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Uropathogen and Resistance Trends of Urinary Tract Infection in Children: Lessons from Longterm Surveillance

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Abstract

Background: Urinary Tract Infections (UTI) are common in children and organisms associated with UTI have shown increasing resistance to commonly used antibiotics. This study aims to evaluate common organisms causing UTI, determine their susceptibility pattern to commonly used oral antibiotics for treatment of UTI and compare trends with past studies in the same geographic region. **Methods:** 4-year retrospective review of positive urine cultures in children < 16 years from 2020 to 2023 in South Staffordshire and surrounding areas in the United Kingdom. Demographic data, culture results and antibiotic susceptibility were analysed using appropriate tools. **Results:** Among the 1818 episodes of confirmed UTI that met inclusion criteria, 87.3% were females while 12.7% were males. 67.4% UTIs were in children < 10 years. *E coli* accounted for 83.3% of all organisms, followed by *Enterecoccus* (5.6%), *Klebsiella* (4.6%) and *Proteus* (2.1%). Analysis of antimicrobial resistance rate showed *E coli* was highly susceptible to nitrofurantoin (95.3%) and cefalexin (92.9%) but had high resistance to trimethoprim (26.7%) and amoxicillin (42.1%). **Conclusion**: Coliform resistance to amoxicillin and trimethoprim remains high. Hence, these antibiotics may not be the right first-line antibiotic choice for empiric treatment of UTI in children.

Keywords

Paediatric Urinary Tract Infection, Antimicrobial Resistance, *Escherichia coli*, Antibiotic Susceptibility

1. Introduction

Urinary Tract Infections (UTI), which are mostly from gastrointestinal organisms, are very common in children. 1 in 10 girls and 1 in 30 boys develop UTI by the age of 16 years [1] [2]. UTI accounts for about 5.6% of acutely ill children < 5 years presenting to general practice surgeries in United Kingdom (UK) [3].

The National Institute for Health and Care Excellence (NICE) in UK recommends empirical use of antibiotics in children with suspected UTI who meet urine dipstick and clinical features criteria [1]. The gold standard for diagnosis of UTI is by isolation of pure organism in an appropriately collected urine specimen [4]-[6].

The prognosis of UTI is good when early diagnosis and prompt treatment with appropriate antibiotics are initiated. However, long-term complications due to delayed or improper treatment can lead to renal scarring, hypertension, and chronic kidney disease [7] [8]. Although there are National recommendations for treatment of paediatric UTI, there are variations in local guidelines for empirical antibiotic treatment due to rising antibiotic resistance to common pathogens causing UTI [9]-[12]. This has made it imperative for continuous local and regional surveillance on commonly used antibiotics and to make necessary policy adjustments in antimicrobial use to treat UTI in children. Routine and inappropriate use of broad-spectrum antibiotics for common paediatric febrile conditions, especially in countries with easy access to over-the-counter antibiotics, has contributed to rising antimicrobial resistance. Recent and frequent use of antibiotics has been shown to be a risk factor for increasing antimicrobial resistance to common UTI pathogens [12]. In addition, organism susceptibility to various antibiotics may change over time. Therefore, it is necessary to have a localized guideline on treatment of paediatric UTI, based on local antimicrobial sensitivity pattern. Equally, it is imperative that monitoring and surveillance of pathogens causing UTI is continued and their resistance pattern to various antibiotics is monitored regularly. This will enable institutions to provide appropriate prescribing guidance and improve antimicrobial stewardship.

Aim and objectives of this study were to:

- Identify the most common bacterial causes of UTI in children.
- Evaluate the resistance pattern and trends of commonly used oral antibiotics in treatment of paediatric UTI.
- Compare the results with previously published data within the same geographic region.

2. Methods

2.1. Subjects and Design

This was a 4-year retrospective data review of UTIs in children aged 0 to 16 years in a district general hospital setting in UK, which serves as a referral centre for all the primary care providers (GP surgeries and community hospitals) in the locality. In order to minimise contamination, only mid-stream clean catch urine samples from the paediatrics department of the hospital as well as from primary care providers were included in the analysis.

