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Trends in antimicrobial resistance in Enterobacterales isolated from children: data from the China Antimicrobial Surveillance Network (CHINET) from 2015–2021

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Abstract

Antimicrobial resistance poses a significant threat to global public health, especially for Enterobacterales. In this study, we investigated the distribution and antimicrobial resistance of Enterobacterales in children in the China Antimicrobial Surveillance Network (CHINET) in 2015–2021. In total, 81,681 strains isolated from children were collected in this period, accounting for 50.1% of Gram-negative organisms. The most frequently isolated Enterobacterales were *Escherichia coli*, *Klebsiella* spp., *Salmonella* spp., and *Enterobacter* spp. The main sources of the isolates were urine and the respiratory tract, accounting for 29.3% and 27.7% of isolates, respectively. The proportions of *E. coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis* expressing extended-spectrum β-lactamase were 48.8%–57.6%, 49.3%–66.7%, and 23.1%–33.8%, respectively. The prevalence of carbapenem-resistant Enterobacterales was 5.7%–9.5%, which showed a decreasing trend from 2015 to 2021. The detection rates of carbapenem-resistant *Klebsiella* spp., carbapenem-resistant *Enterobacter* spp., and carbapenem-resistant *E. coli* were 14.1%–22.6%, 7.1%–15.7% and 2.0%–3.4%, respectively. In Enterobacterales, the resistance rates to ciprofloxacin were higher than to levofloxacin. However, the Enterobacterales strains were highly susceptible to amikacin, polymyxin B, and tigecycline. The resistance rate of *Salmonella* spp. to ampicillin was > 70%, whereas their resistance rate to ceftriaxone was < 30%. These findings indicate that the resistant rates of some Enterobacterales isolates in children to common antimicrobial agents show decreasing trends. Continuous monitoring of bacterial resistance should be strengthened to prevent and control the spread of drug-resistant bacteria.

Keywords Children, Enterobacterales, Bacterial resistance surveillance, Extended-spectrum β-lactamase, Carbapenem-resistant Enterobacterales

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Introduction

Antimicrobial resistance (AMR) occurs when bacteria develop the ability to evade the drugs designed to treat infections. It has become one of the leading threats to public health in the twenty-first century, with substantial morbidity and mortality rates, and mainly affects countries with emerging economies [1]. A previous study commissioned by the UK Government [2] showed that AMR could kill 10 million people per year by 2050. The emergence of AMR has limited the use of these drugs in hospitals, agriculture, and the environment. In China, although a variety of strategies are proposed to control AMR, bacterial resistance among various pathogens, including the order Enterobacterales, the genus *Acinetobacter*, and the species *Pseudomonas aeruginosa*, continues to pose great challenges to clinical anti-infection treatments [3].

Enterobacterales is a large order of medically important bacteria that includes *Escherichia*, *Klebsiella*, *Enterobacter*, and other genera. Members of Enterobacterales are reportedly the pathogens most commonly involved in nosocomial infections, including pneumonia, sepsis, and urinary-tract infections [4]. Cephalosporins and carbapenems are considered the main antibiotics used to defend against the serious infections caused by Enterobacterales. Nevertheless, the wide and unreasonable use of these antibiotics has reduced their efficiency by selecting for the extensive acquisition of genes encoding extended-spectrum β-lactamases (ESBLs) and carbapenemases, respectively [5–7]. However, given the hypoplasia of the immune system in children and their limited antibiotic options, the antimicrobial resistance of pathogens in children is particularly important. Therefore, long-term monitoring of the prevalence of Enterobacteriales in children must be strengthened. In this study, we report the antimicrobial resistance of Enterobacteriales isolated from children in the China Antimicrobial Surveillance Network (CHNET) between 2015 and 2021, which could provide a theoretical basis for guiding the rational use of clinical antibiotics in children.

Results

Distribution of clinical isolates

In 2015–2021, 81,681 Enterobacteriales strains were collected from children, accounting for 29.3% of the total organisms isolated from children and 50.1% of the Gram-negative strains. Enterobacteriales constitutes the largest group of Gram-negative bacteria, although the proportion of Enterobacteriales isolates detected tended to decrease over the 7 years of the study (Table S1). The four most prevalent Enterobacteriales taxa were *E. coli* (44.7%), *Klebsiella* spp. (27.6%), *Salmonella* spp. other than *S. typhi* and *S. paratyphoid* AC (10.4%), and *Enterobacter* spp. (7.6%). As shown in Fig. 1, the proportions of *E. coli* and *Klebsiella* spp. decreased over these 7 years, whereas the proportions of *Salmonella* spp. other than *Salmonella typhi* and *paratyphoid* A–C and *Enterobacter* spp. increased.

