Infection and Drug Resistance

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ORIGINAL RESEARCH

Trends in Antibiotic Resistance Patterns and Burden of Escherichia Coli Infections in Young Children: A Retrospective Cross-Sectional Study in Shenzhen, China from 2014–2018

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Purpose: The emergence of multi-drug resistant ESBL-producing *E. coli* poses a global health problem. In this study, we aimed to investigate the prevalence of *E. coli* infections and their antibiotic susceptibility profiles in paediatric clinical cases in Shenzhen, China from Jan 1, 2014, to Jan 30, 2019, while also determining temporal trends, identifying ESBL-producing strains, and recommending potential empirical antibiotic therapy options.

Methods: We isolated a total of 4148 *E. coli* from different specimens from a single paediatric healthcare centre. Additionally, we obtained relevant demographic data from the hospital's electronic health records. Subsequently, we performed antimicrobial susceptibility testing for 8 classes of antibiotics and assessed ESBL production.

Results: Out of the 4148 isolates, 2645 were from males. The highest burden of *E. coli* was observed in the age group of 0–1 years, which gradually declined over the five-year study period. Antimicrobial susceptibility results indicated that 82% of *E. coli* isolates were highly resistant to ampicillin, followed by 52.36% resistant to cefazolin and 47.46% resistant to trimethoprim/sulfamethoxazole. Notably, a high prevalence of ESBL production (49.54%) was observed among the *E. coli* isolates, with 60% of them displaying a multi-drug resistance phenotype. However, it is worth mentioning that a majority of the isolates remained susceptible to ertapenem and imipenem. Our findings also highlighted a decrease in *E. coli* infections in Shenzhen, primarily among hospitalized patients in the 0–1 year age group. However, this decline was accompanied by a considerably high rate of ESBL production and increasing resistance to multiple antibiotics.

Conclusion: Our study underscores the urgent need for effective strategies to combat multi-drug resistant ESBL-producing *E. coli* Infections.

Keywords: *E. coli* infections, antibiotic susceptibilities, young children, MDR

Introduction

Escherichia coli, a gram-negative pathogen in the *Enterobacteriaceae* family, is a significant cause of bloodstream, urinary tract, gastrointestinal, and respiratory infections worldwide.[1] The global incidence of *E. coli* infections is increasing, according to the Global Burden of Foodborne Diseases report. Approximately 111 million illnesses and 63,000 deaths are attributed to diarrheagenic *E. coli* annually worldwide, Infection rates vary across different regions.[2] This substantial burden necessitates a comprehensive understanding of the pathogen's impact and its growing antimicrobial resistance crisis. This alarming burden highlights the urgent need for effective strategies to tackle *E. coli* infections and their associated challenges. Notably, the impact of *E. coli* on bloodstream infections, while not as clear

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as its role in urinary tract infections, has been identified as a leading cause of bloodstream infections.[3] *E. coli* infections impose a substantial burden on pediatric health, affecting various body sites and warranting a comprehensive understanding of their prevalence and implications for effective disease management.[4] *E. coli* bloodstream infections were not widely recognized as a common issue at the beginning of the 20th century; however, it has been consistently rising worldwide over the decades as shown by numerous studies.[5,6] The gut microbiome is a common source of extraintestinal infections caused by *E. coli* and its population varies among individuals of different ages and lifestyles.[7] The emergence of *E. coli* is a critical issue in the context of antimicrobial resistance, as its resistance rates are increasing worldwide, including in China.[8] The complexity and incomplete understanding of antibiotic resistance development and dissemination are widely acknowledged. Despite numerous studies that demonstrate a correlation between the use of antibiotics and the emergence of antibiotic-resistant bacteria, the extent to which such selection is influenced by ecological or individual factors remains to be further elucidated.[9,10] The impact of prior hospital exposure on trends in *E. coli* bloodstream infections, urinary tract infections and gastrointestinal infections has not been thoroughly investigated specifically in children. Recently, two studies from China were published indicating that among cases of bloodstream infection, 60–70% are caused by gram-negative bacteria, with *E. coli* being the predominant species that have been isolated.[11,12] A MEDLINE database search with keywords such as "bloodstream infection", "urinary tract infection", "antimicrobial susceptibility", and "China" yielded around 286 studies, but none of them focused on the trends of *E. coli* in these infections. A multicentre study revealed that *E. coli* infections with increased antimicrobial resistance occurred in China according to the China Antimicrobial Surveillance Network (CHINET-http://www.chinets.com,2016).[12] A 12-year retrospective study suggests that Extended-spectrum β-lactamase (ESBL) -producing *E. coli* were resistant to ciprofloxacin, cefotaxime, and amoxicillin. However, resistance to these antibiotics has been increasing over time.[11] The reason for the high prevalence of *E. coli* bloodstream infections, and urinary tract infections, as well as the development of antibiotic resistance, may be linked to increased antibiotic usage in the population, individual hospitals and primary care.[13] Our hospital adopted a new antibiotic therapy policy in 2015[14] while monitoring the changes in antibiotic-resistant bacteria to be better equipped to prevent disease. This study aimed to investigate possible changes in antibiotic resistance patterns and the burden of *E. coli* infection in the bloodstream, urinary tract, gastrointestinal tract and other sites from paediatric patients aged 0–14 years in Shenzhen, China.

