Vancomycin-resistant enterococci colonization–infection model: parameter impacts and outbreak risks

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Vancomycin-resistant enterococci (VRE) infections have been linked to increased mortality and costs. A new model of a VRE-infested intensive care unit (ICU) is introduced. It incorporates critical features including the difference between colonization and infection, the role of special preventive care treatment cycles, fitness cost, and antibiotic use. Five patient stages are considered: susceptible, colonized with and without special preventive care, and infected with and without treatment. Parameter ranges are determined representing different ICUs and incorporated to numerically simulate the model. Basic reproductive number of the infection is derived and the impacts of the parameters are analysed. Strategies to minimize VRE infections and outbreak risk are explored with a focus on efficient and simultaneous control of critical parameters. In particular, threshold values of the level of special preventive care and ICU compliance rate are given to achieve desired goals under various constraints.

Keywords: drug resistance; vancomycin-resistant enterococci; parameter impact; basic reproduction number; infection control

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1. Introduction

1.1. Antibiotic resistance and plasmids

Currently, antibiotic resistance is a major health problem. Many nosocomial, or hospital-acquired, infections can be caused by resistant bacteria entering a part of the body during surgery and ending up somewhere where they are not normally found [1,6,8,19,26,27,29,33]. Other infection factors include the role of plasmids, being immunocompromised as a result of other serious treatments, and the use or misuse of antibiotics [3,11,15,30,38,47].

Antibiotics used to treat bacterial infections target only bacterial organelles and prevent the bacteria from replicating. Initially, all bacteria are susceptible to a type of antibiotic. However, a few bacteria, called spontaneous mutants, can be naturally immune to the effects of the antibiotic. If the antibiotic is present in the medium in which the bacteria are grown, these bacteria will be
the only ones able to produce offspring. These offspring will contain the resistance genes and will also be immune to the effects of the antibiotic. However, this resistance comes at a reproductive cost. Since the resistant bacteria have slightly more DNA than the ancestral strain, they cannot produce as many offspring as quickly as the ancestral strain. Moreover, the resistance genes will only be present if the antibiotic is present in the system. Finally, over long periods of time, the bacterial population can overcome the cost of the resistance genes and, if the antibiotic is used for a long enough period, the resistant strain will replace the ancestral strain completely.

Plasmids play a very important role in the amount of resistance that a bacterium has to a given antibiotic. Bacteria have a singular, circular chromosome that stores all their genetic material. Plasmids, floating around the cell, contain extra genes that are not required for cellular function, such as antibiotic resistance. When needed, these plasmids can integrate themselves into the genome of the bacteria and cause resistance factors to be transcribed. Also, plasmids can have intergenerational transfer, as opposed to being passed down from the mother to the daughter cell.

1.2. Vancomycin-resistant enterococci

VRE stands for vancomycin resistant-enterococci. VRE infections in hospitals have been linked to increased mortality and costs [2,9,13,21,24,32,37,41].

Enterococci, as the name suggests, are spherical bacteria and are generally found live in the digestive and genital tracts, bloodstream, and wounds. These bacteria are able to tolerate a wide range of environments, such as temperatures spanning from 10°C to 45°C and pH from 4.5 to 10.0. They can also tolerate a 6.5% NaCl solution and can live in a 60°C environment for up to 10 min. These and other factors make enterococci infections very difficult to treat [25,40].

Vancomycin is a powerful antibiotic used to treat bacteria that are already resistant to penicillin and derivatives of penicillin. Thus, when VRE infection occurs, it can be very difficult to treat and can quickly become life threatening. This is the case in a hospital’s intensive care units (ICUs) when VRE develop in patients with an already compromised immune system, such as in cancer patients going through chemotherapy, patients with organ transplant, and patients with severe illnesses. VRE have been found to be highest among haematology patients and organ transplant recipients. Moreover, hospitals naturally present environments with higher risk of VRE contamination. In this paper, we explore a new VRE model with more factors leading to the spread of VRE and we identify new VRE population stages not covered in pervious models. We also investigate the role and the impact of the parameters involved in VRE infection and determine efficient strategies to control VRE spread and to prevent VRE outbreaks for a whole range of ICUs, at minimum health and monetary costs.

1.3. Plasmids and VRE

For VRE, there are many different plasmids conferring resistance to vancomycin, with the six relevant being VanA, VanB, VanC1, VanC2, VanD, and VanE. VanA confers a strong resistance to vancomycin and teicoplanin (another antibiotic used commonly to treat enterococci infections). VanB offers a strong resistance to vancomycin, but none to teicoplanin. Both VanD and VanE offer a relatively low level of resistance to vancomycin and no resistance to teicoplanin. Finally, VanC1 and VanC2 confer what is called chromosomol resistance; that is, they are resistant genes that are built into the chromosome and not stored as plasmids. They offer a mild resistance to vancomycin and no resistance to teicoplanin, but there is no reproductive cost to carrying these genes since they are built into the chromosome. To date, there has been no clinical outbreak of VRE with only VanC, VanD, or VanE, so this study will focus primarily on VanA and VanB [5,42].

