Prevalence and antimicrobial susceptibility pattern of Staphylococcus Aureus isolated from clinical specimens at the Mater Hospital Nairobi, Kenya.

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Abstract

Background Staphylococcus aureus is a leading cause of hospital and community acquired infections globally. Surveillance of prevalence and antibiotic susceptibility patterns is important to ensure appropriate antibiotic prescription. The aim of this study was to determine the prevalence and susceptibility patterns of Staphylococcus aureus isolated from clinical specimens in a tertiary hospital with diverse and empirical prescribing habits. Methods A retrospective study was conducted at the Mater Misericordiae Hospital, Nairobi. The study involved records of specimens analyzed between January 2014 and December 2018. S aureus was identified using catalase and coagulase tests. Strains phenotypically resistant to <3 non β-lactam antimicrobial categories were defined as non-multidrug-resistant MRSA (nmMRSA) and strains that were resistant to ≥3 non-β-lactam antimicrobial groups were defined as multidrug-resistant MRSA (mMRSA). A specimen was categorized as Penicillin susceptible (PSSA) if susceptible to penicillin and oxacillin, MSSA if resistant to penicillin and susceptible to oxacillin, and MRSA if resistant to oxacillin and penicillin. Isolates were screened for MRSA using 6µg/ml of oxacillin disc in Mueller-Hinton agar supplemented with 4%NaCl.Data was analyzed using Statistical Package for Social Sciences(SPSS) version 20 software. Pearson's chi square and Logistic regression were used to assess association between dependent and independent variables. Results A total of 890 specimens of S. aureus were analyzed in the 5-year period. PSSA was the most prevalent organism seen (45%) while MRSA was the least prevalent (0.45%). There was a fluctuation in the annual prevalence of MRSA between 0-1% over the five years. Most S. aureus was isolated in pus-644(73. 3%). A significant increase in susceptibility of S. aureus to Penicillin and Amoxicillin-clavulanic acid was observed during the study period however, sensitivity to Amoxicillin declined. No mMrsa was detected. Resistance of MRSA to Ampicillin, Penicillin, Tazopiperacillin, Cephalosporins, Erythromycin, Clindamycin, Ciprofloxacin and Meropenem was 100% with both Trimethoprim/sulfamethoxazole and Levofloxacin recording 50% and amoxicillin/clavulanic acid 75% resistance. Conclusion This study demonstrated a steady decline in average annual resistance of S. aureus to commonly used antibiotics. Furthermore, there was a low prevalence of MRSA. No multi-drug Methicillin resistant S. aureus have been isolated in the last five years in this hospital.

Background

[1] *Staphylococcus aureus* (*S.aureus*) is among the most common and devastating human bacterial pathogens, estimated to cause about 20%–30% of bloodstream and surgical site infections globally, as well as up to half of bone and joint infections. [1] Antibiotic resistance is a major problem in the treatment of infections caused by *Staphylococcus aureus*. The emergence of penicillinase-producing *S. aureus* strains occurred shortly after the introduction of penicillin for clinical use, and by the 1970s majority of *S. aureus* infections were penicillin resistant. [1,3] Likewise, methicillin resistance among *S. aureus* was reported in the early 1960s, after the introduction of methicillin following the acquisition of the *mecA*-containing staphylococcal cassette chromosome *mec*(SCC*mec*). [1] Since then, the emergence of Methicillin Resistant *S.aureus* (MRSA) has complicated treatment of Staphylococcus aureus infections

with significant morbidity, mortality and cost [3]. In addition to this, MRSA strains are not only resistant to nearly all beta-lactams, but also other classes of antimicrobials. The epidemiology of MRSA infections has been marked by sequential “waves” of epidemic clones spreading across geographic regions, nations, and continents [1]. [1, 5] As MRSA has become endemic, the use of vancomycin for therapy of invasive MRSA infections has increased, along with concerns about development of vancomycin resistance among MRSA. [2, 7, 9] Evidence shows that the prevalence of MRSA blood infections in the United States and Europe has dropped in recent years. [8, 9] Similarly, MRSA infection rate in Asia is also declining. [6, 9] In contrast, the prevalence of MRSA in most African countries is rising, although the rate is estimated to be below 50%. [9] The changing trajectory of MRSA infection in developed countries has been attributed to implementation of control interventions. Recent data further suggests that penicillin susceptibility may be in a period of renaissance. [4, 11]

