# A Review of Hospital-Acquired Methicillin-resistant *Staphylococcus aureus* (HA-MRSA) and the Mathematical Models Estimating the Reproductive Number

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**Introduction**

In the last decade, Methicillin-resistant *Staphylococcus aureus* (MRSA) has become an important community acquired and nosocomial pathogen requiring investigation due to its sustained prevalence. It is considered to be the cause of hospital associated bloodstream infections, surgical site infections, and pneumonia[1]. While MRSA prevention measures in United States (US) healthcare facilities have made progress in reducing these outcomes, but data from the National Healthcare Safety Network (NHSN) and Emerging Infectious Program (EIP) suggests that this decline has slowed in recent years[2]. Currently, MRSA is the second most common hospital-acquired infection, following closely behind *Clostridium difficile* infection[3].

*Staphylococcus aureus* is a type of bacteria that is naturally occurring primarily on the skin or in the nose. *S. aureus* bacteria is typically harmless. When an antibiotic is taken to treat an infection, the presence of the drug has the potential to evoke defense mechanisms from the bacteria, allowing it to continue to thrive in its environment. If *staph* bacteria growth goes unchecked it can rapidly multiply on the skin or in the nose leading to the aforementioned health outcomes[4]. Methicillin-resistant *Staphylococcus aureus* infection is caused by a type of *staph* bacteria that continues to evolve and is resistant to many different antibiotics. As MRSA becomes more prevalent in society there is a growing understanding of the multiple ways to diagnose and treat the infection with minor adverse effects to the patient. Rapid diagnosis, infection control measures, and adequate treatments ultimately lead to more favorable outcomes. Furthermore, this decreases incidence rates by preventing new cases from being transmitted both inside and outside of the hospital setting.

Due to the impacts of MRSA infections, it is important to understand how infectious this disease is, and how likely it is to spread in healthcare settings. In this review, we aim to compare MRSA reproductive numbers (R) identified in different studies of mathematical models, to understand what

factors yield differing R estimates. First, an overview of the impacts, risk factors, and prevention measures will be discussed. Then, an overview and systematic review of the different model components and their impacts on the R estimates is presented.

**Incidence and Prevalence**

Over the past 20 years, the prevalence and virulence of hospital acquired *Methicillin-resistant Staphylococcus aureus* infection has sustained primarily in developed countries. This is due in part to continuous use of broad-spectrum antibiotics as treatments for various illnesses. In the US from 2005 – 2016, the incidence of hospital-onset MRSA bloodstream infections declined by 74%. However, in March of 2019 the US Centers for Disease Control and Prevention (CDC) released a data report stating that rates of decline of HA-MRSA had been slowing since 2012, and they now appear be increasing. In 2017, the US experienced 120,000 infections and approximately 20,000 associated deaths[8]. While the prevalence and incidence of MRSA is increasing, the CDC states that only around 2% of the population chronically carries MRSA. Therefore, recurrent MRSA infections in a single individual are infrequent[9].

**Risk Factors**

An important step in determining the best hospital infection control practices is to first identify risk factors for acquiring MRSA infections in a healthcare setting. A case control study conducted in 2016 identified a number of individual patient risk factors associated with MRSA acquisition. These were: primary diagnosis of respiratory disease, digestive tract disease, injury or trauma, or other diagnosis compared with cardiocirculatory disease, peripheral vascular disease, mechanical ventilation with pneumonia, and ventricular shunting or ventriculostomy[10]. While these are widely specific factors, many of these are broadly associated with frequent or prolonged hospitalizations. Therefore, prolonged hospitalization is a primary risk factor for transmission of MRSA.

The same case control study, along with previous research, found that fluoroquinolone (the most commonly prescribed class of antimicrobial drugs) use was also a significant risk factor for MRSA

acquisition. Commonly prescribed fluoroquinolones include ciprofloxacin and levofloxacin, which were originally highly regarded for their ability to combat a broad range of pathogens. However, upon screening a large number of staphylococcal bloodstream isolates, the SENTRY Antimicrobial Surveillance Program confirmed resistance to these medications[11].

**Prevention**

There are many precaution measures that can be used to prevent a patient from contracting *MRSA,* especially during a hospital stay. Practices include (1) the use of *MRSA* specific isolation precautions to protect other patients and medical staff, (2) proper use of personal protective equipment (PPE) (3) using good hand hygiene and (4) the implementation of an antibiotic stewardship program that targets inappropriate prescribing practices.

