# Compartmental Mathematical Model with Optimal Control: Can awareness against Methicillin Resistant Staphylococcus aureus prevent its transmission?

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# Compartmental Mathematical Model with Optimal Control: Can awareness against *Methicillin Resistant Staphylococcus aureus* prevent its transmission?

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## Abstract

The number of *Methicillin Resistance Staphylococcus aureus* cases in community and hospitals is on the rise worldwide. Hence, the study aimed to analyze transmission interventions and control strategies that could be used to prevent transmission in this manner. In this regard, compartmental mathematical model was used with and without an optimal control to visualize the effectiveness of awareness in interventions that could be applied in the prevention of transmission. A total of seven years of data gathered from hospital consisting of inpatients and outpatients of MRSA were used in this model. The results suggested that the number of cases of the four compartments: Community-acquired (CA) *Staphylococcus aureus,* CA Methicillin Resistant *Staphylococcus aureus* (MRSA), Hospital-acquired (HA) *Staphylococcus aureus*, HA-MRSA in the designed mathematical model without the control were on an increasing trend. When optimal control was applied as a second model, it was determined that increasing awareness of hand hygiene and wearing a mask were the key controlling measures to prevent the spread of CA-MRSA and HA-MRSA. Lastly, it is concluded that both CA-MRSA and HA-MRSA cases are on the rise and increasing awareness in regard to transmission is significant in preventing further spread.

## Introduction

*Staphylococcus* genus are common inhabitants of the skin and mucous membranes, and under certain circumstances can cause different diseases on a variety of species. *Staphylococcus aureus* (*S. aureus*) is the most important species in this genus which can cause serious infections in various tissues and organs with its many pathogenic factors [1]. *S. aureus* is one of the leading causes of both hospital-acquired and community-acquired infections, such as septic arthritis, osteomyelitis, bacteremia, and especially wound and soft tissue infections which are t among the first nosocomial infections [2, 3, 4].

In 1960, methicillin - a semi-synthetic derivative of the penicillin was developed as a beta-lactam group of antibiotics named penicillinase-resistant penicillin, which achieved a great success in the treatment of staphylococcal infections. However, soon later in the late 1970s and early 1980s methicillin-resistant *Staphylococcus aureus* (MRSA) strains began to emerge hindering the treatment by the use of methicillin caused by these infections. in MRSA is now a very serious problem causing hospital-acquired outbreaks worldwide due to the prevalence of resistance issues. The mecA gene located in a 21-67 kb DNA region called Staphylococcal cassette chromosome mec (SCCmec) is responsible for methicillin resistance in staphylococci [5, 6].

Hence, antibiotics other than the beta-lactam group come to the fore in the treatment of infections caused by MRSA strains and it is important to determine the efficacy of these antibiotics by antibiotic susceptibility tests prior to treatment. These strains are increasingly becoming a serious health problem as a result of multidrug resistance development and the availability of limited treatment options [7, 8].

Although, MRSA infections were first detected in hospitals known as healthcare-acquired/associated MRSA (HA-MRSA), in recent years; infections have emerged in the community named as community-acquired/associated MRSA (CA-MRSA). In addition to CA-MRSA, livestock-associated MRSA (LA-MRSA) has also emerged particularly in humans working in close contact with animals such as pigs, cattle or poultry. As a result, MRSA should be no longer considered only as a healthcare-related problem. Hence, awareness against MRSA as a public health burden should arise since it can no longer be tackled only with hospital infection prevention and control measures [9].

On the other hand, innovative approaches such as the use of mathematical models in forecasting infectious diseases play significant roles in public health. The use of the models is enhanced by constructing compartments which divide the studied population according to the designed model allowing researchers to identify the structure of the disease, predict the future of the disease and introduce necessary control strategies if it is applicable.

These models can be generated for almost every field of health sciences including infectious diseases, cancer, tumors etc. [10, 11, 12]. For example, in our previous study, ESBL resistance in *Escherichia coli* isolates was evaluated via mathematical modelling [13]. In other studies with optimal control theory that can be applied to control bacterial growth [14] antibiotic resistance can be evaluated via sensitivity analysis of a deterministic mathematical model in [15].

This study is proposed to determine the presence of CA-MRSA and HA-MRSA patients in the north side of Cyprus. In this regard, a mathematical model is constructed to discover the situation and forecast the future of MRSA cases in the population. Moreover, a control strategy, efficacy of increase in awareness, is introduced to the constructed model to decide whether this strategy will be effective or not. The main goal of the presented study is to enable a control strategy for the reduction of MRSA cases, especially in the community.

**Data and Methods**

The data used in this paper is gathered from the Near East University Hospital Centre Laboratory with the approval of the Near East University Ethics Review Board (project no: YDU/2022/108-1653). For presenting the study, Near East University Ethics Review Board waived informed consent to the authors of the paper. This study includes retrospective data from 48,835 patients who were administered to Near East University Hospital Microbiology Laboratory on the dates between January, 2016 and December, 2022. Microorganisms were detected in 13,350 of the studied patient samples. *S. aureus* was detected in 612 of the 13,350 samples. Among the 612 *S. aureus* samples, 279 were determined to be MRSA-positive. For the purpose of analysis, 279 MRSA-positive samples were separated into groups according to their types (CA-MRSA/HA-MRSA), years (before the pandemic/after the pandemic) and ages. The details obtained for positive MRSA outpatients from the hospital system data were considered as CA-MRSA and inpatients as HA-MRSA for the purpose of this study. To examine whether there is any significance between these groups, appropriate statistical models and tests were applied to the data groups. As authors,

it is confirmed that all methods were performed in accordance with the relevant guidelines and regulations.