In Africa, MRSA prevalence intra- country and intercountry has been reported to be heterogeneous. In Kenya the data has been variable and inconsistent due to lack of effective and systematic routine surveillance systems [15].

The objective of our study was to establish the prevalence and susceptibility of MRSA, multidrug resistant MRSA, and quantify contemporary penicillin resistance among S*. aureus* over a 5-year period in a tertiary care center. The knowledge acquired will be used to guide the choice of antibiotic therapy and serve as a baseline for measuring the impact of interventions.

Methods

Study setting

The Mater Misericordiae hospital is a private hospital with 179 in- patient bed capacity. It serves mainly a low and middle income population comprising of Kenyans of African and Asian descent and few Caucasians. The Mater hospital microbiological laboratory is ISO 2012 certified. The Mater hospital is unique because prescribing habits in the study location are diverse and empirical. [10]

Data and sample collection

This was a retrospective study based on electronic laboratory records from the Mater microbiological laboratory. The following demographic information was extracted from the hospital administrative database about each patient- location at time of sample collection (in- vs. outpatient), age, gender, type of sample and antimicrobial susceptibility profiles of *S. aureus*. Data from 2014 to 2018 was retrieved from the hospital medical records and for 2018 and 2019 from Vitek 2 (bioMérieux) antibiotic susceptibility system imported to LIFELINE software. [2]

Standard operating procedures were followed in collection of samples in the five-year period.

All *Staphylococcus aureus* isolates were verified with tube coagulase test and catalase tests. Tests were performed in *vitro,* and measured the growth response of an isolated organism to a particular drug or

drugs. These tests were performed under standardized conditions so that the results were reproducible. The raw data was either in the form of a zone size or MIC.

The most common method employed by the Mater hospital diagnostic laboratory between 2014 and 2018 was a simpler agar diffusion test (Kirby–Bauer method).

After incubation, the diameters of the complete growth inhibition zones around each disk were measured. Pre-specified breakpoints were used to interpret the zone sizes and classify them as susceptible(S), intermediate (I), or resistant(R). Clinical Laboratory Standards Institute (CLSI) M100-S19 breakpoints were used for interpretation. Isolates that were “intermediate” by CLSI breakpoints were grouped with resistant isolates for all analyses. [2] Methicillin resistance was determined using Oxacillin. Approval for this study was obtained from the Ethics committee of the Mater hospital. All patient information was anonymized preceding the analysis.

Data Analysis

The data collected were analyzed by SPSS software statistical application version 20 (SPSS INC, Chicago, IL, USA) [10]. In keeping with previous studies, strains that were phenotypically resistant to <3 non β-lactam antimicrobial classes were defined as non-multidrug-resistant MRSA (nmMRSA), and strains that were resistant to ≥3 non-β-lactam antimicrobial classes were defined as multidrug-resistant MRSA (mMRSA).[3] We categorized a specimen a priori, as Penicillin Susceptible *Staphylococci aureus*(PSSA) if it was susceptible to Penicillin and Oxacillin, Methicillin Susceptible *Staphylococci aureus* (MSSA) if it was resistant to Penicillin and susceptible to Oxacillin, and [2] MRSA if it was resistant to Oxacillin and Penicillin. The prevalence of antimicrobial resistance was estimated as the total number of positive results over the entire study sample. The findings were presented in tables, graphs and charts. Pearson’s chi square was used to determine the relationship between antimicrobial resistance and specific categorical variables (gender and in/outpatient status). Kruskal Wallis test was used to compare medians for age. A p value<0.05 was considered statistically significant.