2.2. Data Collection and Analysis

Meditech V6 electronic database of the hospital was used to identify all the urine samples with pure growth of single uropathogen. Sensitivity testing in microbiology laboratory was carried out with Kirby-Bauer disc diffusion method using Muller-Hilton agar medium. All UTI episodes of single organism with pure bacterial growth of $>10^5$ cfu/ml were included. Suspected contaminant with ≥2 pure growths of $>10^5$ cfu/ml or growth of $<10^5$ cfu/ml from clean catch urine specimen were excluded. Only patients with urine samples collected before starting antibiotics were included in the study. Data extracted from the Meditech V6 included organism causing UTI. Local guidelines were followed for antimicrobial susceptibility test and the sensitivity pattern to amoxicillin, trimethoprim, cefalexin, nitrofurantoin and co-amoxiclav was ascertained. In addition, data on subject's age, sex, source and type of urine sample were obtained.

It is common practice for labs in the UK to use European Committee on Antimicrobial Susceptibility Testing (EUCAST) sensitivity breakpoints. EUCAST breakpoints are updated every year and the concentration of the antibiotics along with the zone sizes is provided. The panel of tests also differs depending on the level of resistance.

Analysis was done using SPSS and results were compared to previously published data from paediatric UTIs at the same hospital [9] [13]. Differences in proportion and statistical significance between current and previous findings were tested using the chi square test, and p-value of ≤0.05 was deemed to be statistically significant.

3. Results

There were 1818 episodes of confirmed UTI over the 4-year period. The demographic distribution of children diagnosed with UTI in 2020, 2021, 2022 and 2023 is shown in **Figure 1** and **Figure 2**. Significant gender differences were observed in confirmed UTIs with females accounting for 87.3% (1588) vs 12.7% (230) males (**Figure 1**). During the study period, UTI was 6.9 times more likely in females than in males. There was a statistically significant drop in males developing culture-proven UTI when compared to the published data from 2002 - 2008 (chi square = 48.435; P ≤ 0.0001) and 2009-2019 (chi square = 12.289; P = 0.0005) [9] [13].

1225 (67.4%) of UTI occurred in children < 10 years (**Figure 2**). This represented a statistically significant increase compared to 54.6% seen in 2009 - 2019 review [9] (chi square = 45.313; P ≤ 0.0001). Majority of the children with UTI, 1536 (84%) were seen in the primary care vs 282 (16%) seen in the hospital setting.

Commonly isolated organisms over the 4-year period are shown in **Table 1** & **Figure 3**. For ease of clinical and epidemiological description, organisms are grouped into coliforms (*E coli*) and non-coliforms (any other organism). 1514 (83.3%) and 304 (16.7%) of the cultured organisms were *e coli*forms and non-coliforms respectively (**Table 1**). This represents a statistically significant change compared with 2009 - 2019 review [9] (Total 1002: coliform 94.4%, non-coliform

