

Mathematical Model for Antimicrobial Resistance Transmission Dynamics in Hospitals.

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Abstract

In this study, we formulate and analyze a mathematical model to describe the possible transmission routes of Antimicrobial Resistance (A.M.R) in a hospital setting. We have examined the significant means of transmission of resistance in hospitals and found that the significant means of transmission is the use of antibiotics and through the contamination by health care workers. It has been shown that the resistance free equilibrium point is locally asymptotically stable. We have also shown that the model has a unique positive endemic equilibrium point which is locally asymptotically stable.

Keywords: AMR, Local Stability, Numerical Simulation, Reproduction Number

2010 Mathematics Subject Classification: 34C60; 34D23; 37B25; 92B05; 97M60.

1 Introduction

Antimicrobial resistance (AMR) occurs when disease-causing organisms like bacteria, fungi or parasites change with time and fail to respond to medicines. This makes it more difficult to treat infections thus increasing the risk of disease spread, severe illness and even death. The emergence and spread of AMR is a great public health concern particularly in hospitals and other health care settings [9]. Antibiotics (drugs that inhibits the growth of or destroys bacteria) have drastically reduced deaths and complications caused by bacterial infections and set the stage for modern medicine. However, the predominant factor that has led to the antimicrobial resistance is abuse either by over-using or mis-using of the drugs especially when bought over the counter. Studies show that treatment indications and antibiotic therapy are not proper in nearly 50% of the cases globally [15]. Genetic changes can influence AMR prevalence. Antimicrobial resistant organisms are prevalent in living things (people, animals and plants) as well as food, water, soil and air. They can spread from person to person or between humans and animals, including from food of animal origin. Misuse and overuse of antimicrobials, poor hygiene conditions, poor prevention techniques against infections and disease both in hospitals and farms, inability to afford quality medicine, vaccines and diagnostics, ignorance and lack of enforcement of legislation have been observed to be the key forces of antimicrobial resistance. [3]. Resistance is also enhanced by the irrational use of these drugs as growth supplements in livestock [1]. Moreover, there is an overlap between animals and humans in the transmission of AMR. This is more pronounced in farming communities and is proportional to the intensity of contact [6].

AMR potentially can drain economy with increased economic losses due to reduced productivity caused by sickness of both humans and animals. Therefore, AMR is responsible for high morbidity and mortality rates as well as increased health care costs. It threatens health security, food security and negatively impacts on trade and economy of the country [5].

Resistant-infections have their morbidity and mortality rates on the rise in several countries. For instance, in the United States of America, nearly 3 million people get infected annually with over 35 000 deaths. Similarly, these infections claim over 30 000 lives yearly in Europe [10].

Though antibiotics have cured many infections, their effectiveness is increasingly coming to question. In some hospitals, some patients are presenting infections that are becoming increasingly harder to treat, while others no longer have cure. Studies undertaken in Kenya show that the country is already experiencing increasing levels of antimicrobial resistance. See [7, 4] for more details.

Mathematical models are increasingly used to help understand and control infectious diseases, particularly to identify key parameters driving disease spread, assess the effect of potential interventions

and forecast the trajectory of epidemics, thus making mathematical models powerful tools that can guide policies to control AMR.

Webb et.al. [8] in their study of antibiotic bacterial epidemics in hospitals using a mathematical model, observed that besides the interaction between the infected and uninfected patients, patient-to-Health Care Provider (H.C.P) and patient-to-environment contacts were outstanding means of transmission of the resistance.

Cooper et.al. [2] studied transmission dynamics of MRSA both with and without isolation of the colonized patients. With isolation, they found that Methicillin-Resistant Staphylococcus Aureus (MRSA) - a bacteria resistant to methicillin (an antibiotic) is always eradicated eventually, although this takes a longer time.

Lipsitch et. al. [3] modeled the effects of measures to control nosocomial transmission of bacteria. They observed that any process that cuts down on the rate of between hosts transmission for instance improved hygiene in the hospital environment would reduce the prevalence of the resistant infection. In this work, we intend to extend the work of Cooper et. al. [2], by formulating a model for the ways in which AMR is transmitted in the hospitals. Our model describes transmission dynamics of AMR by incorporating the hospital hygiene and the role of the H.C.P, isolation of patients and use of 2 species of bacteria sensitive to either one or the two drugs.

2 Model Formulation

In this section, we present mathematical model formulated to describe the dynamics of AMR transmission. In this work, we have used an improved SIS compartmental model to incorporate the epidemiological features that depict the AMR transmission using a system of ordinary differential equations (ODE).

Before giving our mathematical model, we make the following assumptions and descriptions:

2.1 Assumptions of the Model

We make various assumptions with this model.

