Research Article

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Evaluation of ESBL resistance dynamics in *Escherichia coli* isolates by mathematical modeling

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Abstract: Antibiotic resistance is becoming one of the threats to global health. This crisis has been attributed to the over-the-counter and overuse of antibiotics leading bacteria to gain the ability to resist and survive even in the presence of antimicrobial agents. *Escherichia coli* (*E. coli*) is one of the major gram-negative bacteria that are the representative indicators of antibiotic resistance. One of the mechanisms of gaining antibiotic resistance is the ability of *E. coli* to gain the production of extended-spectrum beta-lactamases (ESBL). In this study, Near East University Hospital data from 2016 to 2019 were used to study the dynamics of ESBL-producing (ESBL$^+$) and non-ESBL-producing (ESBL$^-$) *E. coli* infections by using a mathematical model. In our study, the aim was to evaluate the distribution of infections caused by resistant *E. coli* strains in later years and to increase the success of treatment in patients infected with *E. coli* by reducing the problem of antibiotic resistance. By using the mathematical model and data of the patients, basic reproduction number (R_0) values were calculated to study epidemiologic dynamics of the disease. The $R_0^{E^-}$ and $R_0^{E^+}$ values for ESBL$^-$ and ESBL$^+$ *E. coli* infections were calculated, respectively. According to the model and the data used within the study, it was calculated that $R_0^{E^-}$ to be 1,266,403 and $R_0^{E^+}$ to be 2,096,747. Since the values for $R_0^{E^-}$ and $R_0^{E^+}$ were equal or greater than 1, this suggests that currently the ESBL$^-$ and ESBL$^+$ *E. coli* infections are in epidemic character for Cyprus. Furthermore, when simulation analyses were carried out for the model, it was predicted that in 2042 the and ESBL$^+$ *E. coli* infection trends will equalize. After 2042, the ESBL$^-$ *E. coli* infections will indicate a descending pattern whereas ESBL$^+$ *E. coli* infection will increase constantly.

Keywords: *Escherichia coli*, mathematical modeling, antibiotic, resistance, ESBL

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1 Introduction

Microorganisms in the Enterobacteriaceae family are the most frequently isolated gram-negative bacteria group from clinical specimens. One example is *Escherichia coli* (*E. coli*), which is a member of the human intestinal normal flora but can also be the cause of infections like urinary tract infections, hemolytic uremic syndrome, pneumonia, sepsis, meningitis, diarrhea, *etc.* [1].

In the last decade, bacteria developing resistance to available antibiotics has become a global threat worldwide. One of the biggest reasons for this is the inappropriate and over-the-counter use of antibiotics. Resistance development in gram-negative bacteria against beta-lactam antibiotics is due to the widespread inappropriate use of new beta-lactam antibiotics. Bacteria acquire resistance by gaining the property of producing the beta-lactamase enzyme. These

enzymes destroy the antibacterial effect by breaking the amide bonds in the beta-lactam ring of beta-lactam antibiotics [2,3].

One of the most important resistance mechanisms against beta-lactam group antibiotics is the production of extended-spectrum beta-lactamase (ESBL). ESBL-producing Enterobacteriaceae isolates are common human pathogens that pose serious problems for individual and public health [4]. Infections originating from ESBL producing *E. coli* strains can lead to long-term hospitalization, high treatment costs, and high mortality rates [5,6].

The first choice of antibacterial agent in the treatment of ESBL producing gram-negative bacterial infections is the carbapenem antibiotic group. Similar to beta-lactam group antibiotic, resistance development in the carbapenem antibiotic group is seen frequently due to the widespread and inappropriate use of carbapenems [7]. Carbapenem-resistant Enterobacteriaceae isolates can also be resistant to many other antibiotics and are considered virulent pathogens. Therefore, serious measures must be taken to prevent the spread of these microorganisms [8].

The distribution of microorganisms that cause infectious diseases and their resistance to antibiotics have changed over the years. For this reason, changes in the causative microorganism and antibiotic resistance status should be constantly monitored by each laboratory to guide the application of empirical treatment [9].

Mathematical modeling is often used to analyze the dynamics of infectious diseases such as influenza, childhood infections, HIV, or vector-borne infections. It has been a widely used technique in recent years for the generation of heath policies as well as supporting the control strategies development of infectious diseases [10,11]. Also, simulations applied in a mathematical model are used to forecast ongoing epidemic spread within the studied population [12]. In addition, with the emergence of coronavirus disease 2019 (COVID-19) pandemic, many studies have successfully used mathematical modeling to control and develop country-based health policies [12,13]. The applied mathematical models generally aim to predict the recurrence, spread, and mortality rates of the disease and to explain their causes [14,15].

In this study, culture samples of patients who were admitted to the Near East University (NEU) Hospital between 2016 and 2019 were evaluated. A mathematical model was created with the data determined and obtained retrospectively. The mathematical model used in this study is $S(t)I(t)$ type model, where $S(t)$ stands for people who are likely to be infected at time t d and $I(t)$ stands for infected individuals who can spread the disease [16].

The very important threshold quantity of the mathematical model is the basic reproduction number denoted as R_0 which is an epidemiologic metric used to analyze the dynamics of infectious diseases. The R_0 is generally reported as a single numeric value and the magnitude of R_0 value is indicative of a potential size of an outbreak or epidemic within the studied population. Interpretations of the R_0 value are made as follows: if the value is equal to or above 1 an outbreak is expected to continue. On the other hand, if R_0 value is below 1, an outbreak is expected to end [17,18].

The created SI type of mathematical model within this study aimed to analyze the antibiotic resistance patterns of *E. coli* infections and the rate of encountering non-ESBL and ESBL producing *E. coli* infections. This study also aims to reveal the emergence rates of *E. coli* strains in patients from the cumulative data of patients visiting NEU Hospital from 2016 to 2019.

Before starting this study, research related to mathematical modeling in the literature was examined. It has been seen that mathematical models are used in the analysis of HIV (human immunodeficiency virus) dynamics [11], in different fields for many purposes during the COVID-19 pandemic [19], in the follow-up of parasitic infections like Hookworm infection [20], in modeling the measles epidemic [21], and in studies related to the investigation of immunological tumor dynamics in cancer patients [22]. In addition, this study was aimed because there are almost no modeling studies on bacteria and antibiotic resistance. The absence of any modeling studies on *E. coli* and antibiotic resistance patterns in Northern Cyprus is one of the main reasons for planning this study.

There are very few articles in the literature about following or predicting the bacteria that cause common diseases and the resistance patterns they develop with mathematical modeling. Our article is especially important in terms of following up *E. coli* infections taking precautions by monitoring resistance strains, and therefore, reducing mortality and morbidity rates. The main goals of this study were to: (i) emphasize the inappropriate use of antibiotics, which is the main reason for the development of resistance in bacteria, (ii) evaluate the status of ESBL producer *E. coli* strains in the future, (iii) make assumptions by discussing the increasing problem of antibiotics, and (iv) estimate the ways to combat these problems and to increase the success rates in the treatment of patients infected with *E. coli*.