Results

Demographic and microbiologic characteristics;

A total of 879 specimens with S. aureus isolates were included in the study. PSSA was the most prevalent organism seen in all S. aureus cultures during the study period (45.62%, 401/879) while MRSA species were the least prevalent (0.46 %(4/879). Two hundred and fifty-five (28.92%) of the S. aureus cultured were Oxacillin sensitive but did not qualify as PSSA or MSSA. Two hundred and twenty (25%) of the isolates were MSSA.

The prevalence of *S. aureus* was highest in 2015, (28.78%) and declined between 2016 and 2018.

The annual prevalence of MRSA fluctuated between 0-1 % during the five-year study period.

Five hundred and thirty-one (60.41 %) specimens were collected from outpatients as compared to 39.59 %(348) from admitted patients. MSSA and PSSA were predominant in outpatients (60.45% and 68.33% respectively) unlike MRSA which was obtained predominantly from inpatients (3/4, 75%). MRSA positive inpatient culture specimens were mainly from patients in the general medical wards (50%, 2/4) and intensive care unit (1/4, 25%).

The median age of all patients with S. aureus infections (N=879) was 28.25years (Q1 14, Q3 41.43, IQR 27.42).

Adolescents (10-19 years) had the highest rates of S. aureus positive cultures (71/257, 27.62%).

(*WHO age classification)

Similarly, MRSA was predominant among patients between the age of 0-19(2/4, 50%).

Five hundred and three of the specimens (57.2%) were isolated from females. MRSA was predominant in male patients (3/4,

75%) unlike MSSA (100/220, 47.27%) and PSSA (156/401, 39.95%).

Most *S. aureus* was detected in pus – (644/879, 73. 3%).The prevalence of *S. aureus* bacteremia was 7.8% (70/879)

Similarly, MRSA was most prevalent in pus. (2/4, 50%).A single isolate of MRSA was identified in cerebrospinal fluid.

Table 1

Susceptibility patterns

Overall, of the S. aureus cultured, 100%(24/24) were sensitive to Linezolid, 100%(8/8) to Clindamycin, 99.30%(626 /630) to Vancomycin, 96%(177/184) to Gentamicin, 95.04% (249/262) to Ciprofloxacin,93.54 %(20/31) to Tetracycline, 82.43 %(516/626) to Erythromycin and 58.85 %(276/469) to Trimethoprim-sulfamethoxazole.

Antibiotic	Resistant N(%)	Sensitive N(%)
Oxacillin(6mcg/ml)	4(0.46)	875 (99.54)
Penicillin G (10u)	220(25.02)	401(45.62)
Vancomycin**	4(0.63)	626 (99.27)
Sxt*(1.25/23.75mcg)	193 (41.15)	276 (58.85)
Gentamycin(10mcg)	7 (3.80)	177 (96.20)
Cefuroxime(30mcg)	15 (2.45)	597 (97.55)
Clindamycin (30mcg)	0	8(100)
Ciprofloxacin(5mcg)	13 (4.96)	249 (97.05)
Linezolid	0	24 (100)
Erythromycin(15mcg)	110 (17.57)	516 (82.43)
Amoxicillin	101(87.83)	14(12.17)
Amoxicillin/clavulanic acid(30mcg)	114 (22.75)	387 (77.25)
Teicoplanin	2(3.39)	57 (96.61)
Nitrofurantoin	3(6.8)	41 (93.18)

*Trimethoprim-sulfamethoxazole

**2mcg-16mcg/ml – vancomycin

The annual resistance to Penicillin and Amoxicillin/clavulanic acid significantly declined during the study period-Penicillin (P value=0.018, 95%CI 4.6376-28.3464) Amoxicillin-clavulanic acid (P value=0.002, 95% CI-37.50-85.83). However, a significant increase in

resistance to Amoxicillin was noted in the same period (P value=0.000, 95%CI -50.4 to -29.44)

MRSA

Four (0.46%) of the isolates were identified as Methicillin Resistant Staphylococcus Aureus. They were all nmMRSA. No mMRSA were isolated.

