(t) - i_r(t))i_s(t) - (\gamma + \chi(t))i_s(t) \\ i'_r(t) = \beta(1 - i_s(t) - i_r(t))i_r(t) - \gamma i_r(t) + \chi(t)\mu i_s(t), \end{cases} \quad (8)$$

and to the initial conditions

$$\begin{cases} i_s(0) = i_{s0} \\ i_r(0) = i_{r0} \end{cases} \quad (9)$$

where $i_{s0}, i_{r0} \in \mathbb{R}_0^+$.

Parameters ω_s, ω_r and ω_χ are positive real constants that can be interpreted as weights associated to the infected individuals and to the treatment rate, respectively. These weights will provide a scaling for the magnitudes of the quantities i_s, i_r, χ . For the sake of simplicity we fix $\omega_\chi = 1$. The goal is to minimize the number of infected individuals i_s and i_r and at the same time the treatment rate χ .

First, define the Hamiltonian

$$\begin{aligned} H(i_s, i_r, \chi, \lambda_1, \lambda_2) \\ = \omega_s i_s + \omega_r i_r + \frac{1}{2} \chi^2 + \lambda_1 (\beta(1 - i_s - i_r)i_s - (\gamma + \chi)i_s) + \lambda_2 (\beta(1 - i_s - i_r)i_r - \gamma i_r + \chi \mu i_s), \end{aligned}$$

where $\lambda_i : [0, T] \rightarrow \mathbb{R}, i = 1, 2$, are two auxiliary functions. Next result gives necessary optimality conditions for problem ($\mathcal{P}_1$).

Theorem 7. ⁽⁴⁾ There exists an optimal control $\bar{\chi}$ and a set of corresponding solutions $(\bar{i}_s, \bar{i}_r)$ that minimize the objective functional (7) subject to (8) and (9). Moreover, there exists an adjoint function $\bar{\lambda} : [0, T] \rightarrow \mathbb{R}^2, \bar{\lambda} = (\bar{\lambda}_1, \bar{\lambda}_2)$, such that $(\bar{i}_s, \bar{i}_r, \bar{\chi}, \bar{\lambda})$ is a solution of the following equations:

1. The control system

$$\begin{cases} i'_s(t) = \beta(1 - i_s(t) - i_r(t))i_s(t) - (\gamma + \chi(t))i_s(t) \\ i'_r(t) = \beta(1 - i_s(t) - i_r(t))i_r(t) - \gamma i_r(t) + \chi(t)\mu i_s(t), \end{cases}$$

that is, system (8);

2. The adjoint system:

$$\begin{cases} \lambda'_1 = -\omega_s + \lambda_1(\beta i_s - \beta(1 - i_s - i_r) + \gamma + \chi) + \lambda_2(\beta i_r - \chi \mu) \\ \lambda'_2 = -\omega_r + \lambda_1 \beta i_s + \lambda_2(\beta i_r - \beta(1 - i_s - i_r) + \gamma); \end{cases} \quad (10)$$