1. That all the patients are admitted into the hospital because they suffer from various primary ailments like malaria, cancer, tuberculosis, cholera or having suffered from accident among other reasons.
2. It is assumed that the population within the hospital remains constant; the total rate of admission is equal to the total rate of discharge.
3. Patients can enter the hospital either colonized with bacteria (proportion n) or uncolonised (a proportion m).
4. Patients stay an average of $\frac{1}{\mu}$ days in the hospital, where μ is the turnover rate in the hospital.

We assume t_i is the per capita treatment rate of drug i , and therefore, the total proportion of the hospital being treated with antibiotics per day is $t_1 + t_2$

5. Furthermore, it is assumed that drugs are prescribed without prior knowledge of the type of bacteria present at the time of the initial prescription as it is not yet common practice to test for resistant bacteria upon entering the hospital. Patients are more likely to be tested for resistant bacteria after one or possibly two drugs have failed to clear the infection. Therefore, it is possible for patients resistant to drug 1, for instance, to be prescribed drug 1; however, these patients will not be cleared until drug 2 is utilized or the patient's immune response causes clearance of the bacteria.

6. It is assumed that without treatment, a patient's immune response will require $\frac{1}{\kappa}$ days to clear the bacteria.

7. We further assume that each patient is equally likely to come into contact with a healthcare provider and, equally likely to become colonized with the resistant strain of bacteria or transmit the bacteria if already colonized upon contact. Patients make β of these effective contacts per unit time.

8. That bacteria is sensitive to drug 2 and therefore application of the drug clears the infection.

9. That new cases occurred at a rate proportional to the product of the number of colonized

and susceptible patients in the hospital.

10. That the population mixes homogeneously. That is, all susceptible individuals are equally likely to be infected by infectious individuals in case of contact.

11. That all patients are tested of resistance on admissions and therefore join either with strains of bacteria that is sensitive to both drugs 1 and 2, or those resistant to drug 1 or those who are uncolonised with either strain.

Here we build a model that describes transmission dynamics of AMR by incorporating the hospital hygiene, isolation of patients and use of 2 species of bacteria sensitive to either one or the two drugs.

2.2 The Model Description

Figure (1) is a flow diagram with five compartments. The first compartment (X) describes the susceptible population. These are patients who do not have the resistant bacteria, but are susceptible to being colonised by either the sensitive bacteria or the resistant type. The bacteria is deemed sensitive to the drugs 1 and 2 if the drugs can clear the bacteria from the patient. However if either of the drugs cannot clear the bacteria, we say it is resistant.

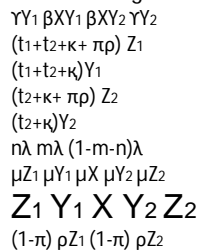


Figure 1: Flow diagram showing the dynamics of AMR transmission in a hospital

The second class comprises patients carrying strains of bacteria that are sensitive to both drugs 1 and 2. This class is represented by Y_1 . The third compartment comprises patients infected with strains of bacteria that are only sensitive to drug 2. This class is resistant to drug 1 and is represented by Y_2 . The fourth class of the model comprises individuals who have strains of bacteria sensitive to drugs 1 and 2 as is the case of Y_1 , but this group is isolated within the hospital facility

and are represented by Z_1 . The fifth class Z_2 consists of patients who are sensitive to drug 2 only; they offer resistance to drug 1.

A description of the variables and parameters used in our model is given in table (1) below, where each of the variables are dimensionless as they are proportions of patients in the hospital. As stated earlier, we assume that all the patients are admitted into the hospital because they suffer from various ailments like malaria, cancer, tuberculosis, cholera e.t.c. λ is the rate of admission of patients into the hospital. A fraction (m) of the admissions are free from the two strains of bacteria. Another fraction (n) are admitted with the bacteria strains sensitive to both drugs 1 and 2. The rest ($1-n-m$) are admitted with the strain resistant to drug 1.

β is the colonization rate of patients in compartment X and incorporates the encounter rate between the non-colonized X and the already colonized patients (Y_1 and Y_2) via HCP. Patients who are infected with the strains of bacteria and are symptomatic are isolated upon testing at a rate γ .

Treatment with drug 1, which occurs at rate t_1 per day, clears carriage of either sensitive or resistant bacteria, converting members of the Y_1 and Z_1 populations into X. Treatment with drug 2, which occurs at rate t_2 per day, clears carriage of sensitive bacteria but has no effect on hosts bearing resistant bacteria. Spontaneous clearance of sensitive and resistant bacteria occurs at a rate κ per day. Patients may be discharged from the hospital at a rate μ .

