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Comparison of Screening for Methicillin-Resistant Staphylococcus Aureus at Hospital Admission and Discharge

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ABSTRACT

Methicillin-resistant *Staphylococcus aureus* (MRSA) contributes greatly to the growing concern of antibiotic-resistant bacteria, especially given its stubborn persistence in healthcare settings. MRSA resists treatment and has colonized an estimated 2% of people worldwide. The CDC reports MRSA prevalence as high as 25–50% in countries like the U.K. and the U.S. Given its resistant nature—it evolves to compensate antibiotic treatment—controlling MRSA levels requires precautionary and defensive measures. This study examines the "search and isolation" approach, which seeks to isolate MRSA-positive patients in hospitals to decrease transmission. Although this strategy is straightforward, whom to screen may vary in practice. We compare screening at admission to screening at discharge, using a mathematical model whose simulations determine MRSA endemic levels in a hospital under either control measure. We found screening at discharge more effective in controlling MRSA endemicity, but at the cost of more isolated patients.

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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 bacterial infections, 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 revolutionary antibiotic (Bondi Jr. and Dietz, 1945). Currently, more than 90% of *S. aureus* cultures are resistant to penicillin (Lowy, 2003). 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% (University of Chicago, 2010).

Since MRSA is both the most prevalent and the most destructive in hospital settings, we restrict our analysis to account only for nosocomial spread. 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, or possess an open wound or skin infection. Recently, screening at discharge has been proposed as an alternative to screening at admission.

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Several mathematical models have attempted to capture the transmission dynamics of MRSA in hospitals. Chamchod and Ruan (2012) present a compartmentalized model for MRSA that considers patients as either uncolonized, colonized, or infectious. Health care workers (HCWs) exist in their own compartments as either contaminated or uncontaminated and behave as vectors for the bacteria. Chamchod and Ruan (2012) consider MRSA transmission dynamics in light of antibiotic usage and subsequent resistance. In their model, patients are considered at a higher risk of developing MRSA if they have a history of antibiotic usage. Cooper et al. (2004) consider additionally the contributions of the community to endemic levels in hospitals. However, the community that Cooper et al. (2004) consider is comprised entirely of previous hospital patients. 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. (2006) constructed two models to study MRSA transmission: one model considers transmission within a single hospital, while another model considers transmission within a system of hospitals. In all of the aforementioned models, screening, if any, 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 hospital 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.

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 (Kluytmans et al., 1997). Robicsek et al. (2009) estimate that MRSA colonization half-life in a patient can be up to 40 months. 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 (Albrich and Harbarth, 2008). Following the example of Chamchod and Ruan (2012), in this study HCWs will be considered separate from the patient population and treated as vectors of the bacteria.

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. Kunori et al. (2002) estimate that the former technique is more expensive than the latter. 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. (2016) found that universal screening-at-admission costs over twice as much as compared to alternative screening methods. 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. For simplicity, no distinction is made between individuals with varying levels of susceptibility to MRSA infection. Although targeted screening is likely to enhance screening effectiveness, the focus of this study is merely to assess efficacy differences when the timing of screening is varied.

Identification of MRSA carriers is critical in health care settings. It is no coincidence then that optimizing how carriers are identified be of utmost importance. Using three mathematical models, each addressing a particular system (control strategies absent, screening at admission, and screening at discharge), we compare the most favored method of screening (that of admission) to screening at discharge in controlling nosocomial transmission of MRSA by using a combination of qualitative and numerical analysis methods to estimate reductions in the number of total contaminated and infected patients.

2 Model Formulation

We used three mathematical models to explore different control strategies for MRSA spread in hospitals. Each model is a system of ordinary differential equations. We first developed a baseline model, which is a simple compartmental model of MRSA transmission in a hospital absent all other control strategies. Each screening strategy is modeled by making corresponding changes to the baseline model. These changes are explained in the subsections to follow.

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 (Chamchod and Ruan, 2012). For the baseline model, patients are considered to be uncolonized (U), colonized (C), or infected (I). A patient is colonized when MRSA bacteria is present on their body, but the bacteria has not entered the body via a break or cut in the skin and progressed to infection. Health care workers (HCWs) are considered to be either uncontaminated (H) or contaminated (H_C).

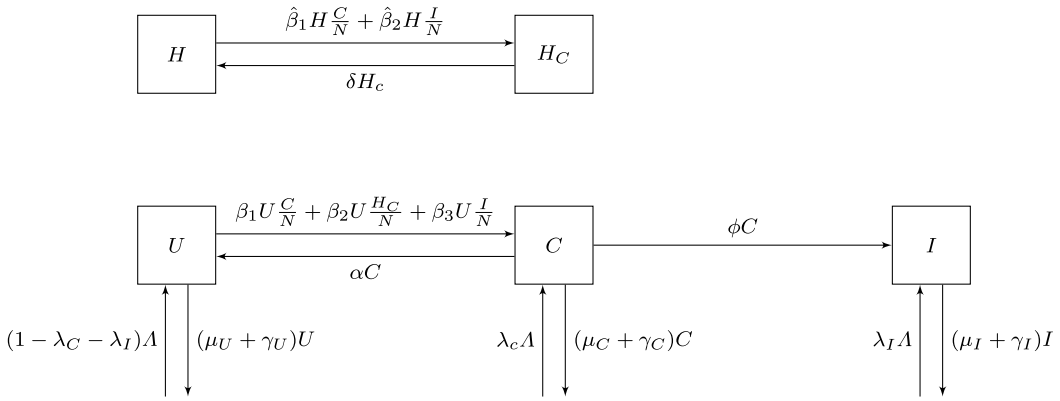

Figure 1: Baseline model diagram.

