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The effect of co-colonization with community-acquired and hospital-acquired methicillin-resistant *Staphylococcus aureus* strains on competitive exclusion

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Abstract

We investigate the in-hospital transmission dynamics of two methicillin resistant *Staphylococcus aureus* (MRSA) strains: hospital-acquired methicillin resistant *Staphylococcus aureus* (HA-MRSA) and community-acquired methicillin resistant *Staphylococcus aureus* (CA-MRSA). Under the assumption that patients can only be colonized with one strain of MRSA at a time, global results show that competitive exclusion occurs between HA-MRSA and CA-MRSA strains; the strain with the larger basic reproduction ratio will become endemic while the other is extinguished. Because new studies suggest that patients can be concurrently colonized with multiple strains of MRSA, we extend the model to allow patients to be co-colonized with HA-MRSA and CA-MRSA. Using the extended model, we explore the effect of co-colonization on competitive exclusion by determining the invasion reproduction ratios of the boundary equilibria. In contrast to results derived from the assumption that co-colonization does not occur, the extended model rarely exhibits competitive exclusion. More commonly, both strains become endemic in the hospital. When transmission rates are assumed equal and decolonization measures act equally on all strains, competitive exclusion never occurs. Other interesting phenomena are exhibited. For example, solutions can tend toward a co-existence equilibrium, even when the basic reproduction ratio of one of the strains is less than one.

Key words:
population model, two-strain model, disease transmission, co-existence, co-infection

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1. Introduction

Methicillin-resistant *Staphylococcus aureus* is a gram-positive bacterium that has historically been associated with hospital-acquired, or nosocomial, infections. Traditionally, infections due to the hospital-acquired MRSA strain (HA-MRSA) occurred predominantly in debilitated and elderly patients [22]. MRSA causes serious infections and is implicated in a large percentage of hospital deaths [19]. Recently, a new strain of MRSA has emerged in the community (CA-MRSA) which is genetically different from HA-MRSA [4, 15]. Unlike HA-MRSA, CA-MRSA infects otherwise healthy young people [4, 15]. Studies show that CA-MRSA is spreading through the community and inevitably into the hospitals [10, 29, 33]. Some studies suggest that CA-MRSA is eclipsing HA-MRSA in hospitals [31]. In [35], a model was presented which supports this hypothesis, exhibiting competitive exclusion, whereby the MRSA strain with the larger basic reproduction ratio out-competes the other strain and becomes dominant in the hospital setting, while the other strain is extinguished [12, 35]. An assumption of the model is that a single patient is never co-colonized with both HA-MRSA and CA-MRSA.

However, recent studies suggest that patients can be co-colonized with different strains of MRSA simultaneously [9]. A single patient can also be co-colonized with MRSA and other bacterial species [23]. Co-colonization can cause serious problems since genes for antimicrobial resistance can be horizontally transferred between different bacterial species resulting in new highly resistant strains. Creating a model that allows for co-colonization in a single patient is necessary to understand the transmission dynamics of multiple strains in a hospital setting. Such a model also allows us to understand how interventions such as hand-hygiene measure compliance and decolonization rate affect the spread of the bacteria through the hospital. Furthermore, the model will help us to understand the effect of co-colonization on competitive exclusion.

We know of no study which examines co-colonization in the hospital setting. However, numerous mathematical models have been developed to examine the dynamic interplay between two or more diseases in a single host [1, 2, 5–8, 11, 16, 20, 24–27, 32, 34]. Mathematically, there is little difference between studying co-infection and co-colonization. However, the modes of transmission, population size and structure, and treatment approaches differ. For instance, mathematical models have been developed to study the co-existence of pathogens, when patients can become immune after infection, or removed from the population for other reasons such as

vaccine [1, 5, 7, 16, 20, 27, 32]. These models are SIR type (susceptible-infected-removed) models, whereas, in the hospital setting, decolonization measures allow patients to return to the susceptible class. Researchers have studied co-infection in SIS (susceptible-infected-susceptible) type models [2, 6, 8, 11, 24–26, 34] which are more appropriate. However, these works studied pathogens other than MRSA, in non-hospital settings, and therefore these models differ in significant ways, such as treatments, possible population size, the number of compartments, ease of deriving global results, and most importantly the paths between compartments, which define the transmission routes.

As a first step to understanding the effect of co-colonization on the transmission dynamics of MRSA in the hospital setting, we develop a reduced version of the model presented in [35], eliminating the infected compartments, which reduces the model to three compartments: S - susceptible, C - only colonized with CA-MRSA, and H - only colonized with HA-MRSA. In the hospital setting, the total population size is well-approximated by a conserved population, N - the number of beds in the hospital. Conserving the population size allows us to reduce the dimension of the model to two, and derive global results showing competitive exclusion always occurs when both diseases are present and have basic reproduction ratios greater than one.

We then extend the model to investigate the effect of co-colonization on competitive exclusion, allowing single patients to be colonized with CA-MRSA and HA-MRSA simultaneously. We add a compartment B - both, which accounts for patients that are co-colonized with HA-MRSA and CA-MRSA. Patients can become co-colonized after first becoming colonized with HA-MRSA or CA-MRSA and through decolonization measures, can return to the susceptible class, making the model SIS type. We then analyze the model and use numerical simulations to understand the effects of co-colonization on competitive exclusion, as well as to determine how different parameters affect the number of patients that are co-colonized. At first, we investigate a general model that assigns different parameters to transmission rates, decolonization rates, and length of stays. Since there is limited evidence that transmission rates differ between MRSA strains, or that decolonization affects the strains differently, we next analyze the model with all of the transmission rates and decolonization rates equal. The difference between strains is then defined by a single parameter, the length of stay in the hospital. We also investigate the efficacy of two standard interventions, decolonization and compliance with hand-hygiene measures.

Although the model is fairly simple, complex dynamics are revealed.

When transmission rates are assumed equal and the difference in the basic reproduction ratios is solely due to the length of stay of patients colonized with HA-MRSA versus colonized with CA-MRSA, competitive exclusion never occurs, and both strains become endemic in the hospital. In the more general case, where transmission rates of the strains are independent, competitive exclusion depends not only on the basic reproduction ratios for CA-MRSA and HA-MRSA, but also on the rates which patients become co-colonized, as well as the efficacy of decolonization and hand-washing compliance. Additionally we find that, due to co-colonization, a strain may become endemic in the hospital even when its basic reproduction ratio is less than one.

The paper is organized as follows. Section 2 gives a brief overview of the models. In section 3, the existence and stability of boundary and co-existence equilibria are analyzed for a model that does not allow a single patient to be co-colonized and then for a model which does allow co-colonization. In section 4, models in which decolonization strategies differ for the strains, which allow patients to be co-colonized directly from the susceptible state, or which allow the total number of patients in the hospital to vary, are presented and analyzed. In section 5, we numerically investigate how two standard interventions, hand-hygiene measures and decolonization, affect transmission dynamics. In section 6, we summarize our findings.

2. Methods

Initially we analyze a reduced model similar to the model presented in [12, 35]. In this model, the "single-colonization model," susceptible patients in a $N = 400$ bed hospital can be colonized with either CA-MRSA or HA-MRSA but not co-colonized. The single-colonization model differs from the model in [35] by focusing on colonization and not including infected states. The single-colonization model produces similar local results as the model in [12, 35]; the MRSA strain with the larger basic reproduction ratio (R_0^C or R_0^H) competitively excludes the other strain from the hospital, even when both basic reproduction ratios are larger than 1. Here, the single-disease basic reproduction ratio R_0^C or R_0^H is a threshold parameter which determines whether CA-MRSA or HA-MRSA will become endemic in the hospital, due to entrance (into a disease free population) of a single colonized patient (notation and description for basic and invasion reproduction ratios are summarized in D.1, Table D.2). Adding the assumption that the total size of the population equals the number of beds in the hospital, we are

able to reduce the model to two dimensions and derive a global competitive exclusion result.

Next, we extend the single-colonization model to the "co-colonization model," by adding a fourth possible patient state, B, in which patients are co-colonized with both CA-MRSA and HA-MRSA. Patients can enter B from either C or H. For instance, the transition to B from C occurs with a transmission rate β_{CH} when a patient in the C state comes into contact with a health care worker who has become colonized with HA-MRSA by coming into contact with a patient in either the H state or B state. Note that patients must enter one of the single colonized states before entering the co-colonized state (results are similar if patients are able to become co-colonized directly, section 4.2). Next we investigate which parameters cause competitive exclusion or lead to indefinite co-existence of both strains in the hospital.

3. Model Description and Results

3.1. Basic SIS model

First assume that there is only one strain of MRSA in the hospital, HA-MRSA. Thereby, patients exist in one of two possible states:

- $S(t)$ = number of patients susceptible at time t
- $H(t)$ = number of patients colonized with HA-MRSA at time t.