Table 1: Description of the model variables.

Variable Description

X The uncolonised population (Patients free of the bacteria sensitive or resistant to drug 1 or drug 2)

Y_1 Patients who carry strains of bacteria that is sensitive to both drugs 1 and 2

Y_2 Patients who carry strains of bacteria that is sensitive to drug 2 only (offers resistance to drug 1)

Z_1 The patients with strains of bacteria sensitive to drugs 1 and 2 and isolated upon testing

Z_2 The patients with strains of bacteria sensitive to drug 2 and isolated upon testing

Parameters Definition

β Is the colonization rate of patients in compartment X and incorporates the encounter rate between the non-colonized X and the already colonised patients (Y_1 and Y_2) via HCP.

λ The rate of admission of patients into the hospital

ρ The rate of discharge from the isolation unit

t_1 The rate of clearance of carriage of bacteria through treatment with drug 1

t_2 The rate of clearance of carriage of bacteria through treatment with drug 2

κ The spontaneous clearance of bacteria (sensitive either to drug 1 or drug 2 or both) from the patient's body

γ The rate of isolation of infected patients

μ The rate of discharge of the hospitalised patient population

m The proportion of patients admitted free of resistance to drug 1.

n The proportion of patients admitted with strain of bacteria sensitive to both drugs 1 and 2.

π The proportion of isolated patients who are completely cleared of resistant bacteria.

2.3 The Model Equations

From the flow diagram, the governing equations describing the transmission dynamics are:

$\frac{dX}{dt}$

$\frac{dY_1}{dt}$

$$= m\lambda + a_1Y_1 + a_2Y_2 + (a_1 + \pi\rho)Z_1 + (a_2 + \pi\rho)Z_2$$

$$- \beta XY_1 - \beta XY_2 - \mu X$$

$\frac{dY_1}{dt}$

$\frac{dZ_1}{dt}$

$$= n\lambda + \beta XY_1 + (1 - \pi)\rho Z_1 - b_1Y_1$$

$\frac{dZ_1}{dt}$

dt

$$= \gamma Y_1 - b_2 Z_1$$

dY₂

dt

$$= (1 - n - m)\lambda + \beta X Y_2 + (1 - \pi)\rho Z_2 - b_3 Y_2$$

dZ₂

dt

$$= \gamma Y_2 - b_4 Z_2 \quad (2.1)$$

Where $a_1 = t_1 + t_2 + \kappa$, $a_2 = t_2 + \kappa$, $b_1 = a_1 + \gamma + \mu$, $b_2 = a_1 + \rho + \mu$, $b_3 = a_2 + \gamma + \mu$ and

$$b_4 = a_2 + \rho + \mu$$

System (2.1) is appended with the initial conditions

$$X(0) \geq 0, Y_1(0) \geq 0, Y_2(0) \geq 0, Z_1(0) \geq 0, Z_2(0) \geq 0.$$

From the model, the total population is given by

$$N = X + Y_1 + Y_2 + Z_1 + Z_2 \quad (2.2)$$

and adding all the equations in system (2.1) we get

dN

dt

$$= \lambda - \mu N \quad (2.3)$$

System (2.1) describes our 5-dimensional model with five variables. We shall first check for the positivity and boundedness of the solutions and since Y_1 and Z_1 do not depend on Y_2 and Z_2 , we shall systematically reduce system (2.1) to two simpler sub-models in what follows.

2.4 Positivity and boundedness of solutions

Lemma 2.1. Suppose that the initial conditions; $X(0) \geq 0, Y_1(0) \geq 0, Y_2(0) \geq 0, Z_1(0) \geq 0, Z_2(0) \geq 0$ hold, then the solutions of system (2.1) will remain positive at all times, $t \geq 0$.

Proof

From the first equation in the system (2.1), we have by comparison method for ODE's

dX

dt

$$\geq m\lambda - (\beta Y_1 + \beta Y_2 + \mu)X$$

From which we obtain

$$X(t) \geq X(0)e^{-$$

\int_0^t

$$(\beta Y_1 + \beta Y_2 + \mu) ds + e^{-$$

\int_0^t

$$(\beta Y_1 + \beta Y_2 + \mu) ds$$

\int_0^t

\geq

$$m\lambda e^{-$$

\int_0^t

$$(\beta Y_1 + \beta Y_2 + \mu) dw du \geq 0$$

Similarly, it can be shown that Y_1, Z_1, Y_2 and Z_2 are positive. Therefore all solutions of the system of equations (2.1) are positive for all $t \geq 0$.

