Develop mathematical models to control the diffusion of antibiotic resistant bacteria to avoid a serious public health hazard

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Abstract: The phenomenon of emergence and diffusion of resistant bacteria in populations involve microbial, individual and population scales simultaneously. In that context, modelling, which allows formalization and simulation of the different scales, can help in analyzing, predicting and understanding better the spread of bacteria. The aim of this paper is to build some mathematical models to study and to control the diffusion of antibiotic resistant bacteria.

Key-Words: - Mathematical models; Antibiotic; resistant; control; Bacteria.

1 Introduction

The application of mathematics and statistics in modern biomedical research has developed significantly in recent years. The successive developments in medical sciences and the regular production of vast amounts of data and information have led to additional needs for new mathematical equations and models and new statistical methods. It is necessary to be able to organize and analyze this amount of data, to extract useful information.

The modeling of biological phenomena has many benefits, it can help to describe and understand certain real phenomena. In fact, modeling makes it possible to formalize complex biological systems and its representational techniques make it possible to summarize and organize information. Thus, modeling makes it possible, from aggregated data, to estimate key parameters, hidden, known or even unknown. The main objective of this research is to introduce and develop mathematical equations to study the dynamics of the transmission of pneumococcal strains in society.

The phenomena at the origin of the emergence and diffusion of resistant bacteria in the population are complex and difficult to anticipate. In this context, mathematical modeling and simulation, which make it possible to formalize the phenomena, taking place at different scales and to set up virtual experiments that are not feasible under real conditions, become essential research tools.

Here, we will consider a mathematical problem given in the form of equations related to some important biological phenomena in various fields of application, and try to propose and develop some new mathematical models for a new study of the output of interactions between some associated effects. We try to develop a mathematical modeling tool to control the diffusion of antibiotic resistant bacteria.

The dynamics of emergence and the diffusion of resistant bacteria in the population is difficult to anticipate and its number is not easy to calculate it in a period of time, because this phenomenon occur at different scales and under many factors (bacteria,

host and population) and it is well known that the bacteria circulate in human environments.

A mathematical formalization and simulation can contribute to better understanding and anticipating the phenomena involved to avoid a serious public health hazard. In particular, the fundamental cause of the matter is under consideration by many mathematicians to answer biologist's questions to achieve a complex and new structure, by merging several phenomena into one side and considering their effectiveness.

The emergence and diffusion of resistant bacteria originates from a combination of phenomena occurring at different scales: microbiological (genetic evolution of microorganisms and acquisition of new mechanisms of resistance, "fitness"), individual (colonization of individual ecosystems, competition between strains, natural or acquired immunity, selection of resistant pathogens), and lastly, population (direct or indirect transmission of pathogens). In terms of research, the study of these phenomena is necessarily multidisciplinary, involving microbiologists, physicians and epidemiologists.

However, if in each of these disciplines it is possible to study and interpret the phenomena of resistance in the present or the past, they do not allow us to project ourselves into the future. Only mathematical modeling makes it possible to work on evolution schemes.

It also allows formalizing and simulating the phenomena that take place at different microscopic and macroscopic levels. A crosscutting tool can help to understand the phenomenon and make it possible to make prospective hypotheses.

The main questions raised in this paper is: What are the roles played by antibiotics and viral infections in the dynamics of pneumococcal infections resulting from sensitive and resistant strains? To answer each of these questions, a specific mathematical model will be developed.

2 Mathematical Model

The phenomena at the origin of the emergence and diffusion of resistant bacteria in the population are complex and difficult to anticipate. In this context, mathematical modeling and simulation, which make it possible to formalize the phenomena, taking place at different scales and to set up virtual experiments that are not feasible under real conditions, become essential research tools.

The application of mathematics, physics and computer science in biomedical research has evolved considerably in recent years. Advances in genetics and the systematic production of large amounts of data have created new needs for computer tools and statistical methods. It is necessary to be able to organize and analyze these new data, extract relevant and useful information and possibly structure and graphically represent new knowledge derived from it.

Modeling biological phenomena has several interests. First, modeling can help describe and better understand certain phenomena. Indeed, modeling makes it possible to formalize complex biological systems and to equate knowledge by taking into account several levels of biological organization. His representational techniques also make it possible to summarize and organize knowledge. The modeling then makes it possible, from collected data, to estimate key parameters hidden or poorly known or unknown.

