Comparison of screening for methicillin-resistant *Staphylococcus aureus* (MRSA) at hospital admission and discharge

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Abstract

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a significant contributor to the growing concern of antibiotic resistant bacteria, especially given its stubborn persistence in hospital and other health care facility settings. In combination with the general persistence of *S. aureus* (colloquially referred to as staph), MRSA presents an additional barrier to treatment and is now believed to have colonized two of every 100 people worldwide. According to the CDC, MRSA prevalence sits as high as 25-50% in countries such as the United Kingdom and the United States. Given the resistant nature of staph as well as its capability of evolving to compensate antibiotic treatment, controlling MRSA levels is more a matter of precautionary and defensive measures. The subject of the following research is the method of "search and isolation" which seeks to isolate MRSA positive patients in a hospital so as to decrease infection potential. Although this strategy of search and isolate is straightforward, the question of just whom to screen is of practical importance. We compare screening at admission to screening at discharge. To do this, we develop a mathematical model and use both stochastic and deterministic simulations to determine MRSA endemic levels in a hospital with either control measure implemented. The more successful control measure will better control endemic potential and proliferation of MRSA.

1 Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a bacterium that colonizes the skin of human beings as well as their proximate environment. Although this is intrinsically true for staph, antibiotic resistance has made eradication much more difficult. The evolution of antibiotic resistance in staph, however, is not a new development. The discovery of penicillin in the 1920s allowed for a very effective treatment for *S. aureus* and other infectious diseases, remaining effective until only a few decades later when Bondi and Dietz identified the enzyme penicillinase being produced by staph, completely nullifying any power of the drug [2]. Currently, more than 90% of *S. aureus* cultures are resistant to penicillin [20]. Methicillin was developed as a response to penicillin resistance, but as early as the 1960s, the same decade it was developed, MRSA had already been isolated in the United Kingdom. Fifty years following initial isolation, MRSA has spread worldwide and has developed potent endemicity in health care facilities across the United States and Europe. Currently, approximately 90,000 Americans suffer from MRSA infections every year with a mortality rate of 22% [29].

Since MRSA is both the most prevalent and the most destructive in hospital settings, this is the context which the following paper assumes. Screening and isolation is a very common control strategy implemented in hospitals battling MRSA outbreaks. Screening typically involves the swabbing of the nares of a patient to determine colonization, and is performed at admission. A positive result yields the placement of the patient into a region of the hospital where bacterial spread is hindered, aptly termed an isolation unit (IU). Here, further transmission of the bacteria is assumed to be zero. Preference may or may not be given to certain patients with higher susceptibility to MRSA carriage, including any individuals who have a history of hospital admission, have a history of antibiotic use, belong to a certain age group, have an open wound or skin infection, etc. However, screening at discharge has been proposed as an alternative to screening at admission.

Several mathematical models have attempted to capture the transmission dynamics of MRSA in hospitals. Chamchod and Ruan present a compartmentalized model for MRSA that considers patients as either uncolonized, colonized, or infectious [6]. Health care workers (HCWs) exist in their own compartments as either contaminated or uncontaminated and behave as vectors for the bacteria. Chamchod and Ruan consider MRSA transmission dynamics in light of antibiotic usage and subsequent resistance. Patients are considered at a higher risk of developing MRSA if they've a history of antibiotic usage. Cooper et al. consider additionally the contributions of the community to endemic levels in hospitals [7]. However, the community that Cooper et al. considers is comprised entirely of previous patients of the hospital. The authors highlight that timing of intervention, resource provision, isolation practices, and the correct combination of procedures is the key to successful eradication. Bootsma et al. constructs two models to study MRSA transmission: one model considers transmission within a single hospital, while another model considers transmission within a system of hospitals [3]. In all the aforementioned models, screening, if any occurred, is performed at admission.

MRSA is classified in accordance with where it originates: community-acquired MRSA (CA-MRSA) and hospital-acquired MRSA (HA-MRSA). As a result of its persistence and antibiotic resistance, MRSA is able to maintain endemic rates within health care facilities for extended periods of time. MRSA epidemics in hospitals are responsible for the majority of deaths attributed to the bacteria, and its endemicity yields exorbitant costs of treatment and precautions in lieu of effective antibiotic treatment.

Hospitals with high endemic rates become sources of infection instead of facilities for recovery. Consequently, the attention of this research focuses on HA-MRSA only.

1.1 Epidemiology

One aspect deserving elaboration is the notion of colonization. A patient is considered colonized when the bacteria is present on his physical person. Common places include the nares, throat, and groin [18]. Robicsek et al. estimate that MRSA colonization half-life in a patient can be up to 40 months [24].

Carrying the bacteria is different from being infected. Infection occurs when MRSA is allowed to enter the body, typically by way of skin lesions or wounds. Thus, from this information it can be inferred that health care workers (HCWs) are the main carriers of MRSA, as they interact with individual patients the most and are likely to be contaminated for longer periods of time due to continuous exposure to the bacteria [1]. Following the example of Chamchod and Ruan, HCWs will be considered separate from the patient population and treated as vectors of the bacteria.

1.2 Screening strategies

Screening is used to detect patients who have been colonized by MRSA. There is no unique screening procedure followed by hospitals in general. Molecular techniques, such as polymerase chain reaction (PCR) methods, are generally faster and more accurate in comparison to culture techniques. Nonetheless, Kunori et al. estimates that the former technique is more expensive than the latter [19]. For the purposes of our study, we assume that the hospital uses rapid MRSA testing. The question of just how many patients should be screened is important. Universal screening-at-admission is costlier and generally inefficient. Roth et al. found that universal screening-at-admission costs over twice as much as compared to alternative screening methods [25]. One such common alternative is targeted screening, whereby patients deemed at high-risk of developing MRSA colonization/infection are screened. Such patients include those with frequent hospital stays, a history of antibiotic usage, or are hospitalized with skin wounds/lesions on their skin.

1.3 Research Question

This article extends the mean field approach of MRSA models to include novel aspects with respect to screening and isolation processes. Typical methods of screening occur only at admission. We introduce the "screening-at-discharge" method, which will "flag" patients at discharge if they are colonized with MRSA. Upon readmission, flagged patients are moved to isolation. Our final goal is to determine which strategy is more effective in reducing MRSA endemicity.

2 Methodology

2.1 Baseline model

Our model considers a town of $58,000$ with a single hospital of 600 beds and a health care staff of 150 HCWs [6]. For the baseline model, patients are considered to be uncol-

onized (U), colonized (C), or infected (I). A patient is colonized when MRSA bacteria is present on his/her body, but the bacteria has not progressed to infection. Health care workers (HCWs) are considered to be either uncontaminated (H) or contaminated (H_C).

Admitted patients are either colonized or infected with probabilities λ_C and λ_I, respectively; they are uncolonized, otherwise. Our baseline model is represented by the following system of ordinary differential equations:

$$\begin{aligned}
\frac{dH}{dt} &= \delta H_C - \hat{\beta}_1 H \frac{C}{N} - \hat{\beta}_2 H \frac{I}{N} \\
\frac{dH_c}{dt} &= \hat{\beta}_1 H \frac{C}{N} + \hat{\beta}_2 H \frac{I}{N} - \delta H_c \\
\frac{dU}{dt} &= (1 - \lambda_C - \lambda_I)\Lambda - (\mu_U + \gamma_U)U - \beta_1 U \frac{C}{N} - \beta_2 U \frac{H_c}{N} - \beta_3 U \frac{I}{N} + \alpha C \\
\frac{dC}{dt} &= \lambda_C \Lambda - (\mu_C + \gamma_C)C + \beta_1 U \frac{C}{N} + \beta_2 U \frac{H_c}{N} + \beta_3 U \frac{I}{N} - (\phi + \alpha)C \\
\frac{dI}{dt} &= \lambda_I \Lambda - (\mu_I + \gamma_I)I + \phi C
\end{aligned} \tag{1}$$

where β_1 denotes the transmission rate between colonized and uncolonized patients, β_2 refers to the transmission rate between contaminated HCWs and uncolonized patients, and β_3 is the transmission rate between infected and uncolonized patients. An uncolonized patient must first be colonized before becoming infected. μ and γ are used to denote death and discharge/treatment rates of each compartment. ϕ is the rate at which colonized patients become infected. Colonized patients are decolonized at a rate of α; thus $1/\alpha$ captures the average time of decolonization. $1/\delta$ gives the average time an HCW remains contaminated. $\hat{\beta}_1$ is the rate of contamination between uncontaminated HCWs and colonized patients, while $\hat{\beta}_2$ denotes the transmission efficiency between uncontaminated HCWs and infected patients.