There are distinct types of enterococci that are usually found to exhibit some resistance to vancomycin. They are divided into two types based on their resistances: intrinsic and acquired.
The are said to be intrinsic when the resistance to vancomycin is not caused by plasmid transmission. They are said to be acquired when the resistance is caused by a plasmid giving the bacterium the necessary genetic code to produce resistance genes. Species with an intrinsic resistance include *Enterococcus gallinarum* and *Enterococcus casseliflavus/flavus*. Acquired resistances are most often found in *Enterococcus faecium*, *Enterococcus faecalis*, *Enterococcus raffinosus*, *Enterococcus avium*, and *Enterococcus durans*. There have been no clinical outbreaks caused by VRE intrinsic resistance, so for the purposes of this model, only acquired resistance will be used [10]. Furthermore, 85–99% of all VRE cases are caused by either *E. faecium* or *E. faecalis*, and these are the two species that the model and the data focus on [36,40].

### 1.4. VRE detection and prevention

Early detection and isolation can help prevent VRE infection and its spread. There are currently two major ways to screen for VRE: a rectal swab every couple of days to be grown on an agar plate and the use of polymerase chain reaction (PCR). PCR can be used to make many copies of a certain strain of DNA. For example, if the PCR machine is set to make copies of VanA, it can be used to test the presence of that sequence of DNA. Often PCR is not the first choice made by hospitals since it has the tendency to give false positives because certain sequences seem like the VanA plasmid even though they are not. The use of agar plates is more reliable and cheaper; however, it takes more time to get the results. There is a need to identify new methods for cheap and efficient screening of VRE. Once this method is determined, quick identification and isolation of patients with VRE infection can help control VRE [12,31,39].

### 1.5. Stages of VRE infection

We identified five VRE stages of patients in a given ICU. Initially, everyone is considered susceptible. Once a positive VRE culture is produced without the patient showing symptoms, the patient is considered to be colonized by VRE. The symptoms of a VRE infection depend on where the infection is located. It is not well known why a patient colonized with VRE will progress to a full-blown infection. The current finding is that most patients who develop a VRE infection are already in the ICU and therefore on antibiotics. Also, most patients have just had some sort of major surgery and are immunosuppressive. Since VRE are resistant to most antibiotics, the antibiotics kill off the majority of the bacteria around it, but leave VRE unharmed. This gives the VRE plenty of room to expand and leads to an increase in the VRE density and virulence, leading to an infection. Once the infection sets in, only a few antibiotics are powerful enough to overcome the VRE broad spectrum of resistance. Two major drugs, Linezolid and Tygacil, have been developed recently and can be effective. If the infection is cleared by the immune system and antibiotics, the patient is considered to be recovered. The HIPAC recommends three consecutive negative agar growth plates spaced at least one week apart [12,25,35]. However, a recovered patient is not immune to another VRE infection and therefore the patient either leaves the ICU or joins the susceptible stage. In general, there is no known VRE immunity.

Special preventive care can help a colonized patient move back to the susceptible stage instead of to the infected stage. Initially, it was thought that there was no treatment for colonized individuals, but recent studies have shown that chlorhexidine baths can help clear the colonization. Also, a patient testing positive for VRE should be put into contact isolation [49]. This includes requiring health workers to change gowns and gloves after each contact with the patient. In addition, specific equipments, such as stethoscopes, are designated for contact with isolated patients. In this project, we used two classes for the colonized: those under special preventive care and those without due to economical factors, misdiagnosis, or limited ICU resources. We analysed the impact of the
variations of the proportions of these classes and effective strategies to adjust the parameters in order to control VRE or prevent outbreaks.

2. New contamination–infection VRE model

Recently, Yahdi and Much [46] have developed a VRE model that was used as a starting point for this work. Other relevant models are reported in [4,11,22]. This paper includes stages and transition factors of VRE infection not modelled before, in particular, the distinction between colonization and infection, as well as the role of fitness cost, preventive care, and treatment cycles. The model started out with seven variables. With a focus on the common practices in most ICU environments and main factors involved in the VRE dynamics, the model was reduced to five variables representing five VRE stages in ICUs as well as 19 independent parameters. A flow diagram of the new model is shown in Figure 1, where the box represents an ICU, the blue short arrows represent patients entering or leaving the ICU, the red right arrows represent transitions that are bad for the patients but good for VRE, the green left arrows represent transitions that are good for the patients but bad for VRE, and the yellow dashed arrows show the transitions within the same category of patients depending on the use or no use of special preventive care or treatments.

2.1. Five variables

Each of the five variables in the model is designed to represent a distinct VRE-related stage.

- Susceptible, $S$: Encompasses all patients who are classified as VRE free, that is, not producing a positive culture, so not colonized or infected since there is no natural immunity [14,25]. An ICU patient with a VRE infection who clears the infection returns to $S$, since having a VRE infection once does not confer immunity [40].

![Figure 1. VRE compartmental model in an ICU.](image-url)
Colonized, $X$: Once a patient produces a positive culture, he or she is considered to be colonized. In this stage, no treatment can be offered since most treatments only make the infection worse [10,35].

Colonized and under special preventive care, $Y$: According to the Centers for Disease Control and Prevention (CDC), when someone is colonized with VRE, he or she must be put under contact isolation to prevent further spread. This variable represents all colonized under contact isolation as well as other special preventive care described earlier.

Infected without VRE treatment, $V$: Once VRE hit a high density and the patient shows symptoms, the patient is considered to be infected. If VRE get into the skin, the area could be red and sore. VRE can be present in the form of urinary tract infections due to catheterization since many ICU patients need catheters. Moreover, a patient may not receive VRE treatment because of the reasons described in Section 2.2.

