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The Dangers of *Staphylococcus aureus* and Antimicrobial Resistance

Madison Pines
Lynn University

THE DANGERS OF *STAPHYLOCOCCUS AUREUS* AND ANTIMICROBIAL RESISTANCE

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Madison Pines

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Abstract

Methicillin-resistant *Staphylococcus aureus* (MRSA) is the etiological agent responsible for many problematic infections. The signs and symptoms of an infection caused by MRSA differ based on the route of transmission and type of infection. *Staphylococcus aureus* can secrete toxins that act as virulence factors and aid host invasion. Obesity, old age, being a health care worker, playing contact sports, living in a crowded place, hospitalization, recent antibiotic use, and HIV patients are more at risk of developing an infection caused by MRSA. An abundance of factors has contributed to antimicrobial resistance, like misuse of antibiotics in clinical and agricultural settings and overuse of antibiotics. MRSA can be multidrug resistant via efflux pumps and resistance genes, rendering infections caused by MRSA challenging to treat. Resistance patterns of *Staphylococcus aureus* differ geographically due to surveillance programs and antibiotic usage. The production of new antibiotics, antibiotic surveillance programs, diagnostic testing, and educational programs are imperative to slowing the spread of MRSA. Staphylococcal infection and MRSA infections can be prevented by handwashing, sterilizing medical equipment, maintaining a clean healthcare setting, having clear isolation protocols, cleaning gym equipment, not sharing personal care products like razors, and taking the entire course of antibiotics as prescribed by a medical professional. Overall, MRSA is a dangerous pathogen capable of causing opportunistic nosocomial infections that require immediate attention and research.

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Abbreviations and Acronyms

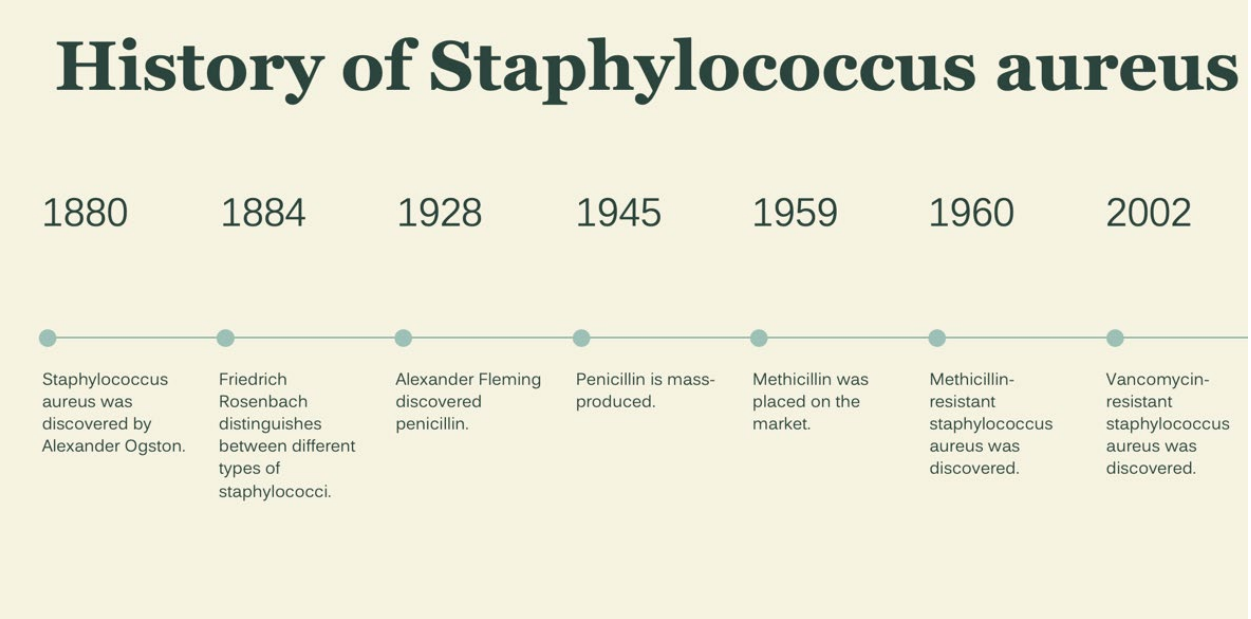
CA-MRSA	**Community-associated methicillin-resistant *Staphylococcus aureus***
Erm	**Erythromycin ribosome methylase genes**
ET	**Exfoliative toxin**
HA-MRSA	**Healthcare-associated methicillin-resistant Staphylococcus Aureus**
HIV	**Human immunodeficiency virus**
MDR	**Multidrug resistant**
MRSA	**Methicillin-resistant *Staphylococcus aureus***
MSSA	**Methicillin-sensitive *Staphylococcus aureus***
PBP	**Penicillin-binding proteins**
PBP2a	**Penicillin-binding protein 2a**
PVL	**Panton valentine leucocidin**
SCCmecs	**Staphylococcal cassette chromosome *mec***
STRAMA	**Swedish Strategic Programme Against Antibiotic Resistance**
TSST-1	**Toxic shock syndrome toxin-1**
VRSA	**Vancomycin-resistant *Staphylococcus aureus***

The Dangers of Staphylococcus aureus and Antimicrobial Resistance

Introduction

Staphylococcus aureus was first discovered in 1880 by a surgeon named Alexander Ogston (Lakhundi & Zhang, 2018). Ogston observed staphylococci from a puss specimen and called the colonies staphylococci, which comes from the Greek word "staphyle," which means a cluster of grapes, and "kokkos," meaning berries (Licitra, 2013). Four years later, Friedrich Rosenbach was able to distinguish between different types of staphylococci by color (Adhikari, 2021). Rosenbach looked at staphylococci under a microscope and was able to differentiate between *Staphylococcus aureus* and *Staphylococcus albus* (Lakhundi & Zhang, 2018). Many years later, penicillin was discovered by Alexander Fleming in 1928, and in 1945, penicillin was mass-produced (Tan & Tatsumura, 2015). In 1959, methicillin was placed on the market to treat infections caused by gram-positive bacteria resistant to penicillin (Enright et al., 2002). By 1960, Jevons and Parker discovered a methicillin-resistant strain of *Staphylococcus aureus* (Parker & Jevons, 1964). Lastly, vancomycin-resistant *Staphylococcus aureus*, or VRSA, was discovered in 2002 in Michigan (Cong et al., 2020).

