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Staphylococcus aureus Skin and Soft Tissue Infection Recurrence Rates in Outpatients: A Retrospective Database Study at 3 US Medical Centers

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Background. *Staphylococcus aureus* skin and soft tissue infections (SA-SSTIs) are common in healthcare and community settings, and recurrences occur at variable frequency, even after successful initial treatment. Knowing the exact burden and timing of recurrent disease is critical to planning and evaluating interventions to prevent recurrent SSTIs.

Methods. In this retrospective study, SSTI cases in patients aged ≥18 years at 3 US medical centers (Columbia, Chicago, Vanderbilt) between 2006 and 2016 were analyzed according to a biennial cohort design. Index SSTIs (with or without key comorbidities), either microbiologically confirmed to be SA-SSTI or not microbiologically tested (NMT-SSTI), were recorded within 1 calendar year and followed up for 12 months for recurrent infections. The number of index cases, proportion of index cases with ≥1 recurrence(s), time to first recurrence, and number of recurrences were collected for both SA-SSTI and NMT-SSTI events.

Results. In the most recent cohorts, 4755 SSTI cases were reported at Columbia, 2873 at Chicago, and 6433 at Vanderbilt. Of these, 452, 153, and 354 cases were confirmed to be due to *S. aureus*. Most cases were reported in patients without key comorbidities. Across centers, 16.4%–19.0% (SA-SSTI) and 11.0%–19.2% (NMT-SSTI) of index cases had ≥1 recurrence(s). In patients without key comorbidities, more than 60% of index SSTIs with recurrences had only 1 recurrence, half of which occurred in the first 3 months following primary infection.

Conclusions. SA-SSTI recurrences are common among healthy adults and occur in at least 1 in 6 individuals during the 1 year following the primary event.

Keywords. *Staphylococcus aureus*; skin and soft tissue infection (SSTI); SSTI recurrence; methicillin-resistant *Staphylococcus aureus*; antimicrobial resistance.

Staphylococcus aureus causes infections of varying severity, ranging from minor ailments to life-threatening events. Skin and soft tissue infections (SSTIs) are the most common clinical manifestation of *S. aureus* [1]. *Staphylococcus aureus* is the second most common cause of healthcare-associated infections in the United States and ranks first among the pathogens that cause surgical site infections and ventilator-associated pneumonia [2, 3].

Over the last 3 decades, methicillin-resistant *S. aureus* (MRSA) has remained a major public health problem. Although the incidence of MRSA in hospitalized patients has recently declined [4], the emergence of community-acquired MRSA poses new challenges [5, 6]. Many countries routinely screen patients admitted to hospitals for MRSA in order to decolonize carriers and use a variety of healthcare infection prevention modalities (ie, antimicrobial stewardship, hand hygiene, and hospital cleaning) to reduce hospital transmission of MRSA [1, 7–10]. Although these measures have decreased the risk of MRSA infection, the incidence of recurrent infections remains high both in discharged patients and in the community [11–15]. Though frequent, there is considerable variation reported for *S. aureus* SSTI (SA-SSTI) recurrence rates [13, 16–18], which could be attributed to the lack of standardized case definitions across studies. The definition of SSTI is typically based on *International Statistical Classification of Diseases and Related Health Problems* (ICD)-9 or ICD-10 codes [19], ICD [21] *Current Procedural Terminology* codes [20], or limited to microbiologically confirmed cases from laboratory data [16].

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The emergence of antimicrobial-resistant MRSA strains, particularly in the community [6], necessitates the development of new prevention strategies. Developing an effective vaccine against *S. aureus* could be pivotal for containing emergence of resistant strains. Our main objective in this study was to use a standardized methodologic basis for SSTI case ascertainment and provide reliable estimates of SA-SSTI recurrence rates in 3 academic medical centers. These data will be used to strengthen the design of prevention studies that evaluate the efficacy of candidate vaccines, monoclonal antibodies, or novel antibiotics. A summary contextualizing the outcomes of this study is displayed in Figure 1 for the convenience of healthcare professionals.

METHODS

Study Design and Population

This was a retrospective hospital database study of outpatients aged ≥18 years with 1 or more SSTIs as defined by ICD-9 or ICD-10 codes [21] (Supplementary Table 1). Records were retrieved from the outpatient department (OPD) and emergency department (ED) databases of 3 US medical centers (Columbia University Irving Medical Center, University of Chicago Medicine, and Vanderbilt University Medical Center, referred to hereafter as Columbia, Chicago, and Vanderbilt) between 2006 and 2016. Cases were linked through their unique identifier with the records of the clinical microbiology laboratory database at each center to categorize each patient as tested or not tested for *S. aureus* and confirm the microbiological diagnosis. Patients were further categorized by the presence/absence of the following key comorbidities that have been associated with higher risk for developing SSTI: complicated diabetes, hemodialysis, human immunodeficiency virus (HIV)/AIDS, and malignant neoplasia, determined by the presence of appropriate ICD-9 or ICD-10 codes (Supplementary Table 2). Patients with an SSTI who presented with open wounds, post-operative wounds, wound infections, or burns were excluded.

Data were analyzed according to a cohort study design intended to mimic a clinical trial. As a primary infection cannot be differentiated from a recurrent event, a cohort approach was adopted. Data for cases were considered biennially to ensure a 12-month follow-up for all identified SSTI events. The first SSTI event (index case) was collected between 1 January and 31 December (year 1), and each index case was evaluated in the next 12 months (year 2) for any recurrences (Figure 2). Patients included in one cohort were eligible to be included in the following biennial cohorts; the first SSTI event reported in year 1 of the new cohort was considered as a new index case.