**Mathematical Model**

In the presented paper, the model consists of 8 compartments as follows: susceptible individuals $(S)$, individuals that are infected with community-acquired *Staphylococcus aureus* $(C_C)$, individuals that are infected with CA-MRSA $(C_I)$, individuals that are infected with hospital-acquired *Staphylococcus aureus* $(H_C)$, individuals that are infected with HA-MRSA $(H_I)$, antibiotic group oxazolidinones $(O)$, antibiotic group glycopeptides $(G)$, antibiotic group trimethoprim-derivatives $(T)$. The model is constructed by using ordinary differential equations at time $t$ and it is given below.

$$\frac{dS}{dt} = \Lambda(1 - k_1 - k_2 - k_3 - k_4) - \beta_1 C_c S - \beta_2 C_I S - \beta_3 H_c S - \beta_4 H_I S + \gamma_1 O + \gamma_2 G + \gamma_3 T + a\delta_1 C_C + b\delta_3 H_C - \mu S,$$

$$\frac{dC_C}{dt} = \Lambda k_1 + \beta_1 C_c S - [a\delta_1 + (1-a)\delta_2]C_C - \mu C_C,$$

$$\frac{dC_I}{dt} = \Lambda k_2 + \beta_2 C_I S + (1-a)\delta_2 C_C - (o_1 + g_1 + r_1)C_I - \mu C_I,$$

$$\frac{dH_C}{dt} = \Lambda k_3 + \beta_3 H_C S - [b\delta_3 + (1-b)\delta_4]H_C - \mu H_C,$$

$$\frac{dH_I}{dt} = \Lambda k_4 + \beta_4 H_I S + (1-b)\delta_4 H_C - (o_2 + g_2 + r_2)H_I - (\mu + d)H_I,$$

$$\frac{dO}{dt} = o_1 C_I + o_2 H_I - \gamma_1 O,$$

$$\frac{dG}{dt} = g_1 C_I + g_2 H_I - \gamma_2 G,$$

$$\frac{dT}{dt} = r_1 C_I + r_2 H_I - \gamma_3 T.$$

In this current model, three groups of antibiotics, Oxazolidinones, Glycopeptides and Trimethoprim-derivatives, were used in the treatment alternative to methicillin in MRSA infections. According to the data of MRSA-positive 277 patients, it was found that at least 85% of the patients could be treated with the aforementioned three groups of antibiotics (Table 1). The definition of variables and parameters are given in Table 2 and Table 3.

**Table 1.** The sensitivity of Methicillin-resistant *Staphylococcus aureus* bacteria in patients.

| **The group of antibiotics** | **Sensitivity percentage** |
|---|---|
| Oxazolidinones | 93% |
| Glycopeptides | 92% |
| Trimethoprim-derivatives | 86% |

**Table 2.** Definition of variables used in the model.

| **Variables** | **Definition** |
|---|---|
| $S$ | Individuals that are susceptible to *Staphylococcus aureus* |
| $C_C$ | Community-acquired *Staphylococcus aureus* infected individuals |
| $C_I$ | Community-acquired Methicillin Resistant *Staphylococcus aureus* infected individuals |
| $H_C$ | Hospital-acquired *Staphylococcus aureus* infected individuals |
| $H_I$ | Hospital-acquired Methicillin Resistant *Staphylococcus aureus* infected individuals |
| $O$ | Oxazolidinones antibiotic groups |
| $G$ | Glycopeptides antibiotic groups |
| $T$ | Trimethoprim-derivatives antibiotic groups |

**Table 3.** Definition of parameters used in the model.

| **Variables** | **Definition** |
|---|---|
| $\Lambda$ | Admissions to the hospital laboratory |

| | |
|---|---|
| $k_1$ | The rate of patients admitted as $C_C$ |
| $k_2$ | The rate of patients admitted as $C_I$ |
| $k_3$ | The rate of patients admitted as $H_C$ |
| $k_4$ | The rate of patients admitted as $H_I$ |
| $\beta_1$ | Transmission rate from $S$ to $C_C$ |
| $\beta_2$ | Transmission rate from $S$ to $C_I$ |
| $\beta_3$ | Transmission rate from $S$ to $H_C$ |
| $\beta_4$ | Transmission rate from $S$ to $H_I$ |
| $\gamma_1$ | Recovery rate when treated with oxazolidinones |
| $\gamma_2$ | Recovery rate when treated with glycopeptides |
| $\gamma_3$ | Recovery rate when treated with trimethoprim-derivatives |
| $\delta_1$ | Transmission rate from $C_C$ to $S$ |
| $\delta_2$ | Transmission rate from $C_C$ to $C_I$ |
| $\delta_3$ | Transmission rate from $H_C$ to $S$ |
| $\delta_4$ | Transmission rate from $H_C$ to $H_I$ |
| $a$ | Cure rate of $C_C$ |
| $b$ | Cure rate of $H_C$ |
| $d$ | Hospital discharge |
| $\mu$ | Natural death rate |

***Model Analysis***

**Theorem 1.** Assume that $(S, C_C, C_I, H_C, H_I, O, G, T)$ is one of the solutions of the proposed system with the following initial conditions:

$$S \geq 0, C_C \geq 0, C_I \geq 0, H_C \geq 0, H_I \geq 0, O \geq 0, G \geq 0, T \geq 0.$$

Then, the set $W$ below is biologically feasible and all of the solutions in $\mathbb{R}_+^8$ stay in $\Lambda$ with respect to the proposed system [12].

$$W = \{(S, C_C, C_I, H_C, H_I, O, G, T) \in \mathbb{R}_+^8 : S, C_C, C_I, H_C, H_I, O, G, T \leq \Lambda\}.$$

**Proof.** Let $N$ denote the whole population. That is, $N = S + C_C + C_I + H_C + H_I + O + G + T$. Addition of all of the terms that are on the right side of the system gives

$$\frac{dN}{dt} = \Lambda - \mu(S + C_C + C_I + H_C + H_I) - dH_I.$$

From the equality, it is clear that $\frac{dN}{dt} \leq \Lambda$. Applying integration to the both sides with respect to $t$ yields

$$N(t)e^t \leq \Lambda e^t + p,$$

for some arbitrary constant $p$. With the use of Rota and Birkhoff for the above differential inequality, it can be obtained that as $t$ tends to infinity, $\infty$, $0 \leq N \leq \Lambda$. Consequently, the solutions of the given system enter the region $\Lambda$. Thus, it is certain that the model is feasible by means of biology and it is enough to consider the dynamics on the model in $\Lambda$.

