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Demographics Of Those In Clinical Trials To Treat S. Aureus

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DEMOGRAPHICS OF THOSE IN CLINICAL TRIALS TO TREAT S. AUREUS

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Abstract:

This study aims to identify potential discrepancies between the racial/ethnic demographics of participants enrolled in randomized controlled trials of antibacterials used to treat *Staphylococcus aureus* and the demographics for those who contract the disease. 115 clinical trials were analyzed for gender, racial, and ethnicity of clinical trial participants. Of the included studies, 95.7% included data on gender, 71.3% included racial data, and 27.0% included ethnicity data. Black/African American individuals were substantially underrepresented in trials when compared to the burden of disease that they share. Black/African American representation in *S. aureus* clinical trials needs to be ensured in order to properly investigate clinical efficacy of new antibiotics. Ethnicity data should be gathered by researchers on all clinical trials. A standard reporting method for race/ethnicity needs to be implemented for clinical trials to ensure comparability and to allow for analysis on more specific racial/ethnic groups.

Key words: Staphylococcus aureus, racial groups, ethnicity, anti-bacterial agents, clinical trials

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Introduction:

The importance of representation in clinical trials cannot be overstated. Disparities in morbidity and mortality by race can be found in the United States even after controlling for socioeconomic and treatment differences.[1] The United States is in need of new antibiotics to treat infections due to antibiotic resistant pathogens, however, recent research on cancer and heart disease clinical trials has shown that trial participants are not representative of the populations that are impacted by the disease.[2,3] Research also shows that members of different sexes, races and ethnicities may respond differently to treatments.[4-6] No prior research into the demographics of current antibacterial clinical trial participants exist.

Staphylococcus aureus is a bacteria that can asymptomatically colonize humans and also lead to infection, commonly referred to as a "staph" infection.[7] Methicillin-resistant *S. aureu*s (MRSA) infections are difficult to treat because of resistance to antibiotics. Methicillin susceptible *S. aureus* (MSSA), like MRSA, can be deadly but differ as they are susceptible to treatment using antibiotics. MRSA and MSSA can cause a range of infections including pneumonia, bloodstream and surgical site infections.[8] In 2019, the Center for Disease Control and Prevention (CDC) announced that MRSA was categorized as a "serious risk", the second highest risk category, in their Antibiotic Resistance Threats in the United States publication.[9] The same report estimated 323,700 MRSA cases in hospitalized patients and 10,600 deaths in 2017.

This study aims to identify potential discrepancies between the racial/ethnic demographics of participants enrolled in randomized controlled trials of antibacterials used to treat MSSA and MRSA including those with skin and soft tissue infections (SSTI), bloodstream infections, and pneumonia caused by *S. aureus* in the United States and those traditionally infected with the bacteria. Over 100 clinical trials were analyzed for participant demographics and compared to the demographics of those afflicted with MRSA using a participant to prevalence ratio.

Methods:

This paper was designed to investigate the proportion of *S. aureus* clinical trials reporting gender, race, and ethnicity of trial participants and investigate whether these trials accurate represent the burden *S. aureus* has in the United States.

Papers were collected using Covidence in order to facilitate systematic review management. Two databases were searched, the "Cochrane CENTRAL" database, which includes PubMed, Embase, CT.gov, ICTRP, and CINAHL and the U.S. National Library of Medicine's ClinicalTrials.gov database.

The following search strategy was used for Cochrane CENTRAL:

1) One of the following:

-MeSH descriptor: [Anti-Bacterial Agents] OR

-MeSH descriptor: [Anti-Infective Agents] OR

-"anti-infective" OR antimicrobial OR antimicrobials OR antimicrobially OR "antimicrobial" OR "anti-bacterial" OR antibiotic OR antibiotics OR "antibiotic's" OR antibiotical OR antiinfective OR antiinfectives OR antiinfection OR antibacterial OR bacteriocide OR bacteriocides OR antibacterials OR antibacterially

2) And one of the following:

-MeSH descriptor: [Staphylococcal Infections] OR

-MeSH descriptor: [Staphylococcus aureus] OR

-"Staphylococcus aureus" OR "Methicillin-resistant Staphylococcus aureus" OR MRSA

3) And publication year from 2000 to 2021, in Trials

4) And publication year from 2000 to 2021, in Trials (Word variations have been searched)

This search criteria resulted in 1,790 results.