The total population (N) is given as the sum of total HCWs (N_H) and total patients (N_P). N_H is assumed constant, as well as N_P. This latter assumption can be made with the correct choice of Λ, or the rate at which patients are admitted into the hospital. A patient is admitted into the hospital whenever an existing patient leaves, either by death or discharge. For the baseline model, $\Lambda = (\mu_U + \gamma_U)\,U + (\mu_C + \gamma_C)\,C + (\mu_I + \gamma_I)\,I$. With these assumptions, total population within the hospital is constant.

Patients and HCWs are assumed to mix homogeneously.Strictly speaking, the assumption of homogeneous mixing can be challenged, since most patients are confined to their rooms for the majority of the time and do not necessarily contact other patients directly. However, they may be in contact with equipment and surfaces, and thus indirectly contaminate both HCWs and other patients. We consider these indirect contacts when calculating transmission rates.

There are two assumed mechanisms of contamination for uncontaminated health care workers. The first mechanism is contact with colonized patients while the second mechanism is contact with infected patients. We assume that a health care worker does not become contaminated from other HCWs [27][4]. Because it is possible for a HCW to become contaminated more than once in the same day, we do not account for frequency of particular patient contacts.

The baseline compartmental model is shown in the following diagram:

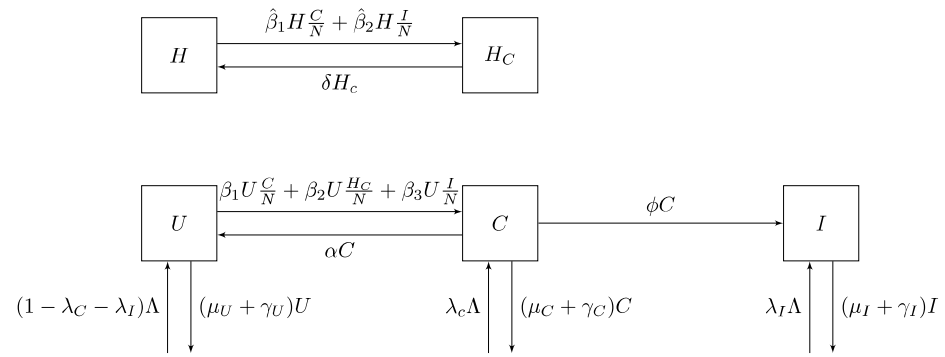

Figure 1: Baseline model diagram.

2.2 Screening at admission

Next, we consider screening at admission. We maintain the structure of the baseline model with the addition of the isolation compartment, denoted by Z, referred to as the isolation unit (IU). For simplicity, we assume that the IU has infinite capacity. If a patient is tested positive for MRSA at admission, he/she will be moved to the IU for the remainder of his/her time in the hospital. No distinction is made between infected and colonized patients when screened for MRSA. Only newly admitted patients may be placed in the IU, with the exception being an identified infected patient in the hospital according to some rate κ. $1/\kappa$ is taken to be the sum of the average incubation period of MRSA infection (4.5 days) and the average duration of culture and sensitivity testing (2.5 days according to [15]). It is assumed that patients are screened at admission with probability ρ. The model representing the aforementioned MRSA hospital dynamics is as follows

$$\begin{aligned}
\frac{dH}{dt} &= \delta H_C - \hat{\beta}_1 H\frac{C}{N} - \hat{\beta}_2 H\frac{I}{N}\\
\frac{dH_c}{dt} &= \hat{\beta}_1 H\frac{C}{N} + \hat{\beta}_2 H\frac{I}{N} - \delta H_c\\
\frac{dU}{dt} &= (1-\lambda_C-\lambda_I)\Lambda - (\mu_U+\gamma_U)U - \beta_1 U\frac{C}{N} - \beta_2 U\frac{H_c}{N} - \beta_3 U\frac{I}{N} + \alpha C\\
\frac{dC}{dt} &= \lambda_C\Lambda(1-\rho) - (\mu_C+\gamma_C)C + \beta_1 U\frac{C}{N} + \beta_2 U\frac{H_c}{N} + \beta_3 U\frac{I}{N} - (\phi+\alpha)C\\
\frac{dI}{dt} &= \lambda_I\Lambda(1-\rho) - (\mu_I+\kappa)I + \phi C\\
\frac{dZ}{dt} &= (\lambda_C+\lambda_I)\Lambda\rho + \kappa I - (\mu_Z+\gamma_Z)Z
\end{aligned} \tag{2}$$

For this model, $\Lambda = (\mu_U+\gamma_U)\,U + (\mu_C+\gamma_C)\,C + (\mu_I)\,I + (\mu_Z+\gamma_Z)\,Z$. Note that patients infected with MRSA are not discharged, but are treated in isolation. As with the baseline model, the population remains constant. Note also that we omit consideration of Z regarding transmission between contaminated and uncontaminated groups. This is because we assume that $Z << N$. Admitted patients tested positive for MRSA move into the IU at a rate given by $(\lambda_C+\lambda_I)\rho\Lambda$. Patients in isolation are assumed to die at a rate of μ_Z and are discharged/treated at a rate of γ_Z. Patients infected with MRSA are not treated outside the IU. The schematic for this system is shown on the next page.

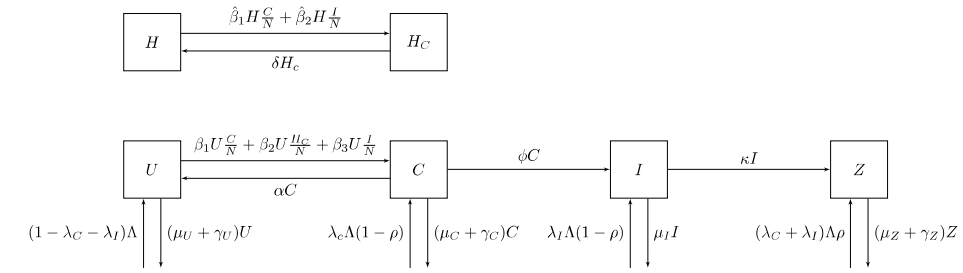

Figure 2: Screening at admission model diagram.

2.3 Screening at discharge

In order to reformulate the model so as to consider screening at discharge, we compartmentalize the community in terms of flagged (F) and unflagged (F_U) individuals. Patients are flagged if they test positive for MRSA at discharge, and are unflagged otherwise. Patients who are flagged, when readmitted to the hospital, are placed in the isolated compartment. Our model becomes:

$$\begin{aligned}
\frac{dH}{dt} &= \delta H_C - \hat{\beta}_1 H\frac{C}{N} - \hat{\beta}_2 H\frac{I}{N} \\
\frac{dH_C}{dt} &= \hat{\beta}_1 H\frac{C}{N} + \hat{\beta}_2 H\frac{I}{N} - \delta H_c \\
\frac{dU}{dt} &= (1-\lambda_C-\lambda_I)\Lambda\Big(\frac{F_U}{kF+F_U}\Big) - (\mu_U+\gamma_U)U - \beta_1 U\frac{C}{N} - \beta_2 U\frac{H_C}{N} \\
&\quad - \beta_3 U\frac{I}{N} + \alpha C \\
\frac{dC}{dt} &= \lambda_C\Lambda\left(\frac{F_U}{kF+F_U}\right) - (\mu_C+\gamma_C)C + \beta_1 U\frac{C}{N} + \beta_2 U\frac{H_C}{N} + \beta_3 U\frac{I}{N} \\
&\quad - (\phi+\alpha)C \\
\frac{dI}{dt} &= \lambda_I\Lambda\left(\frac{F_U}{kF+F_U}\right) - (\mu_I+\kappa)I + \phi C \\
\frac{dZ}{dt} &= \Lambda\Big(\frac{kF}{kF+F_U}\Big) + \kappa I - (\mu_Z+\gamma_Z)Z \\
\frac{dF}{dt} &= \rho(\gamma_C C + (1-\tau)\gamma_Z Z) - \Lambda\Big(\frac{kF}{kF+F_U}\Big) - \mu_F F \\
\frac{dF_U}{dt} &= (1-\rho)(\gamma_C C + (1-\tau)\gamma_Z Z) + \gamma_U U + \tau\gamma_Z Z - \Lambda\left(\frac{F_U}{kF+F_U}\right) \\
&\quad - \mu_{F_U} F_U + b_{F_U}
\end{aligned} \tag{3}$$

In addition to the previous model, success of patient treatment is included. Treatments are successful of complete eradication with probability τ and otherwise fail with probability $1-\tau$. We also consider the factor k, which represents the number of times more likely that a flagged patient is to be readmitted to the hospital as compared to an unflagged patient.