In the study, most *Enterobacterales* isolates were cultured from urine (29.3%, 23,966/81,681), followed by respiratory-tract samples (27.7%, 22,600/81,681), wound secretions (12.6%, 10,319/81,681), stools (11.1%, 9104/81,681), and blood (7.8%, 6388/81,681). During the 7-year study, the constituent ratios of the isolates from urine and respiratory-tract samples continued to decline, whereas the constituent ratios of isolates from

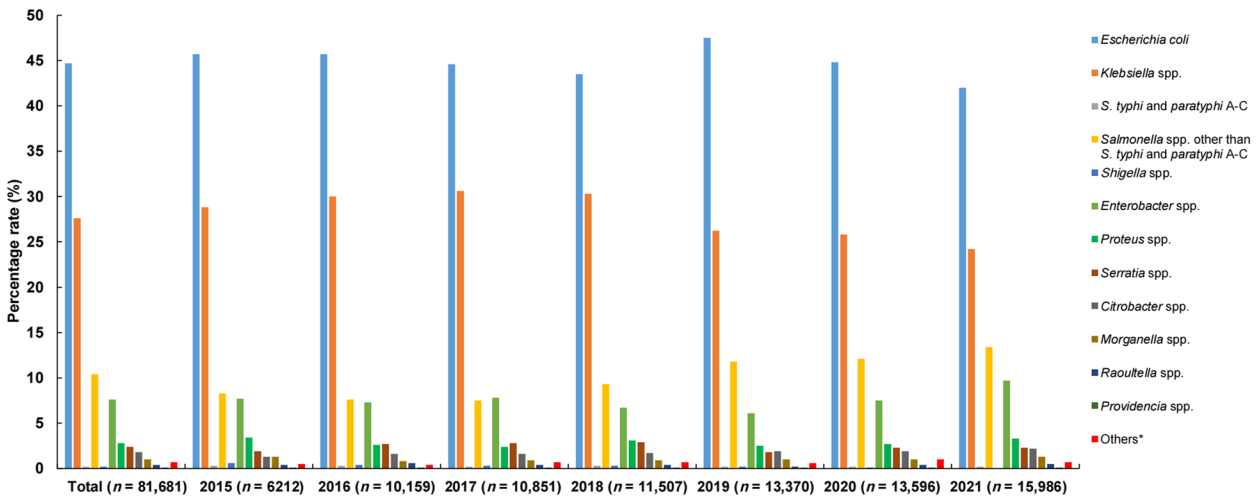

Fig. 1 Species distribution of Enterobacterales isolates from children in CHINET program over the period between 2015 and 2021. **Pantoea* spp., *Yersinia* spp., *Cronobacter* spp., *Kluyvera* spp., *Budvicia* spp., *Buttiauxella* spp., *Edwardsiella* spp., *Hafnia* spp., *Cedecea* spp

stools, wound secretions, and blood increased (Table S2). It is noteworthy that *E. coli* was mainly isolated from urine, wound secretions, and respiratory-tract samples. *Klebsiella* spp. and *Enterobacter* spp. were frequently detected in respiratory-tract samples, urine, and blood. *Salmonella* spp. other than *S. typhi* and *S. paratyphoid* A-C were commonly isolated from stools and blood (Table S3).

As shown in Table S4, the proportions of Enterobacterales isolates collected from children in different hospital departments in 2015–2021 were 19.0% (15,497 strains) from outpatient and emergency departments and 81.0% (66,184 strains) from inpatient departments. Of the 15,497 strains isolated in outpatient and emergency departments, *E. coli* (43.7%) and *Salmonella* spp. other than *S. typhi* and *S. paratyphoid* A–C (27.1%) were the primary species isolated from urine (49.9%) and stools (27.8%). Of the 66,184 strains isolated in inpatient departments, *E. coli, Klebsiella* spp., and *Enterobacter* spp. constituted 43.8%, 30.3%, and 8.6% of isolates, respectively, and were mainly from internal medicine departments (19.2%), neonatology departments (19.2%), and general surgery departments (15.4%). They were primarily isolated from respiratory-tract samples (28.9%) and urine (23.2%).

The constituent rates of Enterobacterales in infants (>28 days–12 months) were 35.1%–43.5%, followed by 11.4%–21.5% in neonates (0–28 days), and 13.5%–17.7% in preschoolers (2–5 years). The constituent rate of Enterobacterales in school-age children (6–12 years) was relatively low at 5.9%–8.0% (Table S5). *Escherichia coli* (42.0%) and *Salmonella* spp. other than *S. typhi* and *S. paratyphoid* AC (23.2%) were most common in infants (>28 days–12 months), whereas *E. coli* (36.3%–61.0%) and *Klebsiella* spp. were commonly detected in the other age groups.