3. The transversality condition

$$\lambda_1(T) = 0 = \lambda_2(T). \quad (11)$$

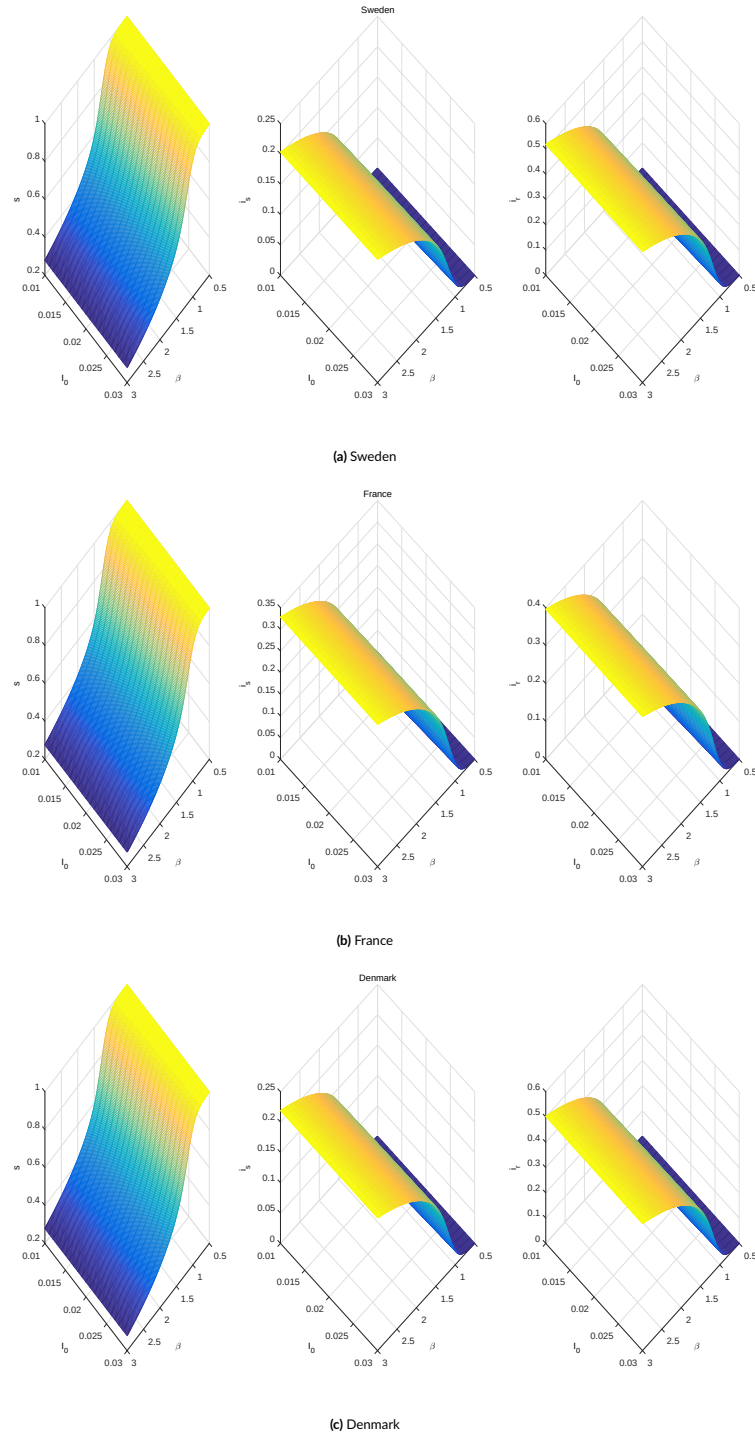


FIGURE 3 Dependence on I_0 and β .

Furthermore, the following minimization condition is fulfilled:

$$H(\bar{i}_s, \bar{i}_r, \bar{\chi}, \bar{\lambda}_1, \bar{\lambda}_2) = \min_{\chi \in \Omega} H(\bar{i}_s, \bar{i}_r, \chi, \bar{\lambda}_1, \bar{\lambda}_2).$$

Proof. The existence of an optimal control $\bar{\chi}$ is an immediate consequence of ^{5, Corollary 4.1}. In fact, it follows due to:

1. the convexity of integrand of $\mathcal{J}_1$ with respect to the control χ ;

2. a priori boundedness of the state solutions;
3. the state system (8) satisfies the Lipschitz property with respect to the state variables since state solutions are bounded.

The deduction of the necessary optimality conditions is a standard result from the Pontryagin's minimum principle. If $\bar{\chi}$ is an optimal control, there exists a nontrivial mapping $\bar{\lambda} : [0, T] \rightarrow \mathbb{R}^2$, such that the following equations are satisfied for $(\bar{i}_s, \bar{i}_r, \bar{\chi}, \bar{\lambda})$:

1. The control system

$$i'_s = \frac{\partial H}{\partial \lambda_1} \quad \text{and} \quad i'_r = \frac{\partial H}{\partial \lambda_2};$$

2. The adjoint system:

$$\lambda'_1 = -\frac{\partial H}{\partial i_s} \quad \text{and} \quad \lambda'_2 = -\frac{\partial H}{\partial i_r};$$

3. the transversality condition $\lambda_1(T) = 0 = \lambda_2(T)$;

and also the minimization condition:

$$H(\bar{i}_s, \bar{i}_r, \bar{\chi}, \bar{\lambda}_1, \bar{\lambda}_2) = \min_{\chi \in U} H(\bar{i}_s, \bar{\lambda}_1, \chi, \bar{\lambda}_2).$$

□

Observe that the minimization condition is deduced from the following fact:

$$\frac{\partial H}{\partial \chi} = 0 \Leftrightarrow \chi = (\lambda_1 - \lambda_2 \mu) i_s,$$

whenever χ is on the interior of the set Ω , that is, when $0 < \chi < \chi_{\max}$. Thus, we need to solve the system

$$\begin{cases} i'_s = \beta(1 - i_s - i_r)i_s - (\gamma + \chi)i_s \\ i'_r = \beta(1 - i_s - i_r)i_r - \gamma i_r + \chi \mu i_s \\ \lambda'_1 = -w_s + \lambda_1(\beta i_s - \beta(1 - i_s - i_r) + \gamma + \chi) + \lambda_2(\beta i_r - \chi \mu) \\ \lambda'_2 = -w_r + \lambda_1 \beta i_s + \lambda_2(\beta i_r - \beta(1 - i_s - i_r) + \gamma), \end{cases}$$

together with the boundary conditions

$$\begin{cases} i_s(0) = i_{s0} \\ i_r(0) = i_{r0} \\ \lambda_1(T) = 0 \\ \lambda_2(T) = 0, \end{cases}$$

where

$$\chi(t) = \begin{cases} 0, & \text{if } (\lambda_1(t) - \lambda_2(t)\mu)i_s(t) < 0 \\ (\lambda_1(t) - \lambda_2(t)\mu)i_s(t), & \text{if } 0 \leq (\lambda_1(t) - \lambda_2(t)\mu)i_s(t) \leq \chi_{\max} \\ \chi_{\max}, & \text{if } (\lambda_1(t) - \lambda_2(t)\mu)i_s(t) > \chi_{\max}. \end{cases}$$

