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Epidemiological profile and antimicrobial resistance trends of *Staphylococcus aureus* in Chinese pediatric intensive care units from 2016 to 2022: a multi-center retrospective study

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Abstract

Objective This study aimed to analyze the profiles and evolution of *Staphylococcus aureus* in the pediatric intensive care units (PICUs) of 17 hospitals in China from 2016 to 2022.

Methods Susceptibility testing was performed to bacterial strains with a uniform monitoring protocol, which was provided by the US Clinical and Laboratory Standards Institute (CLSI) and used by the China Antimicrobial Surveillance Network (CHINET). The results were interpreted in accordance with the performance standards for antimicrobial susceptibility testing issued by the US Clinical and Laboratory Standards Institute.

Results Twenty-six thousand six hundred thirteen bacterial strains were isolated from 17 PICUs in China from 2016 to 2022, 3,147 of which were *Staphylococcus aureus*, ranking second among etiological agents of infections from PICUs. In 2022, *Staphylococcus aureus* had the highest detection rate, being 36.19%. And in 2021, MRSA had the highest detection rate, being 10.35% in *Staphylococcus aureus*. There were statistically significant differences in the annual detection rate of gram-positive bacteria, *Staphylococcus aureus* and MRSA between the years from 2016 to 2022 ($P < 0.05$). More males were found with *Staphylococcus aureus* or *methicillin-resistant Staphylococcus aureus*, but there were no statistical differences in gender distribution between any two years ($P < 0.05$). The top 3 highest

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detection rate of *Staphylococcus aureus* in age groups were infants (1244, 39.7%), toddlers (741, 23.7%), and children at school age and older (731, 23.4%). For MRSA, The top 3 in age groups were infants (91, 38.9%), children at school age and older (87, 29.1%), and toddlers (48, 20.5%). The detection rate of *Staphylococcus aureus* was statistically different in the distribution of age stratification ($P < 0.05$). There was no statistically significant difference in these two aspects of MRSA ($P > 0.05$). The top 3 highest detection rate of *Staphylococcus aureus* in infected sites were the lower respiratory tract (2,552, 81.7%), bloodstream (217, 6.5%), and skin wounds (110, 3.9%). For MRSA, The top 3 in infected sites were the lower respiratory tract (156, 77.9%), skin wounds (47, 8.8%), and bloodstream (15, 6.6%). The detection rate of *Staphylococcus aureus* and MRSA was statistically different in the distribution of infected sites ($P < 0.05$). All the strains of *Staphylococcus aureus* were sensitive to tigecycline, nitrofurantoin, vancomycin, and linezolid. The resistant rate of *Staphylococcus aureus*, to penicillin G was as high as 87.5% at least, to erythromycin was as high as 51.8% at least, to benzocillin was as high as 38.0% at least, to cefoxitin was as high as 35.5% at least, and to clindamycin was as high as 32.7% at least. All the strains of MRSA were sensitive to vancomycin, linezolid, quinupristin/dalfopristin, and tigecycline. Of these 234 strains of MRSA, 179 (76.5%) were resistant to erythromycin, 116 (49.6%) to clindamycin, 39 (16.7%) to tetracycline, 29 (12.4%) to levofloxacin, 27 (11.5%) to ciprofloxacin, 27 (11.5%) to moxifloxacin, 14 (6.0%) to TMP-SMX, eight (3.4%) to rifampicin, and six (2.6%) to gentamicin.

Conclusions *Staphylococcus aureus* is the most common gram-positive bacterium in PICUs. Infants are most likely to be infected by *Staphylococcus aureus* and *methicillin-resistant Staphylococcus aureus*. And the lower respiratory tract is the most common infected site of *Staphylococcus aureus*. *Staphylococcus aureus* has a high resistant rates to commonly used antimicriobials in pediatrics, but no strains resistant to vancomycin and/or linezolid were found. When considering *Staphylococcus aureus* infection clinically, it is necessary to select antimicrobials reasonably based on the patient's age, infected site and local epidemiological characteristics.

Keywords Pediatric intensive-care unit, *Staphylococcus aureus*, Antimicrobial resistance, Evolution

Background

As a major cause of community-acquired and nosocomial infections, *Staphylococcus aureus* (*S. aureu*) can trigger a variety of infectious diseases, including skin and soft tissue infections, endocarditis, osteomyelitis, septicemia, pneumonia, and many other serious and even fatal conditions [1]. Antimicrobial resistance (AMR) refers to the ability of microorganisms to have intrinsic resistance to antimicrobial drugs or to develop extrinsic resistance through acquired mechanisms. Unfortunately, the overuse of broad-spectrum antimicrobials has led to the development of AMR in *S. aureus*, resulting in poor anti-infective efficacy, and thus has become a major challenge in clinical settings [2]. *S. aureus* can be categorized into two groups according to its resistance to benzoxacillin: *methicillin-sensitive S. aureus* (MSSA) and *methicillin-resistant S. aureus*(MRSA). MRSA has rapidly become the most common drug-resistant pathogen in many countries around the world, including Europe, the United States, North Africa, the Middle East, and East Asia [3, 4]. In China, the proportion of MRSA obtained by hospitals has reached 50.4% [5]. Children suffering from skin and soft tissue infections with the detection rate of S. aureus was 62.57%, among which MRSA accounted for 14.79% [6]. Very immature preterm infants, especially those with a birth weight less than 1,500 g may account for approximately 80% of all cases of neonatal MRSA infections [5–7]. These make it become a focus of global public health. Therefore, monitoring the epidemiological characteristics of *S. aureus* can help us cope with the harm better.

Children in PICUs often experience critical conditions with Immunosuppressive state, frequent invasive procedures, intensive and prolonged antimicrobial use, and poor infection prevention and control, which are all associated with the development of AMR [8–10]. Dynamically monitoring the prevalence, clinical distribution, and AMR profiles of *S. aureus* infections in PICUs is crucial for the diagnosis and treatment of these infections. Here, we retrospectively analyzed clinical *S. aureus* isolates from the PICUs of 17 hospitals in the China paediatric Intensive care Unit Pathogen Surveillance Network (CHIPS) from 2016 to 2022, to provide evidence for the clinical treatment and infection control of this pathogen.