Figure 1



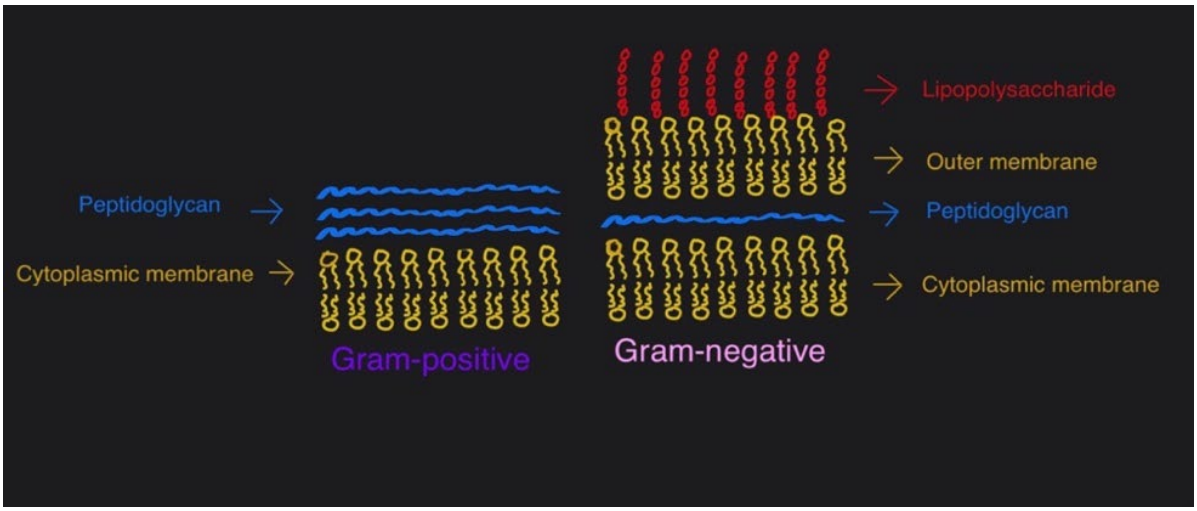
Pictured above is a timeline of historical events relating to MRSA and antibiotic development from 1880 to 2002.

Due to the fact that MRSA was discovered a year after methicillin was put on the market, it was assumed that methicillin was the driving force in the development of antibiotic resistance of *Staphylococcus aureus*. However, antibiotics like methicillin were synthesized to annihilate resistant strains of *Staphylococcus aureus; this* is likely due to earlier beta-lactam usage, which is associated with the *BlaZ* and the *MecA* gene. The *BlaZ* gene encodes a beta-lactamase, which is an enzyme that allows staphylococcus aureus to survive in the presence of a beta-lactam antibiotic, like penicillin, by inactivating it. By the same token, the SCC*mec* element houses the *MecA* gene, which allows *Staphylococcus aureus* to continue to carry out cell wall synthesis in the presence of a beta-lactam antibiotic. The overutilization of penicillin allowed the *Staphylococcus aureus* strains carrying the *MecA* or the *BlaZ* gene to survive. Harkins et al. sequenced MRSA isolates and concluded that the evolution of *Staphylococcus aureus* resistance was due to early beta-lactam utilization (Harkins et al., 2017). Indicating that the early use of antibiotics like penicillin is responsible for the evolution of *Staphylococcus aureus* to MRSA.

Bacteria are divided into two categories, gram-positive and gram-negative (See Figure 2). *Staphylococcus aureus* is a gram-positive coccus. Gram-positive bacteria lack an outer membrane, they have a thick peptidoglycan layer, and they lack lipopolysaccharide. Gram-negative bacteria have lipopolysaccharides, an outer membrane, and a thin layer of peptidoglycan (Silhavy et al., 2010). Peptidoglycan is a polymer consisting of N-acetylglucosamine, N-acetylmuramic acid, and glycan. The glycans are cross-linked by peptide chains in peptidoglycan by Penicillin-binding proteins (PBP) that carry out transpeptidation. The methicillin-resistant strains of *Staphylococcus aureus* have penicillin-binding protein 2a or (PBP2a), encoded by the *MecA* gene; MecA is located on staphylococcal cassette chromosome *mec* (SCCmec), which is a mobile genetic element (Liu et al., 2017). Mobile genetic elements are gene sequences capable of moving from one location on the genome to another or to another bacteria. Penicillin and methicillin are beta-lactam antibiotics, as they contain a beta-lactam ring in their chemical structure. PBP2a allows MRSA to synthesize cell walls by allowing cross-linking even if a beta-lactam antibiotic is present. Beta-lactam antibiotics inhibit bacterial cell wall synthesis by binding to the penicillin-binding proteins, which can lead to lysis of the bacteria (Bush & Bradford, 2016).

Another form of resistance can be achieved with beta-lactamases. Beta-lactamases are enzymes synthesized by some bacteria, including MRSA. Beta-lactamases hydrolyze the beta-lactam ring in beta-lactam antibiotics, rendering these antibiotics useless. The *BlaZ* gene, for instance, is also a beta-lactamase; the *BlaZ* gene allows *Staphylococcus aureus* to resist penicillin (Pence et al., 2015).

Figure 2



The structural difference between gram-positive and gram-negative is depicted here. Gram-negative bacteria have a cytoplasmic membrane, outer membrane, lipopolysaccharide, and a thin layer of peptidoglycan. However, gram-positive bacteria have a cytoplasmic membrane and a thick layer of peptidoglycan.

Resistance Mechanisms

Researchers develop antibiotics by targeting structures specific to bacteria and exploiting these targets. Typical targets for antibiotics include enzymes or cellular components vital to prokaryotic survival. These targets aim for structures unique to bacteria, which makes them safe for human consumption. Beyond methicillin, MRSA has developed resistance to multiple antibiotics due to their overuse and misuse (Zhao et al., 2021). *Staphylococcus aureus* can resist antibiotic treatment with both resistance genes and efflux pumps.

First, the *erm* genes or erythromycin ribosome methylase genes are responsible for macrolide, lincosamides, and streptogramin resistance in *Staphylococcus aureus* (Matsuoka et al., 2002). Macrolides are a class of bacteriostatic antibiotics that are used to treat gram-positive bacteria and some gram-negative bacteria. Macrolides work by interfering with translation (Vázquez-Laslop & Mankin, 2018). Lincosamides are a class of antibiotics used to treat

infections caused by gram-positive bacteria; lincosamides work to obstruct protein synthesis, which in turn kills bacteria (Schwarz et al., 2016). Streptogramins are a class of antibiotics used to treat infections caused by gram-positive infections, and streptogramins work by interrupting bacterial protein synthesis (Cocito et al.,1997). *Erm* genes work by preventing the binding of a macrolide, lincosamides, or a streptogramin antibiotic by methylating 23s rRNA, and this decreases the likelihood of macrolide, lincosamides, or a streptogramin antibiotic from attaching to the bacterial ribosome allowing the bacteria to survive in the presence of these antibiotics (Leclercq, 2002).