Consequently, the total admission into the hospital is given by $\Lambda = (\mu_U+\gamma_U)\,U + (\mu_I)\,I + (\mu_C+\gamma_C)\,C + (\mu_Z+\gamma_Z)\,Z$ in order to retain a constant hospital population. The unflagged population is comprised of the wider community as well as patients who were not identified as MRSA-positive when they were discharged from the hospital.

Recruitment rate and death rate for the unflagged group are denoted by μ_{F_U} and b_{F_U}, respectively. Individuals in the flagged compartment die at a rate of μ_F. The birth and death rates of the community were chosen so that the community population is asymptotically constant. The disease dynamics of this model is represented graphically as follows:

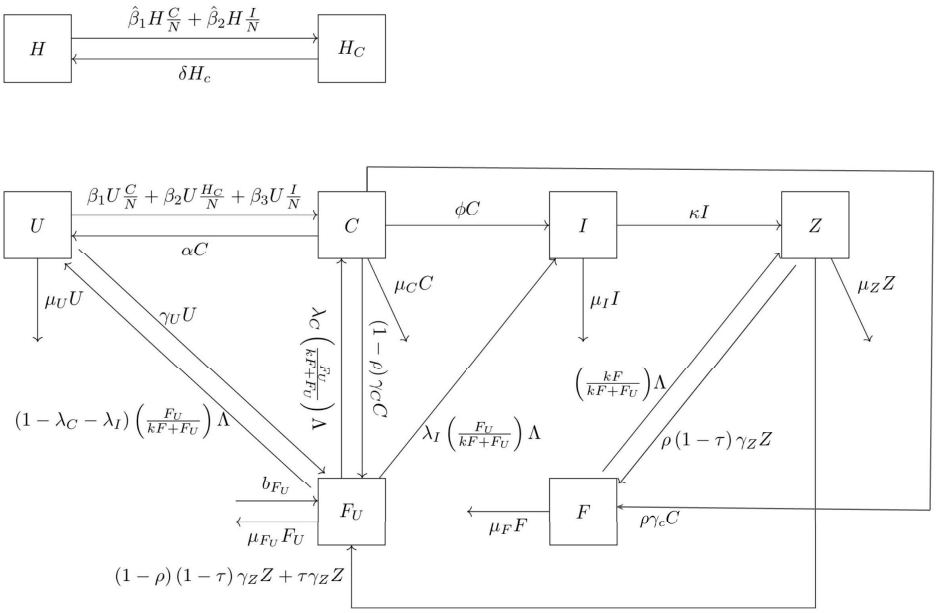

Figure 3: Screening at discharge diagram.

2.4 Parameter estimation

Several parameters discussed prior deserve further elaboration, contained within this subsection. For β_2, the transmission rate between contaminated HCWs and uncolonized patients, we assumed that patients could not be colonized more than once during a single day. We further assumed that patients, on average, will have contact with three distinct HCWs any given day. [14] reports that HCWs make 7.6 contacts per patient per day. If HCWs make 84 patient contacts every day, this means that each HCW will have 11.05 unique patient contacts every day. Thus, β_2 is calculated to be the product of unique patient contacts and the transmission efficiency. On the other hand, HCWs can be contaminated more than once in any given day, so we disregard unique patient contacts when making this calculation. That is, transmission rate from colonized patients to uncontaminated HCWs, denoted by $\hat{\beta}_1$, is the product of total contacts per day and the transmission efficiency. The transmission efficiency between infected patients and uncontaminated HCWs is double that of colonized patients and uncolonized HCWs.

$1/\delta$ gives the average time an HCW remains contaminated. Because data for this term is either lacking or varies greatly (e.g. an HCW can become decontaminated by merely washing his hands or an HCW can be colonized with MRSA for weeks at a time), we computed δ numerically based on the findings of Albrich and Harbarth (2008), who found that average MRSA carriage amongst HCWs is around 4.6% [1]. Furthermore, γ_Z and μ_Z are assumed to be averages of the discharge/treatment and death rates, re-

spectively, of colonized and infected patients. That is, $\gamma_Z = \frac{\gamma_I + \gamma_C}{2}$ and $\mu_Z = \frac{\mu_I + \mu_C}{2}$.

The term κ represents the rate at which patients develop MRSA infection, are identified as having MRSA, and subsequently isolated. Assuming a 4.5-day incubation period, followed by a 2.5-day period for culture and susceptibility testing, our value of κ comes out to 0.13. This value is close to the value of 0.14 used by [3]. Since patients who develop infection are identified and isolated over the span of 7 days and are assumed to stay in the hospital for 16 days, each transmission rate concerning infected patients is multiplied by a factor of 7/16, as they are assumed to be no longer infectious in isolation.

k represents the number of times more likely that a flagged patient is to be readmitted to the hospital as compared to an unflagged patient. Stochastic simulations revealed that regardless of our value of k, the rate of patient admission from the flagged compartment would approach a stable equilibrium. This follows intuitively from the fact that, for large k, F will become small quickly and remain small for $t \to \infty$. On the other hand, if k is small, F will remain large and remain so for all t. The death rate for either community compartment is just the average lifespan of an American, and the birth rate of the unflagged compartment is chosen so that the population of the community is asymptotically constant.

3 Analysis

3.1 Disease Free Equilibrium and Reproductive Number

3.1.1 Baseline model

The rate of patients being admitted per unit time Λ is a function of the number of patients leaving the hospital, in order to retain a constant hospital patient population. We should have

$$\Lambda = \omega_U U + \omega_C C + \omega_I I \tag{4}$$

where ω_J is the sum of the death (μ_J) and discharge (γ_J) rates of compartment J, i.e. $\omega_J = \gamma_J + \mu_J$.

For the system of equations found in (1), a disease-free equilibrium (DFE) does not exist when either $\lambda_C > 0$ or $\lambda_I > 0$. There are proportions of colonized and infected patients, given by the probabilities λ_C and λ_I, being admitted at each time step. This forbids the existence of a state without any contaminated patient. Therefore, we consider the case where all new patients are uncolonized ($\lambda_I = \lambda_C = 0$) in order to analyze the potential spread of MRSA bacteria within the hospital and calculate an adjusted reproduction number.

Equating the right hand side of system (1) to zero with $\lambda_C = \lambda_I = 0$, the system at DFE has conditions given by

$$\begin{aligned} H^* &= N_H \\ U^* &= N_P \\ {H_C}^* = C^* &= I^* = 0 \end{aligned} \tag{5}$$

To calculate the basic reproduction number R_0 of this adjusted system, we employ the next-generation matrix method [11, 30]. The basic reproduction number is the largest eigenvalue or spectral radius of FV^{-1}, where F and V are the Jacobian matrices

Parameter definition	**Symbol**	**Values**	**Reference**
Total number of patients	N_P	600	N/A
Total number of HCWs	N_H	150	N/A
Prob. that admitted patient is colonized	λ_C	0.0374	[13]
Prob. that admitted patient is infected	λ_I	0.0067	[26]
Death rate of uncolonized patients	μ_U	5.58x10^{-5} day^{-1}	[16]
Death rate of colonized patients‡	μ_C	8.25x10^{-5} day^{-1}	[21]
Death rate of infected patients	μ_I	4.87x10^{-4} day^{-1}	[23]
Death rate of isolated patients‡‡	μ_Z	2.85x10^{-4} day^{-1}	estimated
Death rate of unflagged individuals***	μ_{F_U}	3.48x10^{-5} day^{-1}	N/A
Death rate of flagged individuals	μ_F	3.48x10^{-5} day^{-1}	N/A
Birth rate of community	b_{F_U}	2.018 day^{-1}	N/A
Discharge rate of uncolonized patients	γ_U	0.189 day^{-1}	[13]
Discharge rate of colonized patients	γ_C	0.143 day^{-1}	[10]
Treatment rate of infected patients	γ_I	0.063 day^{-1}	[12], [17], [8]
Treatment rate of isolated patients	γ_Z	0.1015 day^{-1}	estimated
Decontamination rate of HCWs	δ	1.813 day^{-1}	[14]
Decolonization rate of colonized patients	α	0.001 day^{-1}	[21], [6]
Progression rate from colonized to infected	ϕ	0.04 day^{-1}	[6]
Progression rate from infected to isolated	κ	0.13 day^{-1}	estimated
Prob. of successful treatment	τ	0.68	[22]
Screening probability	ρ	varies	N/A

Table 1: Parameter definitions, values, and references

of vectors $\mathscr{F}$ and $\mathscr{V}$, evaluated at the disease free equilibrium of the system (5).