The following search strategy was used for ClinicalTrials.gov:

1) Other terms:

"anti-infective" OR antimicrobial OR antimicrobials OR "antimicrobial" OR "anti-bacterial" OR antibiotic OR antibiotics OR antiinfective OR anttinfectives OR antibacterial OR bacteriocide OR bacteriocides OR antibacterials OR antibacteriocides

2) And condition or disease:

"Staphylococcus aureus" OR "Methicillin-resistant Staphylococcus aureus" or MRSA

3) And recruitment status:

Recruiting, Not yet recruiting, Active, not recruiting, Completed, Enrolling by invitation, Suspended, Terminated, Unknown status Studies

4) And country:

United States

5) And first posted:

1/1/2000 to 12/31/2021

Each study's abstract was analyzed to ensure the scope of the study fell under the auspices of this literature review. Excluded studies included:

-Animal studies

-Studies of nonbacterial infections

-Interventions/trials of substances that do not have direct anti-bacterial activity (e.g., honey, tea tree oil)

-Studies not published in English

-International studies with no patients in the United States

-Conference abstracts, book chapters, case studies or case series, editorials, letters, preprints, review articles, systematic reviews

-Studies of antibiotic stewardship

-Studies of antibiotic prophylaxis (e.g., for surgery or in cystic fibrosis patients)

-Cost-effectiveness studies

-Studies including diagnostic devices

-Intra-abdominal infections

-Upper gastrointestinal perforations

-Nasal colonization or decolonization studies

-Studies of nasal carriage

-Studies about mupirocin

-Studies of essential oils (e.g., tea tree oil)

-Perforation caused by surgical error

-Studies of probiotics

-Topical antibiotics

-Pharmacokinetic-Pharmacodynamic (PK/PD) studies

-MIC and molecular epidemiology studies

-Otitis media

-Exclude but flagged (articles of interest)

This search criteria resulted in 1,893 results (Figure 1). There were 56 duplicate studies found and removed. Each study's title and abstract were reviewed for relevance to the research question which resulted in the removal of 1,489 studies that did not meet our criteria. Full text review removed 267 articles resulting in a final 115 studies to be included in this literature review.

After full text review, a Qualtrics database was created for extraction of relevant data. Trial participants were categorized based on the published papers. Data extracted for each study included participant's age, gender, ethnicity, and race. For age, participants were classified as "adult" (>= 18) or pediatric (<=17). With regards to gender, participants were classified as "male", "female", or "non-binary". The race of participants was designated to the following categories: Black, White, Asian, Native (including Native American, Native Alaskan, and Native Hawaiian), Multiracial, Unknown, and Other. When a given racial breakdown was not consistent with this study's, the most similar classification was used (e.g. Navajo nation was classified as Native American). Finally, the ethnicity of participants was classified as "Hispanic", "non-Hispanic", or "unknown Hispanic". Because some studies did not include gender, racial, or ethnicity breakdowns the total number of participants for which data is available changes by how the data is broken down.

Study characteristics were also recorded, including funder (academic, industry, or both), trial phase (1, 2, 3, 4, post-licensure, or unknown), and infection type (bloodstream infections (BSI), respiratory tract infections, acute bacterial skin and skin structure infections (ABSSIs), bone/joint infection, or other). If the infection type was a respiratory tract infection, the type of infection was also recorded as ventilator-associated pneumonia (VAP), hospital-associated pneumonia (HAP), or community-associated pneumonia (CAP). The entity (or entities) that sponsored each trial was also collected; sponsors were classified as either academic or industry. Included studies were coded as including pediatric patients if they included any participants under the age of 18 (non-inclusive) and adult patients if the study included participants over 18 years old (inclusive).

