Infection and Drug Resistance

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ORIGINAL RESEARCH

Bacterial Epidemiology and Antimicrobial Resistance in Children in Shandong Province, China, 2017–2022: A Multicentre Retrospective Study

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Introduction: Bacterial antimicrobial resistance is becoming increasingly serious, but there are very limited studies in children. Shandong Province Pediatric bacterial & fungal Antimicrobial Resistance Surveillance System (SPARSS) program was established in 2017 to monitor and analyze the trends of bacterial epidemiology and antimicrobial resistance in children. Clinical bacterial isolates were collected from 59 tertiary hospital in Shandong Province China during 2017 to 2022.

Methods: We conducted a retrospective analysis of bacterial distribution and resistance patterns, utilizing data from the SPARSS network and analyzed with WHONET 5.6 software.

Results: A total of 185,274 isolates were collected, and the top 5 bacteria were *Staphylococcus aureus* (19.0%), *Escherichia coli* (12.8%), *Streptococcus pneumoniae* (12.3%), *Haemophilus influenzae* (11.0%) and *Klebsiella pneumoniae* (7.1%). In the composition of strain specimens, most of the strains came from the respiratory tract (59.8%), followed by pus (11.4%). The resistance rate of *Staphylococcus spp*. to penicillins remains high at 90%, while the resistance rate to linezolid is low but shows an upward trend. Vancomycin-resistant strains have emerged in *Enterococcus spp*. which due to its complex genetic structure, possesses inherent resistance to most drugs. The resistance rate of *Enterobacter spp*. to meropenem remains low, although it exhibits a high resistance rate to β-lactams. Notably, carbapenem-resistant *Salmonella spp*. has been identified since from 2022. *Acinetobacter baumannii* and *Pseudomonas aeruginosa* demonstrate high drug resistance to most antibiotics. *H. influenzae* and *Moraxella catarrhalis*, primarily isolated from respiratory tract samples, show an increasing trend in β-lactamase-producing strains annually. The detection rates of multi-drug-resistant bacteria, including MRSA, CREO, CRKP, CRPA, and CRAB, have been decreasing annually, with their distribution varying among children of different ages. The resistance rate of *Candida tropicalis* to fluconazole was 43.6%, which was much higher than the detection rate of adults in China and Europe.

Discussion: Despite restrictions on antibiotic use in China, the situation of bacterial drug resistance remains critical, particularly in children. Therefore, long-term monitoring of bacterial drug resistance in this population is essential to develop effective strategies for the early and accurate treatment of childhood infections.

Keywords: bacteria, antimicrobial resistance, children, China, Multi-Drug-Resistant Organisms, MDROs

Introduction

Bacterial antimicrobial resistance (AMR) is becoming increasingly serious with the unreasonable use of antibiotics, which is a serious threat to human public health security.[1] It has been estimated to cause 10 million deaths worldwide by year 2050 if the current trend of inappropriate and excessive use of antibiotics continues.[2] In addition to being associated with a high mortality rate, bacteria AMR imposes a significant financial burden on health-care systems. For instance, in

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the United States, more than 2.8 million multidrug-resistant (MDR) bacterial infections occur annually, causing at least 35,000 deaths and $20 billion in health-care expenditures.[3] So, both preventing bacterial AMR and increasing microbiological laboratory and data collection capacity to improve scientific understanding of this health threat should be a very high priority for global health policy makers. Although there has been a lot of testing in the world to detect the prevalence of AMR and MDR bacteria in humans, such as Global Antimicrobial Resistance and Use Surveillance System (GLASS), European Antimicrobial Resistance Surveillance Network (EARS-Net), CARSS (China Antimicrobial Resistance Surveillance System) and CHINET (China Antimicrobial Surveillance Network),[4–6] there are very limited studies in children,[7] and the quality of published studies assessing the distribution of Multi-Drug-Resistant Organisms (MDROs) in children is mixed. At the same time, there is no monitoring data report on the rate of fungal resistance in children for consecutive years from China. Therefore, AMR surveillance network unique to children is essential for pediatric antimicrobial stewardship. To focus on the AMR surveillance in pediatric patients, we established the Shandong Province Pediatric bacterial and fungal Antimicrobial Resistance Surveillance System (SPARSS) program in 2017, which currently comprises 59 hospitals. We presented a large amount of bacteria data in the past six years from SPARSS and made a comprehensive analysis on the evolution of bacteria epidemiology and the AMR profiles.

On the basis of our data, we analyzed the bacterial epidemiology and resistance profiles of primary pathogens in Shandong Province's children from 2017 to 2022 for the first time, analyzed the MDROs distributions with time and/or with age, and described MDROs' potential threaten to children, especially to the low-immunity neonates. Our study will be very useful to guide the anti-infection therapy in Shandong Province's children as well as the worldwide pediatric patients.

Materials and Methods

Enrollment of Bacteria and Patients

During 2017 to 2022, all unduplicated aerobic bacteria were collected from 59 tertiary hospitals in Shandong Province, China. For the repeated strains: only the first isolate from the same species and the same patient was enrolled in this study.

Neonatal patients were defined as the discharge with age in days between 0 and 28 days (inclusive), while non-neonatal patients were defined as the children with 29 days to 18 years (exclusive).

Isolate Inclusion and Exclusion Criteria

Unified standard was conducted stringently in each hospital. Inclusion and exclusion criteria from different samples were conducted as follows. Respiratory tract includes: upper respiratory tract specimens (throat swabs) and lower respiratory tract specimens (sputum and BALF). All α-hemolytic *Streptococcus spp*. were excluded, except *Streptococcus pneumoniae*. Blood: all unduplicated aerobic bacteria collected from blood culture were involved. Stool: only enteropathogenic bacteria were involved. Urine: only involved the bacteria $>10^4$ colony forming units (CFU)/mL and the bacterial species were ≤ 2.

Strain Identification

We used Matrix assisted laser desorption ionization (MALDI) TOF MS to identify the strains.