Specifically, $\mathscr{F}$ is a matrix of terms that account for newly contaminated patients and HCWs, while $\mathscr{V}$ contains terms corresponding to the transitions and outflow of patients and HCWs from these compartments. Recall that newly sick individuals are going to either the contaminated HCW compartment, H_C, or to the colonized patient compartment, C. We have

$$\mathscr{F} = \begin{pmatrix} \hat{\beta}_1 H \frac{C}{N} + \hat{\beta}_2 H \frac{I}{N} \\ \beta_1 U \frac{C}{N} + \beta_2 U \frac{H_c}{N} + \beta_3 U \frac{I}{N} \\ 0 \\ 0 \\ 0 \end{pmatrix} \quad \text{and} \quad \mathscr{V} = \begin{pmatrix} \delta H_c \\ \omega_C C + \alpha C + \phi C \\ \omega_I I - \phi C \\ \hat{\beta}_1 H \frac{C}{N} + \hat{\beta} H \frac{I}{N} - \delta H_c \\ -\Lambda + (\mu_U + \gamma_U) U - \alpha C + \\ \quad \beta_1 U \dfrac{C}{N} + \beta_2 U \dfrac{H_c}{N} + \beta_3 U \dfrac{I}{N} \end{pmatrix}$$

Parameter definition	Symbol	Parameter values	Reference
Rate of patient colonization after contact w/colonized patients	β_1	0.27 day^{-1}	[14], [9]
Rate of patient colonization after contact w/contaminated HCWs	β_2	1.68 day^{-1}	[14]
Rate of patient colonization after contact w/infected patients	β_3	0.03 day^{-1}	[12]
Rate of HCW contamination after contact w/colonized patients	$\hat{\beta}_1$	0.27 day^{-1}	[14], [28]
Rate of HCW contamination after contact w/infected patients	$\hat{\beta}_2$	0.24 day^{-1}	estimated

Table 2: Transmission rates, values, and references

Furthermore, the F and V matrices are

$$F = \begin{pmatrix} 0 & \frac{\hat{\beta}_1 N_H}{N_H+N_P} & \frac{\hat{\beta}_2 N_H}{N_H+N_P} \\ \frac{\beta_2 N_P}{N_H+N_P} & \frac{\beta_1 N_P}{N_H+N_P} & \frac{\beta_3 N_P}{N_H+N_P} \\ 0 & 0 & 0 \end{pmatrix} \quad \text{and} \quad V = \begin{pmatrix} \delta & 0 & 0 \\ 0 & \alpha+\phi+\omega_C & 0 \\ 0 & -\phi & \omega_I \end{pmatrix}$$

Each element n_{ij} of the next generation matrix is the average number of new colonized or infected individuals of the ith compartment produced by the interaction with or progression from individuals of the jth compartment, at each time step. For example, the first element is zero because we assumed that no new contaminated HCWs will be the result of interactions with other contaminated HCWs. Proceeding with our calculations,

$$FV^{-1} = \begin{pmatrix} 0 & \frac{{N_H}^*(\hat{\beta}_2\phi+\hat{\beta}_1\omega_I)}{(\alpha+\phi+\omega_C)\omega_I} & \frac{{N_H}^*\hat{\beta}_2}{\omega_I} \\ \frac{{N_P}^*\beta_2}{\delta} & \frac{{N_P}^*(\beta_3\phi+\beta_1\omega_I)}{(\alpha+\phi+\omega_C)\omega_I} & \frac{{N_P}^*\beta_3}{\omega_I} \\ 0 & 0 & 0 \end{pmatrix} \tag{6}$$

where ${N_P}^* = \frac{N_P}{N_H+N_P}$, and ${N_H}^* = \frac{N_H}{N_H+N_P}$.

The reproduction number is thus:

$$R_0 = \frac{1}{2}\left(\frac{N_P^*(\beta_3\phi+\beta_1\omega_I)}{(\alpha+\phi+\omega_C)\omega_I} + \sqrt{\left(\frac{N_P^*(\beta_3\phi+\beta_1\omega_I)}{(\alpha+\phi+\omega_C)\omega_I}\right)^2 + 4\left(\frac{N_H^*(\hat{\beta}_2\phi+\hat{\beta}_1\omega_I)}{(\alpha+\phi+\omega_C)\omega_I}\right)\left(\frac{N_P^*\beta_2}{\delta}\right)}\right) \tag{7}$$

We can represent the reproduction number as

$$R_0 = \frac{1}{2}\left(R_P + \sqrt{R_P^2 + 4\cdot R_H^2}\right) \tag{8}$$

where R_P is the colonization/infection potential of patients and R_H is the contamination potential of HCWs. These two represent processes occurring simultaneously: a direct transmission between patients and a two-step cycle of transmission between patients and HCWs.

R_H is the geometric mean of (1) the average number of new contaminated HCWs by transmission from colonized patients and (2) the average number of new colonized patients by transmission from contaminated HCWs. The first factor, as seen in equation (9), has two terms that account for different transmission pathways: one direct (HCWs being contaminated by colonized patients) and the other indirect (HCWs being contaminated by infected patients). This term is

$$R_H = \sqrt{N_H^* \left(\frac{\hat{\beta}_1}{\alpha + \phi + \omega_C} + \frac{\phi}{\alpha + \phi + \omega_C} \cdot \frac{\hat{\beta}_2}{\omega_I} \right) \left(\frac{N_P^* \beta_2}{\delta} \right)} \tag{9}$$

Now, rewriting the expression for R_P, we find that it is the average number of new colonized patients produced by contacts between uncolonized and colonized patients. As in the first term of R_H, R_P is the sum of two terms: direct transmission characterized by colonized patient transmission, and indirect transmission characterized by infected patient transmission. Thus,

$$R_P = N_P^* \left(\frac{\beta_1}{\alpha + \phi + \omega_C} + \frac{\phi}{\alpha + \phi + \omega_C} \cdot \frac{\beta_3}{\omega_I} \right) \tag{10}$$

Furthermore, since $R_H, R_P > 0$, we have from (8) that:

$$R_0 = \frac{R_P}{2} + \frac{1}{2}\sqrt{R_P^2 + 4R_H^2} > \frac{R_P}{2} + \frac{1}{2}\sqrt{R_P^2} = R_P \tag{11}$$

Applying the triangle inequality, we also find that:

$$R_0 = \frac{R_P}{2} + \frac{1}{2}\sqrt{R_P^2 + 4R_H^2} < \frac{R_P}{2} + \frac{1}{2}\left(R_P + 2R_H\right) = R_P + R_H. \tag{12}$$

Combining these results, we can say that, in general, $R_P < R_0 < R_P + R_H$. The latter part of this inequality means that the two infection potentials R_P and R_H have a net effect (given by the reproduction number R_0) which is less than their sum. We can explain this by the fact that patients transmit MRSA to both patients and HCWs, but HCWs can transmit the bacteria back to patients. So, this overlap of transmission explains the aforementioned result. Recall that, as no new infected or colonized patients are being admitted into the system, this reproduction number accounts only for the spread of MRSA within the hospital facilities.

3.1.2 Screening at Admission

In order to achieve a constant population inside the hospital we let $\Lambda = (\gamma_U + \mu_U)\, U + (\gamma_C + \mu_C)\, C + \mu_I I + (\gamma_Z + \mu_Z)\, Z$. As before, we assume that there are no incoming colonized nor infected patients in order for a DFE to exist. At the DFE we have

$$\begin{aligned} H^* &= N_H \\ U^* &= N_P \\ {H_C}^* = C^* = I^* &= Z^* = 0 \end{aligned} \tag{13}$$

Using the next-generation matrix approach, we obtain:

$$\mathscr{F} = \begin{pmatrix} \hat{\beta}_1 H \frac{C}{N} + \hat{\beta}_2 H \frac{I}{N} \\ \beta_1 U \frac{C}{N} + \beta_2 U \frac{H_C}{N} + \beta_3 U \frac{I}{N} \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \qquad \mathscr{V} = \begin{pmatrix} \delta H_C \\ (\mu_C + \gamma_C)C + (\phi + \alpha)C \\ (\mu_I + \kappa)I - \phi C \\ -\kappa I + (\mu_Z + \gamma_Z)Z \\ -\delta H_C + \hat{\beta}_1 H \frac{C}{N} + \hat{\beta}_2 H \frac{I}{N} \\ -\Lambda + (\mu_U + \gamma_U)U + \beta_1 U \frac{C}{N} \\ \qquad + \beta_2 U \frac{H_C}{N} + \beta_3 U \frac{I}{N} - \alpha C \end{pmatrix}$$

$$F = \begin{pmatrix} 0 & \hat{\beta}_1 N_H^* & \hat{\beta}_2 N_H^* & 0 \\ \beta_2 N_P^* & \beta_1 N_P^* & \beta_3 N_P^* & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \qquad V = \begin{pmatrix} \delta & 0 & 0 & 0 \\ 0 & \alpha + \mu_C + \gamma_C + \phi & 0 & 0 \\ 0 & -\phi & \kappa + \mu_I & 0 \\ 0 & 0 & -\kappa & \mu_Z + \gamma_Z \end{pmatrix}$$