Method

Study Setting, Design, and Population

This study was in line with the Declaration of Helsinki guidelines and was approved by the Research Ethics of Shenzhen Children's Hospital (Decision No 2018/03) which complies with global ethical standards. In the course of this retrospective study, we obtained a total of 4723 non-duplicate specimens, including urine, sputum, pus, blood, stool, and throat swab samples, collected between January 1, 2014, and December 30, 2018. These specimens were systematically gathered as part of a routine antimicrobial resistance surveillance initiative, encompassing patients from distinct age groups (0–1, 2–5, 6–10, and 11–14 years), each exhibiting specific clinical symptoms indicative of various infection types. The collection was tailored to encompass patients with suspected bloodstream infections, urinary tract infections, gastrointestinal infections, and respiratory infections. In particular, symptoms such as severe body pain, fever, rapid breathing, and rash were used as criteria for identifying potential bloodstream infections, while signs like pyuria were indicative of urinary tract infection or inflammation. Similarly, gastrointestinal and respiratory infections were characterized by abdominal pain, diarrhoea, bronchitis, and lung abscess symptoms. Our comprehensive analysis evaluated the interplay of patient demographics with the incidence of *E. coli* infections across these distinct categories, accounting for age and sex adjustments based on population estimates provided by the Shenzhen Children's Hospital's record room. Notably, verbal consent was procured from patients for the use of anonymized data in research, following the standard operating procedures of Shenzhen Children's Hospital. This retrospective design was approved by the Research Ethics Committee of Shenzhen Children's Hospital, and our central research laboratory strictly adhered to good clinical and laboratory practice (GCLP) guidelines, ensuring the reliability and validity of our findings.

Specimen and Data Collection

Shenzhen Children's Hospital has implemented an extensively defined standard operating procedure (SOP) for sample collection during paediatric clinical practices including rapid transportation of specimens to central laboratories. To assess the *E. coli* burden in the paediatric population urine, appendix, sputum, pus, blood, stool, and throat swab specimens were collected from patients suspected of having an *E. coli* infection using an aseptic technique and placed in sterile containers to prevent contamination by highly trained nursing staff. The samples were transported to the central laboratory, department of microbiology, within 30 minutes, and patient data, including age, gender, specimen type, and department of admission, was collated from the hospital record room in an Excel sheet.

Isolation and Identification of *E. Coli*

Samples suggestive of bloodstream infections, urinary tract infections, gastrointestinal infections, and respiratory infections were cultured on an enriched lauryl sulfate-aniline blue agar medium, MacConkey agar and 5% human blood agar. The plates were incubated aerobically at 37 °C/24 hrs and characterised phenotypically. The purity of the isolates was assessed and a colony count of $\geq 10^4$ CFU/mL was considered significant. Bacterial identification was performed by the VITEK-2 system (bioMérieux, Lyon, France) which was further confirmed by the API-20E tests. Results were analysed and interpreted as per the manufacturer's instructions.

