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Lily McNulty Date

Racial, Ethnic, and Socioeconomic Disparities in Pediatric Community-Acquired Methicillin-resistant *Staphylococcus aureus*: A Systematic Review and Meta-Analysis

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Racial, Ethnic, and Socioeconomic Disparities in Pediatric Community-Associated Methicillin-resistant *Staphylococcus aureus*: A Systematic Review and Meta-Analysis

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Abstract

Racial, Ethnic, and Socioeconomic Disparities in Pediatric Community-Acquired Methicillin-resistant *Staphylococcus aureus:* A Systematic Review and Meta-Analysis

By Lily McNulty

Background Marginalized communities suffer from poorer health outcomes due to systemic and structural discrimination. Antimicrobial resistance is an emerging health threat, yet it's unclear to what extent community-acquired methicillin-resistant Staphylococcus aureus (CA-MRSA) burdens these groups.

Methods A scoping review was conducted to identify studies that reported colonization or infection with 8 bacteria of interest by participant race, ethnicity, or socioeconomic status (SES). Studies that reported pediatric CA-MRSA were included for a systematic review and meta-analysis. Two independent reviewers extracted data using Covidence and conducted quality assessments. Meta-analyses and subgroup analyses were conducted using RStudio version 4.2.2.

Results Fifteen studies including 609,641 children from 5 countries were included. Compared to children of non-minority race or ethnicity (e.g., White, Jewish), minority children (i.e., Black, Hispanic, Bedouin, Aboriginal) had a higher risk for MRSA versus methicillin-susceptible *S. aureus* (MSSA) (RR: 1.51, 95% CI [1.26; 1.80], I^2=44%). A sensitivity analysis with low-bias studies (n=3) showed a significant difference between minority and non-minority groups when comparing the risk of MRSA versus no MRSA (RR: 2.02, 95% CI [1.18; 3.46], I^2=66%). Compared to higher SES children (e.g., private insurance, low deprivation), children of lower SES had a higher risk for MRSA versus MSSA (RR: 1.54, 95% CI [1.17; 2.02]) in studies with a low risk of bias.

Conclusion Minority children have statistically significantly higher risks of MRSA colonization or infection across multiple countries. More research is needed to identify and dismantle systems that perpetuate barriers to equitable healthcare, prevention, and treatment of CA-MRSA.

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Chapter 1: Introduction

Background

In recent decades, human health and behavior have been heavily influenced by the ability to cross international borders at a rate not previously seen. Globalization, or interactions on an international scale, has created significant opportunities for political, social, and economic collaboration (Smith et al., 2007). However, it is also an important consideration in the protection of human health, as globalization allows for increased movement of people and disease. There is a threat to global public health when communicable diseases can jump from one country to the next in hours, and the origins of these diseases are difficult to identify. One of these threats is antimicrobial resistance. Antimicrobial resistance, as explained by the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC), occurs when microbes develop resistance to previously effective treatment drugs (WHO, 2020; CDC, 2022). More specifically, antibiotic resistance occurs when bacteria become resistant to drugs that are used to treat bacterial infections (WHO, 2020). Antibiotic resistance did not follow far on the heels of the discovery of antibiotics in the early twentieth century; after Fleming discovered penicillin in 1928, the bacterial penicillinase was discovered before penicillin was even brought to the market as a treatment, thus introducing the spread of bacteria resistant to penicillin (Smith et al., 2007). Bacteria that are classified as major threats to human health began developing resistance to treatments that had just been introduced. Of these bacteria, *Staphylococcus aureus* became a highly virulent "superbug," meaning its resistance to treatments was complex and it caused high rates of sickness and death when infected (Smith et al., 2007).

Staphylococcus aureus is a Gram-positive bacterium that is round, cocci-shaped, and can grow aerobically or anaerobically (Taylor et al., 2022). It is a common bacterium as humans are

suitable reservoirs; typically, it can be found on the skin or mucus membranes, and one of the most common locations for *Staphylococcus aureus* carriage is in the lower nostrils, or anterior nares (Taylor et al., 2022). *Staphylococcus aureus* has several mechanisms of resistance. The staphylococcal chromosomal cassette mec (SCCmec) can have either the mecA or mecC genes that encode for PBP-2a, rather than normal PBP, the penicillin-binding protein that synthesizes the bacterial cell wall; PBP-2a, because it does not bind well to beta-lactams, can continue to synthesize the cell wall (Liu et al., 2016; Taylor et al., 2022). This means that *Staphylococcus aureus* strains with these genetic elements can continue to proliferate and cause disease in the presence of beta-lactam antibiotics and derivative classes (Enright et al., 2002; Liu et al., 2016; Noel et al., 2010).

What makes MRSA a uniquely harmful organism is its virulence; shortly after its inception in the 1960s, nosocomial MRSA infections became commonplace, and severe infections from MRSA were cropping up in healthy populations (Liu et al., 2016). As MRSA clones appeared around the world, more attention was being called to their ability to manifest as invasive infections with high levels of morbidity and mortality, and in the late 1990s, treatment failure began to be documented among otherwise healthy populations (Liu et al., 2016). What was typically a healthcare-associated infection was now seen emerging in the community. Community-acquired MRSA (CA-MRSA) infections began emerging in the late 1990s and early 2000s in individuals who did not have the characteristics normally associated with typical MRSA patients, such as recent hospitalization, prior surgery, recent MRSA infection, etc. (Baba et al., 2002), and CA-MRSA strains are now more prevalent than HA-MRSA strains in many settings (Mediavilla et al., 2012). Otto discusses the increased virulence in CA-MRSA strains, indicating that continued infections in individuals without predisposing risk factors can be

attributed to its level of severity (2013). An increase in morbidity and mortality from CA-MRSA in both vulnerable and non-vulnerable communities has created the need for a comprehensive understanding of the burden of the disease.

The pediatric population is a vulnerable population that has increased exposure to CA-MRSA infections. In the US, a substantial proportion of children attend daycare centers where communicable diseases, like MRSA, are common (Miller et al., 2011). Children under 18 have a variety of other risk factors, such as playing on sports teams, and having sustained close contact with peers, among other factors (Mayo Clinic, 2022). Given its virulence and rapid rise in community settings, it is critical to consider the factors at play in the spread, acquisition, morbidity, and mortality of community-acquired MRSA among the pediatric population.

Rationale and Problem Statement

CA-MRSA is a prevalent health threat. In recent years, there has been a critical shift in focus toward health equity and social justice. In discussing the epidemiology of CA-MRSA, it is important to do so through a lens of health equity. Early in the COVID-19 pandemic, it was clear that some populations were shouldering a heavier burden of morbidity and mortality than others. Increased number of cases, severe illness, and death were largely seen among minority communities and communities of color (Ma et al., 2021; Mude et al., 2021). These racial disparities are not limited to just the recent COVID-19 pandemic, however. Across the world, historically marginalized communities tend to have poorer health outcomes when compared to their non-vulnerable counterparts (Jones et al., 2023; Levy et al., 1998). Systemic and structural racism and discrimination result in factors that perpetuate these disparities, like unequal access to health care, education, and economic opportunity, among others (Nelson et al., 2002; Williams et al., 2000). There have been several papers that reported results indicating that children of color

or low socioeconomic status saw more infection with CA-MRSA (Ali et al., 2019; Immergluck et al., 2019), but the body of evidence is still scarce, especially outside of the United States.

While the discourse around racial disparities in infectious disease is growing, there persists a gap in the cumulative evidence around racial, ethnic, and socioeconomic disparities in CA-MRSA infection and colonization among the pediatric population. By conducting a systematic review and meta-analysis, this research aims to close the gap in evidence of these disparities in order to inform and shape health policy.

Purpose Statement

The purpose of this research is to shed light on the existing evidence of racial, ethnic, or socioeconomic disparities in the burden of community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) in children. The aim of gathering, synthesizing, and presenting this evidence is to examine the extent to which CA-MRSA disproportionately affects these minority groups so that the public health community can better advocate for health equity, and work to identify and change systems that contribute to the burden of disease.

Research Question and Hypotheses

Research question: Is there evidence of racial, ethnic, or socioeconomic disparities in the burden of CA-MRSA in pediatric populations in the US and globally?

Null hypothesis: Children belonging to racial or ethnic minority groups or children who are socioeconomically disadvantaged do not have a higher risk for CA-MRSA when compared to children belonging to non-minority or non-socioeconomically disadvantaged groups.

Alternative hypothesis: Children belonging to racial or ethnic minority groups or children who are socioeconomically disadvantaged have a higher risk for CA-MRSA when compared to children belonging to non-minority or non-socioeconomically disadvantaged groups.

Significance Statement

This research will attempt to bridge the existing knowledge gap in the disparities that exist in the burden of pediatric CA-MRSA. It will present cumulative findings from peer-reviewed research to assess the current epidemiology of pediatric CA-MRSA and has the potential to inform community- and national-level entities of how it may disproportionately impact vulnerable communities. This can be utilized to create infectious disease interventions for high-risk populations, whether it be on an individual, healthcare provider, or policy level. For example, a study conducted by Chamie et al. discussed the "test and respond" model, designed by Unidos en Salud in response to the Latino communities across the US being disproportionately impacted by the COVID-19 pandemic (2022). By utilizing a community-based, low-barrier, mass testing program, the burden of disease among Latinos in the regions where it was adopted could be accurately assessed and addressed. Public health programs are only as successful as the evidence and research behind them; Unidos en Salud used the evidence of racial disparities in COVID-19 infection to create a tailored intervention to lessen the burden of the disease (Chamie et al., 2022). This research aims to do just that – provide evidence to inform public health interventions related to CA–MRSA in the pediatric population.

Chapter 2: Literature Review

Major Threats to Human Health and an Introduction to Antibiotic Resistance

As globalization increases and changes in populations and health behaviors occur, major threats to human health evolve in response to these transitions. In 2019, the World Health Organization (WHO) named antimicrobial resistance among the top ten major threats to global health (2019). Antibacterial resistance occurs when treatment for bacterial infections is no longer effective; the bacteria themselves, rather than the host, become resistant to medicine that usually clears the pathogen (WHO, 2023). In turn, treating infections in communities with a higher incidence of antimicrobial-resistant infections can become incredibly difficult.