In order to accurately compare trial participant demographics to the demographics of the population experiencing MRSA and MSSA infections, incidence rates and racial demographics were extracted from 15 years of CDC MRSA report data (2005-2019) and three years of CDC MSSA report data (2016-2019).[11-25] To compare MRSA rates to national demographics, race and ethnicity estimates

were taken from the United States Census Bureau.[26] Four studies were found that estimated the burden of *S. aureus* by gender (Table 1).[27-30]

We calculated the proportion of male participants, White participants, Black participants, and Hispanic participants for each study. Participant to prevalence ratios (PPRs) were calculated as described by Poon and Varma[10-11]) by dividing the percentage of study participants in each demographic group by the percentage of the MRSA population in each group. Underrepresentation was defined as a PPR less than 0.8. Overrepresentation was defined as PPR over 1.2. Prevalence was estimated using CDC reporting statistics. Since CDC reporting was not available for Hispanic/Latino populations, census data was used and the prevalence of Hispanic/Latino individuals in the United States was used as the estimate for Hispanic/Latino burden of MRSA.

Results:

After extraction and full text review, 115 studies were included in the analysis. An overwhelming majority of studies (n=110, 95.7%) included the gender of all participants. Only 82 of the evaluated studies (71.3%) included the race of participants. Thirty-one studies (27.0%) included ethnicity data for participants (Table 2).

When pooling all the studies that supplied gender data, the total number of clinical trial participants was 48,461. Of those, 29,247 (60.4%) identified as male and 19,214 (39.6%) identified as female. No study indicated that participants identified as or were given an option to indicate as any other gender identity (Table 3).

The minimum proportion of men in a given study was 0.36, the maximum proportion was 0.99, with a mean proportion of 0.61 and a standard deviation of .08. Most studies were adequately representative of gender (n=97, 88%). The minimum proportion of White individuals was 0 and a maximum proportion of .99. The mean and standard deviation (SD) proportion of White individuals was 0.69 SD± 0.22. The mean proportion of White participants was significantly higher when compared to the

mean proportion of White individuals with MRSA as reported by the CDC ($p<0.01$). A majority of studies overrepresented white individuals (n=45, 57%; Table 4). Only 6 studies (7%) had adequate representation for Black/African American individuals; in 87% of studies (n=71) this population was underrepresented (Table 4).

The range of Hispanic or Latino individuals in a study was 0.04-0.34 with a mean of 0.17 SD± 0.1. Hispanic/Latino populations were often underrepresented (n= 15, 48%), but in 32% (n=10) of studies analyzed they were also overrepresented (Table 4).

The earliest any included study began enrolling participants was in June of 1995, while the most recent data collected by any study was in April of 2019. Academic sponsors included the National Institutes of Health (NIH), universities, and university-associated healthcare systems (Table 5). Only 13 studies (11.3%) included exclusively pediatric patients. Most studies (n=87, 75.7%) included exclusively adult patients. Studies that included both pediatric and adult populations totaled 14 and represented 12.2% of all studies. One study (0.9%) did not indicate the age of participants (Table 5).

The CDC data shows that over the last 15 years, approximately 60% of MRSA cases are among White identifying individuals, 36% are Black identifying individuals, and 4% are by other race identifying individuals. CDC data also shows that the number of MRSA cases has been declining since 2005 but shifted to a small upward trend since 2015 (Table 6). Although limited, the MSSA data supplied by the CDC shows that a much larger proportion of other races experience infection due to MSSA (Table 7). Data also shows a steady increase in MSSA cases since the data became available (Table 7). Prevalence ratios are provided in Table 9.

Importantly, the CDC also publishes incidence rate information. Data collected showed a steep decline in MRSA incidence rates among the black population, dropping from 78.3 cases per 100,000 individuals in 2005 to 29.5 cases per 100,000 individuals in 2019 (a 62% decline). Comparatively smaller declines were experienced by the white and other racial incidence rates, falling from 29.9 cases per 100,000 individuals in 2005 to 21.2 cases per 100,000 individuals in 2019 for whites (a 29% decline) and

from 12.9 cases per 100,000 individuals in 2005 to 7.3 cases per 100,000 individuals in 2019 for other races (a 43% decline). Incidence rate data for MSSA was only available for the years 2016 through 2019 (inclusive), however both white and black populations experienced a rise in MSSA incidence rates during that time period (an 18% and 6% increase for white and black populations, respectively). Only members of other races experienced a decline in MSSA cases throughout the four-year time period, from 31.3 cases per 100,000 individuals in 2016 to 24.8 cases per 100,000 individuals in 2019 (a 21% decline) (Tables 8-9).