Antimicrobial Susceptibility Testing

Antibiotic susceptibility testing (AST) was conducted on each isolate using the automated VITEK-2 system (bioMérieux, Lyon, France) and an ASTGN335 card, following the manufacturer's instructions. The minimum inhibitory concentrations (MICs) were interpreted based on the clinical breakpoints published by the European Committee on Antimicrobial Susceptibility Testing (EUCAST, Version 9.0).[15] Additionally, a broth microdilution method was employed, and the results were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) guidelines (CLSI: M100-S22).[16] The antibiotic susceptibility results were categorized as susceptible, intermediate, or resistant for antibiotics that belonged to the following classes categories: Penicillin's - ampicillin, ampicillin/sulbactam, piperacillin/tazobactam; Monobactam - aztreonam; Fluoroquinolones - ciprofloxacin, levofloxacin; Cephalosporins - cefazolin, cefotetan, ceftazidime, ceftriaxone, cefepime; Aminoglycosides - amikacin, gentamicin, tobramycin; Carbapenems - ertapenem, imipenem; Nitrofurans - nitrofurantoin; and Sulfonamides - trimethoprim/sulfamethoxazole. Bacterial isolates that were resistant to at least one antibiotic of three or more antimicrobial classes were classed as multi-drug resistant (MDR).[17] The results were validated by using *E. coli* (ATCC 25922) as a control strain. Furthermore, ESBL detection was performed by both the VITEK-2 system and double-disc diffusion method (DDDM) which includes a disc of amoxicillin-clavulanic acid (20/10 mcg), along with ceftriaxone (30 mcg), ceftazidime (30 mcg) and cefotaxime (30 mcg) to observe a synergistic reaction, a well-characterized strain of *Salmonella typhimurium* (SP-15-127) from our laboratory was used as a positive control.[18] The distance between the discs is critical and 20 mm centre-to-centre. To assess the effect of antimicrobial resistance, which might also affect the treatment outcome we investigated resistance trends over the past 5 years among males and females, as well as assessed the prevalence of bloodstream infections, urinary tract infections, gastrointestinal infections and respiratory infections. We also evaluated the current choice of drugs available to treat these infections and sought to understand the severity of *E. coli* infection in young children.

Statistical Analysis

A chi-square test was performed to analyse the data using GraphPad Prism software, version 9, (GraphPad Software, San Diego, CA, USA). p-value ≤ 0.05 was considered to be statistically significant. Figures were created by using R ggplot2.

Results

Between Jan 1, 2014, to Dec 30, 2018, a total of 4214/4723 (89.22%) specimens' cultures were positive on an enriched lauryl sulfate-aniline blue agar plate and primarily identified by the VITEK-2 system, of which 4148 (98.34%) were confirmed as *E. coli* by the API-20E system and colony morphology along with Gram staining. 66/4214 (1.57%) were false positives recorded by the VITEK-2 system and were subsequently excluded from the study. There were very few discrepancies in the

identification of *E. coli* using both the VITEK-2 automated system and the API-20 method. Of which 2750 (66.31%) of the specimens were collected from hospitalised patients and 1398 (33.69%) from the outpatient department. The distribution of samples by the department was as follows: Infectious diseases had the highest number of cases with 1700 (40.98%), followed by our specialized respiratory infection department with 481 (11.59%), endocrinology 435 (10.48%), intensive care unit 396 (9.54%). Other departments with notable numbers of cases included surgery 279 (6.72%), haematology and oncology 252 (6.07%), immunology 236 (5.68%), gastrointestinal department 124 (2.98%), neurology 93 (2.24%), neonatology 87 (2.09%), and from an unknown source 65 (1.56%) (Supplementary Figure 1). Out of the 4148 cases of *E. coli* infection, 2645 (63.76%) were identified in male patients, and 1503 (36.23%) were identified in female patients with a mean age of 6.5 yrs. (median age 7 yrs.; SD 3·59 yrs.) (Figure 1). The overall prevalence of *E. coli* infection declined over the years but show the highest peak of each year in the mid (April to June) of 2014 and 2017. The age group 0–1 yr. had the highest burden of *E. coli* infection and further details on the burden of *E. coli* infections among the age groups are shown in Figure 1. The prevalence of *E. coli* infection was significantly higher in males than in females in the ages 11–14. group, [chi-square = 17.0533 (*p-value* is 0.0018)] while lower in the age group 6–10 yrs, [chi-square is 2.5942 (*p-value* is 0.62)] (Figure 2). Overall, between 2014–2018, the mean prevalence of *E. coli* infections was 829 with SD 238.10 (two-tailed p-value 0.005) but this number varied substantially across the study period. Out of 4148, 1481 (35.70%) isolates were recovered from urine samples, while 1343 (32.37%) were from sputum, 531 (12.80%) from pus, 423 (10.19%) from bloodstream infections and 230 (5.54%) from stool samples and 140 (3.37%) were recovered from throat swabs (Figure 3). The overall prevalence of *E. coli* gastrointestinal infection increased but that of respiratory infections declined year after year. The *E. coli* infection burden in urinary tract infections declined at a lower rate across the study period.