Lemma 2.2. The system (2.1) has solutions which are bounded in the feasible region

$\Psi =$

n

$$X, Y_1, Y_2, Z_1, Z_2 \in R_5 : N(t) \leq \lambda$$

μ
0

Proof. From the equation (2.3), we have $\frac{dN}{dt} + \mu N = \lambda$. This gives

$\frac{d}{dt}(Ne^{\mu t}) = \lambda e^{\mu t}$. By use of the

integrating factor we have $N(t)e^{\mu t} = N(0) +$

$\int_0^t \lambda e^{\mu s} ds$. This simplifies to

$N(t) = N(0)e^{-\mu t} + \frac{\lambda}{\mu}(1 - e^{-\mu t})$. Thus $N(t) = e^{-\mu t}[N(0) - \frac{\lambda}{\mu}] + \frac{\lambda}{\mu}$.

Therefore as $t \rightarrow \infty$, $N(t) \rightarrow \frac{\lambda}{\mu}$.

Hence $\lim_{t \rightarrow \infty} N(t) \leq \frac{\lambda}{\mu}$.

λ

μ

Hence

$\lim_{t \rightarrow \infty} N(t) \leq$

$\frac{\lambda}{\mu}$

λ

μ

This implies that the solutions of the model are bounded for $t \geq 0$ and is therefore biologically meaningful.

Thus, from Lemma 2.1 and 2.2 the model is well-posed epidemiologically and mathematically and hence, it is feasible to study the dynamics of the system (2.1) in Ψ .

2.5 Model Analysis

The model in (2.1), consists of two independent sub-models which we will analyze as follows;

2.5.1 Sub model 1: Resistance to drugs 1 and 2.

$\beta XY + \gamma Y$
 $t_1 + t_2 + \kappa + \pi \rho Z_1$
 $(1 - \pi) \rho Z_1$
 $m\lambda - n\lambda$
 μX
 $\mu Y_1 + t_1 + t_2 + \kappa + \gamma Y_1$

$X \ Y_1 \ Z_1$

μZ_1

From the schematic diagram, we obtain the governing equations as;

$$\frac{dX}{dt} = m\lambda + a_1 Y_1 + (a_1 + \pi \rho) Z_1 - (\beta Y_1 + \mu) X$$

$$\frac{dY_1}{dt} = n\lambda + (1 - \pi) \rho Z_1 + \beta X Y_1 - b_1 Y_1$$

$$\frac{dZ_1}{dt} = \gamma Y_1 - b_2 Z_1 \quad (2.4)$$

Where $a_1 = t_1 + t_2 + \kappa$, $b_1 = a_1 + \gamma + \mu$, and $b_2 = a_1 + \rho + \mu$

2.5.2 Resistance Free Equilibrium Point (RFE), E_0

To obtain the equilibrium points of the sub-model (2.4), we equate the right hand side of the submodel system to zero. At the Resistance Free Equilibrium point E_0 , there is no resistance in the population and hence $Y_1 = Z_1 = 0$. Thus the R.F.E point is;

$$E_0 = (X_0, Y_0,$$

$$Z_0,$$

$$R_0) = \left(\frac{m\lambda}{\mu}, 0, 0 \right)$$

2.5.3 Basic Reproduction Number, R_{12}

The basic reproduction number is defined as the expected number of secondary cases, produced, in a completely susceptible population, by a typical AMR-infected individual during his/her entire period of infectiousness.

The effective reproduction number R_{12} is defined to be the number of secondary cases caused by a single AMR-infected patient in the presence of treatment with drug 1 and drug 2.

R_{12} is computed using the next generation matrix method [14]. Therefore, R_{12} is given by

$$R_{12} = \frac{\beta X_0}{b_1}$$

$$\text{where where } X_0 = \frac{m\lambda}{\mu}$$

Similarly the effective reproduction number R_2 which is the number of secondary cases caused by a single AMR-infected patient in the presence of treatment with drug 2 only as is discussed in model 2 is given by

$$R_2 = \frac{\beta X_0}{b_3}$$

$$\text{where where } X_0 = \frac{m\lambda}{\mu}$$

2.5.4 Existence of positive Endemic Equilibrium Point, E^*

Theorem 2.3. There exists a unique positive endemic equilibrium point, E^* for the sub model (2.4)

Proof. Let $E^* = (X^*, Y^*, Z^*, R^*)$ be the endemic equilibrium point. We can check for the existence of a positive E^*

$$X^* = \frac{m\lambda}{\mu} - \frac{a_1 Y^*}{(a_1 + \pi\rho)\gamma Y^*}$$

βY^*

$1 + \mu$

and Z^*

$1 =$

γY^*

1

b_2

(2.5)