The next-generation matrix is

$$FV^{-1} = \begin{pmatrix} 0 & \frac{N_H^*\left[\hat{\beta}_1(\kappa+\mu_I)+\hat{\beta}_2\phi\right]}{(\kappa+\mu_I)(\alpha+\mu_C+\gamma_C+\phi)} & \frac{N_H^*\hat{\beta}_2}{\kappa+\mu_I} & 0 \\ \frac{N_P^*\beta_2}{\delta} & \frac{N_P^*[\beta_1(\kappa+\mu_I)+\beta_3\phi]}{(\kappa+\mu_I)(\alpha+\mu_C+\gamma_C+\phi)} & \frac{N_P^*\beta_3}{\kappa+\mu_I} & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \tag{14}$$

The basic reproduction number, given by the largest eigenvalue of the next-generation matrix, has the same form as (8) and satisfies (11) and (12). R_P and R_H are given by

$$R_P = N_P^* \left(\frac{\beta_1}{\alpha + \mu_C + \gamma_C + \phi} + \frac{\phi}{\alpha + \mu_C + \gamma_C + \phi} \cdot \frac{\beta_3}{\kappa + \mu_I} \right) \tag{15}$$

$$R_H = \sqrt{N_H^* \left(\frac{\hat{\beta}_1}{\alpha + \mu_C + \gamma_C + \phi} + \frac{\phi}{\alpha + \mu_C + \gamma_C + \phi} \cdot \frac{\hat{\beta}_2}{\kappa + \mu_I} \right) \frac{N_P^* \beta_2}{\delta}} \tag{16}$$

The difference between the baseline reproduction number and the reproduction number for the discharge screening model is the introduction of the rate κ, which is the progression of infected patients to the isolation unit. Also, note that the discharge rate γ_I, which was implicit in the ω_I rate, is excluded. Then, in order to make R_0 smaller than in the baseline model, κ has to be greater than γ_I.

A clear disadvantage of setting $\lambda_C = \lambda_I = 0$ in the analysis is that the screening parameter ρ does not appear in the expression for the reproductive number. Then, it is not possible to evaluate via the reproduction number the impact of the control strategy.

3.1.3 Screening at discharge

At the disease-free equilibrium, for $\lambda_C = \lambda_I = 0$, we have

$$\begin{aligned} H^* &= N_H \\ U^* &= N_P \\ {F_U}^* &= \frac{b_{F_U} - \mu_U N_P}{\mu_{F_U}} \\ {H_C}^* = C^* = &I^* = Z^* = F^* = 0 \end{aligned}$$

and the reproduction number, given by the largest eigenvalue of the next-generation matrix, is the same as that found for the screening at admission model. Once again, our R_P and R_H terms are

$$R_P = N_P^* \left(\frac{\beta_1}{\alpha + \mu_C + \gamma_C + \phi} + \frac{\phi}{\alpha + \mu_C + \gamma_C + \phi} \cdot \frac{\beta_3}{\kappa + \mu_I} \right) \tag{17}$$

$$R_H = \sqrt{N_H^* \left(\frac{\hat{\beta}_1}{\alpha + \mu_C + \gamma_C + \phi} + \frac{\phi}{\alpha + \mu_C + \gamma_C + \phi} \cdot \frac{\hat{\beta}_2}{\kappa + \mu_I} \right) \frac{N_P^* \beta_2}{\delta}} \tag{18}$$

3.2 Sensitivity analysis of R_0

3.2.1 Baseline model

The sensitivity analysis performed assumes that parameters are obtained from normal distributions. Coefficients of sensitivity are estimated from the partial derivatives of R_0. Figure 4 summarizes the indices of sensitivity for the basic reproduction number of the (adjusted) baseline model, as it appears in equation (7). The most relevant parameters affecting R_0 are the rate of transmission between uncolonized and colonized patients (β_1) and the discharge rate of colonized patients (γ_C). These results suggest that the colonization rate β_1 has a major impact on the outbreak potential of MRSA in a hospital.

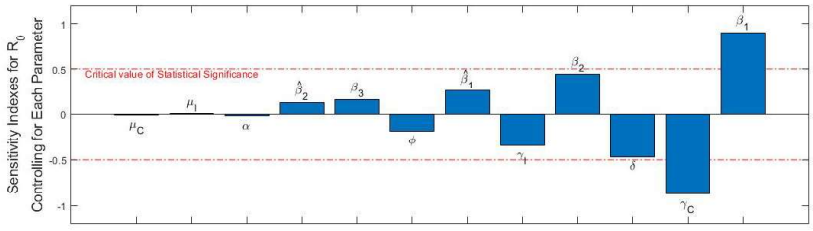

Figure 4: Sensitivity in the baseline model

The parameter γ_C summarizes the flow out from the colonized compartment due to treatment or discharge. As more colonized patients leave the hospital, net MRSA transmission rate drops. In the baseline model, only two other parameters have statistically significant influence on the reproduction number. The rest of the parameters, with sensitivity indices within the critical threshold, exhibit statistically negligible effects on

R_0.

The time it takes for a contaminated HCW to become decontaminated can vary between 6 hours and 24 days [14]. It can be seen in Figure 5 that the basic reproduction number of the baseline model is always greater than 1 for any value of δ. This means that reducing the decontamination rate can decrease the value of the basic reproduction number, but it is never enough to prevent an outbreak in absence of any other control effort.

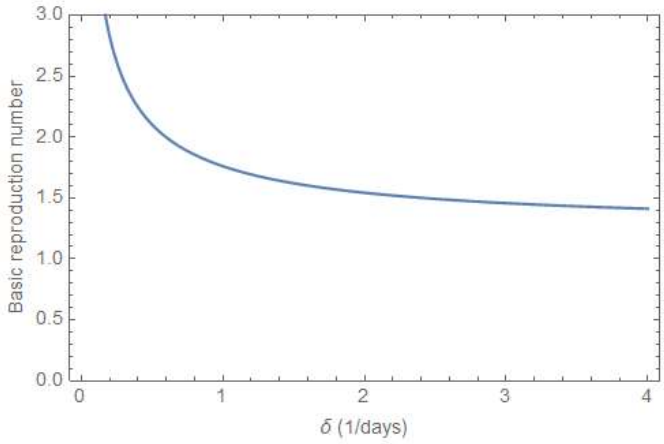

Figure 5: Basic reproduction number versus the decontamination rate of HCWs (δ).

3.2.2 Screening at admission and discharge

In the screening at admission and discharge models we introduce the parameter κ, denoting the rate of progression from infected to isolated. Once again, we find that β_1 and γ_C have more influence on R_0 than other parameters (see Figure 6). This means β_1 and γ_C play an important role in controlling MRSA for both implemented control strategies.

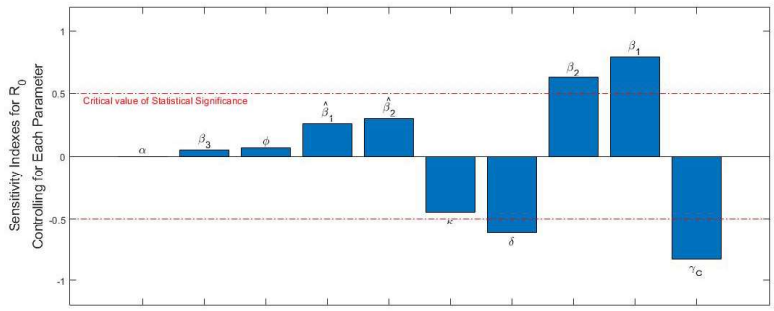

Figure 6: Sensitivity index for screening models.

Unlike the baseline model, the rate of patient colonization after contact with contaminated HCWs, β_2, has a greater effect on the screening models. This means that

patients are more sensitive to colonization by contacts with contaminated HCWs. Another difference with the baseline model is that the sensitivity index of δ, the rate of decontamination of contaminated HCWs, is higher. Thus, δ has more impact on reducing R_0 in the screening models. In the screening models, $1/\kappa$ denotes the average time that an infected patient takes to move to the isolated unit. Note in Figure 7 that when reducing δ and κ, it is always the case that $R_0 > 1$. This means that, in order to reduce the prevalence of MRSA in hospitals, it is necessary to adjust other parameters.