There was a significantly higher White population in studies that included international participants ($F=.412$, $p=.032$).

Discussion:

In this study, 115 clinical trials for antibiotics to treat *S.* aureus infections were analyzed for their gender, race, and ethnic representation. This study shows that Black/African American individuals are not adequately represented in clinical trials for *S. aureus.* It is also evident that better race and ethnicity reporting needs to be implemented to ensure comparability between studies. Hispanic/Latino populations were often over- and underrepresented indicating that more time and focus needs to be placed on ensuring these populations are accurately reflected in clinical trial participants.

There is a clear need to improve racial and ethnicity reporting in relation to clinical trials. A mere 27% of all *S. aureus* reporting ethnicity. Over a quarter of studies did not publish data related to race of clinical trial participants.

There is much credit to studies that indicate race/ethnicity should not be a data point collected or considered in medicine as it stems from the centuries of racism in the medical field.[29] There is a vast body of literature shedding light on the racial bias that still exist in medicine.[30] This study does not intend to contribute or contradict any of these arguments, rather is meant to ensure that clinical trials include

people of all identities as a comment on American social cohesiveness and represents those that experience this disease.

While a majority of trials were considered reasonably representative by these parameters, the pooled demographic data for all included clinical trials shows that this is not the whole story. It is interesting to note that members of "other" races may actually be overrepresented in clinical trials. While pooled statistics show roughly 14% participation in clinical trials for non-White and non-Black individuals, CDC data reports 5% of the MRSA and 10% of the MSSA burden is experienced by this population.

A vast majority of studies included gender information when reporting their clinical trial results. Over half of the studies were adequately representative when analyzing PPRs and the pooled demographics from all included clinical trials fell within the range published by previous investigations (Table 9). This is important since for much of history medicine was male-centric and focused exclusively on the efficacy of medicine in men.[31]

While MRSA cases have substantially dropped since 2005, there has been a concerning increase since 2015. There has been a substantial drop in incidence rates per 100,000 individuals for the entire period. While the gap between White incidence rates and Black/African Americans has decreased extensively, there is clearly still work to be done. There has been a concerning increase in MSSA incidence among White and Black/African American individuals as shown in the CDC MSSA data. While the total number of MSSA cases has been increasing steadily, it is important to note that the MSSA incidence for "Other races" has been decreasing for the entirety of time data is available. While the rise in cases and incidence is of great concern, an advantage is the far lower mortality rate for MSSA cases compared to MRSA.[32] This also could be a result of the focus on antimicrobial resistance around the world.

It would be worthwhile to begin collecting *S. aureus* data in a different way. Currently the CDC only supplies racial data for three racial groups (Tables 6-9) and for no ethnic groups. It would be

worthwhile to create a template for all clinical trials to collect the same racial/ethnic data among all clinical trials to ensure proper representation and to prevent any miscommunications or errors in data collection. This standardization would be helpful for current research to ensure compliance and efficacy data is comparable across clinical trials. It will also allow future researchers to find new uses and information concerning a given drug by other racial/ethnic groups should it be needed at a later time. The current method is incompatible to determine potential issues or uses among other racial/ethnic groups. Having a more specific racial breakdown could allow for more particular recommendations on representation for clinical trials. For example, Native American populations may compose most "Other Race" *S. aureus*, yet only account for .04% of clinical trial participants. While current data suggests "Other Race" participants are adequately represented, standardized data collection and reporting methods may allow for more particular focuses to be needed.

Limitations:

As with most studies, there is always the limitation of human error; with several data checks there are still concerns that the extracted data may have in some way be entered inconsistently or with mistakes. There is also the inherent concern in meta-analysis that the papers examined were in some way flawed or that the search criteria were in some way non-inclusive of all papers with pertinent data to the topic. Unique to this study is the possibility that there are better ways to investigate "reasonable representation" in a given study. A final limitation is the inability to break down beyond three racial groups. CDC data does not report MRSA or MSSA cases outside of these three categories. Many clinical trials that were analyzed follow this pattern. Due to this, it is impossible to estimate the true burden or representation in clinical trials of *S. aureus* on racial groups outside of "White/Caucasian", "Black/African American" and "Other".