Detection rates of ESBLs and carbapenem-resistant Enterobacterales (CRE)

The prevalence rates of ESBL production in *E. coli*, *K. pneumonia*, and *P. mirabilis* isolated from children were 48.8%–57.6%, 49.3%–66.7%, and 23.1%–33.8%, respectively (Fig. 2a). An epidemiological trend analysis indicated that the proportions of EBSL-producing *E. coli* isolates and EBSL-producing *K. pneumoniae* isolates gradually increased from 2015 to 2021, whereas the proportion of ESBL-producing *P. mirabilis* isolates increased only slightly from 2015 to 2021. The ESBLs rates of *K. pneumoniae* were always higher than those of *E. coli* in 2015–2020, but these rates were reversed in 2021.

Among the 81,681 isolates examined in this study, 6254 were considered CRE and the overall detection rate was 7.7% (5.7%–9.5%), Of these CRE, the rates of carbapenem-resistant *Klebsiella* spp., carbapenem-resistant *Enterobacter* spp., and carbapenem-resistant *E. coli* were 14.1%–22.6%, 7.1%–15.7%, and 2.0%–3.4% (Fig. 2b). The carbapenem resistance in other species of Enterobacterales was also observed, with different detection rates ranging from 1.0% to 11.9%. We detected a decreasing trend in carbapenem-resistant *Klebsiella* spp. and carbapenem-resistant *E. coli*, and an increasing trend in carbapenem-resistant *Enterobacter* spp. over the 7 years of the study. The distribution of CRE strains varied among the different age groups and they were most commonly detected in neonates (6.3%–14.1%), followed by infants (6.6%–11.1%) and adolescents (6.4%–10.8%) (Fig. 2c).

Susceptibility and resistance rates of antimicrobial agents in Enterobacterales

As summarized in Fig. 3, the resistance rates of *E. coli* to the majority of antimicrobial agents tested showed a decreasing trend from 2015 to 2021, except for ciprofloxacin (from 39.6% to 46.0%) and levofloxacin (from 31.8% to 34.2%). The resistance rates of *E. coli* to three carbapenems (ertapenem, imipenem, and meropenem) were < 5%, and increased slowly from 2015 to 2017, but then decreased slowly from 2018 to 2021. The rate of resistance to gentamicin for *E. coli* was > 30%, whereas < 3% of strains were resistant to amikacin. Most *E. coli* strains were strongly susceptible to polymyxin B and tigecycline (> 95%).

From 2015 to 2021, the resistance of *Klebsiella* spp. strains to most test antimicrobial agents showed a gradual decreasing trend, except to ciprofloxacin (from 32.5% to 34.8%), levofloxacin (from 17.0% to 19.4%), and trimethoprim–sulfamethoxazole (from 29.3% to 30.9%) (Fig. 4). The resistance rates of *Klebsiella* spp. to imipenem and meropenem decreased from 20.9% and 20.9%, respectively, in 2015 to 12.7% and 13.5%, respectively in 2021. More than 30% of *Klebsiella* spp. were resistant to ciprofloxacin. The rates of resistance to polymyxin B and tigecycline remained in a low level, ranging from 0% to 5.0%.

Over the 7 years of the study, the resistance of the *Enterobacter* spp. strains to most antimicrobial agents tested showed a increasing trend, except for amikacin (from 1.8% to 0.4%) and gentamicin (from 14.9% to 8.6%) (Fig. 5). The resistance rates of *Enterobacter* spp. to imipenem and meropenem increased from 4.4% and 5.0%, respectively, in 2015 to 9.8% and 9.7%, respectively, in 2021. The resistance rates of *Enterobacter* spp. to ciprofloxacin and levofloxacin were < 15%. Most *Enterobacter* spp. strains were sensitive to polymyxin B and tigecycline, with high susceptibility rates of 95%.

The resistance rates of *S. typhi* and *S. paratyphi* AC strains to ampicillin were 50.0%–89.3%, with large

