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A MODEL OF DRUG RESISTANCE WITH INFECTION BY HEALTH CARE WORKERS

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Abstract. Antibiotic resistant organisms (ARO) pose an increasing serious threat in hospitals. One of the most life threatening ARO is methicillin-resistant staphylococcus aureus (MRSA). In this paper, we introduced a new mathematical model which focuses on the evolution of two bacterial strains, drug-resistant and non-drug resistant, residing within the population of patients and health care workers in a hospital. The model predicts that as soon as drug is administered, the average load of the non-resistant bacteria will decrease and eventually (after 6 weeks of the model's simulation) reach a very low level. However, the average load of drug-resistant bacteria will initially decrease, after treatment, but will later bounce back and remain at a high level. This level can be made lower if larger amount of drug is given or if the contact between health care workers and patients is reduced.

1. **Introduction.** Antibiotic resistant organisms (ARO) pose an increasing serious threat in hospitals. Factors which contribute to the spread of ARO in hospitals are poor immune system of most patients, close living quarters, and the contact with health care workers (HCWs) as, for example, in patients with intravenous drip or catheter. One of the most life threatening ARO is the methicillin-resistant staphylococcus aureus (MRSA). Indeed, MRSA is increasing in hospitals world wide to alarming levels [3, 11, 12] and [14]. There have been a number of mathematical models that focused on the transmission dynamics of resistant bacteria, using population-level approaches such as differential equation models or individual- based models [1, 2, 5, 7, 9, 13, 16, 20, 21] and [22].

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Another series of papers [6, 8, 10, 22] and [23] addressed the major role played by HCWs in the transmission of resistant bacteria from one patient to another. In the study by D'Agata et al. (2007) an individual based model (IBM) was developed to describe the transmission of the bacterial disease by means of HCWs. Each visit of a patient by a HCW results in contamination of either the HCW by the patient or the patient by the HCW. During each shift, the length of each visit by the HCW and the sequence of the visited patients are stochastic events. Simulations of the model suggest that early initiation of treatment reduces the non-resistant bacterial load.

Another approach developed by D'Agata et al. (2007, 2008) and Webb et al. (2005) is based on a dynamical equations model (DEM). The population of patients is divided into compartments: colonized, uncolonized, contaminated, uncontaminated, with the drug-resistant, or non-drug resistant bacteria. The proportion of the population in each compartment is considered as a variable, x_i. A system of differential equations for the x_i is then introduced to describe bacterial transmission among the various compartments and to explore optimal strategies of drug treatment.

In the present paper we develop a mathematical model for the evolution of the bacterial strains within population of patients in a hospital. Our aim is to provide a framework for a generic situation where non-drug resistance strain may mutate into drug resistant strain as a result of drug treatment. As in some of the work cited above the bacterial infection may spread by contact between patients and HCWs. We assume that patients bacterial load can be monitored and, when it exceeds a threshold T_H, drug is administered at strength (or amount) σ for time duration T^*. We wish to determine the best dosing strategy, that is, the values of T_H, σ and T^* under which the average increase of bacterial load of the drug-resistant strain is the smallest.

Our model is based on the simplest possible assumptions. Thus, we assume that during the six weeks of the simulations time of the model patients do not enter or leave the hospital. We also make simple assumptions on the immune response of the patients to the bacterial infection, on the rate of mutation from non-resistant strain to drug-resistant strain, and on the HCWs-patients infection rate. Subsequent work should include long term carriage of bacteria by HCWs, the difference between various HCW sterilization methods, and the ratio of HCWs to patients. Many of the parameters used in the model are not known experimentally at this time. Nevertheless we believe that the present simple model can serve as a starting point for deeper investigations of the various factors that are associated with drug-resistant bacterial growth in a hospital.

2. **Method: The dynamics of bacteria.** We consider two bacterial strains: non-drug resistant bacteria b_1 and drug-resistant bacteria b_2. We assume that each patient carries bacterial strains of some load (b_1, b_2). Denote by $P(t, b_1, b_2)$ the number density of patients with bacterial load (b_1, b_2), that is, number of patients at time t with bacterial load between (b_1, b_2) and $(b_1 + \Delta b_1, b_2 + \Delta b_2)$ is approximately $P(t, b_1, b_2)\Delta b_1 \Delta b_2$, provided Δb_1 and Δb_2 are small numbers. Similarly, the number density of HCWs with bacterial load $(\bar{b}_1, \bar{b}_2)$ is denoted by $H(t, \bar{b}_1, \bar{b}_2)$. We introduce the dynamics of the bacteria in a patient and in a HCW respectively, by

$$\frac{db_i}{dt} = A_i(t, b_1, b_2, H)\,, \quad \frac{d\bar{b}_i}{dt} = B_i(t, \bar{b}_1, \bar{b}_2, P),\ (i = 1, 2). \tag{1}$$

The function A_i depends on the natural growth of b_i, the bacterial transmission from H which contributes to an increase of b_i, the response of the immune system of patients to b_i, the effect of drug treatment, and the mutation rate from non-drug resistant bacteria to the drug-resistant bacteria. The function B_i depends on the growth of $\bar{b}_i$ and on the bacterial transmission from P. We assume that HCWs undergo sterilization by the end of each shift, and therefore we do not include infection, drug treatment and immune response in the dynamics of the HCWs.