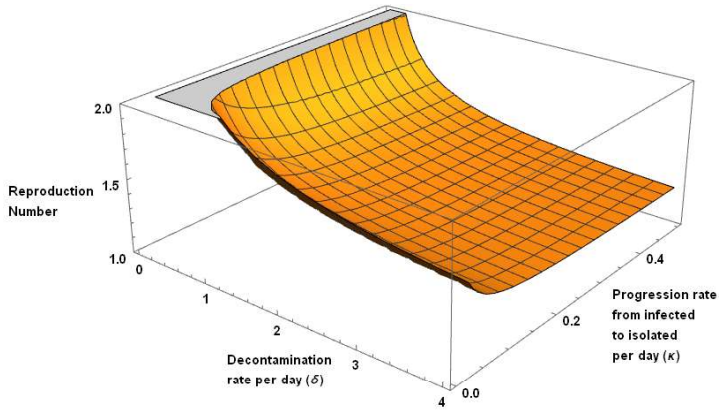

Figure 7: Basic reproduction number with respect to the decontamination rate of HCWs (δ) and the rate of progression from infected to isolated (κ).

4 Results

4.1 Endemic Equilibria

The endemic equilibrium corresponds to a steady state where the disease remains in the population [5]. The baseline compartmental model for uncolonized (U), colonized (C) and infected (I) individuals differs from a classic SIR model in that it includes a level of HCWs with two states (contaminated and uncontaminated). The high level of complexity associated with our model does not allow us to find a closed form solution, hence results will be explored using numerical solutions.

In order to find the endemic equilibria of the baseline and screening models, we reduced the system of equilibrium conditions to one algebraic equation with one variable and to two algebraic equations with two variables, respectively. Figure 8 shows the solutions to these resulting equations in terms of the screening probability ρ.

It can be observed that the endemic levels of colonized and infected patients and contaminated HCWs within the hospital decrease as ρ increases. Furthermore, the screening at discharge strategy (dashed lines) has a bigger impact on the infected and colonized patient populations than the screening at admission strategy (solid lines). Specifically, the former strategy decreases the colonized patient population at equilibrium more significantly than the latter. However, patients in isolation for discharge screening grows much larger for larger ρ than the isolated patient population for admission screening. We also observe that the infected patient and contaminated HCW populations do not differ significantly between models.

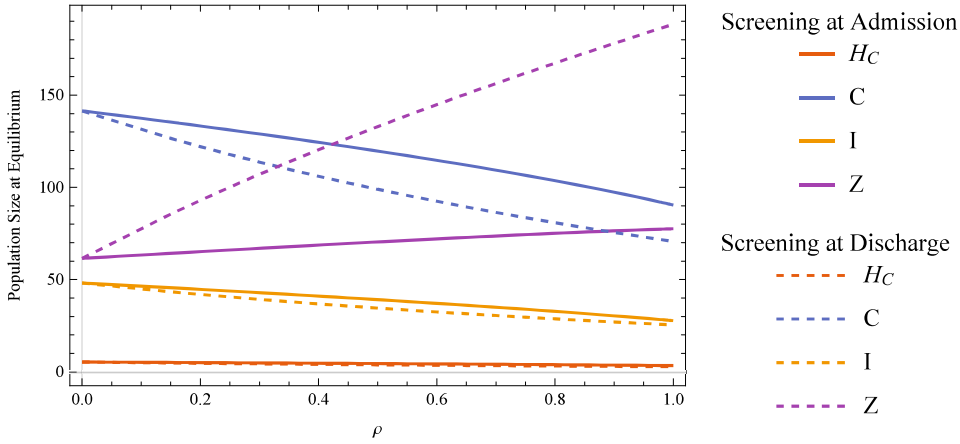

Figure 8: Population sizes at the endemic equilibrium as ρ varies. The solid lines correspond to screening at admission, whereas the dashed lines correspond to screening at discharge.

For the rest of this subsection we explore the influence of specific parameters affecting the endemic equilibria at the screening at admission model of subpopulations levels. We use graphical approximations to understand the asymptotic behavior of solutions with respect to these critical parameters.

Figure 9 depicts the number of contaminated HCWs as a function of screening probability (ρ) and rate of decontamination (δ). It would seem that screening does not affect the contaminated HCW population. Contaminated HCW population drops to considerably low levels after a threshold of δ is achieved. This occurs when $\delta \approx 1$. This result illustrates that small efforts toward decontamination make a considerable difference in reducing levels of MRSA prevalence, at least for contamination levels among HCWs. This is an extension of the result found in Figure 5, in this case for all ρ belonging to the interval $[0, 1]$.

Figure 10 presents the sum of colonized, infected, and isolated patients in terms of the same parameters ρ and δ. We shall refer to this sum as the contaminated patient population. The decontamination rate of HCWs affects the final outcome of the total contaminated population more significantly than ρ. Naturally, as δ increases, the total contaminated population decreases. However, when δ falls below the threshold $\delta \approx 1.5$, the contaminated patient population grows significantly, suggesting that HCW hygiene practices are very important in controlling MRSA.

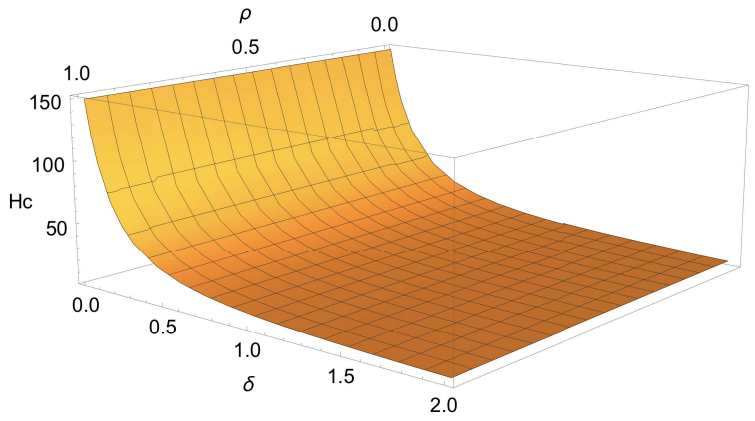

Figure 9: Contaminated HCW population as function of screening probability (ρ) and decontamination rate (δ).

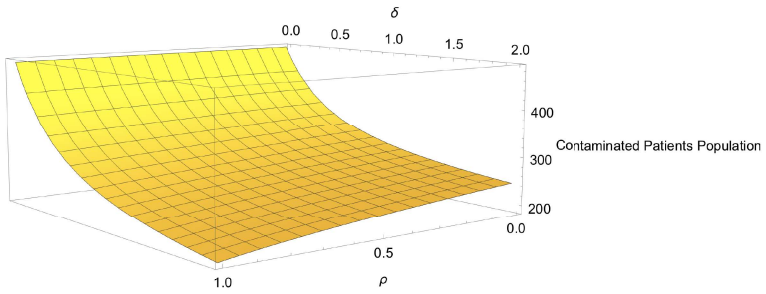

Figure 10: Contaminated population as function of screening probability (ρ) and decontamination rate (δ).

In Figures 11 and 12 we plot contaminated HCW and contaminated patient populations as functions of the discharge rate of colonized patients (γ_C) and the screening probability (ρ). For the contaminated HCW population, when ρ and γ_C increase, the contaminated population naturally decreases. As hospitals discharge/treat more colonized patients they reduce the MRSA endemicity levels inside the hospital. For the colonized patient population, the situation is similar. However, since patient discharge directly affects the contaminated population, the sensitivity is much more significant. For both populations, the most significant change occurs when $\gamma_C \leq 0.2$.

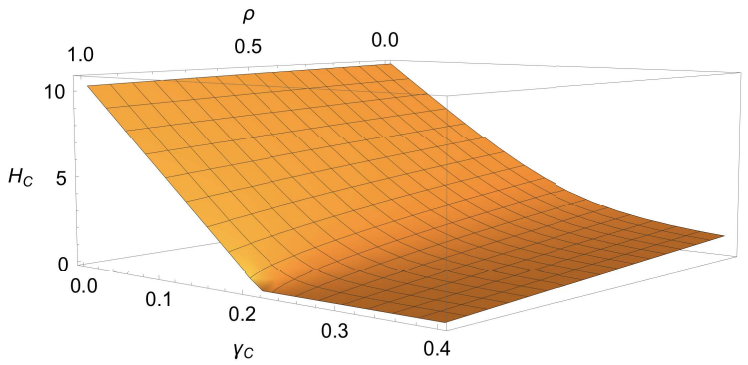

Figure 11: Contaminated HCW population as a function of screening probability (ρ) and the discharge rate of colonized patients (γ_C).