After a breakdown in hand-hygiene practices, healthcare workers can become colonized by coming into contact with colonized patients. Susceptible patients can become colonized when visited by contaminated healthcare workers. Susceptible patients become colonized with HA-MRSA at a transmission rate $(1-\eta)\widehat{\beta_H}$. Here, η represents compliance with hand-hygiene practices ($0 \leq \eta \leq 1$). The lengths of stay for susceptible patients and patients colonized with HA-MRSA are $1/\delta_S$ and $1/\delta_H$, respectively. Decolonization efficacy is given by α_H. The percentage of patients entering the hospital colonized with HA-MRSA is given by $100\lambda_H$. The total number of patients entering the hospital per day is given by Λ. The equations that govern the transmission dynamics of HA-MRSA in the hospital are given by

$$\frac{dS}{dt} = \Lambda(1-\lambda_H) - \frac{(1-\eta)\widehat{\beta_H}SH}{N} + \alpha_H H - \delta_S S \tag{1}$$

$$\frac{dH}{dt} = \Lambda\lambda_H + \frac{(1-\eta)\widehat{\beta_H}SH}{N} - (\delta_H + \alpha_H)H. \tag{2}$$

To simplify the analysis, we absorb $(1-\eta)/N$ into the transmission term so that

$$\beta_H = \frac{(1-\eta)\widehat{\beta_H}}{N}. \tag{3}$$

We then conserve the total population of patients at size N, the number of beds in the hospital. Allowing the population size to vary does not qualitatively change the local results of any of the following models, while conserving the population allows us to reduce the dimensionality of the models and therefore to derive the global stability of the systems. Here, the conservation condition reduces the system to a single equation, by replacing S with $N - H$.

To determine if transmission dynamics alone cause the strains to remain in the hospital indefinitely, we let $\lambda_H = 0$. This can be seen as a perfect screening model, where all patients are screened for bacteria upon entrance and screening is 100% effective. Under these refinements, transmission dynamics are governed by the basic SIS model under conservation,

$$\frac{dH}{dt} = \beta_H(N-H)H - (\delta_H + \alpha_H)H. \tag{4}$$

We define R_0^H as the basic reproduction ratio when only HA-MRSA exists in the hospital. R_0^H is easily found using standard linearization techniques,

$$R_0^H = \frac{\beta_H N}{(\delta_H + \alpha_H)}. \tag{5}$$

The disease-free equilibrium (DFE, E_0^H) (see D.1, Table D.1 for description of all equilibria),

$$E_0^H\colon\ H = 0 \tag{6}$$

for the basic SIS model is globally asymptotically stable when $R_0^H < 1$. Note that here $S = N$. Otherwise there is a unique boundary equilibrium, where HA-MRSA remains indefinitely in the hospital,

$$E_H\colon\ H = \frac{N\beta_H - \delta_H - \alpha_H}{\beta_H} = N\left(1 - \frac{1}{R_0^H}\right), \tag{7}$$

which is globally asymptotically stable [21].

Symmetrically, for the community strain in the absence of the hospital strain, ($C(t)$ = number of patients colonized with CA-MRSA at time t, and

$S = N - C$),

$$R_0^C = \frac{\beta_C N}{(\delta_C + \alpha_C)}. \tag{8}$$

Here, R_0^C is the basic reproduction ratio when only CA-MRSA exists in the hospital. Susceptible patients become colonized with CA-MRSA with a transmission rate of $(1-\eta)\widehat{\beta_H}$ and $\beta_C = (1-\eta)\widehat{\beta_C}/N$. The length of stay for patients colonized with CA-MRSA is $1/\delta_C$ and decolonization efficacy is given by α_C. The percentage of patients entering the hospital colonized with CA-MRSA ($100\lambda_C$) would be included in the model in the same form as in system 2, but here has also been set to zero.

Again, the DFE,

$$E_0^C\colon\ C = 0, \tag{9}$$

is globally asymptotically stable when $R_0^C < 1$ (here also, S = N). Otherwise there is a unique boundary equilibrium,

$$E_C\colon\ C = \frac{N\beta_C - \delta_C - \alpha_C}{\beta_C} = N\left(1 - \frac{1}{R_0^C}\right), \tag{10}$$

which is globally asymptotically stable [21].

R_0^C and R_0^H increase when transmission (β_H or β_C) increases. The basic reproduction ratios are also dependent on the length of stay of patients colonized with the strains ($1/\delta_C$ and $1/\delta_H$), as well as the efficacy of decolonization (α_C and α_H). Therefore, if one strain is more highly transmissible than the other, its basic reproduction ratio will be higher. Additionally, if one strain causes more severe infections or only affects populations of the hospital that on average stay longer in the hospital (such as the elderly), then the length of stay will be longer and the R_0 value for that strain will be larger.

3.2. Single-colonization Model

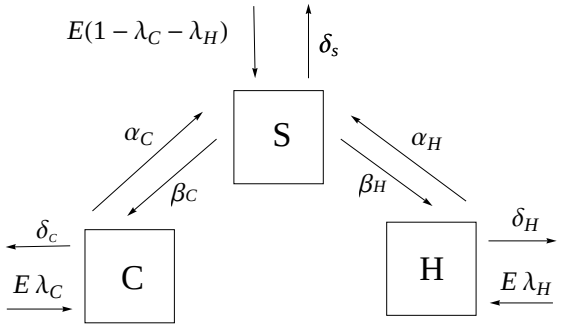
Next, we extend the model to be similar to [35], where patients can only be colonized with a single strain of MRSA (co-colonization with HA-MRSA and CA-MRSA is not included but both strains exist in the hospital). Therefore, patients are in one of the three states, S, H or C, which are now included in the model together. The equations that govern the transmission

dynamics of CA-MRSA and HA-MRSA in the hospital are then given by

$$\frac{dC}{dt} = \beta_C(N - C - H)C - (\delta_C + \alpha_C)C \tag{11}$$

$$\frac{dH}{dt} = \beta_H(N - C - H)H - (\delta_H + \alpha_H)H, \tag{12}$$

where the parameter definitions are the same as in the basic SIS models and where now, $S = N - C - H$ (figure 3.2).



3.3. Single-colonization Results

The single-colonization model, equations (11) and (12), shows qualitatively similar local results as [35]. These local results suggest that competitive exclusion occurs. When $1 < R_0^C < R_0^H$, the boundary equilibrium E_H^{sc}: $(C, H) = (0, N(1 - 1/R_0^H))$ is stable while the boundary equilibrium E_C^{sc}: $(C, H) = (N(1 - 1/R_0^C), 0)$ is unstable (see D.1 for equilibria and local stability results). When $1 < R_0^H < R_0^C$, E_C^{sc} is stable while E_H^{sc} is unstable.

Since the single-colonization model is two-dimensional, we are able to extend these results to show global competitive exclusion occurs.

Theorem 3.1. *The disease-free equilibrium, $E_0^{sc} = (C, H) = (0, 0)$ exists for all parameters for the single-colonization model, equations* (11) *and* (12)*, and is globally asymptotically stable if R_0^C and R_0^H are both less than one.*

This global result shows that, independent of the initial number of patients colonized with either strain, if neither strain would become endemic in the absence of the other, neither will become endemic when both are present.

Theorem 3.2. *If $1 < R_0^C < R_0^H$ and if there are initially some patients colonized with HA-MRSA (the initial condition does not start on the C-axis),*

the boundary equilibrium E_H^{sc} exists and is globally asymptotically stable. Also, the boundary equilibrium E_C^{sc} exists and is globally unstable. Therefore, competitive exclusion occurs.

A symmetric result (exchange C's with H's) holds when $1 < R_0^H < R_0^C$.

These global results show that if either strain would have become endemic in the absence of the other strain, then the dominant strain (the one with the larger basic reproduction ratio) will become endemic while the other will be extinguished. Global stability, as opposed to local stability, shows that competitive exclusion will occur independently of how many patients are originally colonized with each strain (as long as there is initially at least one patient colonized with each strain).

Note here that if the inferior strain has an $R_0 < 1$ while the dominant strain has an $R_0 > 1$, then the dominant strain will become endemic and the inferior strain will be extinguished over time. In this case, the boundary equilibrium associated with the inferior strain does not exist.

Proofs for theorems 3.1 and 3.2 are given in Appendix A.