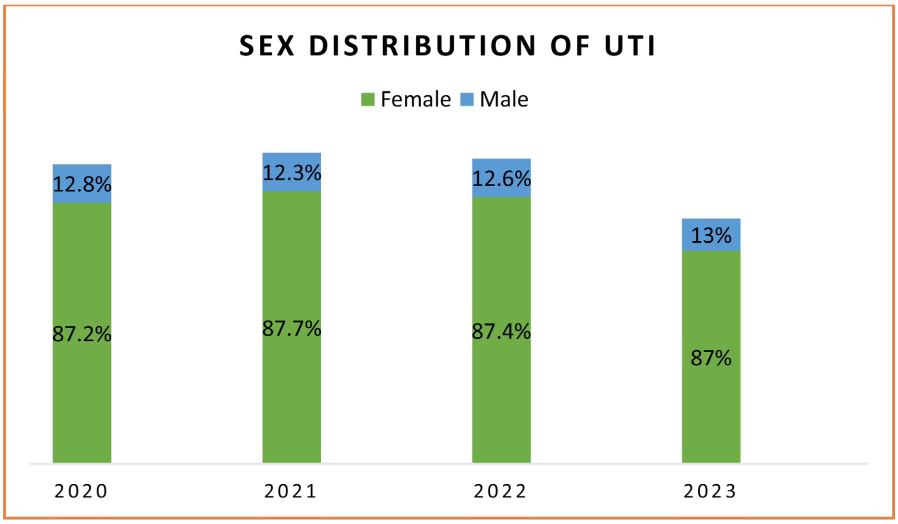

Figure 1. Sex distribution.

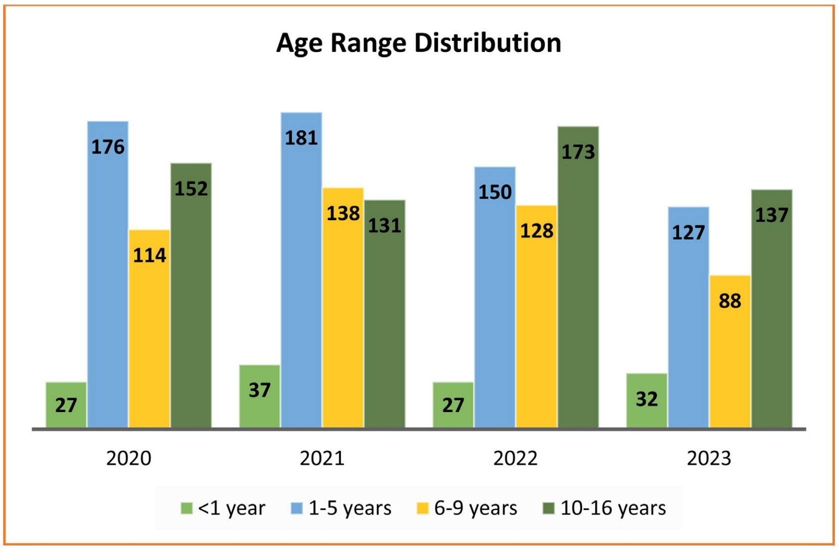

Figure 2. Age distribution.

Table 1. Frequency of coliform and non-coliform organisms causing UTI from 2020 to 2023.

Year	Coliform	Non coliform	Total
2020	388 82.7%	81 17.1%	469
2021	407 83.7%	80 16.4%	487
2022	398 83.3%	80 16.7%	478
2023	321 83.3%	63 16.7%	384 1818

5.6%. Chi square = 71.492; P ≤ 0.0001) and compared with 2002 - 2008 review [13] (Total 547: coliform 92%, non-coliform 8%. Chi square = 25.389; P ≤ 0.0001). In this study, *Enterococcus* (5.6%) and *Klebsiella* (4.6%) species were the most commonly isolated non-coliform organisms (Figure 3).

Figure 4 depicts the resistance pattern and trend of coliforms to four commonly used oral antibiotics from 2020 to 2023. Figure 5 illustrates the mean resistance compared with past UTI review cycles (2009 - 2013 and 2016 - 2019). Coliform resistance to nitrofurantoin (4% to 5.4%; mean 4.7) and cefalexin (6.6% to 7.5%;