2.1. **Dynamics of the bacteria within the patients.** We make the following assumptions:

(i) Patients initially in the hospital remain in the hospital during the period of the simulations of the model, and no new patients are admitted.
(ii) The HCWs change every shift, where 1 shift = 8 hours.
(iii) A patient becomes infective if $\max(b_1, b_2)$ exceeds a threshold T_H and, when this occurs, a drug is administered for time duration T^*.
(iv) During a visit, if the HCW has higher load of bacteria, the visited patient will be contaminated by the bacteria carried by the HCW. More precisely, when HCWs with bacterial load (a_1, a_2) visit patients with bacterial load (b_1, b_2) and $a_i > b_i$ for i=1 or i=2, then the patients bacterial load b_i will increase proportionally to $a_i - b_i$; hence the total increase rate resulting from such visits is proportional to
$$\int H(t,a)(a_i - b_i)^+ da_i.$$
Similarly, if the patient has higher bacterial load, then the HCW will be contaminated by the patient according to a similar formula.
(v) The non-resistant and the resistant bacteria grow at rates λ_1 and λ_2 respectively, where $\lambda_1 > \lambda_2$ [8].
(vi) The immune system of the patients acts to reduce the bacterial population.
(vii) The drug kill rate for the non-resistant bacteria, σ_1, is larger than the drug kill rate, σ_2, for drug-resistant bacteria [15].
(viii) As result of drug treatment, the non-resistant bacteria mutates into a drug-resistant bacteria at constant rate θ; we neglect mutation in the reverse direction.

Based on the above assumptions, the dynamics of the bacteria in the patients is described by equations (2) and (3):

$$\frac{\mathrm{d}b_1}{\mathrm{d}t} = \underbrace{\lambda_1 b_1}_{\text{growth}} - \underbrace{\nu M_1(t,b) b_1}_{\text{immune response}} - \underbrace{\sigma_1(t) b_1}_{\text{drug response}} - \underbrace{\mu(t) b_1}_{\text{mutation}} + \underbrace{\eta_1 \int_\Omega H(t,a)(a_1 - b_1)^+ \mathrm{d}a}_{\text{infection of patients by HCWs}}, \tag{2}$$

$$\frac{\mathrm{d}b_2}{\mathrm{d}t} = \underbrace{\lambda_2 b_2}_{\text{growth}} - \underbrace{\nu M_2(t,b) b_2}_{\text{immune response}} - \underbrace{\sigma_2(t) b_2}_{\text{drug response}} + \underbrace{\mu(t) b_1}_{\text{mutation}} + \underbrace{\eta_2 \int_\Omega H(t,a)(a_2 - b_2)^+ \mathrm{d}a}_{\text{infection of patients by HCWs}}, \tag{3}$$

where $b = (b_1, b_2)$ varies in a domain Ω.

The immune response, the drug response and the mutation, as well as the dynamic of the patients and of the HCWs will be described below.

We introduce two important quantities: the threshold T_H at which the drug is administered, and the time duration T^* of drug treatment.

In our model, only the relative values of b_1, b_2 and T_H are relevant since the variables b_i and T_H can be rescaled by $b_i \to \frac{b_i}{\zeta}$, $T_H \to \frac{T_H}{\zeta}$ for any parameter ζ. We shall then assume, for simplicity, that $\Omega = \{(b_1, b_2); 0 < b_1 < 1, 0 < b_2 < 1\}$, the initial bacterial loads of (b_1, b_2) in patients and HCWs are in the region $5b_1 + 10b_2 < 1$, and that the range of T_H varies between 0.2 and 0.8. As will be shown, the b_i will remain smaller than 1 during the simulation period (6 weeks).

2.2. **Immune response.** The immune response is represented by dimensionless quantities M_1 (for b_1) and M_2 (for b_2). The dynamics of the immune system response is given by [15]:

$$\frac{\mathrm{d}M_1}{\mathrm{d}t} = \gamma_1 \frac{b_1 M_1}{\kappa + b_1}(1 - M_1), \tag{4}$$

$$\frac{\mathrm{d}M_2}{\mathrm{d}t} = \gamma_2 \frac{b_2 M_2}{\kappa + b_2}(1 - M_2) - \frac{\alpha b_2}{\kappa + b_2} M_2, \tag{5}$$

with initial conditions:

$$M_i(0, b) = 0.1 \quad \text{in } b \in \Omega, \tag{6}$$

for all $i = 1, 2$.