***Patient Isolation Measures, PPE, and Hand Hygiene***

To ensure MRSA is not contracted by other patients or medical personnel it's necessary to separate patients that are identified as positive carriers of MRSA or have active MRSA infection into a state of isolation during their hospital stay. As previously mentioned, staph bacteria can survive on fomites in adequate conditions. Therefore, adherence to isolation measures plays an important role in reducing nosocomial transmission. Hospital isolation procedures should include: (1) Placing MRSA positive patients in a private room. (2) If patients must share a room, patients that are colonized with the same organisms should be placed together. (3) Patients should be placed on MRSA specific precautions while awaiting laboratory test results. These isolation precautions also require the wearing of gowns and gloves by medical staff upon entering a patients' isolated room. After providing care, medical personnel should remove all PPE before exiting the room and proceeding with the care of other patients. In addition, hand hygiene with soap and water or alcohol-based hand sanitizer should be completed prior to and after providing any patient care[12].

***Antibiotic Stewardship Programs (ASP)***

Lastly, antibiotic stewardship plays a very important role in controlling MRSA transmission in a hospital setting. Antibiotic usage is a major contributing risk factor to MRSA infection. As such frequency and duration of high-risk antibiotic therapies should be monitored thoroughly. Alternative therapies should be researched and proposed in an effort to reduce the incidence of HA-MRSA. Antibiotic stewardship programs should primarily target fluoroquinolones. A time-series study conducted in Scotland found that the introduction of a national ASP caused a 47% reduction of broad-spectrum antibiotic prescribing in hospitals. As a result, hospitals experienced a 54% decrease in MRSA prevalence[13].

ASPs can be classified as being either restrictive, persuasive or structural[14]. Restrictive intervention programs limit physicians to what prescriptions that they can provide. Persuasive interventions focus on coaching physicians to stop therapy for MRSA if the patient no longer has MRSA infection or prescribe other antibiotics (beta-lactams) in patients that are high risk for developing MRSA infection. Structural interventions require the review of hospital wide prescribing practices and move to alter prescribing on a system wide basis. While antibiotic stewardship is not the single answer to targeting antibiotic resistant *staph* bacteria and hospital acquired MRSA, it has a positive impact on decreasing incidence when integrated with other infection prevention strategies[15].

**Modeling Terms**

In order to understand the impacts of MRSA in healthcare settings, it is important to understand how we predict the infectiousness of this disease. The reproductive number (R) is the average number of secondary infections caused by one infectious case[16]. If this number is greater than 1 it indicates that the disease is spreading and causing an outbreak. If R is less than 1 the outbreak will not be able to continue. Within the definition of R there are further classifications of the value. The basic reproductive number ($R_0$) is used when we consider everyone in the population susceptible to the disease. When there is immunity introduced into the population, then the effective reproductive number ($R_{eff}$) is used.

Determining what R actually is for an infectious disease requires consideration of multiple parameters that can affect its value. These factors include transmission rates, susceptibility, environmental factors and many more parameters are necessary for estimating R. The creation of models allows for estimation of the value of R under these different circumstances. When creating models, there are two types to consider. The first being a deterministic model. With this type of model, the outcome is determined by the parameters set at the beginning. No matter how many times the model is run, the same result always occurs. The benefit of this model is that it can be simple to create and understand. On the other hand, there is no consideration of randomness that typically occurs in a normal biological system. Alternatively, a stochastic model can be used to account for randomness. Stochastic models in this case can be considered more realistic than deterministic but also can be much more complex[16]. Both types of models should be considered for the estimation of R for MRSA.

**Methods**

Due to the variability in R, we aimed to search the literature for studies that created models to estimate the R of MRSA and will compare their similarities and differences. We took a systematic approach to identifying studies and searched the Medline database for pertinent studies. We set inclusion criteria as studies written in English, done only in human populations, and studies that used either empirical or simulation data based on a mathematical model to estimate R. Studies were not included in our review if they did not report an estimate of R, were related to animal transmission of MRSA, did not discuss hospital transmission of MRSA, and were not original research. We then used the following search terms to identify studies:

("MRSA"OR "methicillin-resistant staphylococcus aureus") and (“reproductive number”[tiab] or “reproduction number”[tiab] or “reproductive rate”[tiab] or “reproduction ratio” [tiab] or

"reproduction value"[tiab] or "R0" [tiab] or "secondary infections" [tiab] or "secondary cases" [tiab])

The results of our search are included in Figure 1. In total we identified 65 studies of which 18 were reviewed in full after abstract review and 5 were deemed relevant to our review.