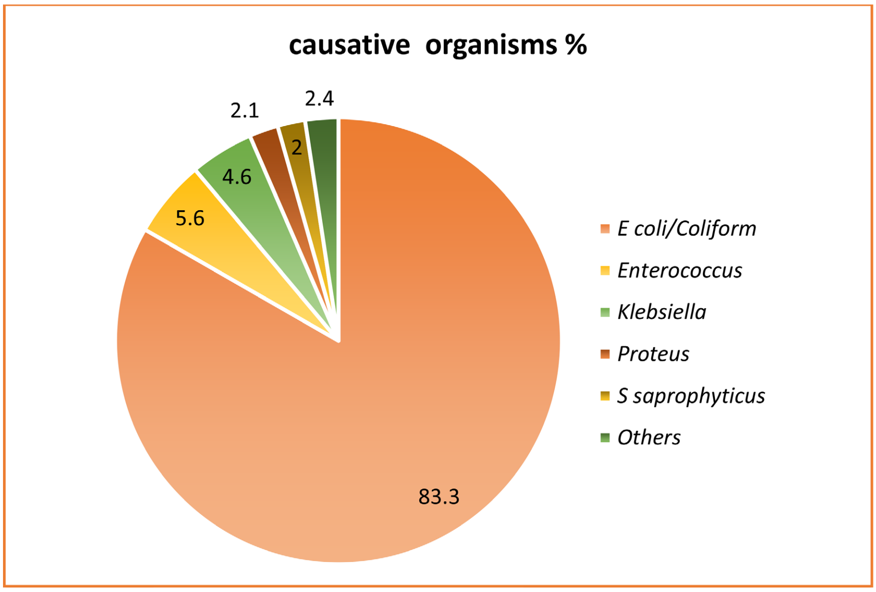

Figure 3. Common organisms causing UTI in children.

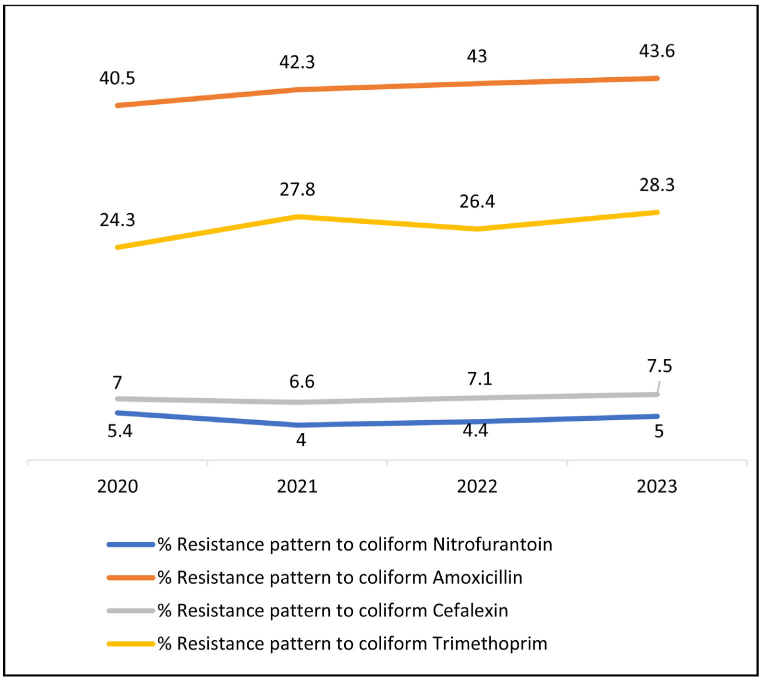

Figure 4. Resistance pattern and trend of coliform to common oral antibiotics.

mean 7.1) was low and remained stable over the 4-year period. On the other hand, resistance to trimethoprim (24.3% to 28.3%; mean 26.7) and amoxicillin (40.5% to 43.6%; mean 42.1) remained high. Mean coliform resistance to nitrofurantoin decreased from 6.0% in 2016-2019 review [9] to 4.7% (chi sq. 6.553; p = 0.0105) in 2020 - 2023. However, statistically significant decrease in mean coliform resistance to cefalexin (22% vs 7.1%; chi sq 12.648; p = 0.0004) and trimethoprim (42% vs 26.7%; chi sq 16.614; p < 0.0001) was noted when compared to 2016 - 2019 data [9]. **Figure 6** shows non-coliforms' resistance to commonly used oral antibiotics.