Infected undergoing VRE treatment, $W$: In this stage, the infected patient is undergoing treatment for VRE infection. There are only a few drugs to rely on to treat this disease, such as Tygacil and Linezolid.

### 2.2. Transitions between the stages

The model includes all possible VRE-related transitions between the different stages as well as between the ICU and the outside.

Transitions out of the susceptible stage $S$: There are three ways to leave the susceptible stage. The first two are linked. Patients who acquire VRE can move on to the colonized stage either with or without special preventive care. Transition to either $X$ or $Y$ depends on how severe the case of VRE is, how quickly the infection is detected, the high health risk to the ICU patient, and the resources. Also, patients can leave the susceptible stage by leaving the ICU.

Transitions to the susceptible stage: There are several ways to be in the susceptible stage. Recovering from a VRE infection does not confer immunity. Thus, a patient who has recovered from a VRE infection by treatment or from VRE colonization can return to the susceptible stage or leave the ICU. There is no known treatment to help colonized patients, rather time, spontaneous curing, and special preventive care are typical means. Chlorhexidine baths can be used to treat a colonized individual, but the results are currently experimental. Finally, the majority of patients enter the ICU VRE free.

Transitions into the colonized stages $X$ and $Y$: Susceptible patients who test positive for VRE are put into one of the colonized stages. Patients who produce positive VRE culture should be placed immediately in contact isolation according to the CDC [42]. In addition, some of the special preventive care measures stated earlier are recommended. A colonized patient may or may not be under special preventive care due to several factors, including higher risk issues, preventive care policy, compliance of the hospital and health-care workers with guidelines, hospitals resources such as the number of beds, specially equipped rooms and the availability of adequate number of health workers, or simply misdiagnosis of VRE colonization. There are also factors related to the patient such as economical factors.

Transitions out of the colonized stages: A colonized individual can become infected when the density of VRE in the bloodstream increases [10,12]. Also, a patient can leave the ICU at any time during the colonization stages. A patient may be colonized with VRE for up to four years without reaching the infected level.

Transitions into the infected stages $V$ and $W$: A patient showing symptoms of a VRE infection is classified as infected. A patient can enter the ICU with a full-blown VRE infection. The transitions between the two infected stages $V$ and $W$, with and without VRE treatment, are due
to many factors. To prevent the bacteria from becoming more resistant to new antibiotics, many
drugs can only be used for 7–10 days. Patients can be put on treatment cycles including stopping
of the treatment. In addition, an ICU patient suffering from other serious health complications
may not be able to receive a VRE treatment. Others do not receive adequate treatments due to
misdiagnosis or delay of diagnosis.

- Transitions out of the infected stages: There are two ways to leave the infected stage: VRE free
by treatment or by spontaneously curing without treatment. A patient can leave the ICU for
other reasons including cost or death.

2.3. Nineteen independent parameters

The parameters involved in the different transitions were investigated and reduced to 19 inde-
pendent parameters. The ranges of the parameter values were gathered from recent data available
from scientific resources, including professional journals and reports from the Harvard School of
Public Health, National Institutes of Health and ClinicalTrials.gov. They were accurately deter-
mined to reflect the diversity among ICUs and to allow for an investigation of the combinations of
parameters that can lead to a better control of VRE. Table 1 gives a summary of these parameters,
followed by their descriptions. The total number of ICU patients is assumed to be constant in
average.

- \( \mu \) represents the general ICU admission rate, while \( m_1, m_2, m_3, m_4, \) and \( m_5 \) represent the
percentages among the admitted patients into each of the five stages with \( m_5 = 1 - m_1 - m_2 - m_3 - m_4 \).
- \( \delta \), contamination rate: It encompasses all factors leading to contamination, including contact
with health-care workers, contact with other patients, contact with contaminated instruments,
etc.
- \( f \), fitness cost: Fitness cost relates to the bacteria and their cost of living with the plasmid.
Using \((1 - f)\), we take into account that the more fit the bacteria become, the easier it is to
live with the plasmid, and thus the worse it is for the patient. In these cases, \( f \) is close to zero.

| Parameter | Description | Mean value | Range value | Sources |
|-----------|-------------|------------|-------------|---------|
| \( \mu \) | General admission rate | 0.0956 | \(0.03 \leq \mu \leq 0.14\) | [11,23,28] |
| \( \delta \) | Contamination rate | 0.29845 | \(0.2657 \leq \delta \leq 0.3312\) | [20] |
| \( m_1 \) | Admission rate of susceptible | 0.7 | \(0 \leq m_1 \leq 1\) | [11,28] |
| \( m_2 \) | Admission rate of colonized \( X \) | 0.1 | \(0 \leq m_2 \leq 1\) | [11,28] |
| \( m_3 \) | Admission rate of colonized under special preventive care | 0.1 | \(0 \leq m_3 \leq 1\) | [11,28] |
| \( m_4 \) | Admission rate of infected \( V \) | 0.05 | \(0 \leq m_4 \leq 1\) | [11,28] |
| \( \gamma \) | Rate of curing due to treatment | 0.46 | \(0 < \gamma < 1\) | [23] |
| \( \beta \) | Rate of spontaneous curing | 0.095 | \(0.03 < \beta < 0.16\) | [16,18,20,48] |
| \( \epsilon \) | Factors leading to infection | 0.2083 | \(0 < \epsilon < 1\) | [11,48] |
| \( r \) | Colonized \( X \) moving to infected \( V \) | 0.2 | \(0 < r < 1\) | [48] |
| \( q \) | Colonized under preventive care \( Y \) moving to infected \( V \) | 0.5 | \(0 < q < 1\) | [48] |
| \( 1 - k \) | % new colonized moving to special preventive care | 0.3 | \(0 < k < 1\) | [48] |
| \( 1 - p \) | Hospital and health-care worker compliance rate | 0.5 | \(0 < p < 1\) | [11,48] |
When $f$ is close to 1, the cost of keeping the plasmid is high and so the bacteria will regress to a non-resistant strain, which makes it easier for the patient.