If the index case had a biological specimen (collected from the infected skin area) microbiologically confirmed as *S. aureus*, the index case was categorized as SA-SSTI. If the index case was

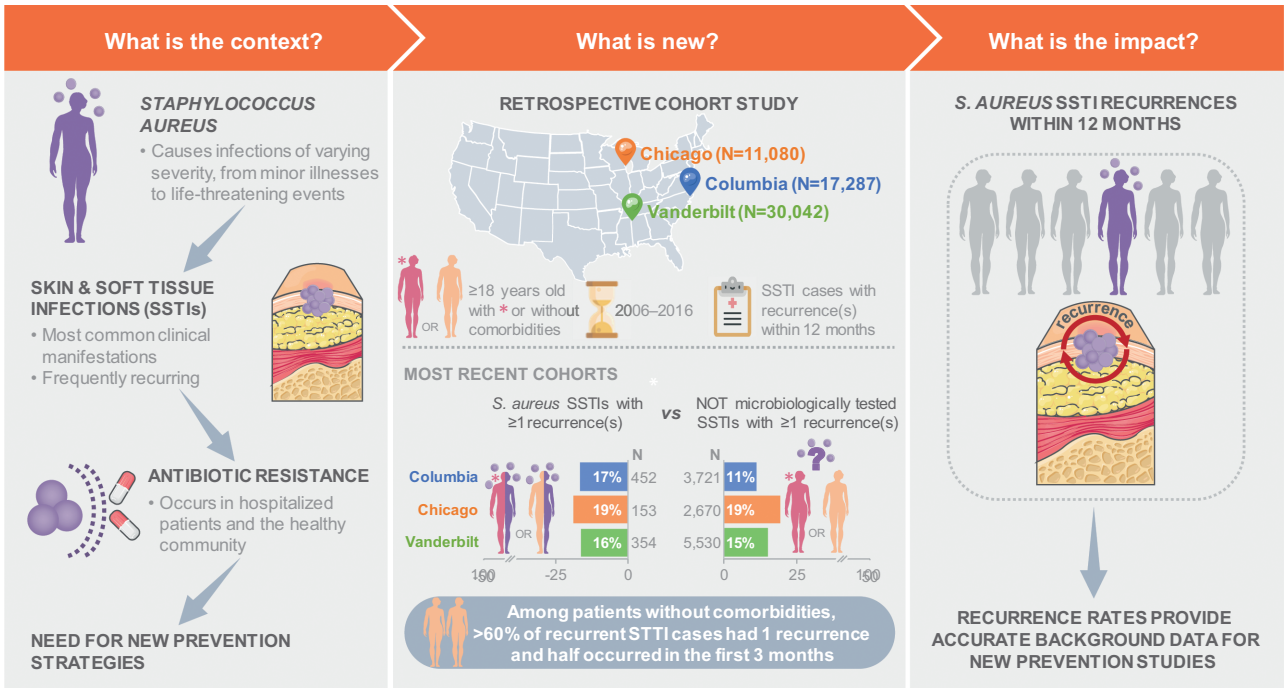

Figure 1. Plain language summary of the outcomes of the study. Purple human, human with *Staphylococcus aureus* infection; dark rose human, human with comorbidities; light rose human, human without comorbidities; half dark rose/purple human, human with *S. aureus* infection and comorbidities; half light rose/purple human, human with *S. aureus* infection and without comorbidities; gray human, general population. Abbreviations: N, total number of cases; SSTI, skin and soft tissue infection. SSTI Icon taken and modified from Servier Medical Art (https://smart.servier.com/image-set-download/), licensed under a Creative Commons Attribution 3.0 France. Hourglass and medical record icons made by Flat Icons and Freepik, respectively, from www.flaticon.com.