*Equilibrium Points and Basic Reproduction Numbers*

For the constructed model, there exists a disease-free equilibrium point, denoted by $E_0$. At this point, the disease is expected to die out in the population. In this case, $E_0$ is the point where MRSA patients do not exist in the population and hence no one is diagnosed with MRSA. In order to reach $E_0$, $R_0$ value(s) of the disease should be less than 1. $E_0$ of this model is unique and it is obtained as

$$E_0 = \left(S_0, C_{C,0}, C_{I,0}, H_{C,0}, H_{I,0}\right) = \left(\frac{\Lambda}{\mu}, 0, 0, 0, 0\right).$$

It is clear that the disease-free equilibrium point attracts the region so that

$$E_0 = \left\{\left(S_0, C_{C,0}, C_{I,0}, H_{C,0}, H_{I,0}\right) \in \mathbb{R}_5^+ : C_{C,0} = C_{I,0} = H_{C,0} = H_{I,0} = 0\right\}.$$

In this model, since there are 4 different categories of disease, 4 different basic reproduction numbers, denoted by $R_0$, are obtained for each disease compartment. For the calculation of $R_0$ formulas, Next Generation Matrix (NGM) Method is used as follows [12]:

The matrix that consists of new infections with MRSA is

$$F = \begin{bmatrix} \beta_1 S_0 & 0 & 0 & 0 \\ (1-a)\delta_2 & \beta_2 S_0 & 0 & 0 \\ 0 & 0 & \beta_3 S_0 & 0 \\ 0 & 0 & (1-b)\delta_4 & \beta_4 S_0 \end{bmatrix},$$

and the rest of the system is included in the below matrix:

$$V = \begin{bmatrix} a\delta_1 + (1-a)\delta_2 + \mu & 0 & 0 & 0 \\ 0 & o_1 + g_1 + r_1 + \mu & 0 & 0 \\ 0 & 0 & b\delta_3 + (1-b)\delta_4 + \mu & 0 \\ 0 & 0 & 0 & o_2 + g_2 + r_2 + d + \mu \end{bmatrix}$$

According to the NGM method, $R_0$ formulas are computed by finding the dominant eigenvalues of the matrix $F.V^{-1}$. Hence, $R_0$ formulas for the compartments $C_C, C_I, H_C$ and $H_I$ are obtained as below, respectively.

$$R_{0,C_C} = \frac{\beta_1 S_0}{a(\delta_1 - \delta_2) + \delta_2 + \mu},$$

$$R_{0,C_I} = \frac{\beta_2 S_0}{o_1 + g_1 + r_1 + \mu},$$

$$R_{0,H_C} = \frac{\beta_3 S_0}{b(\delta_3 - \delta_4) + \delta_4 + \mu},$$

$$R_{0,H_I} = \frac{\beta_4 S_0}{o_2 + g_2 + r_2 + d + \mu}.$$

**Theorem 2.** The disease-free equilibrium (DFE) point of the system, $E_0$, is locally asymptotically stable if $R_{0,C_C} < 1, R_{0,C_I} < 1, R_{0,H_C} < 1$ and $R_{0,H_I} < 1$.

**Proof.** The Jacobian matrix [16] evaluated at the DFE point $E_0$ is calculated as

$J$

$$= \begin{bmatrix} -\mu & a\delta_1 - \beta_1 S_0 & -\beta_2 S_0 & b\delta_3 - \beta_3 S_0 & -\beta_4 S_0 & \gamma_1 & \gamma_2 & \gamma_3 \\ 0 & \beta_1 S_0 - a\delta_1 - (1-a)\delta_2 - \mu & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & (1-a)\delta_2 & \beta_2 S_0 - o_1 - g_1 - r_1 - \mu & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \beta_3 S_0 - b\delta_3 - (1-b)\delta_4 - \mu & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & (1-b)\delta_4 & \beta_4 S_0 - o_2 - g_2 - r_2 - d - \mu & 0 & 0 & 0 \\ 0 & 0 & o_1 & 0 & o_2 & -\gamma_1 & 0 & 0 \\ 0 & 0 & g_1 & 0 & g_2 & 0 & -\gamma_2 & 0 \\ 0 & 0 & r_1 & 0 & r_2 & 0 & 0 & -\gamma_3 \end{bmatrix}.$$

Here, $S_0 = \frac{\Lambda}{\mu}$ and the eigenvalues of the matrix are $-\gamma_1, -\gamma_2, -\gamma_3, -\mu, \beta_1 S_0 - a\delta_1 - (1-a)\delta_2 - \mu, \beta_2 S_0 - o_1 - g_1 - r_1 - \mu, \beta_3 S_0 - b\delta_3 - (1-b)\delta_4 - \mu$ and $\beta_4 S_0 - o_2 - g_2 - r_2 - d - \mu$. It is obvious that the eigenvalues $-\gamma_1, -\gamma_2, -\gamma_3$ and $-\mu$ are always negative since the parameters are always positive. The eigenvalues $\beta_1 S_0 - a\delta_1 - (1-a)\delta_2 - \mu, \beta_2 S_0 - o_1 - g_1 - r_1 - \mu, \beta_3 S_0 - b\delta_3 - (1-b)\delta_4 - \mu$ and $\beta_4 S_0 - o_2 - g_2 - r_2 - d - \mu$ are negative under the conditions $R_{0,C_C} < 1, R_{0,C_I} < 1, R_{0,H_C} < 1$ and $R_{0,H_I} < 1$. Thus, the DFE point is locally asymptotically stable if $R_{0,C_C} < 1, R_{0,C_I} < 1, R_{0,H_C} < 1$ and $R_{0,H_I} < 1$ and unstable if $R_{0,C_C} > 1, R_{0,C_I} > 1, R_{0,H_C} > 1$ and $R_{0,H_I} > 1$.