Antimicrobial Susceptibility

Antimicrobial susceptibility test was carried out using Kirby-Bauer method or automated systems interpreted according to the criteria of Clinical and Laboratory Standards Institute (CLSI) 2024 breakpoints.[8] Penicillin susceptibility of *S. pneumonia* was detected by E-test, its breakpoint in meningitis and nonmeningitis samples were different.

CRE were defined as the *Enterobacteriaceae spp*. strains, which presented resistance to one of ertapenem, imipenem or meropenem. CRAB and CRPA were identified as imipenem or meropenem resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. Penicillin-nonsusceptible *S. pneumoniae* (PNSP) was defined as penicillin-intermediate or resistant. PNSP was tested using penicillin E-test and interpreted according to 2024 CLSI standard.

β-Lactams Test

Oxoid™ touch stick β-lactams product was used to detect the β-lactams activity according to the instructions. This product exhibits a rapid distinctive color change from yellow to red. Positive result was defined as yellow to pink-red color change of the disk. Negative result was considered as no color change. Positive control: *Staphylococcus aureus* ATCC 29213 or the β-lactams product positive strain has been confirmed in the lab; negative control: *Haemophilus influenzae* ATCC 10211 or the β-lactams product negative strain has been confirmed in the lab.

Reference Strains

S. aureus ATCC 29213, *Escherichia coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 were included to ensure reproducibility of the antibiotic susceptibility testing procedure.

Statistical Analysis

Statistics analyses were performed using GraphPad Prism 7.0 (GraphPad Software, Inc., San Diego, California, USA). Differences among the groups were analyzed with independent samples *t* test. Two side P values of less than 0.05 were considered as statistically significance.

Results

Distribution of Clinical Isolates

From 2017 to 2022, a total of 185,274 bacterial strains isolated from children were enrolled in the SPARSS program, of which 3.2% (5,886) were collected from outpatients and 96.8% (179,388) were collected from inpatients. There were 77,804 Gram-positive bacteria (42.0%) and 105,110 Gram-negative bacteria (56.7%). The top 10 bacteria were *S. aureus* (19.0%), *E. coli* (12.8%), *S. pneumoniae* (12.3%), *H. influenzae* (11.0%), *Klebsiella pneumoniae* (7.1%), *Moraxella catarrhalis* (6.4%), *P. aeruginosa* (4.6%), *A. baumannii* (3.2%), *Enterobacter cloacae* (2.6%), and *Staphylococcus epidermidis* (2.3%). In the composition of strain specimens, most of the strains came from the respiratory tract (59.8%), followed by pus (11.4%), blood specimen (7.1%) and urine specimen (4.7%) (Table S1). Notably, the constituent proportion in the respiratory tract dropped from 64.18% in 2017 to 53.28% in 2022. Compared to other specimen types, there have been significant changes in the composition of respiratory tract specimen strains over the past six years. The proportion of *H. influenzae* and *S. pneumoniae* in respiratory specimens decreased significantly in 2020, while the proportion of *S. aureus* increased markedly (Figure 1A). The proportion of *M. catarrhalis* reached its peak in 2020, and overall, there was a decreasing trend in the proportions of *E. coli* and *K. pneumoniae* in respiratory specimens. The *E. coli* in pus samples and urine samples are the most frequently detected bacteria. In blood samples, the main bacteria detected are *S. epidermidis* and *Staphylococcus hominis,* the main bacteria detected are *E. coli* and *Enterococcus faecium* in urine specimen and in the pus specimen it is mainly *E. coli* and *S. aureus* (Figure 1B–D).

AMR Trends in Main Bacteria

Staphylococcus spp

S. aureus exhibits the highest resistance rate to penicillin G at 95.8%, with no declining trend observed in recent years. The resistance rate to oxacillin is 28.3% and remains stable, showing a relatively stable trend. In contrast, there has been a declining trend in resistance rates to aminoglycosides and fluoroquinolones. Coagulase-negative staphylococci (CoNS) has the highest resistance rate to penicillin G (93.2%), but there has been a gradual decrease in recent years (P=0.0129). Additionally, there is a downward trend in resistance rates to erythromycin (P=0.0034), trimethoprim-sulfamethoxazole (SXT) (P<0.0001). The resistance rates of *S. aureus* and CoNS to linezolid are generally low, and no vancomycin-resistant *Staphylococcus. spp*. was identified. Overall, CoNS exhibits a higher resistance compared to *S. aureus* (Table S2).

The prevalence of antibiotic resistance in Methicillin-resistant *S. aureus* (MRSA) is generally higher than that in Methicillin-sensitive *S. aureus* (MSSA), with a statistically significant difference (P< 0.05). However, the resistance rates to gentamicin and SXT in MRSA are lower than those in MSSA, with no significant differences in resistance rates to