2.1 Model

A mathematical model of a system describes the operation of this system using a mathematical language. In 1974, Eykhoff defined models as "representations of the essential aspects of a system providing a knowledge of this system in its usual form". The description of the system is then made from a set of variables and equations establishing relations (functions) between these variables. There are different types of variables that can play different roles in the model: input variables that can be of different natures: known / unknown, constant / random ...; the observed variables, which are the so-called, output variables. On the other hand, it is possible to classify the models according to different criteria such as linearity, the taking into account of the random aspects (deterministic or probabilistic) or the taking into account of temporal aspects (static or dynamic).

2.1. Different types of models

The most classical methods of dynamic modeling can differentiate according to their deterministic or

stochastic nature and according to the description of individuals in the population.

2.1.1. Deterministic versus stochastic

In deterministic models, transitions from one state to another are described by a fixed transition rate. Thus, for the same initialization of the model and the same set of parameters, the simulations of the model always produce the same dynamics. In stochastic models, the random aspects of dynamics are taken into account. Variables and input parameters are not defined by a constant but are characterized by probability distributions. Therefore, in such models, each simulation produces a distinct result.

2.1.2. Description of individuals: population versus individual

The two major classes of models used are compartmental models and agent models.

Compartmental models are Markovian models in which compartment dynamics are described by a system of differential equations.

The population is divided according to a finite number of subgroups or compartments, and variables (rate) characterize the transitions (or changes of states) between the compartments. Thus, the simulations make it possible to calculate, as a function of time, the average numbers of the different subgroups.

By contrast, in multi-agent or self-centered models, it is possible to model and simulate individually the different entities (individuals or bacteria for example). These models can describe the bacterial level, the human level and they can be spatially explicit. In these models, it is possible to follow over time each individual and the characteristics associated with it. A major interest of multi-agent simulations is to be able to describe the global consequences of local interactions between members of a population.

21.3. Intra-host models

Intra-host models most often describe the growth dynamics of bacterial colonies within a host. Colonization of the host is a multifactorial phenomenon that depends on the pathogen and the antibiotic studied. Thus the models, according to the targeted precision and the question asked can formalize the bacterial growth, the mutations associated with the acquisition of resistance, the sensitivity of the strain to the antibiotic, the "fitness" of the strain, etc. . .

It should be noted that in this section, the term "fitness" is used in its microbiological definition, which corresponds to the ability of a bacterium to multiply.

Depending on their complexity, the intra-host models take into account one or more strains competing for the niche, a constant or time-varying antibiotic pressure, an immune reaction of the host, etc. These models are most often coupled with data collected in vitro or in vivo in order to estimate certain parameters or to validate predictions. A simple model of intra-host bacterial dynamics can be described by the following equation

$$\frac{dM}{dt} = \alpha M(t)\left[1 - \frac{M(t)}{M_{max}}\right] - k\big(C(t)\big)M(t) - \mu(t)M(t),$$

$$M(0) = M_0, \qquad (2.1)$$

where

$M(t)\left[1 - \frac{M(t)}{M_{max}}\right]$ Is Multiplication,

$k\big(C(t)\big)M(t)$ Is Effect of antibiotic,

$\mu(t)M(t)$ Is Immunity.

Here M(t) is the number of bacteria at time t, M_{max} is the maximum size of the colony in the niche (Due to limited resources, for example), $\boldsymbol{\alpha}$ is the growth rate effective of the bacterium (Integrating the division and natural death of the bacteria), *k(C(t))* the antibiotic induced bacterial elimination rate as a function of the antibiotic concentration *C(t)* and $\boldsymbol{\mu(t)}$ is the elimination rate of the bacterium by the immune system at a time *t*.

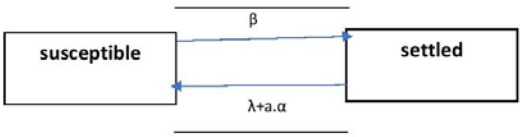
Thus, $\alpha\ M(t)$ represents the colony growth term, k(C(t)) $M(t)$ the term of elimination of bacteria under the effect of a concentration C(t) et $\mu(t)$ M(t) the term of elimination of bacteria by the immune system. The form of k(C) depends on the bacterial species and the antibiotic. Its value can be associated with the level of resistance of the bacterium for the concentration of antibiotic C.

3 Relationship Between Antibiotics and Resistances

A compartmental model that describes the colonization dynamics of members of a population by a bacterial strain is constructed. The population is divided into two compartments: colonized individuals (number Y), and no colonized individuals or likely (effective X). Individuals may be exposed to an antibiotic, with antibiotic exposure being evenly distributed among the population.

Let β is the transmission rate for the strain studied; $1/\theta$ the colonization time by the strain; α the rate of exposure to antibiotics; and ρ the decolonization frequency under antibiotic exposure (or efficacy of the antibiotic).