The remainder of the article proceeds as follows. In Section 2, collection of *E. coli* data and applied models are described. In Section 3, the values of the model in numerical simulation and sensitivity analysis of the dynamics of resistant *E. coli* strains are explained in the light of the

data obtained as a result of the modeling. In the last sections, a discussion of the results and concluding remarks are presented.

2 Experimental procedures

2.1 Collection of data

E. coli strains detected in patients who visited the NEU Hospital between 2016 and 2019 were taken from the *Nucleus* data system in the hospital with their associated pre-determined parameters. These parameters included age, gender, and culture samples (urine, blood, aspirate, *etc*.). Also, the parameters included the departments where these samples arrived from such as internal medicine, intensive care, *etc*. Furthermore, the strains of *E. coli* were grouped into ESBL negative and ESBL producing *E. coli* strains according to their antibiotic resistance profile. In this study, to simplify the flow of the text, ESBL producing *E. coli* strains are referred to as ESBL$^+$ and non-ESBL producing *E. coli* strains as ESBL$^-$.

2.2 Identification of strains and antimicrobial susceptibility tests

The samples taken from the relevant services and polyclinics of the NEU Hospital during the study period were delivered to the microbiology laboratory. The delivered samples were cultured on blood agar and eosin methylene blue (EMB) agar. These media were kept in an incubator at 35°C for 24–48 h depending on the growth status.

For the samples with gram-negative bacterial growth, McFarland bacterial suspensions in the range of 0.50–0.63 MFU were prepared based on the manufacturer's recommendations. These prepared suspensions were loaded into the Biomerieux VITEK® 2 Compact (bioMerieux, Inc. Durham, USA) device for identification of the bacterial species and analysis of antimicrobial susceptibility tests. VITEK® 2 GN (bioMerieux, Inc. Durham, USA) cards were used to identify the gram-negative bacterial species. The antimicrobial resistance of the detected bacteria was determined by the type of sample (urine, sputum, *etc*.) by using VITEK® 2 AST-N327 (bioMerieux, Inc. Durham, USA), VITEK® 2 AST-N325 (bioMerieux, Inc. Durham, USA), and VITEK® 2 AST-N326 (bioMerieux, Inc. Durham, USA) cards.

2.3 Application of obtained data to the mathematical model

The study used SI type of mathematical model. Basic reproduction numbers for *E. coli* non-ESBL and ESBL producing infections were calculated and represented as $R_0^{E^+}$ and $R_0^{E^-}$, respectively. The R_0 values were calculated using the next-generation matrix method. In addition, local and global sensitivity analyses were performed to illustrate the impact of each parameter on R_0 value within the mathematical model.

In the constructed model, populations within the hospital were grouped into three mutually exclusive ways: The susceptible $S(t)$, infected with ESBL$^+$ *E. coli* named as $E^+(t)$, and infected with ESBL$^-$ *E. coli* named as $E^-(t)$. It was assumed that individuals entered one of these classes with the constant variable Λ when they first entered the hospital. However, for the study, the model was continued only with *E. coli* ESBL$^+$ individuals.

Within the created model, the rate of admission to the hospital with infected ESBL$^-$ *E. coli* was referred to as m_1 and individuals infected with ESBL$^+$ *E. coli* was m_2. Furthermore, the individual's discharge from hospital by death was stated as μ or hospital discharge as d. The susceptible class can be infected with ESBL$^-$ *E. coli* (δ_1) or ESBL$^+$ *E. coli* (δ_2). The recovery rate from ESBL$^-$was β_1 and the recovery rate from ESBL$^+$ was given by β_2. The rate of transmission from ESBL$^-$ *E. coli* to ESBL$^+$ *E. coli* is β_3. With these assumptions, the model is given by the system of differential equation in (1), where the definitions and the values of each parameter are given in Table 1.

$$\begin{aligned}
\frac{dS}{dt} &= \tau(1 - m_1 - m_2) - \delta_1 E^- S - \delta_2 E^+ S + \alpha_1 K + \alpha_2 T \\
&\quad + c\beta_1 E^- - (\mu + d)S, \\
\frac{dE^-}{dt} &= \tau m_1 + \delta_1 E^- S - (c\beta_1 + (1 - c)\beta_3)\beta_1 E^- - \mu E^-, \\
\frac{dE^+}{dt} &= \tau m_2 + \delta_2 E^+ S + (1 - c)\beta_3 E^- - \beta_2 E^+ - (k + p)E^+ \\
&\quad - \mu E^+, \\
\frac{dK}{dt} &= kE^+ - \alpha_1 K, \\
\frac{dT}{dt} &= pE^+ - \alpha_2 T.
\end{aligned} \tag{1}$$

The most often used treatment options for ESBL$^+$ *E. coli* stated as $E^+(t)$ within the model were indicated as K (carbapenems) and T (piperacillin-tazobactam). In this study, the model used in [23] was extended by adding two treatment classes K and T. The constructed mathematical model can be visualized in Figure 1.

Table 1: Descriptions and the values of the parameters within the mathematical model

Parameters	Descriptions	Values
S	Susceptible to *E. coli*	17,579
E^-	ESBL negative *E. coli*	1,279
E^+	ESBL positive *E. coli*	601
K	Carbapenems	518
T	Piperacillin-tazobactam	472
Λ	The number of hospital admissions	67.064
m_1	The fraction of patients admitted with ESBL$^-$	0.5099
m_2	The fraction of patients admitted with ESBL$^+$	0.0239
c	The probability that a person takes drug one and be resistant to the drug	0.7
δ_1	The transmission rate of a susceptibility patient infected with ESBL$^-$	0.00000045
δ_2	The transmission rate of susceptible to ESBL$^+$ *E. coli*	0.00000052
β_1	Removed from ESBL$^-$ *E. coli* to susceptible class	0.007819
β_2	Transmission rate from ESBL$^+$ *E. coli* to susceptible class	000655
k	Rate of individuals that can be treated with K	0.000861897
p	Rate of individuals that can be treated with T	0.000078536
β_3	Transmission rate from ESBL$^-$ to ESBL$^+$	0.00218
μ	Natural death	0.0002

It is assumed that the individual with ESBL$^+$ can be treated with K (carbapenems) and T (piperacillin-tazobactam) with the rate of k and t, respectively. With these assumptions, newly created differential equation in (2) were used for the model, with the parameters presented in Table 1 [24].

$$\begin{aligned}
\frac{dS}{dt} &= \tau(1 - m_1 - m_2) - \delta_1 E^- S - \delta_2 E^+ S + \alpha_1 K + \alpha_2 T \\
&\quad + c\beta_1 E^- - (\mu + d)S, \\
\frac{dE^-}{dt} &= \tau m_1 + \delta_1 E^- S - (c\beta_1 + (1 - c)\beta_3)\beta_1 E^- - \mu E^-, \\
\frac{dE^+}{dt} &= \tau m_2 + \delta_2 E^+ S + (1 - c)\beta_3 E^- - \beta_2 E^+ - (k + p)E^+ \\
&\quad - \mu E^+, \\
\frac{dK}{dt} &= pE^+ - \alpha_1 K, \\
\frac{dT}{dt} &= tE^+ - \alpha_2 T.
\end{aligned} \tag{2}$$

2.4 Stability of disease-free equilibrium (DFE) point and basic reproduction ratio

With equalizing to zero of each equation in the system (2) and with the assumption $m_1 = m_2 = 0$, the DFE was obtained as $E_0 = \left(\frac{\Lambda}{\mu + d}, 0, 0\right)$.