Admitted patients are colonized or infected with probabilities λ_C and λ_I, respectively; they are uncolonized, otherwise, with probability $1 - \Lambda_C - \Lambda_I$. Our baseline model is represented by the following system of ordinary differential equations:

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

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. The variables μ and γ denote death and discharge/treatment rates of each compartment. The rate at which colonized patients become infected is given by the Greek letter ϕ. Colonized patients are decolonized at a rate of α; thus $1/\alpha$ captures the average time to decolonization. HCWs remain contaminated for an average time of $1/\delta$ days. The rate of contamination between uncontaminated HCWs and colonized patients is given by $\hat{\beta}_1$, while $\hat{\beta}_2$ denotes the transmission efficiency between uncontaminated HCWs and infected patients.

The total hospital population (N) is the sum of HCWs (N_H) and patients (N_P). Both aforementioned subpopulations of patients and HCWs are assumed constant. The patient population can be made constant 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, $\Lambda = (\mu_U + \gamma_U)\, U + (\mu_C + \gamma_C)\, C + (\mu_I + \gamma_I)\, I$. The HCW population is kept constant since we ignore consideration of death for the HCW compartments.

Patients and HCWs are assumed to mix homogeneously. Strictly speaking, the assumption of homogeneous mixing can be challenged, since patients may be confined to their rooms for the majority of their hospital stay. However, in normal wards this may not always be the case, and so transmission between colonized/infected and uncolonized patients is included.

There are two assumed mechanisms of contamination for uncontaminated health care workers: contact with colonized patients and contact with infected patients. We assume that a health care worker cannot be contaminated by other HCWs (Boyce and Pittet, 2002; Sopena and Sabrià, 2002). 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. A schematic of the baseline model is shown in Figure 1.

2.2 Screening at admission

For the model of screening at admission, we maintain the structure of the baseline model while adding an isolation compartment, denoted by Z, henceforth referred to as the isolation unit (IU). For simplicity, we assume that the IU has infinite capacity. Screening is successful with probability ρ. Any patients who test positive for MRSA at admission will be moved to the IU for the remainder of their hospital stay. No distinction is made between infected and colonized patients when screened for MRSA.

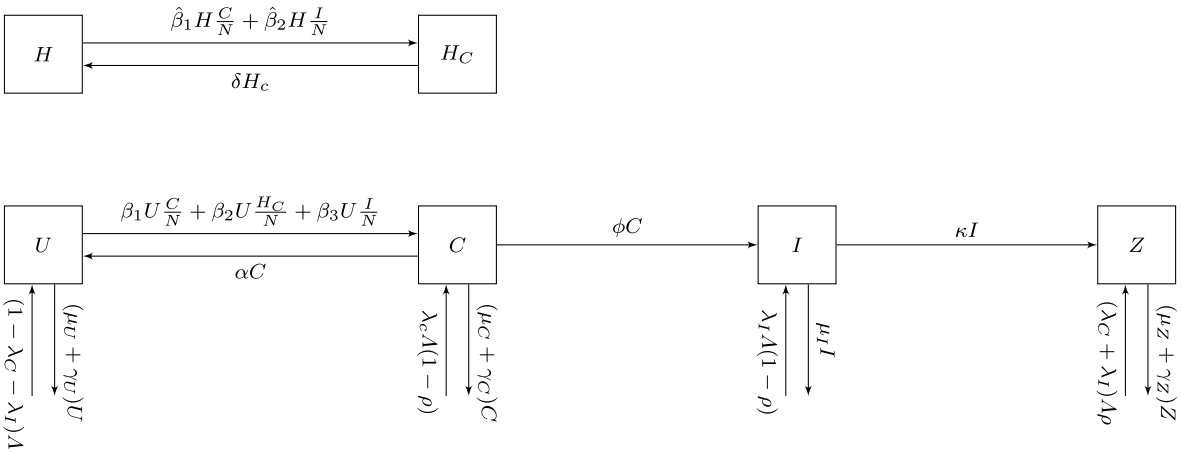

Figure 2: Screening at admission model diagram.

Patients who test negative at admission enter the general hospital population (compartment U, C, or I depending on true MRSA status regardless of test result). Only newly admitted patients may be placed in the IU, with the exception being infected patients identified while in the hospital, which occurs at a rate we denote by κ. That is, $1/\kappa$ is taken to be the sum of the average incubation period of MRSA infection (4.5 days) and the average duration of culture and susceptibility testing (2.5 days according to Hal et al. (2007)). 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 may only leave the infected compartment as the result of death or identification and subsequent treatment in the IU. 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 for patients treated in isolation, the precautions are such that transmission is negligible. Admitted patients testing 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, meaning that they must be identified as being infected with MRSA in order to receive treatment. The schematic for this system is given in Figure 2.

2.3 Screening at discharge

Screening at discharge tests all patients returning to the community for MRSA. Again the screening is assumed to identify MRSA-positive patients with probability ρ. In order to track screening results, we compartmentalize the community in terms of flagged (F) and unflagged (F_U) individuals. Patients who test positive are flagged in the hospital's records and enter the F compartment. Patients who test negative enter the general (unflagged) community F_U. The flagged compartment consists entirely of discharged patients, while the unflagged compartment consists of both discharged patients who were not colonized/infected with MRSA during their stay in the hospital and individuals in the wider community. Individuals in the wider community serve as a patient pool that more realistically captures readmission probabilities. The alternative of this is a community consisting of only previous patients, or no community at all, in which case flagging at discharge becomes indistinguishable from flagging at admission. Patients who are flagged, when readmitted to the hospital, are placed in the isolated compartment for the duration

of their hospital stay. Our model then becomes

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

In addition to the previous model, success of patient treatment is included. Proportion τ of treatments are successful of complete eradication and fail otherwise. 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, 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. The recruitment rate and death rate for the unflagged group are denoted by b_{F_U} and μ_{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 in Figure 3.