## Results

Table 1 includes a summary of all included studies, model specifications, and their estimation of R. All included studies used some variant of a deterministic model or stochastic model, each with a variation of parameters based on their research interest. Considerations of environmental transmission and person to person transmission of MRSA were made in each of the models.

### *Compartments*

All included models are compartmental, classifying individuals into several groups within the system. Both Huang papers considered prior antibiotic exposure in their models. Their models included 7 compartments including uncolonized patients with and without antibiotic exposure, colonized patients with and without antibiotic exposure, uncontaminated or contaminated healthcare workers, and free-living bacteria in the environment. Similarly, both Wang studies used the same classifications except they did not include prior antibiotic exposure resulting in 5 compartments. These papers ensure to look at transmission between the general population, between healthcare workers, and between the two groups within healthcare settings. These compartments were used within both deterministic and stochastic models.

Alternatively, Ruscio opted to use an individual-based model (IBM) which is a variant of a stochastic model. Within this type of model consideration of individual characteristics of each person is

considered. This could include age, occupation, race, or gender for example. Within this model the compartments are more simple expanding to just susceptible, colonized, and infectious individuals. This study looked at transmission in both community and healthcare settings and does not include individual compartments for healthcare workers. The benefit of this type of model is that it allows you to track individual characteristics. When the number of compartments gets too large under a typical compartmental model, an IBM allows us to track as many characteristics of individuals as we wish. While this helps to make the model more realistic and true in comparison to what is actually happening, it can become very complex.

***Parameters***

Table 2 provides a summary of included parameters in each of the models. Both Huang and Wang studies have similar parameters included. These studies include parameters related to hospital stay, compliance to interventions such as hand hygiene, and transmission from the surrounding environment. Along with interventions such as hand washing, Wang 2012 includes a parameter for isolation precautions in the prevention of MRSA transmission. Both Huang studies consider previous exposure to antibiotics including an antibiotic prescription rate parameter and a parameter for the change in this rate. The Huang paper that aims to measure the seasonality of MRSA transmission considers a changing rate in antibiotic prescriptions based on the time of year. As previously stated, all consider transmission between individuals as well as with the surrounding environment.

The Ruscio paper included parameters aimed at identifying transmission from abroad as well as parameters for the likelihood of someone with a travel history to be tested for MRSA while hospitalized. Furthermore, they considered each of their parameters in the community, healthcare setting, and nursing homes. Within this model they accounted for the sensitivity of the MRSA test as well as the time it takes to process one of these tests. Lastly, instead of individual parameters for transmission between

healthcare workers to other populations and vice versa, parameters for nurse to bed ratio and length of hospital stay were included to account for hospital transmission of MRSA.

***Reproductive Number***

As a result of these different models, various R estimates were made. Estimates of R, for all studies, were made from either hospital collected data or national surveillance data on cases of MRSA. Of the five included studies, four estimated $R_0$ and one estimated $R_{eff}$. The specific values of R are included in Table 1. The estimates of R ranged from 0.68 to 1.48. The two estimates made in the Huang studies were both greater than one indicating a potential outbreak. The R estimates from the remaining three studies were all less than one. The four studies that estimated $R_0$ generally used their deterministic model to get this value and used the stochastic models to observe the model behavior. Ruscio was the only study to use an IBM model, and they were also the only ones to estimate $R_{eff}$. The $R_{eff}$ value estimated by this study was also the lowest R value at 0.68.

**Discussion**

Overall, the type of model and its components can lend to differing estimates of R for MRSA. It can be seen that the more specific the model is, the more representative of reality the model can be. By adding compartments and parameters to these models they are able to simulate what is actually happening with this infectious disease. In each of these models, the compartments and parameters act and interact differently resulting in different estimates of R. Consideration of different interventions, different populations, or even different exposures can lend to these differences as described above. While models are not always accurate, they can come close to mirroring the true processes that are occurring, by allowing for the correct components to be included.

