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Effective antimicrobial therapies of urinary tract infections among children in low- and middle-income countries: A systematic review

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ABSTRACT

Importance: Urinary tract infection (UTI) is one of the most common infections encountered in infancy and childhood. Despite the emerging problem of antibiotic resistance in recent years, the use of antibiotics for better management of UTIs is inevitable.

Objective: This study aims to explore the efficacy and adverse effects of the available antimicrobial agents that are used in pediatric UTIs in low- and middle-income countries (LMICs).

Methods: Five electronic databases were searched to identify relevant articles. Two reviewers independently performed screening, data extraction, and quality assessment of the available literature. Randomized controlled trials providing antimicrobial interventions in both male and female participants within the age range of 3 months to 17 years in LMICs were included.

Results: Six randomized controlled trials from 13 LMICs were included in this review (four trials explored the efficacy). Due to high heterogeneity across the studies, a meta-analysis was not performed. Other than attrition and reporting bias, the risk of bias was moderate to high due to poor study designs. The differences in the efficacy and adverse events of different antimicrobials were not found to be statistically significant.

Interpretation: This review indicates the necessity for additional clinical trials on children from LMICs with more significant sample numbers, adequate intervention periods, and study design.

KEYWORDS

Antimicrobial agents, Children, Efficacy, LMICs, Urinary tract infection

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INTRODUCTION

Urinary tract infection (UTI), one of the most common bacterial infections among infants and children, is usually characterized by a range of conditions caused by the existence of microorganisms in the urinary tract.[1] Both symptomatic and asymptomatic UTIs are frequent in children. Lower UTI or cystitis is usually symptomatic and may show dysuria, urinary incontinence, frequency, and urgency; upper UTI or acute pyelonephritis (highly increased inflammatory markers) shows symptoms like fever, back pain, abdominal pain, and vomiting.[2] Nonspecific symptoms in young children aged below 2 years often make it more difficult to distinguish pyelonephritis from cystitis.[2]

According to age and sex, the incidence of UTI varies and is known to be more common in boys during the first year of life,[3] but the incidence changes with increasing age and is found to be more frequent among girls than in boys (3% of girls, 1% of boys) during the pre-pubertal period.[4] The most common etiology for infection of the urinary tract of neonates is *Escherichia coli*, the same as in the other age groups.[5] In developing countries, UTI prevalence rates among children range from 6% to 37%, with Gram-negative coliform organisms such as *E. coli* and *Klebsiella* species being the most common bacterial isolates.[6] More importantly, pediatric UTI is associated with poor nutritional status in developing countries,[7] but despite reporting a high prevalence of UTI among these children, there is insufficient data about thorough research utilizing standardized microbiological techniques.[8] Thus, it creates concerns over antibiotic resistance as it is significant as many children require proper antibiotics for UTI treatment.[6]

After an initial UTI, children often encounter recurrent infections, especially 6–12 months after the initial infection of the urinary tract.[3] Children below 12 months of age are more vulnerable to long-term renal complications such as permanent renal scarring, poor renal growth, recurrent pyelonephritis, early hypertension, and impaired glomerular function due to recurrent UTI (rUTI).[9] Therefore, antibiotic prophylaxis is as important as a treatment to prevent a recurrence. UTIs and their recurrence management continue challenging pediatric care providers in developing countries as the treatment guidelines are not included in the generic Integrated Management of Childhood Illness algorithm.[10] With the upsurging of antibiotic resistance, oral treatment options are getting limited. Even though prophylactic antibiotics are commonly used to treat rUTIs, this elevates the risk of rUTIs with antibiotic-resistant strains due to a lack of proper guidelines.[11] Treatment with antibiotics often started empirically, even before the availability of urine culture for causative pathogens, antibiotic sensitivity, and resistance reports. More frequently, UTIs are managed with broad-spectrum antibiotics, whereas a small range of activities might be relevant to consider. Thus, concerns about infections with antibiotic-resistant strains are rising. Over the past years, the antibiotic sensitivity status of pathogens causing UTIs has been altered in communities and hospitals.[12] In recent years, many studies portrayed high resistance to antimicrobial agents like ampicillin, trimethoprim, and cephalosporins, leading to a shortage of options for first-hand treatment of UTIs.[13] Despite the burden of pediatric UTIs, accurate information regarding the resistance pattern of pathogens against antimicrobial agents in low- and middle-income countries (LMICs) is scarce.