3.4. Co-colonization model

Next we extend the model, equations (11) and (12), to allow patients to be concurrently colonized with CA-MRSA and HA-MRSA. The compartment dynamics are now governed by the equations:

$$\frac{dC}{dt} = (\delta_S S + \delta_C C + \delta_H H + \delta_B B)\lambda_C + \beta_C S(C+B) - \beta_{CH} C(H+B) - (\delta_C + \alpha_C)C \tag{13}$$

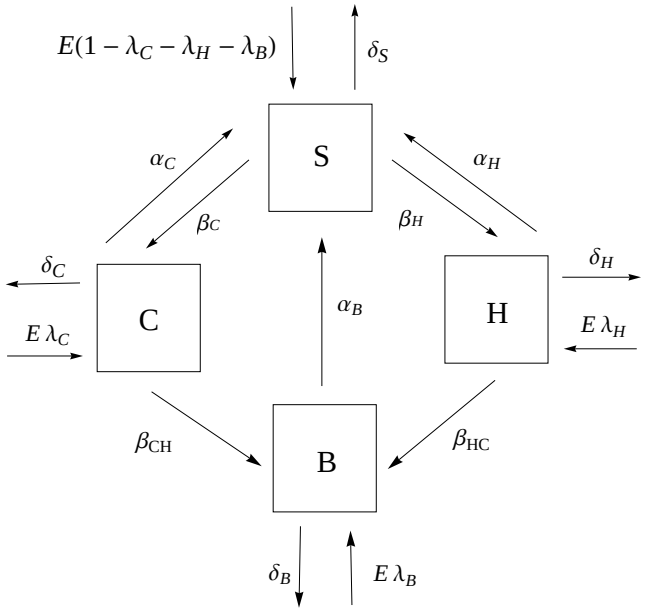
$$\frac{dH}{dt} = (\delta_S S + \delta_C C + \delta_H H + \delta_B B)\lambda_H + \beta_H S(H+B) - \beta_{HC} H(C+B) - (\delta_H + \alpha_H)H \tag{14}$$

$$\frac{dB}{dt} = (\delta_S S + \delta_C C + \delta_H H + \delta_B B)\lambda_B + \beta_{CH} C(H+B) + \beta_{HC} H(C+B) - (\delta_B + \alpha_B)B. \tag{15}$$

Here, B signifies the compartment of patients co-colonized with CA-MRSA and HA-MRSA. Also now, from the conservation condition, $S = N - C - H - B$. The transmission rates are $(1-\eta)\widehat{\beta_{CH}}$ for patients colonized with CA-MRSA becoming co-colonized with both strains, and $(1-\eta)\widehat{\beta_{HC}}$ for patients colonized with HA-MRSA becoming co-colonized; $\beta_{CH} = (1-\eta)\widehat{\beta_{CH}}/N$ and $\beta_{HC} = (1-\eta)\widehat{\beta_{HC}}/N$. The length of stay for co-colonized patients is $1/\delta_B$.

Decolonization efficacy is given by α_B for co-colonized patients. All other parameters remain the same (figure 3.4).

Again, to analyze the transmission dynamics in the hospital, thinking of this as a perfect screening model, we let $\lambda_C = \lambda_H = \lambda_B = 0$, where $100\lambda_B$ is the percentage of patients entering the hospital co-colonized.



3.5. Co-colonization Results

Theorem 3.3. *The DFE, E_0^{cc}: $(C, H, B) = (0, 0, 0)$, of the co-colonization model, equations 13 - 15, exists and is locally asymptotically stable if R_0^C and $R_0^H < 1$. (The basic reproduction ratio for the co-colonization model, $R_0^{cc} = \max\{R_0^H, R_0^C\}$.)*

This result suggests that, even with the allowance of co-colonization, if neither strain would have become endemic in the hospital in the absence of the other, neither will be endemic in the presence of the other.

Besides the DFE, there are two other analytically known equilibria, the boundary equilibria. Each of these represents the state where one strain

of MRSA is endemic in the hospital while the other strain is extinguished. If one of these is locally stable while the other is unstable, competitive exclusion is suggested. If both are unstable, competitive exclusion does not occur. These equilibria are

$$E_H^{cc}\text{: } (C, H, B) = (0, N(1 - 1/R_0^H), 0) \tag{16}$$

$$E_C^{cc}\text{: } (C, H, B) = (N(1 - 1/R_0^C), 0, 0). \tag{17}$$

We use the corresponding invasion reproduction ratios, I_H^{cc} and I_C^{cc}, to determine when only the hospital strain or only the community strain exclusively remains endemic in the hospital over time. I, the invasion reproduction ratio, is a threshold parameter similar to R_0. The difference between them is that R_0 is a threshold parameter, which, when greater than one, signifies that at least one strain will become endemic in the hospital and when less than one signifies that both strains will be extinguished over time. In this way, it describes the stability of the DFE; when $R_0 > 1$ the DFE is unstable and when $R_0 < 1$ the DFE is stable. Whereas, I is a threshold parameter that determines when a secondary strain will become endemic in the presence of another strain which is endemic in the hospital [11, 34, 37]. This can mean that the new strain replaces the old strain, and the old strain is extinguished over time or that both strains are endemic over time leading to co-existence. For the co-colonization model, I describes the stability of the boundary equilibria (see D.1, Table D.2). For example, I_C^{cc} is the invasion reproduction corresponding to the boundary equilibrium E_C^{cc}, which represents only CA-MRSA being endemic in the hospital. When $I_C^{cc} > 1$, then E_C^{cc} is unstable (just as the DFE is unstable when $R_0 > 1$); the introduction of one patient with HA-MRSA would push the system away from the boundary equilibrium containing only CA-MRSA and susceptible patients, (E_C^{cc}), towards an equilibrium where H is positive and HA-MRSA becomes endemic.

It is not possible to have an equilibrium where both C and H are positive and $B = 0$. This is apparent if we look at the equation describing the rate of change of B. If $C > 0$ and $H > 0$ then $\frac{dB}{dt} > 0$, and therefore B cannot equal zero in the asymptotic state.

There is a fourth equilibrium, the "co-existence equilibrium," that is found in numerical solutions which has a known form under realistic assumptions (shown below) but does not have a general known form. All compartments are positive in the fourth equilibrium, and both diseases remain endemic over time. We expect this equilibrium to be stable when the three analytically known equilibria are concurrently unstable.

Theorem 3.4. *E_H^{cc} exists if $R_0^H > 1$, is locally asymptotically stable if $I_H^{cc} < 1$ and is locally asymptotically unstable if $I_H^{cc} > 1$, where I_H^{cc} is the invasion reproduction ratio given by*

$$I_H^{cc} = \frac{R_0^C}{R_0^H}\left(\frac{\frac{\beta_{CH}}{(\alpha_B+\delta_B)}N\left(1-\frac{1}{R_0^H}\right)+1}{\frac{\beta_{CH}}{(\alpha_C+\delta_C)}N\left(1-\frac{1}{R_0^H}\right)+1}\right)+\frac{\beta_{HC}}{\alpha_B+\delta_B}N\left(1-\frac{1}{R_0^H}\right). \quad (18)$$

Symmetric results hold for E_C^{cc} and I_C^{cc}, the boundary equilibrium and invasion reproduction ratio where only CA-MRSA is endemic.

I_H^{cc} has a complicated form, but we can extract some interesting biological ideas from the equation. First, if we let $\beta_{CH} = \beta_{HC} = 0$, the system reduces to the single-colonization model, and $I_H^{cc} = I_H^{sc} = R_0^C/R_0^H$. Otherwise, I_H^{cc} differs from I_H^{sc} in that it is dependent not only on R_0^C and R_0^H, but also on the rates of transmission to the co-colonized state, as well as the lengths of stay of patients colonized only with CA-MRSA as well as patients co-colonized.

When $I_H^{cc} > 1$, the boundary equilibrium E_H^{cc} is unstable. This means that over time, HA-MRSA will not be the only strain remaining in the hospital, and it is likely that CA-MRSA invades, also becoming endemic. The system then tends toward the co-existence equilibrium. The only other possibilities are both strains are extinguished or CA-MRSA alone remains endemic. Both strains cannot be extinguished, because that would mean the DFE would be stable, and since we assumed $R_0^H > 1$, the DFE is unstable. When $1 < R_0^C < R_0^H$, most parameters that make $I_H^{cc} > 1$ also make $I_C^{cc} > 1$. This is because $R_0^C/R_0^H < R_0^H/R_0^C$ and $(1 - 1/R_0^H) < (1 - 1/R_0^C)$, the smaller terms being part of I_H^{cc} and the larger terms being part of I_C^{cc}. When both I_H^{cc} and I_C^{cc} are greater than one, both strains become endemic in the hospital over time, because neither boundary equilibria nor the disease-free equilibrium is stable.

There is limited evidence that transmission rates differ between MRSA strains, or that antimicrobial agents affect the strains differently. Therefore, we next assume that all transmission rates are equal and antimicrobial agents act equally.

Theorem 3.5. *If $\beta = \beta_C = \beta_H = \beta_{CH} = \beta_{HC}$, and if $\alpha = \alpha_C = \alpha_H = \alpha_B$,*

$$I_H^{cc2} = \frac{1}{1-\frac{1}{R_0^H}+\frac{1}{R_0^C}} + R_0^H - 1, \quad (19)$$

and competitive exclusion will not occur.

Under these conditions (all $\beta's$ are equal and all $\alpha's$ are equal) a known form exists for the co-existence equilibrium (see Appendix C for the form of the co-existence equilibrium).