By using the next-generation matrix method, $R_0^{E^+}$ and $R_0^{E^-}$ values were calculated as follows:

$$F = \begin{pmatrix} \Lambda m_1 + \delta_1 S E^- \\ \Lambda m_2 + \delta_2 S E^+ \end{pmatrix}, \; V = \begin{pmatrix} c\beta_1 E^- + (1 - c)\beta_3 E^- + \mu E^- \\ -(1 - c)\beta_3 E^- + \beta_2 E^+ + \mu E^+ \end{pmatrix}.$$

$$f = \begin{pmatrix} \delta_1 \frac{\Lambda}{\mu} & 0 \\ 0 & \delta_2 \frac{\Lambda}{\mu} \end{pmatrix}, \; v = \begin{pmatrix} c\beta_1 + (1 - c)\beta_3 + \mu & 0 \\ -(1 - c)\beta_3 & \beta_2 + \mu \end{pmatrix}.$$

$$fv^{-1} = \begin{pmatrix} \frac{S\boldsymbol{\delta}_1}{c\beta_1 + (1 - c)\beta_3 + \mu} & 0 \\ \frac{S\boldsymbol{\delta}_2(1 - c)\beta_3}{(c\beta_1 + (1 - c)\beta_3 + \mu)(\beta_2 + \mu)} & \frac{S\boldsymbol{\delta}_2}{\beta_2 + \mu} \end{pmatrix}.$$

Then, $\frac{\Lambda\delta_1}{\mu(c\beta_1 + (1 - c)\beta_3 + \mu)}$ and $\frac{\Lambda\delta_2}{\mu(\beta_2 + \mu)}$ are the dominant eigenvalues of fv^{-1}. Therefore, the basic reproduction numbers are given as:

$$R_{0,E^-} = \frac{\Lambda\delta_1}{\mu(c\beta_1 + (1 - c)\beta_3 + \mu)}, \tag{3}$$

$$R_{0,E^+} = \frac{\Lambda\delta_2}{\mu(\beta_2 + \mu)}. \tag{4}$$

Then, parameters represented in Table 1 were integrated into equations. (3) and (4) and the below values of R_{0,E^-} and R_{0,E^+} were obtained:

$$R_{0,E^-} = 1{,}266{,}403,$$

$$R_{0,E^+} = 2{,}096{,}747.$$

Theorem 1. *For model (2), the disease-free equilibrium was locally asymptotically stable when* $R_{0,E^-} < 1$ *and* $R_{0,E^+} < 1$.

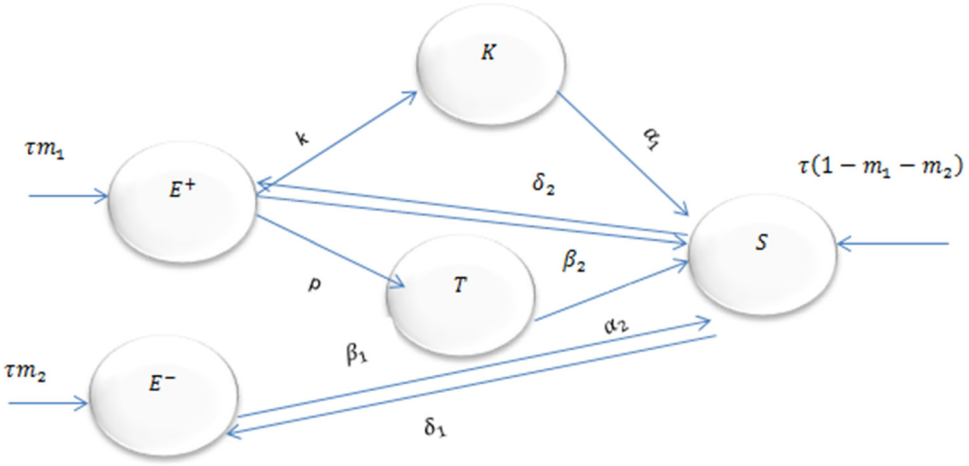

Figure 1: The flowchart representing compartments and their interaction with ESBL$^+$ and ESBL$^-$ *E. coli* strains within the model.

Proof. The Jacobian matrix at the DFE point of the model (2): □

$$J = \begin{pmatrix} -(\mu+d) & c\beta_1 - \delta_1 S_0 & -\delta_2 S_0 & \alpha_1 & \alpha 2 \\ 0 & \delta_1 S_0 - (\beta_1+\mu) & 0 & 0 & 0 \\ 0 & (1-c)\beta_1 & \delta_2 S_0 - (\beta_2+k+p+\mu) & 0 & 0 \\ 0 & 0 & k & -\alpha_1 & 0 \\ 0 & 0 & t & 0 & -\alpha_2 \end{pmatrix}.$$

The eigenvalues of the Jacobian matrix were: $\lambda_1 = \delta_1 S_0 - (\beta_1 + \mu)$,

$$\lambda_2 = \delta_2 S_0 - (\beta_2 + k + p + \mu),$$

$$\lambda_3 = -(\mu + d),$$

$$\lambda_4 = -\alpha_1,$$

$$\lambda_5 = -\alpha_2.$$

The λ_3, λ_4, and λ_5 were always less than zero and λ_1 was less than zero when $R_{0,1}$ was less than zero and λ_2 was less than zero when $R_{0,2}$was less than zero. Therefore, DFE was locally asymptotically stable when both $R_{0,1}$ and $R_{0,2}$ were less than zero.

Sensitivity analysis of R_0

Local sensitivity analyses were applied in order to highlight the sensitivity of some key associated parameters to the value of R_0 in the model.

This was performed to analyze the sensitivity of R_0 in relation to the important parameters used throughout the model. The computation of the expression of R_0 was carried out using the technique of next-generation matrix and it is denoted by

$$R_0 = \left\{ R_{0,E^-} = \frac{\Lambda\delta_1}{\mu(c\beta_1 + (1-c)\beta_3 + \mu)},\ R_{0,E^+} = \frac{\Lambda\delta_2}{\mu(\beta_2 + k + p + \mu)} \right\}.$$

Then, computation of the normalized local sensitivity was performed which indicates that R_0 is proportional to the parameters in connection to the model.