3 Parameter Estimation

All model parameters are defined, and estimates given, in Tables 1 and 2. Several parameters discussed prior deserve further elaboration, contained within this section. 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. The authors Grundmann et al. (2002) report that HCWs make 7.6 contacts per patient per day. The proportion of contacts yielding successful transmission is taken to be 0.01 (Grundmann et al., 2002). With this, the rate of successful transmission per day is $1-(1-0.01)^{7.6} = 0.0735$. To account for transmission from colonized/infected patients to uncolonized patients, we used the transmission rate $\beta_1 = 0.27\ \text{day}^{-1}$ derived in D'Agata et al. (2009) in the case of colonized patients, and similarly for transmission from infected patients (with appropriate scaling depending on how long infected individuals are capable of transmission), denoted by β_3. We do not include environmental contamination in our transmission parameters, although this is likely an important consideration (Dancer, 2008; Huang et al., 2019). Explicit consideration of environmental contamination is found in the works of Wang and Ruan (2017) and Wang et al. (2012), for example.

If HCWs make 84 patient contacts per day (this includes contacts with all patients), then the rate of transmission from colonized patients to HCWs is $\hat{\beta}_1 = 84\times 0.152$, where 0.152 is the probability of successful contamination (Grundmann et al., 2002). For convenience, we assume that the probability of contamination is double that for infected patients. However, since infected patients are only considered to be truly infectious for 7 days (before they move to isolation, in the case of the models with control strategies), the true rate is given as $\hat{\beta}_2 = 0.304\times 7/16\times 84 = 11.17$. The 7/16 term is introduced as individuals are considered infectious for only 7 of their 16 day stay, on average (see below for details). For the baseline model, which lacks an isolation compartment, corresponding adjustments would have to be made when computing these parameters.

The average time an HCW remains contaminated is $1/\delta$ days. 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%. Thus, the value of δ changes between models to reflect this percentage. In particular, the screening models will have lower values of δ than the baseline model as they include an IU, which restricts contamination of HCWs. For the model with screening at admission, $\delta = 48.23\ \text{day}^{-1}$, while for the model with screening at discharge, $\delta =$

Table 1: Parameter definitions, values, and references.

Parameter Definition	Symbol	Value	Reference
Total number of patients	N_P	600	N/A
Total number of HCWs	N_H	150	N/A
Colonized proportion of newly admitted patients	λ_C	0.0374	Fishbain et al. (2003)
Infected proportion of newly admitted patients	λ_I	0.0067	Seybold et al. (2006)
Death rate of uncolonized patients	μ_U	$5.58\text{x}10^{-5}$ day^{-1}	Hall et al. (2013)
Death rate of colonized patients	μ_C	$8.25\text{x}10^{-5}$ day^{-1}	Mendy et al. (2016)
Death rate of infected patients	μ_I	$4.87\text{x}10^{-4}$ day^{-1}	Klevens et al. (2007)
Death rate of isolated patients	μ_Z	$2.85\text{x}10^{-4}$ day^{-1}	estimated
Death rate of unflagged individuals	μ_{F_U}	$3.48\text{x}10^{-5}$ day^{-1}	N/A
Death rate of flagged individuals	μ_F	$3.48\text{x}10^{-5}$ 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}	Fishbain et al. (2003)
Discharge rate of colonized patients	γ_C	0.143 day^{-1}	Davis et al. (2004)
Treatment rate of infected patients	γ_I	0.063 day^{-1}	Cosgrove et al. (2005); D'Agata et al. (2005); Hassoun et al. (2017)
Treatment rate of isolated patients	γ_Z	0.1015 day^{-1}	estimated
Decontamination rate of HCWs	δ	varies	Grundmann et al. (2002)
Decolonization rate of colonized patients	α	0.001 day^{-1}	Chamchod and Ruan (2012); Mendy et al. (2016)
Rate of progression from colonized to infected	ϕ	0.04 day^{-1}	Chamchod and Ruan (2012)
Rate of progression from infected to isolated	κ	0.13 day^{-1}	estimated
Proportion of successful treatment	τ	0.68	Mollema et al. (2010)
Screening proportion	ρ	varies	N/A

Table 2: Transmission rates, values, and references for the models with screening.

Parameter Definition	Symbol	Value	Reference
Rate of patient colonization after contact w/colonized patients	β_1	0.27 day^{-1}	D'Agata et al. (2009); Grundmann et al. (2002)
Rate of patient colonization after contact w/contaminated HCWs	β_2	0.0735 day^{-1}	Grundmann et al. (2002)
Rate of patient colonization after contact w/infected patients	β_3	0.03 day^{-1}	D'Agata et al. (2009)
Rate of HCW contamination after contact w/colonized patients	$\hat{\beta}_1$	12.77 day^{-1}	Grundmann et al. (2002); Spetz et al. (2008)
Rate of HCW contamination after contact w/infected patients	$\hat{\beta}_2$	11.17 day^{-1}	estimated