The control can be written in a more concise way:

$$\chi(t) = \min \{ \max \{ (\lambda_1(t) - \lambda_2(t)\mu)i_s(t), 0 \}, \chi_{\max} \}. \quad (12)$$

Based on the a priori boundedness of the state and adjoint functions and the resulting Lipschitz structure of the ODEs, we can ensure a unique optimal control $\bar{\chi}$ for a small value of T . The uniqueness of the optimal control follows from the uniqueness of the optimality system, given by the control system (8) and the adjoint system (10), together with the transversality condition (11) and with characterization (12).

The second optimal control problem ($\mathcal{P}_2$) to be considered is the following:

$$\min_{\chi \in \Omega} \mathcal{J}_2 = \int_0^T \frac{\omega_\chi}{2} \chi^2(t) dt + \omega_s i_s(T) + \omega_r i_r(T) \quad (13)$$

subject to the system (8) and to the initial conditions (9). Again, we consider $\omega_\chi = 1$.

In this case, the goal is to minimize the number of infected individuals only at the final time and at the same time minimizing the treatment rate during the entire process.

The necessary conditions are given by

$$\begin{cases} i'_s = \beta(1 - i_s - i_r)i_s - (\gamma + \chi)i_s \\ i'_r = \beta(1 - i_s - i_r)i_r - \gamma i_r + \chi \mu i_s \\ \lambda'_1 = \lambda_1(\beta i_s - \beta(1 - i_s - i_r) + \gamma + \chi) + \lambda_2(\beta i_r - \chi \mu) \\ \lambda'_2 = \lambda_1 \beta i_s + \lambda_2(\beta i_r - \beta(1 - i_s - i_r) + \gamma), \end{cases}$$

together with the boundary conditions

$$\begin{cases} i_s(0) = i_{s0} \\ i_r(0) = i_{r0} \\ \lambda_1(T) = w_s \\ \lambda_2(T) = w_r, \end{cases}$$

where

$$\chi(t) = \min \{ \max \{ (\lambda_1(t) - \lambda_2(t)\mu) i_s(t), 0 \}, \chi_{\max} \}. \quad (14)$$

The two optimal control problems are solved using a Matlab code based on Forward-Backward Sweep Method¹¹. The system of ordinary differential equations is solved numerically using a fourth order Runge-Kutta method.

6 | NUMERICAL SIMULATIONS

Numerical simulations are shown in Figures 4 and 5 for both optimal control problems, where two values of the parameter β are tested: $\beta = 0.7 \text{ person}^{-1}\text{y}^{-1}$ and $\beta = 2 \text{ person}^{-1}\text{y}^{-1}$. The remaining parameters are $\gamma = 0.8 \text{ y}^{-1}$ and $\mu = 12\%$. The values of the weights and the initial conditions are $w_s = w_r = 1$, and $(s_0, i_{s0}, i_{r0}) = (0.98, 0.013, 0.007)$, respectively. The corresponding dynamics are evaluated for $T = 20$ years.