By using the R_0 indexes, $\gamma = \{\Lambda, \mu, c, \beta_1, \beta_2, \beta_3, \delta_1, \delta_2, k, t\}$, R_0, the normalized local sensitivity was defined as shown below:

$$\Omega_\gamma^{R_0} = \frac{\partial R_0}{\partial \gamma}\frac{\gamma}{R_0}. \tag{5}$$

Using the above definition (5), the model was computed by the following indices for the output R_0 concerning every parameter presented in

$$\Omega_\Lambda^{R_0,\mathrm{ESBL}^-} = \frac{\delta_1}{\mu(c\beta_1 + (1-c)\beta_3 + \mu)}\frac{\mu(c\beta_1 + (1-c)\beta_3 + \mu)}{\delta_1\Lambda} = 1, \tag{6}$$

$$\Omega_{\delta_1}^{R_0,\mathrm{ESBL}^-} = \frac{\Lambda}{\mu(c\beta_1 + (1-c)\beta_3 + \mu)}\frac{\mu(c\beta_1 + (1-c)\beta_3 + \mu)}{\Lambda\delta_1} = 1, \tag{7}$$

$$\begin{aligned} \Omega_\mu^{R_0,\mathrm{ESBL}^-} &= \frac{-\Lambda\delta_1[c\beta_1 + (1-c)\beta_3 + 2\mu]}{\mu^2(c\beta_1 + (1-c)\beta_3 + \mu)^2} \times \frac{\mu^2(c\beta_1 + (1-c)\beta_3 + \mu)}{\delta_1\Lambda} \\ &= \frac{-[c\beta_1 + (1-c)\beta_3 + 2\mu]}{c\beta_1 + (1-c)\beta_3 + \mu}, \end{aligned} \tag{8}$$

$$\begin{aligned} \Omega_c^{R_0,\mathrm{ESBL}^-} &= \frac{-\Lambda\delta_1[\beta_1 - \beta_3]}{\mu(c\beta_1 + (1-c)\beta_3 + \mu)^2}\frac{\mu c(c\beta_1 + (1-c)\beta_3 + \mu)}{\delta_1\Lambda} \\ &= \frac{-c[\beta_1 - \beta_3]}{c\beta_1 + (1-c)\beta_3 + \mu}, \end{aligned} \tag{9}$$

$$\Omega_{\beta_1}^{R_{0,\mathrm{ESBL}^-}} = \frac{-\Lambda\delta_1 c}{\mu(c\beta_1 + (1-c)\beta_3 + \mu)^2} \times \frac{\mu\beta_1(c\beta_1 + (1-c)\beta_3 + \mu)}{\delta_1\Lambda} = \frac{-\beta_1 c}{c\beta_1 + (1-c)\beta_3 + \mu}, \quad (10)$$

$$\Omega_{\beta_3}^{R_{0,\mathrm{ESBL}^-}} = \frac{-\Lambda\delta_1(1-c)}{\mu(c\beta_1 + (1-c)\beta_3 + \mu)^2} \times \frac{\mu\beta_3(c\beta_1 + (1-c)\beta_3 + \mu)}{\delta_1\Lambda} = \frac{-\beta_3(1-c)}{c\beta_1 + (1-c)\beta_3 + \mu}, \quad (11)$$

$$\Omega_{\Lambda}^{R_{0,\mathrm{ESBL}^+}} = \frac{\delta_2}{\mu(\beta_2 + k + p + \mu)} \frac{\mu(\beta_2 + k + p + \mu)}{\Lambda\delta_2} = 1, \quad (12)$$

$$\Omega_{\delta_2}^{R_{0,\mathrm{ESBL}^+}} = \frac{\Lambda}{\mu(\beta_2 + k + p + \mu)} \frac{\mu(\beta_2 + k + p + \mu)}{\Lambda\delta_2} = 1, \quad (13)$$

$$\Omega_{\mu}^{R_{0,\mathrm{ESBL}^+}} = \frac{-\Lambda\delta_2[\beta_2 + k + p + 2\mu]}{\mu^2(\beta_2 + k + t + \mu)^2} \frac{\mu\mu(\beta_2 + k + p + \mu)}{\Lambda\delta_2} = \frac{-[\beta_2 + k + p + 2\mu]}{(\beta_2 + k + p + \mu)}, \quad (14)$$

$$\Omega_{\beta_2}^{R_{0,\mathrm{ESBL}^+}} = \frac{-\Lambda\delta_2\mu}{\mu^2(\beta_2 + k + p + \mu)^2} \frac{\beta_2\mu(\beta_2 + k + p + \mu)}{\Lambda\delta_2} = \frac{-\beta_2}{(\beta_2 + k + p + \mu)}, \quad (15)$$

$$\Omega_{k}^{R_{0,\mathrm{ESBL}^+}} = \frac{-\Lambda\delta_2\mu}{\mu^2(\beta_2 + k + p + \mu)^2} \frac{k\mu(\beta_2 + k + p + \mu)}{\Lambda\delta_2} = \frac{-k}{(\beta_2 + k + p + \mu)}, \quad (16)$$

$$\Omega_{p}^{R_{0,\mathrm{ESBL}^+}} = \frac{-\Lambda\delta_2\mu}{\mu^2(\beta_2 + k + p + \mu)^2} \frac{t\mu(\beta_2 + k + p + \mu)}{\Lambda\delta_2} = \frac{-p}{(\beta_2 + k + p + \mu)}. \quad (17)$$

3 Results

In this model, the patients who were diagnosed from 2016 to 2019 solely with *E. coli* strains were used to study *E. coli* infections and estimate the simulations on the antibiotic resistance analysis. Based on the collected data, sensitivity analysis was applied to each of the parameters indicated in Table 1 within the model. The parameters in Table 1 were integrated into Eqs. (6–17) and the sensitivity analysis for each parameter in R_0 is represented in Table 2.

For ESBL$^-$ *E. coli*, increasing the parameters Λ and δ_1 to 10% also increased the R_0 by 10%. On the other hand, when increasing the c, β_1, β_3, and μ parameters to 10% within the model, R_0 value decreased. For the ESBL$^+$ *E. coli* analysis, when $\boldsymbol{\Lambda}$ and $\boldsymbol{\delta_2}$ parameters increased by 10% the R_0 value also increased. Whereas, when the parameters β_1, μ, k, and t were increased by 10%, the R_0 value decreased.

Table 2: Sensitivity analysis of R_0 to the designed model

Sensitivity	Sensitivity values
$\Omega_{\Lambda}^{R_{0,\mathrm{ESBL}^-}}$	1
$\Omega_{\delta_1}^{R_{0,\mathrm{ESBL}^-}}$	1
$\Omega_{c}^{R_{0,\mathrm{ESBL}^-}}$	−0.9599
$\Omega_{\beta_1}^{R_{0,\mathrm{ESBL}^-}}$	−0.98545
$\Omega_{\beta_3}^{R_{0,\mathrm{ESBL}^-}}$	−0.01095
$\Omega_{\mu}^{R_{0,\mathrm{ESBL}^-}}$	−1.0036
$\Omega_{\Lambda}^{R_{0,\mathrm{ESBL}^+}}$	1
$\Omega_{\delta_2}^{R_{0,\mathrm{ESBL}^+}}$	1
$\Omega_{\beta_2}^{R_{0,\mathrm{ESBL}^+}}$	−0.87212
$\Omega_{\mu}^{R_{0,\mathrm{ESBL}^+}}$	−0.87745
$\Omega_{k}^{R_{0,\mathrm{ESBL}^+}}$	−0.09817
$\Omega_{p}^{R_{0,\mathrm{ESBL}^+}}$	−0.01046

Furthermore, dynamics of the *E. coli* ESBL$^+$ and ESBL$^-$ diagnosed patient numbers with their corresponding years have been studied. Figure 2 indicates the ESBL$^+$ and ESBL$^-$ patient distribution according to years simulated with the parameters used in the model.