From (5)-(6) it follows that $0 \leqslant M_i(t, b) \leqslant 1$ and $M_i(t, b) = 0.1$ if $t > 0$, $b_i = 0$. The term $-\frac{\alpha b_2 M_2}{\kappa + b_2}$ represents a decrease of the immune response to the drug resistant bacteria.

2.3. **Drug treatment.** The HCWs work in shifts of 8 hours. At the end of each shift, the HCWs undergo sterilization and become uninfected. We divide the time t into shifts of 8 hours, $t_0 = 0 < t_1 < t_2 < \cdots < t_m < \cdots$ where $t_m = 8m$ hours. Set

$$\rho_m = \frac{1}{t_m - t_{m-1}} \int_{t_{m-1}}^{t_m} (|b| - T_H)^+ dt,$$

where $|b| = \max(b_1, b_2)$. ρ_m represents the average of the difference between the bacteria b in the patient and the threshold T_H in the time interval between t_{m-1} and t_m, that is the shift m.

Suppose $\rho_m = 0$ for $m = 1, 2, \cdots, n-1$ and $\rho_n > 0$.

Since T_H is the bacterial threshold at which drug is administered, treatment should start as soon as the average of the difference between the bacteria b in the patient and the threshold T_H is positive $\rho_n > 0$, that is drug treatment is administered at time t_n. However, since the measurement of T_H is not precise, thereafter the average of the difference between the bacteria b in the patient and the threshold T_H; ρ_n, is not precise too, some doctors may decide not start the treatment if ρ_n is quite small.

To model this fact, we assume that all doctors will prescribe medication to the patient at time t_n if the average of the difference between the bacteria b in the patient and the threshold T_H is bigger than 10% of the threshold T_H in the shift n; $\rho_n > 0.1T_H$. But only a fraction $\frac{10}{T_H}\rho_n$ of the doctors will prescribe medication to the patient at time t_n if the average of the difference between the bacteria b in the patient and the threshold T_H is less than 10% of the threshold T_H in the shift n; $\rho_n < 0.1T_H$.

We represent the probability in which the doctor gives the drug treatment to the patient by the quantity

$$h_1(\rho_n) = \begin{cases} \dfrac{10}{T_H}\rho_n & \text{if } \rho_n < 0.1T_H, \\ 1 & \text{if } \rho_n > 0.1T_H, \end{cases}$$

and we take the drug treatment administered to the patient by the doctor to be the quantity

$$\sigma_i(t) = h_1(\rho_n)\mathbb{1}_{(t_n, t_n+T^*)}\sigma_i,\ (i = 1, 2)$$

where $\mathbb{1}_{(\alpha,\beta)} = 1$ if $\alpha < t < \beta$ and $= 0$ otherwise.
If $\rho_n > 0.1T_H$, then the total amount of drug (σ_1, σ_2) is delivered to the patient during the period $(t_n, t_n + T^*)$, and no additional drug will be given.
If however $\rho_n < 0.1T_H$, then with probability $h_1(\rho_n)$ the patient began to receive drug at $t = t_n$. Additional probability of beginning drug treatment will occur at a later time t_k if:

$$\begin{aligned} &\rho_l = 0 \ \text{ if } \ n < l < k, \\ &\rho_k > 0. \end{aligned}$$

Again, because the decision of the doctor on initiation the drug treatment at time t_k, depends on imprecise reading of T_H, the probability of starting drug treatment at time t_k is

$$h_2(\rho_k) = \begin{cases} h_1(\rho_k) & \text{if } \ h_1(\rho_n) + h_1(\rho_k) \leqslant 1, \\ 1 - h_1(\rho_n) & \text{if } \ h_1(\rho_n) + h_1(\rho_k) > 1, \end{cases}$$

and the duration of the treatment is again T^*. Hence, if $h_1(\rho_n) + h_1(\rho_k) = 1$, then the total drug treatment is expressed by

$$\sigma_i(t) = [h_1(\rho_n)\mathbb{1}_{(t_n, t_n+T^*)} + h_2(\rho_k)\mathbb{1}_{(t_k, t_k+T^*)}]\sigma_i,\ (i = 1, 2).$$

If however $h_1(\rho_n) + h_1(\rho_k) < 1$, then additional probabilities of drug treatment may occur at later times according to the same principle as above, but the total amount of drug never exceeds (σ_1, σ_2) for the duration of T^*.

2.4. **Mutation of the bacteria.** We assume that at the end of the first drug-treatment, a mutation from b_1 to b_2 will occur at rate $\theta h_1(\rho_n)b_1$. This means that b_1 will decrease by $\theta h_1(\rho_n)b_1$ and b_2 will increase by the same amount:

$$\begin{aligned} b_1(t_n + T^* + 0) &= b_1(t_n + T^* - 0)(1 - \theta h_1(\rho_n)), \\ b_2(t_n + T^* + 0) &= b_2(t_n + T^* - 0) + \theta h_1(\rho_n)b_1(t_n + T^* - 0), \end{aligned}$$

where θ is a parameter, $0 < \theta < 1$; for simplicity we assume that θ does not depend on σ_1.