The "why" behind the increase in the prevalence of antimicrobial resistance is not a straightforward answer. The development and spread of antibacterial resistance are complex, and transmission routes largely depend on the type of bacteria. Antibacterial resistance can be caused by misuse and/or overuse of antibiotics for preventing and treating bacterial infections, inappropriate use for non-bacterial infections, the spread of resistant bacteria due to poor infection control practices, agricultural practices, and the wide array of uses for antibiotics across settings such as the veterinary field (WHO, 2014; CDC, 2019). The threat of antibacterial resistance has the power to derail years of advancement in public health and safety. The Centers for Disease Control and Prevention (CDC) "Antibiotic Resistance Threats in the United States, 2019" report outlines the gains made in the prevention of antibiotic resistance-related morbidity and mortality over six years, but the threat remains (2019). This report estimates that, as of 2019, resistant bacteria can lead to over two million infections and over 35,000 deaths nationally (CDC, 2019). Despite gains in infection control, antibiotic-resistant bacteria pose a significant risk to both healthcare and non-healthcare populations. By understanding the populations who

are most impacted by resistant bacterial colonization and infection, prevention measures and public health recommendations can be made to curb transmission, understand the burden of antibacterial-resistant disease, and create strategies to equitably prevent and treat colonization and infection events.

Transmission Overview & Community-acquired antibacterial resistance

Our understanding of the epidemiology of antibacterial-resistant infections has evolved with an increase in available data and research, and its mechanisms of transmission have become more understood. Though transmission routes depend on the type of bacteria and if they are gram-negative versus gram-positive, antibacterial-resistant bacteria can be spread through close or sexual contact, they can be airborne, spread through contaminated surfaces or water, or be transmitted by animals or animal products (CDC, 2019). However, there exists a gap in the depth of research concerning community-associated resistant colonization and infections.

Hospital-acquired resistant infections, or infections that are due to healthcare exposures, are a risk to those in contact with the healthcare setting (CDC, 2019). Zimlichman et al. detail the burden of general healthcare-associated infections and paint a grim picture of healthcare-associated infection outcomes for both the patients and healthcare systems (2013). Apart from their exorbitant cost and burden on the healthcare system, healthcare-associated infections have the potential to reach communities outside of healthcare facilities (Zimlichman et al., 2013). Healthcare-associated infections pose a huge risk for vulnerable populations seeking care; however, it is possible to implement prevention and infection control techniques at a facility level (CDC, 2019). On the other hand, community-acquired infections, or infections that are contracted outside of a healthcare setting, are harder to track and prevent than healthcare-associated infections. If resistant infections originate from a healthcare facility and are

transmitted from the movement of patients, there is the risk of healthcare-associated infections becoming a danger to the general population (CDC, 2019). While definitions of community- and healthcare-associated infections can differ depending on the context in which they are used, van Duin et al. describes several common definitions:

1. Community-onset: If the onset of infection was within the first 48 hours of a patient's admission to a healthcare facility (van Duin et al., 2020).
    a. Community-acquired: no previous healthcare-related exposures, such as hospital admission within the previous three months, before a positive culture.
    b. Healthcare-associated: had a healthcare-related exposure within three months of a positive culture, such as hospital admission, received acute care, dialysis, or other intravenous treatments, or resided in a long-term care facility.
2. Nosocomial: onset of infection was after the first 48 hours of a patient's admission to a healthcare facility (van Duin et al., 2020).

It is important to note that the 48-hour timeframe is not used across every setting. There is variation in how "community-acquired" is defined; some settings may use a 72-hour timeframe, and samples collected in the community or through population-based surveillance may be assumed as community-acquired. Additionally, van Duin et al. highlight the fact that most individuals are infected with organisms with which they were first colonized; so, the timing of colonization with resistant bacteria is another important consideration (2020). There exists a lack of harmony in definitions that creates a potential need for a standardized meaning; this has

the potential to further our understanding of the risks of community- or healthcare-associated resistant bacterial infections.

Disparities in the burden of Infectious Diseases

A gap in the study of antibacterial resistance is understanding the disparities in individuals or populations carrying the burden of these infections. The world has seen the scale of how infectious diseases of public health significance can impact vulnerable communities. The COVID-19 pandemic has been a deadly force for the past three years. Ma et al. utilized mathematical modeling to understand and evaluate the impact of both racial and ethnic disparities on the burden of COVID-19 (2021). This study found that these disparities in healthcare access, underlying medical conditions that are risk factors for more severe COVID-19 disease, and exposure to COVID-19 have led to both higher morbidity and mortality associated with the disease among minority populations (Ma et al., 2021). However, the existing demographic data that exists may not be comprehensive enough to wholly understand the impact of infectious diseases on vulnerable communities or individuals. Studies in infectious disease have identified gaps in the collection of demographic data that measures the burden of disease; Ansari et al. demonstrated that missing race and ethnicity information, though in the realm of sexually transmitted infections, can impact how disparities are measured, and in turn, can determine the extent of said disparities (2022). If demographic factors like race, ethnicity, or socioeconomic factors are not being uniformly collected, it is difficult to accurately portray disparity measures.

The COVID-19 pandemic gave way to a still-growing breadth of literature that provides evidence that minority populations have been burdened with higher morbidity and mortality from infectious diseases. Chaturvedi et al. describe the risk factors associated with COVID-19

transmissions, such as close contact and shared spaces; typically, minority populations tend to live in closer contact either due to household crowding or live in areas with higher population density due to systematic forces of oppression that have created largely disparate living situations (Chaturvedi et al., 2020; Ali et al., 2019). From a health standpoint, African Americans are less likely to have and access adequate healthcare and generally receive a poorer level of care due to implicit biases of healthcare practitioners; Chaturvedi discusses the concept of the "Iron Triangle", which encompasses cost, access, and quality of healthcare systems, and how the United States historically has not delivered upon the three tenets equally, if at all, to minority populations (Bakullari et al., 2014; Chaturvedi et al., 2020; Pollack et al., 2018). Tai et al. reported the burden of COVID-19 on minority populations in the United States, providing an update in 2021 from their previous findings in 2020; severe health outcomes like hospitalization and death are more likely to occur among Black, Hispanic, and American Indian populations than Whites (Tai et al., 2021; Tai et al., 2022). This, paired with socioeconomic disparities like higher rates of unemployment among minorities and inequalities in the level of housing and healthcare services, created a different kind of pandemic for vulnerable populations, one more severe that impacted more than just human health (Tai et al., 2021; Tai et al., 2022).

When sociodemographic factors compound to create certain outcomes for populations, a pandemic can disproportionately impact these groups; this is not only true for the COVID-19 pandemic but for other large events that affect many communities at one time. It is vital that studies are conducted in both healthcare and community-based settings to fully capture the racial, ethnic, and socioeconomic factors that lead to disparities in disease acquisition, morbidity, and mortality.

Methicillin-resistant *Staphylococcus aureus* (MRSA)

Infections, including skin and soft tissue infections (SSTIs), and deaths can be attributed to a variety of drug-resistant bacteria, but the severity of morbidity and mortality differs dependent on the kind of bacteria itself. For example, the 2019 CDC report outlines urgent, serious, and concerning resistant threats – methicillin-resistant *Staphylococcus aureus* (MRSA) is categorized as a serious threat (CDC, 2019). Lowy et al. created a timeline of the emergence of resistant bacteria, one of the earliest and most notable being *Staphylococcus aureus* (2003). *S. aureus* poses a great concern to the public health and medical communities: it is the cause of many healthcare-associated infections, and its high mortality rate is even more burdensome as it continues to develop new resistance mechanisms (Lowy et al., 2003; Alvarez et al., 2019). Methicillin resistance arose after resistance against penicillin treatments was formed in *S. aureus;* the rapid spread of MRSA quickly became a pathogen of major concern and was causing morbidity and mortality in countries that had not yet introduced methicillin treatments (Peacock et al., 2015; Otto et al., 2014). *S. aureus* clones (both human and animal strains) developing into MRSA and MRSA's adaptability as a pathogen means that it can develop resistance to a wide array of antibiotics, creating the need to home in on prevention efforts at a healthcare and community level (Chambers et al., 2009; Lee et al., 2018). Chambers et al. remarked that part of MRSA's unique nature is the sheer number of clones associated with CA-MRSA and the severity of the disease that they were causing (2009). Perhaps more concerning, however, was the spread of the virulent pathogen into communities that didn't have any risk for nosocomial infection, creating a new threat for already-vulnerable communities (Lee et al., 2018).

Community-associated MRSA quickly rose as a top threat in the 21st century as these clones disseminated globally (Chambers et al., 2009; Otto et al., 2014). Its adaptability,

virulence, and its multiplicity of clones call for the global community to unite efforts in CA-MRSA prevention at a community-centered level (Lakhundi et al., 2018).

Pediatric CA-MRSA

Knowing how resistant bacteria affect the most vulnerable populations is critical to building and prioritizing prevention efforts. There is a growing body of research looking at how CA-MRSA affects the pediatric population in both the US and globally; Purcell et al. conducted a study over the course of 14 years that examined the burden of CA-MRSA on the hospitalized pediatric population (2005). Not only did CA-MRSA cases increase exponentially after the year 2000, but 89% of these new cases, both inpatients and outpatients, were among otherwise healthy children with no healthcare-related risk factors, something that is more common among HA-MRSA cases (Purcell, 2005; Zaoutis et al., 2006). Though this specific study is focused on a pediatric population in South Texas, the prevalence of CA-MRSA among the healthy population is worrisome.

Similar studies have been conducted that show a rapid increase in the proportion of CA-MRSA in *S. aureus* isolates or infections; Zaoutis' study spanned over the course of three years and found a nearly threefold increase in CA-MRSA cases, not unlike the increase that Purcell et al. saw in Texas in the early 2000s (Paintsil, 2007; Purcell et al., 2005; Zaoutis et al., 2006). Another quintessential example is the rise of CA-MRSA among pediatric populations in Chicago, IL, where Herold et al. saw a dramatic increase in MRSA cases among children that had no previously identified risk factors (1998). The researchers conducted an epidemiological investigation and determined that the rise in CA-MRSA among children without risk factors was not confined to an outbreak, but rather spread out and relatively sustained; other hospitals in the

Chicago area saw a similar increase in pediatric CA-MRSA, reaffirming the conclusions from Herold et al. (Herold et al., 1998; Hussain et al., 2001).

The treatment of MRSA cases with antibiotics among children is dependent on several factors. Examples include where and how the infection manifests, the risk factors of the individual, and the epidemiology of MRSA in the community (Paintsil, 2007). For example, the resistance profile among healthy children with MRSA may be different from that of children with risk factors, such as recent hospitalization, previous MRSA infection, or previous antibiotic treatment, among others; children with risk factors have been found to have an increased likelihood of resistance to ciprofloxacin or clindamycin (Paintsil, 2007; Zaoutis et al., 2006). Assessing the state of MRSA in the community of the child and whether there has been a change in incidence among HA- or CA-MRSA can inform healthcare practitioners and public health personnel of the epidemiologic status of MRSA. Across the board, researchers have seen an increase in healthy children presenting to healthcare facilities with CA-MRSA with no predisposing risks.