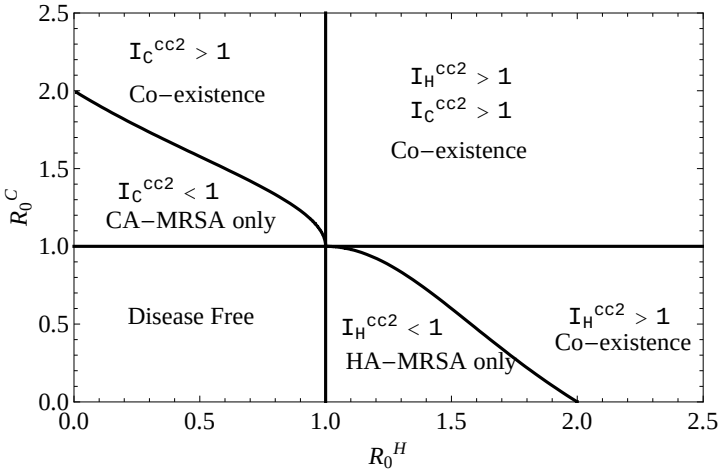
Corollary 3.6. *Under the assumptions of theorem 3.5,*

$$I_H^{cc2} > 1 \tag{20}$$

whenever

$$R_0^C > \frac{1}{\frac{1}{2-R_0^H} + \frac{1}{R_0^H} - 1}. \tag{21}$$

Notice that $I_H^{cc2} > 1$ even for some values where $R_0^C < 1$. In fact, when $R_0^H > 2$, $I_H^{cc2} > 1$ for all possible values of R_0^C ($R_0^C > 0$) (see figure 3.5). This counterintuitive result says that the invasion reproduction ratio of the dominant strain can be larger than one even when the basic reproduction ratio of the inferior strain is less than one. When $R_0^C < 1$ and condition 21 is true, co-colonization causes CA-MRSA to become endemic in the hospital. Under the same parameters, CA-MRSA would have been extinguished over time without co-colonization.



Since all $\beta's$ are equal and all $\alpha's$ are equal, the only difference between R_0^C and R_0^H lies in the lengths of stay of patients colonized with CA-MRSA and patients colonized with HA-MRSA, $CLOS = 1/\delta_C$ and $HLOS = 1/\delta_H$, respectively. The length of stay of co-colonized patients ($BLOS$) is assumed to be the longer of $CLOS$ and $HLOS$ ($BLOS = 1/\delta_B = \max\{1/\delta_C, 1/\delta_H\}$), since they are colonized with the dominant strain. But co-colonized patients

are also colonized with the inferior strain. Therefore, due to co-colonization, the effective length of stay of patients with the inferior strain increases, causing it to remain in the hospital even for parameters where $R_0^C < 1$ if they also make condition 21 true.

Numerical simulations suggest that the co-existence equilibrium exists and is globally asymptotically stable if and only if the invasion reproduction ratio of the dominant strain, the strain with the larger basic reproduction ratio, is greater than one (see Appendix C for details). All numerical simulations were performed using Mathematica (Wolfram Research, Inc).

If there are other differences between the strains besides the lengths of stay, such as different transmission rates or different rates of decolonization (not all $\beta's$ or $\alpha's$ are equal), then equation 18 determines when $I_H^{cc} > 1$. In this case, I_H^{cc} is not dependent only on R_0^H and R_0^C. It is also dependent on the rates that patients become co-colonized, as well as the decolonization rates, and $CLOS$ and $BLOS$. For example, if patients that are colonized with HA-MRSA are more likely to become colonized with CA-MRSA (increase the transmission rate β_{HC} while keeping all other transmission rates equal) then the second term in equation 18 increases. In this case, there are smaller values of R_0^C than those from condition 21 which would make $I_H^{cc} > 1$, and therefore co-existence likely.

Proofs of theorems 3.3, 3.4, and 3.5 are given in Appendix B.

4. Model Variations

4.1. Different Antimicrobial Strategies

In the case where strains are removed with different antimicrobial agents [4], decolonization will remove one strain at a time and patients will transfer to either the C compartment or to the H compartment before being able to transfer to the S compartment.

The equations governing transmission dynamics are then

$$\frac{dC}{dt} = (\delta_S S + \delta_C C + \delta_H H + \delta_B B)\lambda_C + \tag{22}$$
$$\beta_C S(C+B) - \beta_{CH} C(H+B) - (\delta_C + \alpha_C)C + \alpha_{BC} B$$
$$\frac{dH}{dt} = (\delta_S S + \delta_C C + \delta_H H + \delta_B B)\lambda_H + \tag{23}$$
$$\beta_H S(H+B) - \beta_{HC} H(C+B) - (\delta_H + \alpha_H)H + \alpha_{BH} B$$
$$\frac{dB}{dt} = (\delta_S S + \delta_C C + \delta_H H + \delta_B B)\lambda_B + \tag{24}$$
$$\beta_{CH} C(H+B) + \beta_{HC} H(C+B) - (\delta_B + \alpha_{BC} + \alpha_{BH})B.$$

Here, α_{BC} and α_{BH} represent the efficacy of removing the CA-MRSA strain or the efficacy of removing the HA-MRSA strain from a co-colonized patient, respectively. The parameters are written in the most general form but are likely to be equal to α_H and α_C, respectively.

Analyzing the new equations with the same methods used for the co-colonization model shows that the invasion reproduction ratio is the same (equation 18), except we replace α_B with $\alpha_{BC} + \alpha_{BH}$.

4.2. Patients are Directly Co-colonized

We can modify the model by allowing patients to become co-colonized with both CA-MRSA and HA-MRSA directly from the susceptible state, due to contact with healthcare workers who are co-colonized. The only change to the system of equations is adding $\beta_B SB$ patients per time from the S to the B compartment. Then

$$\frac{dB}{dt} = (\delta_S S + \delta_C C + \delta_H H + \delta_B B)\lambda_B + \tag{25}$$
$$\beta_{CH} C(H+B) + \beta_{HC} H(C+B) - (\delta_B + \alpha_B)B + \beta_B SB.$$

If the system remains conserved with $S = N - C - H - B$, and if we let

$$T_B = \beta_{HC} N \left(1 - \frac{1}{R_0^H}\right) - (\alpha_B + \delta_B) + \frac{N\beta_B}{R_0^H} \tag{26}$$

$$T_C = \frac{\beta_C N}{R_0^H} - \left(\alpha_C + \delta_C + \beta_{CH} N \left(1 - \frac{1}{R_0^H}\right)\right) \tag{27}$$

$$N_B = \beta_{HC} N \left(1 - \frac{1}{R_0^H}\right) + \beta_{CH} N \left(1 - \frac{1}{R_0^H}\right) \tag{28}$$

$$N_C = \frac{\beta_C N}{R_0^H}, \tag{29}$$

E_H is locally asymptotically stable when the following two conditions are met

1. $T_B + T_C < 0$
2. $N_B N_C < T_B T_C$.

The proof is the same as for theorem 3.4, except that we can no longer say that $N_B > T_B$. Therefore, both conditions must be met for stability.

4.3. The Hospital Population is Not Conserved

If instead of conserving the population, we allow entrance at a rate of Λ, the invasion reproduction ratio is similar. The same methods show that under this condition, I_H^{pnc} is

$$I_H^{pnc} = \frac{R_0^C}{R_0^H} \left(\frac{\frac{\beta_{CH}}{(\alpha_B + \delta_B)} \frac{\Lambda}{\delta_H} \left(1 - \frac{1}{R_0^H}\right) + 1}{\frac{\beta_{CH}}{(\alpha_C + \delta_C)} \frac{\Lambda}{\delta_H} \left(1 - \frac{1}{R_0^H}\right) + 1} \right) + \frac{\beta_{HC}}{\alpha_B + \delta_B} \frac{\Lambda}{\delta_H} \left(1 - \frac{1}{R_0^H}\right), \tag{30}$$

where in this case E_H^{pnc}: $(S, C, H, B) = ((\alpha_H + \delta_H)/\beta_H, 0, \Lambda/\delta_H - \delta_S(\alpha_H + \delta_H)/(\beta_H \delta_H), 0)$, $R_0^H = \Lambda\beta_H/(\delta_S(\alpha_H + \delta_H))$ and $R_0^C = \Lambda\beta_C/(\delta_S(\alpha_C + \delta_C))$.

5. Numerical Results

Two standard interventions, hand-hygiene measures and decolonization, affect transmission. Therefore, we next investigated the effect of these two interventions on the transmission dynamics of the co-colonization model. We assume that all transmission rates and decolonization rates are equal.