Similar jumps will occur at the end of the second drug treatment, that is, at $t = t_k + T^*$, etc. We can express these jumps by the functions $-\mu(t)b_1$ in (2) and $+\mu(t)b_1$ in (3) where

$$\mu(t) = \delta_{t_n+T^*}(t)\theta[h_1(\rho_n)\mathbb{1}_{(t_n, t_n+T^*)} + h_2(\rho_k)\mathbb{1}_{(t_k, t_k+T^*)} + \cdots],$$

and δ is the Dirac function.

2.5. **The dynamic of the bacteria within HCWs.** Denote by $\bar{b}_1$ and $\bar{b}_2$ the non-resistant and the resistant bacteria, respectively, carried by the HCWs. Equations (7) and (8) describe their dynamics:

$$\frac{\mathrm{d}\bar{b}_1}{\mathrm{d}t} = \underbrace{\lambda_1 \bar{b}_1}_{\text{growth}} + \underbrace{\eta_1 \int_\Omega P(t,a)(a_1 - \bar{b}_1)^+ \mathrm{d}a}_{\text{contamination of HCWs by patients}}, \tag{7}$$

$$\frac{\mathrm{d}\bar{b}_2}{\mathrm{d}t} = \underbrace{\lambda_2 \bar{b}_2}_{\text{growth}} + \underbrace{\eta_2 \int_\Omega P(t,a)(a_2 - \bar{b}_2)^+ \mathrm{d}a}_{\text{contamination of HCWs by patients}}, \tag{8}$$

Since HCWs undergo sterilization by the end of their shift, they do not become infected.

2.6. **Parameters values.** The parameters values of the model are given in the Table 1. Because of the lack of experimental results, most of the parameters in the model equations are not known, and are arbitrarily chosen; we refer to them by TW ("this work").

We proceed to explain the choice of some of the parameters.
Since b_2 is drug-resistant, the drug kill rate σ_2 for the resistant bacteria is taken to be smaller than the drug kill rate σ_1 for the non-resistant bacteria. Similarly, we take the immune response growth rate for drug-resistant bacteria, γ_2, to be smaller than the immune response growth rate,γ_1, for non-resistant bacteria. We also included additional deterioration rate of the immune response to b_2 in the term $-\dfrac{\alpha b_2 M_2}{\kappa + b_2}$. We assume that in the contact between patients and HCWs, the drug-resistant bacteria is transmitted more easily than the non-resistant bacteria, that is, $\eta_2 > \eta_1$. However, the simulation results will not change qualitatively if η_1 is chosen to be larger than η_2.

The immune response plays an important role in fighting the bacteria, especially the non-resistant strain. For example, if we ignore the contamination between patients and HCWs, then even with full continuous administration of the drug, in order to decrease the bacterial load b_1, M_1 must be such that

$$\lambda_1 - \sigma_1 - \nu M_1(t,b) < 0,$$

that is

$$M_1(t,b) > \frac{\lambda_1 - \sigma_1}{\nu} = \frac{2.77 - \sigma_1}{3}.$$

Symbol	Interpretation	Value	Reference
λ_1	growth rate of non-resistant bacteria	2.77 /shift	[8]
λ_2	growth rate of resistant bacteria	0.92 /shift	[8]
ν	immune response rate	3 /shift	TW
σ_1	drug kill rate of non-resistant bacteria	$1.7 \leqslant \sigma_1 \leqslant 2.2$ / shift	TW
σ_2	drug kill rate of resistant bacteria	0.28 /shift	TW
η_1	non-resistant bacteria exchange rate	10^{-4} /shift	[1], [8], TW
η_2	resistant bacteria exchange rate	1.5×10^{-4} /shift	[1], [8], TW
γ_1	immune response growth rate	0.7 /shift	TW
γ_2	immune response growth rate	0.5 /shift	TW
κ	immune response 'pseudo carrying capacity'	1	TW
θ	mutation rate	1/12	TW
α	degradation rate of the immune response by the resistant bacteria	0.1 /shift	TW

TABLE 1. Parameters of the model

3. **Method: The dynamics of patients and HCWs.** Recall that patients do not enter or leave the hospital during the time period considered in the model. The dynamics of the patients is then described by the conservation law

$$\frac{\partial P}{\partial t} + \operatorname{div}(P\vec{A}) = 0, \tag{9}$$

where $\vec{A} = (A_1, A_2)$ and the $A_i = \dfrac{\mathrm{d}b_i}{\mathrm{d}t}$ are given by the right hand sides of (2), (3). Similarly, the HCW dynamics is described by the conservation law

$$\frac{\partial H}{\partial t} + \operatorname{div}(H\vec{B}) = 0, \tag{10}$$

where $\vec{B} = (B_1, B_2)$ and the $B_i = \dfrac{\mathrm{d}\bar{b}_i}{\mathrm{d}t}$ are given by the right hand side of (7), (8). We take the initial bacterial load of the patients to be a positive constant in the region $\{b_1 > 0,\ b_2 > 0,\ 5b_1 + 10b_2 < 1\}$ and zero elsewhere, and normalize it so that $\int P(0, b)db = 1$. Hence

$$P(0, b) \equiv P_0(b) = \begin{cases} 100 & \text{if } 5b_1 + 10b_2 < 1, \\ 0 & \text{elsewhere in } \Omega. \end{cases} \tag{11}$$