Substituting equation (2.5) into the right hand side of the second equation of system (2.4) and equating to zero, we obtain after simplification

$$w_2 Y^{*2} + w_1 Y^* + w_0 = 0 \quad (2.6)$$

where

$w_2 =$

$$-\beta\mu(a_1 + \rho + \gamma + \mu)$$

b_2

$$w_1 = \beta n\lambda + \beta m\lambda +$$

$$\mu \{(1 - \pi)\rho\gamma - b_1 b_2\}$$

b_2

This is a quadratic equation in Y^*

w_1, w_2 is negative and the constant term w_0 is positive since all the parameters are positive by definition. Therefore by the Descartes' rule of signs [11], the quadratic equation (2.6) has only one positive root irrespective of the sign of w_1 .

2.5.5 Stability analysis of the equilibrium points

In this section, we analyze the stability of the equilibrium points E_0 and E^* . For Resistance Free Equilibrium (R.F.E) point, E_0 , we have the following;

Theorem 2.4. The Resistance Free Equilibrium (R.F.E) point, E_0 of the sub-model (2.4) is locally asymptotically stable if $R_{12} < 1$ and $b_1 b_2 (1 - R_{12}) > (1 - \pi)\rho\gamma$

Proof

It suffices to show that the Jacobian matrix has all its eigenvalues having negative real parts. The Jacobian of the sub-model (2.4) at R.F.E is given by

$$J(E_0) =$$

\cdot
 \cdot

$$-\mu a_1 - \beta X_0 a_1 + \pi\rho$$

$$0 \quad \beta X_0 - b_1 (1 - \pi)\rho$$

$$0 \quad \gamma - b_2$$

\cdot

$$\cdot \quad (2.7)$$

The characteristic polynomial in Q (where Q is the spectral parameter) is given by $|J(E_0) - QI| = 0$, which yields after simplification

$$(-\mu - Q)$$

$-$

$$Q^2 + \{b_2 + b_1(1 - R_{12})\}Q + b_1 b_2 (1 - R_{12}) + \pi\rho\gamma - \rho\gamma$$

$-$

$$= 0 \quad (2.8)$$

From (2.8), we have

$$Q = -\mu Q_2 + \{b_2 + b_1(1 - R_{12})\}Q + b_1 b_2(1 - R_{12}) - (1 - \pi)\rho\gamma = 0 \quad (2.9)$$

Equation (2.9) above has all its roots having negative real parts provided $R_{12} < 1$ and $b_1 b_2(1 - R_{12}) > (1 - \pi)\rho\gamma$. Thus, all the eigenvalues of $J(E_0)$ have negative real parts provided $R_{12} < 1$ and $b_1 b_2(1 - R_{12}) > (1 - \pi)\rho\gamma$.

Next we investigate the stability of the endemic equilibrium point, E^* .

Theorem 2.5. The endemic equilibrium point, E^* is locally asymptotically stable if $b_1 b_2 > b_2 b_5 + \gamma c_4$ and $b_2 b_5 > a_1 b_2 + \gamma c_2$

Proof. It suffices to show that the Jacobian matrix has all its eigenvalues having negative real parts.

The Jacobian matrix $J(E^*)$ of sub-model (2.4) at E^* is given by

$$J(E^*) = \begin{pmatrix} \cdot & & & & & \\ \cdot & & & & & \\ -c_1 a_1 - b_5 c_2 & & & & & \\ c_3 b_5 - b_1 c_4 & & & & & \\ 0 & \gamma & -b_2 & & & \\ \cdot & & & & & \\ \cdot & & & & & \end{pmatrix} \quad (2.10)$$

Where $c_1 = \beta Y^*$

$$c_1 = \beta Y^*, \quad c_2 = a_1 + \pi \rho, \quad c_3 = \beta Y^*$$

$$c_4 = (1 - \pi)\rho, \quad b_1 = a_1 + \mu + \gamma, \quad b_2 = a_1 + \mu + \rho \text{ and}$$

$$b_5 = \beta X^*$$

The characteristic equation in x (where x is the spectral parameter) is obtained using the formula

$$|J(E^*) - xI| = 0 \text{ and is given by}$$

$$x^3 + h_2 x^2 + h_1 x + h_0 = 0$$

where

$$h_2 = b_1 + b_2 + c_1 - b_5$$

$$h_1 = b_2(b_1 - b_5 -$$

$$\gamma c_4$$

$$b_2$$

$$) + (b_2 + b_1 - b_5)c_1 + (b_5 - a_1)c_3$$

$$h_0 = (b_1 - b_5)b_2 c_1 + (b_5 - a_1)b_2 c_3 - \gamma c_1 c_4 - \gamma c_2 c_3$$