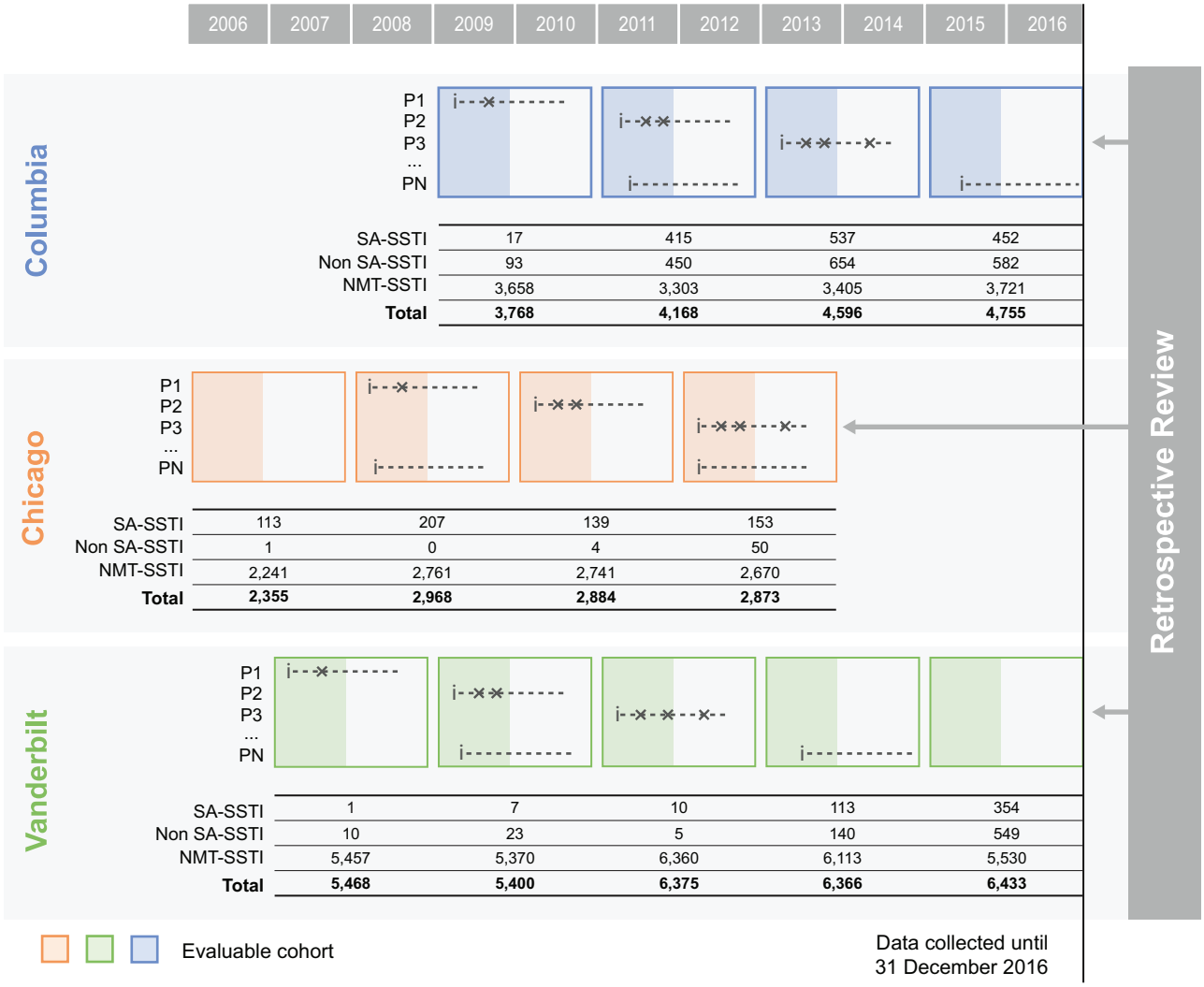

Figure 2. Overview of study design and SSTI cases reported by cohorts. Abbreviations: i, index case; NMT-SSTI, skin and soft tissue infection not microbiologically tested; non SA-SSTI, SSTI cultured and confirmed negative for *Staphylococcus aureus*; P, patient; SA-SSTI, skin and soft tissue infection cultured and confirmed positive for *S. aureus*; x, recurrence.

not microbiologically tested (NMT), it was categorized as NMT-SSTI. An SSTI event was considered recurrent if any patient returned to the OPD or ED with an SSTI that occurred more than 14 days later (a minimum of 14 days is defined to differentiate a recurrence from a relapse [17]) and within 12 months after the index case (common time frame used for recurrent SSTI [13, 19]). Recurrence rates were measured for outpatients with both SA-SSTI or NMT-SSTI index cases. To overcome the very few recurrences that were microbiologically evaluated, any SSTIs (tested or not tested) were accepted as a recurrence. The number of SA-SSTI index cases and recurrences where the reference primary infection was caused by *S. aureus* (monomicrobial) or by *S. aureus* with other bacteria (polymicrobial) were reported separately.

The study protocol was approved by the institutional review board of each center. The study was conducted in accordance with all applicable regulatory and subject privacy requirements and the guiding principles of the Declaration of Helsinki. For this study, anonymized data were used, thus no patient consent was requested.

Study Objectives

The primary objectives of the study were to estimate the proportion of SA-SSTI cases with at least 1 recurrent SSTI, defined as a new SSTI occurring after 14 days and up to 12 months following the index SSTI; to estimate the time to first recurrence; and to assess the number of recurrent SSTIs per SA-SSTI cases. As secondary objectives, the above-mentioned outcomes stratified by monomicrobial or polymicrobial *S. aureus* infections and by methicillin-susceptible *S. aureus* (MSSA) or MRSA isolates were also analyzed. Tertiary objectives were to assess the number of NMT-SSTI cases, the proportion of NMT-SSTI cases with at least 1 recurrent SSTI, the time to first recurrence, and the number of recurrent SSTIs per NMT-SSTI cases.

Statistical Analyses

All years with available clinical and microbiological records were included, starting with the most recent one. The analysis focused on the most recent evaluable cohorts as these cohorts were characterized by comparable SA-SSTI cases across centers. As shown on Figure 2, other cohorts at Vanderbilt had very few SA-SSTIs, thus, a meaningful comparison of index cases and recurrence rates across centers was possible only in the last cohort. The annual number of SA-SSTI and NMT-SSTI cases and the annual cumulative incidence of cases with 1 or more recurrences were estimated by center, with exact 95% confidence intervals using the binomial distribution model for each evaluable cohort. The cumulative proportion of SA-SSTI cases having at least 1 recurrence within 3, 6, 9, and 12 months following the index case and the proportion of recurrent SSTI cases with 1, 2, or more than 2 recurrences within 12 months following the index case were computed. The number of SA-SSTI cases and the recurrence rates stratified by monomicrobial or polymicrobial primary infection and disaggregated into MRSA and MSSA were also reported. Cox proportional hazard models that included covariates such as sex and age (18–50, >50 years), cause of infection (*S. aureus* only or *S. aureus* and other bacteria; MSSA or MRSA), history of recurrence (none or ≥1), and medical center were fitted to investigate the effect of several factors on the time to first recurrence after the index infection. Sensitivity analyses were conducted to determine whether the recurrence rate statistically changes if a different case definition for recurrence is adopted: greater than 1 month (instead of a minimum of 14 days) after the index infection.

RESULTS

Description of the Samples

The total number of SSTI cases (tested and not tested) was stable across the available cohorts (Figure 2). Except for the first cohorts, Chicago and Vanderbilt had similar numbers of cases for the evaluable period (2873–2968 and 6366–6433, respectively). Columbia had a small but steady increase in SSTI cases by year from 3768 in 2009 to 4755 in 2015 (Figure 2).