Similarly, we take the initial bacterial load for the HCW to be a constant in the smaller region $\{\bar{b}_1 > 0,\ \bar{b}_2 > 0,\ 20\bar{b}_1 + 20\bar{b}_2 < 1\}$ and zero elsewhere, and normalize it so that $\int H(0, \bar{b})d\bar{b} = \frac{1}{4}$ (assuming that there are 4 patients per one HCW [8]).

Hence

$$H(0,\bar{b}) \equiv H_0(\bar{b}) = \begin{cases} 200 & \text{if } 20\bar{b}_1 + 20\bar{b}_2 < 1, \\ 0 & \text{elsewhere in } \Omega. \end{cases} \tag{12}$$

Furthermore, at the beginning of each shift $t = t_n$ we take

$$H(t_n,\bar{b}) = H_0(\bar{b}). \tag{13}$$

Since $M_i(0,b) = 0.1$ if $b_i = 0$ and (by Table 1)

$$\lambda_1 - \sigma_1 - 0.1\nu > 0, \quad \lambda_2 - \sigma_2 - 0.1\nu > 0, \tag{14}$$

we have

$$A_1(t,0,b_2) > 0, \quad A_2(t,b_1,0) > 0. \tag{15}$$

Also, as mentioned earlier, the bacterial load b_i (under the initial condition (11)) will not exceed 1 for the duration of the simulation. Consequently, the characteristic curves $\dfrac{db_i}{dt} = A_i$ initiating in Ω do not exit Ω. We therefore do not prescribe boundary conditions for P. Then, for all $t > 0$, $P(t,b)$ is also supported in Ω and, by integrating (9) over Ω, we obtain

$$\int_\Omega P(t,b)db = \int_\Omega P(0,b)db = 1, \tag{16}$$

for any $t > 0$.

Similarly, the characteristic curves $\dfrac{d\bar{b}_i}{dt} = B_i$ initiating in Ω do not exit Ω, $H(t,\bar{b})$ is supported in Ω, and

$$\int_\Omega H(t,\bar{b})d\bar{b} = \int_\Omega H(0,\bar{b})d\bar{b} = \frac{1}{4}, \tag{17}$$

for all $t > 0$.

4. **Results.** We are interested to determine the effect of the drug treatment on the growth of the bacteria, especially the drug-resistant bacteria. We measure the load of the drug-resistant bacteria by the first b_2-moment of P :

$$Q_2(t) = Q_2(t,\sigma,T_H,T^*) = \int b_2 P(t,b_1,b_2)db_1db_2, \tag{18}$$

where $\sigma = (\sigma_1,\sigma_2)$. In view of (16), $Q_2(t)$ is also the average value of b_2 taken over the entire patients population.
Similarly, we define

$$Q_1(t) = Q_1(t,\sigma,T_H,T^*) = \int b_1 P(t,b_1,b_2)db_1db_2, \tag{19}$$

as average of b_1 taken over the entire patients population. We wish to evaluate $Q_1(t)$ and $Q_2(t)$ for different values of σ, T_H and T^*.
Since b_2 is drug-resistance, we fix σ_2, say at $\sigma_2 = 0.28$, and vary σ_1 from low level $\sigma_1 = 1.7$, to intermediate level $\sigma_1 = 2.0$, to high level $\sigma_1 = 2.2$. We choose, for T_H, the values 0.2, 0.4, 0.6 and 0.8 and take $T^* = 1$ week or $T^* = 2$ weeks.

We solve the six ordinary differential equations, (2)-(5) and (7), (8), using the fourth-order Runge-Kutta method and the partial differential equations (9), (10) using the Lax-Friedrichs method [17] and [18].

The integrals in (2), (3), (7), (8) and (18)-(19) are computed by the trapezoidal rule. The algorithm of the simulations is given in the Appendix A.