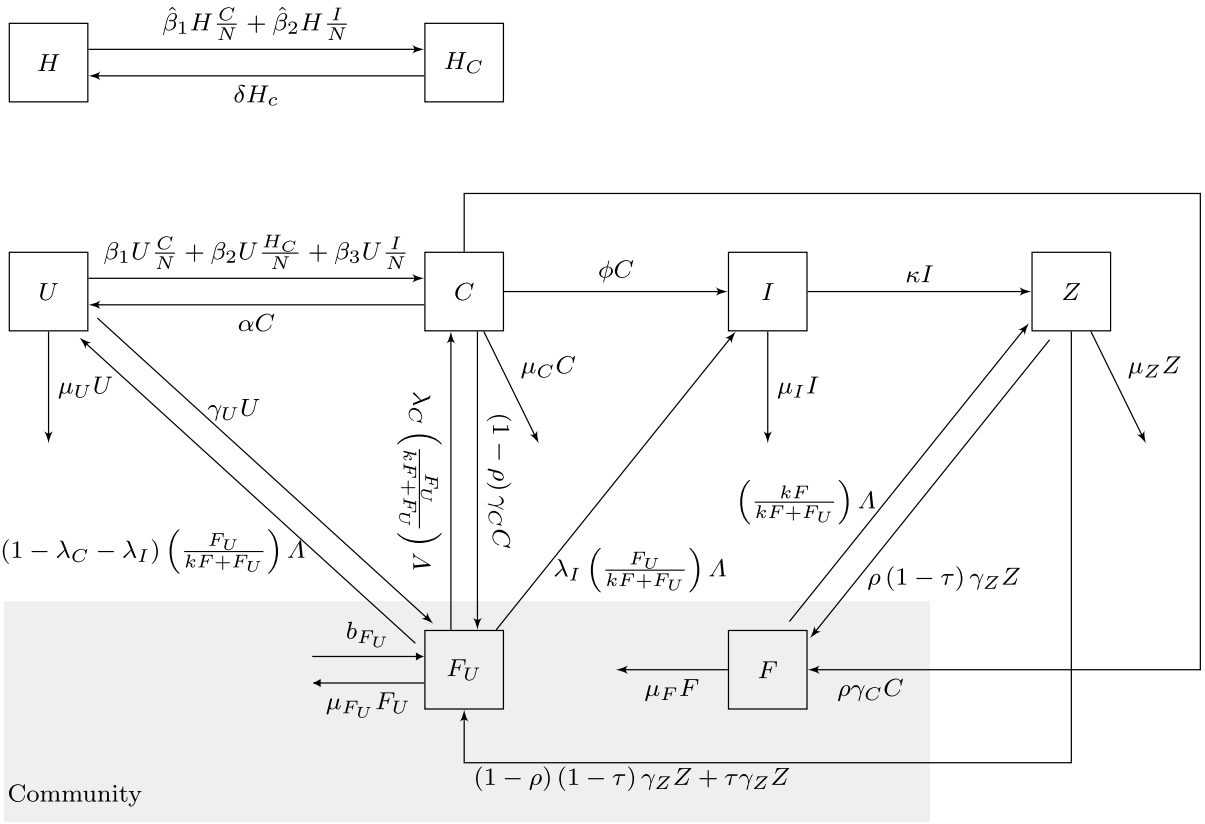

Figure 3: Screening at discharge model diagram.

50 day^{-1}. For the baseline model, δ was determined to be 108 day^{-1}. The value of δ is large for the baseline model because the model lacks any means to isolate patients in the event of colonization/infection, so infected patients remain infectious for the entire duration of their stay in the hospital; thus, in order to fit the given 4.6% HCW contamination, the corresponding decontamination rate must be higher.

The discharge and death rates in isolation, γ_Z and μ_Z, are taken to be the averages of the respective discharge/treatment and death rates 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 while in the hospital, are identified as having MRSA, and are 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 day^{-1}. This value is close to the value of 0.14 used by Bootsma et al. (2006). 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, on average, 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. Note that this only applies to the models where a control strategy is present.

The variable 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. Numerical 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 individual in the United States, and the birth rate of the unflagged compartment is chosen so that the population of the community is asymptotically constant.

4 Analysis

For each model we calculate an adjusted reproduction number using the next generation matrix method (Diekmann et al., 1990). We then perform a sensitivity analysis to determine the extent to which each parameter affects this value. Finally, we look at the endemic equilibria of our models.

4.1 Disease-free equilibrium and adjusted reproduction number R_0

A disease-free equilibrium (DFE) is obtained when the contaminated and infected populations are zero, i.e.,

$$\begin{aligned} H_C^* = C^* = I^* = Z^* = 0, \\ H^* = N_H, \\ U^* = N_P. \end{aligned} \tag{4}$$

For any of the three models, a DFE as in (4) does not exist when either $\lambda_C > 0$ or $\lambda_I > 0$. Colonized and infected patients are being admitted at each time step, forbidding the existence of a hospital state absent any contaminated patients. Nonetheless, these parameters can be set to zero to allow insight into the spread of MRSA bacteria within the hospital. That is, the model is simplified to consider the case where all newly admitted patients are uncolonized ($\lambda_I = \lambda_C = 0$). By doing so, we were able to calculate an *adjusted* reproduction number, denoted by R_0.

To calculate reproduction numbers, we employed the next-generation matrix method (Diekmann et al., 1990; van den Driessche and Watmough, 2002). Full details are given in the Appendix.

The adjusted reproduction number for the baseline model is

$$R_0 = \frac{1}{2}\left(R_P + \sqrt{R_P^2 + 4 \cdot R_H^2}\right), \tag{5}$$

where

$$R_P = N_P^*\left(\frac{\beta_1}{\alpha + \phi + \omega_C} + \frac{\phi}{\alpha + \phi + \omega_C} \cdot \frac{\beta_3}{\omega_I}\right) \tag{6}$$

and

$$R_H = \sqrt{N_H^*\left(\frac{\hat{\beta}_1}{\alpha + \phi + \omega_C} + \frac{\phi}{\alpha + \phi + \omega_C} \cdot \frac{\hat{\beta}_2}{\omega_I}\right) N_P^*\left(\frac{\beta_2}{\delta}\right)}. \tag{7}$$

Here, R_P is the colonization potential of patients and R_H is the contamination potential of HCWs. In the equations above, $\omega_J = \mu_J + \gamma_J$ for some compartment J. These two values represent processes occurring simultaneously: a direct transmission between patients and a two-step cycle of transmission between patients and HCWs.

Equation (6) is the average number of newly colonized patients as result of contacts with other colonized or infected patients. The first term accounts for contacts with colonized patients; and the second term accounts for contacts with infected patients who transitioned from the colonized compartment. Equation (7) measures MRSA transmission in the two-step cycle between HCWs and patients. Thus the average one-step transmission potential is given by the geometric mean of the two one-step transmission potentials: the average number of new contaminated HCWs per colonized patient and per infected patient, and the average number of new colonized patients per contaminated HCW.