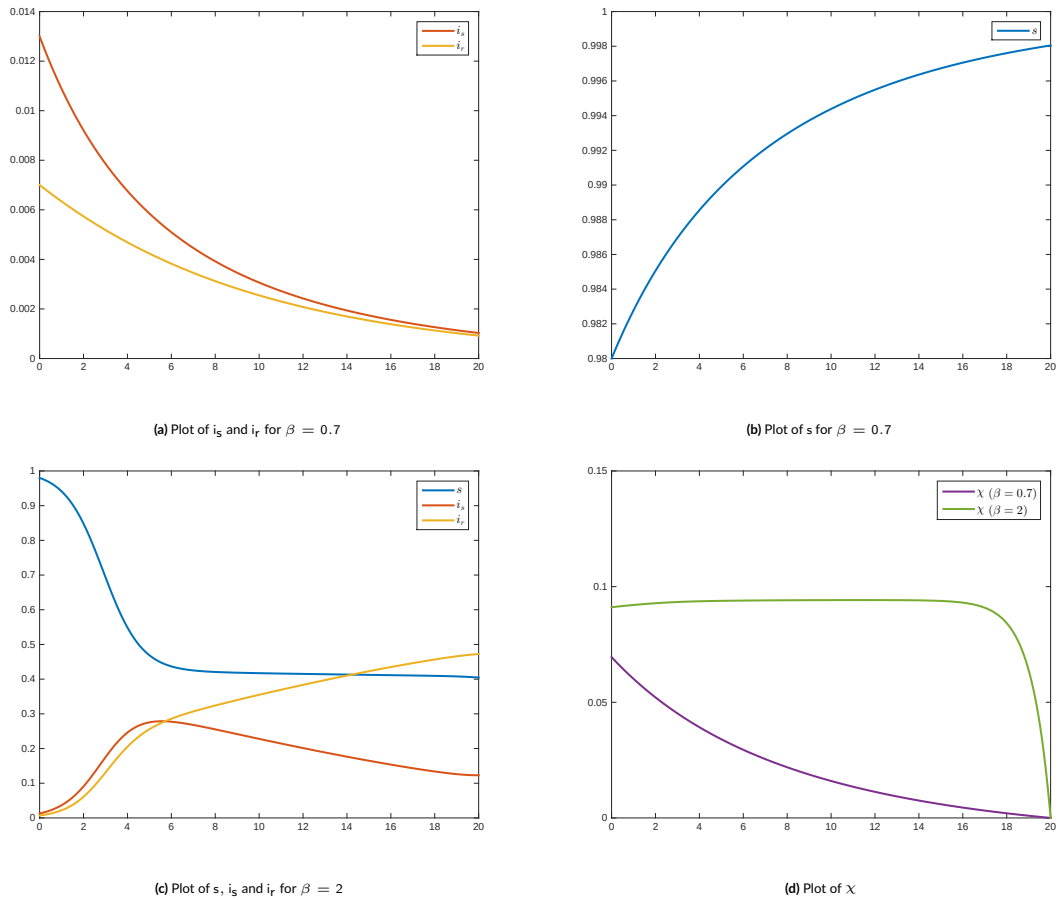


FIGURE 4 Dynamics of susceptible, infected population and treatment rate for problem $(\mathcal{P}_1)$.

According to the values of the parameters that we fixed previously, a comparison between the performance of the two optimal control problems is shown in Table 2 for different values of β .

As it can be observed, the optimal control problem $(\mathcal{P}_2)$ seems to be a better strategy to implement even for high rate of the bacterium spread. Indeed, the treatment rate in the whole time horizon $[0, T]$ for problem $(\mathcal{P}_2)$ is considerably lower than the treatment rate for problem $(\mathcal{P}_1)$. Also, for