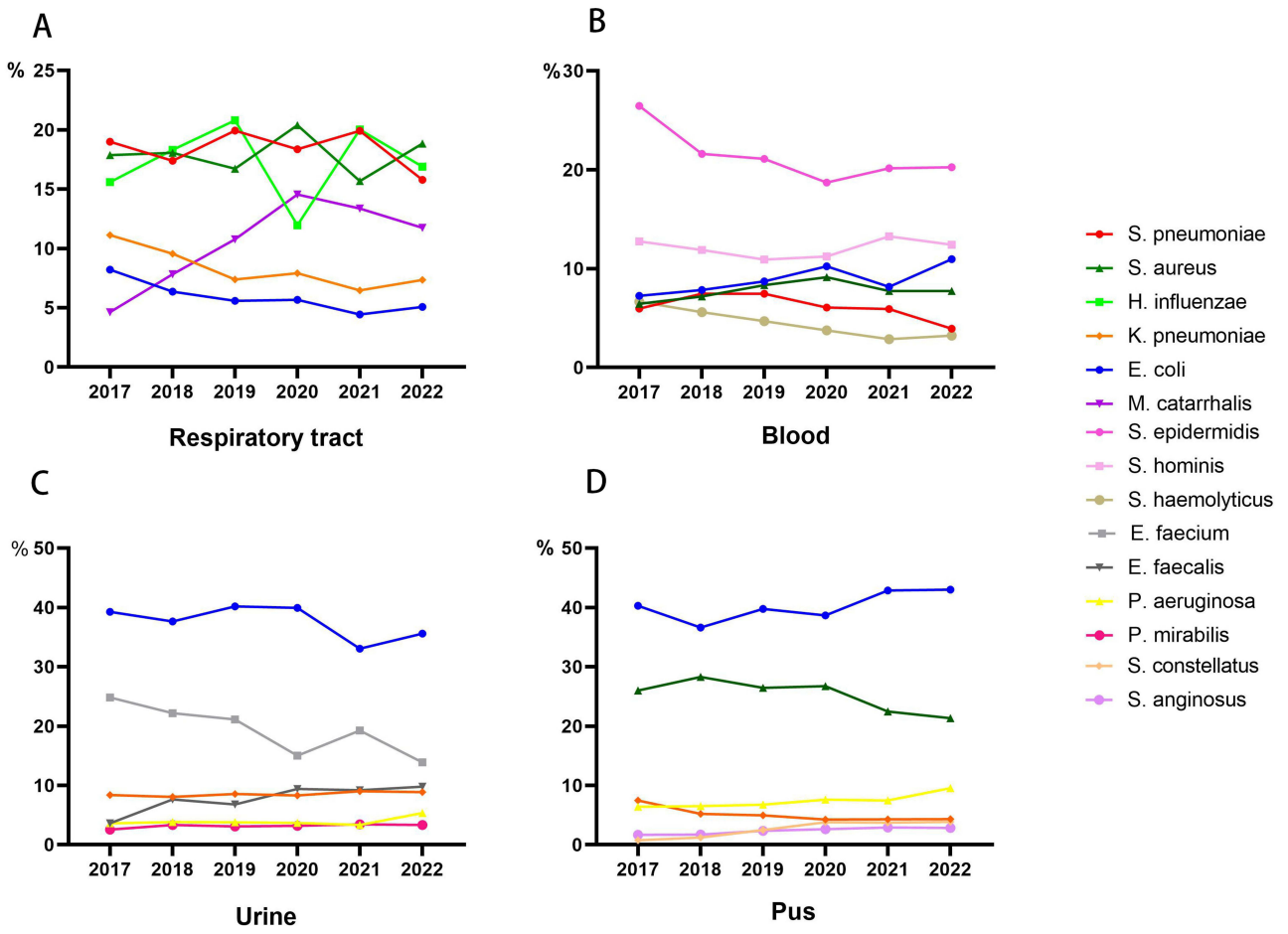

Figure 1 Distributions of the top six pathogens from different specimens reported by the SPARSS program in 2017 to 2022. (**A**) Distributions of the top six pathogens from respiratory tract; (**B**) Distributions of the top six pathogens from blood; (**C**) Distributions of the top six pathogens from urine; (**D**) Distributions of the top six pathogens from pus.

levofloxacin and moxifloxacin between MRSA and MSSA. There is no significant decreasing trend in resistance rates of MRSA to SXT (P=0.926), ciprofloxacin (P=0.0764), and rifampin (P=0.183). In MSSA, there is no significant decreasing trend in resistance rates to penicillin, but there is a decreasing trend in resistance rates to erythromycin, clindamycin, tetracycline and fluoroquinolones (P<0.05) (Table 1).

Streptococcus spp

S. pneumoniae and *Streptococcus pyogenic* are highly sensitive to penicillin, while *Streptococcus mitis* exhibits lower sensitivity to penicillin compared to the first two. All three species demonstrate relatively high resistance to clindamycin and erythromycin, with *S. pneumoniae* and *S. pyogenic* being more pronounced. *S. mitis* has a significantly higher resistance rate to levofloxacin than the others. The resistance rate of *S. pneumoniae* to SXT and ceftriaxone remains relatively stable, while the resistance rate of *S. pyogenic* to levofloxacin has shown a downward trend over the years (P<0.0019) (Table S3).

Enterococcus spp

The resistance of *E. faecium* is generally higher than that of *E. faecalis* (except for tetracycline). Both species show low rates of vancomycin resistance, no *E. faecalis* strains resistant to linezolid were found, but resistant strains of *E. faecium* do exist. The resistance rates of *E. faecalis* to high concentrations of gentamicin, ciprofloxacin, and levofloxacin have been decreasing annually (P<0.05). In contrast, *E. faecium* shows a decreasing trend in resistance rates to tetracycline, erythromycin, ampicillin, and penicillin (P<0.05) (Table S4).

Table 1 AMR Profiles of MRSA and MSSA Reported by SPASS Program in Shandong Province, China, 2017 to 2022