Subjects and methods

Specimen sources

The specimens sent for testing were collected from children admitted to 17 PICUs, including Children's Hospital of Fudan University, Shanghai Children's Medical Center affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai Children's Hospital affiliated to Shanghai Jiaotong University, Children's Hospital Affiliated to Zhejiang University Medical School, Children's Hospital of Soochow University, Ningbo Women and

Children's Hospital, Wuxi Children's Hospital, The First Affiliated Hospital of Xiamen University, Xiamen Children's Hospital, Anhui Children's Hospital, Shenzhen Children's Hospital, Henan Children's Hospital, Kaifeng Children's Hospital, Hunan Children's Hospital, Jiangxi Provincial Children's Hospital, Kunming Children's Hospital and Guiyang Children's Hospital, during the period from 1 January 2016 to 31 December 2022. All the PCUs belong to CHIPS member hospitals, that means they all basically the same in terms of level, disease diagnosis and treatment, specimen collection and testing. Blood, cerebrospinal fluid, urine, pus, exudates, tissue specimens from the respiratory tract and gastrointestinal tract, and specimens from catheter tips were examined. The inclusion criteria were: (i) age 30 days to 18 years; and (ii) culture specimens that were positive for *S. aureus*. Duplicate strains at the same site in the same patient were eliminated.

Age stratification of the specimen

The specimens were stratified according to age,including infant (30 days −1 year), toddler (1 year −3 years), preschool children (3 years−6 years), and children at school age and older (> 6 years).

Isolation and identification of bacterial strains and drug susceptibility testing (DST)

The bacterial strains were isolated and cultured with reference to the National Guide to Clinical Laboratory Procedures (4th edition) [11]. The Vitek 2 Compact fully automated system (Mérieux, France) was used for strain identification. The methods and standards of antimicrobial susceptibility test of CLSI in the United States are the standards followed by China. We took the performance standards for antimicrobial susceptibility testing issued by the US CLSI study. DST and the interpretation of its results were based on the US Clinical and Laboratory Standards Institute (CLSI) guidelines (2020 edition) [12]. DST was performed for the following drugs: cefoxitin, ceftaroline, benzoxicillin, ampicillin/sulbactam, penicillin G, sulfamethoxazole-trimethoprim (TMP-SMX), erythromycin, clindamycin, nitrofurantoin, vancomycin, rifampicin, teicoplanin, linezolid, tigecycline, levofloxacin, amikacin, ciprofloxacin, moxifloxacin, tetracycline, minocycline, chloramphenicol, amoxicillin/clavulanic acid, ceftriaxone, cefoperazone/sulbactam, tobramycin, clarithromycin, azithromycin, quinupristin/dalfopristin, fosfomycin, and gentamicin. The quality control strain, ATCC 25923 (*S. aureus*), was provided by Shanghai Municipal Centre for Disease Control and Prevention (Shanghai CDC) (Shanghai, China), and the quality control of DST was performed on a weekly basis.

Definition of susceptibility

S. aureus can be categorized into two groups, MSSA and MRSA. MSSA refers to *S. aureus* that is not resistant to methicillin, whereas MRSA refers to *S. aureus* that is resistant to all penicillins, including methicillin and other antibiotics that are resistant to β-lactamase.

Statistical analysis

Statistical analyses were performed with the WHONET 5.6 and SPSS 26.0 software, and graphs were drawn with the GraphPad software. The count data are presented as cases and percentages. Comparisons between multiple groups were analyzed by χ^2 *test*. If the frequency of a single cell was less than 5, *Fisher's exact test* was used for comparison between multiple groups. *χ2 test* or *Fisher's exact tes*t was followed by *Z-test*, which was used for comparison between two groups within multiple groups. A two-tailed *P-value* < 0.05 was considered statistically significant.

Results

Overview of the distribution of bacterial strains

From 2016 to 2022, a total of 26,613 bacterial isolates were identified, 9,743 of which were gram-positive bacteria. 3147 strains of gram-positive bacteria were *S. aureus*, accounting for 32.30%. 234 strains of *S. aureus were* MRSA, accounting for 7.44% (Table 1). The top 10 bacterial isolates were shown in Fig. 1. *S. aureus* ranked second in all, and occupied the first place in gram-positive bacteria. From 2016 to 2019, with the increase of the total number of bacterial strains, the number and proportion of *S. aureus* showed an upward trend. From 2020 to 2022, the total number of strains detected fluctuated, as did the number and proportion of *S. aureus* (Table 1 and Fig. 2). The annual detection rate of *S. aureus* was shown in Table 1. In 2022, *S. aureus* had the highest detection rate, being 36.19%. And in 2021, MRSA had the highest detection rate, being 10.35% in *S. aureus*. There were statistically significant differences in the annual detection rate of gram-positive bacteria, *S. aureus* and MRSA between the years from 2016 to 2022 ($P < 0.05$), and the statistical differences between any two years were shown in Table 1 for details. The detection rate of MRSA differed significantly between 2020 and 2021 ($P < 0.05$), with the lowest rate being 4.99% in 2020 and the highest rate being 10.35% in 2021 (Table 1).

Table 1 Isolation of related strains in PICUs of 17 hospitals in China from 2016 to 2022

The year	Total number of bacterial isolates	Number of GM^+ isolates (%)	Number of *S. aureus* isolates (%)	Number of MRSA isolates (%)
2016	3,650	1,220 (33.42%)[a]	302 (24.75%)[a]	28(9.27%)[a,b]
2017	3846	1315 (34.19%)[a]	385 (29.28%)[a,b]	20(5.19%)[a,b]
2018	3734	1322 (35.40%)[a,b]	420 (31.77%)[b,c]	22(5.24%)[a,b]
2019	4326	1584 (36.62%)[a,b,c]	526 (33.21%)[b,c]	49(9.32%)[a,b]
2020	3697	1449 (39.19%)[c]	521 (35.96%)[c]	26(4.99%)[b]
2021	4045	1604 (39.65%)[c]	541 (33.73%)[b,c]	56(10.35%)[a]
2022	3315	1249 (37.68%)[b,c]	452 (36.19%)[c]	33(7.30%)[a,b]
Total number	26,613	9743 (36.61%)	3147 (32.30%)	234 (7.44%)
χ^2 value	***	56.404	57.018	21.155
P value	***	< 0.001	< 0.001	0.002

*GM^+*Gram-positive bacteria, *MRSA methicillin-resistant Staphylococcus aureus*

*** The specific values were not calculated separately; please refer to Note 1 for specific statistical significance

[a, b, c] The same letters between any 2 years indicate $P > 0.05$, whereas different letters between any 2 years indicate $P < 0.05$