- $\tau$, antibiotic use alone: Previous antibiotic use or misuse is a risk factor for contracting a VRE infection, including frequency and the length of antibiotic use [11].

- $\alpha$ and $\alpha_p$, transitions between the colonized with and without special preventive care $X$ and $Y$: This includes all the transition factors cited earlier, such as high density of VRE, previous surgeries, and resource limitations.

- $\theta$ and $\theta_t$, transitions between infected patients with or without VRE treatment $V$ and $W$: $\theta$ is the rate of infected who will start VRE treatment and $\theta_t$ represents the rate of infected patients under VRE treatment for which the treatment will be (temporarily) stopped as explained earlier.

- $\beta$, spontaneous curing: VRE infections can vary in severity, and sometimes a patient can be spontaneously/naturally cured over a period of time.

- $\gamma$, rate of curing due to treatment: Antibiotics such as Tygacil and Linezolid can clear the infection. Isolation and compliance with new stethoscopes, washing hands, and limited contact can also help to clear the infection.

- $\epsilon$, factors leading to infection: This encompasses any factor that can lead to an infection including previous antibiotic use, risk factors, such as cancer, organ transplants, gastrointestinal infections, critical surgeries, prior hospital stay, whether immunosuppressives are used, and previous nosocomial infection.

- $r$ and $q$, transitions from the colonized stages $X$ and $Y$ to the infected stages $V$ and $W$: This is a weight that distributes the colonized patients becoming infected into infected with or without VRE treatment.

- $(1 - k)$, transitions from the susceptible stages to the colonized stages: This is a weight that distributes the susceptible patients becoming colonized into the colonized with or without special preventive treatment.

- $(1 - p)$, hospital and health-care worker compliance rate with preventive measures: This includes the compliance with regulations, hand hygiene, contact rate between patients, health-care worker contact rate with patients, probability of contamination per contact, rate of health-care worker/patients, changing of stethoscopes, gowns, and gloves, as well as any preventive measures put in place to clear contamination such as chlorhexidine baths. A lower $p$, that is, a higher $(1 - p)$, leads to a more beneficial impact of special preventive measures.

### 2.4. Mathematical representation of the model

We consider that, on average, the total number of patients in the ICU remains constant. Taking into consideration the transitions between the stages described above as well as the roles played by the parameters, the model is shown in Figure 1. $S, X, Y, V,$ and $W$ denote the ICU patients who are susceptible (VRE free), colonized without special preventing care, colonized under special preventive care, infected without VRE treatment, and infected with VRE treatment, respectively.

The corresponding system of five nonlinear differential equations is given below:

\[
\frac{dS}{dt} = \mu m_1 + \beta Y + \beta X + \beta V + \gamma W - \mu S - (1 - f)(\delta S(V + W + X + (1 - p)Y) + \tau S),
\]
\[
\frac{dX}{dt} = m_2 \mu - \mu X + k(1 - f)(\delta S(X + pY + V + W) + \tau S) + \alpha_p Y - X(\beta + \alpha + (1 - f)\epsilon),
\]
\[
\frac{dY}{dt} = m_3 \mu - \mu Y + (1 - k)(1 - f)(\delta S(X + pY + V + W) + \tau S)
+ \alpha X - Y(\beta + \alpha_p + (1 - f)\epsilon p),
\]
\[
\frac{dV}{dt} = m_4 \mu - \mu V + (1 - f)\epsilon (rX + qpY) + \theta W - (\theta + \beta)V,
\]
\[
\frac{dW}{dt} = (1 - m_1 - m_2 - m_3 - m_4)\mu - \mu W + (1 - f)\epsilon ((1 - r)X + (1 - q)pY)
+ \theta V - (\theta + \gamma)W
\]

with the following initial conditions: \(S(0) = S_0, X(0) = X_0, Y(0) = Y_0, V(0) = V_0, W(0) = W_0,\)
and \(S_0 + X_0 + Y_0 + V_0 + W_0 = 1.\)

### 3. Simulations

The parameters vary within their respective ranges as they differ from one ICU to the other and to account for uncertainties in their values. To represent all possible ICU scenarios, Mathematica was used to develop interactive numerical simulations (Figure 2) of the effect of the variation of each of the 24 parameters within their respective ranges.

For further validation of the model, we looked at extreme cases where some variables and parameters are at critical values.