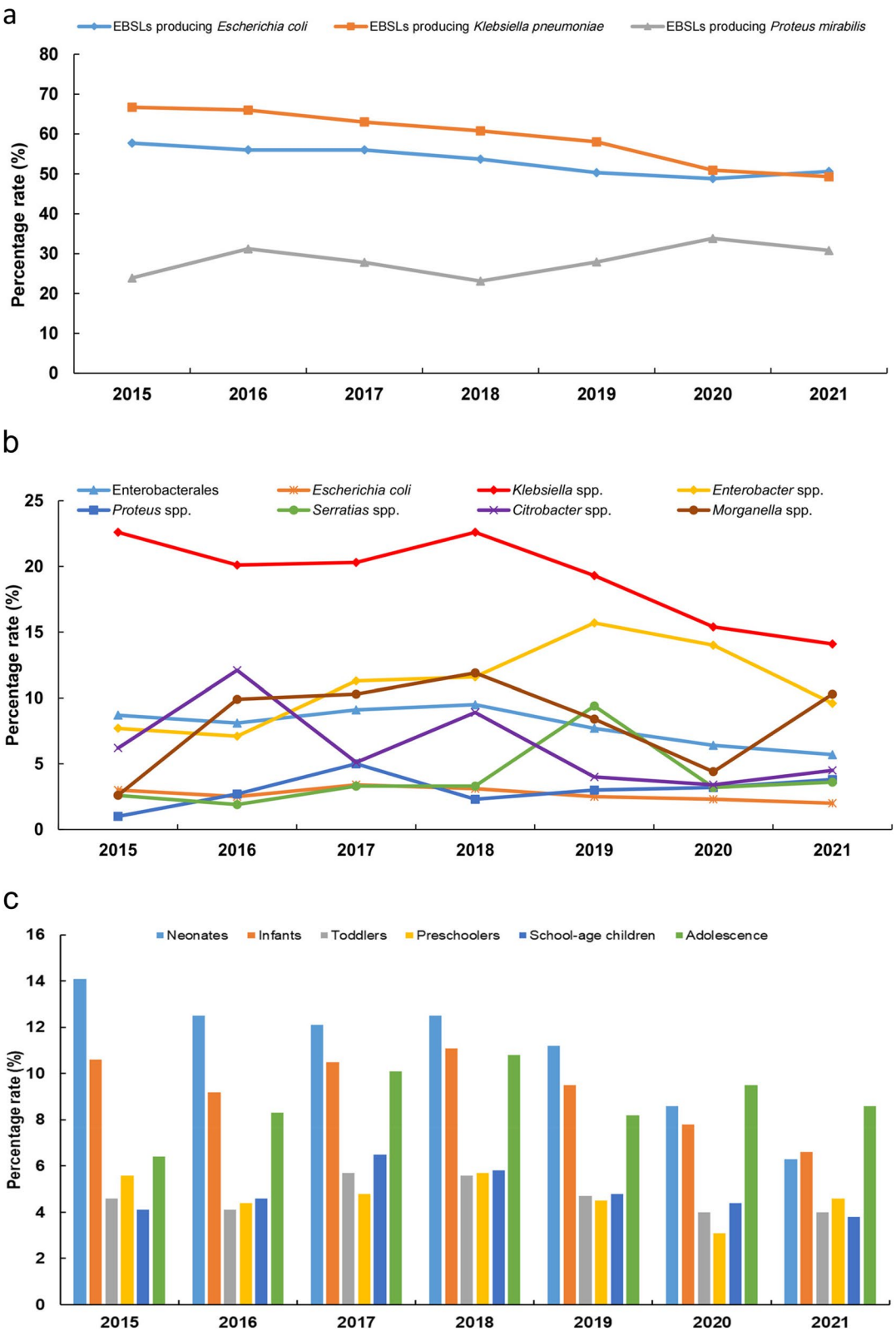

Fig. 2 Surveillance of EBSLs and CRE among Enterobacterales from children from 2015 to 2021. **a** The detection rates of ESBLs. **b** Prevalence of CRE among common species. **c** Prevalence of CRE among different ages. ESBLs: Extended-spectrum beta-Lactamases; CRE: Carbapenem-resistant Enterobacterales