While it is critical to look at the overall epidemiologic profile of who is acquiring CA-MRSA, it's equally important to understand how these colonization or infection events may disproportionately impact vulnerable populations more than others. The next review of literature will dive into disparities in the burden of infectious diseases, and more specifically, CA-MRSA.

Disparities in MRSA and CA-MRSA

In recent years, as institutions have seen an increase in the spread of both MRSA and CA-MRSA strains globally, studies have been conducted to attempt to understand the implications of the disease and the epidemiology of who is being impacted the most. Healthcare or hospital-associated MRSA has typically been studied in more depth, and demographic

information can sometimes be more easily collected from medical charts or case report forms from inpatients. Studies like that of Leys et al. found that hospital-acquired infections not limited to, but including MRSA, were more common among Native American minority groups with a study sample of over twelve million individuals (2020). Similarly, Bakullari et al. reported findings to connect the dots between healthcare-associated infections in US adults and the racial and ethnic disparities in these infections; it was found that when hospitalized for specific conditions requiring surgery, Asian and Hispanic patients had higher rates of hospital-acquired infections when risk-adjusted, though Black patients were not found to be at a statistically significant higher risk (2014). Studies like this show how not only socioeconomic or racial factors are at play, but how linguistic barriers and biases from practitioners also influence the risk for infection (Bakullari, 2014).

Burden of MRSA

As the decline in HA-MRSA contrasts with the rise in CA-MRSA, more evidence is being gathered to understand mechanisms of transmission and disease susceptibility. Despite recent downward trends in the incidence of HA-MRSA, Gualandi et al. found that Black patients are still more than two times more likely to have HA-MRSA than White patients (2018). To answer the question of how racial, ethnic, or socioeconomic factors play into the burden of resistant infections, a relatively limited number of studies have been conducted. See et al. investigated how socioeconomic factors affect the racial disparity in CA-MRSA between White and Black populations in the United States (2017). They found that socioeconomic factors, like urbanicity and household crowding, were more indicative of invasive CA-MRSA infection when looking at disease rates by race (See et al., 2017). Fridkin et al. found that when comparing the two cities of Atlanta and Baltimore, only in Atlanta did they see a significant difference in

MRSA incidence among Black and White individuals (Fridkin et al., 2005). These studies emphasize that there is more at play than simply race or ethnicity as risk factors for disease, but rather the social factors (such as socioeconomic status, housing conditions, and comorbidities) as touched on by See et al. (2017). Research conducted by Mohnasky et al. reported racial disparities in *S. aureus* bacteremia and discussed how patient characteristics were more indicative of infection, such as comorbidities; these characteristics, however, are often linked to social factors as discussed in See's paper like poverty, crowding, or level of access to care (Mohnasky et al., 2021; See et al., 2017). In a similar vein, Beltrán et al. investigated the association between markers of poverty and CA-MRSA in Argentina and found a statistically significant relationship between skin and soft tissue infections and household overcrowding in lower SES neighborhoods (2018). Results from a UK study by Tosas Auguet et al. reinforced this link between lower SES and increased risk for CA-MRSA; social factors that are indicators of low socioeconomic status play a significant role in the acquisition of CA-MRSA (2016). Lower socioeconomic status is often found in marginalized communities that have been systematically excluded from accessing high-quality education and healthcare, among other major institutions that contribute to an individual's physical, social, and economic well-being. Indigenous populations, both in the United States and globally, have typically been marginalized populations that suffer from disparities in access to often-basic healthcare services and resources (Bailie et al., 2004; Tong et al., 2012). Tong et al. examined racial and socioeconomic differences in the Indigenous population in Australia and found a large disparity in the incidence of *S. aureus* bacteremia between the indigenous and non-indigenous populations (2012).

There is a growing number of studies that highlight the racial, ethnic, and socioeconomic disparities in who is not only acquiring but also suffering from MRSA and CA-MRSA. To fully

understand the burden of disease, we need to critically evaluate how racial, ethnic, and socioeconomic characteristics influence CA-MRSA acquisition, morbidity, and mortality. The subsequent examination of the literature focuses on assessing what exists in terms of racial, ethnic, and socioeconomic disparities of CA-MRSA, specifically in the pediatric population.

Disparities in Pediatric MRSA and CA-MRSA

Though there is limited evidence of racial, ethnic, and socioeconomic disparities in CA-MRSA in the general population, there exist even fewer studies focusing on these disparities in the pediatric population. What does exist, however, echoes previously discussed studies; that there are differences in CA-MRSA acquisition and morbidity based on race, ethnicity, and socioeconomic status. A Brazilian study conducted by Neves et al. found that both income and income stability are significantly associated with colonization with MRSA, and children with unstable income are more than two times more likely to be colonized (Neves et al., 2019). The rise in the number of children being hospitalized with MRSA causes concern about the potential of rapid CA-MRSA transmission among healthy pediatric populations; Ali et al. conducted a spatial analysis of disparities in community-onset MRSA (CO-MRSA) and looked at both individual- and neighborhood-level characteristics that may be predictors of CA-MRSA infection (2019). The authors found that among children, Black and public health insurance groups were more likely to have CO-MRSA, and crowding and a higher level of poverty were neighborhood-level indicators for CO-MRSA risk (Ali et al., 2019). Another pediatric population of concern is remote, Indigenous populations. While Campbell et al. predominantly discusses the role of nurse practitioners in the clinical care of pediatric CA-MRSA, they emphasize how rural children often have less than adequate conditions, both at a household- and community level, and how this

contributes to the overall burden of CA-MRSA in indigenous communities (Campbell et al., 2020).

Concluding comments

There are a limited number of studies that explicitly discuss the burden of racial, ethnic, and socioeconomic disparities among children with CA-MRSA. It is up to researchers, clinical personnel, and the field of public health to call attention to the importance of standardizing demographic data collection and shedding light on the danger of pediatric CA-MRSA. Ensuring that both pediatric and adult minority populations have adequate access to healthcare services, as well as recognizing the social factors that lead to these disparities in healthcare access and disease burden, is a collective responsibility.

Chapter 3: Methodology

Eligibility Criteria

Inclusion criteria

The systematic literature review and meta-analysis focusing on pediatric MRSA is part of a larger scoping review, focused on examining evidence of racial, ethnic, and socioeconomic disparities in the burden of community-acquired resistant bacterial infections. The eligibility criteria for the scoping review are overarching and guided the pediatric MRSA systematic review criteria. The inclusion criteria for the larger review required that colonization or infection with at least one of the nine bacterial strains was reported: *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter species, Escherichia coli, Enterobacteriaceae,* or *Enterobacterales*. The papers needed to report colonization or infection by either race, ethnicity, or socioeconomic factors, and all ages, genders, and countries were accepted from any year. The criteria for these colonization events or infections were that they were community-acquired; if the paper included nosocomial or hospital-acquired infections, then the community-acquired versus healthcare-associated infections needed to be reported separately, with race, ethnicity, or SES factors reported separately as well. For this pediatric MRSA systematic review, the inclusion criteria were that the population was strictly pediatric (however the paper defined pediatric, either below eighteen or nineteen years of age) and limited to MRSA infection or colonization. It was also required that there was a comparator group for these papers, i.e., MRSA versus no MRSA colonization or infection, and/or MRSA versus MSSA colonization or infection, to complete a meta-analysis. Colonization and infection events were combined for this systematic review and meta-analysis as

this research is focused on the prevalence of MRSA among children belonging to minority and low-SES groups, and less so on the clinical presentation of MRSA.

Exclusion criteria

Exclusion criteria for the larger scoping review excluded papers that did not report one of the bacteria of interest, the cause of infection was unclear, the paper did not report race, ethnicity, or SES information, the infection was hospital-acquired or device-associated, or only country-level measures of SES were described (i.e., low or middle-income countries). Additionally, case studies, narrative reviews, systematic reviews, and papers without abstracts were excluded. For the pediatric MRSA review, papers were excluded if there was no comparator group for MRSA, the patient population included groups other than pediatrics, race, ethnicity, or socioeconomic characteristics were not reported separately by comparator groups, community-acquired and hospital- or healthcare-acquired infections were reported together, or MRSA infections included concurrent infection with MSSA. Papers were excluded if the raw data could not be extracted from the paper, or if the comparator group was not also community-acquired (for example, CA-MRSA versus MSSA, but MSSA was not community-acquired). Additionally, papers that pooled *S. aureus* with other organisms that were not of interest for the scoping review were excluded if *S. aureus* did not comprise more than 50% of colonization events or infections.

Information Sources and Search Strategy

On January 11th and 12th of 2022, a Tufts University Librarian (RM) conducted literature searches in the following databases: MEDLINE (Ovid), MEDLINE Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, and Daily (Ovid), Global Health

(Ovid), Embase (Elsevier), Cochrane Database of Systematic Reviews (Wiley), Cochrane Central Register of Controlled Trials (Wiley), and Web of Science Core Collection.

Search strategies utilized both controlled vocabulary and free-text keywords. All searches were based on an initial MEDLINE search developed in collaboration with the other authors and utilizing MeSH terminology and related keywords for the following concepts: Community-Acquired Infections, Outpatients, Ambulatory Care, Socioeconomic Factors, Health Status Disparities, Healthcare Disparities, Continental Population Groups, Ethnic Groups, Gram-Negative Bacteria, and individual ESKAPE pathogens. The MEDLINE strategy was translated to each of the listed databases by RM, and all databases were searched from inception through January 2022, except for MEDLINE Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, and Daily, where the search covered 2017 through 10 January 2021. References were collected and deduplicated using Endnote X9, prior to export to Covidence for screening and management (Covidence, 2022). The selection process involved at least two reviewers at each stage, including title and abstract screening and full-text review. Screened studies were included or excluded at each stage, requiring consensus between reviewers.

Data Collection Process

A data extraction template was created in Covidence in the fall of 2022 by LM, NN, MN, and EA. The extraction template included the below elements: PMID (search in PubMed), title, country, study design (choose from list), study duration (in years), study funding (choose from the list: academic, federal, internal, etc.), conflicts of interest (if reported), participant demographics (race, ethnicity, SES), inclusion criteria – the strain of bacteria (*Staphylococcus aureus*), age (pediatric, adult, senior) (all papers pediatric), age mean, median, and range, infection type (infection or colonization, or both), the definition of community-acquired (part of

our inclusion criteria), inclusion criteria, exclusion criteria, method of recruitment (inpatient, outpatient, or community-based), the total number of participants recruited, total number analyzed, percent male, outcome, and outcome table (outcome one-ten with name, arm one-arm four).