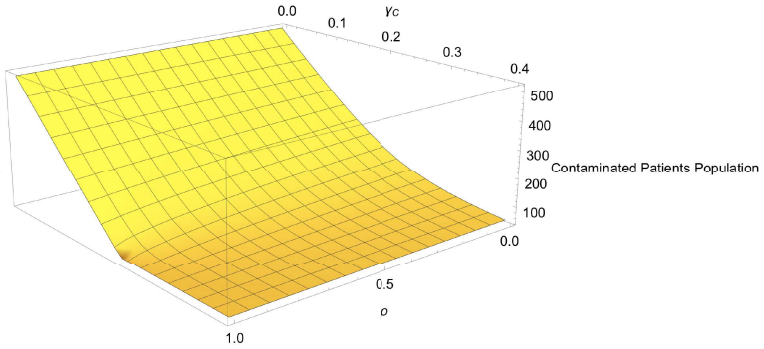

Figure 12: Contaminated population as a function of screening probability (ρ) and the discharge rate of colonized patients (γ_C).

Figure 13 shows the contaminated HCW population as a function of the screening probability (ρ) and the discharge rate of isolated patients (γ_Z). The discharge rate of isolated patients has a biggest effect on the contaminated HCW population when $\gamma_Z \leq 0.2$. As γ_Z increases the contaminated HCW population also increases. This is because we had assumed that each time a patient is discharged from the hospital, a new patient from the community is admitted. As this number grows, the greater the chance that these newly admitted patients will be either colonized or infected.

As can be seen in Figure 14, contaminated patient population is given as a function of γ_Z and ρ. The effect of discharging isolated patients directly impacts the number of contaminated patients in the hospital, consequently yielding a greater effect on the contaminated patient population than the contaminated HCW population. When $\gamma_Z \leq 0.02$ (that is, when the average length of stay of isolated patients exceeds 50 days), the contaminated patient population explodes. Otherwise, changes in the length of stay of isolated patients has negligible overall effects.

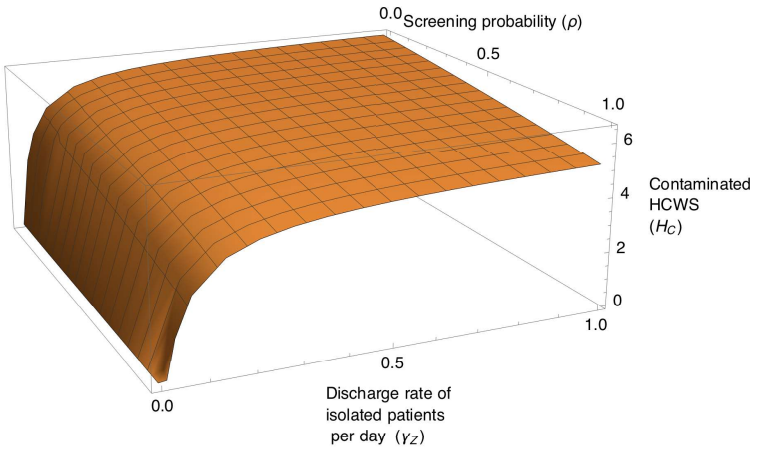

Figure 13: Contaminated HCW population as a function of screening probability (ρ) and the discharge rate of isolated patients (γ_Z).

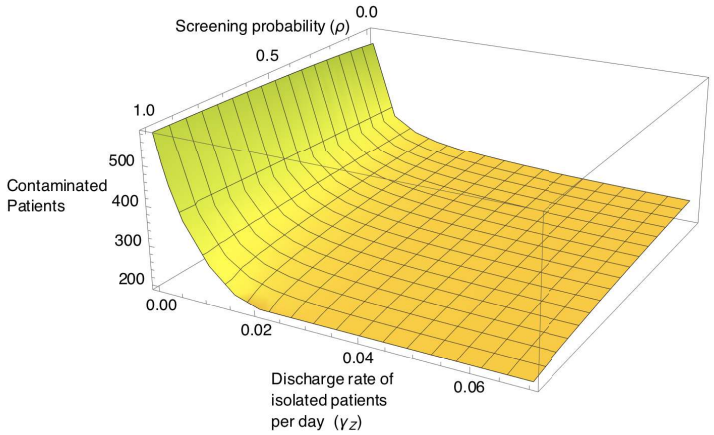

Figure 14: Contaminated patient population as a function of screening probability (ρ) and the discharge rate of isolated patients (γ_Z).

4.2 Deterministic and stochastic simulation comparisons

Stochastic simulations were run for both models over the time span of three years. Stochastic simulations were utilized to look at the variation of data from the mean-field results reported in the deterministic models, and helped to account for variability in the model simulations and consistency within the results. Data from infected, colonized, contaminated, and isolated populations were recorded for different values of ρ between 0 and 1. The trivial case of $\rho = 1$ was omitted from the figures, as complete screening made all populations carrying the bacteria go to zero. Naturally, as shown in Figure 14, larger values of ρ correspond to smaller endemic populations of infected and colonized patients. Larger values of ρ do not, however, significantly affect the contaminated HCW population, as shown in Figure 13.

Figures 15 and 16 show a superposition of fifty stochastic simulations against the mean-field results of the deterministic solution.

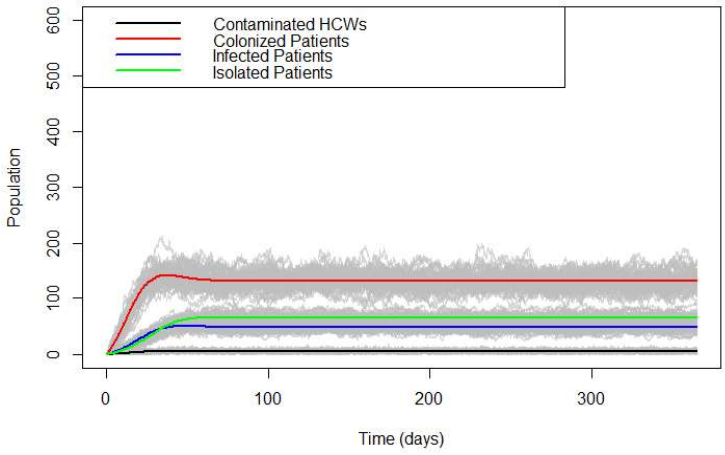

Figure 15: Admission screening simulations - deterministic model superimposed on fifty stochastic simulations ($\rho = 0.1$).

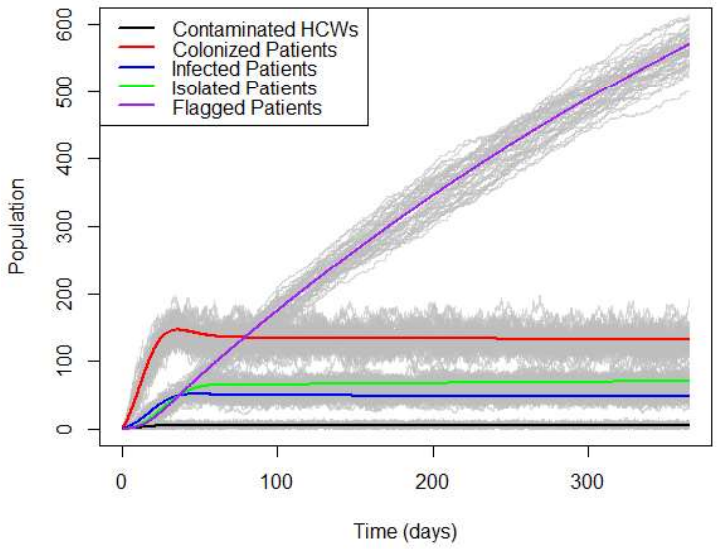

Figure 16: Discharge screening model simulations - deterministic model superimposed on fifty stochastic simulations ($\rho = 0.1$).

Observed but not shown in Figure 16 is that the population of the flagged compartment asymptotically approaches a limit in finite time, determined by the rate at which

flagged individuals are readmitted and the death rate of flagged individuals.

A more careful analysis was performed to determine deviation of the results of either model. Populations at equilibrium for infected patients and contaminated HCWs did not change significantly with screening procedures. Thus, these results were omitted, and effectiveness was measured based on colonized and isolated patient populations alone. For values of ρ between 0 and 1, 100 stochastic simulations were run using the parameter values found in Tables 1 and 2. For each simulation the colonized and isolated patient population sizes at endemic equilibrium were recorded. The results are shown in Appendixes A and B. Colors are used to indicate the frequency with which endemic populations occurred. These graphs are shown on the following pages. Discharge screening yields lower colonized patient population equilibria and also appears to have a lower variation about the mean-field result. However, isolated patient population increase significantly faster to over twice that achieved with admission screening for the same value of ρ. The greater deviation in endemic equilibria found with the admission screening model implies that the endemic equilibria are less predictable than those generated by the discharge screening model.