Since the microorganisms causing UTIs and their susceptibility to antibiotics show regional differences, the susceptibility pattern of antibiotics found in regional data is more valuable than those of international studies.[14] In each area, the antibiotic choice should be selected as specified by the local antimicrobial sensitivity patterns as per suggestions of the American Academy of Pediatrics and the European Society for Pediatric Urology. Hence, it is essential to consider the antibiotic susceptibility status of bacteria regionally detected as a reference to the preferred antibiotics in the case of empirical therapy.[4] Although several randomized controlled trials (RCTs) have been done on UTI treatment in the case of children. Moreover, most studies in LMICs are from a single site, have a small sample size, or lack adequate methodologies for diagnosing UTIs, identifying pathogens, and measuring drug susceptibility. Therefore, this study aims to investigate the available appropriate antimicrobial therapies for better management of UTI among children in LMICs and assess their efficacy and adverse events. So, all the RCTs conducted in LMICs have been included in this review.

METHODS

Ethical approval

This systematic review has been completed following the methodology of Cochrane systematic reviews[15] and labeled the requirements stated in preferred reporting items for systematic reviews and meta-analysis protocols guidelines.[16,17] The approval for this systematic review was given by the Ethics Review Committee of North South University, Bangladesh (2020/OR-NSU/IRB-No.602), and the protocol was published after peer review.[18] This systematic review is registered in the International Prospective Register of Systematic Reviews. The registration number is CRD42021260415.

Patients or the public involvement: Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

Search strategy and selection criteria

A broad search strategy was developed by the team and a search expert, using the PICO format and the keywords such as "Children", "Pediatrics", "LMICs", "Developing countries", "Antibiotics", "Antimicrobial therapies", "Antibacterial treatment", "Efficacy", "Adverse events", "Urinary tract infection", "UTI", "Acute cystitis", "RCTs" to search different electronic bibliographic database including MEDLINE, The Cochrane Library (Cochrane Central Register of Controlled Trials), Scopus, Web of Science, and ClinicalTrials.gov. Studies were selected in compliance with the following inclusion criteria: all the articles in the English language and published between 2000 to February 2022, RCTs providing pharmacological intervention on both male and female participants within the age range of 3 months to 17 years in LMICs were included. Articles other than the English language were excluded due to the unavailability of a translator in the team. We decided to have articles from 2000 because we aimed to find out the details about the antibiotics of recent generations and primarily used.

We extracted data based on the key points, such as publication year, targeted countries, study design, sample size (both intervention and control group), population age and gender, identified pathogens, details about the interventions, primary and secondary outcomes of the selected studies, and recorded them in a structured excel format. Both the "title and abstract" and "full text" screening of the retrieved articles were executed by two reviewers independently, and a third reviewer resolved any disagreement. Every study was evaluated critically to assess the risk of bias by two independent authors.[19]

Meta-analysis was not done in this review because extracted data were dissimilar, and none of the studies performed analysis using odds ratio or risk ratio. The prespecified subgroup analysis planned to be done for covariates, such as ethnicity, sex, and age, could not be done. This analysis was not possible since most studies did not give data for distinct pediatric subpopulations.