Antimicrobial Susceptibility Profile

MICs determined by the automated AST VITEK-2 systems and by broth microdilution showed no discrepancies. Overall antimicrobial susceptibility results revealed that 3404 (82%) *E. coli* were highly resistant to ampicillin followed by cefazolin [n=2172, 52.36%], trimethoprim/sulfamethoxazole [n=1969, 47.46%], ampicillin/sulbactam [n=1895, 45.68%], ceftriaxone [n=1727, 41.63%], gentamicin [n=1496, 36.06%], aztreonam [n=1253, 30.20%], ciprofloxacin [n=1070, 25.79%] and levofloxacin [n=787, 18.97%], while lower resistance was observed against, cefepime [n=364, 8.77%], tobramycin [n=290, 6.99%], ceftazidime [n=264, 6.36%], piperacillin/tazobactam [n=82, 1.97%], cefotetan [n=79, 1.90%], amikacin [n=62, 1.49%] and nitrofurantoin [n=49, 1.18%]. Moreover, the results indicate that the majority of the *E. coli* isolates were sensitive to ertapenem, and imipenem (Figure 4). Out of the 4148 isolates tested, 744 (17.93%) were found to be sensitive to all tested antibiotics. The prevalence of ampicillin-resistant *E. coli* declined over subsequent years (Figure 5). An increase was observed in the case of cefepime, cefazolin, and ceftriaxone-resistant *E. coli*, whereas not many changes were observed in resistance against ciprofloxacin, gentamicin and ceftazidime. Our observations reveal that isolates obtained from gastrointestinal infection and urinary tract infections cases exhibit multiple drug-resistance phenotypes (the chi-square statistic is 0.7914, a *p*-value is 0.9396) (Supplementary Figure 2). We have found no

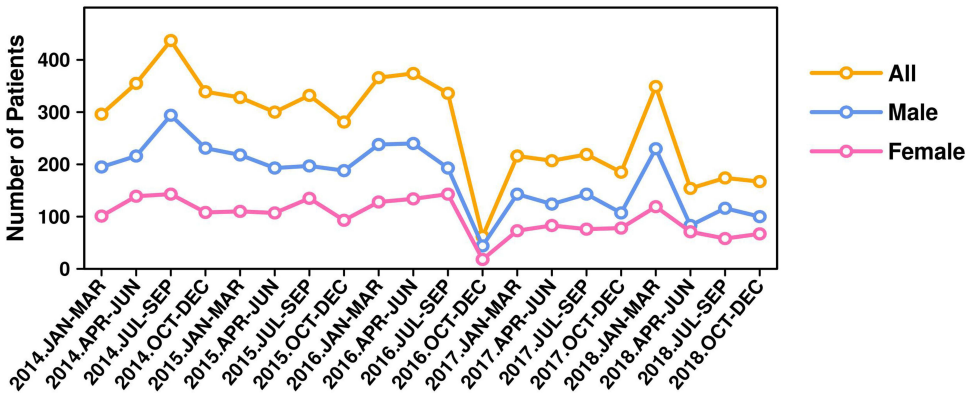

Figure 1 Gender structured and trimester prevalence of *Escherichia coli* infection in young children in Shenzhen from 2014–2018.

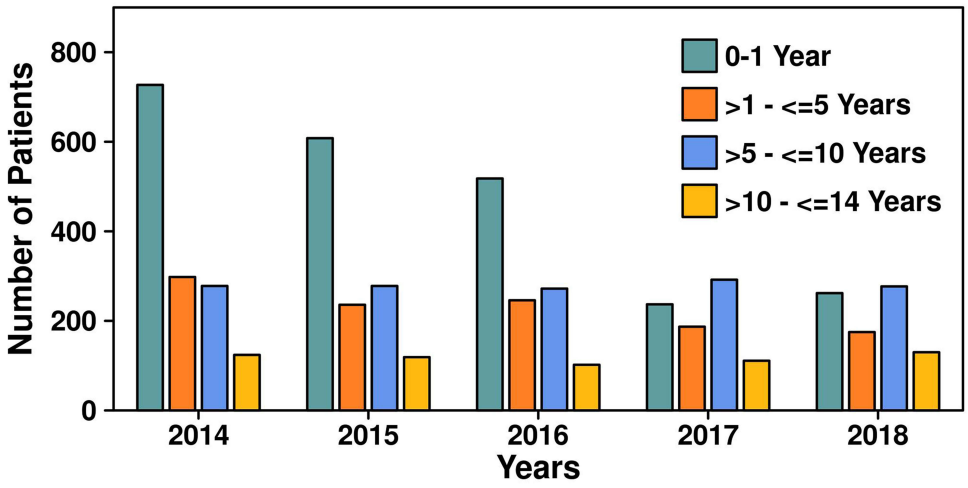

Figure 2 Age Structured *Escherichia coli* infection in young children in Shenzhen from 2014–2018.