5 Discussion

MRSA prevalence in hospital facilities is a concern of increasing priority since it jeopardizes the health of patients and health care workers alike. However, MRSA cannot be treated exclusively with antibiotics due to the very realistic possibility of further resistant strains. Thus, control strategies and protocols should be emphasized in health care facilities so as to control bacterial spread and further proliferation. Screening followed by isolation is a very common method of controlling MRSA. Of practical consideration is the most effective means of screening. Here we evaluated the effectiveness of discharge screening as compared to the typical alternative of admission screening.

In order to compare the two proposed strategies for MRSA control in hospitals, we evaluated three compartmental models: a baseline model and two models for either screening strategy. The difference in the design of the models is intended to answer questions otherwise not addressed in the current literature regarding patients leaving hospitals and the effect on MRSA transmission dynamics in hospitals.

Screening at discharge appears to be the more effective strategy in reducing endemic populations within the hospital. However, discharge screening also yields a very rapid growth in the number of isolated patients, suggesting that the strategy may not be entirely practical if considering an IU with finite capacity. Admission screening also had larger variations in endemic equilibria around the mean-value result, suggesting more variability than what was seen with discharge screening. Infected patient and contaminated HCW populations were ignored, as there was no significant difference in these populations between screening strategies.

Many areas of further research and elaboration remain. The most significant of which include an isolation unit (IU) with finite capacity (e.g. 20 beds). This consideration would clarify the practicality of discharge screening and resolve the issue of whether or not the growth seen in the stochastic models can't be accommodated. Another important consideration is cost. Although we can mathematically express the results of the above models in a concise and simple manner, the true pragmatism must be evaluated in terms of cost. A significant problem associated with controlling MRSA is the cost it incurs in treatment and various methods to prevent its spread. Future work

can include cost-benefit analysis. MRSA represents a growing financial burden for both families and the public health system. This situation involves more complexity due to the antibiotic-resistant feature of the bacteria. Consequently, increasing resources, both financial and human, have to be devoted to control the spread of this disease. These results might guide policy makers to improve control strategies. However, a detailed cost analysis might produce more sound results. This will help to plan budgets adequately and to recognize needs for future infrastructure. In performing our research, parameter values were chosen conservatively so as to provide a lower bound for any results later on.

As mentioned earlier, patients and HCWs are assumed to be mixed homogeneously. Although greatly simplifying analysis, this is not entirely the case in reality. Some patients have more contacts with HCWs than others naturally, such as those who may visit the intensive care unit (ICU). However, elaboration on this would require a more narrow scope regarding our system, as is the case with Bootsma et al [3].

Parameters were taken, for the most part, from primary sources and various papers discussing MRSA endemic dynamics. Admittedly, not all parameters were obtained the same way. A more exhaustive analysis could include confidence intervals and hypothesis testing. Finally, admission rate is chosen so that population within the hospital is constant. That is, whenever a patient is discharged or dies, a new patient is admitted to take his place. HCW population is also assumed to be constant. Although these assumptions greatly simplify analysis, they are unrealistic.

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Appendix A Stochastic simulations for colonized patient populations

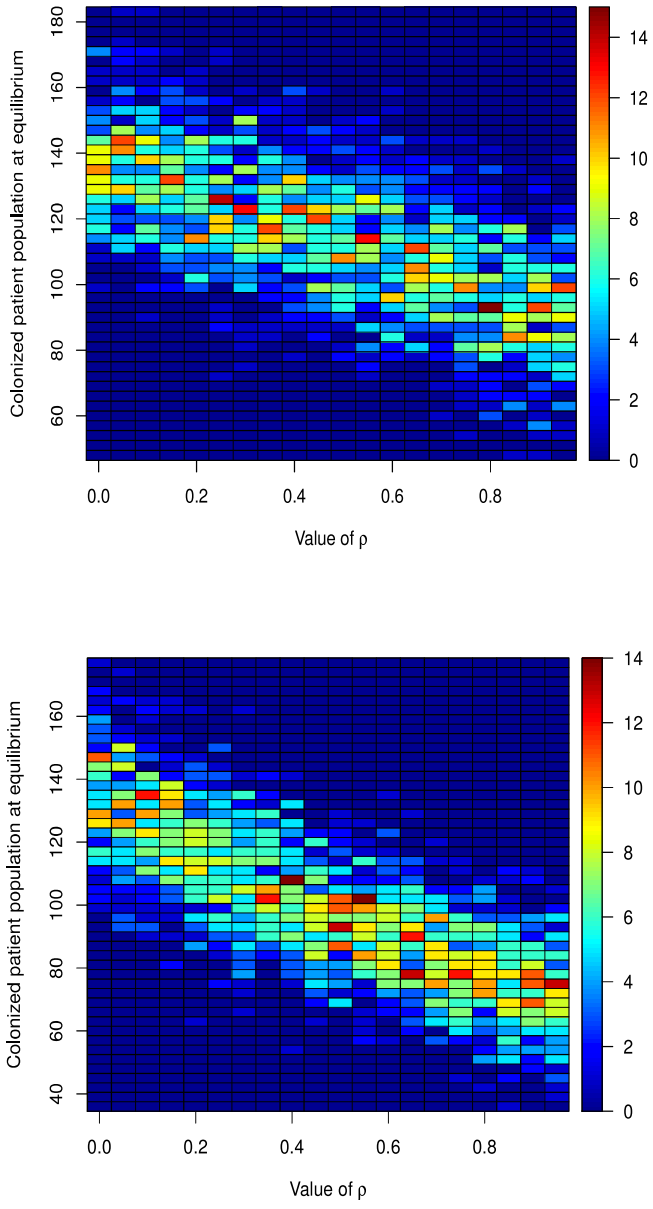

Figure 17: Comparison of colonized patient populations at equilibrium between admission screening (top) and discharge screening (bottom) using stochastic simulations.

Appendix B Stochastic simulations for isolated patient populations

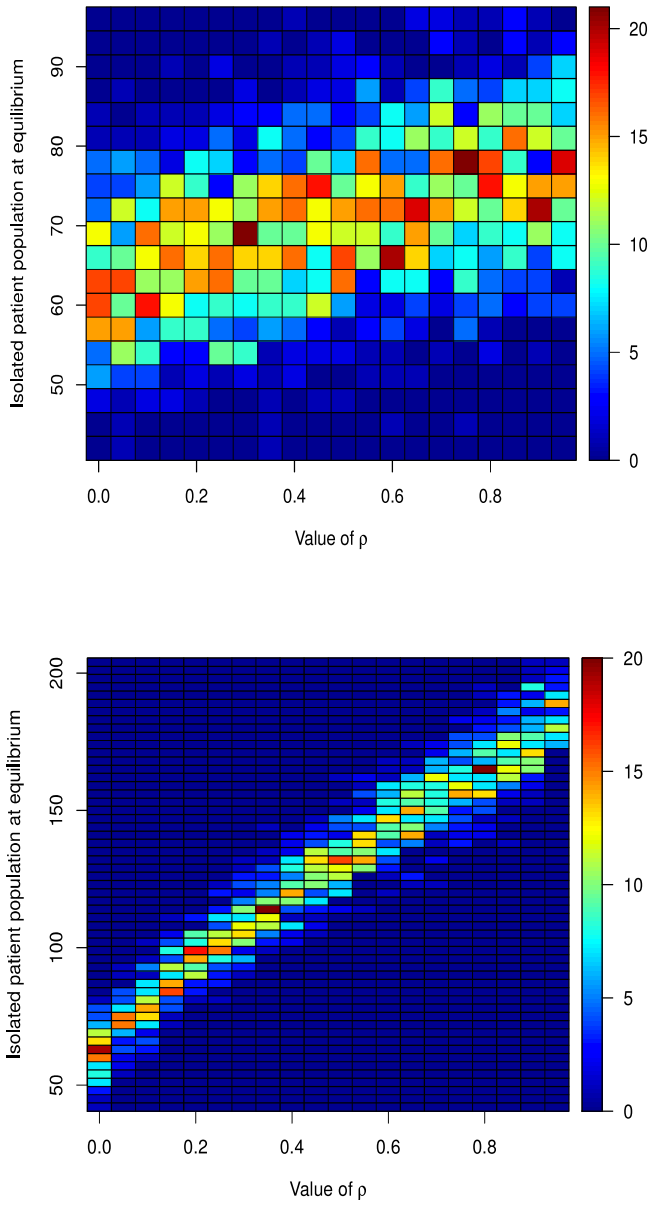

Figure 18: Comparison of isolated patient populations at equilibrium between admission screening (top) and discharge screening (bottom) using stochastic simulations.

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