RESULTS

Selection of studies

A comprehensive search of five electronic databases recognized 1070 potential studies. After removing 142 duplicates, the titles and abstracts of 928 articles were reviewed to identify relevant literature. We excluded 883 articles based on the inclusion and exclusion criteria, leaving 45 papers for the full-text evaluation. In the final stage of selection, 39 more studies were rejected due to the following reasons: nine articles were not in English; full texts were not available for one article; 24 studies did not represent LMIC countries; five studies did not have a randomized controlled design. We attempted to contact that one author regarding access to the full texts but did not receive any response to the e-mails. After the complete screening, six studies were selected for the final systematic review. Figure 1 presents the PRISMA flow diagram of the detailed selection process of the studies. Four of the included trials explored the efficacy of drugs in treating UTIs and compared safety and tolerability.[20–23] Two of the trials were prophylaxis studies and explored the safety and adverse events only.[24,25]

Study sites

The reviewed studies were from 13 different LMICs around the globe. Seven countries were from the North and South American regions (Mexico, Costa Rica, Colombia, Brazil, Venezuela, Argentina, and Peru); two countries were from Europe (Russia and Ukraine); two countries were from Asia (Malaysia, and Iran); South Africa was from the African region; and one transcontinental country–Turkey. Three of the studies were multi-centered,[20–22] and the rest were single-center trials,[23–25] the maximum number of study centers located in South American countries. The multi-centered studies were conducted both in LMICs and high-income countries.[20–22]

Study characteristics

Table 1 comprises the basic characteristics of the included RCTs. All the research was active-controlled trials comparing a relatively newer drug to a standard intervention for UTIs in pediatric patients. However, the study by Belet et al.[24] alone had three arms comparing the efficacy of three different antibiotics. One of the trials was a pilot study by Mohseni et al.[25] from Iran. All the included studies had data on 511 children collectively within the age range of 3 months to 17 years. The different antimicrobial agents under trial were ertapenem, ceftriaxone, trimethoprim-sulfamethoxazole (TMP-SMX) combination, cefadroxil, cefprozil, ceftazidime-avibactam combination, doripenem, cefixime, ceftizoxime, and nitrofurantoin. Mohseni et al.[25] assessed the efficacy of a probiotic-antibiotic combination. The probiotics were given in intervals over a mean period of 2 years. The study by Belet et al.[24] was a prophylaxis study with a duration of three months. The other trials had lengths of 2 weeks or less.

Risk of bias within the studies

Figures S1 and S2 demonstrate the risk of bias assessment within individual studies according to the Cochrane risk of bias tool. There is a potential risk of selection bias within the trials as only two out of six reported the generation of random sequences aptly.[24,25] Moreover, none of the