Across medical centers, NMT-SSTI cases exceeded SA-SSTI cases (Figure 3). Overall, 18.5% of SSTI cases were microbiologically tested at Columbia, 6.0% at Chicago, and 4.0% at Vanderbilt; 44.4%, 91.8%, and 40.0% of cases, respectively, were found positive for *S. aureus*. Outpatients with an SA-SSTI were slightly younger and more frequently male than patients with a NMT-SSTI. Approximately 10%–20% of SSTI cases had

	SA-SSTI			NMT-SSTI		
	Columbia	Chicago	Vanderbilt	Columbia	Chicago	Vanderbilt
Number of cases	1,421	612	485	14,087	10,413	28,830
Age (years), mean ± SD	44.9 ± 18.7	42.1 ± 17.6	45.6 ± 17.8	48.7 ± 20.4	44.4 ± 18.6	47.2 ± 18
Gender (males), %	54.8	48.9	53.8	47.0	41.3	46.4
Key comorbidities, %						
Complicated diabetes	4.2	1.1	0.6	3.6	0.7	0.4
Renal dialysis	0.0	0.2	0.8	0.0	0.3	0.3
HIV/AIDS	3.2	7.7	1.2	1.6	8.6	0.4
Malignant neoplasms	3.4	3.3	13.4	4.7	2.7	14.2
Multiple comorbidities	0.4	9.3	0.4	0.5	5.6	0.7
Total comorbidities	11.2	21.6	16.4	10.4	17.9	16.0
No key comorbidities, %	88.8	78.4	83.5	89.5	82.1	84.0

Figure 3. Sample characteristics. Abbreviations: HIV, human immunodeficiency virus; SA-SSTI, skin and soft tissue infection caused by *Staphylococcus aureus*; NMT-SSTI, skin and soft tissue infection not microbiologically tested; SD, standard deviation. People and malignant cells Icons taken and modified from Servier Medical Art (https://smart.servier.com/image-set-download/), licensed under a Creative Commons Attribution 3.0 France.

key comorbidities. Comorbidity profiles were similar among SA-SSTI and NMT-SSTI cases. Columbia had the lowest proportion of SSTI cases with comorbidities, with an equal representation of complicated diabetes, malignancies, and HIV/AIDS. Chicago had the highest proportion of SSTI cases with multiple comorbidities, and Vanderbilt had the highest proportion of patients with malignant neoplasia.

Variation of Recurrence Rates

Overall, the proportion of SSTI cases with at least 1 recurrence was consistent across cohorts (Figure 4). In the SA-SSTI groups, excluding the years with sample size less than 100 cases, the proportions of cases with at least 1 recurrence (bold text in Figure 4) were 13.6%–16.6% at Columbia, 19.0%–22.7% at Chicago, and 16.4%–16.8% at Vanderbilt. Of the total number of recurrent cases following an SA-SSTI index infection, 92 of 217 cases at Columbia, 16 of 125 at Chicago, and 17 of 81 at Vanderbilt were tested microbiologically; 68 (73.9%), 16 (100%), and 15 (88.2%) of these cases were found positive for *S. aureus*. In the NMT-SSTI groups, the recurrence rates were 11.0%–13.7% at Columbia, 15.9%–19.3% at Chicago, and 15.1%–17.4% at Vanderbilt. Recurrence rates were comparable between SA-SSTI and NMT-SSTI groups, except for the most recent cohort at Columbia.

SSTI Incidence in the Most Recent Cohorts

Of the total SSTI cases collected in the most recent evaluable cohorts (2015 for Columbia and Vanderbilt and 2012 for Chicago), 21.7% were microbiologically tested at Columbia, 7.1% at Chicago, and 14.0% at Vanderbilt (Supplementary Table 3); 43.7%, 75.4%, and 39.2% of cases, respectively, were found positive for *S. aureus*. A total of 452 SA-SSTI index cases were reported at Columbia, 153 cases at Chicago, and 354 at Vanderbilt. Most of these cases (398 of 452 [88.1%], 115 of 153 [75.2%], and 296 of 354 [83.6%], respectively) were reported in patients without key comorbidities. In the NMT-SSTI groups, 3721 (Columbia), 2670 (Chicago), and 5530 (Vanderbilt) index cases were recorded; 3335 (89.6%), 2191 (82.1%), and 4584 (82.9%) of these cases were reported in patients without key comorbidities. The proportion of microbiologically tested SSTI cases in the latest evaluable cohorts ranged from 6.4% to 21.0% across centers if the patients did not have comorbidities and from 10.0% to 27.3% in cases of key comorbidities.

A higher proportion of patients with key comorbidities had recurrences compared with patients without comorbidities (Figure 5). However, due to the sample size, this difference was more evident for NMT-SSTIs. In patients without key comorbidities, approximately half of first SSTI recurrences occurred within the first 3 months (Figure 6). Of the SSTI cases with recurrence, more than 60% had a single recurrence (Figure 7), while the remaining patients had 2 or more recurrences. Overall results (including all evaluable cohorts) on the recurrence rates and proportional distribution in the number of recurrences for each center are provided in Supplementary Table 4 and Supplementary Figures 1 and 2.