Furthermore, since $R_H, R_P > 0$, we have from (5) that

$$R_0 = \frac{R_P}{2} + \frac{1}{2}\sqrt{R_P^2 + 4R_H^2} > \frac{R_P}{2} + \frac{1}{2}\sqrt{R_P^2} = R_P. \tag{8}$$

Applying the triangle inequality, we also find that

$$R_0 = \frac{R_P}{2} + \frac{1}{2}\sqrt{R_P^2 + 4R_H^2} < \frac{R_P}{2} + \frac{1}{2}\left(R_P + 2R_H\right) = R_P + R_H. \tag{9}$$

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 adjusted reproduction number, R_0) which is less than their sum. This is explained by the fact that patients are capable of transmitting MRSA to both patients *and* HCWs, while HCWs can only transmit MRSA to patients, and not to other HCWs. Recall that, as no new infected or colonized patients are being admitted into the system, this adjusted reproduction number accounts only for the spread of MRSA within hospital facilities absent colonized/infected patient admission.

When all patients are assumed to enter the hospital MRSA-negative ($\lambda_I = \lambda_C = 0$), both screening models at admission and discharge simplify to the same adjusted system. Therefore, they share the adjusted reproduction number and no comparison based on this parameter can be made between the screening models. The adjusted reproduction number has the same form as in (5) and satisfies inequalities (8) and (9). R_P and R_H for the screening models are given by

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

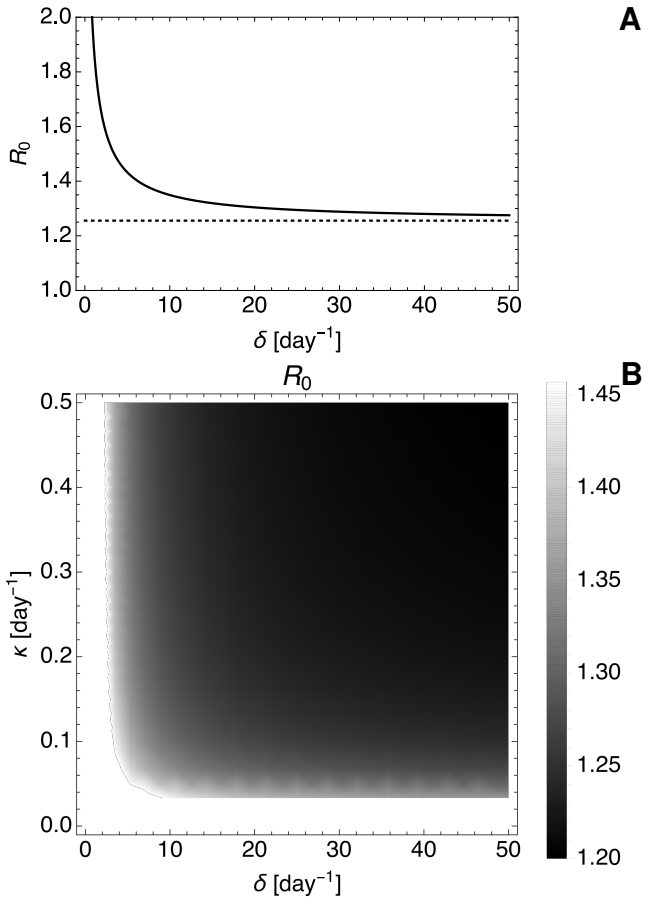

Figure 4: (A) The adjusted reproduction number R_0 of the baseline model is shown with respect to the decontamination rate of HCWs, δ. The adjusted reproduction number is always bigger than $R_0 \approx 1.26$ (dotted line). (B) The adjusted reproduction number of the screening models is shown as a function of the decontamination rate of HCWs, δ, and the rate at which infected patients move to isolation, κ. Note that $R_0 > 1$ for all values of δ and κ plotted.

and

$$R_H = \sqrt{N_H^* \left(\frac{\hat{\beta}_1}{\alpha + \phi + \omega_C} + \frac{\phi}{\alpha + \phi + \omega_C} \cdot \frac{\hat{\beta}_2}{\kappa + \mu_I} \right) N_P^* \left(\frac{\beta_2}{\delta} \right)}, \tag{11}$$

respectively. The difference between the adjusted reproduction numbers for the baseline and screening models is the introduction of the rate κ, which is the rate of progression of infected patients to the isolation unit. Note also that the discharge rate γ_I is excluded from the adjusted number of the screening models. 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 adjusted reproduction number.

The time it takes for a contaminated HCW to become decontaminated can vary between 6 hours and 24 days (Grundmann et al., 2002), and it can be seen in Figure 4A that the adjusted reproduction number of the baseline model is always greater than 1 for any of these values of δ. This means that reducing the decontamination rate can decrease the value of the adjusted reproduction number, but it is never enough to prevent an outbreak in the absence of any other control effort.

To determine how both κ and δ affected the adjusted reproduction number in the models with screening, the latter was graphed as a function of either variable. The results are shown in Figure 4B. We found that when increasing δ or κ and keeping other parameters constant, it is always the case that $R_0 > 1$. Therefore, in order to reduce the prevalence of MRSA in hospitals, it is not sufficient to only ensure that HCWs are adhering to hygiene policies and screening patients regularly for MRSA infection: it is necessary to control for other parameters.