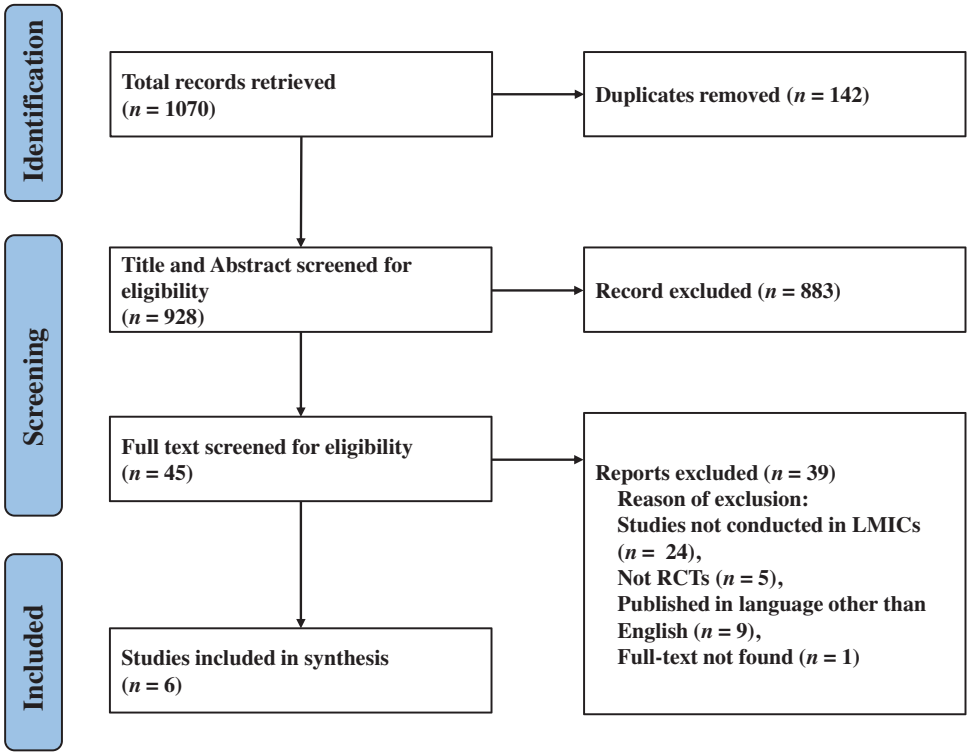

FIGURE 1 Flowchart of the selection of studies. LMICs, low- and middle-income countries; RCTs, randomized controlled trials.

studies clearly stated the allocation concealment process. Two out of six were blinded at the level of participants and implementers,[20,22] whereas two of the trials did not report any blinding at all.[24,25] The other studies were unclear about blinding the patient parties or the study personnel. The outcome assessors were blinded in two trials only.[20,21] The information was indeterminate in the rest. We could not detect any attrition or reporting bias, as data on the principal outcome and other outcomes of interest have been recorded precisely. In the trial by Belet et al.,[24] it was mentioned that the calculation of sample size and power was not done primarily. However, the rest of the articles were not explicit about other potential biases.

Study participants

In total, six RCTs included 511 pediatric patients of both sexes. However, the three multicountry studies did not differentiate between the participants from LMICs and high-income countries. The age of the participants ranged from 3 months to 17 years across the studies. However, Gok et al.[23] did not mention any specific age criterion. Belet et al.[24] and Mohseni et al.[25] had a slightly narrower range, 6 months to 15 years and 3 to 15 years, respectively. No justification or reason was given for their choices.

The studies commonly defined UTI as the presence of $\geq 10^5$ colony-forming units (CFU) of any recognized uropathogen in mid-stream, clean-catch urine samples. Belet et al.[24] and Mohseni et al.[25] specifically targeted rUTI patients for their studies. Recurrence was defined as two or more infections in the last 6 months by Belet et al.[24] Mohseni et al.[25] considered rUTI as an infection that occurs after the full resolution of a previous one. Gok et al.[23] included UTI patients of any type. The rest of the studies were on patients with complicated UTI (cUTI).[20–22] cUTI referred to urinary infection combined with any other urological abnormality, such as pyelonephritis, which did not respond well to traditional treatments.

Interventions

The studies included in this systematic review were diverse in terms of study settings, duration, and interventions. Two of the trials were prophylaxis studies. The rest of the studies were primarily on the efficacy of drugs in treating UTIs and comparing safety and tolerability.

Belet et al.[24] studied the efficacy of TMP-SMX, cefprozil, and cefadroxil as prophylactics in children suffering from rUTI. Patients with at least two or more urinary infections in the last 6 months were chosen for the study and divided into three groups. The doses were as follows: TMP-SMX 1–2 $mg \cdot kg^{-1}$, cephadroxil 5 $mg \cdot kg^{-1}$, and cefprozil 5 $mg \cdot kg^{-1}$. The drugs were given once daily in the evening for 3 months, followed by a follow-up period of six months.