Similarly, vancomycin is a glycopeptide bactericidal antibiotic effective against gram-positive bacteria. Like penicillin and methicillin, vancomycin functions by inhibiting cell wall production. There are strains of *Staphylococcus aureus* that are resistant to vancomycin, called vancomycin-resistant *staphylococcus aureus* (VRSA). Vancomycin interacts with the D-Ala-D-Ala region of peptidoglycan, which interrupts crosslinking and can cause lysis, leading to the death of the bacteria (Wang et al., 2018). Some strains of bacteria have *Van* genes, like *Staphylococcus aureus*. These van clusters mitigate resistance by altering D-Ala-D-Ala to D-Ala-D-Lactose; this exchange removes a hydrogen bond, which decreases the likelihood of vancomycin binding and causing lysis (Miller et al., 2014). It is also possible to mutate D-Ala-D-Ala to D-Ala-D-Ser; this alteration also decreases the likelihood of vancomycin binding as well (Miller et al., 2014). There are three types of vancomycin-resistant *Staphylococcus aureus*: vancomycin-resistant *Staphylococcus aureus* is a form of *Staphylococcus aureus* that is resistant to vancomycin, vancomycin-susceptible *Staphylococcus aureus* is a form of *Staphylococcus aureus* that is receptive to vancomycin, and vancomycin-intermediate *Staphylococcus aureus* is

somewhat susceptible to vancomycin *(*Cong et al., 2019). To determine if VRSA is present, van clusters should be in attendance (Cong et al., 2019).

Fosfomycin is a phosphonic acid antibiotic that interrupts cell wall synthesis (Cao et al., 2019). Fosfomycin is used to treat infections caused by both gram-positive and gram-negative bacteria (Falagas et al., 2016). Some strains of MRSA contain the *Fos*B enzyme, which can lead to fosfomycin resistance by epoxide ring-opening, which renders fosfomycin ineffective in killing some strains of *Staphylococcus aureus* (Lima et al., 2021; Thompson et al., 2014).

Mupirocin is an antibiotic used to treat skin infections caused by gram-positive bacteria like *Staphylococcus aureus* (Conly & Johnston, 2002). Mupirocin prevents protein synthesis in gram-positive bacteria by blocking bacterial isoleucyl-tRNA synthetase (Cohen et al., 2017; Chung et al., 2020). The *ileS2* gene allows *Staphylococcus aureus* to resist mupirocin by encoding a substitute isoleucyl-tRNA synthetase (Ho et al., 2016; Poovelikunnel et al., 2015). Therefore allowing *Staphylococcus aureus* to prosper in the presence of mupirocin.

Efflux pumps are also a method bacteria can use to confer resistance to antibiotics. *NorA, mdeA*, and *qacA/B* are a few genes that encode efflux transporters. Efflux pumps are transport proteins that eliminate noxious materials from bacteria, like antibiotics or toxins (Soto, 2013). Efflux pumps allow MRSA to resist fluoroquinolone antibiotics (Hassanzadeh et al., 2017). Hassanzadeh et al. conducted a study regarding efflux pumps and MRSA resistance and concluded that 70% of the MRSA strains were resistant to ciprofloxacin, with a majority of *mdeA* gene present with a frequency of 61.7% and a minority of the *qacA/B* genes with 3.3% (Hassanzadeh et al., 2017). The *fexA* gene is also another gene that encodes an efflux pump. Chloramphenicol works by targeting protein synthesis (Oong & Tadi, 2022). Chloramphenicol is an antibiotic used to treat infections caused by gram-positive and gram-negative bacteria.

Chloramphenicol is typically prescribed to treat eye infections. The *fexA* gene allows *Staphylococcus aureus* to pump out chloramphenicol. Lastly, tetracyclines are a class of antibiotics that are effective against gram-positive and gram-negative bacteria. Tetracycline antibiotics can decrease bacterial growth by attaching to the bacterial ribosome, interrupting protein synthesis (Chopra & Roberts, 2001). Some strains of MRSA have *tet* genes, which allow for resistance via efflux pumps as well, effectively allowing MRSA or *Staphylococcus aureus* to extrude tetracycline (Schmitz et al., 2001; Li et al., 2013).

Toxins

Staphylococcus aureus can secrete toxins that aid in invading the host (Sharma et al., 2017). These toxins aid in bacterial growth and can cause problematic symptoms in the host. Some virulence factors are encoded in the genome or can be found on a mobile genetic element (Otto & Peschel, 2013). Staphylococcal toxins are classified into three kinds of toxins: superantigens, pore-forming toxins, and exfoliative toxins (Grumann et al., 2014). For example, Phenol-soluble modulins are pore-forming toxins that are involved in the development of a MRSA infection by launching inflammatory reactions and disintegration of leukocytes and erythrocytes (Otto & Peschel, 2013).

Panton valentine leucocidin (PVL) exotoxin is synthesized by some strains of *Staphylococcus aureus* and has been associated with community-associated MRSA (Vandenesch et al., 2003). PVL is a virulence factor commonly seen in skin and soft-tissue infections (Darboe et al., 2019). PVL can lyse leukocytes in small numbers; PVL is also known to trigger inflammation (Yoong & Pier, 2012).

There is also exfoliative toxin (ET) or epidermolytic toxins, which are encoded by *ET* genes. Exfoliative toxins are serine proteases that can cause skin exfoliation. Exfoliative toxins

are secreted by *Staphylococcus aureus* and cause scalded skin syndrome. Scalded skin syndrome is mainly seen in young children, scalded skin syndrome is characterized by exfoliation of the skin and a rash that can occur on the entire body or just one region of the body (Ross & Shoff, 2022; Ladhani et al., 1999). Mohseni et al. conducted a molecular analysis and observed that 87.3% of their isolates had no less than one *ET* gene (Mohseni et al., 2018).