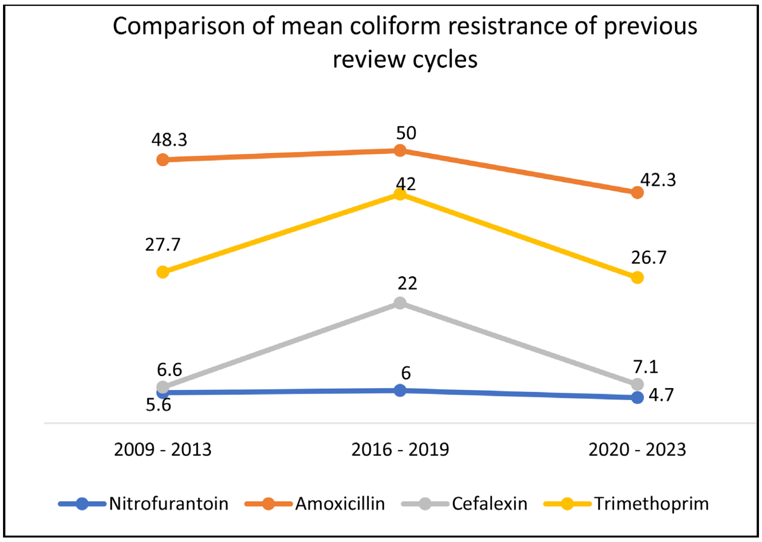

Figure 5. Comparison of mean coliform resistance to common antibiotics from past reviews.

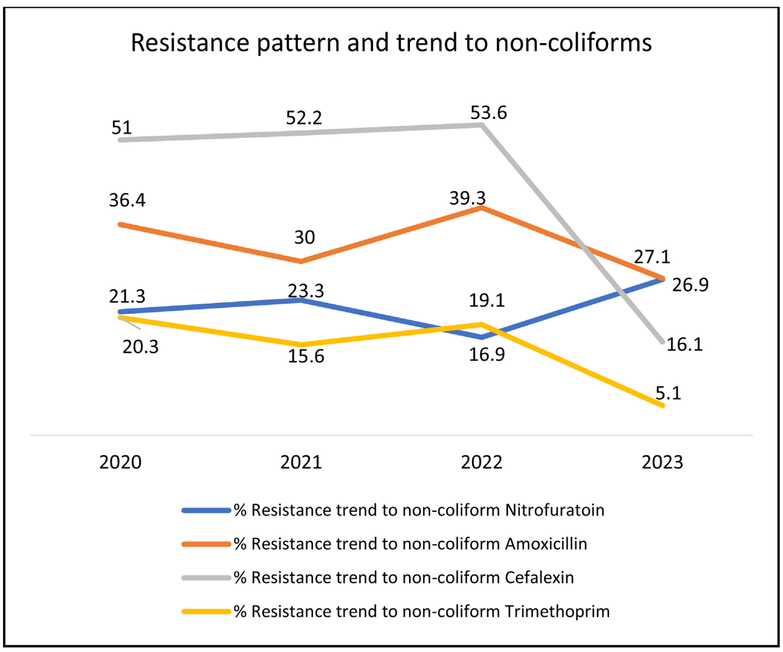

Figure 6. Resistance pattern and trend of non-coliforms to common oral antibiotics.

4. Discussion

This study findings highlight common bacterial organisms causing UTI in children and the increasing resistance trend to some commonly used oral antibiotics for treatment of UTI. These findings are significant as they will guide antibiotic choice in empiric treatment of UTI, before sensitivity results are available.

The demographic distribution in this study showed 67.4% of paediatric UTI occurred in children < 10 years, and females accounted for 87% of overall cases. This is in keeping with several hospital-based and community-based studies globally with reported female predominance ranging from 68% to 92% and a higher likelihood of UTI in younger children [9]-[15]. Our findings showed a slight increase in female predominance when compared with observations by Ahmed *et al.* [9] where they reported 82% UTIs in females. This could be due to practice changes over time or increase in frequency of collection of samples from one gender.