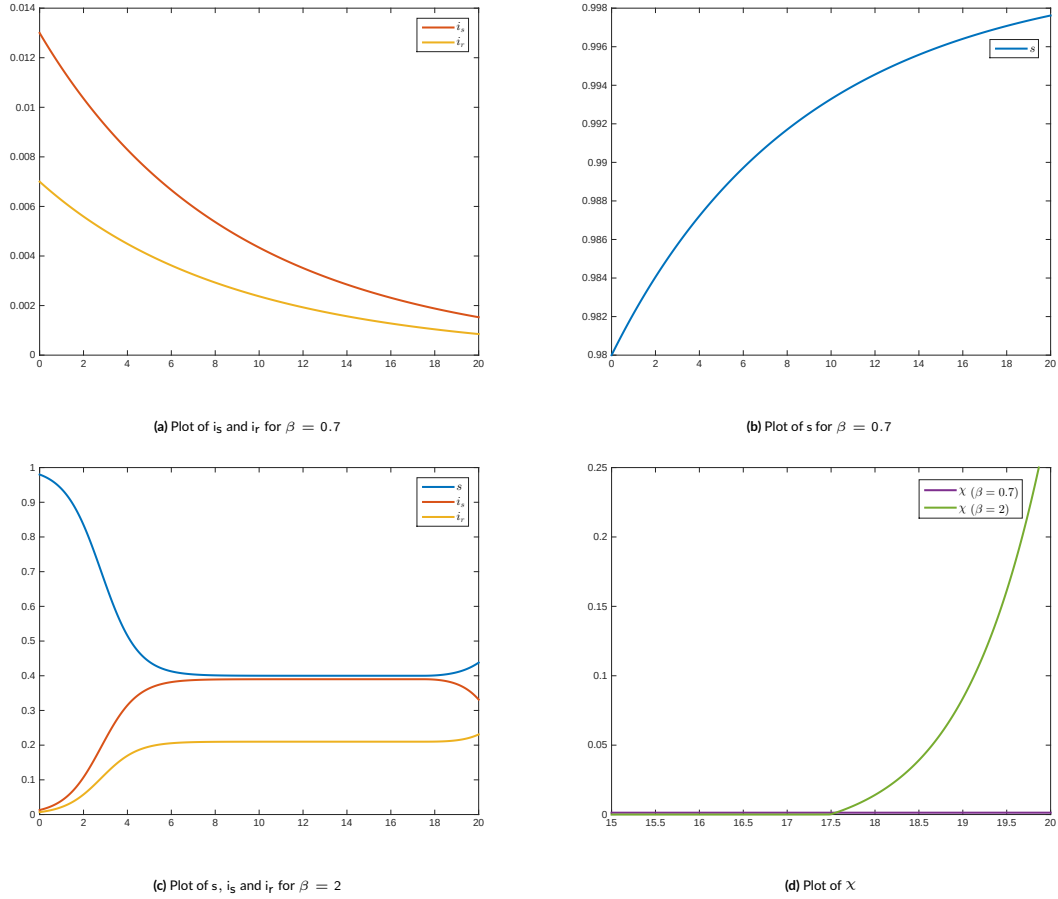


FIGURE 5 Dynamics of susceptible, infected population and treatment rate for problem $(\mathcal{P}_2)$.

small values of β , there are no substantial difference between the number of infected individuals i_s and i_r at the final time T for the two problems. In both situations, independently of applying problems $(\mathcal{P}_1)$ or $(\mathcal{P}_2)$, the total number of infected individuals at the final time, $i_s(T) + i_r(T)$, is similar. However, the number of drug-susceptible individuals either at the final time or along the time horizon is always lower with method $(\mathcal{P}_1)$. The reverse situation occurs when we consider the number of drug-resistant individuals.

With respect to the administration of treatment, it can be noticed in Figures 3 and 4, that for $\beta = 2 \text{ person}^{-1} \text{y}^{-1}$, when we consider procedure $(\mathcal{P}_1)$, the treatment rate χ is almost constant during the whole process except near the final time, where it decreases and vanishes. In opposite, in problem $(\mathcal{P}_2)$, the treatment rate is close to zero, except near the final time, where the treatment rate increases considerably. This is the reason why the number of infections by drug-resistant bacterium increases and overtakes the number of infections by drug-susceptible bacterium when we apply the treatment given by $(\mathcal{P}_1)$. With the second approach, since the treatment is applied mostly near to the final time, the number of infections by drug-resistant bacterium is always lower than the number of infections by drug-susceptible bacterium. Even though near the final time i_r is increasing as a consequence of the treatment increment.

Overall, the technique given by problem $(\mathcal{P}_2)$ seems to be more efficient since it involves less financial costs and a lower number of individuals infected by drug-resistant strain of *M. genitalium*. This can be helpful for health organizations to outline a strategy to control the propagation of macrolide resistant mutations.

Remark 1. Although in the endemic equilibrium, $i_s = 0$ and it is globally stable, we can not ignore the class i_s in the optimal control model, since in this case the results will be different. For example, using the same data as the one used in Figure 4, but considering $\omega_s = 0$, the results are displayed in Figure 6. As it can be seen, the evolution of infected individuals is distinct when $\omega_s = 0$.

β		$i_s(T)$	$i_r(T)$	$\int_0^T i_s(t) dt$	$\int_0^T i_r(t) dt$	$\frac{1}{2} \int_0^T \chi^2(t) dt$
0.5	$(\mathcal{P}_1)$	2.7935e-5	1.7204e-5	0.0402	0.0232	9.6752e-4
	$(\mathcal{P}_2)$	3.1170e-5	1.6795e-5	0.0425	0.0229	7.4323e-9
0.7	$(\mathcal{P}_1)$	0.0010	9.2380e-4	0.0838	0.0602	0.0082
	$(\mathcal{P}_2)$	0.0015	8.5032e-4	0.1052	0.0572	1.6815e-5
0.9	$(\mathcal{P}_1)$	0.0125	0.0355	0.2154	0.3797	0.0703
	$(\mathcal{P}_2)$	0.0326	0.0274	0.4655	0.3168	0.0037
1.0	$(\mathcal{P}_1)$	0.0251	0.1170	0.3670	0.9924	0.1130
	$(\mathcal{P}_2)$	0.0796	0.0727	1.0364	0.7009	0.0080
1.2	$(\mathcal{P}_1)$	0.0501	0.2713	0.9945	2.7739	0.1212
	$(\mathcal{P}_2)$	0.1685	0.1325	2.7244	1.5413	0.0134
1.5	$(\mathcal{P}_1)$	0.0809	0.3797	2.1466	4.6418	0.1028
	$(\mathcal{P}_2)$	0.2469	0.1832	4.6403	2.5509	0.0164
2.0	$(\mathcal{P}_1)$	0.1231	0.4724	3.6664	6.3128	0.0821
	$(\mathcal{P}_2)$	0.3313	0.2309	6.6560	3.6171	0.0173

TABLE 2 Comparison between the two optimal control problems for several values of β .