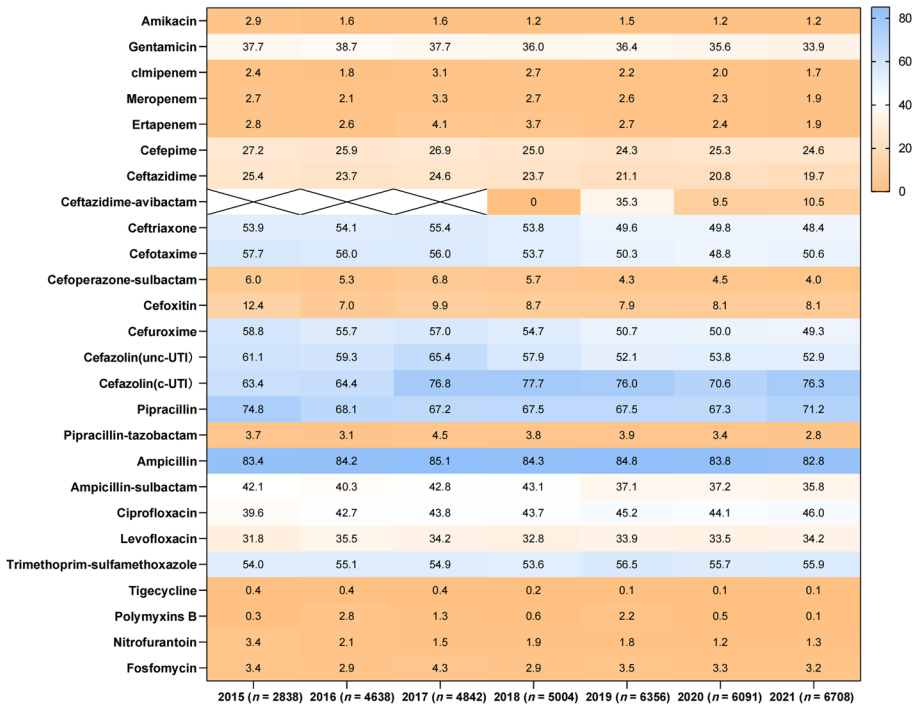

Fig. 3 Resistance rates of *Escherichia coli* to antimicrobial agents from children from 2015 to 2021 (%). UTI: urinary tract infection; Ceftazidime-avibactam: only for carbapenem-resistant *E.coli*. Nitrofurantoin and Fosfomycin: only for urinary tract isolates

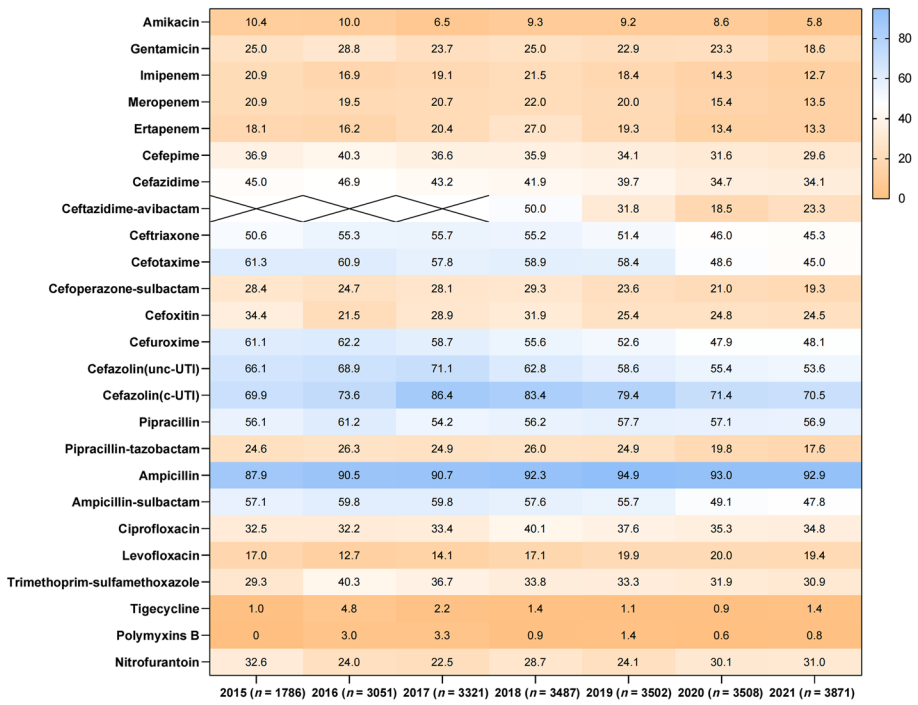

Fig. 4 Resistance rates of *Klebsiella* spp. to antimicrobial agents from children from 2015 to 2021 (%). UTI: urinary tract infection; Ceftazidime-avibactam: only for carbapenem-resistant *Klebsiella* spp. Nitrofurantoin: only for urinary tract isolates