Other model parameters were analyzed similarly (not shown). Having $\delta > 5$ day^{-1}, $\beta_1 < 0.21$ day^{-1} ensures that the reproduction number is less than 1. If $\delta \leq 5$ day^{-1}, however, this may not be sufficient in order to prevent endemicity of MRSA in the system. A similar phenomenon can be observed with the parameter γ_C. This indicates that as long as competent hygiene policies are enforced, an endemic free system can be achieved so long as both $\beta_1, \gamma_C < 0.2$ day^{-1} in a system with screening (i.e.,

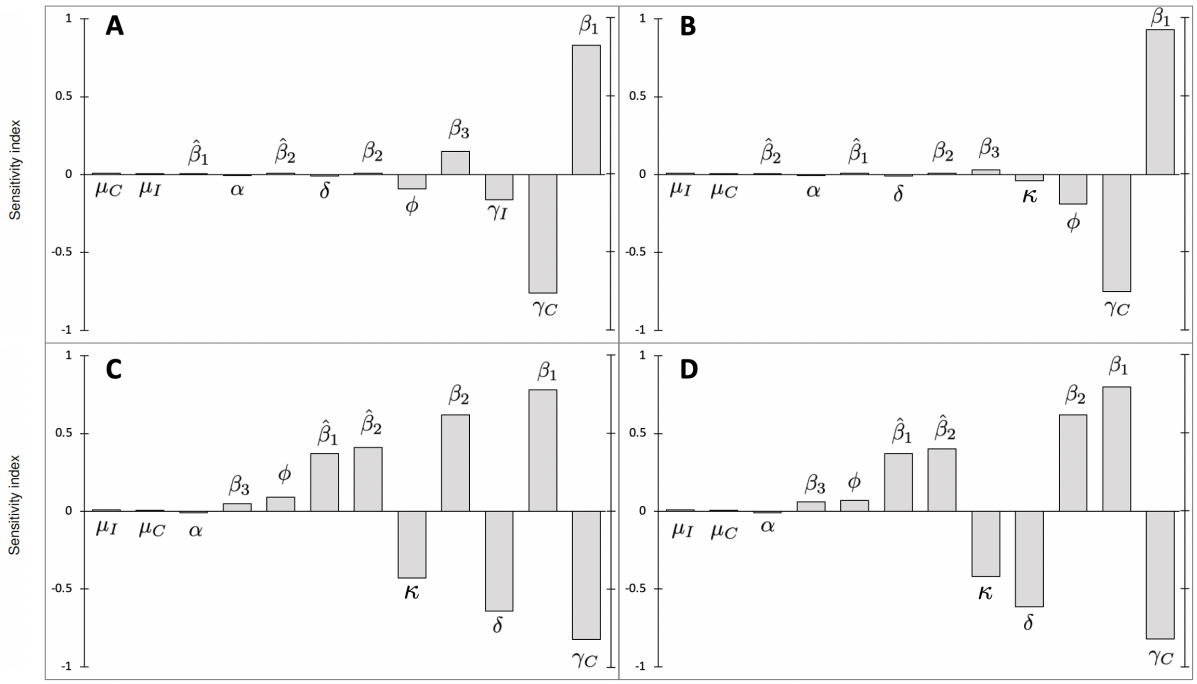

Figure 5: Sensitivity analysis of the adjusted reproduction number R_0 with respect to some parameters for (A) the baseline model and (B) the models with screening strategies, using Table 1 values. Sensitivity scenarios for a 10% increase (C) and 10% decrease (D) in values for β_1 and γ_C, respectively.

strict precautions are taken when contacting colonized patients and colonized patients are treated as soon as possible, ideally at a rate of 1 in every 5 days).

4.2 Sensitivity analysis of R_0

For the sensitivity analysis, we assumed that the parameters were obtained from normal distributions. Local sensitivity indices are estimated from the partial derivatives of R_0. In practice, parameter values are changed by a factor of 0.01 and the corresponding percent change in R_0 is plotted. Figure 5A summarizes the indices of sensitivity for the adjusted reproduction number of the baseline model, as given by equations (6) and (7). As one can see, the parameters to which R_0 is most sensitive are the rate of transmission between uncolonized and colonized patients (β_1) and the discharge rate of colonized patients (γ_C).

In our baseline model there are several mechanisms by which an uncolonized patient may become colonized with MRSA. This sensitivity analysis supports the hypothesis that the most important mechanism to mitigate is direct colonization via other colonized patients. The parameter γ_C summarizes the flow out from the colonized compartment due to treatment or discharge. This means that as more colonized patients leave the hospital, net MRSA transmission rate drops. In the baseline model, only these two parameters exhibited significant effects on R_0 when changed by small amounts. The remaining parameters produced negligible effects on R_0.

For the models with screening at admission and discharge, (10) and (11), we found that the contamination rate, β_1, and the recovery rate of colonized patients, γ_C, were the most influential parameters (see Figure 5). These results continued to hold when we varied β_1 and γ_C by ±10%. Figure 5C shows the sensitivity indices when $\beta_1 = 0.24$ and $\gamma_C = 0.13$ (a parameter change of −10%), while Figure 5D shows the sensitivity indices when $\beta_1 = 0.3$ and $\gamma_C = 0.16$ (a parameter change of +10%). This analysis shows consistent sensitivity results with γ_C and β_1 presenting the largest effects. The decontamination rate, δ, and contamination rate, β_2, are the third most sensitive parameters for Figures 5C and 5D, respectively.

4.3 Endemic equilibria

The adjusted reproduction number calculation allowed us to compare the criteria for outbreaks of the baseline model and the screening models. In this subsection, we make a comparison between both screening models by calculating their endemic equilibria. An endemic equilibrium corresponds to a steady state where the disease remains in the population (Brauer, 2008). The