The differences in R estimates can lend directly to the components of the model. The $R_0$ values in the Huang studies are the only ones greater than one. This is likely to be the case because they considered prior use of antibiotics. As mentioned, there are issues with prevention of MRSA due to antibiotic resistance. Presence of antibiotic resistance makes it more difficult to prevent MRSA and stop further transmission. With considering this in the model, it makes sense that the estimates for these $R_0$ values would indicate an outbreak. In the Ruscio study, $R_{eff}$ was estimated. This estimation of R considers some sort of immunity in the population. While this is not necessarily always the case with MRSA, the body does have some immune response to the pathogen that could lend to some individuals being less susceptible than others. This would then make sense as to why this estimate of R is lower than the other included studies. However, it does also have to be considered that the aim of this study was to look at transmission of MRSA in a low prevalence country. This would also lend to the decreased estimate of $R_{eff}$.

While not all the R estimates indicate an outbreak of MRSA, all studies do highlight the importance of prevention measures to stop its spread. To decrease new cases of nosocomial MRSA infection, it is necessary to utilize best isolation and hand hygiene practices not only for patient protection but also to protect healthcare workers from transmission. It is crucial for hospitals to consider implementing antibiotic stewardship programs with the understanding that this cannot only positively affect overprescribing practices but can also reduce antibiotic resistance that can lead to MRSA infections. Further research should be done to find more innovative methods for treatment of MRSA that do not rely on additional antibiotic use. Together, all of these factors aid in the reduction of R to prevent the transmission of MRSA.

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**Tables and Figures**

Table 1. Model characteristics and R estimates for included studies

| Author, Year | Method (model type) | Assumptions | Basic/Effective Reproductive Number | Reproductive Number Estimate |
|---|---|---|---|---|
| Huang, 2019[17] | ODE model for antibiotic exposure and environmental contamination | No cross infection, hospital fully occupied, bacteria in environment are uniformly distributed | Basic | 1.29 |
| Huang, 2019[18] (season) | Periodic deterministic model assess effect of seasonality on transmission | Only uncolonized patients with antibiotic exposure at admission | Basic | 1.48 |
| Wang, 2017[19] | Deterministic and stochastic models considering environmental contamination | Fully occupied unit, number of patients remains constant, number of HCW constant, no cross-infection between patients | Basic | 0.76 |
| Ruscio, 2019[20] | Individual based model in healthcare environments and community settings | Homogenous mixing of individuals | Effective | 0.68 |
| Wang, 2012[21] | Deterministic and stochastic models - direct transmission of HCW to patients/volunteers & indirect transmission of HCW/Volunteers and environmental bacteria | Bacteria in the ward is uniformly distributed, environment in the ward is one compartment, only modeled dynamics of HCW, patients, and bacteria assuming that volunteers are the same as their patient | Basic | 0.98 |

Table 2. Summary of included parameters in each model

| **Huang, 2019** | **Huang, 2019 (season)** | **Wang, 2017** | **Rusico, 2019** | **Wang, 2012** |
|---|---|---|---|---|
| Antibiotic prescription rate | Antibiotic prescription rate | Admission rate | proportion of person with foreign background | Person to person transmission |
| Change of antibiotic prescription rate | Change of antibiotic prescription rate | Total patients | Nurses to bed ratio | Environmental transmission |
| Admission rate | Admission rate | Total HCW | Length of stay | Admission rate |
| Discharge rate | Discharge rate | Contact rate | Colonization to infections ratio for imported cases | Admission already colonized when being hospitalized |
| Cleaning rate | Cleaning rate | Probability of colonization | Duration of carriage | Shedding rate |
| Contact rate | Contact rate | Probability of contamination | Initial prevalence | Discharge rate |
| Probability of colonization | Probability of colonization | Discharge rate | Screening probability for hospitalized patients with travel history | Recovery rate |
| Probability of contamination | Probability of contamination | Cleaning rate | Sensitivity of MRSA test | Clearance rate |
| Hand hygiene compliance | Hand hygiene compliance | Colonization rate from the environment | Turnaround time for MRSA test | Hand hygiene compliance |
| Decontamination rate | Decontamination rate | Hand hygiene compliance | Transmission rate | Isolation rate |
| Shedding rate | Shedding rate | Decontamination rate | | Total HCW |
| Colonization rate from the environment | Colonization rate from the environment | Contamination rate to the environment | | |
| Total patients | Total patients | Total patients | | |
| Total HCW | Total HCW | Total HCW | | |

Figure 1. Flow diagram of included studies