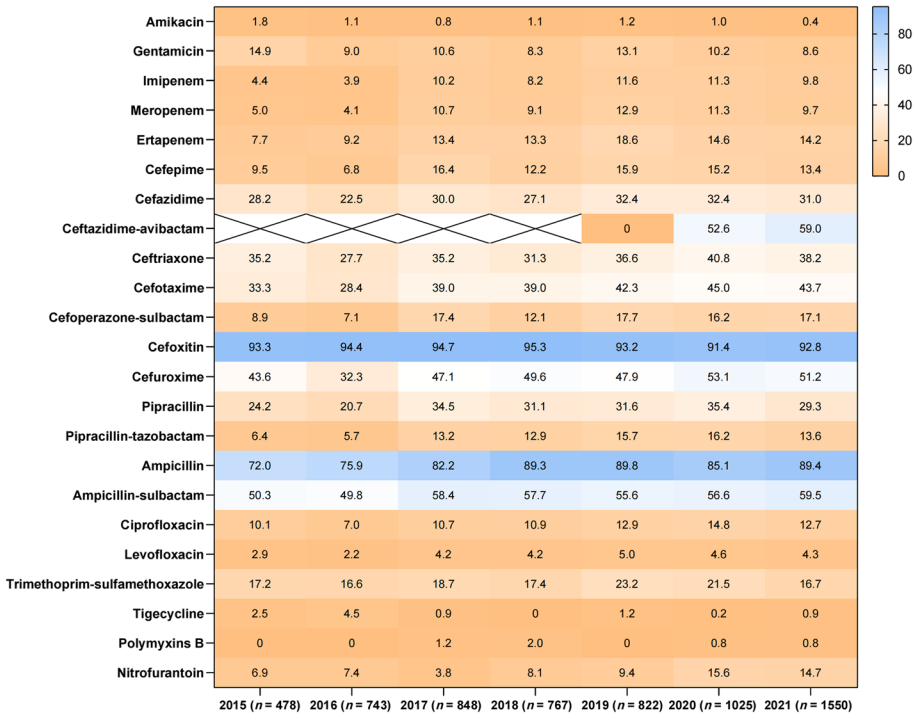

Fig. 5 Resistance rates of *Enterobacter* spp. to antimicrobial agents from children from 2015 to 2021 (%). Ceftazidime-avibactam: only for carbapenem-resistant *Enterobacter* spp. Nitrofurantoin: only for urinary tract isolates

fluctuations. The resistant rates of *S. typhi* and *S. paratyphi* A–C strains to ceftriaxone decreased, while the resistant rates of ampicillin–sulbactam, ciprofloxacin, trimethoprim–sulfamethoxazole, and chloramphenicol increased (Fig. 6). However, as shown in Fig. 7, the resistance rate of *Salmonella* spp. other than *S. typhi* and *S. paratyphoid* A–C to the common antimicrobial agents tested increased to different degrees. More than 70% of *Salmonella* spp. other than *S. typhi* and *S. paratyphoid* A–C were resistant to ampicillin, whereas < 30% of these strains were resistant to ampicillin–sulbactam and ceftriaxone. The resistance rate of *Enterobacter* spp. to ciprofloxacin was < 15%. All *Salmonella* spp. isolates were high susceptible to imipenem.

Discussion

The results of monitoring drug resistance in Enterobacteriales isolated from children in China recorded in CHINET from 2015–2021 were as follows. (i) *Escherichia coli* was the most common Enterobacteriales species,

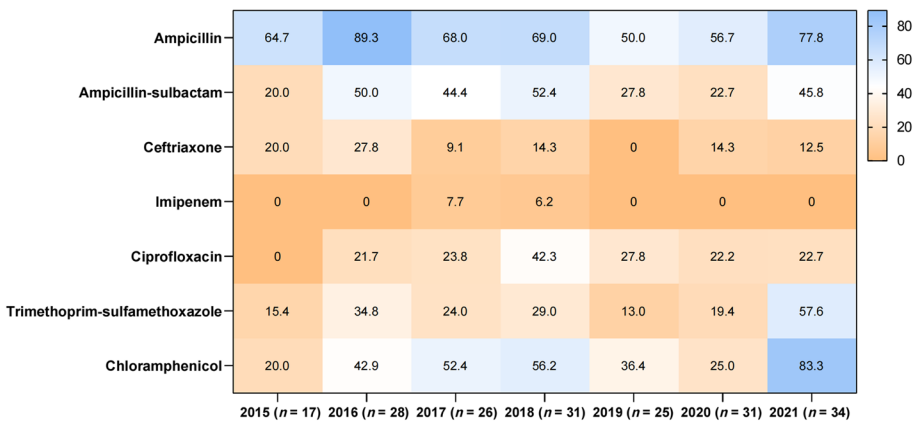

Fig. 6 Resistance rates of *S. typhi* and *paratyphi* A–C to antimicrobial agents from children from 2015 to 2021 (%)