With the present data, non-ESBL *E. coli* (ESBL$^-$ *E. coli*) infection numbers collected in NEU Hospital for the study period (2016–2019) were higher compared to the ESBL producing (ESBL$^+$) *E. coli* infections. For the future predictions, the mathematical model simulation indicated that ESBL$^+$ *E. coli* infections will increase steadily. According to the data, the ESBL$^+$ and ESBL$^-$ *E. coli* infections number will become equal in the 23rd year. After the 23rd year, the ESBL$^+$ *E. coli* infections will start to rise with an increasing pattern than the ESBL$^-$ *E. coli*.

3.1 Sensitivity analysis of R_0 within the model for *ESBL$^+$ E. coli* patients

From here, the rest of the study has emphasized the ESBL$^+$ *E. coli* infection analysis. Five parameters: k, p, Λ, δ_2 and β_2 used in the model were further increased by 10% to study the effect on the R_0 value for *E. coli* ESBL$^+$ infection, referred to as the sensitivity analysis.

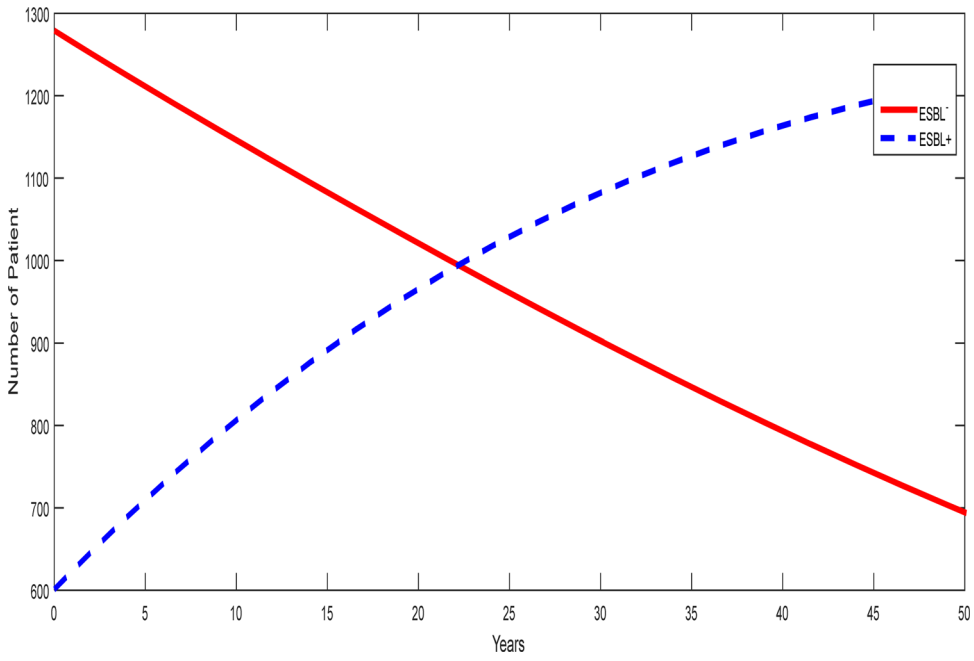

Figure 2: Dynamics of ESBL$^+$ and ESBL$^-$ *E. coli* infections.

The parameter represents the carbapenemase treatment. Figure 3a represents the original data and Figure 3b represents the 10% increase in carbapenemase treatment to the original data. In this way, the model sensitivity could be analyzed. According to our application, when k is increased within the model, the ESBL$^+$ patient number decreases.

The parameter t represents the piperacillin-tazobactam antibiotic treatment in the model. Figure 4a represents the original pattern of t applied to the collected data and Figure 4b represents the 10% increased piperacillin-tazobactam antibiotic treatment to the original data. When t was increased by 10%, the ESBL$^+$ patient indicated a decreasing pattern.

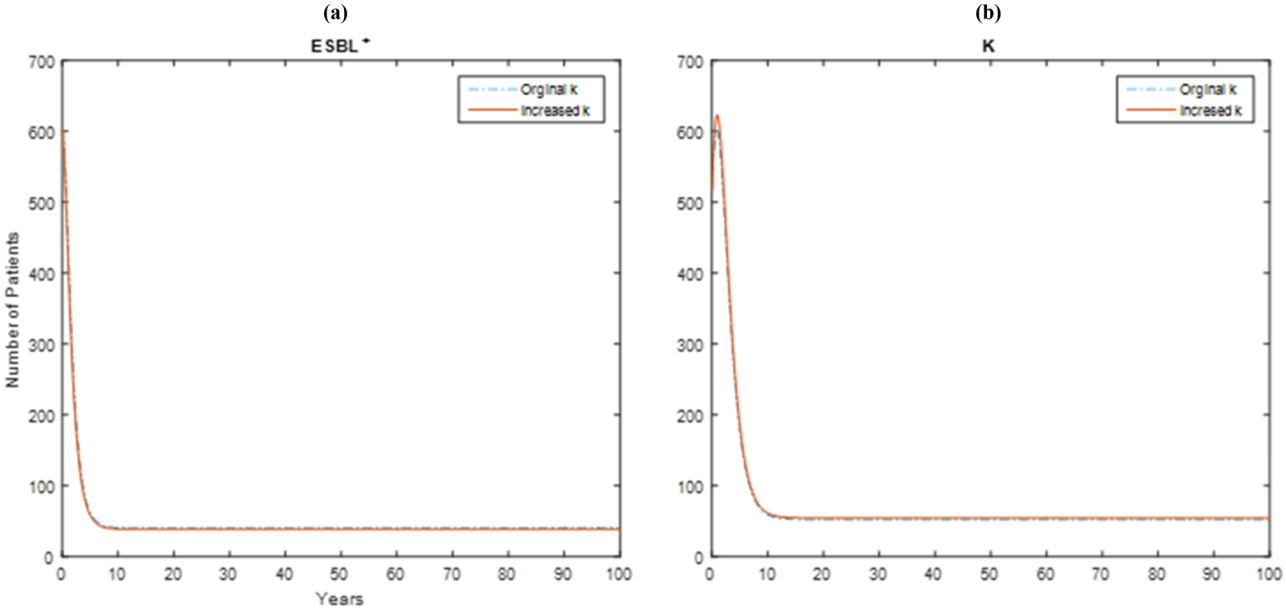

Figure 3: Impact of the variation in k on the number of infectiveness of ESBL$^+$ *E. coli* patients.