Figure 1



3.1. The mathematical equations

Let x, y the proportions of susceptible and colonized individuals given by $\boldsymbol{x + y = 1}$ as:

$$\begin{cases} x = \dfrac{X}{X+Y} \\ y = \dfrac{Y}{X+Y}. \end{cases} \tag{3.1}$$

The model is described by the following differential equations

$$\begin{cases} \dfrac{dx}{dt} + \beta xy = (\theta + a\alpha)y \\ \dfrac{dy}{dt} - \beta xy = -(\theta + a\alpha)y. \end{cases} \tag{3.2}$$

We can rewrite the equation (3:2)1 as

$$\frac{dx}{dt} + \beta x(1-y) = (\theta + a\alpha)(1-y), \tag{3.3}$$

then,

$$\frac{dx}{dt} = \frac{dy}{dt} = y(\beta x - \theta - a\alpha)(1-y), \tag{3.4}$$

The equilibrium states of the system are as follows

1. $x = 1, y = 1$, this equilibrium state is said to be trivial: the pathogen tends to disappear in the population.

2. $x = \frac{\theta + a\alpha}{\beta}, y = 1 - x$, this state of equilibrium is said to be endemic: the prevalence of the pathogen in the population tends to stabilize towards a non-zero value.

3.2. Reproduction number

Let's get into the state of endemic non-trivial equilibrium. Let R_0^{env} be the number of basic reproduction in the environment, it is the variable that characterizes the epidemic of the strain in the environment considered, where

$$\begin{cases} x = \dfrac{\theta + a\alpha}{\beta} = \dfrac{1}{R_0^{env}} \\ \\ R_0^{env} = \dfrac{\beta}{\theta + a\alpha}. \end{cases} \quad (3.5)$$

If $R_0^{env} > 1$, the strain is epidemic and remains in the population to become endemic. More than $R_0^{env} > 1$ is strong, more than the strain is epidemic in the environment.

1- If $\alpha = 0$, the antibiotic exposure is zero in the population and we have:

$$R_0^{env} = \frac{\beta}{\theta}$$
$$= R_0, \quad (3.6)$$

where R_0 is the number of basic reproduction, or intrinsic R of the strain. It represents the number of secondary cases generated by a first case in a totally healthy population.

2- If $\alpha > 0$, antibiotic exposure is non-zero. In this case, two different situations can be considered, depending on the efficacy rate of the antibiotic on the decolonization of the strains *a*:

A. If $a > 0$, we have $a\alpha > 0$ and the number of breeding in the environment considered, where R_0^{env} is weaker than R_0 the intrinsic of the strain:

$$R_0^{env} = \frac{\beta}{\theta + a\alpha} < R_0$$
$$= \frac{\beta}{\theta} \quad (3.7)$$

Thus, when the antibiotic effectively eliminates the strain, it is called antibiotic-sensitive strain *(S)*, the epidemic capacity of the strain is reduced by antibiotic exposure which gives it a disadvantage in the environment.

B. If $a = 0$, we have then $a\alpha = 0$, and the number of breeding in the environment considered, where R_0^{env} is close to R_0 the intrinsic of the strain:

$$R_0^{env} = \frac{\beta}{\theta + a\alpha} = R_0$$
$$= \frac{\beta}{\theta} \quad (3.8)$$

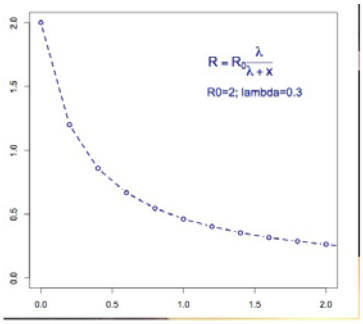
Thus, when the strain is resistant *(R)* or diminished susceptibility to the antibiotic, its epidemic of the strain is not affected by the antibiotic exposure.

We can then quantify the impact of the edicamentous environment on the epidemic of the strains. It consists of a modification of the natural R_0 or intrinsic R of the strain

$$R_0^{env} = \frac{\beta}{\theta + a\alpha}$$
$$= R_0 \frac{\beta}{\theta + a\alpha} \quad (3.9)$$

In Figure 2, the Y vertical axis is epidemiology of the strain and the X horizontal axis is Effect of antibiotic.

Figure 2



Values taken by the number of reproduction of the strain according to the effect of antibiotic exposure. The values of R_0 and θ are respectively fixed at *2* and *0.3*.

Thus, this simple model is sufficient to highlight the importance of the role of antibiotic exposure in the dissemination of strains.