The initial pediatric MRSA papers were extracted by LM, NN, MN, EA, and AB. LM was an extractor on each of the papers. In March of 2023, three additional papers were extracted by LM, EA, MN, AB, and SA. Once each paper had two unique reviewers that completed data extraction, papers were sent to consensus in Covidence, where one individual resolved conflicts between the two reviewers. Many conflicts were due to errors in punctuation, capitalization, or differences in wording. If there were issues in consensus or the reviewer had questions, they would bring the issue to a weekly meeting where the group would discuss how to resolve it. Once consensus was reached, the data was exported into an Excel spreadsheet for data cleaning, organization, and analysis. The initial papers were exported in December 2022, and the remaining three papers were exported in March 2023. Two papers that did not meet eligibility criteria were retroactively excluded during preparations for data analysis.

Quality Assessment

A modified Cochrane risk-of-bias template (Higgins et al., 2011) was created by LM in collaboration with EA to be used when assessing the quality of each study included. They were measured with 3 options: low bias, high bias, or unsure/some concerns. The indicators measured were:

1. Selection bias: Were the sample groups drawn from the same population?
2. Assessment of exposure: how was the exposure information obtained? i.e., through medical records, one-time interviews, etc.

3. Detection bias: was statistical analysis used appropriately to adjust, match, or correct?
4. Detection bias: was missing data handled appropriately?
5. Outcome described clearly (e.g., the definition of acquisition reported clearly)?
6. Was the outcome measured objectively (lab measurement)?

Two reviewers (LM and AB) independently completed the risk of bias for each of the papers. Each indicator had a comment box for the two reviewers to record justifications, notes, or questions. The consensus was completed by LM, and each paper had a cumulative score of low risk of bias, unsure/some concerns, or high risk of bias.

Data Analysis

Data were organized in two Excel sheets, one for Race and Ethnicity, and one for Socioeconomic indicators. The referent groups were designated as Arm one in both sheets; these groups were the number of events reported in the minority populations (e.g., Black race, Aboriginal, Hispanic, or Bedouin ethnicity, low-income, household crowding, etc.). Arm two was the comparator group, the non-minority population (e.g., White race, European or Jewish ethnicity, high-income, no household crowding, etc.). The raw numbers for the minority groups were then summed, so the effect measures could be calculated against the comparator group. This data was then put into a data shell to be uploaded to RStudio, which reported variables event.e, noevent.e, n.e, event.c, noevent.c, n.c, and analysis. Analysis one or two was designated to each study, analysis one being MRSA versus MSSA, and analysis two being MRSA versus no *S. aureus*. These data were uploaded into R Studio where separate analyses for race/ethnicity and SES were run. For studies reporting race and ethnicity, six analyses were run with two comparator groups, MSSA colonization or infection, or no MRSA colonization or infection.

Analyses were determined a priori. Analyses included MRSA versus MSSA (all studies), MRSA versus MSSA (low-bias studies only), MRSA versus MSSA (Black versus White), MRSA versus No MRSA (all studies), MRSA versus No MRSA (low-bias studies only), and MRSA versus No MRSA (Black versus White). For studies reporting socioeconomic characteristics, three analyses were run with the same two comparator groups: MRSA versus MSSA (all studies), MRSA versus MSSA (low-bias studies only), and MRSA versus No MRSA (all studies). There were not enough studies that reported socioeconomic characteristics to run the same sensitivity and subgroup analyses. For subgroup and sensitivity analyses, original and alternative results were produced. The subgroup analyses of Black versus White were conducted to examine the risk of MRSA among children in the United States; seven unique studies reported Black and White race. R package meta (Balduzzi et al., 2019) was utilized to run the meta-analyses of binary outcome data. A forest plot was generated for all analyses to present the risk ratios and 95% confidence intervals, common effects model, random effects model, prediction interval, and the I^2 variable for quantifying heterogeneity. It is important to note that studies Ali 2019 and Immergluck 2019 were pulled from the same study population but were run in separate analyses so there was no risk of double case counts. Submission to IRB was not necessary as this project did not conduct primary human subject research.

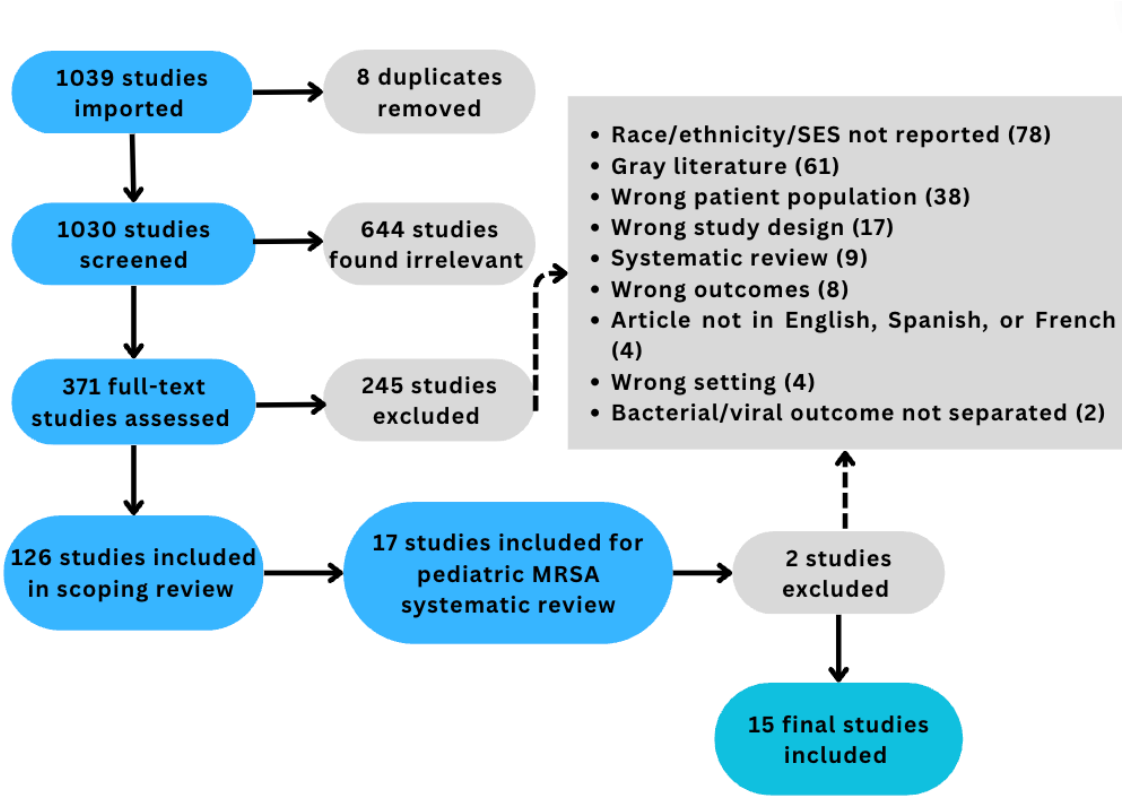
Chapter 4: Results

Study Characteristics

Study selection

In Covidence, NN, MN, and CC conducted title and abstract screening for 1,030 imported papers, where 644 papers were found to be irrelevant according to the broad eligibility criteria. LM, NN, and MN conducted the full-text review for the remaining 371 studies. 245 of these papers were excluded, and 126 studies were included in the scoping review. From these 126, studies were screened independently by LM to identify papers that met the pediatric MRSA SRMA and found fourteen initial studies that met this criterion in January of 2023. Three studies were included in March of 2023, and two were later excluded. A total of fifteen studies were included in this systematic review and meta-analysis. See the PRISMA diagram below:

Figure 1: PRISMA flow diagram



Overview of studies

Of the 126 studies included in the broader scoping review, fifteen studies met the eligibility criteria for the pediatric CA-MRSA systematic review and meta-analysis. Studies were from five countries: the US (n=10), Israel (n=1), Iran (n=1), New Zealand (n=1), and Australia (n=2), and included 671,692 participants. Table 1 describes study characteristics, including authors, study title, country, type of recruitment (or how they obtained their sample), the number of participants analyzed, study type and duration, the definition of community-acquired that was used, whether MRSA infection or colonization was reported, race, ethnicity, or socioeconomic characteristics reported, the comparator group, the author's outcomes of interest (e.g., skin and soft tissue infections, MRSA, community-acquired pneumonia), and any relevant findings about differences seen between racial, ethnic, or socioeconomic groups. Children belonging to "unknown" race or ethnicity groups or with missing indicators of socioeconomic status (e.g., insurance) were excluded from the meta-analyses as were children that did not belong to outcomes of interest (for example, children with positive cultures for bacteria that were not of interest). A total of 609,641 children were included in the analysis.

Table 1: Study Characteristics

Authors	**Title; Country**	**Recruitment type**	**Participants analyzed, (n)**	**Study type & duration**	**Definition of CA; Infection or colonization**	**Characteristics reported (race, ethnicity, SES)**	**Comparator group**	**Outcome of Interest**	**Relevant findings**
Ali et al., 2019	A Spatial Analysis of Health Disparities Associated with Antibiotic Resistant Infections in Children Living in Atlanta (2002–2010); USA	Inpatient, outpatient	39,371	Case-control study, 8 years	Samples collected within 48 hours, and all outpatients; infection	Race/ethnicity (White NH, Black NH, Hispanic, Other) and insurance status (private, public, self-pay)	No MRSA (uTBI patients)	Community-onset MRSA infection	Characteristics such as race, insurance status, and geographic location influence the risk for CO-MRSA infections.
Bar-Meir et al., 2010	Staphylococcus aureus Skin and Soft Tissue Infections: Can	Inpatient	81	Prospective cohort; 1.5 years	Samples collected within 48 hours and	Race (Black, White, Hispanic, other), SES:	MSSA	CA-MRSA skin and soft tissue infection	Authors found a high prevalence of CA-MRSA in the community;