In Figure 3(a), all colonized patients are immediately put under special preventive care with other parameters around their mean values. This is assuming that the hospital has enough space and resources and that economical factors are not an issue for the patients to continue this care as long as needed. As expected, the infection rate is very low. Figure 3(b) shows a simulation when there is no special preventive care for colonized patients while the other factors remain around the mean values. For example, this is the case for a hospital that does not comply with the CDC’s recommended procedures or is without adequate resources for both the ICU and patients. In this case, the infection rate increases noticeably. Figure 3(c) represents one of the worst-case scenarios:
no colonized patient is able to receive a special preventive care nor is he or she able to obtain any treatment for his or her VRE infections. The other parameters are around their mean values. It is not surprising that the level of infection is significantly higher than in any other scenario. The death rate of a VRE-infected patient would also increase significantly. Figure 3(d) represents one of the best-case scenarios. All colonized and infected patients have unlimited access to special preventive care and VRE treatment with other parameters at their mean values. This scenario assumes the availability of all needed resources for both the patients and the hospital. Also, it is assumed that there are an adequate number of effective drugs that can be used to treat VRE infections. The rate of infection is remarkably low.

4. Parameter impact on the infection at the steady states

4.1. Equilibria

We are now interested in finding the long-term behaviour of the model. We investigate the equilibria of the system of differential equations with $S + X + Y + V + W = 1$ and $0 \leq S \leq 1, 0 \leq X \leq 1, 0 \leq Y \leq 1, 0 \leq V \leq 1, 0 \leq W \leq 1$. 
The parameters vary within their respective ranges. Numerical techniques (Mathematica) were used to numerically solve the system of equations for the equilibria. With a set of parameters the same as that shown in Figure 2, it was found that in the long term, there will be 37% of susceptible patients, 14% of colonized without special preventive care and 34% with preventive care, and 7.5% of infected without VRE treatment, while 7.5% with VRE treatment. The parameters can vary in the qualitative investigation of the parameters with the largest impact to determine ways to control the spread of VRE for each particular ICU.

4.2. Impact of the parameters at the equilibria

We are interested in quantifying the impact of each of the parameters on the long-term total number of VRE-infected patients $V$ and $W$. By introducing a small change on one parameter, we would like to measure the change at the equilibria of the total number of infected patients $V + W$ and then normalize these measures to determine the parameters that are most sensitive. For a given fixed set of the 19 parameters, the sensitivity of the total number of VRE-infected patients $V + W$ to a parameter $n$ at a given value $n_0$ of $n$ is given by the partial derivative $\partial (V + W) / \partial n$ evaluated at $n_0$ then normalized [7,17,43,45]. Numerical approximations represent the summary results when each parameter $n$ is increased or decreased slightly using a set of small percentage values.

Figure 4 shows the amplitudes of the impact of the parameters on the total number of infected patients for similarly normalized changes in parameters; the larger the amplitude is, the greater the impact is. A positive amplitude represents an increase in VRE infection as the corresponding parameter is increased, while a negative amplitude represents a decrease in VRE infection as the corresponding parameter is increased. This helps decide a strategy as to which parameters are to be altered first in order to control VRE or to balance the negative effect of a sudden change in another parameter. For example, $p$, related to the effectiveness of compliance, has a large impact, thus critical for controlling VRE spread. Overall, we found that controllable parameters that were the most sensitive include factors leading to infection $\epsilon$, compliance rate $(1 - p)$, admission rate of

Figure 4. Normalized impact of the parameters on VRE infection with mean parameter values: $m_1 = 0.7, m_2 = 0.1, m_3 = 0.1, m_4 = 0.05, \mu = 0.0956, \delta = 0.29845, f = 0.25, r = 0.302, \alpha_p = 0.1, \alpha = 0.2, \theta_i = 0.1, \theta = 0.2, \beta = 0.095, \gamma = 0.46, \epsilon = 0.2083, r = 0.2, q = 0.5, k = 0.3,$ and $p = 0.5$. 
susceptible patients $m_1$, rate of curing due to treatment $\gamma$, antibiotic use $\tau$, and general admission rate $\mu$. Other parameters include the fitness cost $f$ and the rate of spontaneous curing $\beta$. Small change in $\epsilon, p, \tau, \gamma, f$, and $\beta$ greatly impacts VRE infection and should be the priority for a VRE control strategy in the context of this ICU.

For example, an increase in $\mu$ corresponds to a reduction in the length of stay $1/\mu$, leading to a reduction in contamination and infection instances and thus to a reduction in VRE infection. For a higher value of $\epsilon$, the infection will be rapidly spreading, and patients are quickly moving through the colonized stages to the infected stages. A reduction in $\epsilon$ can lower the virulence of these bacteria. It is clear that as $p$ increases, the compliance rate $(1 - p)$ drops, and the disease will spread further. An overuse or misuse of antibiotics can lead to an increase in the resistance to these drugs, giving the bacteria an advantage against the immune system. An increase in $\gamma$ leads to a decease in the number of infected patients. Similarly, if the fitness cost $f$ increases, the infection rate drops. Indeed, it costs more for the bacteria to reproduce, giving the immune system time to destroy the bacteria and clear the infection. Finally, for $\beta$, as the number of spontaneously cured people increases, the rate of infection decreases.