We must note here that, no competition for the colonization of the ecological niche has been modeled. Thus, in a context without competition, the R strains would not be favored by the presence of antibiotics, and the strains *(S)* would be disadvantaged.

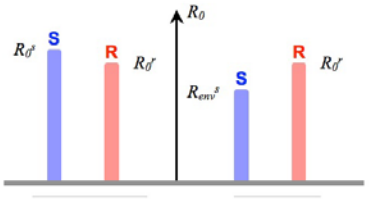
Still in a context without competition, let us look at all susceptible strains colonizing an unexposed or weakly exposed population. In a highly exposed population, only a portion of these strains can spread. The persistent strains are those whose intrinsic R_0 is sufficiently high for the $\boldsymbol{R_0^{env}}$ to remain greater than *1* when *a* is large. We can then define, for a given antibiotic exposure, a threshold from which the strains are competitive and can persist in the environment:

$$R_0^{env} = \frac{\beta}{\theta_s + a\alpha} \geq 1, \quad then, \beta_S^{threshold}$$
$$\geq \theta_s + a\alpha, \quad (3.10)$$

where θ_s and , β_S are the parameters relating to susceptible strains.

For a non-competitive model assuming that, the resistant strains are intrinsically less epidemic than the sensitive strains (decrease in "fitness" associated with resistance).\\
The effect of antibiotic exposure on R_0 changes can be summarized in Figure 3.

Figure 3



Epidemiology of the strains *(S)* and *R* according to the antibiotic exposure, the term designating the antibiotic exposure.

4. Model of Nosocomial Infection

4.1. Formulation of the Model

It well known that infection with strains resistant to antibiotics is very common in hospital area; here we introduce a mathematical model (Ordinary Differential Equations) governing the transmission dynamics. Let X represents the proportion of patients who are note colonized by the bacterial species, S represents the proportion of patients colonized by the bacterial species susceptible to both drugs and R_1, R_2, and R_{12}, representing patients colonized by strains resistant to drug 1, drug 2, and both drugs 1 and 2, respectively. The parameter μ represents the patient turnover rate in the hospital. Drug 1 and drug 2 are used at rates τ_1 andτ_2. The primary transmission rate, proportional to the frequencies of each strain, is described using the rate constantβ. The fitness costs to bacteria are described byc_1, c_2, and c_{12}. The rate of secondary transmission to that of primary is described by σ.

Patients enter the hospital in any of the states X, S, R_1, R_2, and R_{12} at rates μ $(1-m-m_1-m_2-$ $m_{12})$, μm, μm_1, μm_2, and μm_{12} per day.

$$\frac{\mathrm{dS}}{\mathrm{dt}} = (m-S)\mu - (\tau_1+\tau_1+\gamma)S + \sigma\beta(c_1R_1 + c_2R_2 + c_{12}R_{12})S + \beta SX,$$

$$\frac{\mathrm{d}R_1}{\mathrm{dt}} = (m_1-R_1)\mu - (\tau_2+\gamma)R_1 + \beta(1-c_1)R_1X + \sigma\beta c_{12}R_{12}R_1 - \sigma\beta(c_1S + (c_1-c_2)R_2)R_1,$$

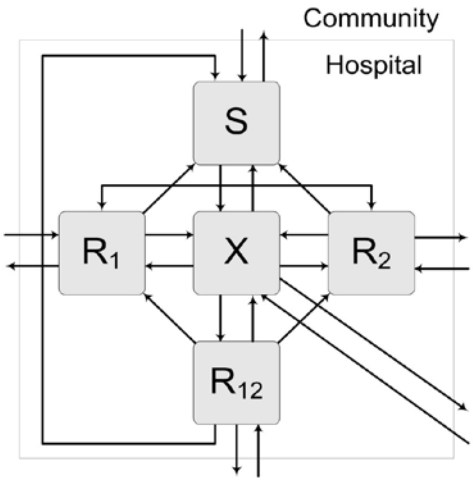
$$\frac{\mathrm{d}R_2}{\mathrm{dt}} = (m_2-R_2)\mu - (\tau_2+\gamma)R_2 + \beta(1-c_2)R_2X + \sigma\beta c_{12}R_{12}R_2 \quad - \sigma\beta(c_2S + (c_2-c_1)R_1)R_2,$$

$$\frac{\mathrm{d}R_{12}}{\mathrm{dt}} = (m_{12}-R_{12})\mu - \gamma R_{12} + \beta(1-c_{12})R_{12}X - \sigma\beta c_{12}(S + (1-c_1)R_1 + (1-c_2)R_2)R_{12},$$

$$\frac{\mathrm{d}X}{\mathrm{dt}} = (1-m-m_1-m_2-m_{12}-X)\mu + (\tau_1+\tau_2+\gamma)S + (\tau_2+\gamma)R_1 + (\tau_1+\gamma)R_2 + \gamma R_{12} - \beta X(S + (1-c_1)R_1 + (1-c_2)R_2 + (1-c_{12})R_{12})$$

This model**,** shown in Figure 4**,** tracks several patient populations in a hospital based on their colonization status

Figure 4



The model incorporating resistance

We are mainly interested in the dynamics of transmission between patients rather than the dynamics due to conjugation and mutation at the bacterial level.