Several studies have shown *E coli* as leading cause of UTI in children [3] [5] [9]-[11] [14] [16]. *E coli* remained the most common cause of paediatric UTI in our locality (83.3%), although there has been a statistically significant drop when compared to 2002-2008 (92%) and 2009-2019 (94.4%) in the similar population [9] [13]. Chakupurakal *et al.* [13] in a previous review of 547 confirmed UTI in children < 16 years from 2002-2008 found *E coli* (92%) as leading cause, followed by *Pseudomonas* (3%) and *Proteus* (2%). Ahmed *et al.* [9] in a follow-up review of 1002 children < 16 years between 2009 to 2019 observed that 94.4% of UTIs were caused by *E coli*. Majority of UTIs in their study were in children seen in secondary care settings as they were not able to capture 5-year data (2014 - 2019) from the primary care providers. In contrast, 84% of the UTIs in the current review were from primary care providers. This may well explain potential selection bias resulting in differences in organism mix and resistance rates compared to previous studies in the same locality [9] [13]. Children being seen for UTIs in a secondary care setting may either have a failed treatment in primary care or have atypical UTI features from the outset. This may partially explain higher proportion of non-coliform organisms in our study. In a nationwide retrospective review of 53,203 UTI in children <18 years between 2007 and 2021 in Israel, Shkalim *et al.* [11] observed *E coli* (82.1%), *Proteus* (7.1%), *Pseudomonas* (3.7%) and *Enterococcus* (3.2%) as most common causes of UTI. Our study showed similar proportion of *E coli* (83.3%), as well as *Enterecoccus* (5.6%) being the leading gram-positive organisms causing UTI. On the other hand, *Klebsiella* (4.6%) and *Proteus* (2.1%) were found to be common gram-negative organisms. Marol *et al.* [14] in India, in a 2-year retrospective review of UTI in children < 13 years, found *E coli* (84%), *Proteus* (8.6%) and *Klebsiella* (6.4%) as the most common organisms causing UTI.

This study observed that coliforms are highly susceptible to nitrofurantoin and cefalexin. This is similar to several studies from United Kingdom and globally, which have reported good susceptibility of *E coli* to nitrofurantoin and cefalexin but rising resistance to amoxicillin, ampicillin and trimethoprim [9]-[11] [15]

[17]-[19]. In our study, coliform resistance to nitrofurantoin was the lowest and remained stable, ranging from 4% to 5.4% (mean 4.7%) from 2020 to 2023. This was followed by cefalexin with a mean resistance of 7.1% (6.6% to 7.5%) over the same 4-year period. Bean *et al.* [18] in a 12-month review of 1227 cases of community and hospital confirmed *E coli* UTIs in children < 16 years, in East London, reported coliform resistance to nitrofurantoin and cefalexin of 3.8% and 8.2% respectively. They also found a very high resistance of 62.3% and 46.3% of *E coli* to ampicillin and trimethoprim respectively. The susceptibilities of coliform to nitrofurantoin and cefalexin in our study were similar to their findings, although their resistance to ampicillin and trimethoprim was significantly higher compared to our findings. The two studies shared similar comparative methodology but were conducted at different time periods (2005 Vs 2020 - 2023). Practice changes over years with improving antimicrobial stewardship, may be partly responsible for the difference in some of the results. Butler *et al.* [17] in review of 1458 confirmed *E coli* UTIs in children < 5 years in primary care setting in Wales, reported *E coli* susceptibilities to amoxicillin, trimethoprim, cefalexin and nitrofurantoin of 45%, 74%, 95% and 98% respectively. This is similar to our study findings.

Ahmed *et al.* [9] in a retrospective review of UTI in children < 16 years from 2009 to 2019 in the same location as our study, reported high susceptibility of coliform to nitrofurantoin with a low mean resistance of 5.8%, which is similar to our recent findings. However, their study observed a mean coliform resistance of 14.5% and 32.4% to cefalexin and trimethoprim respectively. The reason for the higher resistance of *E. coli* to cefalexin (twice that observed in our study) remains unclear. Their study was mostly in children with confirmed UTI in secondary care setting while about 84% of UTIs in our study were in children seen in the primary care setting. Dean *et al.* [18] in London observed that *E coli* susceptibility to common oral antibiotics was higher for community UTI compared with those seen in the hospital settings. Some of these children may have had failed antibiotic treatment for UTI or received antibiotics for suspected other acute paediatric febrile illnesses by the general practitioner before being referred to secondary care.