Resistance to Trimethoprim/sulfamethoxazole and levofloxacin was comparable at 50% whereas resistance to amoxicillin/clavulanic acid was seen in 75%of specimens tested. MRSA displayed 100% resistance to Ampicillin, Penicillin, Tazopiperacillin, Cephalosporins, Erythromycin, Clindamycin Ciprofloxacin and Meropenem.

Trend in mean antibiotic resistance

In 2014 a *S. aureus* infection was on average resistant to 3.02 antibiotics and by 2018 this decreased to 1.8 antibiotics.

Discussion

The current study demonstrates that there has been a high prevalence of PSSA (45.62%) and MSSA (25%) in the five-year period and a low prevalence of MRSA (0.45%). [25] A similar prevalence of MSSA has been reported in Eritrea.

The overall prevalence of MRSA was low (4/879, 0. 46%).The annual prevalence of MRSA fluctuated between 0-1%. This is lower than the prevalence recorded at other centres. [14, 15] Other studies have depicted a higher prevalence of MRSA in the range of 3.7% to 50%. Differences in patient type, use of antibiotics, laboratory procedures, sample size and length of study may contribute to variations in prevalence of MRSA.

MSSA and PSSA were predominantly isolated in outpatients unlike MRSA which was more in inpatients. This has similarly been observed in a study in Japan where MRSA was more prevalent in admitted patients [17]. Even though this study was not designed to identify risk factors for MRSA acquisition, risk factors that have previously been associated with acquisition of MRSA in hospitals such as broad-spectrum antimicrobial therapy, admission to an intensive care unit and proximity to other patients with MRSA [16] could play a major role in our study site.

Majority of *S. aureus* isolates were from patients between the ages of 0-19, particularly in adolescents (10-19years). However, there were no significant differences in age between patients with MRSA and MSSA or MRSA and PSSA but there were significant differences in age in patients with MSSA and PSSA.

Similarly, in a study carried out in Australia, MRSA infections were found to be more likely in younger patients (under 40) [24]

There were statistically significant differences in gender between patients who grew MRSA and PSSA. Similarly, there were significant differences in gender between patients with MSSA and PSSA however there were no significant differences in gender between patients whose cultures were positive for MRSA and MSSA

Most *S. aureus* isolates were from female patients. This difference could have arisen from the fact that female patients constituted majority of the study population (57.2%).

MRSA infections were highest in male patients unlike MSSA and PSSA. Several studies have found the isolation, carriage and infection of MRSA to be higher in males [16, 18]. This could be because hand-hygiene behavior varies according to gender.

MSSA, PSSA and MRSA were all predominantly isolated from pus. This finding is similar to what was found in Ethiopia [16]. MRSA was also isolated from a tracheal aspirate specimen and cerebrospinal fluid. The three clinical situations that predispose to the development of *S aureus* meningitis are neurosurgical intervention, contiguous infection and *S aureus* bacteremia. Until recently, most cases have been caused by methicillin-susceptible *S aureus* strains. There are now an increasing number of reports of severe infections attributed to methicillin-resistant strains of *S aureus* (MRSA). [26].

Overall *S. aureus* showed highest sensitivity to Linezolid, Vancomycin and Clindamycin. Similarly, in other studies in Kenya, *S. aureus* had low resistance to Linezolid and Vancomycin [10, 14].