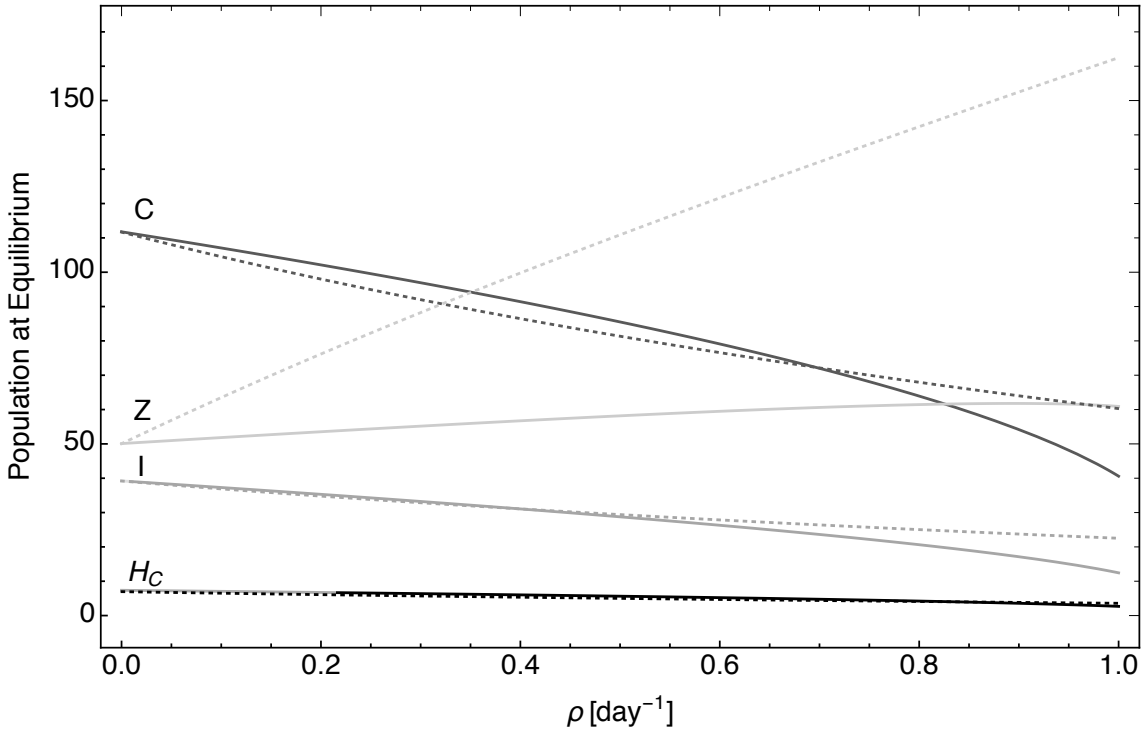

Figure 6: Population sizes at the endemic equilibrium as ρ varies. The solid lines correspond to screening at admission model, whereas the dotted lines correspond to screening at discharge model. The populations shown are contaminated health care workers H_C, colonized C, infected I and isolated Z patients.

high level of complexity associated with our models does not allow us to find a closed form solution for the endemic equilibria, hence solutions were found using numerical methods.

Figure 6 shows the in-hospital populations H_C, C, I and Z, at the endemic equilibrium, as functions of the screening proportion ρ. For screening probabilities below 60%, screening at patient discharge, shown with dotted lines, produced marginally better endemic conditions than screening at patient admission, shown with solid lines. Although endemic conditions were more favorable for the model with screening at discharge, the isolated patient population was much larger than in the model with screening at admission. For higher screening probabilities, screening at patient admission produced better endemic conditions. For all but the highest screening proportions ($\rho > 0.8$), contaminated HCW and infected patient populations were very similar in size for either screening model.

Figure 7A presents the sum of colonized patients, infected patients, and contaminated HCWs as a function of parameters ρ and δ for the model with screening at admission. We shall refer to this sum as the contaminated population. Sufficiently large values of δ ($\delta > 10$ day^{-1}) produced little overall influence on the contaminated population when compared to ρ.

The same comparison was made for the model with screening at discharge in Figure 7B. There was little difference between screening models in how the parameter δ affected the contaminated population. Interestingly, even for very high screening proportions, the contaminated population in the model with discharge screening was still greater than 100. This is a consequence of the mechanism of screening, as discharge screening does not stop individuals colonized or infected with MRSA from entering the hospital. For higher values of ρ the model with screening at admission produced more favorable results, indicated by a smaller contaminated population.

5 Results and Discussion

We developed and analyzed three models of nosocomial MRSA transmission to find the superior screening strategy. Popular hospital practice favors screening at admission, while screening at discharge had yet to be tested. We found that, for screening values of $\rho < 0.6$ (i.e., less than 60% of new/outgoing patients are screened at admission/discharge), screening at discharge produced marginally better results in the form of a smaller overall colonized patient population. For $\rho < 0.6$, the effect of either control strategy on the infected patient population was nearly equivalent. For $\rho > 0.6$, on the other hand, screening at admission was the better screening method, as it better controlled both colonized and infected patient populations. For all values $\rho > 0$,

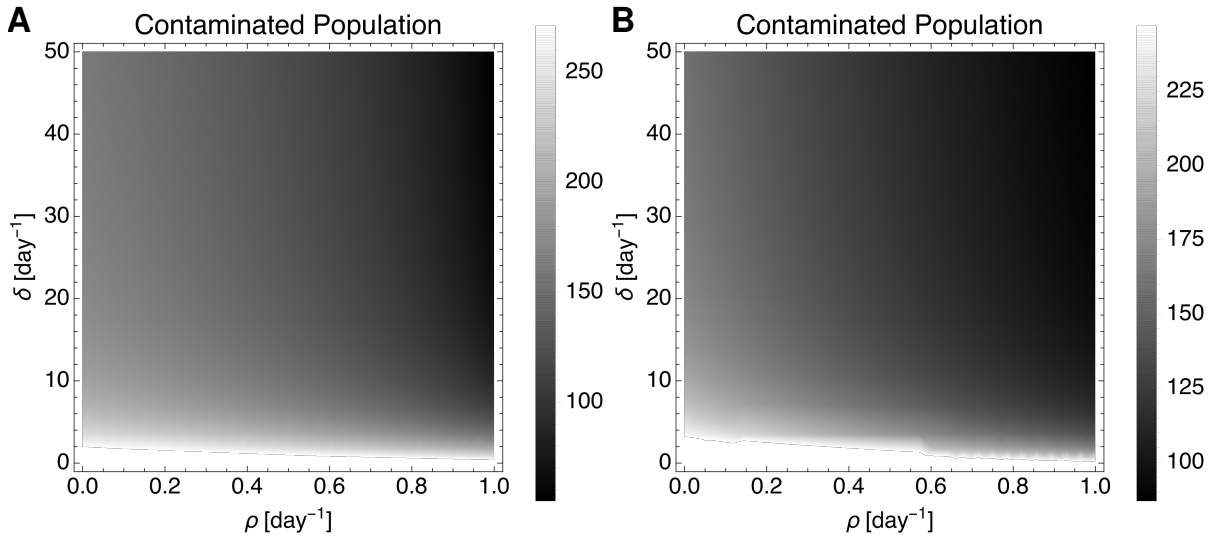

Figure 7: Contaminated population as a function of screening proportion (ρ) and the decolonization rate of contaminated HCWs (δ) for the model with screening at (A) admission and (B) discharge.

screening at discharge yielded more isolated patients than the alternative control strategy, suggesting cost limitations.