Although a small change in the level of special preventive care $(1 - k)$ does not appear to have a large impact on the number of infected patients, it is still an important parameter since changes in $k$ are at a larger scale. Moreover, $k$ has a critical role in the outbreak risk as it is shown later in the paper. Finally, the impact of each parameter depends on the combination of parameters used, this is to say the ICU particular environment, though the parameters are independents. Local sensitivity diagrams are indeed different when various sets of parameter values are considered. One should use the ICU’s proper set of parameters and related sensitivity diagram to determine specific strategies to control the parameters.

5. Outbreak risk analysis

In this section, we determine the critical factors that can cause a VRE outbreak. We considered the disease-free state, with no VRE-infected or colonized patients in the ICU. We determined the basic reproduction number $R_0$ of VRE infection as a function of a given set of parameters. The VRE infection is endemic if $R_0 > 1$. We investigated the impact of various parameters on the risk of VRE outbreak. The goal is to manipulate the parameters to ensure that the basic reproductive number is always far below 1, as a good strategy to reduce the outbreak risk. The next generation matrix technique is used to determine $R_0$ [44], and an outline is included in Appendix 1.

5.1. Basic reproductive number

The basic reproduction number for the model is given by

$$R_0 = \frac{1}{2} \left( [k(\beta + \mu + \alpha_1)] + (1 - k)p(\beta + \mu + \alpha) + p(1 - f)\epsilon \right) + \left[ [k(\beta + \mu + \alpha_1)] + (1 - k)p(\beta + \mu + \alpha) + p(1 - f)\epsilon \right]^2 - 4pk(1 - k)[(\beta + (1 - f)p\epsilon + \mu + \alpha)] \left[ \beta + (1 - f)\epsilon + \mu + \alpha - \alpha\alpha_1 \right]^{1/2}.$$

With the exception of a few cases, covered in the next section, simulations of the variation of the values of the basic reproduction number as the parameters vary matched anticipated outbreak risk behaviour. Table 2 presents the examples of combinations of parameter values with and without outbreak for the corresponding ICU.

With the eight parameters kept at mean values, $R_0$ is small, as it is currently the case for most ICUs. For the second case, the compliance rate $(1 - p)$ is dropped and the factors leading to
infection ($\epsilon$) are increased, which leads to an increase in $R_0$. However, the negative effect of $(1 - p)$ and $\epsilon$ was balanced by the positive effect of an increase in admission rate $\mu$ (thus a decrease in the length of stay) and an increase in the fitness cost $f$ (thus harder for the bacteria to reproduce), resulting in $R_0$ staying below 1. The last case has a high value of $R_0$ even with the level of special preventive care $(1 - k)$ at 100% and high rates of admission $\mu$ and of spontaneously curing $\beta$. This is due to the extremely low compliance rate $(1 - p)$ and fitness cost $f$.

### 5.2. Parameter impact on the basic reproduction number

The basic reproduction number depends on eight parameters. Similar to the previous section, sensitivity diagrams shown in Figures 5 quantify these parameter impacts on the outbreak risk. In Figure 5(a), the compliance rate $(1 - p)$ has the largest effect on the basic reproductive number. As $(1 - p)$ decreases, $p$ increases and the basic reproductive number increases the fastest as shown in Figure 5(a), which confirms the results given in Table 2. In addition, this emphasizes the importance of compliance rate in reducing both the total number of infected patients and the outbreak risk. Special preventive care should be increased in order to lower the outbreak risk. A similar analysis can be performed for the other parameters. In particular, the level of special preventive care for newly colonized patients $(1 - k)$, the rate of colonized moved out of special preventive care ($\alpha$), and the factors leading to infection ($\epsilon$) have a significant impact on $R_0$.

Figure 5(b) represents an ICU with higher factors leading to infection and lower level of special preventive care, compliance rate, and admission rate. It shows an example of how the impact of the parameters can vary significantly for each combination of parameters.

The level of special preventive care for newly colonized patients, $(1 - k)$, stands out with a peculiar behaviour: in Figure 5(a), an increase in $k$, that is, a decrease in $(1 - k)$, has a very high impact on decreasing the basic reproduction number $R_0$, while in Figure 5(b), an increase in $k$, that is, a decrease in $(1 - k)$, increases $R_0$. This is also visible through simulations performed on both the values of $R_0$ and the total number of infected patients ($V + W$).

### Table 2. Basic reproduction number for a set of parameter values.

| ICU context                                | $\mu$ | $f$  | $p$  | $\alpha$ | $\beta$ | $\epsilon$ | $(1 - p)$ | $(1 - k)$ | $R_0$ |
|-------------------------------------------|-------|------|------|-----------|---------|------------|-----------|-----------|-------|
| Mean parameter values                     | 0.0956| 0.25 | 0.1  | 0.2       | 0.095   | 0.2083     | 0.5       | 0.8       | 0.22  |
| Balanced change in parameter values       | 0.1198| 0.347| 0.1  | 0.2       | 0.094   | 0.858      | 0.3       | 0.8       | 0.55  |
| Extreme and unbalanced changes            | 0.14  | 0    | 0.5  | 0.5       | 0.16    | 1          | 0         | 1         | 1.8   |

Figure 5. Normalized impacts of the parameters on the outbreak risk. (a) Mean parameter values: $\mu = 0.0956, f = 0.25, \alpha_p = 0.1, \alpha = 0.2, \beta = 0.095, \epsilon = 0.2083, k = 3,$ and $p = 0.5$. (b) Special set of parameter values: $\mu = 0.036, f = 0.25, \alpha_p = 0.324, \alpha = 0.035, \beta = 0.095, \epsilon = 1, k = 0.94,$ and $p = 0.74$. 
5.3. Strategies to minimize outbreak risk

Earlier in the paper, we discussed ways to control the number of VRE-infected patients. In this section, we discuss strategies to prevent VRE outbreaks with a focus on the parameters $k$ and $p$ for the reasons described above.