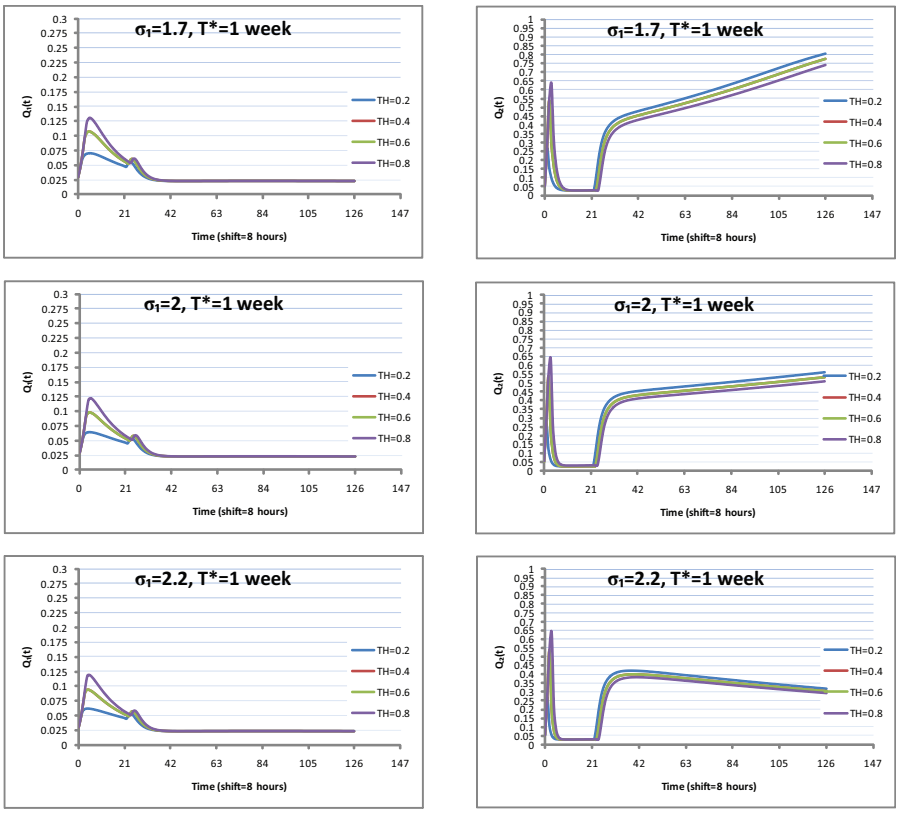

FIGURE 1. The first b_1-moment (left column) and b_2-moment (right column) in the patients during 6 weeks of observations when they undergo 1 week (21 shifts) treatment and when the drug killing rate takes three values: small (first row), and intermediate (second row) and large (third row).

In Figure 1 the time duration of the drug treatment is $T^* = 1$ week and Figure 2 the time duration of the drug is $T^* = 2$ weeks. The first row represents the values of $Q_1(t)$ and $Q_2(t)$ for the low dose $\sigma_1 = 1.7$, the second row represents the values of $Q_1(t)$ and $Q_2(t)$ for the intermediate dose $\sigma_1 = 2.0$ and the third row shows the profiles of $Q_1(t)$ and $Q_2(t)$ for the high dose $\sigma_1 = 2.2$. The four curves in each frame correspond to the four levels of the threshold T_H.

A common feature of the first column in Figure 1 is the following: The non-resistant bacterial load $Q_1(t)$ first increases, as no drug is administered, and then, after initiating treatment it decreases steadily during the rest of the 6 weeks period, except for a small reversal. This reversal may be attributed to the fact that since the measurement of the threshold level is not precise, the amount of drug first administered to patients (when the doctor decides that the threshold level has been reached) is not sufficient to reduce the average density of b_1. When the drug is