	We Anticipate the Culture Result?; USA				lacking HA risk factors; infection	insurance status (commercial, Medicaid, self-pay/none)			Black patients were more likely to have CA-MRSA infection than White or Hispanic inpatients.
Britton et al., 2013	Paediatric community-associated Staphylococcus aureus: A retrospective cohort study; Australia	Inpatient	431	Retrospective cohort; 1 year	Samples collected within 48 hours, lacking HA risk factors; infection	Ethnicity (Caucasian, Aboriginal, Pacific Islander, Asian, Middle Eastern, Africa, Subcontinent)	MSSA	CA-MRSA infection	The authors found a high rate of S. aureus in Australian children, and MRSA infection was significantly associated with Aboriginal ethnicity.
Davoodabadi et al., 2016	Nasal colonization in children with community acquired methicillin-resistant Staphylococcus aureus; Iran	Community-based	345	Prevalence study; 1 year	Community-based sample collection, and no risk factors for HA-MRSA; colonization	SES (Urban areas 1-6, 4&6 of high crowding and low SES)	MSSA, no MRSA colonization	MRSA & MSSA colonization	There was a high rate of CA-MRSA among childcare centers, and colonization was positively associated with living in low SES areas.
Duggal et al., 2011	The Increased Risk of Community-Acquired Methicillin-Resistant Staphylococcus aureus Neck Abscesses in Young Children; USA	Inpatient	118	Retrospective cohort study; 5 years	Excluded patients with HA risk factors; infection	Race (African American, Caucasian, Hispanic, Asian)	MSSA, no MRSA infection	Deep neck space infections	Though African American children accounted for the majority of deep neck space infections with MRSA, race was not found to be statistically significant – younger age and lateral abscesses were significant risk factors.
Frei et al., 2010	Emergence of community-acquired methicillin-resistant Staphylococcus aureus skin and soft tissue infections as a common cause of hospitalization in United States children; USA	Inpatient	616,375 (495,760+	Retrospective cohort study; 11 years	CA-MRSA defined by ICD-9 codes; infection	Race (Black, White, Other), SES: insurance status (private, Medicaid, Medicare, no charge, self-pay, worker's compensation, other)	No SA and MSSA (Not a valid comparator because it's not CA)	CA-MRSA skin and soft tissue infection (SSTI)	Risk factors for CA-MRSA infection include White race and not having health insurance.
Galper et al., 2021	Assessment of infections rate due to community-acquired Methicillin-resistant Staphylococcus aureus and evaluation of risk factors in the paediatric population; Israel	Inpatient and outpatient	620	Case-control study; 12 years	Samples collected within 48 hours of admission, or in emergency department; infection	Ethnicity (Jewish, Arab)	MSSA infections	CA-MRSA	Incidence of CA-MRSA is increasing in Jerusalem, and being of Arab ethnicity was associated with CA-MRSA infections.

Gautam et al., 2018	Paediatric thoracic empyema in the tropical North Queensland region of Australia: Epidemiological trends over a decade; Australia	Inpatient	123	Retrospective cohort study; 10 years	Required community-acquired ICD-9 code for pediatric thoracic empyema (pTE); infection	Ethnicity (Aboriginal and Torres Strait Islander, non-ATSI)	MSSA or no infection	Pediatric pTE	MRSA was the most common bacteria among pTE patients; ATSI children are more likely to have MRSA infections as a cause for pTE.
Hermos et al., 2009	Epidemiology of community-associated methicillin-resistant Staphylococcus aureus in San Francisco children; USA	Inpatient and outpatient	170	Prospective cohort study; 0.5 years	Samples collected in ED or within 48 hours of admission, excluded most HA risk factors; infection	Race (White, African American, Hispanic, Asian/Native Hawaiian/Pacific Islander, American Indian/Alaska Native, other)	CA-MSSA infections	CA-MRSA	In comparing CA-MRSA to CA-MSSA infections, African American children were statistically more likely to have CA-MRSA infections.
Immergluck et al., 2019	Geographic surveillance of community associated MRSA infections in children using electronic health record data; USA	Inpatient and outpatient	10,642	Retrospective epidemiology study; 9 years	Samples collected within 48 hours of admission; infection	Race (Black, Hispanic, other, White), SES: insurance status (private, public, self-pay)	CA-MSSA infections	CA-MRSA	Having no insurance or public insurance and being Black were significant risk factors for CA-MRSA infection.
Len et al., 2010	Community-Acquired Staphylococcus aureus Pneumonia Among Hospitalized Children in Hawaii; USA	Inpatient	38	Retrospective cohort study; 12 years	Samples collected within 48 hours, lacking HA risk factors; infection	Race (Native Hawaiian/Pacific Islander), SES: insurance (government subsidized/no insurance)	CA-MSSA infections	S. aureus pneumonia	Pneumonia due to CA-MRSA disproportionately affected children of Native Hawaiian/Pacific Islander ethnicity.
Milstone et al., 2010	Community-associated Methicillin-Resistant Staphylococcus aureus Strains in Pediatric Intensive Care Unit; USA	Inpatient	1,210	Retrospective cohort study; 15 months	Samples collected at time of PICU admission or within 3 days, no history of colonization : colonization	Race (White, African American, Other)	No MRSA colonization	CA-MRSA colonization	Patients colonized with MRSA at time of PICU admission were more likely to be African American.
Nerby et al., 2011	Risk Factors for Household Transmission of Community-associated Methicillin-resistant Staphylococcus aureus; USA	Inpatient and outpatient	232	Prospective cohort study: 1 year, 9 months	Samples collected within 48 hours, lacking HA risk factors; colonization	Race (White race), SES: income (annual household income <$30,000)	No MRSA colonization	CA-MRSA colonization	The odds ratio for MRSA vs no MRSA with a 95% CI for white race was 0.469(0.203-1.09), and 0.896(0.375-2.14) for individuals with an annual household income less than $30,000.
Williamson et al., 2013	Increasing Incidence and Sociodemographi	Inpatient	1860	Retrospective cross-sectional	Samples collected within 48	Ethnicity (European, Māori, Pacific	MSSA SSTI	MRSA SSTI	Children of Māori and Pacific Islander

	c Variation in Community-Onset Staphylococcus aureus skin and soft tissue infections in New Zealand children; New Zealand			study; 4 years	hours; infection	Islander, other), SES: NZ Deprivation score (1-3 (low deprivation), 4-7, 8-10 (high deprivation))			ethnicity had the highest incidence of SA infections, and PI children were significantly more likely to have CA-MRSA than their European peers. CA-MRSA was 2.3 times more likely among children in high deprivation areas.
Worley et al., 2015	Suppurative Cervical Lymphadenitis in Infancy: Microbiology and Sociology; USA	Inpatient	76	Retrospectiv e cohort study; 10 years	Samples collected upon admission; infection	Race (Caucasian, African American, Hispanic, other)	MSSA	MRSA in suppurative cervical lymphadeniti s	Race was a significant risk factor in who had resistant blood cultures; African American children were more likely to have MRSA than White or Hispanic children (p=0.004).

Risk of Bias outcomes

The results for the risk of bias outcomes were measured by two independent reviewers, LM and AB, and the consensus conducted by LM is presented below. It is important to note that the risk of bias was assessed for each exposure of interest; for example, Ali et al. reported both racial and socioeconomic factors, so the risk of bias was conducted for both race and SES. While none of the included studies had a high risk of bias, reasons for some concerns of bias were due to exclusion of patients that would impact the sample as an appropriate representation of the larger population, lack of discussion about missing data, lack of clarity in how “community-acquired” was defined when compared to typical definitions (e.g., explicitly stating criteria to avoid healthcare-associated infections), how the assessment of exposure was collected (one-time interviews, for example), and if the outcome was measured objectively (e.g., using lab measurement). Sensitivity analyses were conducted to account for this bias.

Table 2: Individual Study Risk of Bias

Authors	Title	Cumulative Risk of Bias score for each factor
Ali et al., 2019	A Spatial Analysis of Health Disparities Associated with Antibiotic Resistant Infections in Children Living in Atlanta (2002–2010)	Race: low risk of bias SES: low risk of bias
Bar-Meir et al., 2010	Staphylococcus aureus Skin and Soft Tissue Infections: Can We Anticipate the Culture Result?	Race: low risk of bias SES: low risk of bias
Britton et al., 2013	Paediatric community-associated Staphylococcus aureus: A retrospective cohort study	Ethnicity: low risk of bias SES: low risk of bias
Davoodabadi et al., 2016	Nasal colonization in children with community acquired methicillin-resistant Staphylococcus aureus	SES: some concerns
Duggal et al., 2011	The Increased Risk of Community-Acquired Methicillin-Resistant Staphylococcus aureus Neck Abscesses in Young Children	Race: some concerns
Frei et al., 2010	Emergence of community-acquired methicillin-resistant Staphylococcus aureus skin and soft tissue infections as a common cause of hospitalization in United States children	Race: some concerns
Galper et al., 2021	Assessment of infections rate due to community-acquired Methicillin-resistant Staphylococcus aureus and evaluation of risk factors in the paediatric population	Ethnicity: low risk of bias
Gautam et al., 2018	Paediatric thoracic empyema in the tropical North Queensland region of Australia: Epidemiological trends over a decade	Race: low risk of bias
Hermos et al., 2009	Epidemiology of community-associated methicillin-resistant Staphylococcus aureus in San Francisco children	Race/ethnicity: some concerns
Immergluck et al., 2019	Geographic surveillance of community associated MRSA infections in children using electronic health record data	Race: low risk of bias SES: low risk of bias
Len et al., 2010	Community-Acquired Staphylococcus aureus Pneumonia Among Hospitalized Children in Hawaii	Race: some concerns SES: some concerns
Milstone et al., 2010	Community-associated Methicillin-Resistant Staphylococcus aureus Strains in Pediatric Intensive Care Unit	Race: some concerns
Nerby et al., 2011	Risk Factors for Household Transmission of Community-associated Methicillin-resistant Staphylococcus aureus	Race: low risk of bias SES: some concerns
Williamson et al., 2013	Increasing Incidence and Sociodemographic Variation in Community-Onset Staphylococcus aureus skin and soft tissue infections in New Zealand children	Ethnicity: low risk of bias SES: low risk of bias
Worley et al., 2015	Suppurative Cervical Lymphadenitis in Infancy: Microbiology and Sociology	Race: some concerns

Meta-analysis Results

Risk of MRSA among racial and ethnic minority groups

Two main analyses (MRSA versus MSSA, MRSA versus no MRSA), two sub-group analyses for Black and White children only (MRSA versus MSSA, MRSA versus no MRSA), and three sensitivity analyses that only included studies with low risk of bias were conducted. Each meta-analysis produced a risk ratio effect measure with a 95% confidence interval, a common effects model, a random effects model, a prediction interval, and heterogeneity statistics. Below is a summary of the results, and the findings for each meta-analysis with significant results in bolded text.