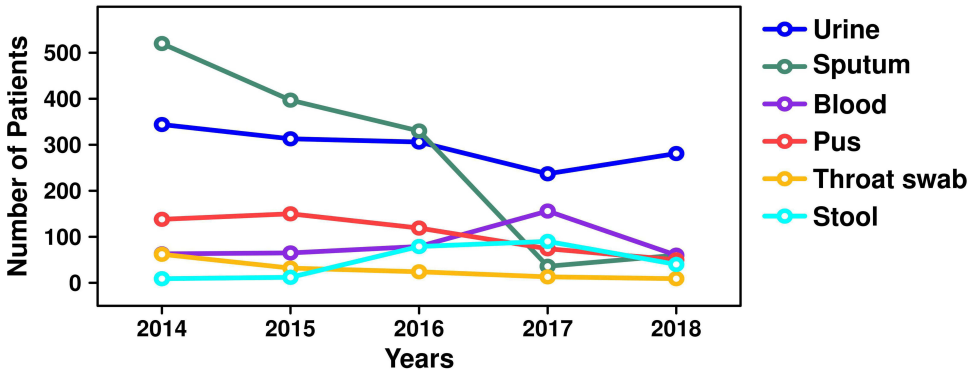

Figure 3 *Escherichia coli* abundance in different patient specimen samples over five years 2014–2018.

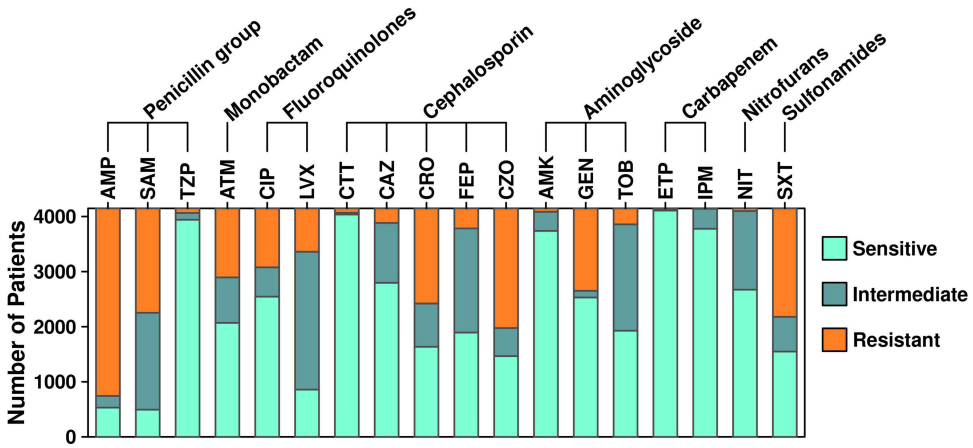

Figure 4 Overall antimicrobial susceptibility of *Escherichia coli* isolates collected from 2014–2018.
Abbreviations: AMK, amikacin; AMP, ampicillin; ATM, aztreonam; CAZ, ceftazidime; CIP, ciprofloxacin; CRO, ceftriaxone; CTT, cefotetan; CZO, cefazolin; ETP, ertapenem; GEN, gentamicin; IMP, imipenem; LVX, levofloxacin; NIT, nitrofurantoin; SAM, ampicillin/sulbactam; SXT, trimethoprim/sulfamethoxazole; TOB, tobramycin; TZP, piperacillin-tazobactam.

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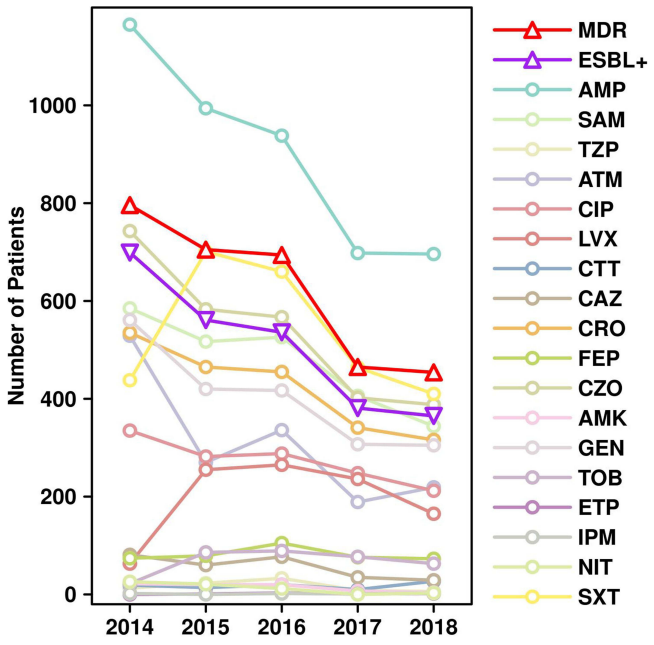