$$= (b_1 - b_5 -$$

$$\gamma c_4$$

$$b_2$$

$$)b_2 c_1 + (b_5 - a_1 -$$

$$\gamma c_2$$

$$b_2$$

$$)b_2 c_3$$

The eigenvalues of the matrix $J(E^*)$ are the roots of the characteristic polynomial in equation (2.11). If we can show that all the roots of the equation (2.11) have negative real parts, then the endemic equilibrium point is locally asymptotically stable. Equation (2.11) has all its roots having

negative real parts if all its coefficients are positive i.e $h_0 > 0$, $h_1 > 0$ and $h_2 > 0$. If $h_2 > 0$, then we have $b_1 > b_5 + \gamma c_4$

b_2

and $b_5 > a_1 + \gamma c_2$

b_2

. This further implies that $b_1 > b_5$ and $b_5 > a_1$.

Consequently $h_1 > 0$ and $h_0 > 0$. Thus if $h_2 > 0$, then equation (2.11) has all its coefficients positive and hence by the Descartes' s rule of signs [11], equation (2.11) has all its roots having negative real parts. The Jacobian matrix, $J(E)$ therefore has all its eigenvalues having negative real parts provided $b_1 > b_5 + \gamma c_4$

b_2

and $b_5 > a_1 + \gamma c_2$

b_2

. 2.6 Sub model 2: Resistance to drug 2 only

In this section we analyze the second sub model when AMR is only sensitive to drug 2. The flow diagram in this case is given below.

γY_2

$(1-\pi) \rho Z_2$

$1 - n - m \lambda$

$\mu X \mu Y_2 \mu Z_2$

$m \lambda$

$\beta X Y_2$

$(t_2+\kappa) Y_2$

$Y X_2 Z_2$

$t_2+\kappa + \pi \rho Z_2$

The equations governing the above sub model are;

dX

dt

$$= m\lambda + a_2 Y_2 + (a_2 + \pi\rho) Z_2 - (\beta Y_2 + \mu) X$$

dY_2

dt

$$= (1 - n - m)\lambda + (1 - \pi)\rho Z_2 + \beta X Y_2 - b_3 Y_2$$

dZ_2

dt

$$= \gamma Y_2 - b_4 Z_2 \quad (2.12)$$

Where $a_2 = t_2 + \kappa$, $b_3 = a_2 + \gamma + \mu$, $b_4 = a_2 + \rho + \mu$

2.6.1 Resistance Free Equilibrium (RFE), E_0

At RFE, $Y_2 = Z_2 = 0$, and we obtain the same Resistance Free Equilibrium, E_0 as in section 2.5.2, i.e

$$E_0 = (X_0, Y_0$$

Z_0 ,

$) = ($

$m\lambda$

μ

$, 0, 0)$

2.6.2 Existence of positive Endemic Equilibrium Point, Σ^*

To obtain the endemic equilibrium point, we equate the right hand side of system (2.12) to zero

with Y_2 and Z_2 assumed to be non zero.

Theorem 2.6. There exists a unique positive endemic equilibrium point, E^* for system of equations (2.12).

Proof. Let $\Sigma^* = (X^*, Y^*$

Z^*

) be the endemic equilibrium point. We can check for the existence of a positive Σ^*

From the sub-model (2.12), we have

$X^* =$

$\frac{m\lambda + a_2 Y^*}{2 + (a_2 + \pi\rho)\gamma Y^*}$

$\frac{b_4}{1 - \beta Y^*}$

and $Z^* =$

$\frac{\gamma Y^*}{2 + \mu}$

(2.13)

Substituting (2.13) into the right hand side of the second equation of system (2.12) and equating to zero, we obtain after simplification

$-\beta\mu(a_2 + \rho + \gamma + \mu)$

b_4

Y^{*2}

$+ \beta K\lambda + \beta m\lambda +$

$\mu \{(1 - \pi)\rho\gamma - b_3 b_4\}$

b_4

$Y^* = 0$ (2.14)

This is a quadratic equation in Y^*

, the coefficient of Y^{*2}

is negative and the constant term is

positive since all the parameters are positive by definition. Therefore by the Descartes' rule of signs [11], the quadratic equation (2.14) has only one positive root irrespective of the sign of the coefficient of Y^*

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2.6.3 Basic Reproduction Number, R_2

The effective reproduction number R_2 is defined to be the number of secondary cases caused by a single AMR-infected patient in the presence of treatment with drug 1 and drug 2.