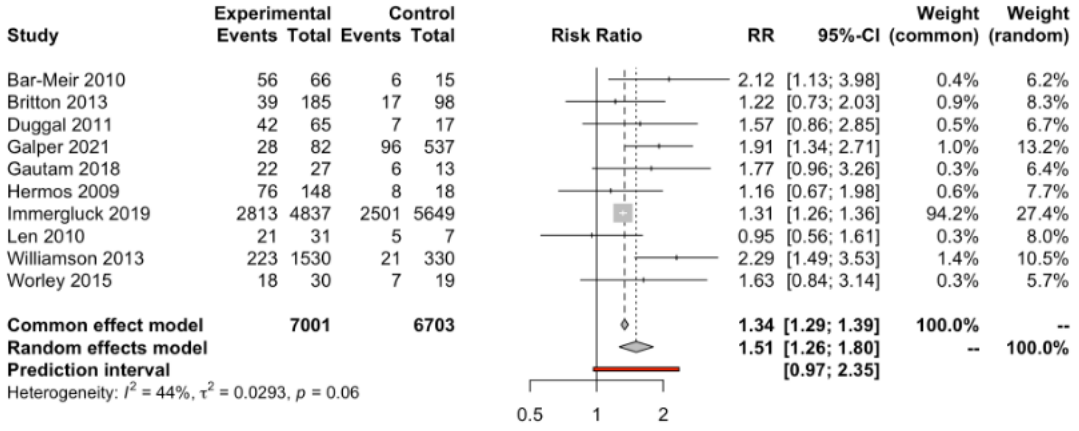
Table 3: Summary of meta-analysis results

Comparison	**RR (95% CI), I^2**
Race/Ethnicity	
MRSA vs MSSA (all)	**1.51 (1.26, 1.80), I^2= 44%**
MRSA vs MSSA (low bias)	**1.62 (1.32, 2.00), I^2= 57%**
MRSA vs MSSA (Black vs. White)	**1.55 (1.28, 1.88), I^2= 6%**
MRSA vs. No MRSA (all)	1.60 (1.00; 2.56), I^2= 99%
MRSA vs. No MRSA (low bias)	**2.02 (1.18; 3.46), I^2=66%**
MRSA vs. No MRSA (Black vs. White)	**1.77 (1.55, 2.01), I^2= 0%**
SES	
MRSA vs MSSA (all)	1.29 (0.83, 1.99), I^2= 74%
MRSA vs MSSA (low bias)	**1.54 (1.17, 2.02), I^2= 56%**
MRSA vs. No MRSA (all)	1.46 (0.54, 3.95), I^2= 82%

Main analyses

Race and ethnicity: MRSA versus MSSA

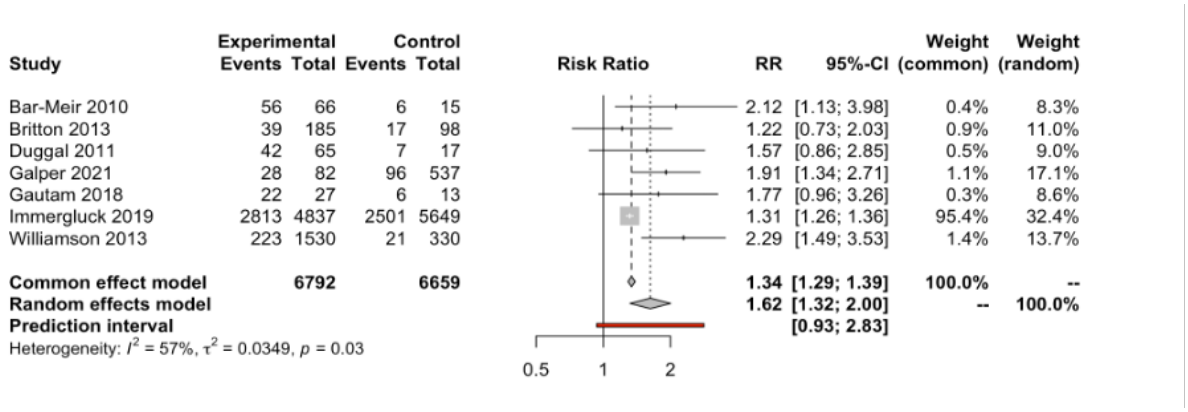
Figure 2: Forest plot MRSA versus MSSA (race, ethnicity)



Ten studies were included in the overall meta-analysis for MRSA versus MSSA. The experimental events include MRSA versus MSSA colonization or infections for racial and ethnic minority groups, including Black, Hispanic, Arab, Aboriginal and Torres Strait Islander, Asian, Native Hawaiian, Māori, American Indian or Alaskan Native, or other. The control group includes MRSA colonization or infections among children that are White, Jewish, not Aboriginal, European, or non-Native Hawaiian or Pacific Islander. Using the random effects model, this analysis demonstrates that children belonging to racial and ethnic minorities are 1.51 times as likely to have MRSA infection or colonization compared to children belonging to non-minority groups (RR: 1.51, 95% CI [1.26; 1.80, I^2=44%]), and has moderate heterogeneity, or moderate variability in the data.

Race and Ethnicity: MRSA versus MSSA (low risk of bias studies only)

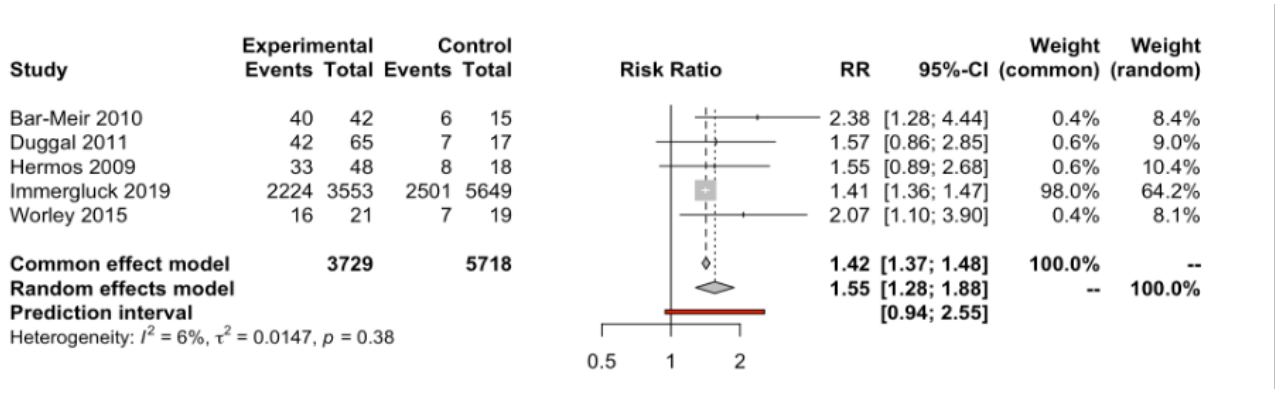
Figure 3: Forest plot MRSA versus MSSA low bias (race, ethnicity)



When conducting the same analysis of race/ethnicity for MRSA versus MSSA with just low-bias studies, the results remain significant and the risk ratio rises to 1.62 (95% CI [1.32; 2.00], I^2=57%), and the heterogeneity increases but remains moderate. The racial and ethnic minority groups included in this analysis are Black, Hispanic, Aboriginal, Pacific Islander, Asian, Middle Eastern, Africa, Subcontinent, Arab, Torres Strait Islander, and Māori children. The non-minority groups are White, Jewish, non-Aboriginal, non-Torres Strait Islander, and non-Native groups. This analysis indicates that children belonging to racial or ethnic minority groups are 1.62 times as likely to have MRSA infection or colonization when compared to children belonging to non-minority groups.

Race and Ethnicity: MRSA versus MSSA (Black versus White)

Figure 4: Forest plot MRSA versus MSSA (Black versus White children)

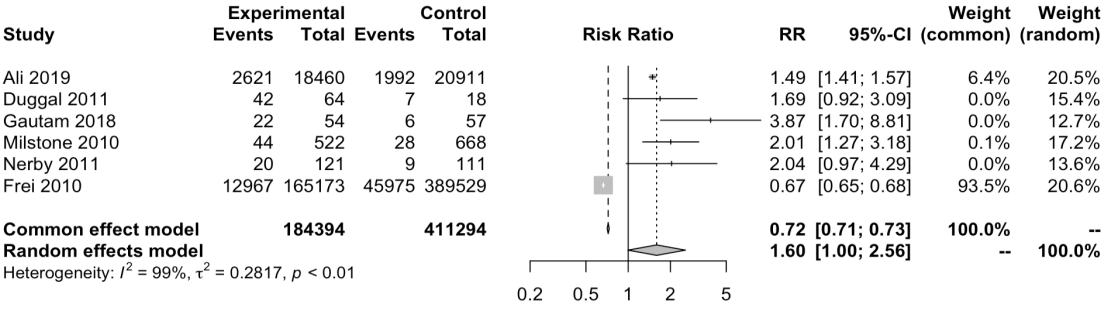


The third analysis for racial and ethnic differences between MRSA and MSSA infection or colonization was conducted among just Black and White children. Across the literature, Black children were found to be at a significantly higher risk of MRSA colonization or infection when compared to White children (RR: 1.55, 95% CI [1.28; 1.88], I^2=6%).

The second analysis looked at racial and ethnic differences between MRSA and no MRSA infection or colonization. The experiment and control groups remained the same as in previous analyses.

Race and Ethnicity: MRSA versus No MRSA

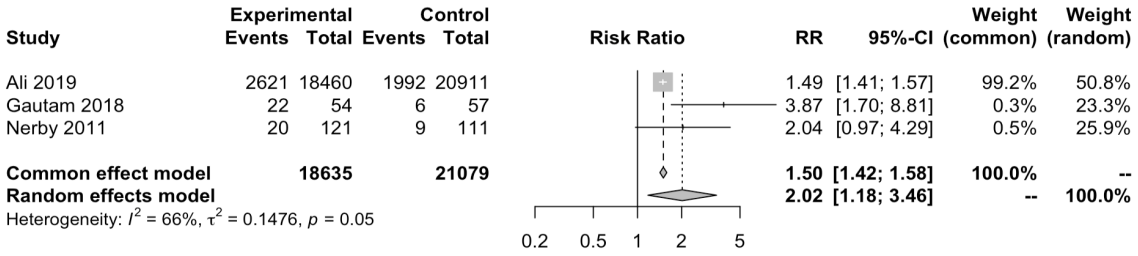
Figure 5: Forest plot MRSA versus no MRSA (race, ethnicity)



When all studies that reported racial or ethnic characteristics for MRSA versus no MRSA were analyzed, children belonging to racial or ethnic minority groups are 1.60 times as likely to have MRSA when compared to children belonging to non-minority groups (RR: 1.60, 95% CI [1.00; 2.56]). However, this result was not statistically significant. The racial and ethnic minority groups in this analysis included Black, Hispanic, Asian, Aboriginal, Torres Strait Islander, and others. It's important to note that this meta-analysis produced I^2=99%, indicating a high level of heterogeneity, or variability, in the data. A sensitivity analysis was conducted to exclude studies with bias.