**Mathematical Model with Optimal Control**

In this section, Optimal Control Theory was introduced to the proposed model to evaluate its efficacy on the disease. The control $u$ denotes the efficacy to precautions taken by peoplewho are aware of MRSA infection, where $0 \leq u \leq 1$. The control is added to the model as $1-u$ since it is assumed that awareness exists in some of the population. The model is revised as follows:

$$\frac{dS}{dt} = \Lambda(1 - k_1 - k_2 - k_3 - k_4) - (1-u)[\beta_1 C_c + \beta_2 C_I + \beta_3 H_c + \beta_4 H_I]S + \gamma_1 O + \gamma_2 G + \gamma_3 T + a\delta_1 C_C + b\delta_3 H_C - \mu S,$$

$$\frac{dC_C}{dt} = \Lambda k_1 + (1-u)\beta_1 C_c S - [a\delta_1 + (1-a)\delta_2]C_C - \mu C_C,$$

$$\frac{dC_I}{dt} = \Lambda k_2 + (1-u)\beta_2 C_I S + (1-a)\delta_2 C_C - (o_1 + g_1 + r_1)C_I - \mu C_I,$$

$$\frac{dH_C}{dt} = \Lambda k_3 + (1-u)\beta_3 H_C S - [b\delta_3 + (1-b)\delta_4]H_C - \mu H_C,$$

$$\frac{dH_I}{dt} = \Lambda k_4 + (1-u)\beta_4 H_I S + (1-b)\delta_4 H_C - (o_2 + g_2 + r_2)H_I - (\mu + d)H_I,$$

$$\frac{dO}{dt} = o_1 C_I + o_2 H_I - \gamma_1 O,$$

$$\frac{dG}{dt} = g_1 C_I + g_2 H_I - \gamma_2 G,$$

$$\frac{dT}{dt} = r_1 C_I + r_2 H_I - \gamma_3 T.$$

The objective functional to be minimized is

$$J(u) = \int_0^T \left[ C_C + C_I + H_C + H_I + \frac{K}{2} u^2(t) \right] dt.$$

The number of individuals diagnosed with MRSA in all compartments and costs of control are expected to be minimized. $K$ is a weight factor representing benefit/cost and the level of the patient's increase of awareness. A quadratic control $\frac{1}{2} K u^2$ is used for convenience in finding an analytic representation of the control $u \in \Omega$. The goal is to find $u^*$ that will satisfy

$$J(u^*) = \min_{u \in \Omega} J(u),$$

where

$$\Omega = \{u(t): 0 \leq u \leq u_{max} = l,$$
$$u \text{ piecewise continuous function}, l \text{ is a fixed constant}, t \in [0, T]\}.$$

For the optimal control, Pontryagin's Maximum Principle's conditions should be satisfied [17]. In this regard, the Hamiltonian $H$ is obtained as

$$H = C_C + C_I + H_C + H_I + \frac{K}{2} u^2(t) + \sum_{i=1}^{8} \lambda_i f_i,$$

where $f_i's$ represent the right-hand side of the proposed system and $\lambda_i's$ represent the adjoint variables for $i = 1, 2, \ldots, 8$. That is,

$$H = C_C + C_I + H_C + H_I + \frac{K}{2}u^2(t) + \sum_{i=1}^{8} \lambda_i f_i$$

$$= C_C + C_I + H_C + H_I + \frac{K}{2}u^2(t)$$
$$+ \lambda_1[\Lambda(1 - k_1 - k_2 - k_3 - k_4) - (1 - u)[\beta_1 C_c + \beta_2 C_I + \beta_3 H_c + \beta_4 H_I]S + \gamma_1 O$$
$$+ \gamma_2 G + \gamma_3 T + a\delta_1 C_C + b\delta_3 H_C - \mu S]$$
$$+ \lambda_2[\Lambda k_1 + (1 - u)\beta_1 C_c S - [a\delta_1 + (1 - a)\delta_2]C_C - \mu C_C]$$
$$+ \lambda_3[\Lambda k_2 + (1 - u)\beta_2 C_I S + (1 - a)\delta_2 C_C - (o_1 + g_1 + r_1)C_I - \mu C_I]$$
$$+ \lambda_4[\Lambda k_3 + (1 - u)\beta_3 H_C S - [b\delta_3 + (1 - b)\delta_4]H_C - \mu H_C]$$
$$+ \lambda_5[\Lambda k_4 + (1 - u)\beta_4 H_I S + (1 - b)\delta_4 H_C - (o_2 + g_2 + r_2)H_I - (\mu + d)H_I]$$
$$+ \lambda_6[o_1 C_I + o_2 H_I - \gamma_1 O] + \lambda_7[g_1 C_I + g_2 H_I - \gamma_2 G] + \lambda_8[r_1 C_I + r_2 H_I - \gamma_3 T].$$

**Theorem 3.** Given an optimal control $u^*$ and solutions $S^*, C_C^*, C_I^*, H_C^*, H_I^*, O^*, G^*, T^*$ pf the corresponding system which minimizes $J(u)$ over Ω. Then there exist adjoint variables $\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6, \lambda_7, \lambda_8$ satisfying

$$\frac{d\lambda_1}{dt} = \lambda_1[\mu - (u - 1)(\beta_1 C_c + \beta_2 C_I + \beta_3 H_c + \beta_4 H_I)] - \lambda_2\beta_1 C_c(1 - u) - \lambda_3\beta_2 C_I(1 - u)$$
$$- \lambda_4\beta_3 H_c(1 - u) - \lambda_5\beta_4 H_I(1 - u),$$

$$\frac{d\lambda_2}{dt} = -1 - \lambda_1[(u - 1)\beta_1 S + a\delta_1] - \lambda_2[(1 - u)\beta_1 S - a\delta_1 - (1 - a)\delta_2 - \mu] + \lambda_3\delta_2(1 - a),$$

$$\frac{d\lambda_3}{dt} = -1 + \lambda_1\beta_2 S(1 - u) - \lambda_3[\beta_2 S(1 - u) - o_1 - g_1 - r_1 - \mu] - \lambda_6 o_1 - \lambda_7 g_1 - \lambda_8 r_1,$$

$$\frac{d\lambda_4}{dt} = -1 + \lambda_1[\beta_3 S(1 - u) - b\delta_2] - \lambda_4[\beta_3 S(1 - u) - b\delta_3 - (1 - b)\delta_4 - \mu] - \lambda_5\delta_4(1 - b),$$

$$\frac{d\lambda_5}{dt} = -1 + \lambda_1\beta_4 S(1 - u) - \lambda_5[\beta_4 S(1 - u) - o_2 - g_2 - r_2 - d - \mu] - \lambda_6 o_2 - \lambda_7 g_2 - \lambda_8 r_2,$$

$$\frac{d\lambda_6}{dt} = (\lambda_6 - \lambda_1)\gamma_1,$$

$$\frac{d\lambda_7}{dt} = (\lambda_7 - \lambda_1)\gamma_2,$$

$$\frac{d\lambda_8}{dt} = (\lambda_8 - \lambda_1)\gamma_3,$$

with transversality conditions

$$\lambda_1(T) = \lambda_2(T) = \lambda_3(T) = \lambda_4(T) = \lambda_5(T) = \lambda_6(T) = \lambda_7(T) = \lambda_8(T) = 0$$

and the optimal control satisfying the optimality condition

$$u^* = \min\left\{\max\left\{\frac{1}{K}[\lambda_2\beta_1 C_c + \lambda_3\beta_2 C_I + \lambda_4\beta_3 H_c + \lambda_5\beta_4 H_I - (\beta_1 C_c + \beta_2 C_I + \beta_3 H_c + \beta_4 H_I)\lambda_1]S\right\}, 1\right\}.$$