Antibiotic Name	MRSA (n=8,746)									MSSA (n=26,443)									MRSA vs MSSA	
	2017	2018	2019	2020	2021	2022	Total	χ^2	*P*	2017	2018	2019	2020	2021	2022	Total	χ^2	*P*	χ^2	*P*
Penicillin G	100	100	100	100	100	100	100	–	–	93.4	93.9	94.8	94.6	94.9	94.1	94.3	3.552	0.0595	–	–
Erythromycin	87.1	86.8	84.4	79.1	77.7	77.9	82.2	82.4	<0.0001	71.4	72.6	73.4	67.3	65.7	67	69.8	67.33	<0.0001	492	<0.0001
Clindamycin	78.8	75.6	72	69.5	70.7	65.8	72	61.52	<0.0001	52.3	51.6	49	49.9	50.2	42.7	49.2	54.58	<0.0001	1315	<0.0001
Tetracycline	29.5	28.4	23.5	22.5	20.4	17.7	24.1	55.9	<0.0001	12.8	10.5	7.6	6.2	6.3	5.9	8.5	132	<0.0001	1099	<0.0001
SXT	4.7	3.6	4.1	4.5	4.9	3.2	4.2	0.008623	0.926	19.8	18.3	16.8	15.2	16.6	13.5	16.6	53.15	<0.0001	835.5	<0.0001
Gentamicin	4.5	4.2	3.2	3.9	2.7	2.9	3.5	7.696	0.0055	16.6	14.4	12.7	8.7	7.8	6.6	11.1	296.9	<0.0001	444.5	<0.0001
Ciprofloxacin	6.8	6.1	5.5	5	4.8	5.8	5.7	3.14	0.0764	5.8	4.8	5.8	3.3	3.8	3.8	4.7	23.6	<0.0001	11.07	0.0009
Levofloxacin	6.3	4.9	4	4.6	3.3	4.9	4.6	4.405	0.0358	5.6	4.6	5.8	4.1	4.1	4.1	4.7	12.21	0.0005	0.141	0.7073
Moxifloxacin	4	4.5	3.7	4.2	2	3.5	3.6	5.252	0.0219	4.6	3.7	4.8	3.5	3.4	3.2	3.9	10.31	0.0013	1.317	0.2511
Rifampin	1.2	1.3	1.3	1	0.5	1.1	1.1	1.773	0.183	0.7	0.6	0.8	0.4	0.4	0.2	0.5	13.41	0.0002	34.79	<0.0001
Vancomycin	0	0	0	0	0	0	0	–	–	0	0	0	0	0	0	0	–	–	–	–
Linezolid	0	0	0	0.2	0	0.2	0.1	–	–	0	0	0	0	0	0	0	–	–	–	–

Abbreviations: MRSA, Methicillin-resistant *S. aureus*; MRSA, Methicillin-sensitive *S. aureus*; SXT, Trimethoprim/Sulfamethoxazole.

Enterobacteriaceae spp

E. coli and *K. pneumoniae* have shown a declining trend in resistance to most antibiotics ($P<0.05$). The resistance of *E. coli* to tigecycline, amikacin, meropenem, and cefoxitin remains relatively stable, while *K. pneumoniae* exhibits consistent resistance to levofloxacin, ciprofloxacin, amikacin, and meropenem. The proportion of carbapenem-resistant *E. coli* (CREO) is 1% (302/23,790), whereas the proportion of carbapenem-resistant *K. pneumoniae* (CRKP) is 6.2% (813/13,129) (Table S5).

Non-Fermentative Gram-Negative Bacilli

The antibiotic resistance rates of *A. baumannii* against cefepime, ceftriaxone, levofloxacin, meropenem, and imipenem have shown a declining trend over the years ($P<0.05$). In contrast, *P. aeruginosa* exhibits stable resistance rates against levofloxacin, ciprofloxacin, and gentamicin. The proportion of carbapenem-resistant *A. baumannii* (CRAB) is 20.8% (1218/5845), while the proportion of carbapenem-resistant *P. aeruginosa* (CRPA) stands at 8.7% (750/8595) (Table S6).

Fastidious Bacteria

The antibiotic resistance rates of *H. influenzae* to levofloxacin remain relatively low and exhibit a consistent annual downward trend ($P<0.05$). However, the prevalence of β-lactamase-producing strains is on the rise ($P<0.05$). The resistance rates to amoxicillin-clavulanate, cefotaxime, chloramphenicol, and SXT are decreasing over the years ($P<0.05$). In contrast, there is an increasing trend in resistance rates to ampicillin-sulbactam and cefuroxime, while the rare strains β-lactamase negative ampicillin resistance (BLNAR) *H. influenzae* is also becoming more prevalent annually ($P<0.05$). For *M. catarrhalis*, the resistance rate to chloramphenicol remains low without a significant upward trend. Nevertheless, the emergence of β-lactamase-producing strains is increasing annually ($P<0.05$). Resistance rate to SXT is also on the rise, whereas resistance to amoxicillin-clavulanate, cefuroxime, cefotaxime, and levofloxacin, have shown a downward trend over the years ($P<0.05$) (Table S7).

Salmonella spp

The resistance rates of *Salmonella spp*. to ampicillin, ceftriaxone, and Aztreonam have been increasing over the years ($P<0.05$). The resistance rate to carbapenems remains at a relatively low level, but resistant strains have emerged. The resistance rates to combination formulations such as ampicillin/sulbactam, piperacillin/tazobactam, and cefoperazone/sulbactam have remained stable, with piperacillin/tazobactam showing a lower resistance rate (0.7~2%). The resistance rate to ampicillin/sulbactam remains at a high level (Table 2). Notably, the detection rate of carbapenem resistant *Salmonella spp*. in 2022 is as high as 0.5%, which deserves further attention and research.

Table 2 AMR Profiles of *Salmonella spp*. Reported by SPARSS Program in Shandong Province, China, 2017 to 2022

Antibiotic Name	*Salmonella spp*. (n=2,821)								
	2017	2018	2019	2020	2021	2022	Total	χ^2	P
Ampicillin	78	72.6	76.2	76.2	82.4	82.3	78.2	7.979	0.0047
Imipenem	0	0	0	0	0	0.5	0.1	–	–
Ertapenem	0	0.7	0	0.4	0	0.6	0.3	–	–
Cefepime	15.4	9.7	11.7	11.7	16.4	13.2	12.9	0.8279	0.3629
Ceftriaxone	22.4	17.4	21.4	22.4	31.1	24.8	23.7	7.242	0.0071
Ceftazidime	14.6	11.5	11.4	12.8	19.4	12.8	13.8	1.668	0.1965
Aztreonam	17.8	14	18.5	18	27	24.2	20.3	10.77	0.001
Levofloxacin	14.5	6.1	6.1	10.5	13.6	10.6	9.9	1.507	0.2196
Ciprofloxacin	27.4	25.6	17	23.2	19.5	7.3	22.9	0.4047	0.5247
Ampicillin/Sulbactam	56.8	62	65.6	64.1	66.8	63.7	63.7	1.362	0.2432
Piperacillin/tazobactam	0.7	2	0.8	1.8	1.8	1.7	1.5	0.5065	0.4767
SXT	26.5	30.5	26.3	24.9	27.9	26.2	26.8	0.2508	0.6165

Abbreviation: SXT, Trimethoprim/Sulfamethoxazole.