TABLE 1 Characteristics of the included studies

Reference	Country†	Study design	Sample size	Age; Gender (Population)	Intervention	Duration of intervention
Arguedas et al. 2008[20]	Colombia, Peru, South Africa, Malaysia, Brazil, Costa Rica, Venezuela	Randomized, double-blind, active-controlled trial	Arm 1: 100; Arm 2: 34	3 months–17 years; both male and female	Ertapenem versus Ceftriaxone	Median duration 4 days
Bradley et al. 2019[21]	Russian Federation, Turkey	Single-blind, randomized, multicenter, active-controlled, phase 2 study	Arm 1: 68; Arm 2: 29	≥3 months to <18 years; both male and female	Ceftazidime-Avibactam versus Cefepime	7–14 days
Cannavino et al. 2015[22]	Argentina, Brazil, Colombia, Mexico, Ukraine	Prospective, multicenter, randomized, double-blind, double-dummy, active-comparator, controlled study	Arm 1: 30; Arm 2: 10	3 months to <18 years; both male and female	Doripenem versus Cefepime	72 h
Gok et al. 2001[23]	Turkey	Randomized, prospective, single-center study	Arm 1: 25; Arm 2: 29	2–13 years; both male and female	Cefixime versus Ceftizoxime + Cefixime	10 days versus Ceftriaxone intramuscular injection for 2 days followed by oral Cefixime for 8 days
Belet et al. 2004[24]	Turkey	Randomized comparative study	Arm 1: 21; Arm 2: 25; Arm 3: 34	6 months–15 years; both male and female	Trimethoprim-Sulfamethoxazole versus Cefadroxil versus Cefprozil	3 months prophylaxis
Mohseni et al. 2013[25]	Iran	Prospective, randomized pilot study	Arm 1: 53; Arm 2: 53	3–15 years; both male and female	*Lactobacillus acidophilus* & *Bifidobacterium lactis* + Nitrofurantoin versus only Nitrofurantoin	Meantime 2 years

†Multicenter trials included participants from low-, middle-, and high-income countries.

Clinical and laboratory investigations, such as urine analysis and cultures, were done on a monthly basis. Patients with symptomatic episodes of UTI during the prophylaxis period were treated with appropriate antimicrobials for 10–14 days. Another prophylaxis research was by Mohseni et al.,[25] who conducted a pilot study to compare the efficacy of a probiotic-nitrofurantoin combination versus nitrofurantoin alone in preventing rUTI in children. Both arms were given 100 ml of plain yogurt without the probiotics daily for 2 weeks prior to the study. The probiotic yogurt (containing *Lactobacillus acidophilus* and *Bifidobacterium lactis*, 107 CFU·ml^{-1}) was taken three times a day concomitantly with a once-daily dose of nitrofurantoin (1 mg·kg^{-1}) at night, while the comparison group received the standard treatment with nitrofurantoin alone (also 1 mg·kg^{-1} at night). The duration of nitrofurantoin doses was not stated. Clinical examination and urine culture were done to confirm febrile UTI in patients during the study period, and appropriate therapeutic doses were given following the treatment guidelines.

Arguedas et al.[20] compared the safety profile, tolerability, and efficacy of ertapenem with ceftriaxone in child patients having cUTI. The doses were different in the 3 months–12 years group from the 13–17 years old children. The doses were as follows: ertapenem 30 mg·kg^{-1}·day^{-1} in two divided doses for 3 months–12 years group, and 1 g daily for the older children; ceftriaxone 50 mg·kg^{-1}·day^{-1} in two divided doses for the younger group, and 50 mg·kg^{-1}·day^{-1} once daily for the rest. All the patients were switched to oral therapy with amoxicillin and clavulanic acid combination (45 mg·kg^{-1}·day^{-1} twice) after 3 days. Children were monitored further for 2 weeks after discontinuation of therapy.