**Proof.** The adjoint system is computed by taking partial derivatives of Hamiltonian function $H$ with respect to the state variables, separately. That is,

$$\frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial S} = \lambda_1[\mu - (u-1)(\beta_1 C_c + \beta_2 C_I + \beta_3 H_c + \beta_4 H_I)] - \lambda_2\beta_1 C_c(1-u) - \lambda_3\beta_2 C_I(1-u) - \lambda_4\beta_3 H_c(1-u) - \lambda_5\beta_4 H_I(1-u),$$

$$\frac{d\lambda_2}{dt} = -\frac{\partial H}{\partial C_C} = -1 - \lambda_1[(u-1)\beta_1 S + a\delta_1] - \lambda_2[(1-u)\beta_1 S - a\delta_1 - (1-a)\delta_2 - \mu] + \lambda_3\delta_2(1-a),$$

$$\frac{d\lambda_3}{dt} = -\frac{\partial H}{\partial C_I} = -1 + \lambda_1\beta_2 S(1-u) - \lambda_3[\beta_2 S(1-u) - o_1 - g_1 - r_1 - \mu] - \lambda_6 o_1 - \lambda_7 g_1 - \lambda_8 r_1,$$

$$\frac{d\lambda_4}{dt} = -\frac{\partial H}{\partial H_C} = -1 + \lambda_1[\beta_3 S(1-u) - b\delta_2] - \lambda_4[\beta_3 S(1-u) - b\delta_3 - (1-b)\delta_4 - \mu] - \lambda_5\delta_4(1-b),$$

$$\frac{d\lambda_5}{dt} = -\frac{\partial H}{\partial H_I} = -1 + \lambda_1\beta_4 S(1-u) - \lambda_5[\beta_4 S(1-u) - o_2 - g_2 - r_2 - d - \mu] - \lambda_6 o_2 - \lambda_7 g_2 - \lambda_8 r_2,$$

$$\frac{d\lambda_6}{dt} = -\frac{\partial H}{\partial O} = (\lambda_6 - \lambda_1)\gamma_1,$$

$$\frac{d\lambda_7}{dt} = -\frac{\partial H}{\partial G} = (\lambda_7 - \lambda_1)\gamma_2,$$

$$\frac{d\lambda_8}{dt} = -\frac{\partial H}{\partial T} = (\lambda_8 - \lambda_1)\gamma_3,$$

with transversality conditions

$$\lambda_1(T) = \lambda_2(T) = \lambda_3(T) = \lambda_4(T) = \lambda_5(T) = \lambda_6(T) = \lambda_7(T) = \lambda_8(T) = 0.$$

On the interior of the given control set, for $0 \leq u \leq 1$, we get

$$0 = \frac{\partial H}{\partial u} = uK + (\beta_1 C_c + \beta_2 C_I + \beta_3 H_c + \beta_4 H_I)\lambda_1 S - \lambda_2 \beta_1 C_c S - \lambda_3 \beta_2 C_I S - \lambda_4 \beta_3 H_c S - \lambda_5 \beta_4 H_I S.$$

Thus,

$$u = \frac{1}{K}[\lambda_2 \beta_1 C_c + \lambda_3 \beta_2 C_I + \lambda_4 \beta_3 H_c + \lambda_5 \beta_4 H_I - (\beta_1 C_c + \beta_2 C_I + \beta_3 H_c + \beta_4 H_I)\lambda_1]S.$$

Therefore,

$$u^* = \min\left\{\max\left\{\frac{1}{K}[\lambda_2 \beta_1 C_c + \lambda_3 \beta_2 C_I + \lambda_4 \beta_3 H_c + \lambda_5 \beta_4 H_I - (\beta_1 C_c + \beta_2 C_I + \beta_3 H_c + \beta_4 H_I)\lambda_1]S\right\}, 1\right\}.$$

**Numerical Simulations for the Constructed Mathematical Model**

Numerical simulations were calculated by the proposed compartmental mathematical model. In Figure 1, Figure 2, Figure 3 and Figure 4, the expected trend of $C_c, C_I, H_C$ and $H_I$ cases are given, respectively. These trends were calculated via MatLab according to the proposed model.

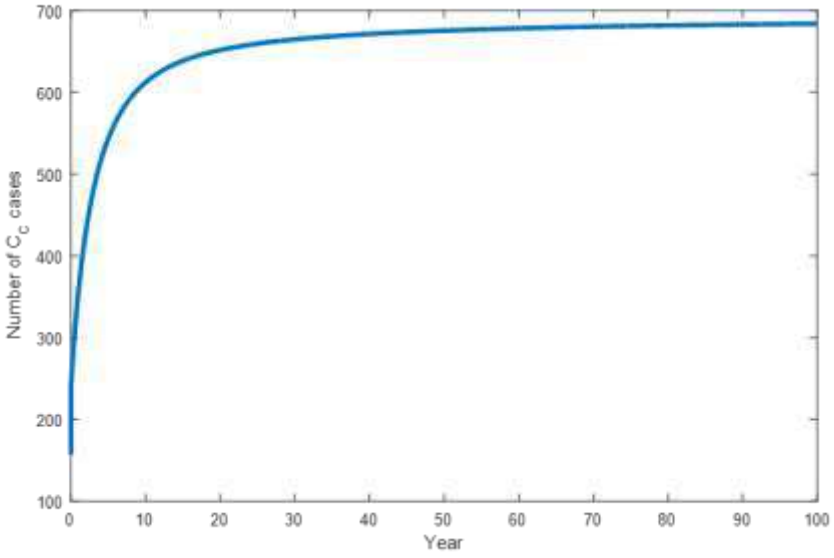


**Figure 1. The trend of community-acquired *Staphylococcus aureus* infected individuals ($C_c$) cases in the community.** The graph demonstrates that according to the constructed model community-acquired *Staphylococcus aureus* cases indicate an increasing trend for 10 years with a start date of early 2023 followed by a plateau up to 700 cases.