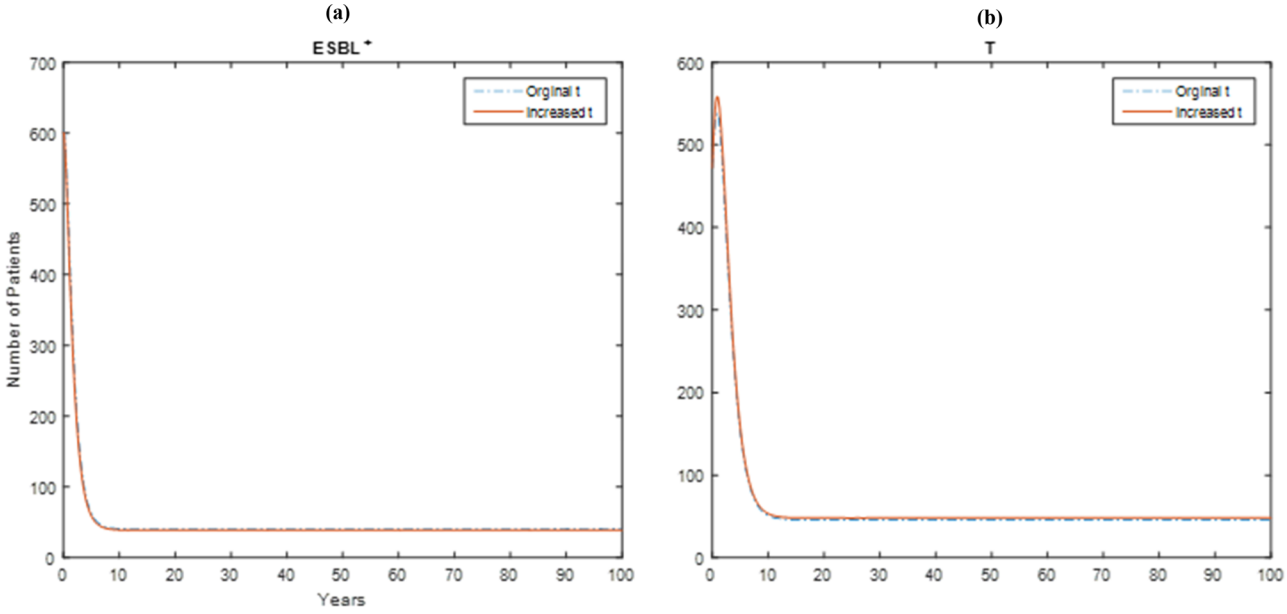

Figure 4: Impact of the variation in p on the number of infectiveness of ESBL$^+$ *E. coli* patients.

The parameter Λ is the total number of hospital admissions to NEU Hospital in the studied period from 2016 January to 2019 December in the model. The original data is depicted in Figure 5a; when Λ is increased by 10%, the number of hospital admissions will increase, the number of ESBL$^+$ patients treated with both k (carbapenemase treatment) and t (piperacillin-tazobactam treatment) will also increase as indicated in Figure 5b and c, respectively.

The parameter δ_2 is the transmission rate of susceptible to ESBL$^+$ *E. coli* as shown in Figure 6a. When δ_2 is increased by 10%, the number of *E. coli* ESBL$^+$ patients treated with k (carbapenemase treatment) and t (piperacillin-tazobactam treatment) will also increase as indicated in Figure 6b and c, respectively.

In the model $\beta_2$is the transmission rate of ESBL$^+$ *E. coli* to the susceptible class as shown in Figure 7a. Hence, when β_2 is increased by 10%, the ESBL$^+$ *E. coli* patients treated with k (carbapenemase treatment) and t (piperacillin-tazobactam treatment) will indicate a decreasing pattern as shown in Figure 7b and c, respectively.

In the model, μ is the natural death rate, any death that is not related to *E. coli* ESBL$^+$ or ESBL$^-$ infections. In

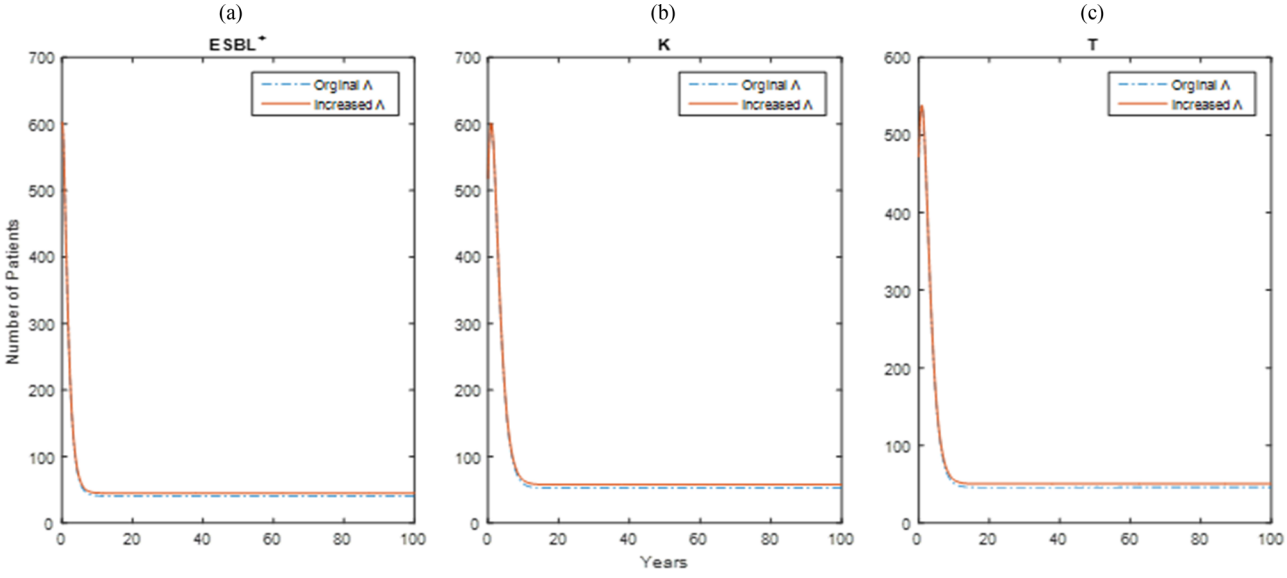

Figure 5: Impact of the variation in Λ on the number of infectiveness of ESBL$^+$ *E. coli* patients.