Evaluable data on mono- and polymicrobial SA-SSTI cases and MRSA/MSSA were only provided by Columbia and Vanderbilt. Most SA-SSTI cases were monomicrobial with an equal representation of MRSA and MSSA (Figure 8). Other secondary end points are not presented due to the small sample

		Columbia		Chicago		Vanderbilt	
		N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Fifth last cohort	SA-SSTI	–	–	–	–	1	100 (2.5; 100)
	NMT-SSTI	–	–	–	–	5,457	15.4 (14.5; 16.4)
Fourth last cohort	SA-SSTI	17	11.8 (1.5; 36.4)	**113**	**19.5 (12.6; 28.0)**	7	0.0 (0.0; 41.0)
	NMT-SSTI	3,658	12.7 (11.6; 13.8)	**2,241**	**17.8 (16.2; 19.4)**	5,370	17.2 (16.2; 18.3)
Third last cohort	SA-SSTI	**415**	**16.1 (12.7; 20.0)**	**207**	**22.7 (17.2;29.0)**	10	30.0 (6.7; 65.2)
	NMT-SSTI	**3,303**	**13.7 (12.5; 14.9)**	**2,761**	**15.9 (14.5; 17.3)**	6,360	16.1 (15.2; 17.0)
Second last cohort	SA-SSTI	**537**	**13.6 (10.8; 16.8)**	**139**	**19.4 (13.2; 27.0)**	**113**	**16.8 (10.4; 25.0)**
	NMT-SSTI	**3,405**	**11.6 (10.5; 12.7)**	**2,741**	**19.3 (17.8; 20.8)**	**6,113**	**17.4 (16.4; 18.3)**
Last (most recent) cohort	SA-SSTI	**452**	**16.6 (13.3; 20.3)**	**153**	**19.0 (13.1; 26.1)**	**354**	**16.4 (12.7; 20.7)**
	NMT-SSTI	**3,721**	**11.0 (10.0; 12.0)**	**2,670**	**19.2 (17.7; 20.7)**	**5,530**	**15.1 (14.2; 16.1)**

Figure 4. Recurrence rate of skin and soft tissue infections (SSTIs) within 12 months following the index SSTI in each evaluable cohort. Evaluable cohorts with >100 SA-SSTI cases are bolded. Abbreviations: %, proportion of cases with at least 1 recurrence; CI, confidence interval; NMT-SSTI, skin and soft tissue infection not microbiologically tested; SA-SSTI, skin and soft tissue infection caused by *Staphylococcus aureus*; N, total number of cases.

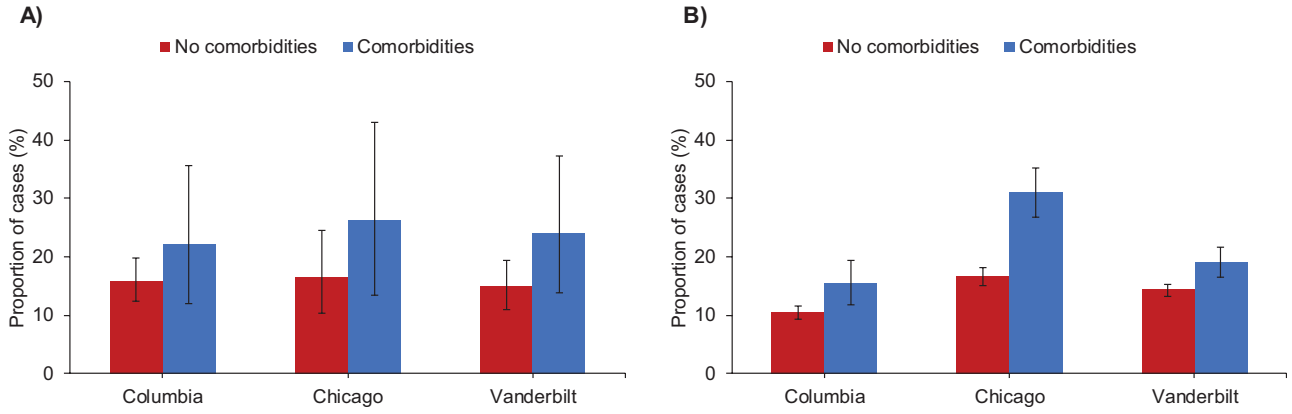

Figure 5. Incidence proportion of skin and soft tissue infections (SSTIs) caused by *Staphylococcus aureus (A)* and SSTIs not microbiologically tested *(B)* with at least 1 recurrent event in the most recent evaluable cohorts. Error bars represent 95% confidence intervals. Key comorbidities: complicated diabetes, hemodialysis, human immunodeficiency virus/AIDS, and malignant neoplasia.

size in all cohorts at Chicago and Vanderbilt, except for the most recent cohort in Vanderbilt.

A Cox proportional hazard model was stratified by age group to maximize the fit of the model for age groups. The group aged >50 years with NMT-SSTI index case had a higher risk for developing recurrences compared with the group aged 18–50 years (hazard ratio [HR] = 1.17, $P < .0001$). The HR for experiencing an SSTI recurrence was significantly higher for patients with key comorbidities compared with those without key comorbidities (HR = 2.01, $P < .0001$ for SA-SSTI index case and HR = 1.43, $P < .0001$ for NMT-SSTI index case). Similarly, the HR for SSTI recurrence was higher for both SA-SSTI and NMT-SSTI cases with a history of at least 1 SSTI in the previous year compared with cases with no SSTI in the past year (HR = 2.27, $P < .0001$ for SA-SSTI and HR = 2.71, $P < .0001$ for NMT-SSTI).

Sensitivity Analysis

For both SA-SSTI and NMT-SSTI index cases, the recurrence rate and the number of recurrent cases did not substantially change when the minimum number of days between index case and recurrences was increased from 14 days to 1 month, though a slight decrease in the number of recurrences and in recurrence rates was observed when applying the 1-month window (Supplementary Table 5, Supplementary Figure 3).