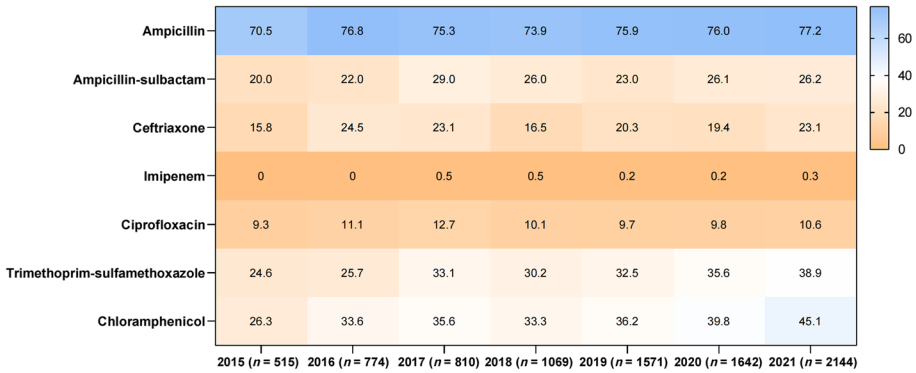

Fig. 7 Resistance rates of *Salmonella* spp. other than *S. typhi* and *paratyphi* A–C to antimicrobial agents from children from 2015 to 2021 (%)

accounting for 44.7% of the total Enterobacteriales, followed by *Klebsiella* spp. (27.6%) and *Salmonella* spp. (10.4%). (ii) The commonest specimens were urine and respiratory-tract samples, with high rates of 29.3% and 27.7%. Members of Enterobacteriales were commonly isolated from children in outpatient and emergency departments, followed by neonatology departments, internal medicine departments, and intensive care units. (iii) The prevalence of ESBL production in *E. coli*, *K. pneumonia*, and *P. mirabilis* isolated from children were 48.8%–57.6%, 49.3%–66.7%, and 23.1%–33.8%, respectively. The proportions of EBSL-producing *E. coli* isolates and EBSL-producing *K. pneumoniae* isolates gradually increased, whereas the proportion of ESBL-producing *P. mirabilis* isolates increased only slightly. (iv) The detection rate of CRE isolates was 7.7%, most of which were *Klebsiella* spp. and *E. coli*, and were most commonly detected in neonates. The Enterobacteriales strains, except *Salmonella* spp., showed low resistance rates to piperacillin–tazobactam, cefoperazone–sulbactam, amikacin, polymyxin B, and tigecycline. (v) The resistance rate of *Salmonella* spp. to ampicillin was > 70%, whereas the resistance rate of *Salmonella* spp. to ceftriaxone was < 30%.

ESBLs are the most important resistance mechanism directed against β-lactam antibiotics in Enterobacteriales. The Clinical and Laboratory Standards Institute (CLSI) states that ESBL testing is mainly useful for epidemiological or infection prevention purposes involving *E. coli*, *K. pneumonia*, and *P. mirabilis*, and is not routinely performed. ESBLs are a class of diverse, plasmid-mediated, complex enzymes that can hydrolyze almost all β-lactamase antibiotics, but do not hydrolyze cephamycins or carbapenems [8]. These surveillance data reveal that the detection rates of ESBLs in *E. coli* and *K. pneumoniae* decreased from 57.7% and 66.7%, respectively, in 2015 to 50.6% and 49.3%, respectively, in 2021, although the rates of these strains at the same period were higher than the total ESBL detection rates reported in the China Antimicrobial Resistance Surveillance System (CARSS) and CHINET [9, 10]. This phenomenon may be related to the limited types of antimicrobial agents available to children and newborns and to the widespread use of cephalosporins in children, which requires further attention. The strict implementation of further training on the rational use of antibiotics in children should be conducted to reduce the overuse of cephalosporins in children. In this study, we also found that the resistance rate to quinolones in Enterobacteriales was > 30%. We speculate that these resistant strains were transmitted from adults to children because quinolones are only used in children with caution.

CRE is a growing concern for patients in healthcare settings because they are not only resistant to carbapenems but also resistant to other antimicrobial agents, including quinolones and aminoglycosides, Therefore, they pose great challenges to clinical anti-infection treatments. These monitoring data show that the rates of detection of carbapenem-resistant *Klebsiella* spp. and carbapenem-resistant *E. coli* decreased from 22.6% and 3.0%, respectively, in 2015 to 14.1% and 2.0%, respectively, in 2021, and the rates of these strains at the same period were lower than the total detection rates in CARSS and CHINET [9, 10]. However, the rate of carbapenem-resistant *Enterobacter* spp. showed an increasing trend and was higher than the rates reported in CARSS and CHINET. Simultaneously, carbapenem-resistant strains also emerged in *P. mirabilis*, *Serratia marcescens*, and *Citrobacter freundii*, which warrants clinical attention. The production of carbapenemases is the main resistance mechanism in these strains and carbapenemase genes can be horizontally transferred among different bacterial species on genetic elements, such as plasmids, resulting in the wide dissemination of CRE strains [11]. In the face of the threat posed by CRE, clinical laboratories must establish long-term monitoring systems for antimicrobial