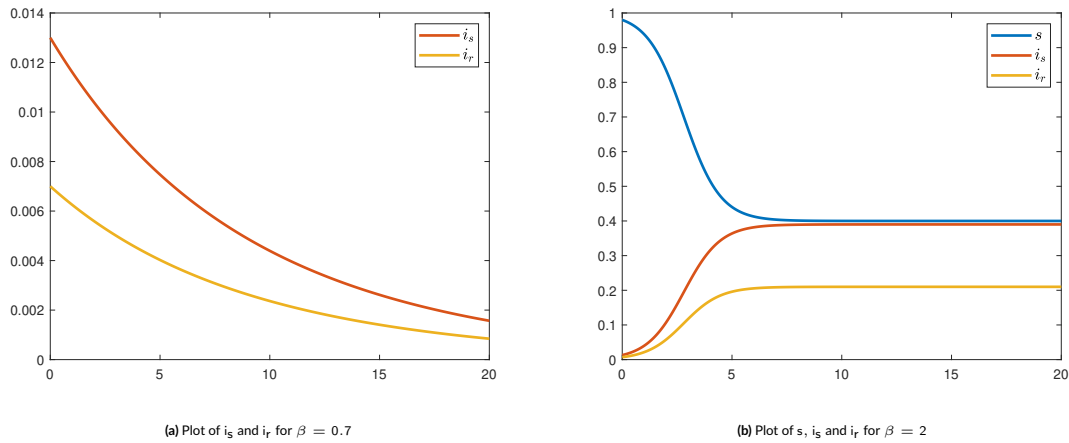


FIGURE 6 Dynamics of susceptible and infected population for problem $(\mathcal{P}_1)$ with $\omega_s = 0$.

7 | A CASE STUDY: THE SPREAD OF *M. GENITALIUM* IN ENGLAND

In this section we study the spread of the disease in England, using real data. In Table 3, the number of *M. genitalium* diagnoses per month in England is displayed. This data was provided by the Public Health England (PHE), from GUMCAD STI Surveillance System. We remark that data represent the number of diagnoses reported, and not the number of people diagnosed. Also, only a small number of sexual health services were reporting *M. genitalium* diagnosis codes (35 in 2016 and 67 in 2017).

	1	2	3	4	5	6	7	8	9	10	11	12	Total
2016	14	14	19	15	15	19	16	14	24	18	18	19	205
2017	13	30	18	21	40	37	44	40	53	38	54	37	425

TABLE 3 Number of *Mycoplasma genitalium* diagnoses per month in England, in the years 2016 and 2017.

As it can be observed, the number of cases diagnosed is much lower than the number of persons infected by the bacterium. This is due to two factors. First, sometimes the disease is asymptomatic. On the other hand, since the means of diagnosis are extremely expensive, the patient may have the symptoms but a general antibiotic treatment, not specific for *M. genitalium*, is applied. To overcome this problem when we model the problem, and the number of total population is required, the following procedure is adopted. In the case of England, previous studies suggest that 1.25% of the population is infected by this bacterium (MG prevalence is 1.2% in men and 1.3% in women²²). So, for the size of population, we take $N = \text{Total} \times 100/1.25$, where Total denotes the total number of cases diagnosed each year. For initial conditions, we consider the number of patients diagnosed in the first month, distributed as follows: 65% is in class i_s and the remaining 35% in class i_r .

The goal is to estimate the disease transmission rate β and the rate of infected individuals who receive treatment χ . The known parameters are, as before, $\gamma = 0.8 \text{ y}^{-1}$ and $\mu = 12\%$. We will determine the unknown parameters β and χ , in order to better approximate our theoretical model (1) to the data given in Table 3. For that purpose, we use the routine `fminsearch` from the Matlab Optimization Toolbox. This routine implements the Nelder-Mead optimization algorithm and the objective function used is based on the least square technique. The procedure is described in the following way: given a theoretical model $t_i \mapsto \Upsilon(t_i, \sigma)$, involving some unknowns $\sigma \in \mathbb{R}^n$, and a sequence of data points $\{(t_i, x_i), i = 1, \dots, m\}$, the routine estimates the unknown parameters for which the error

$$\sum_{i=1}^m (\Upsilon(t_i, \sigma) - x_i)^2$$

attains a minimum value. The results that we obtain in this procedure are displayed in Table 4, for both years. Besides the estimation of the missing parameters, the error of the data fitting is shown. In Figure 7 the obtained results are shown.

	β	χ	Error
2016	1.186471467465153	0.000161634124816	2.810869290229194e-07
2017	2.409736648752084	0.002209748965879	1.398194788165466e-06

TABLE 4 Estimation of parameters with error, in the years 2016 and 2017.