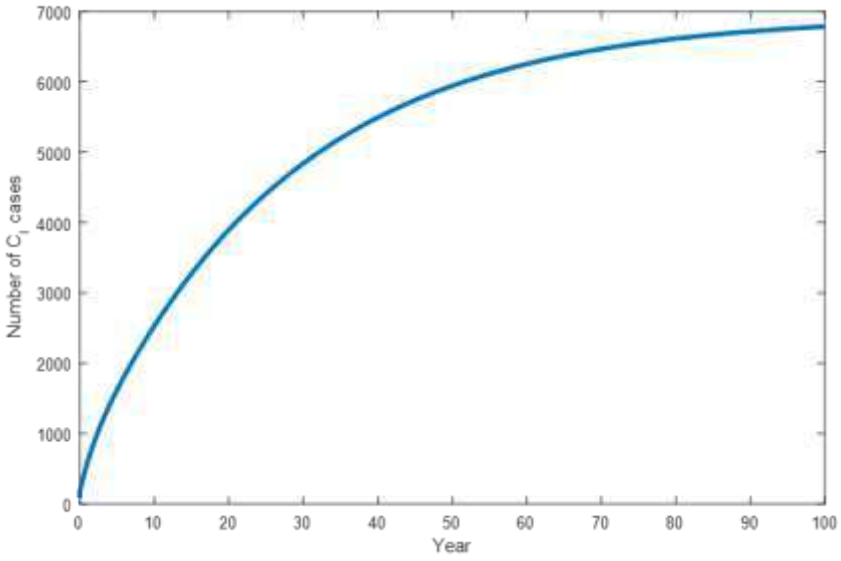


**Figure 2. The trend of community-acquired methicillin resistant *Staphylococcus aureus* infected individuals ($C_I$) cases in the community.** The graph demonstrates that according to the constructed model community-acquired Methicillin Resistant *Staphylococcus aureus* cases indicate an increasing trend starting from the earliest of 2023 and continuing to show an increasing trend for the following years with up to 7,000 cases.

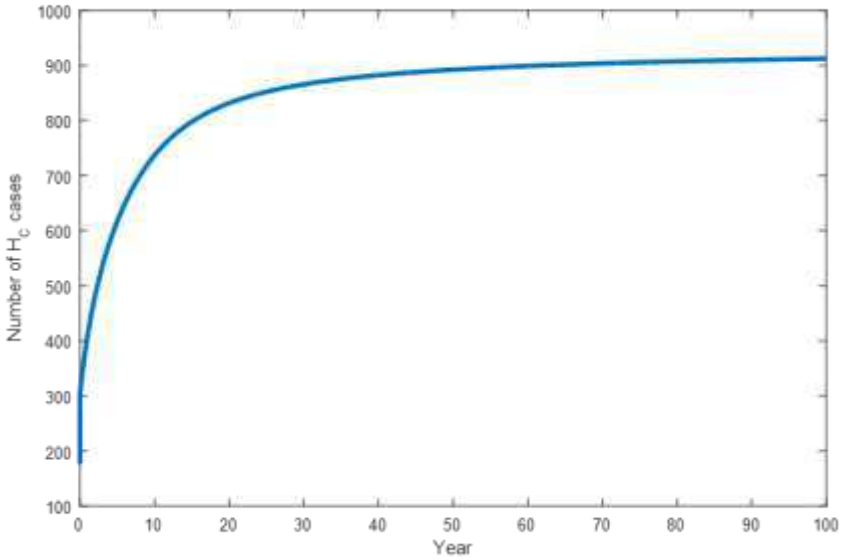


**Figure 3. The trend of hospital-acquired *Staphylococcus aureus* infected individuals ($H_C$) cases.** The graph demonstrates that according to the constructed model hospital-acquired *Staphylococcus aureus* cases indicate an increasing trend for 20 years with a start date of early 2023 followed by a plateau of up to 900 cases.

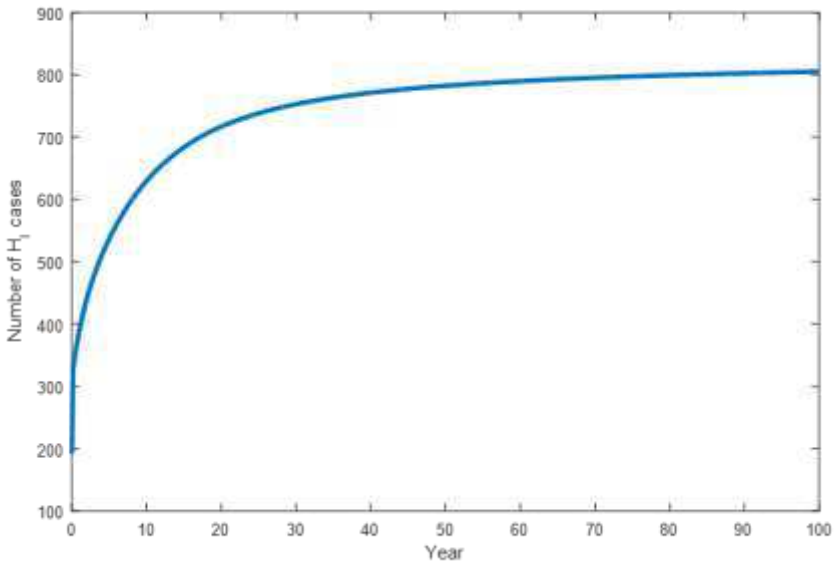


**Figure 4. The trend of hospital-acquired methicillin resistant *Staphylococcus aureus* infected individuals ($H_I$) cases.** The graph demonstrates that according to the constructed model hospital-acquired Methicillin Resistant *Staphylococcus aureus* cases indicate an increasing trend for 30 years with a start date of early 2023 followed by a plateau of up to 800 cases.

**Numerical Simulations for the Constructed Mathematical Model with Optimal Control**

Numerical simulations of the given compartmental mathematical model with optimal control were calculated. Optimal control was applied to the community, and the expected trend of $C_c, C_I, H_C$ and $H_I$ cases were estimated in Figure 5, Figure 6, Figure 7 and Figure 8, respectively. These trends were calculated via MatLab according to the proposed model.