Conclusion:

Black/African American representation in *S. aureus* clinical trials needs to be ensured in order to properly investigate clinical efficacy of new antibiotics. Ethnicity data needs to be gathered by researchers on all clinical trials. A standard reporting method for race/ethnicity needs to be implemented for clinical trials to ensure comparability and to allow for analysis on more specific racial/ethnic groups.

Appendix A: Figures

Figure 1: Flow of papers through the PRISMA process

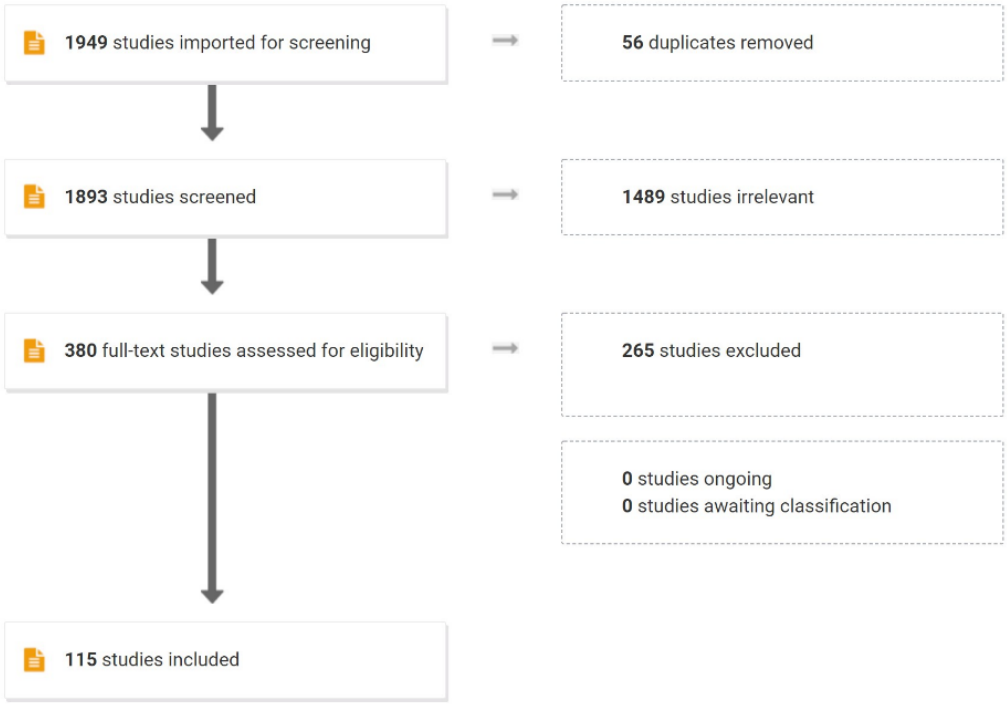

Figure 1 shows where in each step of the review process a given study was removed.

Figure 2: MRSA and MSSA incidence rates per 100,000 individuals by race over time[22-25]