5.3.1. Optimal special preventive care $(1 - k)$

From the simulations on the basic reproduction number, $R_0$ can either increase or decrease with an increase in $k$ near a critical value. This critical value of $k$ is determined by using the derivative of $R_0$ with respect to $k$. Given a specific set of parameters, the critical value for $k$ is given below:

$$k = \left( \frac{\beta}{2} + \frac{1}{2}(1-f)p\epsilon + \frac{\mu}{2} - \frac{1}{2}p(\alpha + \beta + (1-f)\epsilon + \mu) 
- p(\alpha + \beta + (1-f)\epsilon + \mu)(-\beta - (1-f)p\epsilon - \mu + p(\alpha + \beta + (1-f)\epsilon + \mu) 
- \alpha_1) + \frac{\alpha_1}{2} + 2p\alpha_1 - 2p(\alpha + \beta + (1-f)\epsilon + \mu)(\beta + (1-f)p\epsilon 
+ \mu + \alpha_1) \right) (-p(\alpha + \beta + (1-f)\epsilon + \mu)(-\beta - (1-f)p\epsilon - \mu 
+ p(\alpha + \beta + (1-f)\epsilon + \mu) - \alpha_1) + 4p\alpha_1 - 4p(\alpha + \beta 
+ (1-f)\epsilon + \mu)(\beta + (1-f)p\epsilon + \mu + \alpha_1) + (-\beta - (1-f)p\epsilon - \mu 
+ p(\alpha + \beta + (1-f)\epsilon + \mu) - \alpha_1)(\beta + (1-f)p\epsilon + \mu + \alpha_1)).$$

This threshold value $k$ is always a function of seven parameters. For the mean parameter values, the optimal value of $k$ is 0.3978. This means that a good control of the outbreak risk can be achieved by having close to 60% of newly colonized patients under special preventive care. A practical explanation is that with 100% under special preventive care, the larger number of patients can offset the gain made through the preventive care since the probability of incidents leading to contamination will be increased as a result of direct or indirect contacts between patients, in particular, for high-risk patients. On the other hand, if a hospital is not able to get $k$ to its threshold value, other parameters should be controlled to bring the threshold value of $k$ to an accessible level. For example, if the maximum value of $k$ that a certain hospital can obtain is 0.50, $p$ can be adjusted to make the new threshold value of $k$ closer to 0.50.

5.3.2. Outbreak diagram with both $k$ and $p$

It is best to simultaneously analyse $k$ and $p$ to determine how to control the outbreak risk. As $p$ increases, that is, $(1 - p)$ decreases, the compliance of the hospital and the staff with the guidelines is worse. As $k$ increases, $(1 - k)$ decreases and thus fewer high-risk colonized patients are sent to special preventive care. Figure 6 shows contour maps of the basic reproduction number $R_0$ as a function of $p$ and $k$ for two particular sets of the other six parameters. Figure 6(a) shows a worst-case scenario: maximum values of the infection rate and the transitions between the colonized stages, and no fitness cost but with high admission and spontaneously curing rates. The outbreak risk is higher in large ranges of the $k$ and $p$ values. The diagram shown in 6(b) shows low values of $R_0$ along all possible values of $k$ and $p$ when an extremely low infection rate and a high fitness cost but a low spontaneously curing rate are used.
6. Conclusion

The new mathematical model of a VRE-infested ICU is based on the distinction between five VRE-related stages: susceptible, colonized, colonized with special preventive care, infected, and infected undergoing VRE treatment. The model highlights the importance of the distinction between VRE colonization and infection, as well as between the use of special preventive care, compliance rate, and factors leading to infection and treatment cycles. Thus, the model is more representative of actual situations in ICUs. The analysis focused on the simultaneous roles of multiple parameters instead of on a single one. Realistic parameter values were determined using data from research journals and professional health institutions and vary within specific ranges to account for uncertainties of the values and for any ICU scenario. The model, the subsequent analysis, and the computer simulations accurately represented various expected situations inside an ICU. Moreover, the model allowed the investigation of good control strategies to reduce VRE infections and prevent VRE outbreaks, without the risk involved in clinical testing. The values of parameters with significant impacts to control VRE spread and to reduce the outbreak risk.
were identified. Some of the crucial parameters include special preventive care, compliance with health-care standards, length of stay, treatment cycles, and antibiotic use or misuse. For example, it is shown that in certain ICUs, one can lower the risk of outbreak by requiring 60% of patients newly tested as colonized to be under special preventive care instead of 100% and thus at a lower economical cost. Figure 7 shows that in addition the total number of colonized and infected is also lower with just 60% instead of the assumed 100% level of special preventive care. However, if an ICU does not have the resources to achieve 60%, the model suggests alternative ways (using the sensitivity analysis diagrams), that is, control of other parameters, to prevent the spread and outbreaks with a lower special preventive care level.