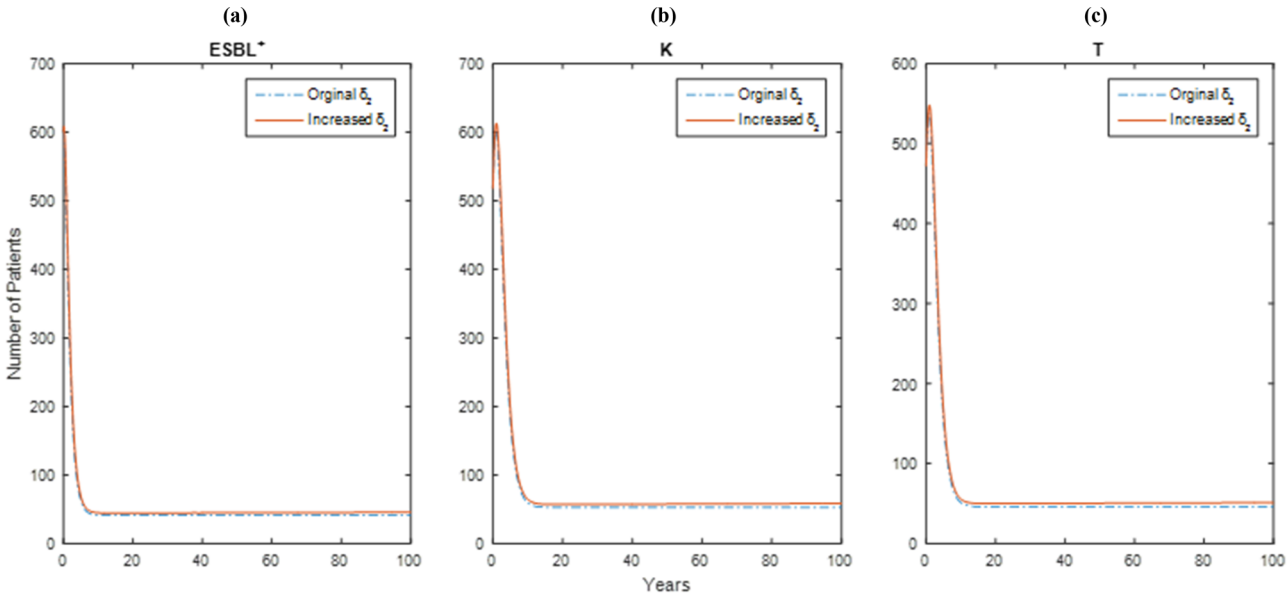

Figure 6: Impact of the variation in δ_2 on the number of infectiveness of ESBL$^+$ *E. coli* patients.

the case when μ is increased by 10%, the number of *E. coli* ESBL$^+$ patients will decrease.

4 Discussion

This study aimed to investigate the near future possibility of the development of antibiotic resistance to *E. coli* producing ESBL infections (ESBL$^+$). To carry out this analysis *SI*-type model was constructed to determine the basic reproduction number (R_0). Next-generation matrix method was used to calculate the values of R_0. In this model, two separate values were calculated for ESBL$^-$ and ESBL$^+$ *E. coli* infections denoted as $R_0^{E^-}$ and $R_0^{E^+}$, respectively.

Moreover, local sensitivity analysis was carried out to evaluate the impact of each parameter used in the model to study the impact on R_0 value. R_0 can be used as an indicator of the transmissibility of infectious diseases. It is often used in epidemiological and public health studies

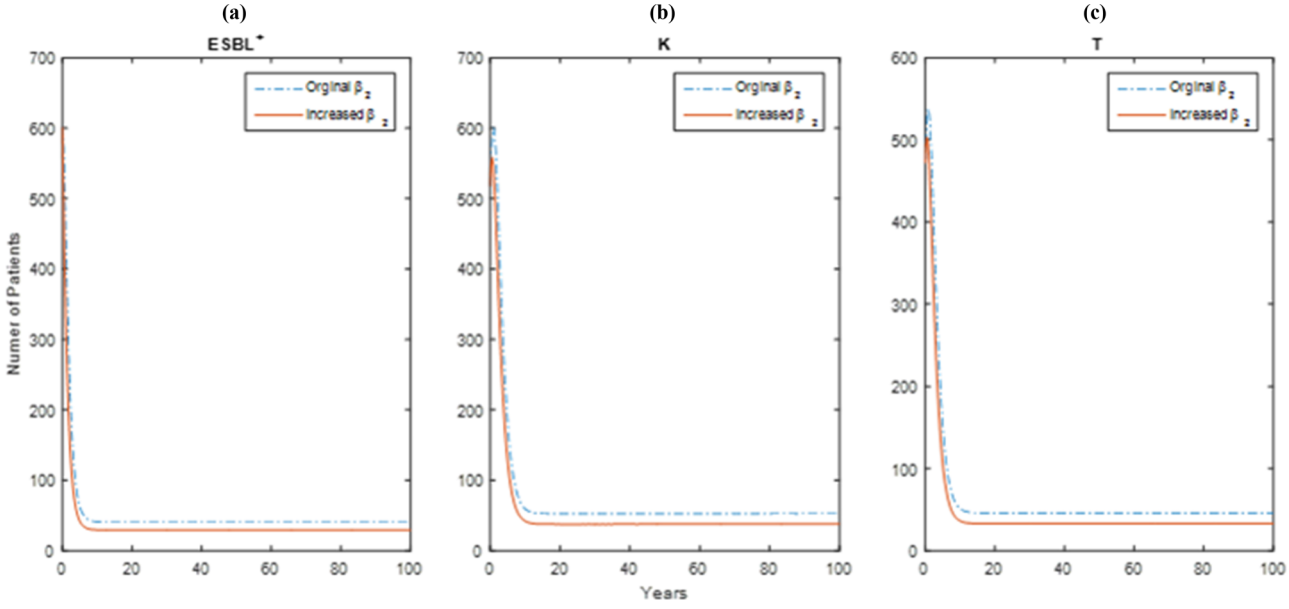

Figure 7: Impact of the variation in β_2 on the number of infectiveness of ESBL$^+$ *E. coli* patients.

to analyze the dynamics of infectious diseases. The calculation of R_0 is generally presented as a single numeric value. If the value of R_0 is greater than or equal to 1 ($\geq$1), the studied outbreak/epidemic is expected to continue whereas if the R_0 value is less than 1 (<1) the outbreak/epidemic is expected to end. Thus, the magnitude of the R_0 represents the potential size of an epidemic or an outbreak within the studied population [18].

For this study, ESBL$^-$ is the *E. coli* infection that can be treated with cephalosporin and other antibiotic groups. Whereas, ESBL$^+$ is the infection that cannot be treated with the cephalosporin group of antibiotics. For this type of infection, carbapenem indicated or piperacillin-tazobactam is preferred for its treatment. For the first choice of treatment, carbapenem antibiotic group is used. If the ESBL$^+$ *E. coli* is resistant to this type of antibiotic group, piperacillin-tazobactam is one of the few options available.

This study was conducted using a total of 17,579 hospital admissions to NEU Hospital in the period between January 2016 and December 2019. Amongst the 17,579 hospital admissions, it was found that 1,871 *E. coli* infections related to hospital admissions occurred in the study period. According to the analysis of the *E. coli* infection, 1,270 were found to be ESBL$^-$ *E. coli* infections and 601 were found to be ESBL$^+$ *E. coli* infections.

By using the *SI*, a type of mathematical model, and the parameters depicted in Table 1, $R_0^{E^-}$ and $R_0^{E^+}$ values were calculated, which were found to be 1,266,403 and 2,096,747, respectively. This indicated that with the current data used, both the *E. coli* infections are in the characteristics of an outbreak. However, the ESBL$^+$ *E. coli* infections have a higher R_0 value than the ESBL$^-$ *E. coli* infections, suggesting that there is a higher possibility for susceptible individuals to acquire ESBL$^+$ *E. coli* than the non-ESBL producing strains of the *E. coli*.

Furthermore, simulation analysis was performed using the mathematical model and data for NEU hospital for the study period. The dynamics of ESBL$^-$ and ESBL$^+$ *E. coli* infections are represented in Figure 2. Within the present time, the ESBL$^+$ *E. coli* infection number is lower than ESBL$^-$ *E. coli* infections. However, with the simulation results, it can be easily seen that although the ESBL$^+$ *E. coli* infection number starts with lower infection rates, as time passes it will follow an increasing trend. The increasing trend of ESBL$^+$ *E. coli* infections will increase constantly and reach the number of ESBL$^-$ *E. coli* infections in the 23rd year of simulation, which is in accordant to the year 2042. After the 23rd year, ESBL$^-$ *E. coli* infections showed descending pattern whereas ESBL$^+$*E. coli* infection indicated an increasing pattern.