Notably, resistance to Amoxicillin-Clavulanic acid and Penicillin G declined gradually over the past five years however, resistance to Amoxicillin rose. This could be explained by the overuse of Amoxicillin which is more readily available and cheaper than amoxicillin-clavulanic acid and a decline in use of Penicillin G over the years. Furthermore, recent publications have reported on the rise of Penicillin-Sensitive Staphylococcus aureus (PSSA). This trend has now been observed on several continents [20] and has been shown to involve bloodstream infections and other serious infections [21]. This increase in the incidence of PSSA infections has also been accompanied by a decrease in methicillin-resistant S. aureus (MRSA) infection rates [3, 19].

All MRSA species were non multidrug resistant. MRSA was completely resistant to Ampicillin, Penicillin, Tazopiperacillin, Cephalosporins, Erythromycin, Clindamycin, Ciprofloxacin and Meropenem.

25% of MRSA demonstrated susceptibility to Amoxicillin-Clavulanic acid. [22] A study in Pakistan found that forty-two percent of isolates were Methicillin Resistant *Staphylococcus aureus* (MRSA) out of which 87.9% were positive for Beta lactamase production and 52.1% of the Beta lactamase producing MRSA were susceptible to Amoxicillin-Clavulanic acid and the rest (47.9%) were resistant.

Our study found that 50% of MRSA were susceptible to trimethoprim-sulfamethoxazole. Pappas, Athanasoulia, and Matthaiou et al reported resistance of MRSA to trimethoprim-sulfamethoxazole to vary worldwide, in general being low in the industrialized world and higher in developing countries [23].

Overall the annual antibiotic *S. aureus* resistance has declined in the past 5 years. One potential explanation for the trend of increasing *S. aureus* antibiotic susceptibility is a change in antibiotic pressures. The declines in the use of narrow-spectrum beta-lactams such as Oxacillin and Penicillin G since 2000 and in the inpatient use of first-generation cephalosporins since 2006 may select against hospital acquired MRSA in favor of PSSA [3].

Our results have important clinical implications in treatment of *Staphylococcus aureus* infections. First, there is a low burden of MRSA in our setting and therefore empiric MRSA cover would not be necessary among patients presenting with *S.aureus* infections. Second, Trimethoprim-sulfamethoxazole is not a suitable first line alternative for treating community acquired *Staphylococcus aureus* infections in this setting unlike in the West. Third, penicillins would be a viable first line option for treating *S.aureus* infections seen in our setting due to the high number of penicillin susceptible organisms.

There are several limitations to our study. First, the testing for inducible beta-lactamase production was not performed, raising the possibility that specimens reported as penicillin susceptible from this time period were in fact penicillin resistant. Secondly, tests were not done to determine the MICs of organisms reported as resistant to Vancomycin. In addition, we did not collect information on a number of vital aspects such as history of antimicrobial use and duration of hospital admission. Furthermore, in the absence of genotyping of specimens, phenotypic MRSA identification methods may not reflect an accurate picture.

Conclusion

The prevalence of MRSA was low when compared with the prevalence rates obtained in previous studies conducted in Kenya. MRSA strains were non-multidrug-resistant and overall there was very low resistance *of S. aureus* to Vancomycin. There has been a decline in resistance of *S. aureus* to Penicillin and Amoxicillin clavulanic acid in the past five years. Good infection control practices and prudent antibiotic use can help to further reduce the burden of MRSA in our setting.

Abbreviations

SCC mec- Staphylococcal cassette chromosome mec

MIC- Minimum inhibitory concentration

SSI- Skin and soft tissue infection

MSSA- Methicillin-susceptible *Staphylococcus aureus*

MRSA-Methicillin-resistant *Staphylococci aureus*

CLSI-Clinical and Laboratory Standard Institute

VRSA- Vancomycin Resistant *Staphylococci aureus*

Declarations

Authors' contributions

CO participated in the study design, literature search, data collection, data analysis, manuscript writing and is the corresponding author, CM, DO, FCFO, LAO and EO participated in the study design, writing the manuscript, interpretation of data, supervision of the microbiological diagnosis and served as scientific advisors. All the above authors read and approved the final manuscript.