Change Trend in MDROs Resistance

We have conducted an analysis on the drug resistance changes of four types of MDR bacteria, namely CREO, CRKP, CRAB, and CRPA. CREO has a significantly lower resistance rate to amikacin compared to other antibiotics. In 2020, the resistance rates of CREO to most antibiotics decreased to their lowest levels (except for ciprofloxacin and SXT), but in 2021, they increased back to the original levels or even higher (Figure 2A). For CRKP, the resistance rates to ciprofloxacin, levofloxacin, gentamicin, amikacin, and tobramycin showed a decreasing trend from 2017 to 2018, but after 2018, they started to increase. Among them, the resistance rate to levofloxacin decreased in 2021, while the rates for ciprofloxacin and gentamicin decreased in 2020, but ciprofloxacin showed an increasing trend after 2021 (Figure 2B). CRAB had resistance rates to most antibiotics above 40%, with the highest resistance rate to ciprofloxacin. The resistance rates of CRAB to fluoroquinolones, ciprofloxacin and levofloxacin increased in 2017, remained relatively stable from 2018 to 2021, and showed a decreasing trend in 2022. The resistance rates of CRAB to amikacin and tobramycin with an overall decreasing trend, reaching their lowest points in 2019 (Figure 2C). The trends of CRPA resistance to fluoroquinolones (ciprofloxacin, levofloxacin), aminoglycosides, and piperacillin-tazobactam were similar, increasing from 2017 to 2018, decreasing from 2018 to 2019, increasing from 2019 to 2021, and decreasing in 2022 (Figure 2D).

We analyzed the annual proportions of MRDOS. Except for MRSA, which showed no significant trend, there was a noticeable year-on-year decline in CREO, CRKP, CRAB, and CRPA. The proportion of fluconazole resistant *Candida tropicalis* (FRCT) increased significantly in 2019, followed by a steady decline in the subsequent years (Figure 3A).

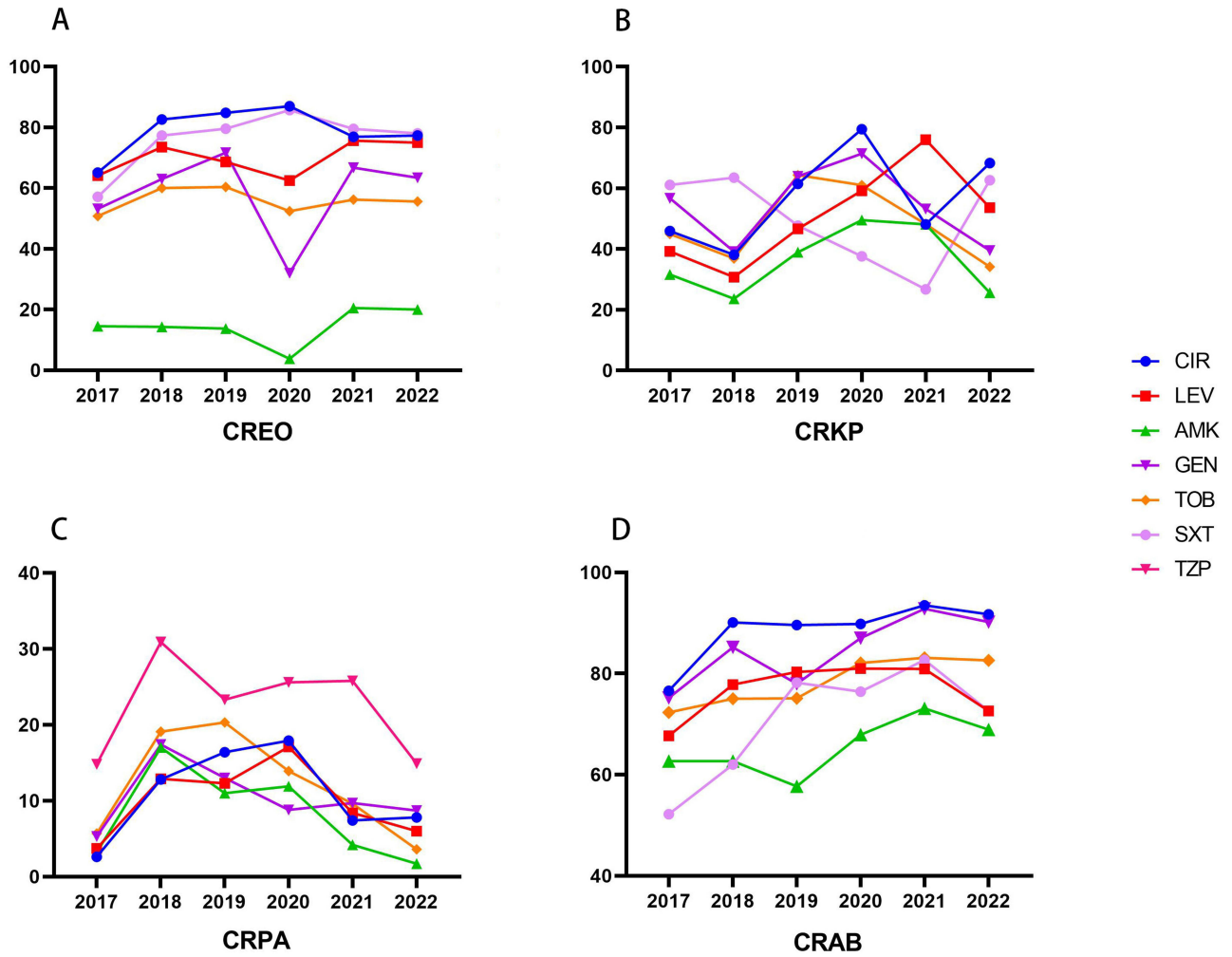

Figure 2 AMR rates of carbapenem-resistant strains reported by the SPARSS Program, 2017 to 2022. (**A**) AMR rates of CREO; (**B**) AMR rates of CRKP; (**C**) AMR rates of CRAB; (**D**) AMR rates of CRPA.