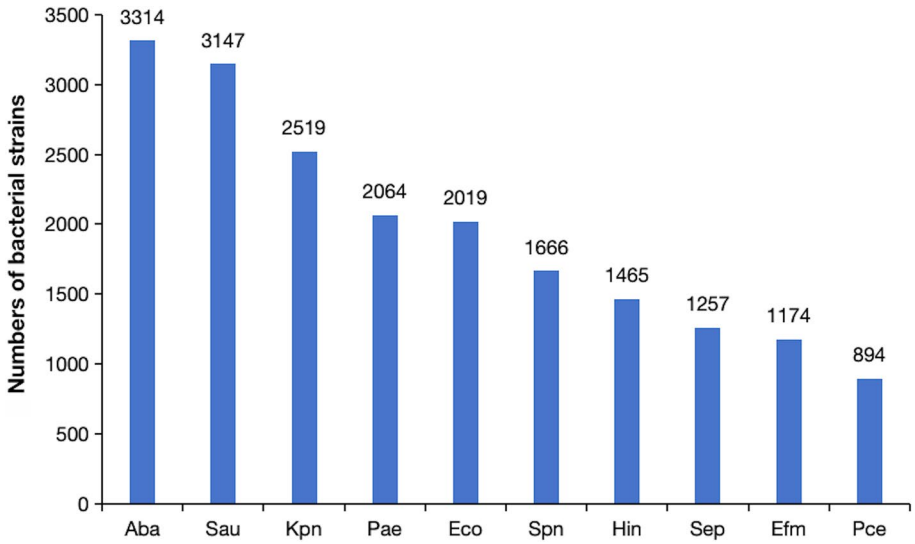

Fig. 1 The top 10 strains of of bacteria from 2016 to 2022. Notes: Aba: *Acinetobacter baumannii;* Sau: *Staphylococcus aureus*; Kpn: *Klebsiella pneumoniae*; Pae: *Pseudomonas aeruginosa*; Eco: *Escherichia coli*; Spn: *Streptococcus pneumoniae*; Hin: *Haemophilus influenzae*; Sep: *Staphylococcus epidermidis*; Efm: *Enterococcus faecium*; Pce: *Burkholderia cepacia*

Distribution of *S. aureus* and MRSA

From 2016 to 2022, more males than females (male:female = 1968:1179) were infected with *S. aureus*, but there was no statistically significant differences in the sex distributions overall and between any 2 years ($P > 0.05$), as shown in Table 2. With regard to MRSA, the above situation is similar to that of *S. aureus* in general, as shown in Table 3.

The detection rate of *S. aureus* and MRSA in children with different ages are shown in Tables 2 and 3 and Fig. 3A. Among the 3147 strains of *S. aureus* in 7 years, the top 3 highest detection rate of *S. aureus* in age groups were infants (1244, 39.7%), toddlers (741, 23.7%), and children at school age and older (731, 23.4%) in order (Table 2). For MRSA, The top 3 in age groups were the same as that of *S. aureus*, but in a different order, infants (91, 38.9%), children at school age and older (87, 29.1%), and toddlers (48, 20.5%). It can be seen that infants were most likely to be infected with *S. aureus*, and showed a higher proportion of MRSA. In the distribution of annual detection rate of *S. aureus*, only in 2022, children at school age and older ranked first. In the other 6 years,

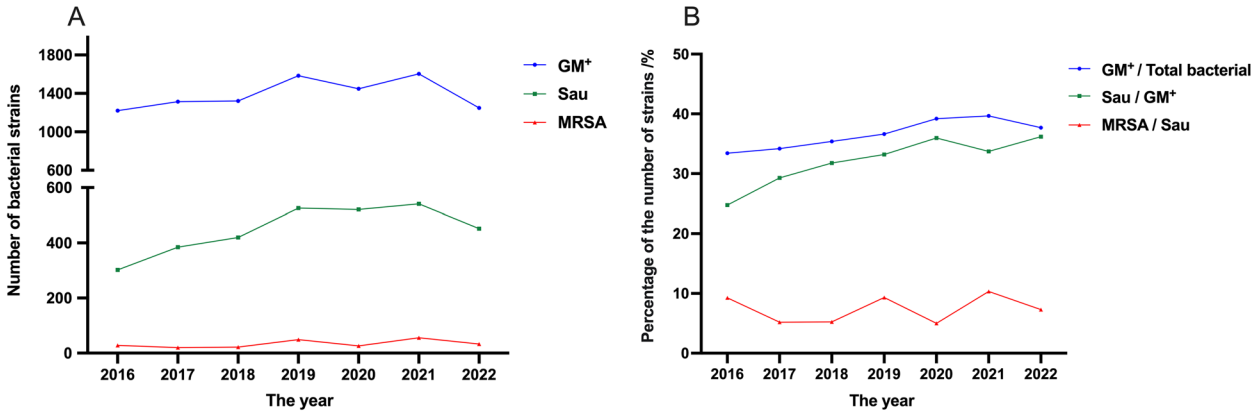

Fig. 2 Related strains in PICUs of 17 hospitals in China from 2016 to 2022. **A** shows annual changes in the number of *S. aureus* strains; (**B**) shows annual changes in the proportion of *S. aureus* strains. Notes: GM + : Gram-positive bacteria; Sau: *S. aureus*; MRSA: *methicillin-resistant S. aureus*

infants ranked first. For MRSA, children at school age and older and infants randomly ranked first. The detection rate of *S. aureus* was statistically different in the distribution of age stratification ($P < 0.05$). And the statistical difference of detection rate of *S. aureus* in the same age group between any two years is shown in Table 2. There was no statistically significant difference in these two aspects of MRSA ($P > 0.05$).

The infected sites of *S. aureus* were shown in Tables 2 and 3 and Fig. 3B. Among all the *S. aureus* isolates from 2016 to 2022, the top 3 highest detection rate of *S. aureus* in infected sites were the lower respiratory tract (2,552, 81.7%), bloodstream (217, 6.5%), and skin