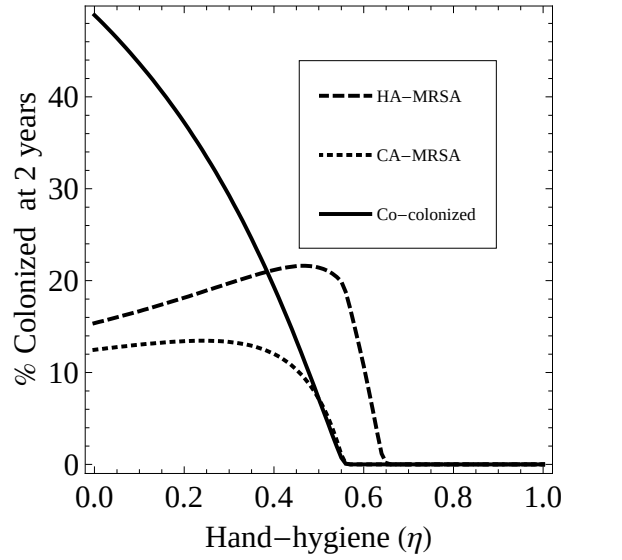
Hand-hygiene is a simple, effective, and inexpensive intervention. However, since washing hands takes time and is necessary after visiting each

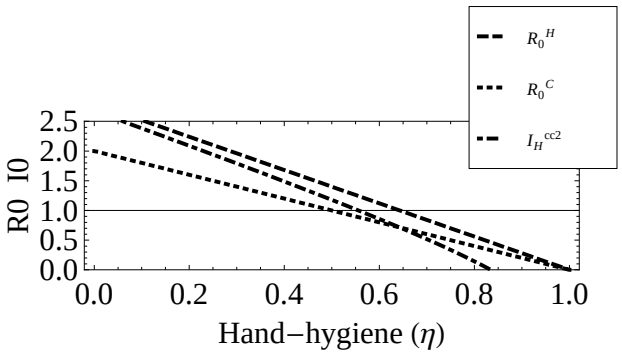
patient, health care workers commonly do not comply completely with hand-hygiene measures. Thus, we varied hand-hygiene compliance, η, between 0 and 1, zero signifying no compliance and 1 signifying perfect compliance. For each η value, we simulated the system for two years. In figure 5, the results of this simulation are shown. As hand-hygiene compliance increases, transmission ($\beta = (1-\eta)\widehat{\beta}/N$) changes, and therefore R_0^C, R_0^H, and I_H^{cc2} change (figure 5 bottom). After two years, both strains remain in the hospital, as long as $I_H^{cc2} > 1$. Notice that this is true, even though R_0^C is less than one for some values of η where $I_H^{cc2} > 1$. Once I_H^{cc2} becomes less than one, E_H becomes stable, and only HA-MRSA remains in the hospital.

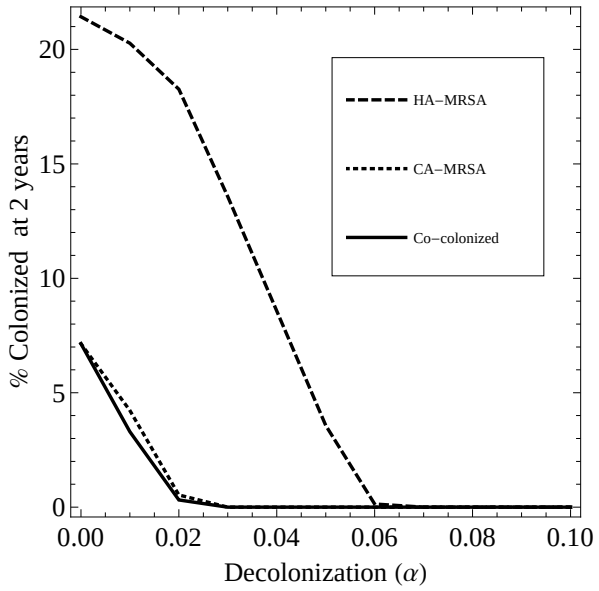
Besides being much more expensive than hand-hygiene measures, decolonization strategies have limited efficacy, since emergence of resistance to the decolonizing agent develops rapidly. To compare the effects of increased decolonization efficacy with hand-hygiene compliance, we next investigated how the efficacy of decolonization affects transmission. We simulated the system for two years, for varying degrees of decolonization efficacy, α, from 0% per day to 100% per day (0% to 10% shown, figure 5). As with hand-hygiene compliance, both strains remain in the hospital until I_H^{cc2} decreases below one (figure 5 bottom). This is true for lower values of α where R_0^C is less than one. Increasing decolonization efficacy quickly reduces the percentage of the patients colonized. The invasion reproduction ratio I_H^{cc2} drops below one with just 2% per day decolonization, leaving only HA-MRSA in the hospital. When decolonization efficacy reaches 6%, both strains are eradicated over time and the system tends towards the disease-free equilibrium.

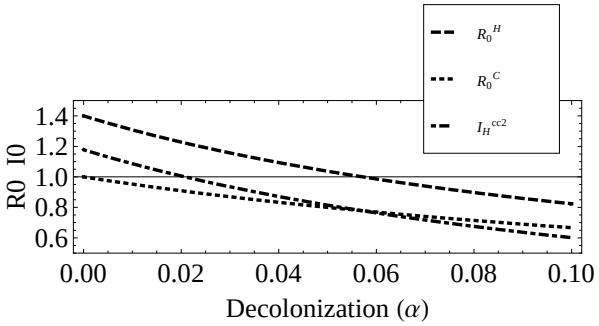
6. Summary

Historically, there has been one known strain of MRSA in the hospital, HA-MRSA. The majority of HA-MRSA infections occurred in elderly or debilitated patients. In recent years, a new strain of MRSA (CA-MRSA) has been found in the population at large, infecting young and otherwise healthy people. As CA-MRSA spreads through the community, it is inevitably entering the hospital, possibly infecting a larger population in the hospital than HA-MRSA would have alone. Understanding how MRSA is transmitted in the hospital setting, when there are multiple strains present, is key to determining appropriate interventions and antimicrobial treatments. Creating mathematical models to elucidate transmission dynamics augments epidemiological studies, which cannot easily determine dynamics because of the numerous factors contributing to bacteria transmission.


HA−MRSA
CA−MRSA
Co−colonized
% Colonized at 2 years
0
10
20
30
40
0.0
0.2
0.4
0.6
0.8
1.0
Hand−hygiene (η)


$R_0{}^H$
$R_0{}^C$
$I_H{}^{cc2}$
R0 I0
0.0
0.5
1.0
1.5
2.0
2.5
0.0
0.2
0.4
0.6
0.8
1.0
Hand−hygiene (η)


20
15
10
5
0
% Colonized at 2 years
HA−MRSA
CA−MRSA
Co−colonized
0.00
0.02
0.04
0.06
0.08
0.10
Decolonization (α)


$R_0{}^H$
$R_0{}^C$
$I_H{}^{cc2}$
1.4
1.2
1.0
0.8
0.6
R0 I0
0.00
0.02
0.04
0.06
0.08
0.10
Decolonization (α)

One issue is whether or not MRSA strains are competing, and if they are, will one strain drive the other strain out of the hospital, causing competitive exclusion. Possible phenotypic characteristics which would distinguish strains are their transmission rates, efficacy of decolonization treatments for each strain, as well as the average length of stay of patients colonized with the strain. If any of these factors differ between CA-MRSA and HA-MRSA, one strain will have a larger basic reproduction ratio (R_0).

Under the assumption that a single patient cannot be colonized with both strains simultaneously, previous work has indicated with local results that competitive exclusion will occur [12, 35]; when both strains have a basic reproduction ratio greater than one, the dominant strain, the one with the larger R_0, will become endemic in the hospital while the inferior strain is extinguished over time. We confirmed these local results using a simplified model, the single-colonization model, and derived global stability results, which showed that competitive exclusion occurred in the hospital independent of how many patients were originally colonized with each strain (theorem 3.2).

The single-colonization model assumed that a single patient could not be concurrently colonized with multiple strains of MRSA. However, recent studies have shown that a single patient can be co-colonized with multiple strains of MRSA simultaneously [9]. Therefore, we next created a model, the co-colonization model, in which patients could be co-colonized with CA-MRSA and HA-MRSA. By determining and analyzing the invasion reproduction ratios, we found that when co-colonization in a single patient is possible, competitive exclusion is parameter dependent, and rare (theorem 3.4). In fact, assuming that the main distinguishing characteristic between strains is the length of stay of colonized patients, competitive exclusion *never* occurs (theorem 3.5 and figure 3.5). Under the same assumptions, numerical simulations suggested that the co-existence equilibrium (which has a known form in this case) exists and is globally stable if and only if the invasion reproduction ratio of the dominant strain is greater than one. Therefore, both strains become endemic in the hospital over time, and the system tends towards the known co-existence equilibrium. Hence, even if CA-MRSA has a competitive disadvantage, it will remain in the hospital, causing higher rates of morbidity and mortality. We also found that both strains can become simultaneously endemic, even when the basic reproduction ratio of the inferior strain is less than one (corollary 3.6). For the same parameters, the inferior strain would have been extinguished in the absence of co-colonization.

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Potential conflicts of interest: EMCD, GFW, JP no conflicts.