Figure 5 Antimicrobial resistance, MDR phenotype and ESBL production of *Escherichia coli* trends based on a year-on-year basis from 2014–2018.
Abbreviations: AMK, amikacin; AMP, ampicillin; ATM, aztreonam; CAZ, ceftazidime; CIP, ciprofloxacin; CRO, ceftriaxone; CTT, cefotetan; CZO, cefazolin; ETP, ertapenem; GEN, gentamicin; IMP, imipenem; LVX, levofloxacin; NIT, nitrofurantoin; SAM, ampicillin/sulbactam; SXT, trimethoprim/sulfamethoxazole; TOB, tobramycin; TZP, piperacillin-tazobactam.

compelling evidence to suggest that the development of drug resistance is linked to the infection site whether it is associated with bloodstream infections, urinary tract infections, or gastrointestinal infections. Our results suggested the use of imipenem and nitrofurantoin as the preferred drugs for treating bloodstream infections, urinary tract infections, respiratory infections and gastrointestinal infections shortly. Our results show that *E. coli* resistance to ciprofloxacin, cefepime, trimethoprim/sulfamethoxazole and piperacillin/tazobactam is significantly higher in females than males compared to other drugs (Supplementary Figure 3). Based on the specimens, all tested drugs were found to be significant (all P values <0.01), is revealed that the infection site of *E. coli was* not more concern but still high resistance was reported in urinary tract infections. The prevalence of ESBL-producing *E. coli* was found to be 49.54% [n=2055], and multidrug-resistant (MDR) phenotype was observed in 60% [n= 1233/2055] of the ESBL-producing isolates. Overall, the mean prevalence of ESBL over the 5 years was 411 with SD 116.8 (Two-tailed p-value 0.00045), but this number varied substantially across the study period, notably; the present study reported the declining prevalence of ESBL *E. coli* from 2014 −2018 in young children at Shenzhen, China (Figure 5). It is worth noting that a high prevalence of ESBL *E. coli* was found in age groups 0–1 years and it has contributed to the MDR phenotype in this organism. During the study period, not much change was observed in the age group 11–14 (Supplementary Figure 4).

Discussion

Escherichia coli is a significant pathogen in bloodstream infections and urinary tract infections, which can potentially lead to fatal outcomes. Proper characterization of these infections requires consideration of various factors such as epidemiology, antimicrobial susceptibility, and host determinants. A comprehensive understanding and analysis of these factors can aid in the development of effective treatment strategies and control measures to prevent the spread of *E. coli* infections in the blood-stream infection, wound infections, respiratory infections and urinary tract infections. This effect might be quantitatively small for an individual, but its overall contribution to the spread of antibiotic resistance in the population is important. The extensive sample size, well-defined sampling departments, and specimens, as well as the inclusion of only gender and age data of individual patients along with their antimicrobial susceptibility profiles, in our study, allowed us to gain further insight into the intricate interplay of factors associated with antibiotic resistance and the trends of *E. coli* infection in young children over five years. Moving forward, we plan to expand our research to include the geographical distribution of *E. coli* and the occurrence of