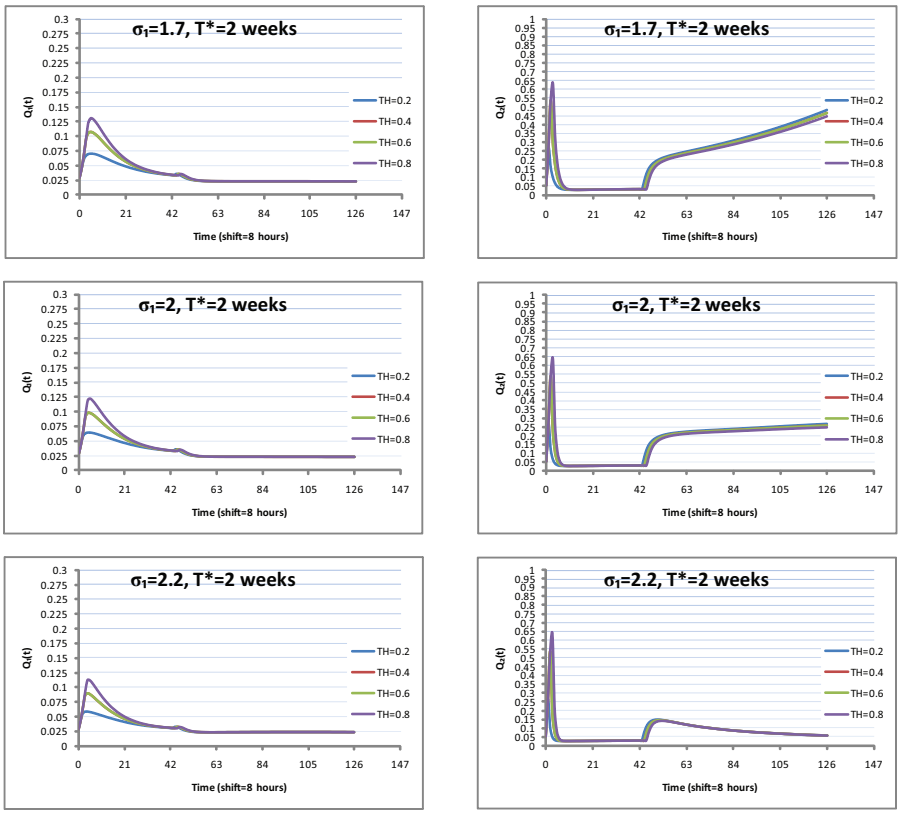

FIGURE 2. The first b_1-moment (left column) and b_2-moment (right column) in the patients during 6 weeks of observations when they undergo 2 weeks (42 shifts) treatment and when the drug killing rate takes three values: small (first row), and intermediate (second row) and large (third row).

administered for two weeks instead of one week (as in Figure 2), this reversal almost disappears. As the drug treatment σ_1 is increased, the bacterial load decreases, but at the end of the sixth week the difference resulting from different doses are negligible. We also see that decreasing the threshold results in smaller bacterial load for the first two weeks, but very little difference is seen thereafter.

The simulation results for the drug-resistance bacteria are quite different. As seen in the second column of Figure 1, after initiating drug treatment the bacterial load decreases, but it remains low only for a short time. It then climbs up to a high level, which depends on the dose σ_1. For small or intermediate doses, $Q_2(t)$ continues to grow, but with the adminstration of the high dose $\sigma_1 = 2.2$ the average level of b_2 eventually decreases and seems to reach an equilibrium, which is nonetheless larger than the initial value $Q_2(0)$.

In Figure 2 (with $T^* = 2$ weeks instead of $T^* = 1$ week) we see the same features as the Figure 1, with few differences with respect to Q_1, but with significant lower values of Q_2. The simulations suggest that the optimal treatment is

$$T^* = 2 \text{ weeks }, \ \sigma_1 = 2.2 \quad \text{(largest dose of drug)}. \tag{20}$$

We note however that the strategy (20) does not take into account possible side-effects of the high dose. We finally note that also in all the frames of Figure 2 there is just a slight advantage in the first 2-3 weeks in choosing the lowest threshold $T_H = 0.2$.

If the contact between HCW and patients is increased then the bacterial load in patients is expected to increase. The increase is more pronounced in the case of b_2, as shown in Figure 3 with $T_H = 0.2$, T^* =2 weeks and exchange rates between HCWs and patients (η_1, η_2), $(10\eta_1, 10\eta_2)$, $(100\eta_1, 100\eta_2)$: the first row corresponds to (η_1, η_2), the second row corresponds to $10(\eta_1, \eta_2)$, and the third row corresponds to $100(\eta_1, \eta_2)$.