Two other similar studies were by Bradley et al.[21] (ceftazidime-avibactam *vs*. cefepime) and Cannavino et al.[22] (doripenem *vs*. meropenem/cefepime). Both the RCTs involved cUTI pediatric patients. In the study by Cannavino et al.,[22] one group received a 30-min infusion of normal saline as a placebo followed by intravenous doripenem (20 mg·kg^{-1}, maximum 500 mg) three times a day. In contrast, the control group was given an 8-hourly dose of intravenous cefepime (50 mg·kg^{-1}, maximum 2 g) or meropenem (20 mg·kg^{-1}) followed by a 60-min infusion of normal saline as a placebo. Bradley et al.[21] did not mention the doses of their interventions in detail. In both cases, a switch to oral drugs was permitted after 3 days with a maximum of 2 weeks of treatment and one or two post-treatment follow up to test if the patients are cured.

Gok et al.[23] assessed the effects of cefixime alone versus the combination of cefixime-ceftizoxime in treating UTIs in pediatric patients.[23] The cefixime group received an oral dose of 8 mg·kg^{-1}·day^{-1} for 10 days, whereas the combination group received parenteral ceftizoxime (50 mg·kg^{-1} twice a day) for 2 days, followed by 8 days of oral cefixime in the dose mentioned. Urinalysis and urine cultures were done multiple times during the treatment phase, 2 days and 3 weeks after the end of the treatment regimen.

Findings

Due to the heterogeneous nature of the trials, we did not perform a meta-analysis of the extracted data. All the studies reported adverse events and cure rates in percentages except the trial by Arguedas et al.[20] where cure rates were not mentioned. A summary of the results from these studies has been presented in Table S1.

Both Belet et al.[24] and Mohseni et al.[25] tested the efficacy of drugs in preventing rUTIs in children. The Belet et al.[24] study tried three different drugs (TMP-SMX, cefadroxil, and cefprozil) on three different arms.[24] Both crude intention-to-treat and per-protocol analyses yielded the same results regarding the incidence of symptomatic and asymptomatic UTIs in the study participants. Both during the prophylaxis period and the follow-up period, no significant difference was observed in the frequency of symptomatic UTIs, but there was a significant difference in the case of asymptomatic bacteriuria episodes. During 225 patient months, no case of asymptomatic UTI was observed in the cefadroxil arm. Also, no adverse event was reported in this group throughout the study. In this trial, the TMP-SMX and cefprozil groups had seven and 12 asymptomatic cases, respectively. Side effects observed in these groups involved vomiting, abdominal pain, rashes, vulvovaginitis, and constipation. Cefadroxil showed the best results among the drugs on trial.

On the other hand, Mohseni et al.[25] tested the efficacy of nitrofurantoin versus nitrofurantoin-probiotics combination in preventing the recurrence of UTI in pediatric patients. The researchers observed a decrease in the incidence of UTIs among the participants, and the difference between the two groups was not significant. However, the probiotic-antibiotic combination group did not have any febrile UTI cases in the last year of treatment, which was significantly different from the antibiotic group (0.13 persons per year). The overall percentage of patients with UTI, as well as renal scarring, was lower in the combination group but was not statistically significant. The researchers concluded that the antibiotic-probiotic combination was more efficient compared to therapy with antibiotics only.

The trials by Arguedas et al.[20] (ertapenem *vs*. ceftriaxone), Bradley et al.[21] (ceftazidime-avibactam *vs*. cefepime), and Cannavino et al.[22] (doripenem *vs*. meropenem/cefepime) were all designed to assess the safety, tolerability, and efficacy of drugs in treating cUTI patients and were comparable to each other in terms of methodology. Arguedas et al.,[20] however, only tested the respective drugs for safety and tolerability and did not report any cure rate.