R_{12} is computed using the next generation matrix method [14]. Therefore, R_2 is given by

$$R_2 =$$

$$\beta X_0$$

$$b_3$$

where where $X_0 = \frac{\rho}{\mu}$

$$\mu$$

2.7 Stability analysis of the equilibrium points

In this section, we analyze the stability of the equilibrium points E_0 and Σ^* . For the R.F.E point, E_0 , we have the following;

Theorem 2.7. The Resistance Free Equilibrium (R.F.E) point, E_0 of sub model 2.12 is locally asymptotically stable if $R_2 < 1$ and $b_3 b_4 (1 - R_2) > (1 - \pi) \rho \gamma$

Proof. It suffices to show that the Jacobian matrix has all its eigenvalues having negative real parts.

The Jacobian matrix of the sub-model 2 at R.F.E is given by

$$J(E_0) =$$

$$\begin{pmatrix} \cdot \\ \cdot \\ -\mu a_2 - \beta X_0 a_2 + \pi \rho \\ 0 \beta X_0 - b_3 (1 - \pi) \rho \\ 0 \gamma - b_4 \\ \cdot \\ \cdot \end{pmatrix} \quad (2.15)$$

The characteristic polynomial in V (where V is the spectral parameter) is given by

$$|J(E_0) - V I| = 0 \quad (2.16)$$

$$\begin{vmatrix} -\mu - V a_2 - \beta X_0 a_2 + \pi \rho \\ 0 \beta X_0 - b_3 - V (1 - \pi) \rho \\ 0 \gamma - b_4 - V \\ \cdot \\ \cdot \end{vmatrix}$$

$$= 0. \quad (2.17)$$

$$\text{from which we obtain after simplification}$$

$$(-\mu - V)$$

$$\begin{vmatrix} V^2 + \{b_4 + b_3(1 - R_2)\} V + b_3 b_4 (1 - R_2) + \pi \rho \gamma - \rho \gamma \\ \cdot \\ \cdot \end{vmatrix}$$

from which we obtain after simplification

$$(-\mu - V)$$

$$\begin{vmatrix} V^2 + \{b_4 + b_3(1 - R_2)\} V + b_3 b_4 (1 - R_2) + \pi \rho \gamma - \rho \gamma \\ \cdot \\ \cdot \end{vmatrix}$$

$$= 0 \quad (2.18)$$

From (2.18), we have

$$V = -\mu \quad (2.19)$$

or

$$V^2 + \{b_4 + b_3(1 - R_2)\} V + b_3 b_4 (1 - R_2) - (1 - \pi) \rho \gamma = 0 \quad (2.20)$$

Equation (2.20) above has all its roots having negative real parts provided $R_2 < 1$ and $b_3 b_4 (1 - R_2) > (1 - \pi) \rho \gamma$. Thus, all the eigenvalues of $J(E_0)$ have negative real parts provided $R_2 < 1$ and $b_3 b_4 (1 - R_2) > (1 - \pi) \rho \gamma$

Next we investigate the stability of the endemic equilibrium point, Σ^* .

Theorem 2.8. The endemic equilibrium point, Σ^* is locally asymptotically stable if $b_3b_4 > b_4d_2 + \gamma d_5$ and $b_4d_2 > a_2b_4 + \gamma d_3$

Proof.

It suffices to show that the Jacobian matrix has all its eigenvalues having negative real parts. The Jacobian matrix, $J(\Sigma^*)$ of sub model (2.12) is given by

$$J(\Sigma^*) = \begin{pmatrix} \cdot & & & & \\ \cdot & & & & \\ -d_1 & a_2 & -d_2 & d_3 & \\ d_4 & d_2 & -b_3 & d_5 & \\ 0 & \gamma & -b_4 & & \\ \cdot & & & & \\ \cdot & & & & \end{pmatrix} \quad (2.21)$$

Where $d_1 = \beta Y^*$

$$d_2 = \mu, \quad d_3 = a_2 + \pi\rho, \quad d_4 = \beta X^*$$

$$d_5 = (1 - \pi)\rho, \quad b_3 = a_2 + \mu + \gamma, \quad b_4 = a_2 + \mu + \rho \text{ and}$$

$$d_2 = \beta X^*$$

The characteristic equation in x (where x is the spectral parameter) is obtained from $|J(E^*) - xI| = 0$ and is given by