resistance and carbapenemase types. It is well known that different bacterial species and populations carry different types of carbapenemases, and previous studies have demonstrated that the major types of carbapenem-resistant *K. pneumoniae* in adults and children are *Klebsiella* pneumoniae carbapenemase and New Delhi metallo-β-lactamase (NDM) carbapenemase, although NDM is the main type in carbapenem-resistant *E. coli* [12]. Therefore, it is recommended that laboratories detect the resistance phenotypes or genes of carbapenem-resistant isolates to improve bacterial drug sensitivity reports. *Enterobacteriales* strains also showed high susceptible to tigecycline and polymyxin B, although there have emerged several isolates resistant to these drugs. This resistance is attributed to the presence of the *mcr-1* gene or the upregulated expression of the resistance–nodulation–cell division (RND) efflux pump [13, 14]. Therefore, it is suggested that the antimicrobial susceptibility testing for tigecycline, polymyxin B, and other novel antimicrobial compounds, such as ceftazidime–avibactam, should be performed routinely for CRE strains to improve drug resistance monitoring.

Conclusions

In conclusion, Enterobacteriales strains are some of the most important bacteria isolated from pediatric patients, and their resistance to common antimicrobial agents has been declining. Nevertheless, the status of antimicrobial resistance in Enterobacteriales cannot be ignored, especially in CRE strains, because it poses a major challenge for the use of antimicrobial agents in the child population. Consequently, monitoring the changes in drug resistance in Enterobacteriales, and strengthening the management of antibiotic stewardship and the prevention and control of hospital infections must be continued, and should provide a theoretical basis for the prevention and control of drug-resistant bacteria.

Materials and methods

Participating hospitals and bacterial strains

In this study, 51 hospitals (45 general hospitals and six children's specialist hospitals) from 29 provinces or cities in China, covering more than 50% of the Chinese population, participated in CHINET from 2015 to 2021. The CHINET program (http://www.chinets.com) was established in 2005 and collects the annual nationwide antimicrobial susceptibility data from all the enrolled hospitals, to analyze the prevalence of bacteria and the changes in the rates of AMR [15]. All Enterobacteriales strains were collected from children ≤ 18 years old. The children were divided into six age groups: neonates (0–28 days), infants (> 28 days–12 months), toddlers (> 12 months–23 months), preschoolers (2–5 years), school-age children (6–12 years), and adolescents (13–18 years). All isolates were identified to the species level with automated systems, such as Vitek 2 Compact (Biomerieux, France), Phoenix M50 (BD, America), or MALDI-TOF. Only one isolate from the same species was included per patient.

Antimicrobial susceptibility testing

Antimicrobial susceptibility testing was performed according to the guidelines of CLSI, with the breakpoints for interpretation recommended by CLSI 2021 [16, 17]. Strains *E. coli* American Type Culture Collection (ATCC) 25,922 and *Pseudomonas aeruginosa* ATCC 27853 were used for quality control. The CLSI breakpoint criteria for cefoperazone was applied for cefoperazone–sulbactam. The breakpoint for polymyxin B was that adopted by domestic expert consensus in 2020 [18]. The interpretive criterion for tigecycline was based on the breakpoint, which was recommended by the Food and Drug Administration (FDA) [19]. The ESBL test was performed for *E. coli*, *K. pneumoniae*, *K. oxytoca*, and *P. mirabilis*. CRE was defined as Enterobacterales resistant to at least one of the carbapenem antibiotics (ertapenem, meropenem, doripenem, or imipenem) or that produced a carbapenemase. However, for some Enterobacterales (e.g., *Proteus* spp., *Morganella* spp., *Providencia* spp.) that have intrinsically elevated minimum inhibitory concentrations to imipenem, it should also include resistance to other carbapenems [20].

Statistical analysis

Antimicrobial resistance data were processed and analyzed with the WHONET 5.6 software (World Health Organization). Data are presented as means ± standard deviations (SD).

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s44280-024-00054-y.

Supplementary Material 1. Table S1. Distribution of 81,681 Enterobacterales isolates from children in CHINET program from 2015 to 2021. Table S2. Distribution of Enterobacterales isolates among clinical specimens between 2015 and 2021. Table S3. Distribution of Enterobacterales isolates among clinical specimens from children between 2015 and 2021. Table S4. The proportion of Enterobacterales isolates among different department from children from 2015 to 2021 (%). Table S5. The proportion of Enterobacterales isolates among different ages from children from 2015 to 2021 (%).

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Authors' contributions

H.Z. and D.Z. designed the study. Y.Y. and Y.G. collected the data. F.P., C.W. and H.Z. analyzed the data. F.P. wrote the manuscript. All authors reviewed, revised, and approved the final report.

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Availability of data and materials

All the data supporting the conclusions of this article is included within the article.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of Huashan Hospital, Fudan University (number 2018–408).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interest.

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