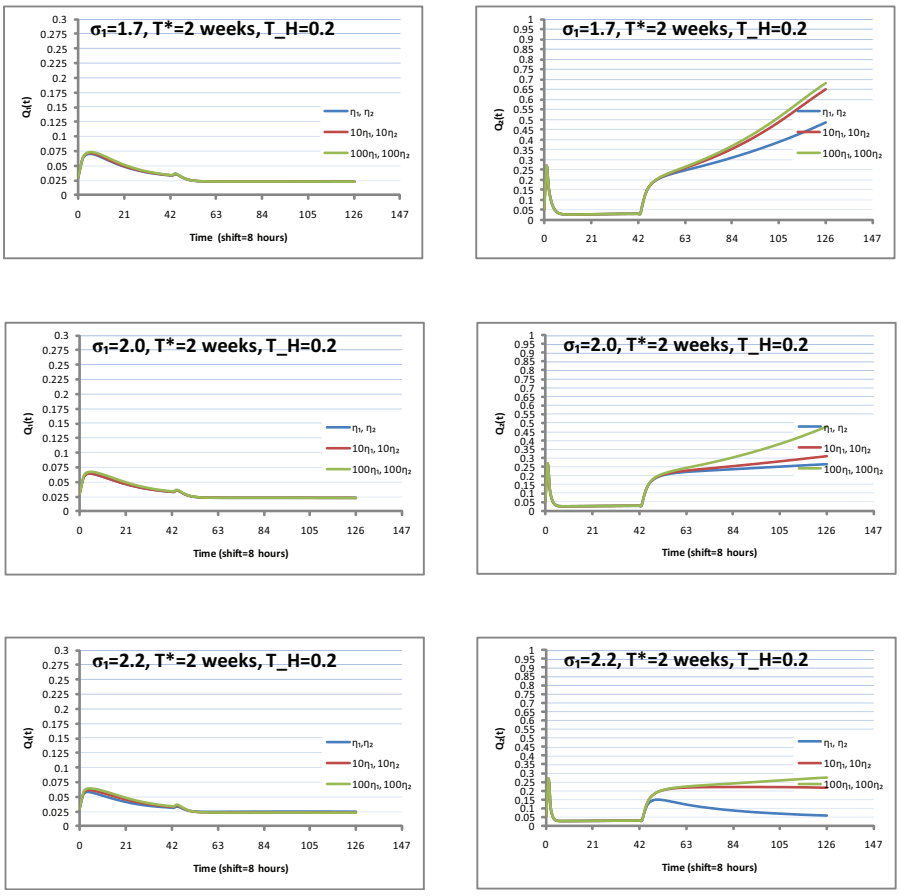

FIGURE 3. Q_1 and Q_2 when the threshold is fixed at $T_H = 0.2$ and the drug treatment is given for 2 weeks for different amount of drug σ_1 (1.7 and 2.0 and 2.2) and different bacterial exchange rates (η_1, η_2), $(10\eta_1, 10\eta_2)$ and $(100\eta_1, 100\eta_2)$.

5. **Discussion.** In the present paper we developed a mathematical model that describes the spread of drug-resistant bacteria in a hospital. The model includes two bacterial strains: non-drug resistant, b_1, and drug resistant, b_2. The model assumes that each patient has a bacterial load (b_1, b_2), and it quantifies the total bacterial

load of each strain b_i within the population of patients by the first moments, or the average, of b_i

$$Q_i(t) = \iint_{\Omega} b_i P(t, b_1, b_2) db_1 db_2 \quad (i = 1, 2),$$

where $P(t, b_1, b_2)$ is the number density of patients with bacterial load (b_1, b_2) with $\iint_{\Omega} P(0, b_1, b_2) db_1 db_2 = 1$. The bacteria evolve according to a dynamical system which includes the effects of patients immune response, drug treatment, mutation from b_1 to b_2, and spread of infection by contact of health care workers with patients.

The model predicts that as soon as drug is administered, the average non-resistant load $Q_1(t)$ will decrease and eventually (i.e., after 6 weeks) will reach a very low level. However, the average load $Q_2(t)$ of the drug-resistant bacteria will initially decrease, after treatment, but then it will bounce back and remain at a high level, dropping off eventually if the drug σ_1 administered to kill b_1 is given in a strong enough dose. The model also predicts that better results for $Q_2(t)$ are obtained if the drug is administered for two weeks instead of one week. It is well known (see for example, Burgess (1999) [4] and a review article by Peter (2005) [19]) that underdosing increases the drug-resistant bacteria. In that sense, our model predictions agree qualitatively with experimental results. However the specific details of how the drug-resistant bacteria evolves under underdosing may depend on the type of bacteria. Since most of our model parameters are not experimentally known, the time evolution of $Q_2(t)$ in our model simulation should not be taken as being universally valid for all types of bacterial infections.

The model also shows (Figure 3) that the bacterial load of patients will increase if the contact (exchange rate) between HCWs and patients is increased; this increase is especially significant for the drug-resistant bacteria.

The model makes a number of simplifying assumptions. For example, it is assumed that a mutation from b_1 to b_2 is given by a constant parameter and that it occurs precisely at the end of the drug treatment. A more serious limitation of the model is due the fact that many of the parameters are not known experimentally. Nevertheless, simulations (not given here) show that the profiles of $Q_1(t)$ and $Q_2(t)$ do not change qualitatively if we modify some of the parameters.

The model is quite flexible and can be refined to include different species of pathogens and hospital conditions. For example:

(i) Suppose each week new patients are admitted and "recovered" patients (those whose bacterial load has remained low for several days) exit the hospital. We can incorporate these conditions into the equation for P by adding two terms on the right-hand side of equation (9), to account for entering and exiting patients.

(ii) Suppose the HCWs are subject to long term carriage of bacteria. We can incorporate this assumption by modifying the right-hand side of equation (13).

(iii) The ratio of HCWs to patients,

$$\int H(0, \bar{b}) d\bar{b} / \int P(0, b) db,$$

can also be introduced as a given parameter, specified for each bacterial disease in each hospital.

The model developed in this paper is for two strains of bacteria. The extension of the model to three strains (b_1, b_2, b_3), or even more strains, is straightforward. But

one would need to have experimental data on the rates of mutations among the various strains.

In summary, we view the present model as a first step to be further developed and refined as more experimental data become available.

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Appendix A. The algorithm

Algorithm 1 During the 6 weeks of observation

Setting the parameters.
Setting the initial conditions.
Runge Kutta method of order 4 scheme for ODEs.
Lax-Friedrichs scheme for PDEs.
First time t_n where $\max(b_1, b_2) > T_H$
if Yes: **then**
    give drug for T^* days
    execute jump at $t = t_n + T^*$
else
    Continue.
    Display $Q_1(t)$ and $Q_2(t)$.
end if

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