Appendix A.

Proof of Theorem 3.1

Proof. Consider the Lyapunov function

$$V = C + H. \tag{A.1}$$

V is positive definite, because $C \geq 0$ and $H \geq 0$ and is radially unbounded.

$$\begin{aligned} \frac{dV}{dt} &= \beta_C(N - C - H)C - (\delta_C + \alpha_C)C + \qquad (A.2)\\ &\quad \beta_H(N - C - H)H - (\delta_H + \alpha_H)H \\ &= (\beta_C N - (\delta_C + \alpha_C))C + (\beta_H N - (\delta_H + \alpha_H))H - \qquad (A.3)\\ &\quad \beta_C(C + H)C - \beta_H(C + H)H. \end{aligned}$$

When $R_0^C < 1$, $\beta_C N - (\delta_C + \alpha_C)$ is negative. Similarly, when $R_0^H < 1$, $\beta_H N - (\delta_H + \alpha_H)$ is negative. For all points other than E_0^{sc}, the third and fourth terms are always negative. Therefore

$$\frac{dV}{dt} < 0 \tag{A.4}$$

everywhere except at E_0^{sc}, where $\frac{dV}{dt} = 0$. Therefore, E_0^{sc} is globally asymptotically stable when R_0^C and R_0^H are both less than one [30]. □

Proof of Theorem 3.2

Proof. Let $F : \mathbb{R}^2 \to \mathbb{R}^2$ and consider

$$\begin{bmatrix} \frac{dC}{dt} \\ \frac{dH}{dt} \end{bmatrix} = \begin{bmatrix} \beta_C(N - C - H)C - (\delta_C + \alpha_C)C \\ \beta_H(N - C - H)H - (\delta_H + \alpha_H)H \end{bmatrix} = F(C, H). \tag{A.5}$$

The only critical points of the system are $(0, 0), (0, N(1 - 1/R_0^H))$ and $(N(1 - 1/R_0^C), 0)$.

Let $\Omega = \{(C, H) \in \mathbb{R}^2 | 0 \leq C \leq N, 0 \leq H \leq N \text{ and } 0 \leq C + H \leq N\}$. We must first show that all trajectories that start in Ω stay in Ω (Ω is a compact forward invariant set for the system). First, consider trajectories starting on the C-axis. $H = 0$ initially, so then $\frac{dH}{dt} = 0$, and thus $H = 0$ for all time. Symmetrically, all solutions that start on the H-axis stay on

the H-axis. Accordingly, solutions that start on the boundary stay on the boundary for all time. Since $F \in C^1(\mathbb{R}^2)$, solutions exist and are unique. Therefore, any solution starting in the interior of Ω cannot cross the axes. Finally, since the system is conserved ($N = S+C+H$), $C+H \leq N$. We see that no solutions can cross the line $H = N - C$. Therefore, Ω is a compact forward invariant set.

Since $F \in C^1(\mathbb{R}^2)$ and the system only has a finite number of critical points in Ω, we know from the Poincaré-Bendixson Theorem, that the ω-limit set of each trajectory is either a critical point, a periodic orbit, or consists of a finite number of critical points and a countable number of limit orbits whose α and ω-limit sets are one of the critical points [30].

We can rule out periodic orbits, for if there were any periodic orbits, we know from index theory that a critical point would lie inside of that orbit. But all critical points lie on the boundary of Ω. We can rule out the critical point $(0, 0)$ because it is locally unstable (both eigenvalues of the linearized system are positive) when $R_0^H > R_0^C > 1$. Additionally, when $R_0^H > R_0^C > 1$, E_H^{sc}: $(C, H) = (0, N(1 - 1/R_0^H))$ is locally asymptotically stable (both eigenvalues of the linearized system are negative), and E_C^{sc}: $(C, H) = (N(1 - 1/R_0^C), 0)$ is a saddle point (one eigenvalue of the linearized system is positive and one is negative) [30]. Since E_H^{sc} is locally asymptotically stable, there can be no trajectory whose α-limit set is E_H^{sc}. Therefore, trajectories either have the ω-limit set E_C^{sc} or E_H^{sc}.

By the Hartman-Grobman Theorem, we know that E_C^{sc} is a topological saddle [30]. Therefore exactly two trajectories approach E_C^{sc}: the trajectory below E_C^{nn} on the C-axis, and the one above it. All other solutions which start in a sufficiently small deleted neighborhood of E_C^{sc} leave the neighborhood as $t \to \pm\infty$. Therefore, all other trajectories must tend to the only possible ω-limit set, E_H^{sc}. Therefore, E_H^{sc} is globally asymptotically stable everywhere in Ω except on the C-axis.

Therefore, competitive exclusion occurs in the single-colonization model. □

Appendix B.

Proof of Theorem 3.3

Proof. If we linearize the co-colonization model about E_0^{cc}, we find that the

eigenvalues of the matrix are:

$$\lambda_1 = -\alpha_B - \delta_B \tag{B.1}$$
$$\lambda_2 = N\beta_C - (\alpha_C + \delta_C) \tag{B.2}$$
$$\lambda_3 = N\beta_H - (\alpha_H + \delta_H). \tag{B.3}$$

λ_1 is always negative. When $R_0^C < 1$ then λ_2 is negative. When $R_0^H < 1$ then λ_3 is negative. Therefore if both R_0^C and R_0^H are less than one, all three eigenvalues are negative and E_0^{cc} is locally asymptotically stable. Otherwise, either λ_2 or λ_3 is positive and E_0^{cc} is unstable. □

Proof of Theorem 3.4

Proof. E_H^{cc} exists if $R_0^H > 1$ because $H = N(1 - 1/R_0^H) > 0$.

To show that E_H^{cc} is locally asymptotically stable, we linearize the system around E_H^{cc}. Next, we compute the eigenvalues of the Jacobian of the system. The first eigenvalue is

$$\lambda_1 = -(\alpha_H + \delta_H + N\beta_H(1 + 2/R_0^H)). \tag{B.4}$$

λ_1 is negative since all values inside of parentheses are positive.

Next, let T_B and T_C equal

$$T_B = \beta_{HC}N(1 - 1/R_0^H) - (\alpha_B + \delta_B) \tag{B.5}$$
$$T_C = \beta_C N/R_0^H - (\alpha_C + \delta_C + \beta_{CH}N(1 - 1/R_0^H)). \tag{B.6}$$

Then, the other two eigenvalues of the Jacobian can be expressed as

$$\lambda_{2,3} = T_B + T_C \pm \sqrt{(T_C + T_B)^2 - 4(T_C T_B - N_C N_B)} \tag{B.7}$$

where $N_C = \beta_C N/R_0^H$ and $N_B = \beta_{HC}N(1 - 1/R_0^H) + \beta_{CH}N(1 - 1/R_0^H)$.

If the following two conditions are met, the real parts of these eigenvalues are negative:

$$T_B + T_C < 0 \tag{B.8}$$
$$N_C N_B < T_C T_B. \tag{B.9}$$

However, we see that $N_C > T_C$, since $T_C = N_C - (\alpha_C + \delta_C + \beta_{CH}N(1 - 1/R_0^H))$ where $(\alpha_C + \delta_C + \beta_{CH}N(1 - 1/R_0^H)) > 0$. Similarly $N_B > T_B$. Also, note that N_C and N_B are always greater than or equal to zero. From these two conditions, we see that $N_C N_B < T_C T_B$ is only possible if both T_C and

T_B are negative. So $T_B + T_C < 0$. Consequently, the only condition we need for E_H to be locally asymptotically stable is

$$N_C N_B < T_C T_B. \tag{B.10}$$

From this condition, I_H^{cc} is derived and is found to be

$$I_H^{cc} = \frac{R_0^C}{R_0^H}\left(\frac{\frac{\beta_{CH}}{(\alpha_B+\delta_B)}N\left(1-\frac{1}{R_0^H}\right)+1}{\frac{\beta_{CH}}{(\alpha_C+\delta_C)}N\left(1-\frac{1}{R_0^H}\right)+1}\right)+\frac{\beta_{HC}}{\alpha_B+\delta_B}N\left(1-\frac{1}{R_0^H}\right). \tag{B.11}$$

I_H^{cc} is less than one when condition B.10 holds. □

Proof of Theorem 3.5

Proof. For competitive exclusion to occur, either $I_H^{cc2} < 1$ or $I_C^{cc2} < 1$.