Race and Ethnicity: MRSA versus No MRSA (low risk of bias studies)

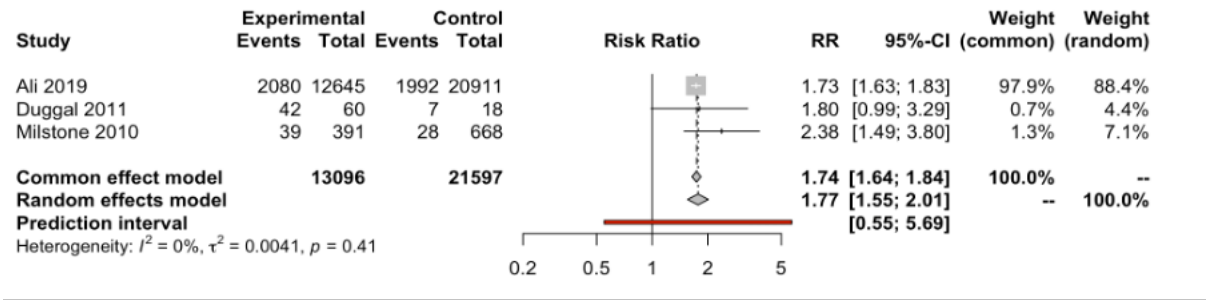
Figure 6: Forest plot MRSA versus no MRSA, low bias (race, ethnicity)



When only studies with a low level of bias were used, three studies were run to assess the relationship between MRSA and race/ethnicity. Racial and ethnic minority groups included Black, Hispanic, Aboriginal, Torres Strait Islander, and other groups. Non-minority groups included White and non-Aboriginal and Torres Strait Islander children. This analysis shows that children of racial or ethnic minority groups are twice as likely to have MRSA than children belonging to non-minority groups (RR: 2.02, 95% CI [1.18; 3.46], I^2=66%) with moderate heterogeneity.

Race and Ethnicity: MRSA versus No MRSA (Black versus White children)

Figure 7: Forest plot MRSA versus no MRSA, (Black versus White children)



There were three studies from the US that reported MRSA versus no MRSA for Black and White children. When comparing just Black versus White children, Black children had a significantly higher risk for MRSA than their White counterparts (RR: 1.77, 95% CI [1.55; 2.01], I^2=0%) with low variability between studies.

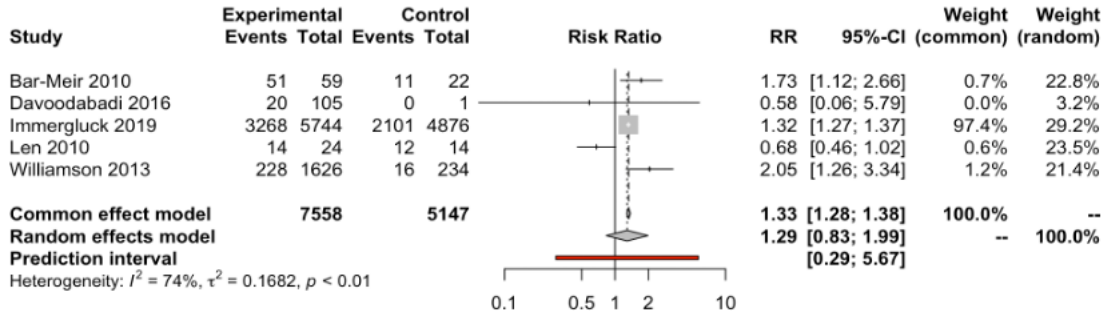
Risk of MRSA among low-SES groups

SES Meta-analyses

These meta-analyses included individuals with low socioeconomic status in the experimental group, versus children of higher socioeconomic status, in the control group. Low socioeconomic status characteristics include living in an area with crowding, low socioeconomic status, or deprivation, living in a crowded household, or having public, self-pay, or Medicaid insurance. The control group included children with private or commercial insurance, living in a non-crowded home or in areas with low deprivation, or in a household with an annual income of over $30,000, the income threshold reported in Nerby et al. (2011).

SES: MRSA versus MSSA

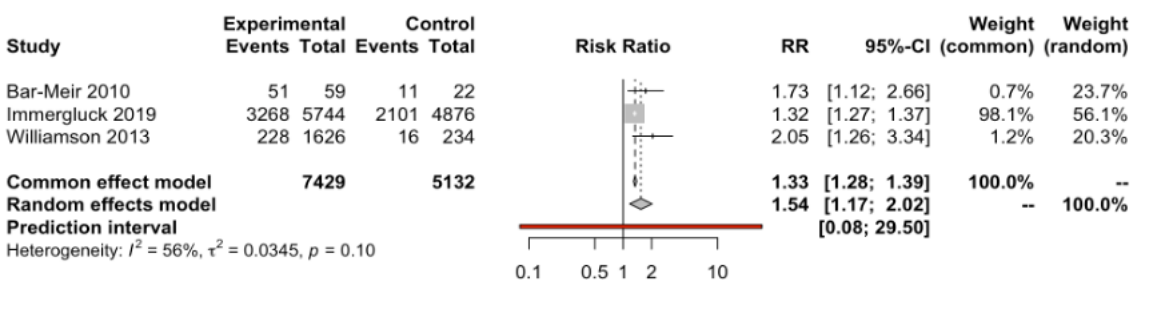
Figure 8: Forest plot MRSA versus MSSA (low SES and high SES)



The first meta-analysis of socioeconomic status was conducted among five studies that reported SES characteristics for MRSA versus MSSA infection or colonization. Low SES groups included Medicaid, public, self-pay, or no insurance, children from areas of high crowding and low SES, and children from areas of high deprivation. The resulting confidence interval for the risk ratio crossed the null, so this analysis was found to be not significant (RR: 1.29, 95% CI [0.83; 1.99], I^2=74%).

SES: MRSA versus MSSA (low risk of bias studies)

Figure 9: Forest plot MRSA versus MSSA, SES low bias

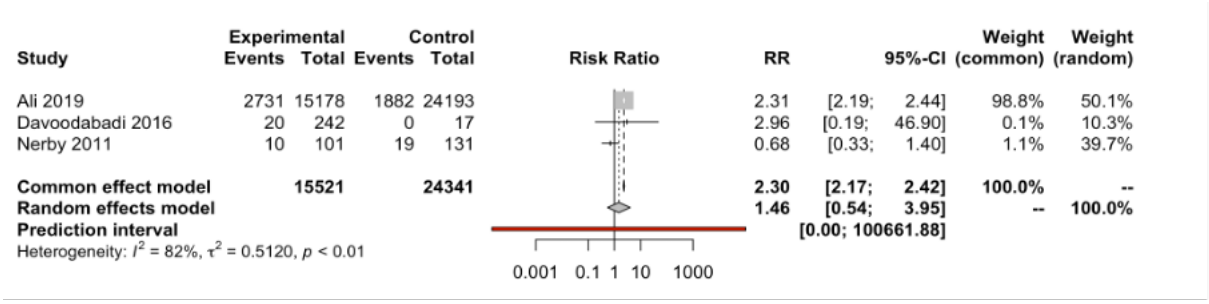


When studies with concerns for bias were excluded from the SES MRSA versus MSSA analysis, three studies were run in the meta-analysis, and children belonging to low SES groups were found to be at a significantly higher risk for MRSA when compared to their high SES

counterparts (RR: 1.54, 95% CI [1.17; 2.02], I^2=56%) with moderate heterogeneity, or variability among studies. This analysis included insurance status and low versus high deprivation characteristics.

SES: MRSA versus no MRSA

Figure 10: Forest plot MRSA versus no MRSA, SES



Only three studies reported SES characteristics for MRSA versus no MRSA infection or colonization, and though children of a lower SES group were at an elevated risk for MRSA, these results were not significant (RR: 1.46, 95% CI [0.54; 3.95], I^2=82%). Characteristics of the low SES group included public or self-pay insurance status, children from high crowding and low SES, and annual income below $30,000.

Summary

Overall, racial and ethnic minorities have a statistically significant increased risk for MRSA infection or colonization when compared to non-minority groups. It is also important to note that five of the six meta-analyses looking at race and ethnicity produced significant results. However, only one analysis of socioeconomic status produced significant results (MRSA versus MSSA, studies of low bias). This may be due to increased variation in how studies reported SES. Results will be further discussed in the following chapter.

Chapter 5: Discussion and Conclusion

Discussion

Racial and ethnic disparities in CA-MRSA

This research aims to investigate the existing evidence of racial, ethnic, and socioeconomic disparities among children with community-acquired methicillin-resistant *Staphylococcus aureus* colonization or infection. Across fifteen studies from five countries included in the systematic review and meta-analysis, consistently statistically significant results were found among children belonging to racial and ethnic minority groups. In five of the six meta-analyses pertaining to MRSA in racial and ethnic groups, including MRSA versus MSSA and MRSA versus no *S. aureus*, the racial and ethnic minority group was found to be at a statistically significantly higher risk of CA-MRSA infection or colonization than their non-minority counterparts. In short, this supports the hypothesis that there are racial and ethnic disparities in the burden of CA-MRSA in children and that children belonging to minority groups are disproportionately impacted by CA-MRSA colonization and infection.

It is essential to question and critically analyze the results presented in this research and other bodies of evidence. Why do children of Black, Hispanic, Aboriginal, Native, and other racial and ethnic minority groups suffer disproportionately from CA-MRSA? A study conducted by See et al. found that after a mediation analysis controlling for socioeconomic status, there was no significant relationship between CA-MRSA and Black race (2017). It is now a matter of health inequities. Feagin and Bennefield's discussion of systemic racism in the U.S. healthcare system builds from the concept of systemic racism theory; it is multidimensional, is not always as obvious as racism on an individual level, and stems from a racial hierarchy that has persisted in systems and institutions over centuries (Feagin et al., 2014). In the U.S. healthcare systems, economy, and institutions, the dominant racial group of the White race has been favored – what

began as land exploitation from Native Americans and enslavement of African Americans in the colonial United States has persisted as white privilege, where non-minority groups continue to benefit from systems that were built to exclude and oppress racial and ethnic minority groups (Feagin et al., 2014; Feagin, 2013). Today, systemic racism is pervasive and impacts many dimensions of life in the United States. The COVID-19 pandemic is the most recent and drawn-upon example of a pandemic that unequally impacted minority groups in the US, including Black and Hispanic groups experiencing higher morbidity and mortality than Whites (Alcendor, 2020; Gravlee, 2020; Hooper et al., 2020; Krieger, 2020; Mude et al., 2021; Rogers et al., 2020). While the impact of the COVID-19 pandemic may be attributed to increased risk factors and comorbidities such as heart disease, obesity, and immunosuppressive conditions like HIV, it is the underlying cause for those comorbidities that must be acknowledged and critically examined (Hooper et al., 2020). These are the systemic forces that reduce access to healthcare, education, and socioeconomic opportunity that historically, and still today, favor non-minority groups.