Table 2 The distribution of *S. aureus* in gender, age and infected sites

Characteristics	The year							X^2 /Fisher value	*P* value
	2016	2017	2018	2019	2020	2021	2022		
Gender No. (%)								7.702	0.261
Male	185(61.3)[a]	258(67.0)[a]	253(60.2)[a]	312(59.3)[a]	325(62.4)[a]	348(64.3)[a]	287(63.5)[a]	***	***
Female	117(38.7)[a]	127(33)[a]	167(39.8)[a]	214(40.7)[a]	196(37.6)[a]	193(35.7)[a]	165(36.5)[a]	***	***
Age No. (%)								110.546	< 0.001
Infant	143(48.1)[a]	190(49.5)[a]	173(41.7)[a,b]	220(41.8)[a,b]	183(35.6)[b,c]	215(39.7)[a,b]	120(26.5)[c]	***	***
Toddler	70(23.6)[a]	79(20.5)[a]	108(26.0)[a]	136(25.9)[a]	135(26.3)[a]	118(21.8)[a]	95(21.1)[a]	***	***
Preschool children	31(10.4)[a]	41(10.6)[a]	45(10.8)[a]	50(9.5)[a]	61(11.8)[a]	70(12.9)[a]	66(14.6)[a]	***	***
Children at school age and older	49(16.5)[a]	65(16.9)[a]	78(18.8)[a]	114(21.7)[a]	128(24.9)[a]	135(25.0)[a]	162(35.8)[b]	***	***
Infected sites No. (%)								---	0.004
Lower respiratory tract	208(73.0)[a]	308(80.0)[a,b]	352(84.0)[b]	448(85.0)[b]	427(82.0)[b]	443(82.0)[a,b]	366(81.0)[a,b]	***	***
Bloodstream	22(7.7)[a]	23(6.0)[a]	36(8.6)[a]	31(5.9)[a]	34(6.6)[a]	35(6.5)[a]	36(8.0)[a]	***	***
Skin wound	19(6.7)[a]	7(1.8)[b]	6(1.4)[b]	16(3.1)[a,b]	26(5.0)[a,b]	22(4.1)[a,b]	14(3.1)[a,b]	***	***
Abscesses	13(4.6)[a,b]	22(5.7)[b]	13(3.1)[a,b]	9(1.7)[a]	12(2.3)[a,b]	17(3.1)[a,b]	16(3.5)[a,b]	***	***
Serous effusion	8(2.8)[a]	9(2.3)[a]	4(1.0)[a]	7(1.3)[a]	7(1.3)[a]	10(1.8)[a]	4(0.9)[a]	***	***
Upper respiratory tract	6(2.1)[a]	5(1.3)[a]	2(0.5)[a]	6(1.1)[a]	2(0.4)[a]	5(0.9)[a]	4(0.9)[a]	***	***
Catheter tip	4(1.4)[a]	1(0.3)[a]	2(0.5)[a]	0(0)[a]	2(0.4)[a]	4(0.7)[a]	1(0.2)[a]	***	***
Others	3(1.1)[a]	6(1.6)[a]	3(0.7)[a]	5(1.0)[a]	3(0.6)[a]	2(0.4)[a]	3(0.7)[a]	***	***
Urinary tract	1(0.4)[a]	2(0.5)[a]	2(0.5)[a]	2(0.4)[a]	6(1.3)[a]	2(0.4)[a]	7(1.5)[a]	***	***
Alimentary canal	1(0.4)[a]	1(0.3)[a]	0(0)[a]	0(0)[a]	0(0)[a]	1(0.2)[a]	1(0.2)[a]	***	***

[a, b,c]The same letters between any 2 years indicate $P > 0.05$, whereas different letters between any 2 years indicate $P < 0.05$

[***] The specific values were not calculated separately; please refer to Note 1 for specific statistical significance

[---] The memory is insufficient to calculate

Table 3 The distribution of MRSA in gender, age and infected sites

Characteristics	The year							X^2 /Fisher value	P value
	2016	2017	2018	2019	2020	2021	2022		
Gender No. (%)								4.791	0.578
Male	17(60.7)[a]	12(60)[a]	16(72.7)[a]	32(65.4)[a]	21(80.7)[a]	38(67.8)[a]	19(57.5)[a]	***	***
Female	11(39.3)[a]	8(40)[a]	6(27.3)[a]	17(34.6)[a]	5(19.3)[a]	18(32.2)[a]	14(42.5)[a]	***	***
Age No. (%)								30.070	0.182
Infant	12(42.8)[a]	11(55.0)[a]	9(40.9)[a]	19(38.8)[a]	7(26.9)[a]	20(35.7)[a]	13(39.4)[a]	***	***
Toddler	5(17.9)[a]	3(15.0)[a]	5(22.7)[a]	13(26.5)[a]	6(23.1)[a]	9(16.1)[a]	7(21.2)[a]	***	***
Preschool children	5(17.9)[a]	1(5.0)[a]	2(9.1)[a]	7(14.3)[a]	2(7.7)[a]	3(5.4)[a]	3(9.1)[a]	***	***
Children at school age and older	6(21.4)[a]	3(15.0)[a]	5(22.7)[a]	9(18.4)[a]	11(42.3)[a]	24(42.8)[a]	10(30.3)[a]	***	***
Infected sites No. (%)								---	< 0.001
Lower respiratory tract	13(65.0)[a]	18(90.0)[a]	3(14.0)[b]	40(82.0)[a]	23(88.0)[a]	50(89.0)[a]	29(88.0)[a]	***	***
Bloodstream	3(15.0)[a]	1(5.0)[a]	3(14.0)[a]	3(6.1)[a]	1(3.8)[a]	2(3.6)[a]	2(6.1)[a]	***	***
Skin wound	0(0)[a]	0(0)[a]	14(64.0)[b]	2(4.1)[a]	29(7.7)[a]	2(3.6)[a]	0(0)[a]	***	***
Abscesses	0(0)[a]	1(5.0)[a]	1(4.5)[a]	0(0)[a]	0(0)[a]	1(1.80	0(0)[a]	***	***
Serous effusion	0(0)[a]	0(0)[a]	0(0)[a]	2(4.1)[a]	0(0)[a]	0(0)[a]	0(0)[a]	***	***
Upper respiratory tract	1(5.0)[a]	0(0)[a]	0(0)[a]	0(0)[a]	0(0)[a]	0(0)[a]	1(2.9)[a]	***	***
Catheter tip	3(15.0)[a]	0(0)[a]	0(0)[a]	0(0)[a]	0(0)[a]	0(0)[a]	0(0)[a]	***	***
Others	0(0)[a]	0(0)[a]	0(0)[a]	1(2.0)[a]	0(0)[a]	0(0)[a]	0(0)[a]	***	***
Urinary tract	0(0)[a]	0(0)[a]	1(4.5)[a]	1(2.0)[a]	0(0)[a]	1(1.8)[a]	1(2.9)[a]	***	***

[a, b]The same letters between any 2 years indicate $P > 0.05$, whereas different letters between any 2 years indicate $P < 0.05$

[***] The specific values were not calculated separately; please refer to Note 1 for specific statistical significance

[---] The memory is insufficient to calculate

MRSA *Methicillin-resistant Staphylococcus aureus*

wounds (110, 3.9%). For MRSA, The top 3 in infected sites were the lower respiratory tract (156, 77.9%), skin wounds (47, 8.8%), and bloodstream (15, 6.6%). Thus, the lower respiratory tract is the most common infected site of *S. aureus* and MRSA.

In the 7 years, the top 2 highest annual detection rate of *S. aureus* in infected sites is the lower respiratory tract and bloodstream. *S. aureus* isolated from abscesses ranked third in 2017 and 2018, and skin wounds ranked third in the other 5 years. For MRSA, the distribution of infected sites is similar to S. aureus, except the skin wound ranked first in 2018 (63.6%). The detection rate of *S. aureus* and MRSA was statistically different in the distribution of infected sites ($P < 0.05$). And the statistical difference of detection rate of *S. aureus* and MRSA in infected sites between any two years is shown in Tables 2 and 3.