Enterotoxins are another virulence factor that can be secreted by *Staphylococcus aureus* and MRSA. There is an abundance of enterotoxins produced by *Staphylococcus aureus*; enterotoxins SEA, SED, SEE, SEG, and SEI have been associated with food poisoning (Argudín et al., 2010; Pinchuk et al., 2010). Staphylococcal enterotoxin targets enterochromaffin cells, and enterochromaffin cells make and release serotonin, which plays a role in inflammation, vomiting, and appetite (Popoff & Poulain, 2010; Diwakarla et al., 2017). A person can become infected with a staphylococcal infection by consuming contaminated food (Argudín et al., 2010). Staphylococcal enterotoxins are associated with gastrointestinal symptoms like stomach pain and vomiting; symptoms can appear as soon as two hours after consuming contaminated food (Argudín et al., 2010; Pinchuk et al., 2010). Staphylococcal food poisoning can be detrimental in at-risk populations like the elderly and lead to hospitalizations (Argudín et al., 2010). Similarly, TSST-1 is an enterotoxin released by *Staphylococcus aureus* and can cause toxic shock syndrome, a deadly infection that can cause multiorgan failure. The *tst* gene encodes TSST-1, and TSST-1 is one of the toxins associated with toxic shock syndrome. A molecular typing study revealed that 27.4% of their staphylococcus isolates have the *tst* gene (Al Laham et al., 2015).

Hemolysins are a type of toxin synthesized and released by *Staphylococcus aureus* and MRSA. There are four different kinds of hemolysins, α-hemolysins, β-hemolysins, γ-hemolysins, and δ-hemolysins (Nasaj et al., 2020). α-hemolysins induce the arrangement of a pore, which

induces cell lysis (Tam & Torres, 2019). β -hemolysins are neutral sphingomyelinase that leads to the lysis of red blood cells (Vandenesch et al., 2012). γ-Hemolysin also forms pores, which can lead to cell lysis (Vandenesch et al., 2012; Yoong & Torres, 2013). δ-hemolysins are also pore-forming hemolysins that can compromise the plasma membrane (Vandenesch et al., 2012). Lastly, Motamedi et al. conducted a study that identified the prevalence of hemolysin genes in the MRSA isolates they collected, and they observed that 63.35% of the isolates had hemolysin genes (Motamedi et al., 2018).

In summary, *Staphylococcus aureus,* or MRSA, is capable of secreting a multitude of toxins that allow for host colonization. Staphylococcal toxins are classified into three kinds of toxins: superantigens, pore-forming toxins, and exfoliative toxins (Grumann et al., 2014). These toxins can cause a wide range of symptoms, and antibiotics are of no assistance in treating these toxins. Overall, the toxins associated with *Staphylococcus aureus* aid in bacterial host invasion and are problematic and sometimes life-threatening to the host.

Origin

Misuse and overuse of antibiotics in clinical and agricultural settings have primarily contributed to antimicrobial resistance (Michael et al., 2014). Due to natural selection, susceptible bacteria should die in the presence of an antibiotic, and the resistant bacteria would be left to multiply (Read & Woods, 2014). A study conducted in China monitored the outpatient prescriptions for antibiotics and observed that about half of the antibiotic prescriptions were inappropriate, and about 15% of the prescriptions were considered appropriate; this study highlights the prevalence of overprescription and misuse of antibiotics (Zhao et al., 2021). While giving a lecture, Alexander Fleming once mentioned that there is a risk to treating microbes with a dose of penicillin that is nonlethal and will likely lead to bacterial resistance (Fleming). This

statement from Fleming provides a possible explanation for how *Staphylococcus aureus* has become resistant over the years. Fleming also points out that antibiotic resistance is not a relatively new problem. Similarly, misuse of antibiotics is just as problematic as overprescribing antibiotics; a study was conducted in the United States by Fleming-Dutra et al. to analyze prescription rates of outpatient antibiotics. Fleming-Dutra et al. observed that about 30% of outpatient antibiotics were possibly inappropriate or unnecessary; as mentioned previously, inappropriate prescription of antibiotics can lead to antimicrobial resistance (2016).

The utilization of antibiotics in food animals also contributes to antibiotic resistance. Antibiotics can be given to food animals to treat and prevent disease (McEwen & Fedorka-Cray, 2002). Food animals can act as a reservoir for bacteria that can become resistant, and these bacteria can be spread to other animals and humans via direct contact (Marshall & Levy, 2011). Furthermore, there is a strain of MRSA specific to food animals, MRSA ST 398. Graveland et al. observed a correlation between humans in direct contact with animals and MRSA carriage (Graveland et al., 2021). Graveland et al. also observed a correlation between antibiotic treatment and MRSA ST398 prevalence (Graveland et al., 2021). This finding implicates the usage of antibiotics in farm animals.

Staphylococcus aureus, among other bacteria, can evolve in the presence of an antibiotic, allowing them to prevail and continue to wreak havoc on the host. The overuse and misuse of antibiotics in both clinical and agricultural settings are primarily responsible for antimicrobial resistance. The agricultural use of antibiotics is so problematic that there is a strain of MRSA specific to food animals (Graveland et al., 2010).

Signs, Symptoms, and Portals of Entry

Table 1

Type of infection	Symptoms	Diagnostic test	Treatment
Bacteremia (bacterial infection in the blood)	Bacteremia presents as a fever, low blood pressure, and tachycardia (CDC, 2022).	A blood culture can identify bacteremia. A positive test would show S*taphylococcus aureus* in the blood.	Bacteremia caused by MRSA can be treated with vancomycin, daptomycin, and telavancin (Choo & Chambers, 2016).
Staphylococcal Skin infection like cellulitis or scalded skin syndrome	Symptoms include red bumps on the skin that can be warm and/or painful and a fever (CDC, 2019).	A tissue sample can identify a staphylococcal skin infection (CDC, 2019).	Skin infections like cellulitis can be treated with trimethoprim-sulfamethoxazole or clindamycin (Brown & Hood Watson, 2022). Skin infections like scalded skin syndrome can be treated by oxacillin (Mishra et al., 2016)
Respiratory infections like pneumonia	Symptoms include fever, a cough, or dyspnea.	A complete blood count can be used to test for respiratory infections caused by *Staphylococcus aureus.* Leukocytosis would indicate a positive test.	Respiratory infections caused by MRSA can be treated with vancomycin (Claeys et al., 2016).
Bone infections	A person may experience pain at the site of infection and a fever (Mayo Clinic, 2022).	A tissue sample can confirm a bone infection.	Bone infections are typically treated with doxycycline or linezolid (Thompson & Townsend, 2011).
Joint infections	A person may experience pain at the site of infection and a fever (Mayo Clinic, 2022).	A tissue sample can confirm a joint infection.	Joint infections can be treated by teicoplanin or vancomycin (Brown et al., 2021).
Endocarditis	Symptoms include chest pain, fever, and shortness of breath (Mayo clinic).	A complete blood culture can confirm endocarditis. Leukocytosis would indicate a positive test.	Endocarditis can be treated by daptomycin and vancomycin (Ruiz et al., 2002; Bamberger, 2007).
Bacterial conjunctivitis	A patient may experience	Bacterial conjunctivitis can be	Bacterial conjunctivitis can be