In the study by Bradley et al.,[21] overall 53.7% and 53.6% of patients in the ceftazidime-avibactam and the cefepime groups respectively experienced adverse events. Most of the events were known adverse effects of the therapies and were mild to moderate in nature. About 11.9% of patients in the ceftazidime-avibactam group had serious adverse events, whereas it was 7.1% in the cefepime group. One of these serious adverse events, a severe neurological dysfunction 2 days after beginning intravenous administration, was thought to be caused by ceftazidime-avibactam therapy. In the Cannavino et al.[22] trial, abdominal pain, nausea, vomiting, and diarrhea were common side effects reported by the patients. 30% of the patients on cefepime experienced at least one serious adverse effect, while it was only 3.3% in the doripenem arm. This difference, however, was not statistically significant. The researchers concluded that the results could not be generalized due to inadequate sample size. Common adverse effects seen in the Arguedas et al.[20] study were diarrhea, vomiting, pain and erythema at the infusion site. Each arm had only one patient with a serious adverse reaction to the drugs (0.33% in the ertapenem arm, 1% in the ceftriaxone arm). Overall, the findings in the two groups were comparable, as stated by the authors.

Bradley et al.[21] observed favorable outcomes both in terms of clinical and microbiologic response rates in both arms of the study. Clinically, 88.9% and 82.6% of the patients responded to the treatment regimen in the ceftazidime-avibactam and the cefepime groups, respectively, whereas normal laboratory findings were observed in 79.6% and 60.9% of the participants. Overall, the response

rate was 72.2% in the ceftazidime-avibactam arm and 60.9% in the cefepime arm during test-of-cure (TOC) visits. Ceftazidime-avibactam was concluded to be preferable over the comparator and showed similar results in curing cUTI in pediatric patients as seen in trials with adult participants. On the other hand, in the trial by Cannavino et al.,[22] 66.7% and 50% of the patients were reported to be clinically cured during the TOC visits. Doripenem is considered slightly better in treating cUTI, although the low enrollment of participants was a limitation, and further research was called to be conducted. Lastly, the Gok et al.[23] study reported 92% and 86% cure rates in the cefixime and ceftizoxime-cefixime arms respectively at the end of the treatment phase. Oral cefixime was concluded to be a safe and effective treatment option for UTIs in children. *E. coli* was identified as the most common etiological agent of UTI in all the studies mentioned above except the Cannavino et al.[22] trial.

DISCUSSION

As UTI is one of the prevalent bacterial diseases among children, proper antibiotic prophylaxis and treatment are necessary. However, integrated management guidelines are lacking in countries with poor socioeconomic status.[26] Already, several RCTs on different antimicrobial therapies to treat pediatric UTIs have been performed in high-income countries to compare various aspects, such as efficacy, safety, tolerability, appropriate duration, and routes of administration, adverse events, and others but there is a significant deficiency of this information in LMICs.[27] Systematic reviews that were previously performed discussed the effective use and duration of multiple antibiotics used in pediatric UTIs. In the case of acute pyelonephritis in children, 14 days of oral treatment with third-generation cephalosporin was found functional as a short-course intravenous antibiotic treatment.[28] Another review compared the durations of different antibiotics and concluded that 10 days of antibiotic treatment is significantly more worthwhile in treating bacteriuria in children.[29] Almost all the RCTs included in these two reviews were conducted in hospital settings in different high-income countries.