bacteraemia and urinary tract infections. To detect the burden of *E. coli* in bloodstream infections, urinary tract infections, RI and GI cases, the determination of its presence in blood, urine, sputum, throat swabs and faecal samples depends on the decision of both physicians and patients to undergo culture tests. As a result, likely, the reported cases do not encompass all incident cases within the population or hospital admissions. It is expected that the missed incident cases are distributed equally across *E. coli*-related bloodstream infections, urinary tract infections, and GI cases. We have discovered that when detecting *E. coli* using an automated system such as Vitek-2 and API-20, we did not observe any significant differences. Moreover, both methods had been validated previously and yielded similar results to ours.[19] Based on our laboratory's practice, we recommend the use of enriched lauryl sulphate-aniline blue agar for culture *E. coli*. Our study indicates that the infectious diseases department has the highest burden of *E. coli* infections among admitted patients, followed by respiratory diseases, endocrinology, and the intensive care unit. The infectious disease departments are in high demand, as they cover a wide variety of infections and have the highest disease burden. Although there may be a higher number of reported cases, there have not been any studies reported from China to the best of our knowledge. Our study supports the previous finding that there is a high prevalence of *E. coli* pathogens in both the intensive care unit and general medicine departments.[20] In our study, it was observed that the prevalence of *E. coli* infections (bloodstream infections and urinary tract infections) was higher in male patients at 63.31% ($p<0.001$) than in female patients at 36.69% among young children. These results were consistent with another study by Randi et al, which reported 77% of *E. coli* bloodstream infections in male adult patients.[21] Although there are few population-based studies on sex differences in the epidemiology of BSI, to our knowledge, all studies have focused on the adult age group, and no previous studies have analysed sex differences in bloodstream infections or respiratory infections among young children. Several studies have suggested that females are more prone to urinary tract infections, due to their shorter urethra, which increases the risk of bacterial ascent from the perianal region into the bladder. However, we have observed a higher number of urinary tract infections in our male patients, which differs from other studies.[22] Moreover, the prevalence of urinary tract infections has been found to vary among children of different ages and ethnic groups. Our observation that *E. coli* urinary tract infections are higher in males is supported by other studies. For instance, Alexander et al reported that *E. coli* is responsible for 80% to 90% of urinary tract infections in children, and the prevalence is higher in boys than in girls.[23] Our findings have demonstrated a consistently higher prevalence of *E. coli* urinary tract infections (35.7%) in young children (excluding 2016 for gastrointestinal), compared to respiratory infection (35.7%), wound infection (12.78%), bloodstream infections (10.13%) and GI (5.55%). This is in line with the results of previous studies.[24] The higher prevalence of *E. coli* urinary tract infections is driven by modifiable risk factors such as being overweight or obese and having poor fluid intake, which increase the risk of urinary tract infections in children.[25] We have assessed the higher number of *E. coli* burden in the hospitalized patients about 2750 (66.31%) and among them, 1908 (46.0%) showed MDR phenotype. We hypothesised that crowded living conditions in hospitals might be associated with increased physical contact between people and with less hygienic conditions that further increase the risk of transmission of *E. coli* and other pathogens. Our hypothesis has been supported by Marcelo et al, which reported fluconazole-resistant *E. coli* transmission in a crowded population.[10] However, generally, more crowded population conditions did not confer an increased risk for urinary tract infections, wound infections and bloodstream infection, except in places like overloaded hospitals where common instruments, washrooms, and shared wards facilitated the transmission of resistant bacteria or resistance genes within the population. Furthermore, molecular analyses such as pulse-feed gel electrophoresis and multi-locus typing /Whole genome sequencing studies are required to warrant the hypothesis. Antimicrobial stewardship has become increasingly crucial with the emergence of multi-drug-resistant *E. coli*, including the production of extended-spectrum beta-lactamases, which we identified in 2055 (49.54%) isolates, and is declining each year. Djuikoue et al, have highlighted a significant prevalence of ESBL-producing *E. coli* in blood samples of young children from Yaoundé, resulting in mortality among infants in Cameroon.[26] Overall antimicrobial susceptibility results revealed that *E. coli* were highly resistant to ampicillin (82%), cefazolin (52.36%), trimethoprim/sulfamethoxazole (47.46%), ampicillin/sulbactam (45.68%), ceftriaxone (41.63%), gentamicin (36.06%), aztreonam (30.20%), ciprofloxacin (25.79%) and levofloxacin (18.97%). Moreover, the results indicate that the majority of the *E. coli* isolates were sensitive to ertapenem, and imipenem. The treatment guidelines suggest cefixime, cefpodoxime, cephalexin, ampicillin, and ceftriaxone being first-line agents used to treat uncomplicated bloodstream infections), wound infections or urinary tract infections.[27] Unfortunately, many studies have suggested the highest growth of resistance against first-line antibiotics in *E. coli*, which is consistent with our findings.[28] With the escalation of antibiotic resistance, managing infections caused by carbapenemase and ESBL-