DISCUSSION

In the United States, staphylococcal SSTI remains a common health condition among patients who seek inpatient and outpatient medical care [22, 23]. Moreover, recurrent infections have been reported to occur in nearly half of patients with an SA-SSTI [24]. In this study, 3 US medical center databases were reviewed for a 10-year period to identify SSTI cases and recurrences. The number of SSTI events was stable over the study period in each center. In the most recent evaluable cohorts, ≤21.7% of cases were microbiologically tested, and ≥39.2% of the tested cases were confirmed positive for *S. aureus* across centers. The proportion of cultured SSTI cases was somewhat

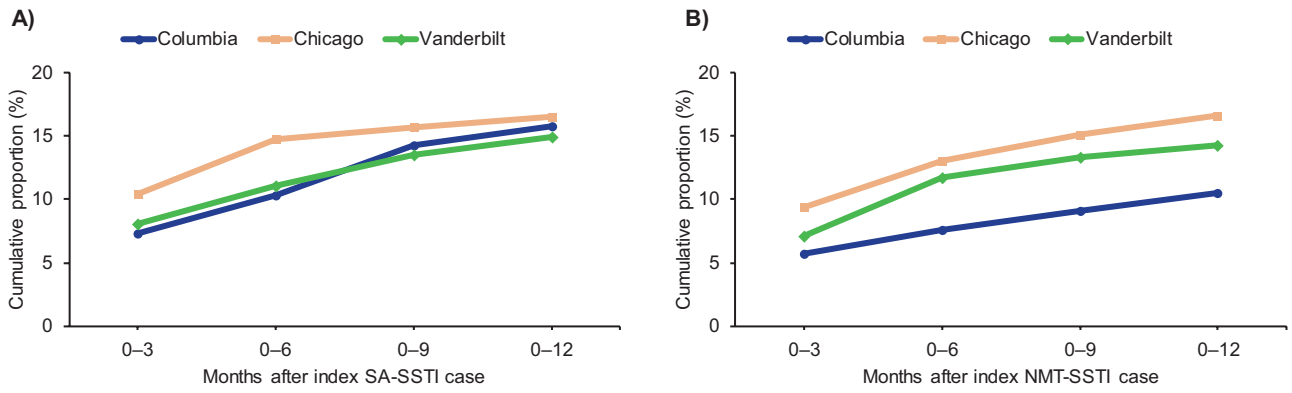

Figure 6. Cumulative recurrence rates for SA-SSTI cases *(A)* and NMT-SSTI cases *(B)* without key comorbidities in the most recent evaluable cohorts. Abbreviations: NMT-SSTI, skin and soft tissue infection not microbiologically tested; SA-SSTI, skin and soft tissue infection caused by *Staphylococcus aureus*.

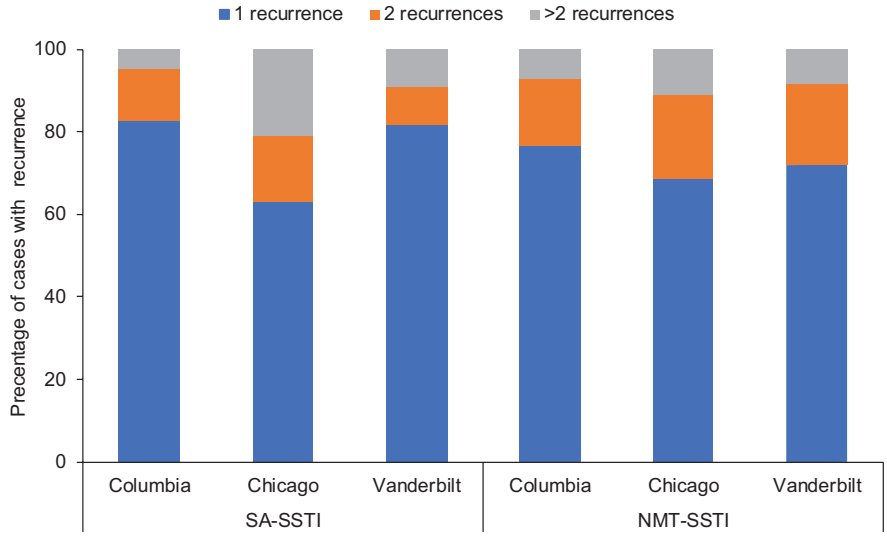

Figure 7. Proportional distribution in number of recurrences for SSTI cases without key comorbidities in the most recent evaluable cohorts. Abbreviations: NMT-SSTI, skin and soft tissue infection not microbiologically tested; SA-SSTI, skin and soft tissue infection caused by *Staphylococcus aureus*.

higher for patients with key comorbidities compared with patients without key comorbidities; this may be explained by the potentially higher severity of abscesses in this population. These data also confirm the lower propensity to microbiologically test SSTI cases in otherwise healthy patients [25].

In the most recent cohorts, 16.4%–19.0% of adults with SA-SSTIs developed 1 or more recurrences within 12 months. Recurrence rates were relatively stable across cohorts and were similar to the recurrence rates reported in California between 2005 and 2011 (6-month follow-up period, patients of all ages) [17] and in Tennessee between 2004 and 2007 (12-month follow-up period, children aged 0–17 years) [18].

Despite current advances as a result of hygiene education, decolonization [11, 12, 14, 26], and antimicrobial prophylaxis [27–29], recurrent SSTIs are frequently reported after an initial SA-SSTI event, and recurrence rates vary greatly among populations and settings [13, 16, 30]. These variations might be related to the different risk factors such as age, type of SSTI, comorbidities (if present), period of follow-up, and other variables [13, 24]. The relative stability of recurrence rates in patients with SA-SSTIs and NMT-SSTIs among different hospitals observed in our study supports the importance of applying the appropriate case definition and inclusion criteria to ensure reliability of estimated recurrent infections.