From the simulation results, the increasing pattern predicted in the ESBL$^+$ *E. coli* infections with no doubt will lead to a major public health problem in the future. This is because for ESBL$^+$ *E. coli* infections, there are a few available antibiotic groups to treat patients as most ESBL$^+$ *E. coli* are resistant to many commonly used antibiotics such as the cephalosporins. To avoid the development of resistance to antibiotics that are currently used, it is very important to use antibiotics after antibiotic

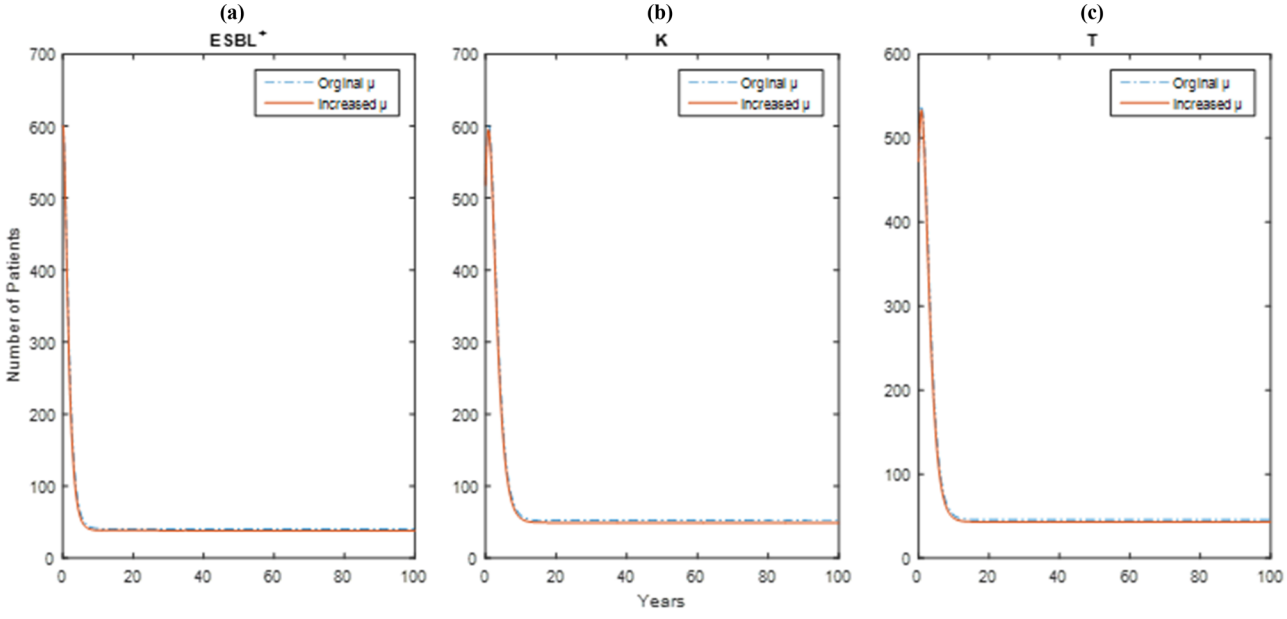

Figure 8: Impact of the variation in μ on the number of infectiveness of ESBL$^+$ *E. coli* patients.

susceptibility tests are performed. Unconscious and over-the-counter antibiotic use is the biggest cause of the development of antibiotic resistance. Hence, prescribed antibiotics should be used in the correct dose and within the advised period.

Another study carried out in 2014 in Cyprus, also emphasized the arising problem of ESBL$^+$ *E. coli* in urinary tract infections. The conducted study revealed that the 389 strains of ESBL$^+$ *E. coli* were isolated from urine samples in Cyprus among the 53% of hospitalized and 44% of outpatients [25].

Furthermore, sensitivity analysis was used to determine which parameters affect the R_0 value and at what magnitude. Determination of the parameters and their influence in either increasing or decreasing the R_0 value is a key factor in the generation of the infectious disease control policies. To determine the key parameters influencing the R_0 values in this study, five parameters: k, p, Λ, δ_2 and β_2 were increased by 10% to perform sensitivity analysis. For this study, sensitivity analyses were only performed for ESBL$^+$ *E. coli* infections. From this analysis it was observed that increasing the parameters of hospital admissions Λ (Figure 5) and transmission of ESBL$^+$ *E. coli* infections to susceptible individuals δ_2 (Figure 6) by 10%, the R_0 value can be increased, indicating that when hospital admissions and ESBL$^+$ *E. coli* infections to susceptible individuals increase, the R_0value of the ESBL$^+$ *E. coli* will be in an epidemic character.

On the other hand, increasing the death rate μ, any death that is not related to *E. coli* infections, by 10%, the R_0value will decrease (Figure 8). Increasing 10% of the individuals that can be treated with k (carbapenemase treatment) (Figure 3) and t (piperacillin-tazobactam treatment) (Figure 4) will also decrease the R_0 value by 10%. However, if any drug resistance develops to these groups of antibiotics, which is a high chance when considering the limited available treatment options, it may lead to the development of persistent infections. Increasing the transmission rate from ESBL$^+$ *E. coli* to susceptible class β_2 by 10% will decrease the R_0 value by 10% (Figure 7). Accomplishment with correct antibiotic choice and adherence to the treatment within the correct period is a critical factor at this point.

5 Conclusion

In conclusion, ESBL$^+$ *E. coli* strains are following an increasing trend in Cyprus and the limited number of options for treatment will be inadequate in near future to treat simple infections. Also, the model predicts that the number of ESBL$^+$ *E. coli* infections will equalize to ESBL$^-$ *E. coli* infections in 2042. After this point, the ESBL$^+$ *E. coli* infections rise constantly. Hence, an immediate rearrangement of the current therapy guidelines should be established. These facts raise the demand for the discovery of a new class of antimicrobial agents and the currently available alternatives should be used efficiently.

The use of over-the-counter antibiotics should be prevented all over the world. Deterrent measures should be strengthened by law to prevent the sale of antibiotics without a prescription. The problems that may be caused by unconscious antibiotic use in the following years should be tried to be shown to people through such studies. In addition, the effective and active functioning of the infection control committee in each hospital and the timely training of all personnel is an important step in slowing down the rate of all infections. This study shows us that when all these are not done, increasing antibiotic resistance will continue to be a major public health problem affecting the whole world.

Selling antibiotics without a prescription may cause bacterial resistance, such as ESBL or carbapenem, in the community. However, it is clear that the spread of resistant bacteria within the hospitals, significantly increases mortality and morbidity rates in patients. For these reasons, effective surveillance studies should be conducted which will provide us with information about these types of infections and give clues for the precautions to be taken in the future. The acceptance and implementation of the concept of "one health" in all countries has an important place among the measures that can be taken. In recent years, the use of mathematical models in health fields gives us the chance to obtain more precise information and to prevent or take early precautions against infections caused by resistant bacteria.

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