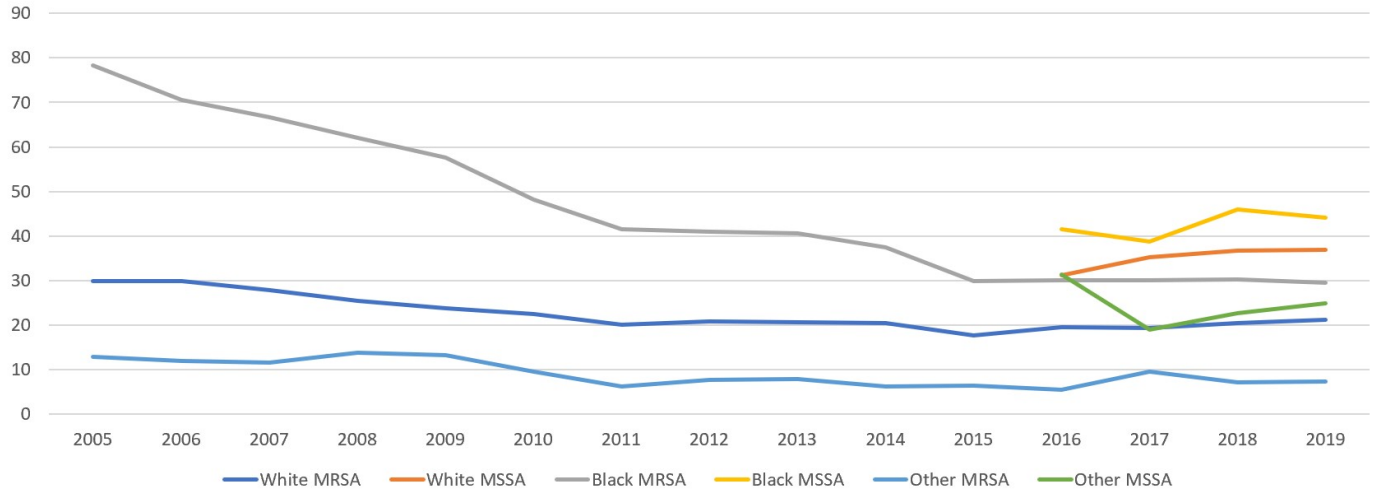

Figure 2 shows the trends over time of MRSA and MSSA incidence rates by a given race. The incidence rates for MSSA are shown in yellow, orange, and green, while the incidence rates for MRSA are shown in light blue, dark blue, and gray. Each value is the incidence rate per 100,000 individuals.

Appendix B: Tables

Table 1: Gender/Sex of samples from studies estimating the burden of *S. aureus*				
Study Title	Trends in Invasive Infection with Methicillin-Resistant *Staphylococcus aureus*, Connecticut, USA, 2001-2010[27]	Socioeconomic Factors Explain Racial Disparities in Invasive Community-Associated Methicillin-Resistant *Staphylococcus aureus* Disease Rates[28]	Public Health Importance of Invasive Methicillin-sensitive *Staphylococcus aureus* Infections: Surveillance in 8 US Counties, 2016[29]	National Burden of Invasive Methicillin-Resistant *Staphylococcus aureus* Infections, United States, 2011[30]
Study First Author Last Name	Hadler	See	Jackson	Dantes
Study Publication Year	2012	2017	2020	2013
Male	60.4%	63.5%	61.4%	60%
Female	39.6%	36.5%	38.6%	40%

Table 2: Demographic breakdown in clinical trials	
n (%)	115 (100)
Studies that include gender breakdown	110 (96)
Studies that include race breakdown	82 (71)
Studies that include ethnicity breakdown	21 (27)

Table 3: Pooled participant demographics	
Demographic:	n (%)
Number of participants for which gender data was available	48,461 (100)
Male	29,247 (60.4)
Female	19,214 (39.6)
Number of participants for which race data was available	38,387 (100)
Black/African American	5,724 (14.7)
White/Caucasian	27,559 (71.0)
Asian	2,400 (6.2)
Native American/Native Hawaiian/Native Alaskan	165 (0.4)
Multi-racial	330 (0.8)
Unknown race	730 (1.9)
Other race	1,929 (5.0)
Number of participants for which ethnicity data was available	15,659 (100)
Hispanic/Latino	2,879 (18.4)
Non-Hispanic/Non-Latino	12,780 (81.6)

Table 4: Calculated patient to prevalence ratios (PPRS)	
PPR for Males	
# of studies for which male proportion was calculated	110
# of studies with accurate male participation – n (%)	97 (88)
# of studies where males are underrepresented – n (%)	6 (6)
# of studies where males are overrepresented - n (%)	7 (6)
PPR Min – Max	.59 - 1.62
PPR for Whites/Caucasians	
# of studies for which White proportion was calculated	79
# of studies with accurate White participation – n (%)	27 (34)
# of studies where Whites are underrepresented – n (%)	7 (9)

# of studies where Whites are overrepresented - n (%)	45 (57)
PPR Min – Max	.50 – 1.62
PPR for Blacks/African Americans	
# of studies for which Black proportion was calculated	82
# of studies with accurate Black participation – n (%)	6 (7)
# of studies where Blacks are underrepresented – n (%)	71 (87)
# of studies where Blacks are overrepresented - n (%)	5 (6)
PPR Min – Max	.00 – 2.11
PPR for Hispanic/Latino	
# of studies for which Hispanic proportion was calculated	31
# of studies with accurate Hispanic participation – n (%)	6 (19)
# of studies where Hispanics are underrepresented – n (%)	15 (48)
# of studies where Hispanics are overrepresented - n (%)	10 (32)
PPR Min – Max	.20 – 1.82