AMR in *S. aureus*

The AMR profiles of 3,147 strains of *S. aureus* from 2016 to 2022 were shown in Table 4. All the strains of *S. aureus* were sensitive to tigecycline, nitrofurantoin, vancomycin, and linezolid. The annual changes in AMR of *S. aureus* from 2016 to 2022 were shown in Table 4 and Fig. 4. The resistant rate of *S. aureus*, to penicillin G was as high as 87.5% at least, to erythromycin was as high as 51.8% at least, to benzocillin was as high as 38.0% at least, to cefoxitin was as high as 35.5% at least, and to clindamycin was as high as 32.7% at least. The resistant rates of *S. aureus* to erythromycin, clindamycin, cefoxitin TMP-SMX and gentamicin were declining annually, to penicillin G and benzoxiline fluctuated within 10%. The resistance trends of *S. aureus* to tetracycline, quinupristin/dalfopristin, and fosfomycin showed a similar trend, increasing initially and then decreasing. *S. aureus* showed similar resistance trend to levofloxacin, ciprofloxacin, and moxifloxacin, with the resistant rate slowly increasing to being less than 10%. It's resistant rate to fosfomycin, rifampicin, and minocycline was less than 5.0%. The significant differences in the AMR of *S. aureus* to commonly used antimicrobials between any 2 years from 2016 to 2022 were shown in Table 4.

AMR in MRSA

The AMR profiles of the 234 strains of MRSA from 2016 to 2022 were shown in Table 5. All the strains

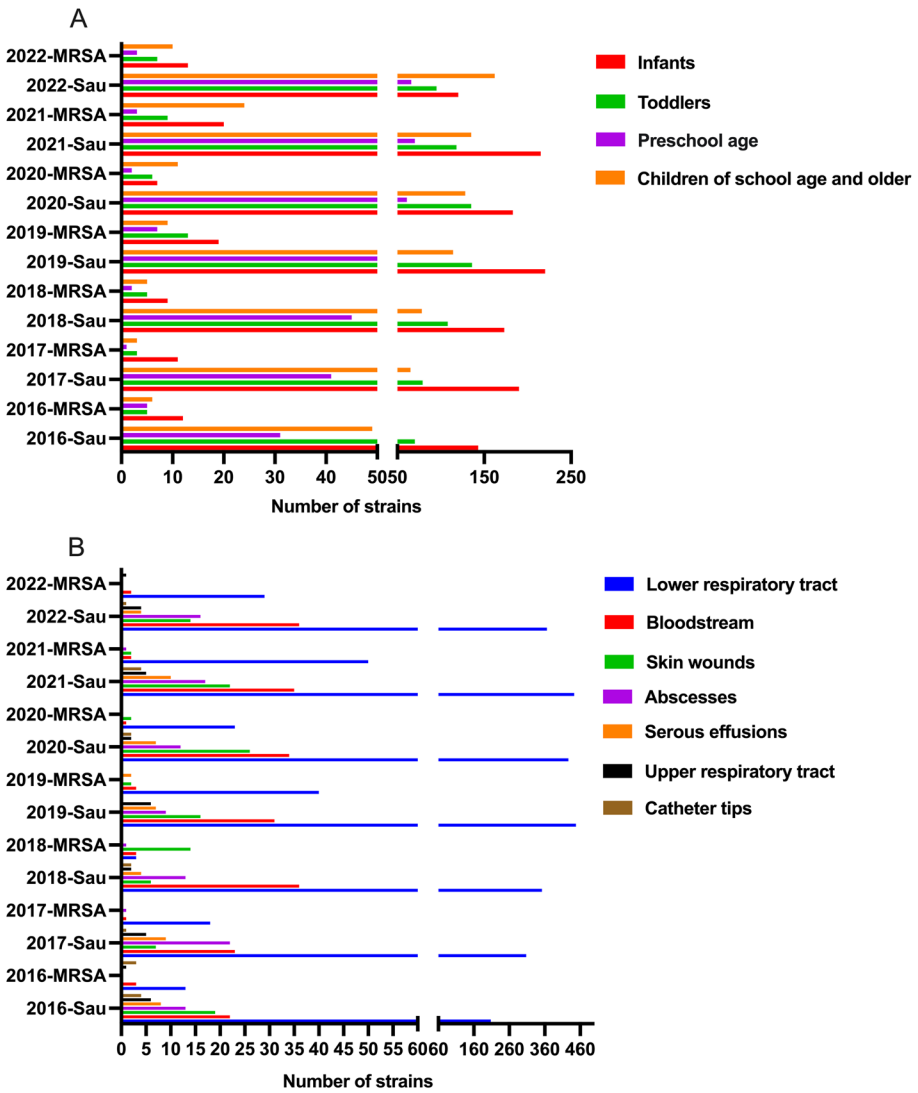

Fig. 3 The distribution of *S. aureus* and MRSA in age and infected sites. **A** shows the distribution of *S. aureus* and MRSA in age (**B**) shows the distribution of *S. aureus* and MRSA. Notes: Sau: *S. aureus*; MRSA: *methicillin-resistant S. aureus*

of MRSA were sensitive to vancomycin, linezolid, quinupristin/dalfopristin, and tigecycline.The annual changes in AMR of MRSA from 2016 to 2022 were shown in Table 5 and Fig. 5. Of these 234 strains of MRSA, 179 (76.5%) were resistant to erythromycin, 116 (49.6%) to clindamycin, 39 (16.7%) to tetracycline, 29 (12.4%) to levofloxacin, 27 (11.5%) to ciprofloxacin, 27 (11.5%) to moxifloxacin, 14 (6.0%) to TMP-SMX, eight (3.4%) to rifampicin, and six (2.6%) to gentamicin. The resistant rates of MRSA to erythromycin, clindamycin, and tetracycline varied considerably, but showed a similar increasing trend. The resistance trends of MRSA to levofloxacin, ciprofloxacin, and moxifloxacin were similar. The resistant rates of MRSA to TMP-SMX, rifampicin, and gentamicin did not exceed 10% after 2017. The significant differences in the AMR of MRSA to commonly used antimicrobials, except tetracyclin, between any 2 years from 2016 to 2022 were shown in Table 5.

Discussion

This is the first multi-center retrospective study, in which we retrospectively analyzed the profile and evolution of *S. aureus* in 17 PICUs in China from 2016 to 2022.