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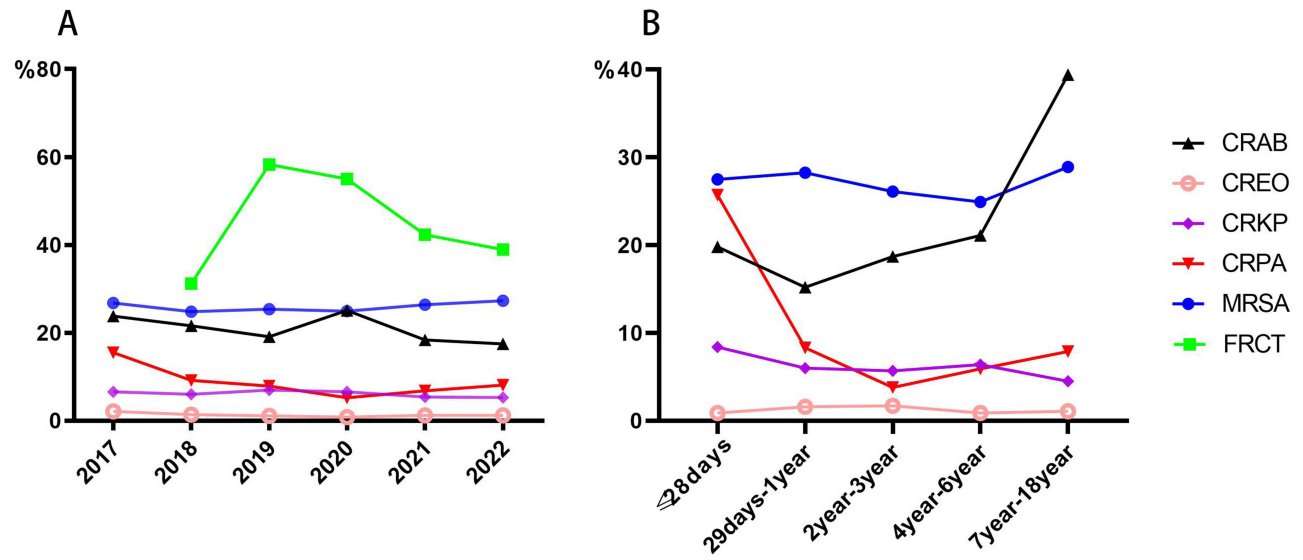

Figure 3 Distribution trends of MDROs as reported by the SPARSS program, 2017 to 2022. (**A**) Distribution trends of MDROs year-by-year; (**B**) Distribution trends of MDROs in different age groups.

CRPA was found to be more prevalent in newborns compared to other age groups, while MRSA showed a higher prevalence among school-aged children. CRAB was significantly more common in school-aged children than in other age groups. In contrast, CRKP exhibited a relatively even distribution across different age groups, with no significant differences observed. CREO maintained a consistently low proportion across all age stages (Figure 3B).

Discussion

Children are major consumers of antimicrobial agents and have high rates of AMR, due to their underdeveloped immune systems make them more susceptible to infectious diseases. The limited use of antibacterial drugs in children has led to the widespread use of carbapenems in children, this antibiotic pressure caused the detection rate of CRE was also higher in children than in adults.[9] Long-term global and national surveillance of AMR trends is thus required to guide the clinic anti-infection treatment. To our knowledge, we firstly described and analyzed the overall AMR profiles of common bacteria isolated from children in Shandong Province, China, indicating that MDROs (which include MRSA, CREO, CRKP, CRAB, and CRPA) were commonly detected from children and presented much higher antimicrobial resistance compared with the sensitive strains. During 2017 to 2022, a total of 185,274 bacteria were enrolled in SPARSS Program, the top ten predominant bacteria isolated from children were *S. aureus, E. coli, S. pneumoniae, H. influenzae, K. pneumoniae, M. catarrhalis, P. aeruginosa, A. baumannii, E. cloacae* and *S. epidermidis*.

According to statistics,[10] respiratory tract infections are the most significant infectious disease factor affecting children's health. Most bacteria we isolated were derived from respiratory specimens (>50%), with the highest proportion being *S. pneumoniae* (19.0%, 21,059/110,720), followed by *H. influenzae* (17.79%, 19,702/110,720). From 2017 to 2022, the proportions of *S. pneumoniae* and *H. influenzae* isolated from respiratory specimens showed a decline in both 2020 and 2022. This phenomenon is associated with the strict COVID-19 containment measures (for example, attending classes at home) implemented in Shandong Province, which not only reduced the transmission rate of COVID-19 but also decreased the spread of other microorganisms transmitted through respiratory secretions. However, the percentage of *M. catarrhalis*, a common cause of respiratory infections,[11] showed an increasing trend from 2017 to 2019, followed by a gradual decline from 2020 to 2022. This trend does not align with that of *H. influenzae* and *S. pneumoniae*, and it also differs from data reported in Xiangtan City, Hunan Province.[12] Aside from respiratory specimens, there were no significant changes in the percentage of bacteria detected in other specimen types, suggesting that the hospital from which our data was sourced was not significantly impacted by COVID-19, leading to a stable dataset.