Our study has several potential limitations. First, records used in this analysis are representative of patients who access OPD and ED care at the 3 medical centers and do not include SSTI cases collected by community-based healthcare providers. Consequently,

		Monomicrobial SA-SSTI		Polymicrobial SA-SSTI	
		MSSA	MRSA	MSSA	MRSA
Columbia	N (%)	n (%)	n (%)	n (%)	n (%)
No comorbidities	398 (100)	141 (35.4)	188 (47.2)	48 (12.1)	21 (5.3)
Comorbidities	54 (100)	25 (46.3)	10 (18.5)	13 (24.1)	6 (11.1)
Total	**452 (100)**	**166 (36.7)**	**198 (43.8)**	**61 (13.5)**	**27 (6.0)**
Vanderbilt	N (%)	n (%)	n (%)	n (%)	n (%)
No comorbidities	296 (100)	147 (49.7)	129 (43.6)	11 (3.7)	9 (3.0)
Comorbidities	58 (100)	36 (62.1)	19 (32.8)	2 (3.4)	1 (1.7)
Total	**354 (100)**	**183 (51.7)**	**148 (41.8)**	**13 (3.7)**	**10 (2.8)**

Figure 8. Distribution of mono- and polymicrobial SA-SSTI cases in the most recent evaluable cohorts. Percentages were calculated using the total number of cases in each category as the denominator. Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*; N, total number of cases; n (%), number and percentage of cases in each category; SA-SSTI, skin and soft tissue infection caused by *S. aureus*.

no inferences can be drawn for the general population of the catchment area of hospitals, though the observed 15%–16% recurrence rates in SA-SSTI cases without comorbidities are consistent with reports from other US states [17, 18]. Second, cases treated at the study centers might represent a biased sample in terms of degree of severity. The records might underestimate the number of recurrent infections because patients who had a recurrent infection might have visited other healthcare facilities and thus might not have been recorded in our data system. This, however, represents a lower bound that would still allow future studies to be adequately powered. Third, as per common clinical practice of microbiologically testing few SSTIs, only a small proportion of SSTIs were microbiologically confirmed to be due to *S. aureus*. Thus, the analyzed sample almost certainly underestimates the actual number of SA-SSTIs. Moreover, patients with a confirmed SA-SSTI who return to the hospital with a new SSTI are unlikely to be reassessed for the presence of *S. aureus* or another pathogen. Indeed, our results confirmed that only a few recurrent infections following SA-SSTI index cases were microbiologically tested. However, of the few recurrences that were tested, most were confirmed as SA-SSTI cases. In our study, any returning SSTI case (confirmed or not for *S. aureus*) was considered as a recurrence, which might have led to an overestimation of SA-SSTI recurrence rates. Last, although the use of ICD codes helps to standardize data collection across centers, the precision of ICD codes for SSTI is highly limited (eg, abscess and cellulitis share the same ICD code), and there is a risk of missing SSTI cases using only ICD diagnostic coding [31].

Despite these limitations, the low variability in the number of SSTIs across cohorts, along with the similarity of recurrence rates between SA-SSTIs and NMT-SSTIs, suggest that severe biases are unlikely to have affected the estimation of SSTI incidence in the catchment area of the centers. Strengths of the study include the large set of index infections, standardized criteria for capturing recurrent SSTI, and evaluation of the presence of key comorbidities. The study also tackled the complexity of case ascertainment by establishing retrospectively an artificial cohort that identifies each index SSTI case as the first recorded episode in a given calendar year and records any recurrent episodes over a 12-month period following the index SSTI. Calendar cohorts were interspaced by 2-year intervals to avoid mixing index cases and recurrences. This study design allowed us to define an artificial time 0 (the time point of the index diagnosis marking the beginning of the 12-month observation period) that is critical for the design of a clinical study that aims to measure the efficacy of an intervention on SSTI recurrences.

CONCLUSIONS

Data from 3 US medical centers revealed that most SSTI patients identified among outpatients during the study period were otherwise healthy people, lacking key comorbidities. Only a small proportion of SSTI cases were microbiologically tested and confirmed to be an *S. aureus* infection. In the most recent cohorts, approximately 1 in 6 individuals experienced at least 1 recurrent SSTI within 12 months following the primary SA-SSTI case. Most of these patients had only 1 recurrent SSTI episode, half of which occurred in the first 3 months after the index infection. The relatively low variation in recurrence rates across centers demonstrates the importance of using a standardized case definition to estimate SSTI recurrences following the first diagnosis of SA-SSTI. In addition to the relevance of our findings, these data may support the development of novel interventions against *S. aureus*. The high incidence rate and homogeneity of recurrences across centers may allow for the design of multicenter clinical studies to evaluate efficacy of candidate vaccines and other treatment options, with a relatively small sample size.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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References