	discomfort of the eyes, redness of the eyes, and photophobia (Pippin & Le).	diagnosed by conducting an eye exam or a swab which will identify the causative agent of the eye infection.	treated with vancomycin or chloramphenicol (Croghan & Lockington, 2018).
Toxic shock syndrome	A patient with toxic shock syndrome may exhibit multiorgan failure, fever, and/or low blood pressure (Ross & Shoff).	Toxic shock syndrome can be identified via a complete blood count and a urine test (Ross & Shoff).	Toxic shock is often treated with vancomycin and clindamycin (Mushlin & Greene, 2010).
Meningitis	Meningitis presents as a stiff neck, sensitivity to light, and headache (Hersi et al., 2022).	Meningitis can be diagnosed with a spinal tap, and a positive result would indicate an increased white blood cell count.	Meningitis can be treated with vancomycin and rifampicin (Brown et al., 2021).
Urinary tract infection	A urinary tract infection is characterized by pain while urinating, fever, or blood in the urine (Alshomrani et al., 2023).	A urinary tract infection can be diagnosed by a urinalysis (Alshomrani et al., 2023).	Urinary tract infections caused by MRSA can be treated with vancomycin (Brown et al., 2021).
Staphylococcal food poisoning	Symptoms of staphylococcal food poisoning include vomiting, fever, and diarrhea.	A diagnosis can be made based on a physical exam.	Drinking fluids and possibly antiemetic medication could be prescribed for staphylococcal food poisoning (CDC, 2023).

Above are common infections caused by *Staphylococcus aureus* and/ or MRSA. The signs and symptoms of an infection caused by MRSA vary depending on the portal of entry. Due to the variability in symptoms, a person must seek medical assistance if they display any of the symptoms listed above. The treatment for an infection caused by MRSA or Staphylococcus aureus varies on the type of infection (Siddiqui & Koirala, 2023). Due to the wide range of infections caused by MRSA or Staphylococcus aureus, there is a wide range of antibiotics used to treat these infections.

Staphylococcus aureus can be found on the skin and does not cause harm if it does not infiltrate the body (Taylor & Unakal, 2022). A MRSA infection can cause skin infections like

cellulitis or surgical site infections, bacteremia, respiratory infections, joint infections, endocarditis, bacterial conjunctivitis, bone infections, toxic shock syndrome, meningitis, bacteremia, and urinary tract infections (Tong et al., 2015). Infections can be local or systemic. A MRSA or staphylococcal infection can be diagnosed via a skin biopsy, a sample of nasal secretion, a blood culture, a complete blood count, saliva, or a urine sample can be used. PCR can also be used to identify MRSA in a sample. There are a few diagnostic methods offered for determining the presence of MRSA in a sample. For instance, the cefoxitin disc test and the oxacillin disc diffusion test can identify the presence of MRSA in a sample. The cefoxitin test and the oxacillin test can identify *mecA* resistance, which allows a medical professional to identify *Staphylococcus aureus*. Pourmand et al. determined that cefoxitin disc diffusion is a practical test that can be used to detect MRSA, and it is inexpensive, which makes this test more accessible to the public (Pourmand et al., 2014).

MRSA can be spread in a hospital or healthcare setting; if a person contracts MRSA from a healthcare setting, it is called HA-MRSA or healthcare-associated methicillin-resistant *Staphylococcus aureus*. The abundance of MRSA infections in healthcare can be attributed to more exposure to bacteria like *Staphylococcus aureus.* MRSA can be transmitted via skin-to-skin contact, by a fomite, or airborne transmission; HA-MRSA can be transmitted via medical devices that have not been sterilized, skin-to-skin contact, or contact with an infected wound. Community-associated methicillin-resistant *Staphylococcus aureus*, or CA-MRSA, is acquired through a non-healthcare setting like a daycare or a locker room. CA-MRSA can be spread by using personal care items that have made contact with an infected person, like a razor and skin-to-skin contact with an infected person. Aside from where a person can catch CA-

MRSA and HA-MRSA, they differ in the toxins they produce and the virulence genes they possess (Otto, 2013).

Risk Factors

Some risk factors associated with MRSA and *Staphylococcus aureus* infections are obesity, being a healthcare worker, old age, playing contact sports, living in a crowded place like a military base or a prison, hospitalization, recent antibiotic use, and patients with an HIV diagnosis, (Khawcharoenporn et al., 2010; Böcker et al., 2008; Befus et al., 2015; Koirala & Siddiqui, 2023; Zeller & Geller, 2011). Obesity adversely affects the immune system, which can complicate the body's ability to fight off infection (De Heredia et al., 2012). Also, if a person is obese, they are more likely to experience antibiotic treatment failure (Longo et al., 2013). Healthcare workers are more likely to be infected with MRSA because they are exposed to MRSA more frequently than non-healthcare workers (Rai et al., 2022). Being hospitalized also increases a person's risk of contracting an infection caused by MRSA or *Staphylococcus aureus* (Thimmappa et al., 2021). Old age puts a patient at risk for MRSA due to immune impairment occurring with age, making an elderly person more vulnerable to opportunistic infection (Lin et al., 2019; Pomorska-Wesołowska et al., 2017). Furthermore, Hasmukharay et al. concluded that an older person is at an increased risk of dying due to a MRSA infection than a younger person due to the possible utilization of medical devices that can carry *Staphylococcus aureus* (Hasmukharay et al., 2023). Playing contact sports has also been associated with higher rates of *Staphylococcus aureus* as well (Jiménez-Truque et al., 2016). *Staphylococcus aureus* can be transmitted via skin-to-skin contact, which is unavoidable in contact sports. Like contact sports, crowded places like prisons or during military service have higher rates of infections caused by *Staphylococcus aureus* or MRSA due to close contact (Aamot et al., 2018; David et al., 2008).

Also, HIV attacks CD4+ cells, CD4+ cells are associated with immune recognition; if these CD4+ levels drop significantly, a person is at risk for opportunistic infection like MRSA (Battistini Garcia et al., 2022; Luckheeram et al., 2012; Lenjiso et al., 2019; Popovich et al., 2010). Lastly, recent antibiotic exposure puts a person at risk for MRSA (Tacconelli et al., 2008). Antibiotics can eliminate the susceptible microbes, leaving behind resistant microbes to reproduce and wreak havoc.