Table 5: Characteristics of *S. aureus* clinical trials	
n	115
Publication Year Range	2000-2021
Study Data Collection	
Earliest	06/1995
Latest	04/2019
Study Location - n (%)	
U.S. Only	62 (54)
U.S. and International	53
Study Location Type – n (%)	
Single-Center	20 (17)
Multi-Center	95 (83)

Phase – n (%)	
1	2 (2)
2	28 (24)
3	32 (28)
Post-Licensure	18 (16)
Not Given	35 (30)
Trial Sponsor – n (%)	
Academic	21 (18)
Industry	83 (72)
Academic & Industry	11 (10)
Placebo Controlled? – n (%)	
Yes	15 (13)
No	100 (87)
Disease Studied – n (%)	
BSI	9 (8)
ABSSIs	73 (63)
Pneumonia	22 (19)
VAP	2 (2)
CAP	9 (8)
HAP	6 (5)
Multiple Types	5 (4)
Bone/Joint Infections	3 (3)
Other	8 (7)
Age Groups – n (%)	
Pediatric Only	13 (11)
Adult Only	87 (76)
Multiple Age Groups	14 (12)
Not Given	1 (1)

Table 6: CDC reported cases of MRSA by race and year[11-25]				
	White - n (%)	Black – n (%)	Other – n (%)	Total
2005	3,578 (58)	2,364 (39)	192 (3)	6,134
2006	3,136 (57)	2,128 (39)	202 (4)	5,466
2007	3,408 (60)	2,109 (37)	179 (3)	5,696
2008	3,375 (59)	2,068 (36)	232 (5)	5,675
2009	3,301 (59)	2,067 (37)	237 (4)	5,605
2010	3,034 (61)	1,773 (36)	187 (3)	4,994
2011	2,743 (62)	1,542 (35)	126 (3)	4,411
2012	2,869 (63)	1,554 (34)	159 (3)	4,582
2013	2,843 (62)	1,563 (34)	170 (4)	4,576
2014	2,842 (64)	1,466 (33)	142 (3)	4,450
2015	1,665 (62)	919 (34)	121 (4)	2,705
2016	1,972 (61)	1,134 (35)	108 (4)	3,214
2017	1,960 (59)	1,161 (35)	198 (6)	3,319
2018	2,073 (62)	1,170 (35)	148 (3)	3,319
2019	2,134 (62)	1,148 (33)	155 (5)	3,437

Table 7: CDC reported cases of MSSA by race and year[22-25]				
	White - n (%)	Black - n (%)	Other - n (%)	Total
2016	1,551 (63)	584 (24)	311 (13)	2,446
2017	2,254 (66)	858 (25)	314 (9)	3,426
2018	2,344 (63)	1,024 (27)	380 (10)	3,748
2019	2,396 (63)	984 (25.9)	420 (11.1)	3,800

Table 8: CDC MRSA incidence rate per 100,000 individuals by race and year[11-25]			
	White	Black	Other
2005	29.9	78.3	12.9
2006	29.9	70.5	12
2007	27.8	66.6	11.5
2008	25.4	62.1	13.8
2009	23.7	57.6	13.3
2010	22.5	48.2	9.5
2011	20.1	41.5	6.2
2012	20.9	40.9	7.6
2013	20.6	40.6	7.9
2014	20.4	37.4	6.3
2015	17.7	29.9	6.4
2016	19.5	30	5.4
2017	19.3	30	9.5
2018	20.5	30.3	7.1
2019	21.2	29.5	7.3

Table 9: CDC MSSA incidence rate per 100,000 individuals by race and year[22-25]				
	2016	**2017**	**2018**	**2019**
White	31.2	35.2	36.7	36.9
Black	41.5	38.7	46.0	44.1
Other	31.3	19.0	22.7	24.8

Table 10: U.S. 2020 census data by race[26]	
Total individuals	331,449,281
Racial Demographics	
% White	76.3
% Black	13.4
% Other	10.3
Ethnic Demographics	
% Hispanic/Latino	18.5
% Non-Hispanic/Non-Latino	60.1

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