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Declarationsss

Competing interests

All the authors declared that they have no competing interests

Availability of data and materials

The data and information supporting the conclusions of this article are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The study protocol and procedure were approved by the ethics committee of the Mater hospital dated 9th November 2017.Our study does not include new clinical procedures, nor was it based on laboratory investigations, only on microbiological surveillance data. Our study did not involve any animals.

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Table

Demographic and microbiologic characteristics of patients' and *S. aureus* subtype

Subtype	No. of isolates	Mean patient age in years(s.d)	% female patients	blood	Lung	SSI	Other
All S.aureus	897	29.73 (21.38)	57.2	7.85%	3.07%	73.27%	15.81%
MRSA	4	31.97 (37.06)	25	0	25%	50%	25%
MSSA	220	28.32 (22.01)	52.73	5.91%	1.36%	83.64%	9.09%
PSSA	401	32.84(20.93)	60.05	5.79%	3.27%	71.54%	19.4%
P-value							

MRSA vs MSSA		0.75	0.705	-	0.003	0.003	0.003
MRSA vs PSSA		0.947	<0.0001	-	<0.0001	<0.0001	<0.0001
MSSA vs PSSA		0.012	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Tests of difference are two-sided and comprised *t* tests for mean age, chi-squared tests for sex and site of infection.

Figures

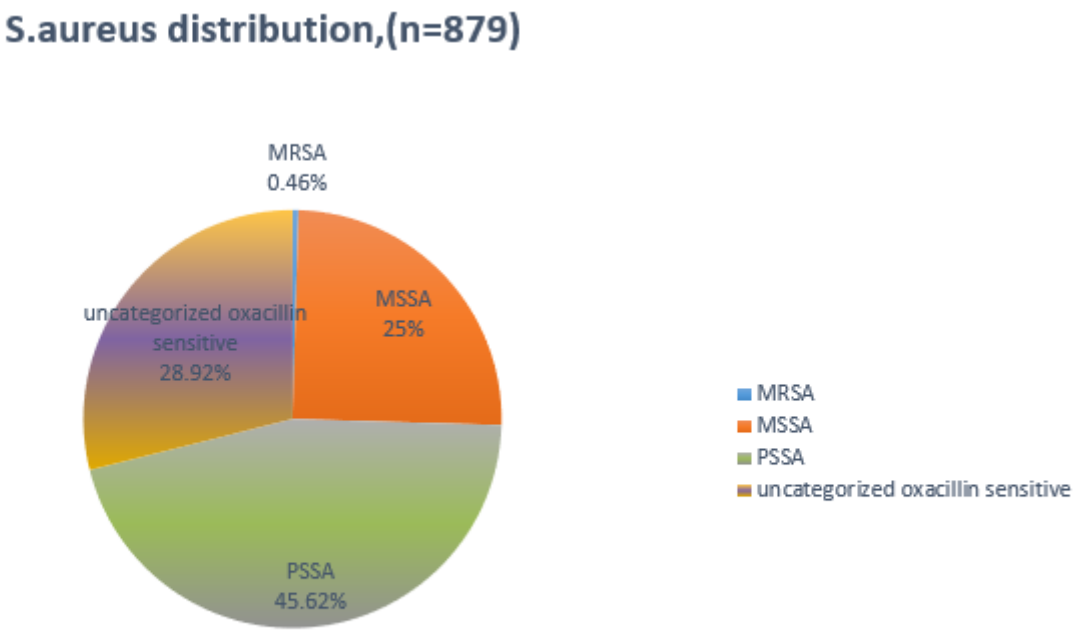

Figure 1

The prevalence of S. aureus was highest in 2015, (28.78%) and declined between 2016 and 2018.