4.2. Stability main results

Let

$$\varphi_S = \frac{\beta}{\tau_1 + \tau_2 + \mu + \gamma}$$

be basic reproductive rate of susceptible bacteria in a hypothetical institution (when $m = m_1 = m_2 = m_{12} = 0$).

And φ_{R_1}, φ_{R_2}, $\varphi_{R_{12}}$ denote, respectively, the basic reproductive rates of bacteria resistant to drug 1, drug 2, and both drugs 1 and 2 in a hypothetical institution, where

$$\varphi_{R_1} = \frac{\beta(1-c_1)}{\tau_2 + \mu + \gamma}$$

$$\varphi_{R_2} = \frac{\beta(1-c_2)}{\tau_1 + \mu + \gamma}$$

$$\varphi_{R_{12}} = \frac{\beta(1-c_{12})}{\mu + \gamma}$$

If $S + R_1 + R_2 + R_{12} + X = 1$, then the population size in hospital is constant and we will need to see the new system

$$\frac{\mathrm{dS}}{\mathrm{dt}} = (m-S)\mu - (\tau_1 + \tau_1 + \gamma)S + \sigma\beta(c_1R_1 + c_2R_2 + c_{12}R_{12})S + \beta S(1 - S - R_1 - R_2 - R_{12}),$$

$$\frac{\mathrm{d}R_1}{\mathrm{dt}} = -R_1\mu - (\tau_2 + \gamma)R_1 + \beta(1-c_1)R_1(1 - S - R_1 - R_2 - R_{12}) + \sigma\beta c_{12}R_{12}R_1 - \sigma\beta(c_1S + (c_1 - c_2)R_2)R_1,$$

$$\frac{\mathrm{d}R_2}{\mathrm{dt}} = -R_2\mu - (\tau_2 + \gamma)R_2 + \beta(1-c_2)R_2(1 - S - R_1 - R_2 - R_{12}) + \sigma\beta c_{12}R_{12}R_2 - \sigma\beta(c_2S + (c_2 - c_1)R_1)R_2,$$

$$\frac{\mathrm{d}R_{12}}{\mathrm{dt}} = -R_{12}\mu - \gamma R_{12} + \beta(1-c_{12})R_{12}(1 - S - R_1 - R_2 - R_{12}) - \sigma\beta c_{12}(S + (1-c_1)R_1 + (1-c_2)R_2)R_{12},$$

Since $m > 0$, there is no balance without disease.

Let

$$S^* = \frac{\beta - (\mu + \tau_1 + \tau_2 + \gamma) + \sqrt{(\mu + \tau_1 + \tau_2 + \gamma - \beta)^2 + 4m\beta\mu}}{2\beta}.$$

By $\omega_0 = (S^*, 0,0,0)$, we mean boundary equilibrium and its Jacobian is given for

$$J_0(2,2) = \beta(1-c_1)(1-S^*) - \sigma c_1\beta S^* - \mu - \gamma - \tau_2$$

$$J_0(3,3) = \beta(1-c_2)(1-S^*) - \sigma c_2\beta S^* - \mu - \gamma - \tau_1$$

$$J_0(4,4) = \beta(1-c_{12})(1-S^*) - \sigma c_{12}\beta S^* - \mu - \gamma$$

by

$$J_0 = \begin{pmatrix} \beta - (\mu + \tau_1 + \tau_2 + \gamma) - 2\beta S^* & \sigma\beta c_1 S^* - \beta S^* & \sigma\beta c_2 S^* - \beta S^* & \sigma\beta c_{12} S^* - \beta S^* \\ 0 & J_0(2,2) & 0 & 0 \\ 0 & 0 & J_0(3,3) & 0 \\ 0 & 0 & 0 & J_0(4,4) \end{pmatrix}$$

Using the results in [9], [10] and the fact that ω_0 is locally asymptotically stable.

5 Conclusion

The models reviewed herein represent some of the first attempts to use mathematical modeling to understand and control the diffusion of antibiotic resistant bacteria to avoid a serious public health hazard. The use of mathematical models to study this type of problems is still in its early stages.

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