Recent antibiotic exposure to children with UTI has been shown to increase the likelihood of antibiotic resistance. Could it also be that the general practitioners are prescribing antibiotics less frequently to children with common respiratory conditions (which are mostly viral)? Decreasing susceptibility of *E coli* to common antibiotics is not unique to United Kingdom. In Türkiye, Kilic *et al.* [10] in a retrospective review of UTI in children < 18 years in a tertiary hospital from 2020 to 2024, reported high susceptibility of *E coli* to nitrofurantoin (1.8% resistance) but significantly high resistance to ampicillin (67.4%), cefazolin (56.6%) and trimethoprim (33.3%). Cefazolin is a first-generation cephalosporin (so is cefalexin) and therefore 56.6% resistance is significantly higher than 7.1% observed in our study. In Organisation for Economic Co-operation and Development countries (OECD), Bryce *et al.* [19] in a systematic review and meta-analysis of *E coli* UTI in children < 17 years found a low pooled *E coli* resistance to nitrofurantoin, ceftazidime (representative for cephalosporin) and amoxicillin/clavulanate of 1.3%, 2.4% and 8.2% respectively. In contrast, pooled resistance for trimethoprim and ampicillin was much higher at 23.6% and 53.4% respectively. The percentage resistance was even higher for each antibiotic in non-OECD countries. Their findings in OECD countries are similar to the observations in our study.

Our study observed varied susceptibility of non-coliform organisms to common oral antibiotics: trimethoprim (85%), nitrofurantoin (77.9%), amoxicillin (66.8%), cefalexin (56.8%); this may be difficult to interpret due to small sample size and a mix of heterogeneous gram-positive and gram-negative organisms.

National Institute for Health and Care Excellence (NICE) [1] recommends use of oral trimethoprim, nitrofurantoin, cefalexin, amoxicillin (only if culture available and susceptible) or co-amoxiclav for treatment of UTI in children, to be guided by local susceptibility. From this study, cefalexin and/or nitrofurantoin would therefore be the best options for empiric treatment of UTI in children in our region. However, nitrofurantoin does not easily reach therapeutic levels in blood and other tissues [20] and therefore may not be very effective against upper UTI in children. Our study also observed increased *E coli* susceptibility to cefalexin compared to previous study in the same location. We therefore recommend cefalexin as first-line empiric antibiotic of choice for treatment of UTI in children in our locality, which should be reviewed as soon as culture results become available. We also recommend continuous urine culture results monitoring and surveillance of antibiotic resistance to detect any changes in susceptibility pattern and make necessary policy review. Antibiotic resistance is likely to increase with the use of broad-spectrum antibiotics, irrational prescriptions and use of continual antibiotic prophylaxis, especially in children with congenital anomalies of kidney and urinary tract [21]. UK published its 20-year vision for Antimicrobial Resistance (AMR) in 2019 with an ambitious target of ensuring AMR is controlled and contained by 2040. To deliver on this vision, the UK government has produced a series of 5-year national action plans to provide sustained and ongoing progress towards achieving the vision. Between 2024 and 2025, UK government aims to a) reduce the need for and unintentional exposure to antimicrobials, b) optimise the use of antimicrobials, c) invest in innovation, supply and access and d) be a good global partner [22]. These initiatives are likely to contribute to controlling global increase in AMR.

5. Conclusion

Local surveillance demonstrates that while nitrofurantoin and cefalexin remain effective against *E. coli*, amoxicillin and trimethoprim continue to exhibit high resistance rates. Cefalexin should be considered the preferred empirical treatment for paediatric UTIs in this locality, with therapy reviewed upon availability of culture results. Continuous monitoring will ensure early identification of shifts in susceptibility patterns.

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Ethics Approval

This study involved analysis of anonymised routine surveillance data and did not require formal ethics committee approval.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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