While much of the literature surrounding systemic and structural racism exists within the context of the United States, structural racism and exclusion of racial and ethnic minorities exist around the world. In Australia, Aboriginal Australians have suffered poorer mental, physical, and emotional health outcomes due to systemic and interpersonal racism (Larson et al., 2007). Larson et al. found that in a cross-sectional study looking at the association between self-reported interpersonal racism and health outcomes, Aboriginal Australians were more likely to have poorer health outcomes if they experienced racism on a personal level, providing evidence that racism can have a direct impact on a person's health or well-being (Larson et al., 2007). A similar cross-sectional study among Aboriginal Australian youth found that experiencing racism on a personal level was associated with poorer mental health outcomes (Priest et al., 2011).

Similar research is found in New Zealand, where Māori, Pacific Islanders, and Asian ethnic minorities collectively experience racism and discrimination, which are then associated with poorer health outcomes (Harris et al., 2006; Harris et al., 2012; Talamaivao et al., 2020). While interpersonal experiences of racism tend to be more overt and outright, Feagin argues that systemic racism has no less of a toll on human health and well-being (Feagin, 2013). It is through explicitly acknowledging and actively working with anti-racist rhetoric and behavior that these systems and structures that perpetuate systemic racism can be disrupted.

Socioeconomic disparities in CA-MRSA

When looking at children belonging to low socioeconomic groups, though each analysis showed that low-SES groups had an elevated risk for MRSA when compared to high-SES groups, only one result was statistically significant. The sensitivity analysis of low-bias studies (n=3) showed that low-SES groups were 1.54 times as likely as high-SES groups to have MRSA colonization or infection relative to MSSA colonization or infection. Studies included in this analysis were from the US (n=2) and New Zealand (n=1) and comprised 12,561 children. Low-SES groups included in the low-bias analysis included children living in high deprivation according to the New Zealand Index of Deprivation (Atkinson et al., 2014) and children with public or self-pay insurance. Other low-SES characteristics of studies in the other analyses include household crowding and income level. A scoping review conducted by Kachmar et al. describes the multitude of ways in which SES can be measured; because of this, it can be hard to accurately measure and control for these factors (2019). However, it is well-understood that health outcomes are positively associated with SES; children of higher SES tend to have better health outcomes than children of low SES (Chen, 2004; Kachmar et al., 2019). Chen and Kachmar et al. discuss the relationship between SES and health as not binary, but a gradient;

instead of being of low or high SES, it is instead an accumulation of factors such as insurance status, crowding, or income, among other things, that places individuals on a gradient between low and high socioeconomic status (Chen, 2004; Kachmar et al., 2019).

Household crowding

The increased risk of resistant infections among children belonging to low-SES groups may be attributed to a variety of factors. A characteristic of socioeconomic status is household crowding which was reported in research by Davoodabadi et al. (2016), Immergluck et al. (2019), and Nerby et al. (2011), and supported by multiple studies that found a positive association between household crowding and MRSA infection or colonization (Calfee et al., 2003; Johansson et al., 2007; Mollema et al., 2010). Household crowding is defined in several ways but is often measured by occupancy rate, persons per room, or persons per bedroom (Gray et al., 2001). Household crowding occurs when individuals share a small space, share personal items, and have sustained physical contact in a smaller space, creating conditions that are conducive to the spread of communicable diseases like MRSA. While there are many other factors at play, such as the type of housing, the environmental conditions of the household, and the social context, several studies have found an association between household crowding and poorer health outcomes and are often found among families belonging to racial and ethnic minorities and of low socioeconomic status (Gray et al., 2001). In conclusion, household crowding can be used as a proxy indicator for socioeconomic status and has been found to be associated with MRSA infections in multiple contexts (Fritz et al., 2009; Vieira et al., 2016). It is critical to design public health interventions that address household crowding as a risk factor for CA-MRSA while acknowledging the root causes of crowding, like poverty and lack of access to affordable housing.

Insurance status

While the studies that reported insurance status as an indicator for SES were limited to the United States, it is important to consider the impacts of affordable access to healthcare for children. Insurance status is a common measure of SES due to federally funded government programs being indicative of an individual or family's ability to pay for health coverage, like Medicaid or Medicare (Casey et al., 2018). Though states have their own eligibility guidelines, federal standards for Medicaid/Medicare programs provide coverage for low-income families, uninsured children, pregnant women, and vulnerable populations (Centers for Medicare & Medicaid Services, 2023). On the other hand, individuals belonging to high SES groups are more likely to have private insurance, either through an employer or a private insurance company. Quality and coverage of healthcare can be a determining factor in the level of care received; uninsured individuals may not receive important preventive care, therefore increasing their likelihood of poorer health outcomes and preventable diseases (Garfield et al., 2016). Within the context of CA-MRSA, multiple studies found that children with public insurance or no insurance had an elevated risk for CA-MRSA infection (Ali et al., 2019; Frei et al., 2010; Immergluck et al., 2019). Future CA-MRSA interventions should be designed knowing that insurance status may significantly influence the risk of infection among children and should be considered alongside other indicators of SES for a comprehensive assessment.

Income and deprivation

Income is a widely used indicator of socioeconomic status. Individuals and families of low income tend to live in crowded, sub-optimal living conditions with limited access to adequate healthcare services, and children of low-income families have higher rates of life-threatening conditions and exposures (Fiscella et al., 2004). In New Zealand, low-income

individuals tend to live in areas of high deprivation according to the New Zealand Index of Deprivation; a study by Tobias and Cheung found that life expectancy was significantly lower in areas of high deprivation, and particularly affected individuals of Māori and Pacific ethnicities (2003). A systematic review conducted by Alividza et al. found that when investigating the risk of antimicrobial resistance among low and middle-income countries, income was not always reported on its own, but rather grouped with other characteristics (2018). Though the results of this review posit that social deprivation is associated with MRSA, more research needs to be conducted to fully understand the impact of poverty and deprivation on CA-MRSA across the globe.

Conclusion

It is critical to note that the analysis of racial and ethnic disparities in CA-MRSA is intricately linked to socioeconomic disparities in CA-MRSA and vice versa. Individuals belonging to racial and ethnic minority groups are more likely to belong to low SES groups, and when compounded, these risk factors can create increased susceptibility to CA-MRSA. Studies suggest that children who are exposed to socioeconomic deprivation at a young age, or even as a fetus, are more likely to carry poorer health outcomes throughout life (Chen, 2004; Fiscella et al., 2004). To combat susceptibility to disease at an early age, public health interventions must be designed to recognize racial, ethnic, and socioeconomic disparities as a public health crisis in antibacterial resistance. Increased risk of CA-MRSA is complex, multifaceted, and a product of systemic and structural discrimination that has persisted throughout time. Acknowledging flaws and exclusion of minority and low-SES groups in access to healthcare, education, and affordable housing is the first step in dismantling systems that create health disparities across the world.

Limitations

This research has several limitations. Most studies included in the analysis were conducted in the United States, and only one other country (Australia) included more than one study. Another limitation may be that the meta-analyses conducted combined both colonization and infection events. Though this was done to examine the prevalence of MRSA among children and not clinical presentation, it is important to note that analyses separating infection and colonization events may produce different results. Another limitation is the lack of standardized definitions of community-acquired MRSA. While this research used the definitions set forth by the authors, variations in the definition can lead to missing data if one definition is less sensitive than others. Another potential limitation is that MRSA infection and colonization events were not stratified by pediatric age groups; some papers reported that infants or younger children were at a higher risk for MRSA than older children (Ali et al., 2019; Duggal et al., 2011; Galper et al., 2021). This is something that could be further investigated. This study did not investigate publication bias and should be considered in the future, along with an overall assessment of the quality of evidence.

Strengths

Despite these limitations, this study has several strengths. The methodology was rigorous and involved two reviewers at each stage, allowing for the accuracy of data ascertainment. The ability to conduct several meta-analyses following a robust methodology ensured quality selection, extraction, and analysis of the included data. This systematic review offers a comprehensive look at the existing evidence examining racial, ethnic, and socioeconomic disparities in the burden of CA-MRSA children. It highlights the gap in research conducted

pertaining to these disparities and offers recommendations that seek to close this gap in research.

Chapter 6: Public Health Implications and Recommendations

The results from this research support the hypothesis that children belonging to racial and ethnic minority groups and children of low socioeconomic status have an increased risk of community-acquired MRSA infection or colonization. The implications of this research can be far-reaching. While infection control measures for healthcare-associated MRSA can be standardized and measured within facilities (Weber, 2005), it is more difficult to fully understand both the scope and the burden of community-acquired MRSA among children, especially considering gaps in consistent healthcare access among low SES groups. An increase in the number of community-based surveillance programs looking at resistant bacterial colonization and infection events in vulnerable communities has the potential to increase knowledge of how far-reaching the problem of CA-MRSA is and can be implemented in areas of high deprivation, low-SES neighborhoods, and among groups with high rates of public or no health insurance. Ali and Immergluck et al. utilized geospatial analysis to characterize and identify neighborhood-level risk factors for CA-MRSA events and found significant associations between characteristics like neighborhood-level crowding and infections (2019). If further research is aimed at identifying both individual- and neighborhood-level risk factors for CA-MRSA, interventions can be tailored on an individual and community basis.

However, the root of the disparities in who carries the burden of CA-MRSA is beyond what reactive public health interventions can address. Taking the proactive, preventive route by addressing the systemic oppression of minority and low-SES groups to increase accessibility to healthcare, education, and economic opportunity can improve health outcomes among these groups. Creating and enacting public health policy that actively works towards the betterment of minority population health is the most efficient way of preventing CA-MRSA, and is the

responsibility of the public health, medical, and legislative groups to work towards the common good of their communities.

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