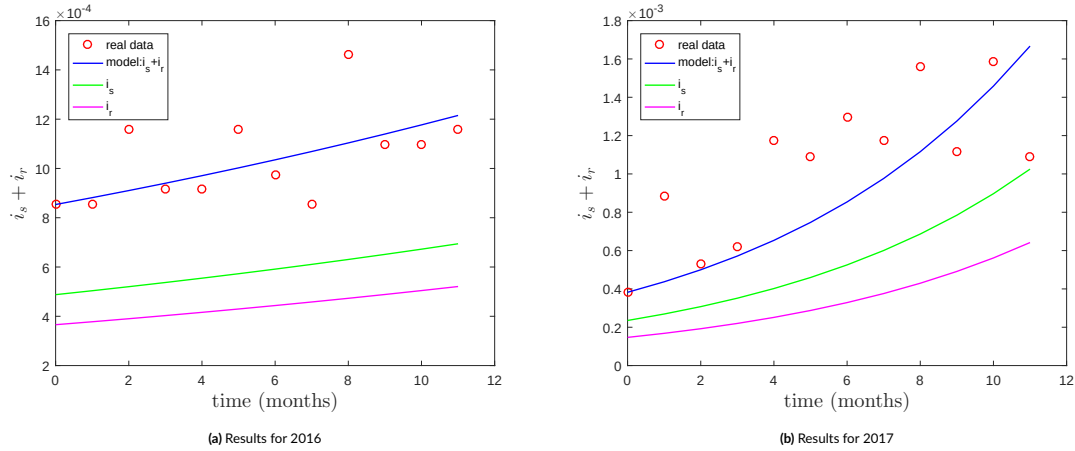


FIGURE 7 Plot of i_s and i_r , and the number of cases in 2016 and 2017.

Based on this data, we observe that the transmission rate has increased from 2016 to 2017. Also, the strain of *M. genitalium* that is resistant to treatment is increasing, which represents a serious problem for health organizations to deal with.

In Figure 8 we present an analysis of the evolution of the disease, considering different values of the treatment rate χ and the disease transmission rate β .

For England the situation is similar to the other countries. In this case it is the parameter χ that does not seem to have any substantial influence on the simulation outcome. As for β , the final population fractions values for $\beta = 0.3$ settle respectively to $s \approx 0.22$, $i_s \approx 0.42$ and $i_r = 0.26$, a situation close, but seemingly slightly better, than Sweden.

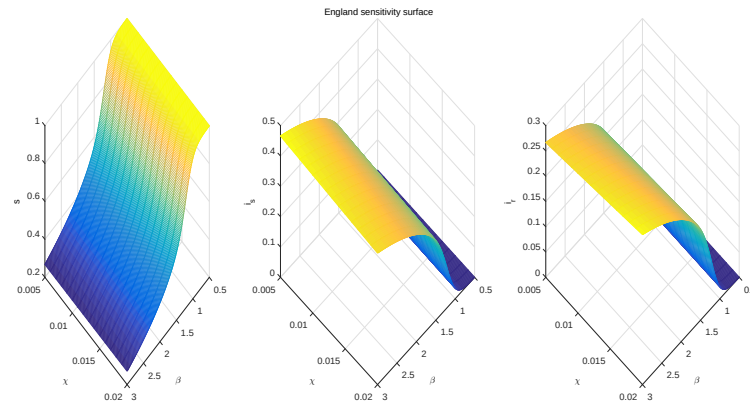


FIGURE 8 Dependence on χ and β .

8 | EPIDEMIOLOGY IMPLICATIONS

In this paper, a mathematical model that simulates the spread of the drug-resistant *M. genitalium* within a population was studied. Equilibrium points and their stability were analyzed. Moreover, two optimal control problems have been proposed where the treatment rate is assumed to vary along the time. In one of them, besides minimizing the treatment rate our interest was also to minimize the number of infected individuals during a certain period of time. On the other one, the objective was to minimize the number of infected individuals only at the final time. Several numerical tests have been performed in order to analyze the trade-off between the number of drug-resistant and drug-susceptible infected individuals by *M. genitalium* and the administration of treatment. In all the situations, the proposed mathematical model is coherent with the clinical practice since the introduction of azithromycin will increase considerably the number of drug-resistant bacterium.

An important issue that must be studied is the evolution of the disease over a long period of time. In Figure 9 we present the results obtained.

The shape of the surfaces qualitatively is the same in all cases. However, at steady state we observe the vanishing of the infected that are susceptible to drugs, while the populations are partitioned only among uninfected and infected but drug-resistant. The proportions are about 75% of infected (drug-resistant) for all the countries, leaving only 25% of the population uninfected. This makes sense, as these quantities are related to the infection. The only difference is the speed at which this steady state is reached, as it depends more on the present conditions in the respective countries, as well as being related to the various populations behaviors, which may differ from country to country.

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Conflict of interest

The authors declare no potential conflict of interests.