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Appendix 1: New generation matrix and the basic reproduction number

Consider the disease-free steady states \( \bar{S}, \bar{X}, \bar{Y}, \bar{V}, \) and \( \bar{W}, \) solutions of the algebraic system for the equilibria, and the corresponding Jacobian matrix \( J \) at the equilibria:

\[
\hat{S} = 1, \quad \hat{X} = \hat{Y} = \hat{V} = \hat{W} = 0, \quad J = \begin{pmatrix} -\mu & N \\ 0 & -M \end{pmatrix}.
\]

\( N \) is given by \( N = (\beta - (1 - f)\delta, \beta - (1 - f)p\delta, \beta - (1 - f)\delta, \gamma - (1 - f)\delta). \) \( M \) is the matrix representing the transitions that involve colonized and infected patients and is defined by

\[
M = \begin{pmatrix} A_{11} & A_{12} \\ A_{21} & A_{22} \end{pmatrix},
\]

\[
A_{12} = (1 - f)\delta \begin{pmatrix} k \\ 1 - k \end{pmatrix}, \quad A_{21} = (1 - f)\epsilon \begin{pmatrix} 0 \\ 1 \end{pmatrix}, \quad A_{22} = \begin{pmatrix} -\beta - \mu \\ 0 \end{pmatrix}.
\]

The basic reproduction number is given by the spectral radius of the matrix \( FG^{-1} \), where \( F \) is the new infection matrix representing transitions leading to new infections, and \( G \) is the matrix representing all other transitions, both extracted from the matrix \( M \) [44]. \( F \) and \( D \) are given by

\[
F = (1 - f)\delta \begin{pmatrix} k \\ 1 - k \end{pmatrix} \begin{pmatrix} k \\ (1 - k)p \\ (1 - k) \end{pmatrix} \begin{pmatrix} k \\ 0 \\ 0 \end{pmatrix} \begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}.
\]

\[
G = \begin{pmatrix} \alpha + \beta + (1 - f)\epsilon + \mu & -\alpha - \alpha_p & 0 & 0 \\ -\alpha & \beta + (1 - f)p\epsilon + \mu + \alpha_p & 0 & 0 \\ 0 & 0 & \beta + \mu & \gamma + \mu \end{pmatrix}.
\]

The product of \( F \) with the inverse matrix \( G^{-1} \) is given by

\[
FG^{-1} = \begin{pmatrix} A & B & 0 & 0 \\ C & D & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix},
\]

\[
A = \frac{(1 - f)k\delta(\beta + (1 - f)p\epsilon + \mu + \alpha_1)}{-\alpha\alpha_1 + (\alpha + \beta + (1 - f)\epsilon + \mu)(\beta + (1 - f)p\epsilon + \mu + \alpha_1)},
\]

\[
B = \frac{(1 - f)kp\delta(\beta\alpha_1 - \mu\alpha_1)}{(\beta + \mu)(-\alpha\alpha_1 + (\alpha + \beta + (1 - f)\epsilon + \mu)(\beta + (1 - f)p\epsilon + \mu + \alpha_1))},
\]

\[
C = \frac{(1 - f)(1 - k)\delta(-\alpha\beta - \alpha\mu)}{(\beta + \mu)(-\alpha\alpha_1 + (\alpha + \beta + (1 - f)\epsilon + \mu)(\beta + (1 - f)p\epsilon + \mu + \alpha_1))},
\]

\[
D = \frac{(1 - f)(1 - k)p\delta(\alpha + \beta + (1 - f)\epsilon + \mu)}{-\alpha\alpha_1 + (\alpha + \beta + (1 - f)\epsilon + \mu)(\beta + (1 - f)p\epsilon + \mu + \alpha_1)}.
\]

Let \( \phi \) and \( \psi \) be as follows:

\[
\phi = \beta + \mu + \alpha_p + (1 - f)p\epsilon, \quad \psi = \beta + \mu + \alpha + (1 - f)\epsilon.
\]
The eigenvalues of $FG^{-1}$ are then reduced to find the eigenvalues $\lambda_1$ and $\lambda_2$ of the matrix $E$:

$$E = \begin{pmatrix} k\phi & kp\alpha \\ (1-k)\alpha & (1-k)p\psi \end{pmatrix},$$

$$2\lambda_1 = (k\phi + (1-k)p\psi) - (k\phi + (1-k)p\psi)^2 - 4[k(1-k)p(\phi\psi - \alpha\alpha_p)]^{1/2},$$

$$2\lambda_2 = (k\phi + (1-k)p\psi) + (k\phi + (1-k)p\psi)^2 - 4[k(1-k)p(\phi\psi - \alpha\alpha_p)]^{1/2}. $$

It is not difficult to see that $\lambda_2$ is larger in absolute value because $p$ and $k$ are always between zero and 1. After substitutions and simplifications, the basic reproduction number $R_0$ is given by

$$2R_0 = [k(\beta + \mu + \alpha_1) + (1-k)p(\beta + \mu + \alpha) + p(1-f)\epsilon]$$

$$+ [[k(\beta + \mu + \alpha_1) + (1-k)p(\beta + \mu + \alpha) + p(1-f)\epsilon]^2$$

$$- 4pk(1-k)(\beta + (1-f)p\epsilon + \mu + \alpha_p)[\beta + (1-f)\epsilon + \mu + \alpha - \alpha\alpha_1)]^{1/2}. $$