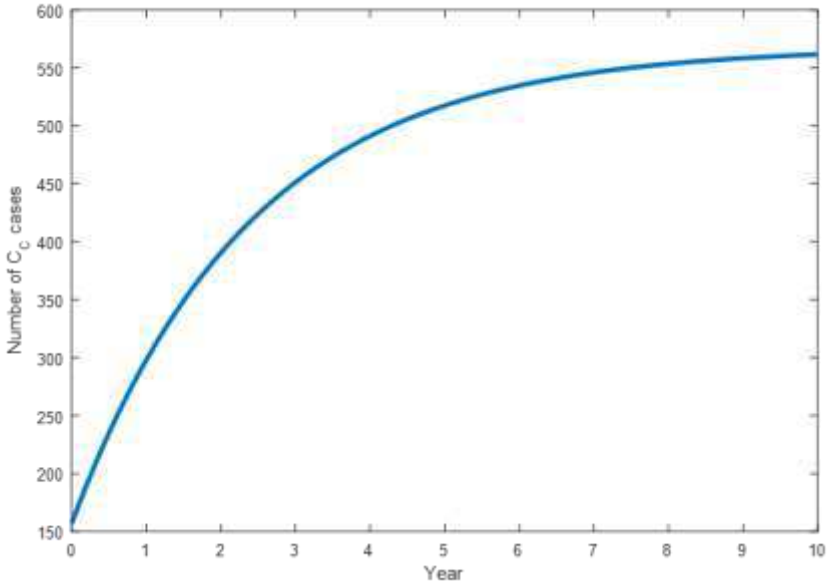


**Figure 5. The trend of community-acquired *Staphylococcus aureus* infected individuals ($C_C$) cases in the community with control.** The graph demonstrates that according to the constructed model with optimal control, community-acquired *Staphylococcus aureus* cases indicate an increasing trend starting from the earliest of 2023 followed by a plateau with up to 550 cases.

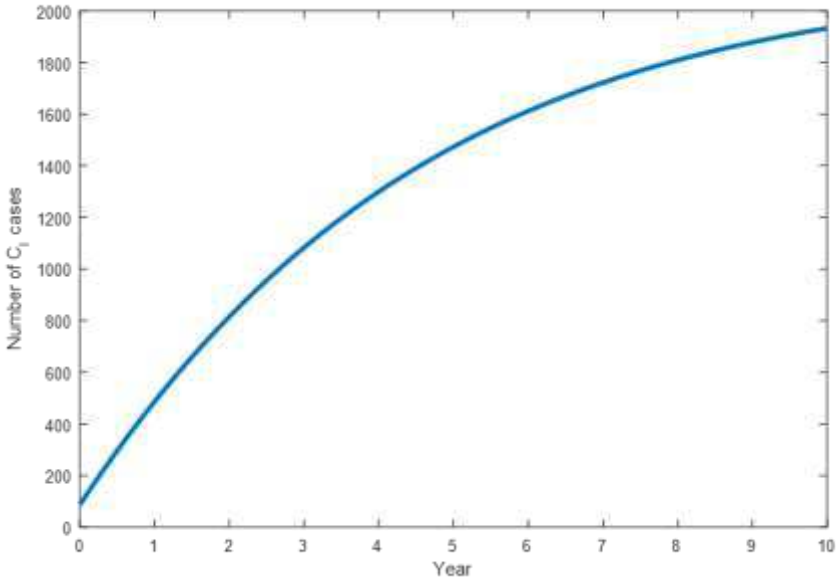


**Figure 6. The trend of community-acquired methicillin resistant *Staphylococcus aureus* infected individuals ($C_I$) cases in the community with control.** The graph demonstrates that according to the constructed model with optimal control, community-acquired Methicillin Resistant *Staphylococcus aureus* cases indicate an increasing trend starting from the earliest of 2023 and continuing to show an increasing trend for the following years with up to 2,000 cases.

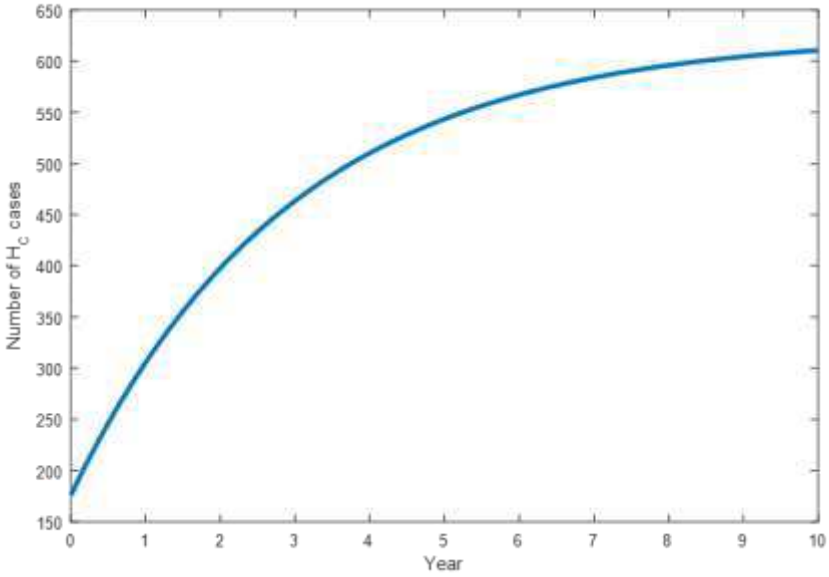


**Figure 7. The trend of hospital-acquired *Staphylococcus aureus* infected individuals ($H_C$) cases with control.** The graph demonstrates that according to the constructed model with optimal control, hospital-acquired *Staphylococcus aureus* cases indicate an increasing trend starting from the earliest of 2023 followed by a plateau with up to 650 cases.