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AUTHOR BIOGRAPHY



Ricardo Almeida received his Bachelor and Master degrees in Mathematics from University of Oporto, Portugal, and Ph.D. degree in Mathematics from University of Aveiro, Portugal. He is currently Assistant Professor in the University of Aveiro. His research interests include fractional calculus, calculus of variations and optimal control theory. He has published 5 books and more than 80 papers in international journals.



Teresa Monteiro received the BS, MS and PhD degrees in Systems and Informatics Engineering (1990), Computational Mathematics (1996), Nonlinear Optimization (2001), respectively, from University of Minho, Portugal. She is researcher in Centre ALGORITMI, University of Minho, Portugal. She started working at the Systems and Production Department, from Engineering School, University of Minho since 1992, being assistant professor. Her research interests are multidisciplinary: Optimal Control and Nonlinear Optimization applied to epidemiological models; applications of Optimization; Numerical Methods; Mathematical Modelling.



Luís Machado received the BS, MS and PhD degrees in Mathematics from the University of Coimbra, Portugal, in 1996, 1999 and 2006, respectively. Since 1996 he has been with the Department of Mathematics, University of Trás-os-Montes e Alto Douro, Vila Real, Portugal, where he is currently an assistant professor. He is also a researcher at the Institute of Systems and Robotics - University of Coimbra, Portugal. His research interests are multidisciplinary and include optimization problems on manifolds, calculus of variations and optimal control problems.



Ezio Venturino received his PhD degree in Applied Mathematics from SUNY at Stony Brook in 1984. He is currently Professor of Mathematics at the Dipartimento di Matematica, University of Torino, Italy. He has visited several international institutions worldwide has a wide scientific collaboration network. His research earlier focused on numerical analysis, mainly methods for integral equations, and currently on nonlinear models for biological and ecological applications.

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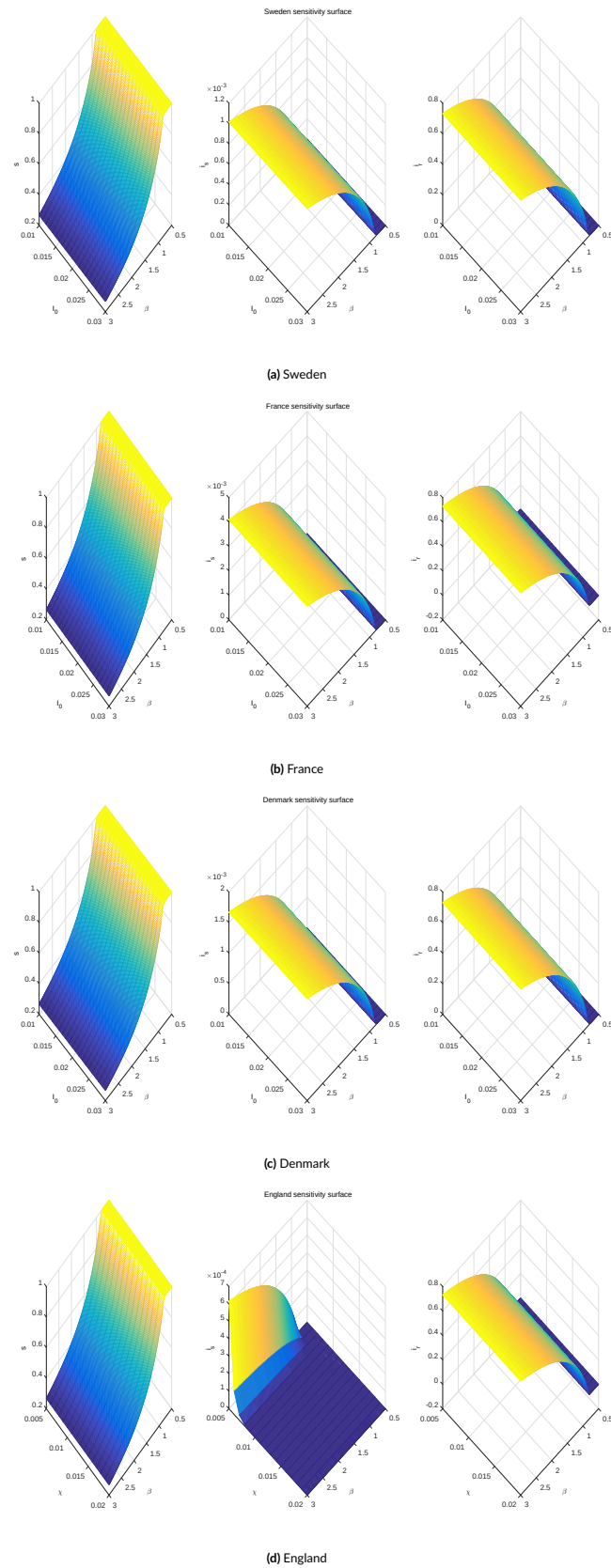


FIGURE 9 Evolution of the disease for a long period of time.