Assume without loss of generality, that E_H^{cc2} is the dominant equilibrium, so that $R_0^H > R_0^C > 1$. Then, I_H^{cc2} is

$$I_H^{cc2} = \frac{R_0^C}{R_0^H}\left(\frac{\frac{\beta_{CH}}{(\alpha_B+\delta_B)}N\left(1-\frac{1}{R_0^H}\right)+1}{\frac{\beta_{CH}}{(\alpha_C+\delta_C)}N\left(1-\frac{1}{R_0^H}\right)+1}\right)+\frac{\beta_{HC}}{\alpha_B+\delta_B}N\left(1-\frac{1}{R_0^H}\right). \tag{B.12}$$

Under the assumptions that $\beta = \beta_C = \beta_H = \beta_{CH} = \beta_{HC}$ and $\alpha = \alpha_C = \alpha_H = \alpha_B$, I_H^{cc} becomes

$$I_H^{cc2} = \frac{1}{1-\frac{1}{R_0^H}+\frac{1}{R_0^C}} + R_0^H - 1. \tag{B.13}$$

Since $R_0^H > R_0^C > 1$, we know that

$$1 > \frac{1}{1-\frac{1}{R_0^H}+\frac{1}{R_0^C}} > \frac{1}{2}. \tag{B.14}$$

Therefore, if $R_0^H > 3/2$

$$I_H^{cc2} > \frac{1}{2} + \frac{1}{2} = 1. \tag{B.15}$$

Next, consider the triangular region $T = \{(R_0^H, R_0^C) | 1 \le R_0^H \le \frac{3}{2} \text{ and } 1 \le R_0^C \le R_0^H\}$. I_H^{cc2} is continuous and has no critical points inside of T. Ergo, we must only check the boundaries to find the absolute extrema of the

function in T. The minimum value in the region is 1, and this occurs at $(R_0^H, R_0^C) = (1, 1)$. Therefore, $I_H^{cc2} \geq 1$ whenever $R_0^H > R_0^C \geq 1$. In fact, for $R_0^H > R_0^C > 1$, $I_H^{cc2} > 1$.

Because the model is symmetric,

$$I_C^{cc2} = \frac{1}{1 - \frac{1}{R_0^C} + \frac{1}{R_0^H}} + R_0^C - 1. \tag{B.16}$$

When $R_0^H > R_0^C > 1$, $I_C^{cc2} > 1$.

Since both I_H^{cc2} and I_C^{cc2} are greater than one, both E_H^{cc2} and E_C^{cc2} are unstable. This shows that competitive exclusion will not occur. □

Appendix C.

The co-existence equilibrium for

$$\frac{dC}{dt} = \beta S(C + B) - \beta C(H + B) - (\delta_C + \alpha)C \tag{C.1}$$
$$\frac{dH}{dt} = \beta S(H + B) - \beta H(C + B) - (\delta_H + \alpha)H \tag{C.2}$$
$$\frac{dB}{dt} = \beta C(H + B) + \beta H(C + B) - (\delta_B + \alpha)B \tag{C.3}$$

is given by

$$\begin{aligned}
C = \frac{1}{2\beta(\delta_C - \delta_H)}\Big[&-2N^2\beta^2 + N\beta(\alpha - 3\delta_C + 4\delta_H) + (\delta_C - \delta_H)(3\alpha - \delta_C + 4\delta_H) \\
&+ (N\beta + \delta_C - \delta_H)\sqrt{\alpha^2 + (2N\beta + \delta_C)^2 - 8(N\beta + \delta_C)\delta_H + 8\delta_H^2 + \alpha(8\delta_H - 4N\beta - 6\delta_C)}\Big] \\
H = \frac{1}{2\beta(\delta_C - \delta_H)}\Big[&-2N^2\beta^2 + 2(\delta_C - \delta_H)(\alpha + \delta_H) + N\beta\Big(\alpha - \delta_C + 2\delta_H \\
&+ \sqrt{\alpha^2 + (2N\beta + \delta_C)^2 - 8(N\beta + \delta_C)\delta_H + 8\delta_H^2 + \alpha(8\delta_H - 4N\beta - 6\delta_C)}\Big)\Big] \\
B = \frac{-1}{2\beta(\delta_C - \delta_H)}\Big[&-2N^2\beta^2 + 4(\delta_C - \delta_H)(\alpha + \delta_H) + N\beta\Big(\alpha - 3\delta_C + 4\delta_H \\
&+ \sqrt{\alpha^2 + (2N\beta + \delta_C)^2 - 8(N\beta + \delta_C)\delta_H + 8\delta_H^2 + \alpha(8\delta_H - 4N\beta - 6\delta_C)}\Big)\Big]
\end{aligned} \tag{C.4}$$

To investigate the existence and the stability of the co-existence equilibrium, we performed the following numerical simulations.

Our first goal was to show that, when $1 < R_0^C < R_0^H$, the co-existence equilibrium only exists for parameters that make $I_H^{cc2} > 1$. The co-existence

equilibrium, E_H^{cc2} exists when all coordinates (given by the forms in Appendix C) are positive. If E_H^{cc2} only exists when $I_H^{cc2} > 1$, E_H^{cc2} should only exist when condition 21 is true. To see if this condition holds, we varied R_0^H between one and two (if $R_0^H > 2$ then $I_H^{cc2} > 1$ for any R_0^C). For each R_0^H, we numerically found the smallest R_0^C for which the co-existence equilibrium exists. We then compared this estimated value of R_0^C with the infimum of condition 21. Since R_0^H is dependent on β, η, δ_H and α, we varied R_0^H by varying each of these parameters independently. Table C.1 lists the ranges of the parameters and the step size taken for each parameter.

Table C.1: Parameter Value Ranges and Step sizes

Parameter	**Minimum**	**Maximum**	**Step size**
α	0% per day	90% per day	10% per day
η	0%	90%	10%
$HLOS$	1 day	50 days	1 day
R_0^H	1.05	1.95	0.05

Next, we let the length of stay of patients colonized with CA-MRSA ($CLOS$) start at 0.01 days, increasing in steps of 0.01, until all coordinates of the co-existence equilibrium were positive (using the formulas for the co-existence equilibrium above). The first estimated $CLOS$ value for which the co-existence equilibrium existed was then compared with the infimum $CLOS$ value that would make condition 21 true. The difference was always less than 0.01 days, our step size. Therefore, when $1 < R_0^H < 2$, the simulations suggest that the co-existence equilibrium only exists for values of R_0^C that make $I_H^{cc2} > 1$.

Our next goal was to show that if $I_H^{cc2} > 1$, then the co-existence equilibrium exists. Therefore, we varied the same parameters above, but let R_0^H range between 1.1 and 10, in steps of 0.1. For each R_0^H, we varied R_0^C by varying the length of stay of patients colonized with CA-MRSA in steps of 1 day. The starting value for R_0^C was either the infimum R_0^C which makes condition 21 true, or if this is less than or equal to zero, then the starting value was 0.1 days. The maximum R_0^C was the largest iterated value less than R_0^H. All other parameters were varied as in the previous simulations. We found that for all choices of parameters, the co-existence equilibrium exists. This suggests that, when $R_0^H > 1$ and $R_0^H > R_0^C$, the co-existence equilibrium exists, if $I_H^{cc2} > 1$.

Finally, we tested the stability of the co-existence equilibrium. For each choice of parameters in the previous simulations, we let the initial values of C

and H vary between 0 and 396 and the initial value of B vary between 1 and 397 in steps of 99, with $C + H + B < 400$. We then numerically simulated the system for $100,000$ days to find the approximate equilibrium point. We calculated the greatest difference, for all initial conditions, between the ending state of our simulation and the co-existence equilibrium. For all values, the coordinates of the numerically simulated equilibrium were within 0.5 of the coordinates of the co-existence equilibrium, suggesting that when the co-existence equilibrium exists, it is globally stable.

Appendix D.

Table D.1: Symbols, values and stability properties for the disease-free equilibria (E_0) and boundary equilibria (E_H and E_C) for the different models. The values and models for the corresponding reproduction ratios in the last column are given in Table D.2.

Equilibrium	**Value**	**Stability**
E_0^H	$H = 0$	$R_0^H > 1$: unstable $R_0^H < 1$: stable
E_0^C	$C = 0$	$R_0^C > 1$: unstable $R_0^C < 1$: stable
E_0^{sc}	$(C, H) = (0, 0)$	$R_0^{sc} > 1$: unstable $R_0^{sc} < 1$: stable
E_0^{cc}	$(C, H, B) = (0, 0, 0)$	$R_0^{cc} > 1$: unstable $R_0^{cc} < 1$: stable
E_H^{sc}	$(C, H) = (0, N(1 - \frac{1}{R_0^H}))$	$I_H^{sc} > 1$: unstable $I_H^{sc} < 1$: stable
E_C^{sc}	$(C, H) = (N(1 - \frac{1}{R_0^C}), 0)$	$I_C^{sc} > 1$: unstable $I_C^{sc} < 1$: stable
E_H^{cc}	$(C, H, B) = (0, N(1 - \frac{1}{R_0^H}), 0)$	$I_H^{cc} > 1$: unstable $I_H^{cc} < 1$: stable
E_C^{cc}	$(C, H, B) = (N(1 - \frac{1}{R_0^C}), 0, 0)$	$I_C^{cc} > 1$: unstable $I_C^{cc} < 1$: stable
E_H^{cc2}	$(C, H, B) = (0, N(1 - \frac{1}{R_0^H}), 0)$	$I_H^{cc2} > 1$: unstable $I_H^{cc2} < 1$: stable
E_C^{cc2}	$(C, H, B) = (N(1 - \frac{1}{R_0^C}), 0, 0)$	$I_C^{cc2} > 1$: unstable $I_C^{cc2} < 1$: stable
E_H^{pnc}	$(S, C, H, B) =$ $((\alpha_H+\delta_H)/\beta_H, 0, \Lambda/\delta_H-\delta_S(\alpha_H+\delta_H)/(\beta_H\delta_H), 0)$	$I_H^{pnc} > 1$: unstable $I_H^{pnc} < 1$: stable
E_C^{pnc}	$(S, C, H, B) =$ $((\alpha_C+\delta_C)/\beta_C, \Lambda/\delta_C-\delta_S(\alpha_C+\delta_C)/(\beta_C\delta_C), 0, 0)$	$I_C^{pnc} > 1$: unstable $I_C^{pnc} < 1$: stable

Table D.2: Explanation and values of symbols for basic reproduction ratios R_0, and invasion reproduction ratios I.