producing pathogens has become a progressively daunting endeavour. As treatment options diminish, colistin has reemerged as a final recourse antibiotic to address infections induced by these profoundly resistant pathogens[29,30] Clinicians must review patient age, and gender-specific culture results and follow local antibiograms and antimicrobial sensitivity patterns available at their institution precisely so that appropriate therapy can be delivered. Our data suggest that imipenem and nitrofurantoin are the drugs of choice to treat multiple antibiotic-resistant E. coli infections in case of bloodstream infections, urinary tract infections, and gastrointestinal infections. Similar to our study, Sara et al have suggested that imipenem is effective in the treatment and control of serious infections caused by MDR *E. coli* and in the reduction of bacterial resistance emergence.[31] As healthcare providers play a pivotal role in patient care, their understanding and recognition of the evolving patterns of antibiotic resistance are essential in guiding appropriate treatment decisions. Monitoring the prevalence of ESBL-producing *E. coli* infections in pediatric patients can offer valuable insights into the local and regional antimicrobial resistance trends, helping healthcare professionals make informed choices when prescribing antibiotics. By regularly assessing the susceptibility profiles of *E. coli* isolates, physicians, pharmacists, and other healthcare professionals can identify emerging trends of resistance and adjust empiric antibiotic therapies accordingly. Tailoring treatment regimens based on local resistance patterns can improve patient outcomes, reduce the risk of treatment failure, and mitigate the development of further antibiotic resistance. Furthermore, fostering collaboration and communication between healthcare facilities, researchers, and public health authorities is vital to effectively combat antimicrobial resistance. This exchange of data and information can lead to a more comprehensive understanding of the epidemiology of ESBL-producing E. coli infections and enable the implementation of evidence-based interventions to curb their spread. Education and awareness campaigns targeted at healthcare professionals can also play a significant role in promoting judicious antibiotic use and antimicrobial stewardship. Our results show the resistance development for ciprofloxacin, cefepime, trimethoprim/ sulfamethoxazole and piperacillin/tazobactam are significantly higher in girls, no gender base supportive studies published yet so further large-scale study required. The present study suggests that the specimen's origin and tested all drugs were found to be significant, first report best of our knowledge. The research has several limitations. We were unable to obtain patient characteristics, accessibility to medical services before arriving at our hospital, self-prescribed consumption of antibiotics, and geographical area. Another limitation is that we could not assess the associations between individual-patient antibiotic use (not available in the research database) and the risk of resistant infections, or between specific empirical regimens and outcomes. These associations are important future research priorities. We only have antibiograms, but representative isolates should be selected for whole-genome sequencing. Their analysis could increase the understanding of the pathogenesis of *E. coli* in young children and provide a further picture of the molecular epidemiology of *E. coli* and identify any clonal relationship. Furthermore, we could not assess the associations between individual-patient antibiotic use and the risk of developing resistant infections. The data on individual antibiotic prescriptions were not included in the research database, which hinders our understanding of the impact of specific empirical treatment regimens on the development of antibiotic resistance. Lastly, the study's retrospective design may have inherent limitations, including incomplete or missing data and potential biases in data collection. While we made efforts to minimize these limitations, they should be taken into consideration when interpreting the results. By acknowledging these limitations, we aim to provide a transparent assessment of the study's scope and potential implications. Future research endeavours can build upon these limitations and address these gaps to further our understanding of *E. coli* infections and antibiotic resistance in pediatric clinical cases.

Conclusion

In summary, there has been a decline in the prevalence of *E. coli* infections burden in young children in Shenzhen, China. *E. coli* urinary tract infections were found to be the most challenging to the healthcare system among children aged 1–5 years. Notably, the use of first-line antibiotics, such as cefixime, cefpodoxime, cephalexin, ampicillin, and ceftriaxone in primary care, was associated with an increased subsequent prevalence of resistant *E. coli* bloodstream infections and urinary tract infections. This supports initiatives aimed at reducing the use of broad-spectrum and inappropriate antibiotics. The high rate of ESBL-producing *E. coli* and multidrug-resistant (MDR) phenotype in paediatric patients is worrisome. Further molecular studies are required to investigate the transmission of drug-resistant genes in *E. coli* among young communities along with additional surveillance to aid and improve antimicrobial stewardship.

Ethics Approval

This study was in line with the Declaration of Helsinki guidelines and was approved by the Research Ethics of Shenzhen Children's Hospital (Decision No 2018/03) which complies with global ethical standards.

Consent to Publish

We did not use the patient's name or personal information; therefore, the Research Ethics Committee of the Shenzhen Children's Hospital waived the requirement for written consent. In addition, Shenzhen Children's Hospital collects verbal consent from patients by asking for their permission to use their anonymised data for research purposes.

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