1. Dayan GH, Mohamed N, Scully IL, et al. *Staphylococcus aureus*: the current state of disease, pathophysiology and strategies for prevention. Expert Rev Vaccines **2016**; 15:1373–92.
2. Hidron AI, Edwards JR, Patel J, et al. NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006–2007. Infect Control Hosp Epidemiol **2008**; 29:996–1011.
3. Weiner LM, Webb AK, Limbago B, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011–2014. Infect Control Hosp Epidemiol **2016**; 37: 1288–301.
4. Centers for Disease Control and Prevention. Invasive *Staphylococcus aureus* (MRSA/MSSA) infection tracking. Available at: https://www.cdc.gov/hai/eip/saureus.html. Accessed 23 September 2019.
5. Sader HS, Mendes RE, Jones RN, Flamm RK. Antimicrobial susceptibility patterns of community- and hospital-acquired methicillin-resistant *Staphylococcus aureus* from United States hospitals: results from the AWARE Ceftaroline Surveillance Program (2012–2014). Diagn Microbiol Infect Dis **2016**; 86:76–9.
6. Calfee DP. Trends in community versus health care-acquired methicillin-resistant *Staphylococcus aureus* infections. Curr Infect Dis Rep **2017**; 19:48.
7. Calfee DP, Salgado CD, Milstone AM, et al.; Society for Healthcare Epidemiology of America. Strategies to prevent methicillin-resistant *Staphylococcus aureus* transmission and infection in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol **2014**; 35:772–96.
8. Fernando SA, Gray TJ, Gottlieb T. Healthcare-acquired infections: prevention strategies. Intern Med J **2017**; 47:1341–51.
9. Kock R, Becker K, Cookson B, et al. Systematic literature analysis and review of targeted preventive measures to limit healthcare-associated infections by methicillin-resistant *Staphylococcus aureus*. Euro Surveill **2014**; 19:20860.
10. Larsen J, David MZ, Vos MC, et al. Preventing the introduction of methicillin-resistant *Staphylococcus aureus* into hospitals. J Glob Antimicrob Resist **2014**; 2:260–8.
11. Huang SS, Septimus E, Kleinman K, et al.; CDC Prevention Epicenters Program; AHRQ DECIDE Network and Healthcare-Associated Infections Program. Targeted versus universal decolonization to prevent ICU infection. N Engl J Med **2013**; 368:2255–65.
12. Huang SS, Singh R, McKinnell JA, et al.; Project CLEAR Trial. Decolonization to reduce postdischarge infection risk among MRSA carriers. N Engl J Med **2019**; 380:638–50.
13. Creech CB, Al-Zubeidi DN, Fritz SA. Prevention of recurrent staphylococcal skin infections. Infect Dis Clin North Am **2015**; 29:429–64.
14. Miller LG, Eells SJ, David MZ, et al. *Staphylococcus aureus* skin infection recurrences among household members: an examination of host, behavioral, and pathogen-level predictors. Clin Infect Dis **2015**; 60:753–63.
15. Huang SS, Platt R. Risk of methicillin-resistant *Staphylococcus aureus* infection after previous infection or colonization. Clin Infect Dis **2003**; 36:281–5.
16. Bocchini CE, Mason EO, Hulten KG, Hammerman WA, Kaplan SL. Recurrent community-associated *Staphylococcus aureus* infections in children presenting to Texas Children's Hospital in Houston, Texas. Pediatr Infect Dis J **2013**; 32:1189–93.
17. May L, Klein EY, Martinez EM, Mojica N, Miller LG. Incidence and factors associated with emergency department visits for recurrent skin and soft tissue infections in patients in California, 2005–2011. Epidemiol Infect **2017**; 145:746–54.
18. Williams DJ, Cooper WO, Kaltenbach LA, et al. Comparative effectiveness of antibiotic treatment strategies for pediatric skin and soft-tissue infections. Pediatrics **2011**; 128:e479–87.
19. Shallcross LJ, Hayward AC, Johnson AM, Petersen I. Incidence and recurrence of boils and abscesses within the first year: a cohort study in UK primary care. Br J Gen Pract **2015**; 65:e668–76.
20. American Medical Association. Current procedural terminology. Available at: https://www.ama-assn.org/practice-management/cpt. Accessed 6 April 2020.
21. Centers for Disease Control and Prevention. International classification of diseases. Available at: https://www.cdc.gov/nchs/icd/icd10.htm. Accessed 6 April 2020.
22. Miller LG, Eisenberg DF, Liu H, et al. Incidence of skin and soft tissue infections in ambulatory and inpatient settings, 2005–2010. BMC Infect Dis **2015**; 15:362.
23. Inagaki K, Lucar J, Blackshear C, Hobbs CV. Methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* bacteremia: nationwide estimates of 30-day readmission, in-hospital mortality, length of stay, and cost in the United States. Clin Infect Dis **2019**; 69:2112–8.
24. Montgomery CP, David MZ, Daum RS. Host factors that contribute to recurrent staphylococcal skin infection. Curr Opin Infect Dis **2015**; 28:253–8.
25. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis **2014**; 59:147–59.
26. Fritz SA, Hogan PG, Hayek G, et al. Household versus individual approaches to eradication of community-associated *Staphylococcus aureus* in children: a randomized trial. Clin Infect Dis **2012**; 54:743–51.
27. Daum RS, Miller LG, Immergluck L, et al.; DMID 07-0051 Team. A placebo-controlled trial of antibiotics for smaller skin abscesses. N Engl J Med **2017**; 376:2545–55.
28. Hogan PG, Rodriguez M, Spenner AM, et al. Impact of systemic antibiotics on *Staphylococcus aureus* colonization and recurrent skin infection. Clin Infect Dis **2018**; 66:191–7.
29. Miller LG, Daum RS, Creech CB, et al.; DMID 07-0051 Team. Clindamycin versus trimethoprim-sulfamethoxazole for uncomplicated skin infections. N Engl J Med **2015**; 372:1093–103.
30. Graber CJ, Jacobson MA, Perdreau-Remington F, Chambers HF, Diep BA. Recurrence of skin and soft tissue infection caused by methicillin-resistant *Staphylococcus aureus* in a HIV primary care clinic. J Acquir Immune Defic Syndr **2008**; 49:231–3.
31. Gu Y, Kennelly J, Warren J, Nathani P, Boyce T. Automatic detection of skin and subcutaneous tissue infections from primary care electronic medical records. Stud Health Technol Inform **2015**; 214:74–80.