In summary, a person is more likely to contract an infection by *Staphylococcus aureus* or MRSA if they have a compromised immune system, which can be caused by aging, a disease like HIV, or a medication. A person who encounters *Staphylococcus aureus* or MRSA frequently may also be at risk, including healthcare workers or people who have been hospitalized recently. Living conditions in which people live in close quarters, like prison or the military, also put a person at risk for contracting MRSA or *Staphylococcus aureus*. Due to the close direct contact, contact sports are also a risk factor for contracting MRSA or *Staphylococcus aureus*. As mentioned previously, antibiotic exposure can lead to antimicrobial resistance, so recent antibiotic usage is also a risk factor.

Epidemiology

MRSA or staphylococcal infections are not considered a pandemic; however, MRSA infections can be found worldwide, and MRSA infections occur in surges or waves (Turner et al., 2019). The resistance patterns of MRSA and *Staphylococcus aureus* vary from one region to the next. The upcoming studies discuss patterns in resistance from different parts of the world.

For instance, a study published by Kot et al. published in 2020 calculated the resistance patterns in hospitals in the Masovian district in Poland from 2015 to 2017. A predominant share of the isolates was resistant to penicillin, ciprofloxacin, erythromycin, clindamycin, and

levofloxacin; the majority of the isolates were also multidrug-resistant (MDR) (Kot et al., 2020). Moreover, from 2016 to 2017, the isolates became significantly more drug-resistant (Kot et al., 2020). This finding indicates how quickly *Staphylococcus aureus* can evolve, highlighting the severity of antibiotic resistance among staphylococcal bacteria. This study also demonstrates the wide range of antibiotics that are ineffective at eradicating *Staphylococcus aureus* or MRSA.

Similarly, a study from Zabol, Iran, observed clinical samples from a teaching hospital using the disk diffusion method. Shahkarami et al. observed complete resistance to both amoxicillin and penicillin in the MRSA strains (Shahkarami et al., 2014). The majority of the MRSA strains were resistant to tetracycline, erythromycin, and nalidixic acid (Shahkarami et al., 2014). Most of the MRSA strains were multidrug-resistant; the researchers speculate the reasoning for this is due to prolonged hospitalizations, employment of various unnecessary antibiotics, and insufficient knowledge regarding MRSA (Shahkarami et al., 2014).

Another study from Kano, northwestern Nigeria, researched antibiotic resistance and sensitivity of different *Staphylococcus aureus* strains. The majority of the isolates were resistant to cloxacillin, streptomycin, tetracycline, cotrimoxazole, and penicillin (Nwankwo & Nasiru, 2011). A preponderance of the isolates was sensitive to vancomycin, chloramphenicol, gentamicin, ciprofloxacin, ofloxacin, levofloxacin, and ceftriaxone (Nwankwo & Nsiru, 2011). There were also more affected males than females in this study; the most affected age group was ages zero to ten. The researchers propose that taking antibiotics improperly and self-medicating could be the reason for high antibiotic resistance (Nwankwo & Nasiru, 2011).

Furthermore, Kaleem et al. conducted a similar study that measured the resistance and sensitivity of different MRSA strains in Pakistan. One hundred and thirty-nine MRSA isolates were collected. The plurality of the isolates was susceptible to linezolid, tigecycline,

vancomycin, teicoplanin, minocycline, vancomycin, chloramphenicol, and quinopristin/ dalfoprisitin (Kaleem et al., 2010). The majority of the isolates were resistant to tetracycline, cotrimoxazole, rifampicin, and clindamycin (Kaleem et al., 2010). This study highlights the wide range of resistance MRSA is capable of.

Moreover, researchers in Dessie, Northeast Ethiopia, conducted another study that observed the resistance and susceptibility of different *Staphylococcus aureus* isolates. All of the isolates were resistant to penicillin, and the majority of the MRSA isolates were resistant to Amoxicillin, Co-trimoxazole, Tetracycline, Chloramphenicol, and Ampicillin (Shibabaw et al., 2014). The methicillin-sensitive *Staphylococcus aureus* (MSSA) isolates were resistant to gentamicin, tetracycline, chloramphenicol, amoxicillin, erythromycin, and ampicillin (Shibabaw et al., 2014). Vancomycin was the most effective antibiotic, and oxacillin was the second most effective for *Staphylococcus aureus* (Shibabaw et al., 2014).

Furthermore, Lohan et al. conducted a study that tracked MRSA prevalence in north India. Lohan et al. found that the prevalence of MRSA increased steadily from 2017 to 2019 (Lohan et al., 2021). The plurality of the MRSA isolates was resistant to ciprofloxacin, erythromycin, and clindamycin (Lohan et al., 2021). All of the isolates were resistant to penicillin, and less than half were resistant to vancomycin, teicoplanin, linezolid, cotrimoxazole, and gentamicin (Lohan et al., 2021). Lastly, more males were affected than females (Lohan et al., 2021).

Additionally, Klevens et al. observed the distribution of MRSA infections and determined the epidemiological trends in *Staphylococcus aureus* infections in nine places in the United States. Klevens et al. observed a higher incidence of MRSA in males, the elderly, and African American people (Klevens et al., 2007). In this study, the most common infection caused

by MRSA was bacteremia, and vancomycin was the antibiotic used most as empirical therapy (Klevens et al., 2007). Klevens et al. also observed 19,382 deaths affiliated with *Staphylococcus aureus* infections in 2017 (Kainet et al., 2019). Klevens et al. demonstrate the severity of staphylococcal infections in the United States.

Additionally, Rao et al. conducted a study to determine the resistance of *Staphylococcus aureus* isolates collected from livestock, humans, and poultry from different labs in the United States. The isolates from the swine were the most resistant; most of the swine isolates were resistant to clindamycin and penicillin, and all of the isolates were resistant to tetracycline (Rao et al., 2022). The preponderance of the *Staphylococcus aureus* isolates from humans were resistant to penicillin, and less than half of the isolates were resistant to erythromycin and clindamycin (Rao et al., 2022). The predominant share of the isolates collected from the beef cattle were resistant to penicillin, and a minority of the isolates were resistant to erythromycin and clindamycin (Rao et al., 2022). As for the isolates from the poultry, the minority was resistant to clindamycin, penicillin, and erythromycin (Rao et al., 2022). Lastly, less than half of the isolates from the dairy cattle were resistant to penicillin, gentamicin, and chloramphenicol (Rao et al., 2022). Overall, Rao et al. demonstrate extensive staphylococcal resistance in food animals.