S. pneumoniae is the most detected bacterium in respiratory specimens. Despite the availability of effective vaccines such as pneumococcal conjugate vaccines (PCV) and the 23-valent pneumococcal polysaccharide vaccine (PPV23), the vaccination rate remains low in China due to the high cost of these vaccines,[13] posing a significant threat to children's health. Our study identified a total of 22,772 strains of *S. pneumoniae*, which exhibited high resistance to macrolide antibiotics and SXT, while showing relatively low resistance to β-lactam antibiotics, with a declining trend observed over the years. This finding is consistent with previous literature.[13] The misuse of macrolide drugs and the clonal spread of MDR strains may contribute to the high prevalence of macrolide resistance in China. Therefore, macrolide antibiotics should be used with caution as empirical treatment for *S. pneumoniae* infections in the current context in China. Most of the resistance patterns observed in *Streptococci spp*. are like those of *S. pneumoniae*; however, *S. mitis* strains of *Streptococci spp*. displayed higher resistance to penicillin, while showing lower resistance rates to macrolide antibiotics, that is also consistent with existing literature.[14]

H. influenzae can cause a range of infectious diseases in children, including pneumonia, invasive diseases, otitis media, upper respiratory tract infections, and vulvovaginitis in preadolescent children, posing a serious threat to their health.[15] In this study, a total of 20,408 strains of *H. influenzae* were detected, with 19,702 strains (96.54%) originating from respiratory specimens. Due to limitations in experimental conditions, not all strains were serotyped. According to relevant literature,[16] since the introduction of the conjugate vaccine against *H. influenzae* type b (Hib), invasive diseases caused by this bacterium are now predominantly attributed to non-typeable *H. influenzae* (NTHi), with most strains detected in China being NTHi. In recent years, there has been an increase in strains producing β-lactamase and BLNAR, as well as strains resistant to ampicillin-sulbactam, cefuroxime, and azithromycin, which aligns with existing literature.[15] Therefore, third-generation cephalosporins may be the preferred treatment option for infections caused by ampicillin-resistant *H. influenzae*.

S. aureus is one of the most prevalent infectious pathogens and is responsible for a range of infectious diseases, including pneumonia, bloodstream infections, and skin infections.[17] In this study, *S. aureus* was found to occupy a significant position across various specimens. Notably, despite ranking second in respiratory specimens, its prevalence trend has remained unaffected by COVID-19 control measures, potentially due to its unique infection mechanisms. The infection mechanisms of *S. aureus* differ depending on the body site. For instance, pulmonary infections often occur as secondary infections following viral pneumonia.[18] Skin infections typically arise after skin injuries,[17] while food poisoning caused by staphylococcal enterotoxin usually results from the consumption of contaminated food.[19] In our study, we detected 8,746 strains of MRSA. Currently, vancomycin is the first-line treatment for MRSA; however, its use should be approached with caution due to its slow bactericidal activity, poor tissue permeability, and potential renal toxicity.[20,21] CoNS, recognized as opportunistic pathogens, are among the leading causes of hospital-associated infections.[22] In this study, CoNS was predominantly isolated from pus and blood, these CoNS found in the bloodstream are considered non-pathogenic. However, due to the lack of relevant clinical information, we cannot further confirm their pathogenicity. As a normal flora of the skin and mucous membranes, CoNS can easily lead to invasive infections following skin injuries.[22] The resistance rate of *Staphylococcus spp*. to penicillin was notably high (>90%), and approximately 50% of strains exhibited resistance to macrolide antibiotics, which was similar to a foreign study.[23] Since their initial report, resistance to linezolid has been steadily increasing.[24] Our study also identified linezolid-resistant *Staphylococcus spp*., though we did not investigate the resistance mechanisms of these strains further. Previous research indicates that the most common mechanisms of resistance involve transmissible *cfr* ribosomal methyltransferase or mutations in 23S rRNA.[25] Thus, it is essential to enhance the monitoring of drug resistance in *Staphylococcus spp*. to provide timely and effective information for clinical empirical treatments.

Enterococcus spp. is a significant pathogen associated with healthcare-related infections.[26] Since the emergence of vancomycin-resistant strains of *E. faecium* and *E. faecalis* in clinical isolates, *E. faecium* has garnered considerable medical and public attention. The primary species detected are *E. faecium* and *E. faecalis*, with 5 strains of *E. faecium* and 2 strains of *E. faecalis* identified as resistant to vancomycin. Notably, the resistance rate of *E. faecium* to β-lactam antibiotics is higher than that of *E. faecalis*, aligning with findings from the literature.[27] *Enterococcus spp*. possesses inherent resistance to various antimicrobial agents, including cephalosporins, aminoglycosides, clindamycin, and SXT. Additionally, due to the plasticity of its genome, *Enterococcus spp*. demonstrates a significant capacity to acquire new resistance determinants.[28] To

mitigate the spread of antibiotic resistance in *Enterococcus spp*., it is crucial to enhance resistance detection and explore new treatment strategies. Furthermore, stricter management of antibiotic usage practices should be implemented.[27]

Enterobacteriaceae spp. bacteria are among the most common human pathogens and are a significant source of both community-acquired and hospital-acquired infections, with *E. coli* being the most important for human health.[29] In this study, *E. coli* was found at a high isolation rate in various samples. As a normal inhabitant of the intestinal flora, *E. coli* can cause a range of infections including cystitis, pyelonephritis, septicemia, pneumonia, peritonitis, meningitis, and device-related infections, presenting a serious threat to children's health.[29] In China, *K. pneumoniae* was responsible for 11.9% of pathogens isolated from ventilator-associated pneumonia (VAP) and intensive care unit (ICU) acquired pneumonia.[30] This high infection and mortality rate has placed a substantial burden on the country's healthcare system. Currently, β-lactam antibiotics are the most used antibiotics.[31] However, their widespread use has led to a dramatic increase in bacteria producing β-lactamases over the past few decades.[32] Our study found high resistance rates in *E. coli* and *K. pneumoniae* to penicillin, first-generation, and third-generation cephalosporins, but lower resistance rates to amoxicillin-clavulanate and fourth-generation cephalosporins. The resistance rate to the carbapenem antibiotic meropenem remained low. Compared with a European study, the resistance rate of the *Enterobacteriaceae spp*. detected in our study was relatively low to the above drugs.[33] Extended-spectrum β-lactamases (ESBLs) are a group of rapidly evolving enzymes that hydrolyze broad-spectrum cephalosporins, penicillin, and aztreonam, but not carbapenems.[34] These enzymes can be inhibited by "classical" β-lactamase inhibitors such as clavulanate, sulbactam, and tazobactam.[35] Due to the limited use of carbapenems in children, they remain the preferred treatment option for treating severe pediatric ESBLs infections.[36] However, increased carbapenem use could lead to the emergence and global spread of carbapenem-resistant *Enterobacteriaceae* (CRE). Our study showed a decreasing trend in CRE rates over the past six years, with CREO and CRKP being distributed relatively evenly across different age groups, a finding that differs somewhat from both domestic and international studies.[37,38] Most of the CRE strains we detected were resistant to cephalosporins, piperacillin, cefoperazone-sulbactam, piperacillin-tazobactam, aztreonam, and carbapenems. Due to some hospitals' limitations, we could not determine enzyme types, so we did not quantify the production of each enzyme type. Research indicates that[39] common enzyme types of CRE isolated from children in China are NDM, KPC, and OXA, in that order, with *K. pneumoniae* producing the blaOXA-232 enzyme being isolated exclusively from children. According to IDSA treatment guidelines, the treatment of CRE infections should begin with identifying the enzyme type produced by the strain,[40] which will guide the subsequent treatment plan based on the enzyme type and infection site.