Our review was designed to include all the RCTs addressing aspects of antibiotic treatment for the children of LMICs with UTIs. However, three multi-country trials included in this review did not differentiate participants between LMICs and high-income countries. We included them as they were conducted in LMICs as well. This is again highlighting the lack of trials in LMICs. Among the six final articles, only one trial included countries in Southeast Asia and African region. Asian guidelines recommend a bundle of empirical antibiotics (both oral and intravenous) depending on different perspectives to treat UTIs in children, but their efficacy and side effects are somewhat unknown.[30] In this review, we learned about nine antibiotics. The six RCTs compared several intravenous antibiotics of different generations (especially cephalosporins and carbapenem), the synergistic effect of combination drug therapy, the comparison of efficacy between oral and IV antibiotics, and the preventive outcome of prophylactic antibiotic use. A new carbapenem (ertapenem) was compared with third-generation cephalosporin to treat cUTI in children.[20] Ertapenem is particularly suitable for community-acquired infections, which has been previously found safe and efficacious to treat complex intra-abdominal and acute pelvic infections in children.[31] This study recommended parenteral ertapenem therapy to treat children with cUTI, community-acquired pneumonia, and skin and soft-tissue infection. Another carbapenem group (doripenem) and cephalosporin (cefepime) showed numerically similar clinical and microbiologic outcomes as effective intravenous antimicrobial therapies to manage pediatric cUTI cases.[22] One of the newest third-generation cephalosporin (ceftazidime) was studied by Bradley et al.[21] in combination with avibactam (non-β-lactam β-lactamase inhibitor) to see the outcome of a combination drug against antibiotics only to treat cUTI in children. In an era of the rising frequency of multidrug-resistant Gram-negative infections, ceftazidime-avibactam may provide clinicians with a beneficial therapy alternative in the initial treatment of children with cUTI caused by susceptible pathogens. Considering the cost and burden of injectable antibiotics, Gok et al.[23] compared 10 days of oral therapy with cefixime to 2 days of intramuscular ceftriaxone followed by 8 days of oral cefixime treatment. Cefixime is the first oral cephalosporin of the third generation, which alone showed similar efficacy as an injectable and oral combined therapy. Two included RCTs' primary objective was to compare the efficacy of different antibiotics as a prophylaxis to treat children with rUTIs. Belet et al.[24] demonstrated the comparison of TMP-SMX, cefprozil, and cefadroxil, where cefadroxil prophylaxis was superior in preventing asymptomatic bacteriuria episodes and somewhat better in preventing symptomatic UTIs in children with recurrence but having a normal urinary system. Lastly, the efficacy of probiotics administration in addition to an antimicrobial agent (nitrofurantoin) brought up a new effective result in Mohseni et al.[25] in the case of preventing rUTI in children.

As meta-analysis could not be done in this review, an overall assumption about the cure rate and side effects after antimicrobial agents were obtained from the targeted RCTs. Here, the median sample size was 88.5, which is small, and making it difficult to conclude any antibiotics or regimens as superior. The deficit of reporting about the

randomization technique, allocation concealment, blinding in most participants, and high losses to follow-up in three studies are likely to contribute to biases in the reported results. Unfortunately, no study analyzed the efficacy of antibiotics by risk ratio and confidence interval. This hampered our efforts to offer a complete picture of the benefits and drawbacks of antibiotic treatment for UTIs in children. Selected original articles also lack information regarding any urological abnormalities, bladder bowel dysfunction, number of previous UTIs, or previous antibiotic exposures, which confronted this review with several limitations. Moreover, no study reported data on resistant organisms. Antibiotic resistance complicates the choice of empiric regimens. It is anticipated to become a more significant concern in the future, especially since the majority of doctors give antibiotics without knowing the findings of urine cultures. It may be favourable to use local antimicrobial susceptibility data (e.g., hospital or laboratory data) to anticipate which antibiotics are likely to be more advantageous. The optimal antibiotic treatment duration in children has both financial and practical concerns. As it is potent and easily affordable, oral treatment can promote compliance in complicated and uncomplicated UTIs. These benefits are much more significant in low-resourced continents and countries with low- and middle-socioeconomic status.

In conclusion, because of the scarcity of scientific evidence in LMICs and the low quality of the studies, no firm conclusions concerning our objectives could be established. Recently, two large multi-centered RCTs on antibiotics of new generations are ongoing, including several LMICs.[32–34] Results from these studies can assist further in being more specific in selecting appropriate antibiotics to treat pediatric UTIs. Moreover, single-dose intravenous or short-course oral antibiotic trials can be the next focus, as these are cost effective and will allow considerable benefits to Asian and African countries. So, our systematic review emphasizes the importance of future research prospects on UTIs in children and the need for additional clinical trial studies with larger sample sizes, appropriate intervention periods, and study design, mainly focusing on LMICs.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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