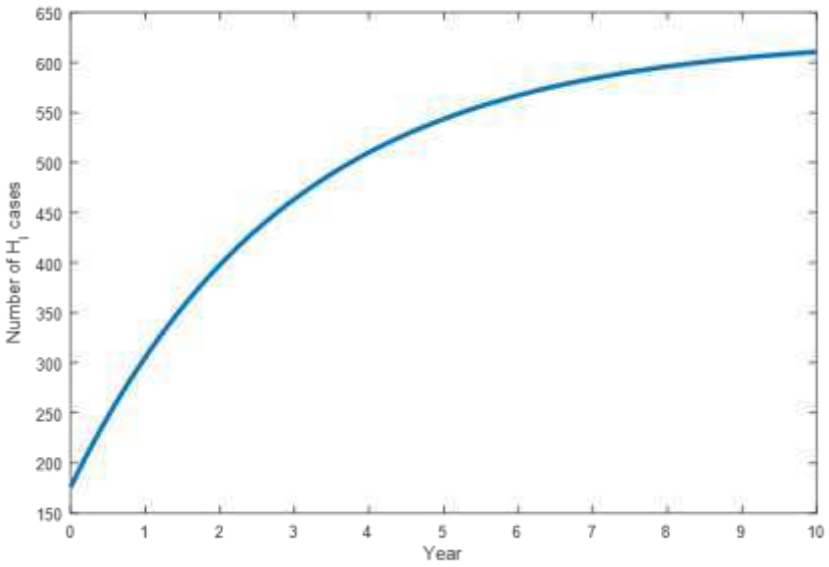


**Figure 8. The trend of hospital-acquired methicillin resistant *Staphylococcus aureus* infected individuals $(H_I)$ cases with control.** The graph demonstrates that according to the constructed model with optimal control, hospital-acquired Methicillin Resistant *Staphylococcus aureus* cases indicate an increasing trend starting from the earliest of 2023 followed by a plateau with up to 650 cases.

## Discussion

In this study, MRSA infections were analyzed in both community and hospitals in the north side of Cyprus. In this regard, a compartmental mathematical model was constructed with and without control to visualize the efficacy of the applied control and increase in the awareness of MRSA cases. According to the results of the compartmental mathematical model without control, a DFE point exists and is locally asymptotically stable in the population. Moreover, numerical simulations of the model without the optimal control revealed that in the upcoming years, there will be a rise in the four compartments studied, including community acquired *Staphylococcus aureus*, community acquired MRSA, hospital acquired *Staphylococcus aureus* and hospital acquired MRSA. On the other hand, these increases are more dangerous for CA-MRSA patients that are MR positive since the trend of these patients is not stable after some point like the other compartments.

When the optimal control theory was applied to the constructed model, it was observed that in all compartments indicated an increasing trend. These increases in the number of cases were almost half of the results of the mathematical model without the control. For example, community-acquired *Staphylococcus aureus* cases indicated an increasing trend for 10 years with a start date of early 2023 followed by a plateau of up to 700 cases with the constructed compartmental mathematical model. Whereas the number of cases for the same group indicated an increasing trend starting from the earliest of 2023 followed by a plateau with up to 550 cases by the constructed compartmental mathematical model with an optimal control. It is clear that there is a significant drop in the number of community-acquired *Staphylococcus aureus* cases when the control is applied. The same decreasing trends of the number of cases occurred in different compartments when the optimal control was applied to the model. Such that in community-acquired Methicillin Resistant *Staphylococcus aureus* cases rise up to 7000 with the compartmental mathematical model. When optimal control was applied, the number of cases dropped to 550. The same pattern of decrease in trend occurred in the hospital-acquired *Staphylococcus aureus* from 900 to 650, and hospital-acquired Methicillin Resistant *Staphylococcus aureus* from 800 to 650. These results firmly suggested that there is an impact of the control measures on the number of cases when applied to the mathematical model.

Others have also implemented deterministic mathematical model to study CA- and HA-MRSA dynamics. D'Agata *et al.*, 's model strongly suggested that CA-MRSA will be replaced with the dominant traditional HA-MRSA strain in hospitals and healthcare facilities. This was due to the well-documented expanding CA-MRSA reservoir and increasing influx of CA-MRSA harboring individuals into the hospitals. CA-MRSA infections result in longer hospitalizations. Hence, D'Agata *et al.* evoked effective strategies for hand hygiene, screening and decolonization for CA-MRSA carriers to prevent this transmission [18].

Another group McBryde *et al.*, also applied stochastic and deterministic mathematical model to determine the transmission dynamics in an intensive care unit. In addition, the group aimed to predict the impact of interventions. The result of this study revealed that increasing the length of stay of all patients, especially the stay of colonized patients increased the transmission. The model predicted that, the most effective intervention was hand hygiene to in preventing transmission of HA-MRSA [19].

**Conclusion**

Overall, MRSA cases are expected to increase over time, which is a threat to public health. Thus, this study aimed to suggest which control measures should be improved in preventing the transmission of MRSA by applying optimal control theory. As a control, one of the parameters was to increase awareness and consciousness in both society and hospital. Here it was assumed that; some part of the society was conscious, meaning that there were aware of the MRSA transmission. In the applied optimal control theory, parameters were increased to evaluate its effectiveness on transmission (the u function in the second model is this control). As a result, the model firmly suggested that the spread of this disease can be reduced if people use masks, disinfectants, gloves (patient relatives, companions) when going to the hospital for a visit or examination. In addition, caregivers and nurses should regularly change gloves, wear masks, pay attention to hygiene, and use disinfectants when examining patients. To conclude, the model showed that the increasing the awareness of control measures in the model can significantly reduce the number of MRSA cases in both the community and hospitals.

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## Author contributions

The contributions of each author to this research are as follows: N.G.: Conceptualization, Methodology, Formal Analysis, Writing—Original Draft, Writing—Review and Editing, Visualization and Numerical Analysis. U.H.: Conceptualization, Methodology, Investigation, Writing—Original Draft, Writing—Review and Editing, Visualization. N.S: Conceptualization, Investigation, Writing—Original Draft, Writing—Review and Editing, Visualization. E.G: Conceptualization, Investigation, Writing—Review and Editing, Visualization. E.H.: Methodology, Formal Analysis, Investigation, Writing—Review and Editing, Visualization. K.S.: Methodology, Investigation, Writing—Review and Editing.

## Competing interests

The authors declare no competing interests.

## Data availability statement

The data for this study are available from the corresponding author upon a reasonable request.

## Additional Information

Correspondence and requests for materials should be addressed to N.G., U.H. and N.S.

## Figure legends

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