S. aureus is a very common human pathogenic microorganism that was first discovered in 1880 by Alexander Ogston, a Scottish surgeon. With the evolution of bacteria and the use of antimicrobial drugs, the AMR

Table 4 Resistance of *S. aureus* to commonly used antimicrobial drugs [Strain (%)]

Antimicrobial drugs	The year						
	2016	2017	2018	2019	2020	2021	2022
Penicillin G	251(93.7)^{a,b}	328(90.9)^{b}	388(92.1)^{a,b}	477(91.2)^{a,b}	471(87.5)^{a,b,c}	551(89.8)^{a,c}	462(93.3)^{c}
Benzocillin	126(47.0)^{a}	155(43.3)^{a}	162(44.1)^{a}	228(43.8)^{a}	197(38.0)^{a}	229(42.6)^{a}	188(42.0)^{a}
Erythromycin	167(60.8)^{a}	227(61.4)^{a}	248(59.3)^{a}	309(59.1)^{a}	292(56.3)^{a}	300(55.6)^{a}	232(51.8)^{a}
Clindamycin	126(42.4)^{a}	153(41.4)^{a}	182(43.4)^{a}	213(41.0)^{a}	207(40.0)^{a}	209(38.8)^{a}	145(32.7)^{a}
Cefoxitin	47(39.5)^{a,b,c}	99(54.7)^{c}	94(44.5)^{b,c}	83(38.0)^{a,b}	60(38.0)^{a}	88(35.7)^{b}	48(35.5)^{a}
Tetracycline	46(16.5)^{a,b}	56(15.1)^{a,b}	52(14.9)^{a,b}	83(19.8)^{b}	79(20.4)^{b}	48(12.8)^{a}	35(12.2)^{a}
Levofloxacin	15(5.7)^{a,b}	19(5.8)^{a,b}	28(7.4)^{a,b}	34(8.1)^{a,b}	29(5.7)^{a,b}	46(9.5)^{a,b}	31(8.3)^{a,b}
Ciprofloxacin	18(6.4)^{a}	19(5.1)^{a}	25(6.2)^{a}	29(6.9)^{a}	24(6.2)^{a}	26(7.0)^{a}	29(10.1)^{a}
Moxifloxacin	11(4.5)^{a}	15(4.8)^{a}	19(6.1)^{a}	26(6.5)^{a}	24(5.2)^{a}	40(8.8)^{a}	25(6.8)^{a}
TMP-SMZ	42(13.9)^{a}	52(14.2)^{a}	44(10.5)^{a,b}	46(8.8)^{a,b}	36(6.9)^{a,b}	37(6.9)^{b}	26(6.8)^{b}
Fosfomycin	2(2.1)^{a}	7(7.1)^{a}	1(0.8)^{a}	4(3.2)^{a}	3(2.2)^{a}	6(3.5)^{a}	3(3.7)^{a}
Rifampicin	9(3.2)^{a}	6(1.6)^{a,b}	5(1.2)^{a,b}	7(1.4)^{a,b}	8(1.8)^{b}	5(1.0)^{a,b}	5(1.2)^{a,b}
Gentamicin	28(9.3)^{a}	29(8.0)^{a,b}	22(5.3)^{a,b,c}	8(1.7)^{d}	19(3.7)^{b,c,d}	21(3.9)^{b,c,d}	10(2.2)^{c,d}
Vancomycin	0^{a}	0^{a}	0^{a}	0^{a}	0^{a}	0^{a}	0^{a}
Minocycline	0^{a}	4(3.7)^{a}	1(1.4)^{a}	3(4.5)^{a}	1(1.2)^{a}	6(3.6)^{a}	0^{a}
Nitrofurantoin	0^{a}	0^{a}	0^{a}	0^{a}	0^{a}	0^{a}	0^{a}
Linezolid	0^{a}	0^{a}	0^{a}	0^{a}	0^{a}	0^{a}	0^{a}
Quinopridin/Dafeptin	22(10.0)^{a}	33(12.5)^{a}	51(17.4)^{a}	46(13.3)^{a}	54(16.2)^{a}	48(15.1)^{a}	26(10.2)^{a}
Tigecycline	0^{a}	0^{a}	0^{a}	0^{a}	0^{a}	0^{a}	0^{a}

$^{a,\ b,\ c}$ The same letters between any 2 years indicate $P > 0.05$, whereas different letters between any 2 years indicate $P < 0.05$

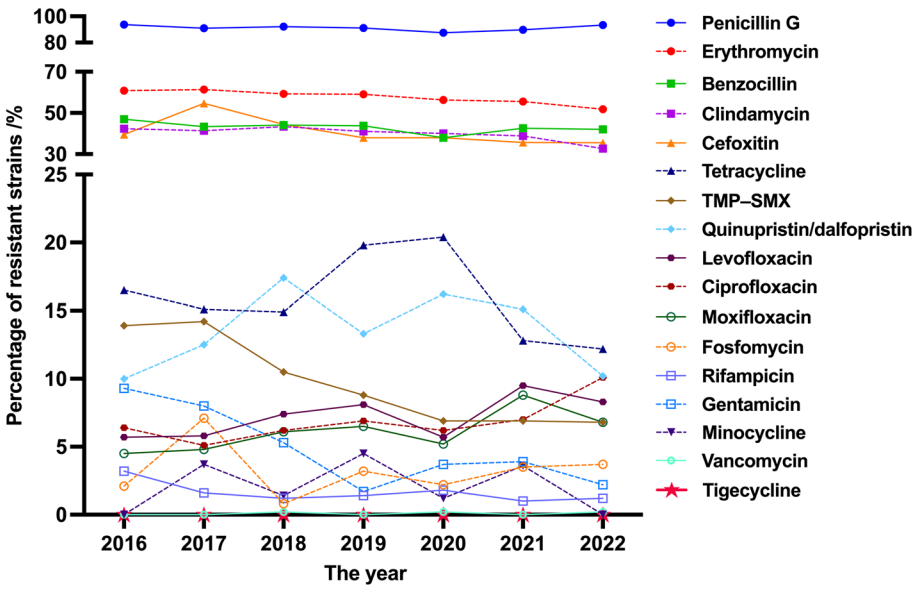

Fig. 4 Resistance of *S. aureus* to commonly used antimicrobial drugs

of *S. aureus*has gradually changed, especially after the emergence of MRSA, which has made the diagnosis and treatment more difficult [13, 14]. Children in ICUs are critically ill and vulnerable to be infected, so that *S. aureus*may cause significant morbidity and mortality in neonatal ICUs and PICUs [15]. Therefore, *S. aureus* in ICUs needs to be continuously monitored. A study in Germany found that the incidence of *S. aureus*and MRSA

Table 5 Resistance of MRSA to commonly used antimicrobial drugs [Strain (%)]