$$x^3 + p_2x^2 + p_1x + p_0 = 0 \quad (2.22)$$

where

$$p_2 = b_3 + b_4 + d_1 - d_2$$

$$p_1 = (b_3 - d_2)b_4 + (b_3 + b_4 - d_2)d_1 + (d_2 - a_2)d_4 - \gamma d_5$$

$$p_0 = (b_3 - d_2)b_4d_1 + (d_2 - a_2)b_4d_4 - \gamma d_1d_5 - \gamma d_3d_4$$

$$= (b_3b_4 - b_4d_2 - \gamma d_5)d_1 + (b_4d_2 - a_2b_4 - \gamma d_3)d_4$$

The eigenvalues of (2.21) are the roots of the characteristic equation (2.22). If we can show that all the roots of the equation (2.22) have negative real parts, then the endemic equilibrium point is locally asymptotically stable. Equation (2.22) has all its roots having negative real parts if all its coefficients are positive i.e $p_0 > 0$, $p_1 > 0$ and $p_2 > 0$. $p_0 > 0$, if $b_3 > d_2 + \gamma d_5$

b_4

$$\text{and } d_2 > a_2 + \gamma d_3$$

b_4

.

This further implies that $b_1 > b_5$ and $b_5 > a_1$. Consequently $p_1 > 0$ and $p_0 > 0$. Thus, if $p_0 > 0$, then equation (2.22) has all its coefficients positive and hence by the Descartes' s rule of signs [11], equation (2.22) has all its roots having negative real parts. The Jacobian matrix, $J(\Sigma^*)$ therefore

has all its eigenvalues having negative real parts provided $b_3 > d_2 + \gamma d_5$

b_4

$$\text{and } d_2 > a_2 + \gamma d_3$$

b_4

3 Numerical Simulation

We carry out numerical simulations to illustrate the long term dynamics of the systems 2.5.1 and 2.6 using Python. The parameter value estimation are in the Table 3 below and have earlier been defined in the text.

Table 2: Parameter Values used in the simulation

Parameters Unit Value (Range) Source

β days⁻¹ 1 [13] [12]

γ days⁻¹ 0.1 [2]

μ days⁻¹ 0.1 [13]

κ days⁻¹ 0.03 [13]

λ days⁻¹ 0.1 [3]

π - 0.25 [2]

t_1 days⁻¹ 0.2-0.05 Estimated

t_2 days⁻¹ 0.1-0.03 Estimated

ρ days⁻¹ 0.05 [2]

m - 0.05 [13]

n - 0.7 [12]

4 Discussion

4.0.1 Model 1

Effects of force of infection, β on the resistance

Increasing the transmission rate β increases the proportion of patients with bacteria strain sensitive to drugs 1 and 2 up to a certain level and then the sensitivity to drugs 1 and 2 is lost as the number of patients with strains of bacteria sensitive to drugs 1 and 2 decreases. The loss of sensitivity to treatment by the two drugs 1 and 2 can be attributed to the fact that treatment clears these sensitive bacteria thereby exposing patients to be colonized by bacteria with the resistant strain.

Effects of use of drugs, $t_1 + t_2$ on the resistance

Treatment of patients with drugs 1 and 2 reduces the duration of clearance of bacteria strains sensitive to drugs 1 and 2. Increasing the rate of treatment with drugs 1 and 2 increases the number of patients with strains of bacteria sensitive to drugs 1 and 2 up to a certain part and then the number decreases significantly. This decrease is attributed to the colonization by strains of the resistant bacteria.

4.1 Model 2

Effects of force of infection, β on the resistance

Increasing the transmission rate β increases the number of patients colonized with bacteria strain sensitive to drugs 2 up to a certain level and then the number reduces. Treatment with drug 2 clears strains of sensitive bacteria making it possible for the patient to be colonized by bacteria resistant to drug 1.

Effects of use of one drug, t_2 on the resistance

Increased treatment with drug 2 increases the number of patients sensitive to it up to a certain level then reduces. Treatment with drug 2 clears the sensitive bacteria and patients begin to be colonized by the resistant bacteria.

5 Conclusion

When treating patients with a drug that is sensitive to an antibiotic $t_1 + t_2$, there is a possibility of the patient developing resistance. Increase in the treatment rate by multiple drugs results into

an increase in the resistance. Therefore the number of drugs used in treating an infection should be minimized as much as is possible since this is one of the routes of transmission of resistance. Similarly, when the force of infection β through interaction with the healthcare providers increases, the resistance also increases. Healthcare provider-to-patient interaction should therefore be reduced for effective control of resistance in hospitals.

5.1 Disclaimer (Artificial Intelligence)

Author(s) hereby disclose that NO generative AI techniques such as Large Language Models (ChatGPT, COPILOT, etc) and text to image have been used during writing or editing manuscripts.

5.2 Acknowledgment

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5.3 Competing Interest

Authors have declared that there is no competing interests.

5.4 Authors' Contribution

Fredrick performed stability analysis of the model, David designed the study and Richard carried out the Numerical simulation. All the authors read and approved the manuscript.

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