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 a hospital for lower screening percentages. Although common practice prefers screening at admission, our results show that, for screening percentages below 60%, screening at discharge is more effective in reducing colonized patient populations within a hospital. For the same range of screening percentages, the infected patient and contaminated HCW populations were nigh indistinguishable (i.e., differences in equilibria were insignificant). However, screening at discharge 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 limited capacity. Consideration of a limited capacity IU was ignored as this would have made our screening at discharge model nonsmooth and thus significantly more difficult to analyze. For screening percentages greater than 60%, screening at admission performed better overall, yielding lower equilibria for both the colonized and infected patient populations. Contaminated HCW populations were once again indistinguishable between models for higher values of ρ.

Some areas of further research and elaboration remain. The most significant of these includes an 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 in the number of isolated patients can 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. These results might guide policy makers to improve control strategies, but a detailed cost analysis might produce more sound results. In performing our research, parameter values were chosen conservatively so as to provide a lower bound for any results later on.

As mentioned earlier, we made the common assumption that patients and HCWs mix homogeneously, and that our patient and HCW populations were constant. To give a more detailed description of heterogeneous mixing would require significantly more data on HCW-patient contact patterns than is presently available.

Parameters were taken, for the most part, from primary sources and various papers discussing MRSA endemic dynamics. A more exhaustive analysis could include confidence intervals and hypothesis testing.

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Appendix: Reproduction Number Calculations

To calculate the reproduction number, we employed the next-generation matrix method (Diekmann et al., 1990; van den Driessche and Watmough, 2002), in which the basic reproduction number is the largest eigenvalue or spectral radius of FV^{-1}, where F and V are the Jacobian matrices of vectors $\mathscr{F}$ and $\mathscr{V}$. F and V are evaluated at the disease free equilibrium (4) obtained when $\lambda_I = \lambda_C = 0$. For the models herein, $\mathscr{F}$ is a vector whose entries are terms that account for newly contaminated patients and contaminated HCWs. Newly contaminated individuals enter either the contaminated HCW compartment H_C, or the colonized patient compartment C. In contrast, $\mathscr{V}$ contains terms of transitions and outflow of patients and HCWs from these compartments.

For the baseline model, the entries in vectors $\mathscr{F}$ and $\mathscr{V}$ correspond to the H_C, C and I compartments:

$$\mathscr{F} = \begin{pmatrix} \hat{\beta}_1 \frac{C(N_H - H_C)}{N} + \hat{\beta}_2 \frac{I(N_H - H_C)}{N} \\ \beta_1 \frac{C(N_P - C - I)}{N} + \beta_2 \frac{H_C(N_P - C - I)}{N} + \beta_3 \frac{I(N_P - C - I)}{N} \\ 0 \end{pmatrix}$$

and

$$\mathscr{V} = \begin{pmatrix} \delta H_C \\ (\alpha + \phi + \omega_C)C \\ \omega_I I - \phi C \end{pmatrix}.$$

The next-generation matrix for the baseline model is thus

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

where $N_P^* = N_P/N$ and $N_H^* = N_H/N$. 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 HCWs could not contaminate each other. The elements of the third row are also zero because there is not any new infected patient at each time step. The newly contaminated people are either colonized HCWs (first row) or colonized patients (second row).

The adjusted reproduction number of the baseline model is

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

where

$$R_P = N_P^*\left(\frac{\beta_1}{\alpha + \phi + \omega_C} + \frac{\phi}{\alpha + \phi + \omega_C} \cdot \frac{\beta_3}{\omega_I}\right) \tag{13}$$

and

$$R_H = \sqrt{N_H^* \left(\frac{\hat{\beta}_1}{\alpha + \phi + \omega_C} + \frac{\phi}{\alpha + \phi + \omega_C} \cdot \frac{\hat{\beta}_2}{\omega_I} \right) N_P^* \left(\frac{\beta_2}{\delta} \right)}. \tag{14}$$

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

When all patients are assumed to enter the hospital MRSA-negative ($\lambda_I = \lambda_C = 0$), both screening models at admission and discharge simplify to the same adjusted system. Therefore, they share the adjusted reproduction number and no comparison based on this parameter can be made between the screening models. The DFE in (4) does not take into account compartments F or F_U because they belong outside the hospital population. Thus only the compartments H_C, C, I and Z are taken into consideration for the entries of the $\mathscr{F}$ and $\mathscr{V}$ vectors, which are

$$\mathscr{F} = \begin{pmatrix} \hat{\beta}_1 \frac{C(N_H - H_C)}{N} + \hat{\beta}_2 \frac{I(N_H - H_C)}{N} \\ \beta_1 \frac{C(N_P - \Sigma)}{N} + \beta_2 \frac{H_C(N_P - \Sigma)}{N} + \beta_3 \frac{I(N_P - \Sigma)}{N} \\ 0 \\ 0 \end{pmatrix}$$

and

$$\mathscr{V} = \begin{pmatrix} \delta H_C \\ (\alpha + \phi + \omega_C) C \\ (\kappa + \mu_I) I - \phi C \\ \omega_Z Z - \kappa I \end{pmatrix}.$$

The next-generation matrix for the screening models is then

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

The adjusted reproduction number has the same form as in (12) and satisfies inequalities (8) and (9). R_P and R_H for the screening models are given by

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

and

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

respectively.

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