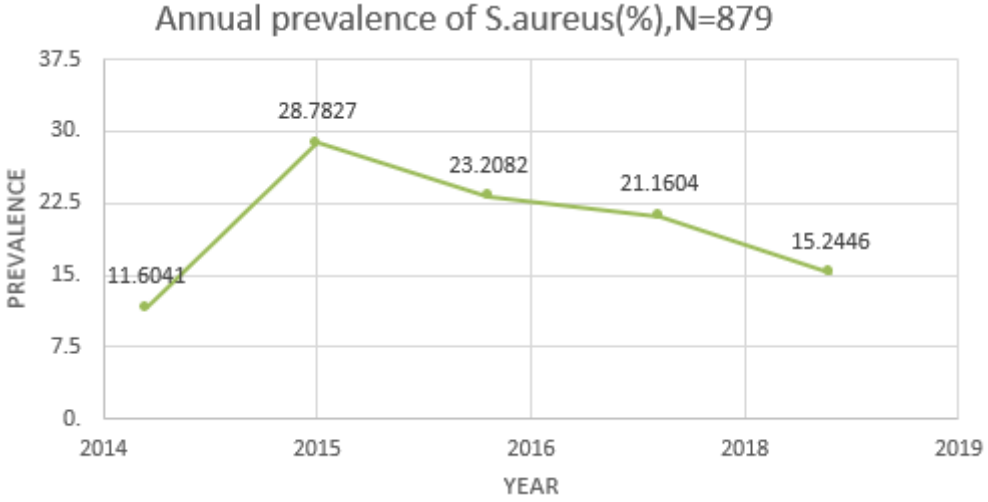

Figure 2

The annual prevalence of MRSA fluctuated between 0-1 % during the five-year study period.

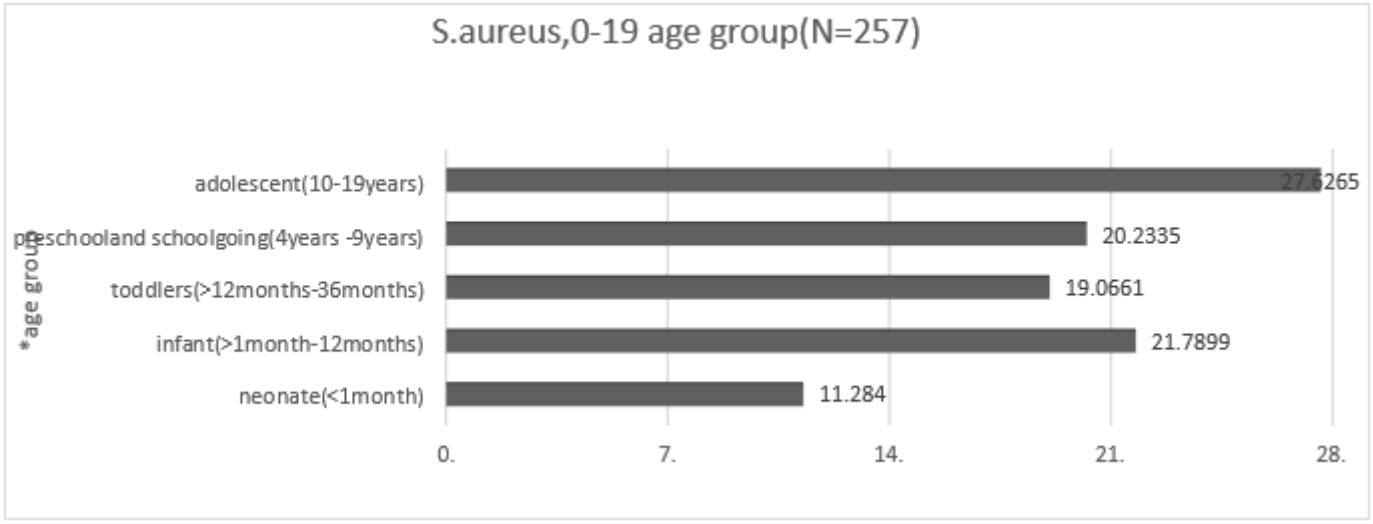

Figure 3

(*WHO age classification)