Symbol	**Model**	**Value**
R_0^H	SIS HA-MRSA	$\frac{\beta_H N}{(\delta_H+\alpha_H)}$
R_0^C	SIS CA-MRSA	$\frac{\beta_C N}{(\delta_C+\alpha_C)}$
R_0^{sc}	single-colonization	$\max\{R_0^C, R_0^H\}$
R_0^{cc}	co-colonization	$\max\{R_0^C, R_0^H\}$
I_H^{sc}	single-colonization	$\frac{R_0^C}{R_0^H}$
I_C^{sc}	single-colonization	$\frac{R_0^H}{R_0^C}$
I_H^{cc}	co-colonization	$\frac{R_0^C}{R_0^H}\left(\frac{\frac{\beta_{CH}}{(\alpha_B+\delta_B)}N\left(1-\frac{1}{R_0^H}\right)+1}{\frac{\beta_{CH}}{(\alpha_C+\delta_C)}N\left(1-\frac{1}{R_0^H}\right)+1}\right)+\frac{\beta_{HC}}{\alpha_B+\delta_B}N\left(1-\frac{1}{R_0^H}\right)$
I_C^{cc}	co-colonization	$\frac{R_0^H}{R_0^C}\left(\frac{\frac{\beta_{HC}}{(\alpha_B+\delta_B)}N\left(1-\frac{1}{R_0^C}\right)+1}{\frac{\beta_{HC}}{(\alpha_H+\delta_H)}N\left(1-\frac{1}{R_0^C}\right)+1}\right)+\frac{\beta_{CH}}{\alpha_B+\delta_B}N\left(1-\frac{1}{R_0^C}\right)$
I_H^{cc2}	co-col. under assump. of th. 3.5	$\frac{1}{1-\frac{1}{R_0^C}+\frac{1}{R_0^H}}+R_0^C-1$
I_C^{cc2}	co-col. under assump. of th. 3.5	$\frac{1}{1-\frac{1}{R_0^H}+\frac{1}{R_0^C}}+R_0^H-1$
I_H^{pnc}	co-col. pop. not conserved	$\frac{R_0^C}{R_0^H}\left(\frac{\frac{\beta_{CH}}{(\alpha_B+\delta_B)}\frac{(R_0^H-1)}{R_0^H\delta_H}+1}{\frac{\beta_{CH}}{(\alpha_C+\delta_C)}\frac{(R_0^H-1)}{R_0^H\delta_H}+1}\right)+\frac{\beta_{HC}}{\alpha_B+\delta_B}\frac{(R_0^H-1)}{R_0^H\delta_H}$
I_C^{pnc}	co-col. pop. not conserved	$\frac{R_0^H}{R_0^C}\left(\frac{\frac{\beta_{HC}}{(\alpha_B+\delta_B)}\frac{(R_0^C-1)}{R_0^C\delta_C}+1}{\frac{\beta_{HC}}{(\alpha_H+\delta_H)}\frac{(R_0^C-1)}{R_0^C\delta_C}+1}\right)+\frac{\beta_{CH}}{\alpha_B+\delta_B}\frac{(R_0^C-1)}{R_0^C\delta_C}$

Table D.3: Parameter values for the transmission dynamics of community-acquired and hospital-acquired methicillin-resistant *Staphylococcus aureus* colonization (CA-MRSA and HA-MRSA).

Parameter	**Symbol**	**Baseline Value**	**Source**
Total number of patients	N	400	
Percent of admissions per day			
Colonized CA-MRSA	100 λ_C	3	[17, 18]
Colonized HA-MRSA	100 λ_H	7	BI, [17, 18]
Length of stay			
Susceptible	$1/\delta_S$	5 days	BI
Colonized CA-MRSA	$1/\delta_C$	5 days	BI
Colonized HA-MRSA	$1/\delta_H$	7 days	[13]
Co-colonized	$1/\delta_B$	7 days	
Hand-hygiene compliance efficacy (as %)	100 η	50%	
Transmission rate per susceptible patient to			
Colonized CA-MRSA per colonized CA-MRSA	β_C	0.4 per day	[3, 28]
Colonized HA-MRSA per colonized HA-MRSA	β_H	0.4 per day	[3, 28]
Transmission rate per patient colonized with CA-MRSA to			
Co-colonized per colonized CA-MRSA	β_{CH}	0.4 per day	[3, 28]
Transmission rate per patient colonized with HA-MRSA to			
Co-colonized per colonized HA-MRSA	β_{HC}	0.4 per day	[3, 28]
Decolonization rate per colonized patient			
per day per length of stay (as %)			
CA-MRSA	100 α_C	0%	[14, 36]
HA-MRSA	100 α_H	0%	
Co-Colonized	100 α_B	0%	

BI: data obtained from the Beth Israel Deaconess Medical Center

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Figure Captions

Figure 1: Diagram for single-colonization model - A compartment diagram describing the transmission dynamics of CA-MRSA and HA-MRSA in a 400-bed hospital, when co-colonization is assumed not possible. The arrows and parameter values correspond to entry and exit from the 3 compartments (S-susceptible patients, C-patients colonized with CA-MRSA, and H-patients colonized with HA-MRSA). The percentages of patients admitted colonized with CA-MRSA or colonized with HA-MRSA are expressed as $100\lambda_C$, and $100\lambda_H$, respectively. Discharge and death rates from the compartments are expressed as follows: δ_S, δ_C, and δ_H for susceptible patients, patients colonized with CA-MRSA, and patients colonized with HA-MRSA, respectively (with mean length of stays defined as $1/\delta_S$, $1/\delta_C$, and $1/\delta_H$). The colonization rates of susceptible patients to the CA-MRSA compartment is β_C and to the HA-MRSA compartment is β_H. The rates of decolonization of patients with CA-MRSA and HA-MRSA are given by α_C and α_H, respectively. To conserve the population, $E = \delta_S S + \delta_H H + \delta_C C$.

Figure 2: Diagram for co-colonization model - A compartment diagram describing the transmission dynamics of CA-MRSA and HA-MRSA in a 400-bed hospital, when co-colonization is possible. B is the compartment for co-colonized patients, $100\lambda_B$ is the percentage of patients admitted already co-colonized, δ_B is the exit rate from B. The co-colonization rate from C to the co-colonized compartment (B) is β_{CH} and from H to B is β_{HC}, and α_B is decolonization rate of co-colonized patients. To conserve the population, $E = \delta_S S + \delta_H H + \delta_C C + \delta_B B$. All other parameters are the same as in figure 1.

Figure 3: Asymptotic behavior of the system - Equilibrium states for different values of R_0^C and R_0^H under the assumption that all transmission rates and rates of decolonization are equal. Co-existence occurs when both R_0^C and R_0^H are greater than one, but also for some values where one reproduction ratio is greater than one and the other is less than one. When $I_H^{cc2} < 1$, E_H^{cc2} is stable and only HA-MRSA is endemic. When $I_C^{cc2} < 1$, E_C^{cc2} is stable and only CA-MRSA is endemic. When both R_0^C and R_0^H are less than one, neither disease remains in the hospital over time.

Figure 4: Varying hand-hygiene compliance - Top: the percentage of patients colonized with HA-MRSA (dashed), CA-MRSA (dotted), and both (solid) after 2 years, versus hand-hygiene compliance (η). The bottom pic-

ture shows R_0^H (dashed), R_0^C (dotted) and I_H^{cc2} (dash-dotted) versus η. Other parameters are given in D.1, Table D.3.

Figure 5: Varying decolonization efficacy - Top: the percentage of patients colonized with HA-MRSA (dashed), CA-MRSA (dotted), and both (solid) after 2 years, versus decolonization efficacy (α). Bottom: R_0^H (dashed), R_0^C (dotted) and I_H^{cc2} (dash-dotted) versus α. Other parameters are given in D.1, Table D.3.