Antimicrobial drugs	The year						
	2016	2017	2018	2019	2020	2021	2022
Erythromycin	21(75.0)[a]	18(90.0)[a]	18(81.8)[a]	42(85.7)[a]	19(73.1)[a]	44(78.6)[a]	17(51.5)[a]
Clindamycin	9(34.6)[a]	9(45.0)[a]	9(40.9)[a]	37(75.5)[a]	14(53.8)[a]	27(48.2)[a]	11(34.4)[a]
Tetracycline	6(22.2)[a,b]	8(40.0)[b]	3(13.6)[a,b]	13(31.0)[a,b]	2(28.6)[a,b]	4(8.5)[a]	3(12.0)[a,b]
Levofloxacin	3(10.7)[a]	1(5.0)[a]	2(9.1)[a]	5(12.2)[a]	3(11.5)[a]	13(28.9)[a]	2(9.1)[a]
Ciprofloxacin	3(10.7)[a]	1(5.0)[a]	2(9.1)[a]	5(11.9)[a]	2(28.6)[a]	9(19.1)[a]	5(20.0)[a]
Moxifloxacin	3(10.7)[a]	0[a]	2(9.1)[a]	5(12.2)[a]	3(11.5)[a]	13(28.9)[a]	1(4.5)[a]
TMP-SMZ	4(14.3)[a]	2(10.0)[a]	1(4.5)[a]	2(4.1)[a]	1(3.8)[a]	2(3.6)[a]	2(6.1)[a]
Rifampicin	4(14.2)[a]	0[a]	1(4.6)[a]	1(2.1)[a]	1(3.8)[a]	0[a]	1(3.0)[a]
Gentamicin	3(10.7)[a]	0[a]	0[a]	1(2.0)[a]	0[a]	0[a]	2(6.1)[a]
Vancomycin	0[a]	0[a]	0[a]	0[a]	0[a]	0[a]	0[a]
Linezolid	0[a]	0[a]	0[a]	0[a]	0[a]	0[a]	0[a]
Quinopridin/Dafeptin	0[a]	0[a]	0[a]	0[a]	0[a]	0[a]	0[a]
Tigecycline	0[a]	0[a]	0[a]	0[a]	0[a]	0[a]	0[a]

[a, b]The same letters between any 2 years indicate $P > 0.05$, whereas different letters between any 2 years indicate $P < 0.05$

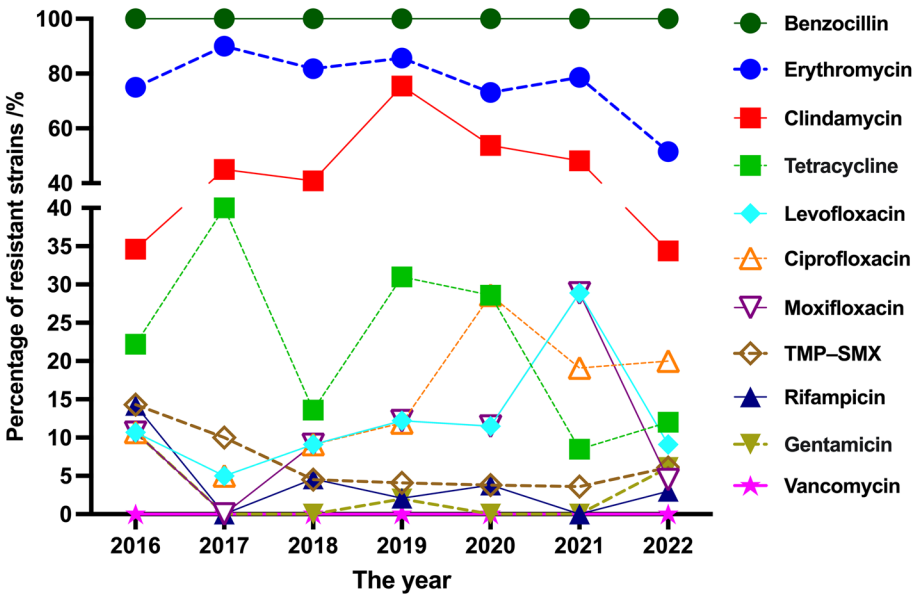

Fig. 5 Resistance of MRSA to commonly used antimicrobial drugs

decreased in hospitals over a 10-year period from 2007 to 2016, but gradually increased in ICUs, with a decrease incidence of MRSA (35.2% to 20.7%) [16]. The China Antimicrobial Surveillance Network (CHINET) reported that the incidence of MRSA in *S. aureus*decreased from 38.4% in 2016 to 30.0% in 2021 [17, 18]. In this study, during the 7 years, from 2016 to 2022, although the top 10 bacterial strains from the 17 PICUs were mainly gram-negative bacilli, *S. aureus* occupied the second place with an absolute advantage, with the incidence of MRSA ranged from 4.99% to 10.35%. The incidence of *S. aureus* in PICUs increased from 24.75% to 36.19%, whereas the incidence of MRSA decreased from 9.27% to 7.30%. Thus, the results of our study are similar to the findings of researches above.Few epidemiological studies have focused on *S. aureus* in PICUs alone, so our study may provide some reference value. The decreased incidence of MRSA in PICUs may be affected by pathogen surveillance and feedback systems and multidisciplinary management of antimicrobial drugs.

The incidence of *S. aureus*is very high [19, 20]. Many previous studies have reported gender differences in *S. aureus*bacteremia (SAB), with some studies showing a higher incidence of SAB in females than in males [21–25], Whereas some others studies have reported that there was no difference in the incidence of MRSA between the sexes [26–28]. In the study, there was no gender difference in the incidence of *S. aureus* and MRSA, which was consistent with the findings of See et al. and Campbell et al. [15, 29] It may be related to the origin of the subjects, the inherent biological differences between men and women, and social factors. Studies undertaken in pediatric wards have shown that the group infected by *S. aureus*is most common in infants [15], and the group infected by MRSA is most common in children younger than 5 year sold [30, 31]. Few studies have investigated the age distribution infected by *S. aureus* and MRSA in PICUs. In our study, both the group infected by *S. aureus* and MRSA were most common in infants. Multiple sites or organs in human can be infected by *S. aureus*. Comprehensive data from home and abroad showed that the most common infected site of MRSA is the respiratory tract (36.3%−48.0%), followed by the bloodstream (15%−35.7%), wounds or catheter exit sites (25.2%−44%), and the urinary tract (2.8%−28%), with the least common source of specimen being puncture fluid [31–33]. Wu et al. [34] reported that the top three most common infected sites of MRSA in children were the lower respiratory tract (58.28%), abscess (16.78%), and secretions (7.61%), and the least common specimen sources were cerebrospinal fluid and urine. Zhang et al. [35] found that MRSA was detected ranging from 40 to 50% in bloodstream infections with *S. aureus*. In the study, the most common infected site of *S. aureus* and MRSA was the lower respiratory tract, followed by the bloodstream and skin wounds. The least common infected sites of *S. aureus* and MRSA were "others" (including peritoneal dialysis fluid, drainage fluid and etc.) and the gastrointestinal tract, respectively. In summary, it can be seen that *S. aureus* is the main pathogen of respiratory tract whether at home or abroad, adults or children, general wards or intensive care units, and the same to MRSA. In this study, we also found that the incidence of *S. aureus* and MRSA in skin wounds was higher in children in PICU, which was mostly related to the colonization of Staphylococcus aureus on the skin surface.