These studies highlight the importance of MRSA surveillance. Most or all of the isolates collected by Kot et al., Shahkarami et al., Nwankwo & Nasiru, Shibabaw et al., and Lohan et al. were resistant to penicillin. Rao et al. found penicillin resistance in human participants, beef cattle, and swine; the minority of the dairy cattle and poultry isolates were resistant to penicillin. Tetracycline resistance was also prevalent in multiple studies, Shahkarami et al., Nwankwo & Nasiru, Kaleem et al., Rao et al., and Shibabaw et al. demonstrate how widespread tetracycline

resistance is among their isolates. A preponderance of isolates was resistant to erythromycin; Kot et al., Shahkarami et al., and Lohan et al. exemplify erythromycin resistance in *Staphylococcus aureus* isolates. Rao et al. also observed erythromycin resistance in human, poultry, and beef cattle isolates. Clindamycin resistance was observed by Kot et al., Kaleem et al., and Lohan et al. Rao et al. also observed clindamycin resistance in humans, beef cattle, and poultry. Both Lohan et al. and Kot et al. observed that the plurality of their *Staphylococcus aureus* isolates was resistant to ciprofloxacin. Kot et al. also observed multidrug resistance in the majority of the isolates and a significant increase in resistance in one year. Lastly, Lohan et al. also observed a steady increase in resistance over a two-year period. These studies demonstrate widespread staphylococcal resistance around the world.

Treatment

It is imperative that new treatments are discovered to treat infections caused by MRSA. Dilsworth et al. conducted an experiment using a combination of therapy with one vancomycin-intermediate *Staphylococcus aureus* strain and two Methicillin-resistant *Staphylococcus aureus* strains. The utilization of Vancomycin and piperacillin-tazobactam together provided significant results compared to vancomycin alone (Dilsworth et al., 2014). Piperacillin is a beta-lactam antibiotic, and tazobactam is a beta-lactamase inhibitor. The combination of these three medications demonstrates an effective course of treatment for infections caused by methicillin-resistant *Staphylococcus aureus* and vancomycin-intermediate *Staphylococcus aureus.* Indicating that a combination of medications may be an effective treatment option for staphylococcal infections.

Similarly, the utilization of TXA709 and Cefdinir together has shown to be effective against MRSA. TXA709 is a prodrug that can target the FtsZ protein, which plays a role in

bacterial cell division. Cefdinir is a cephalosporin antibiotic that can be used to treat infections caused by gram-positive and gram-negative bacteria. Kaul et al. concluded that using both TXA709 and Cefdinir together has a synergistic effect and is effective against resistant infections caused by *Staphylococcus aureus* (Kaul et al., 2016). Kaul et al. also demonstrate that a combination of medications is effective in treating a staphylococcal infection in contrast to only using one medication.

By the same token, biogenic polyamines can be used to treat infections caused by MRSA. Polyamines are ubiquitous polycations; spermine can be used to treat resistant microbes like MRSA (Kwon & Lu, 2007). Kwon & Lu conducted a study monitoring the effects of exogenous polyamines on a few different kinds of bacteria; *Staphylococcus aureus* and MRSA were among the bacteria tested. Kwon & Lu concluded that spermine coupled with a beta-lactam antibiotic increases antibiotic susceptibility in methicillin-resistant *Staphylococcus aureus* and Staphylococcus aureus (Kwon & Lu, 2007).

Diagnostic testing could also be an important tool in antibiotic selection. Antibiotics are only effective against bacteria, and as discussed previously, each antibiotic targets a specific structure or function, which is why each antibiotic is effective against certain bacteria (Patel et al., 2023). Hypothetically, if an antibiotic is prescribed without running a diagnostic test, a medical professional is running the risk of prescribing the wrong antibiotic. However, Sydenham et al. conducted a study regarding diagnostic test usage to assist with antibiotic selection and concluded that diagnostic testing allows for conviction when selecting the appropriate antibiotic (Sydenham et al., 2021). This could prevent the misuse of antibiotics and slow the spread of antibiotic resistance.

Furthermore, the photolysis of staphyloxanthin has been shown to be effective in methicillin-resistant *Staphylococcus aureus* (Dong et al., 2019). Staphyloxanthin is a carotenoid pigment that defends *Staphylococcus aureus* from oxidative stress (Clauditz et al., 2006). Photolysis of staphyloxanthin alters the membrane permeability of *Staphylococcus aureus*, making *Staphylococcus aureus* vulnerable to reactive oxygen species (Dong et al., 2019). It was concluded that the utilization of hydrogen peroxide and photolysis via label-free transient absorption imaging of *Staphylococcus aureus* eliminates *Staphylococcus aureus* (Dong et al., 2019).

Discovering new antibiotics is also an effective way to combat antimicrobial resistance. PM181104 is a newer antibiotic that was discovered recently in MTCC 5269, which is a bacterium that is affiliated with a marine sponge. PM181104 has been shown to be effective against gram-positive bacteria (Mahajan et al., 2013). PM181104 works by interrupting protein synthesis; this new antibiotic was effective in vitro against MRSA (Mahajan et al., 2013).

Similarly, oritavancin is another new antibiotic that was recently approved to treat skin infections caused by gram-positive bacteria like *Staphylococcus aureus* (Belley et al., 2009). Oritavancin is a lipoglycopeptide antibiotic that interrupts cell wall synthesis and can alter membrane permeability (Belley et al., 2009). Oritavancin is considered to be safe and is successful in treating infections caused by gram-positive bacteria with a one-time dose of 1,200 mg or 800mg given as infrequent doses (Dunbar et al., 2011). Overall, Oritavancin has been shown to be an effective treatment for skin infections caused by *Staphylococcus aureus* and MRSA (Dunbar et al., 2011).

New antibiotics research and development is imperative. Some countries have implemented financial incentive plans to tackle the lack of research and development. For

instance, Japan implemented a policy that rewards facilities that did not prescribe antibiotics for the beginning stages of gastrointestinal infections and respiratory infections (Okubo et al., 2022). Okubo et al. observed a decrease in inappropriate prescriptions, indicating that this is a valuable method for curbing inappropriate antibiotic prescriptions, therefore curbing antibiotic resistance. Moreover, Sweden put a program in place called the Swedish Strategic Programme Against Antibiotic Resistance (STRAMA) to assist with antimicrobial resistance. STRAMA tracks antimicrobial resistance trends and tracks antibiotic usage in both humans and animals (Björkman et al., 2021; Mölstad et al., 2017). This program has shown to be effective; Sweden, relative to other European countries, has a low antibiotic outpatient prescription rate ranging from 14.64 to 15.82 from 1997 to 2003 (Ferech et al., 2006). Sweden also has the lowest utilization of antibiotics in animals (Waluszewski et al., 2021). Lastly, MRSA is responsible for less than 2% of infections caused by *Staphylococcus aureus* in Sweden (Holmbom et al., 2020). This evidence highlights the effectiveness of programs like STRAMA in decreasing and even preventing antibiotic resistance and MRSA infection.