Salmonella spp. can lead to diarrhea and even fatal outcomes in children. In addition to the well-known typhoid and paratyphoid types, non-typhoidal *Salmonella spp*. can also have serious consequences.[41,42] This study identified a total of 2,821 strains of *Salmonella spp*., and a comprehensive analysis of their drug susceptibility was conducted. The resistance rates to first-line antibiotics, such as ampicillin and cotrimoxazole, were significantly elevated. Furthermore, the resistance rates to third-generation cephalosporins and fluoroquinolones were also notably high, aligning with findings from international studies.[43–45] While the resistance rate to carbapenem antibiotics remains low (in 2022 is as high as 0.5%) at present, drug-resistant strains have begun to emerge, potentially jeopardizing our last line of treatment for *Salmonella spp*. infections.[45]

P. aeruginosa and *A. baumannii* were the most isolated pathogens among non-fermentative bacteria. *A. baumannii* was predominantly found in respiratory tract, while *P. aeruginosa* accounted for a higher proportion of isolates from pus samples. *A. baumannii* is known to cause hospital-acquired infections such as ventilator-associated pneumonia, bacteremia, urinary tract infections, meningitis, and surgical wound infections.[46] Due to its strong drug resistance and ability for clonal transmission,[47] infections caused by *A. baumannii* can be particularly challenging to treat. In this study, it was observed that the resistance rates of *A. baumannii* to most antibiotics had increased in 2020, possibly linked to the epidemic control measures implemented in Shandong Province during that year. According to the World Health Organization's list of drug-resistant bacteria, carbapenem-resistant *A. baumannii* (CRAB) was identified as the top threat to human health in 2017 in terms of the urgent need for the development of new antibiotics.[48] A total of 1218 CRAB strains were detected in this study, with a higher proportion isolated from school-age children compared to other age groups, which is consistent with findings from a similar study in Shanghai.[49] Treatment of CRAB infections typically involves combination therapy, especially for moderate to severe cases.[50] Infections caused by *P. aeruginosa* pose a

significant challenge due to the pathogen's ability to develop drug resistance, produce multiple virulence factors, and form biofilms.[51,52] Over the years, the resistance of *P. aeruginosa* to commonly used antibiotics has increased significantly,[53] with β-lactam antibiotics being the primary choice for treatment.[52] In this study, the resistance of *P. aeruginosa* to β-lactams was higher compared to other antibiotics, with fluoroquinolones following closely behind. The resistance to meropenem remained relatively low, consistent with findings from other countries.[54] Treatment guidelines from the IDSA recommend tailoring antibiotic therapy based on sensitivity results,[40] with adjustments made as needed and real-time monitoring of sensitivity data. For infections caused by MDR *P. aeruginosa*, preferred antibiotics include ceftazidime-avibactam, cefepime-tazobactam, and imipenem-cilastatin-relebactam.

The detection rate of FRCT in this study was 43.6%, which is higher than that reported in other studies in China,[55] this discrepancy may be attributed to the fact that all specimens were collected from children. Globally, resistance to azole drugs in *C. tropicalis* is primarily observed in the Asia-Pacific region, whereas resistance levels in European and US countries remain low (below 10%).[56] Compared to *Candida albicans*, there is a paucity of research on the mechanisms of drug resistance in *C. tropicalis*, both domestically and internationally. Currently, the mechanisms of *C. tropicalis* resistance to azole antibiotics mainly involve two factors: mutations in the drug's target site and increased expression of efflux pumps.[57,58] Therefore, enhancing the detection of *C. tropicalis* resistance will aid in the development of more accurate diagnostic and treatment strategies.

Our research may have some limitations due to the lack of relevant clinical information, we cannot further confirm their pathogenicity.

Conclusion

The pathogen epidemiology and resistance in children are characteristic and quite different from those for the adult population. MDROs presented much higher AMR profiles and have become an urgent threat to children, with CRKP, CRAB, and CRPA strains showing decreasing but fluctuating trends between 2017 and 2022 due to factors such as COVID-19 and a lower birth rate in China. Keeping effective and continuous surveillance on the trends of bacterial epidemiology and AMR profiles among children is of great significance, because of the emergence of carbapenem-resistant salmonella and the proportion of fluconazole resistant *Candida tropicalis* continued to increase.

Availability of Supporting Data

The authors confirm that the other data supporting the results of this study are available within the article and its supplementary materials. All of the associated data are available from the corresponding author.

Ethic Statement

All experiments involving human participants were performed according to the guidelines and regulations of the Declaration of Helsinki (2013 version). The study guarantees that the identities of the participants and other related data have been kept anonymous and confidential. The requirement for informed consent was waived because of the retrospective nature of the study.

Ethical Approval

This study was reviewed and approved by the Ethical Review Committee of Children's Hospital Affiliated to Shandong University (approval no. SDFE-IRB/P-2022017).

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Disclosure

All authors disclose no competing interests in this work.

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