AMR of *S. aureus* is a major concern and plays a decisive role in the clinical efficacy. There are many researches have reported the resistance of commonly used antimicrobial drugs of *S. aureus*. According to the CHINET report on trends in MRSA resistance from 2016 to 2021, all strains of MRSA were found to be sensitive to vancomycin, teicoplanin, and linezolid, with a decreased trend in resistance to erythromycin, clindamycin, tetracycline, levofloxacin, ciprofloxacin, moxifloxacin, TMP-SMX, gentamicin, and rifampicin [17, 18]. Studies about MRSA in pediatric patients, all strains of MRSA were sensitive to vancomycin and linezolid, and the highest resistant rate to erythromycin was 62%, followed by clindamycin (14%−57%), TMP-SMX (3%−24%), gentamicin (24%), rifampicin (12%), and minocycline (10%) [36, 37]. In this study, we also found that all the all strains of MRSA were sensitive to vancomycin, teicoplanin, and linezolid, with high resistant rates to erythromycin, clindamycin, and tetracycline but low resistant rates to relevofloxacin, ciprofloxacin, moxifloxacin, TMP-SMX, gentamicin, and rifampicin. We also found that the resistance of MRSA to commonly used antimicrobials showed an overall downward trend with wide year-to-year variations, except clindamycin and quinolone antibiotics. The resistant rate of MRSA to clindamycin increased from 34.6% in 2016 to 75.5% in 2019, and then decreased back to 34.4% in 2022. We analysed that the fluctuations resistant rate of MRSA varied widely to these antimicrobials, possibly related to the usage of the drugs. Studies have shown that strains from different sources may exhibit different sensitivity to antimicrobial, and bloodstream-derived MRSAs are more susceptible to drug resistance than than skin-derived and soft tissue-derived MRSAs [38]. Liang et al. [39] reported that resistant rates to gentamicin and ciprofloxacin were significantly higher in MRSAs from the respiratory tract than those from skin and soft tissues or blood.

For staphylococci, resistance to drugs can either develop by horizontal transfer of resistance determinants encoded by mobile genetic elements viz plasmids, transposons and the staphylococcal cassette chromosome or by mutations in chromosomal genes. Horizontally acquired resistance can occur by one of them: enzymatic drug modification and inactivation, enzymatic modification of the drug binding site, drug efflux, bypass mechanisms involving acquisition of a novel drug-resistant target, displacement of the drug to protect the target. Acquisition of resistance by mutation can result from alteration of the drug target that prevents the inhibitor from binding, derepression of chromosomally encoded multi-drug resistance efflux pumps and multiple stepwise mutations that alter the structure and composition of the cell wall and/or membrane to reduce drug access to its target. The development of resistance to many antibiotics by *S. aureus*has involved acquisition of determinants by horizontal gene transfer of mobile genetic elements [40]. Vancomycin was the first choice for pneumonia patients with hospital-acquired MRSA. Recent evidence suggests that the minimum inhibitory concentration for vancomycin is increasing and linezolid is another option [41]. The standard treatment for MRSA bacteremia is vancomycin

or daptomycin. But, the efficacy is limited and there are many disadvantages such as poor tissue permeability and slow killing time. Another strategy is to combine the standard regimen with other drugs, such as antistaphylococcal β-lactam (ASBL). However, whether the combination has obvious better outcomes is still inconclusive [5]. The drug resistance of *S. aureus* inevitably change. Therefore, it is necessary to understand its drug resistance changes in specific areas. Now, there are few studies on the mechanism of S. aureus resistance in PICUs. In this study, the resistance mechanism of *S. aureus* was not explored, which is a major regret. It is planned to be explored in the follow-up related research work.

This study has certain limitations, due to the lack of relevant information that has not been fully matched with clinical data, such as primary disease, seasonal correlation, geographical correlation, isolation of colonized bacteria and pathogenic bacteria, and the difference between community-acquired and hospital-acquired bacteria, etc. We will gradually optimize the CHIPS to incorporate the relevant information in the later data so that these questions will be answered in future studies.

Conclusions

In this study, the 7-year surveillance of bacterial strains in 17 PICUs in China revealed that although gram-negative bacilli were the predominant etiological agents of infections, *S. aureus*, a gram-positive bacterium, ranked second in frequency. Infants were most susceptible to S. *aureus* and MRSA, and the lower respiratory tract was the most common infected site. *S. aureus* showed the highest resistant rate to penicillin G, followed by erythromycin, benzathine, cefoxitin, and clindamycin. The resistant rates of *S. aureus* to levofloxacin, ciprofloxacin, and moxifloxacin were less than 10%, to fosfomycin, rifampicin, and minocycline were less than 5%. MRSA showed a highly resistance to erythromycin and clindamycin, but the resistant rates to tetracycline, levofloxacin, ciprofloxacin, moxifloxacin, TMP-SMX, rifampicin, and gentamicin were low. No strains resistant to vancomycin, linezolid and tigecycline were found in this study, but the supervision of these antimicrobial drugs should not be ignored, and they should be used rationally to maintain the last line of defense in the treatment of *S. aureus*. When considering to be infected by *S. aureus* clinically, it is necessary to select antimicrobial drugs reasonably based on the age, infected site, and local epidemiological characteristics.

Abbreviations

PICU	Pediatric intensive care units
CHINET	China antimicrobial surveillance network
CLSL	Clinical and laboratory standards institute
S. aureu	*Staphylococcus aureus*
AMR	Antimicrobial resistance
MSSA	*Methicillin-sensitive staphylococcus aureus*
MRSA	*Methicillin-resistant staphylococcus aureus*
CHIPS	China paediatric intensive care unit pathogen surveillance network
DST	Drug susceptibility testing
TMP-SMX	Sulfamethoxazole-trimethoprim
GM +	Gram-positive
SAB	*Staphylococcus aureus* Bacteremia

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Authors' contributions

X.L. Zhang, J. Liu, and P. Fu contributed equally to this work as co-first authors. X.L. Zhang, J. Liu, and P. Fu wrote the first manuscript and revised verson. C.Q. Wang, G.P. Lu, and G.F. Yan conceptualized and designed the study, and took responsibility for the integrity of the whole work. The others performed the collection, analysis, and interpretation of data. All authors contributed to the article and approved the submitted version.

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Data availability
Data and materials used in this work are available from the corresponding author upon request.

Declarations

Ethics approval and consent to participate
The study was approved by the institutional review board at the Children's Hospital of Fudan University in Shanghai, and the requirement for informed consent was waived (approval number [2021] 431). The study strictly adheres to the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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