Also, in 2016, an experiment focusing on education and decolonization of MRSA was conducted. Both groups of participants had to test positive for MRSA in order to participate. One group of participants in this study was given literature that contained information on how to care for MRSA at home, which was based on CDC guidelines. The other group was instructed to take part in a decolonization routine which consisted of using a chlorhexidine full body wash two times a month, mupirocin in the nose for five days, and a chlorhexidine oral rinse (Huang et al., 2016). A notable decrease in infection was observed in the group that used chlorhexidine daily. Perhaps a combination of education and chlorhexidine can be used to treat and prevent MRSA infections.

In terms of prevention, there is currently no vaccine on the market that can be used to prevent *Staphylococcus aureus* or MRSA (Clegg et al., 2021). There have been multiple attempts at concocting a vaccine for MRSA or *Staphylococcus aureus*. For example, in 2006 a possible vaccine contender was synthesized, called SA75. SA75 was found to be safe and effective in phase I of the trial. The researchers took *Staphylococcus aureus* and used chloroform to kill the bacteria, and then injected it into the participants (Jahantigh et al., 2022). This vaccine is no longer under development due to the difficulty of replicability (Clegg et al., 2021). The V710 vaccine is another vaccine that was developed to prevent infection caused by *Staphylococcus aureus* (Moustafa et al., 2012). The effectiveness of this vaccine was tested among patients who recently underwent cardiothoracic procedures, and it was recommended that the study should not be completed early due to the low efficacy of the vaccine (Fowler et al., 2013). However, a study published in 2020 discusses a possible solution to the lack of an efficient vaccine; Tam et al. proposed that the MRSA vaccine should target leukocidin-mediated immune evasion instead of directly targeting *Staphylococcus aureus* (Tam et al., 2020). In other words, previous vaccine research has been unsuccessful in preventing Staphylococcal infections.

It is crucial that new antibiotics are synthesized, like oritavancin and PM181104, or different combination therapies are explored, like vancomycin and piperacillin-tazobactam. Diagnostic tests could be used to determine the etiological agent causing a patient's infection, allowing a medical professional to choose an appropriate antibiotic or treatment. Antibiotic resistance monitoring programs like STRAMA should be implemented to track antibiotic prescription rates and resistance rates. Also educating people on how to prevent MRSA transmission could be an effective way to curb resistance.

How to Slow the Spread of Staph infections and MRSA

There are a few methods that can decrease the spread of MRSA in a medical setting; they include handwashing, sterilizing medical equipment, maintaining a clean healthcare setting, and having clear isolation protocols. Education on the dangers of MRSA and antibiotic resistance is imperative to slowing the spread and having appropriate protocols in place (Seibert et al., 2014). Koçak Tufan et al. demonstrate the importance of hand washing in a healthcare setting; Koçak Tufan et al. discovered that hand washing leads to a significant decrease in MRSA colonization, an alcohol-based rub was shown to be the most efficient way of cleaning the hands (Koçak Tufan et al., 2012). Watson et al. conducted a hospital-wide cleaning which consisted of cleaning patients with benzalkonium chloride, isolating patients that tested positive for MRSA, and cleaning surfaces that are frequently touched; these practices revealed a 96% reduction in MRSA rates (Watson et al., 2016). Medical devices must be sterile before making contact with a patient in order to prevent the spread of MRSA, and this could also reduce MRSA transmission (Lei et al., 2017). Outside of a healthcare setting, methods such as cleaning gym equipment, not sharing personal care products like razors, and taking an entire course of antibiotics as prescribed are recommended to reduce the spread of *Staphylococcus aureus* and MRSA (Creech et al., 2015; *Using medication: Using antibiotics correctly and avoiding resistance*, 2008; Maurice Bilung et al., 2018). Sanitizing gym equipment is imperative to avoid spreading infections caused by *Staphylococcus aureus* or MRSA. Lastly, it is imperative that a person takes antibiotics as prescribed to prevent resistance.

By taking preventative measures, the spread of MRSA can be reduced. In a healthcare setting, methods such as handwashing, sterilizing medical equipment, maintaining a clean healthcare setting, and having clear isolation protocols are essential precautions that slow the spread of MRSA. By the same token, in a community setting, precautions like cleaning gym

equipment, not sharing personal care products like razors, and taking an entire course of antibiotics as prescribed are efficient approaches to slowing down the spread of MRSA.

Conclusion

There is an abundance of infections that can be caused by *Staphylococcus aureus* or MRSA, and some strains can secrete toxins that assist with host colonization. *Staphylococcus aureus* is capable of resistance against many different antibiotics via efflux pumps and resistance genes, and it is thought that early beta-lactam usage is responsible for the evolution of resistance in staphylococcus, rendering infections caused by MRSA increasingly challenging to treat. Factors like obesity, old age, being a healthcare worker, living in a crowded region, and having an HIV diagnosis put a person at risk for a MRSA infection (Khawcharoenporn et al., 2010; Böcker et al., 2008; Befus et al., 2015; Koirala & Siddiqui, 2023; Zeller & Geller, 2011). The cause of resistance is thought to be the misuse of antibiotics in a clinical and agricultural setting and the overutilization of antibiotics. The resistance patterns of MRSA differ based on the region, and this is because different countries have different antibiotic prescription rates and the presence or lack of antibiotic resistance plans to slow the spread of resistance. The increase in antibiotic resistance is due to the over-prescription, misuse, and abuse of antibiotics (Zhao et al., 2021; Fleming-Dutra et al., 2016). There are a few methods that have been shown to be effective in slowing the spread or preventing the spread of MRSA and this includes handwashing, sterilizing medical equipment, maintaining a clean healthcare setting, having clear isolation protocols, cleaning gym equipment, financial incentive programs to decrease prescription rates, not sharing personal care products like razors, and taking an entire course of antibiotics as prescribed. Perhaps if these methods are practiced, a decrease in antibiotic resistance is on the horizon. The development of new antibiotics/ treatments is imperative to slowing down the

resistance of *Staphylococcus aureus*. Overall, MRSA is a dangerous nosocomial opportunistic infection that urgently requires monitoring and development of an effective, long-lasting treatment.

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