**Urinary Tract Infection Antibiotic Trial Study Design: A Systematic Review**

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**Abbreviations:**AAP, American Association of Pediatrics

CDC, Center for Disease Control and Prevention

CFU, colonies forming unit

CONSORT, Consolidated Standards of Reporting Trials

CT, clinical trial

EMA, European Medicines Agency

EOT, end of treatment

ESBL, extended-spectrum beta-lactamase

FDA, Food and Drug Administration

OAT, on-antibiotuc therapy

TOC, test of cure

UTI, urinary tract infection

WHO, World Health Organization

**Table of Contents Summary:** A wide variability of inclusion criteria and timing for endpoints assessment was observed in pediatric febrile UTI clinical trials. Harmonized pediatric guidance is required.

**Contributors’ Statement Page**

Dr. Basmaci and Dr. Vazouras conceptualized and designed the study, collected data, carried out the initial analyses and interpretation of data, drafted the initial manuscript.

Dr. Bielicki and Prof. Sharland conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript.

Dr. Folgori conceptualized and designed the study, carried out the initial analyses and interpretation of data, and critically reviewed the manuscript.

Dr. Hsia, Prof. Zaoutis contributed to analysis and interpretation of data, and critically reviewed the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

**Abstract**

**Context:** Urinary tract infections (UTIs) represent a common bacterial infections in children. No guidance on the conduct of pediatric febrile UTI clinical trials (CTs) exist.

**Objective:** To assess the criteria used for patients selection and the efficacy endpoints in febrile pediatric UTI CTs.

**Data Sources:** Medline, Embase, Cochrane central databases and ClinicalTrials.gov between January 1, 1990, and November 24, 2016.

**Study Selection:** We combined MeSH and free-text terms for: “urinary tract infections”, AND “therapeutics”, AND “clinical trials” in children (0–18 years), identifying 3,086 papers.

**Data Extraction:** Two independent reviewers assessed study quality and performed data extraction.

**Results:** Forty CTs investigating 4,381 cases of pediatric febrile UTIs were included. Positive urine culture and fever were the most common inclusion criteria (93% and 78%, respectively). Urine sampling method, pyuria and colonies thresholds were highly variable. Clinical and microbiological endpoints were assessed in 88% and 93% of the studies, respectively. Timing for endpoints assessment was highly variable, and only 3 studies (17%), out of the 18 performed after the Food and Drug Administration 1998 guidance publication, assessed primary and secondary endpoints consistently with this guidance.

**Limitations:** Mixed population of healthy children and with underlying condition. Six trials studied a subgroup of patients with afebrile UTI.

**Conclusions:** We observed a wide variability in the microbiological inclusion criteria and the timing for endpoints assessment. The available guidance for adults appear not to be used by pediatricians and do not seem applicable to the childhood UTI. A harmonized design for pediatric UTIs CT is required.

**Key words:** urinary tract infection; pyelonephritis; clinical trial; study design; antibiotics; children

**Introduction**

Urinary tract infections (UTIs) represent one of the most common bacterial infections in children aged younger than 2 years, especially in febrile infants without localizing signs. 1-3 Appropriately treated UTIs have, overall, a good outcome. However, UTIs can occasionally lead to renal scarring, especially in children with delayed treatment or with a history of underlying vesicoureteral reflux. 4-6 The emergence of resistant strains increases the risk of first-line treatment failure. 7, 8 The World Health Organization (WHO) recently highlighted the increased incidence of *Escherichia coli* resistant to fluoroquinolones and third generation cephalosporins. 7, 8 Extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* have, also, been identified as a serious threat by the Center for Disease Control and Prevention (CDC). 7, 9 A recent systematic review and meta-analysis on ESBL-producing *Enterobacteriaceae* paediatric UTI reported a prevalence of 14%, and identified risk factors such as vesicoureteral reflux, history of UTI and recent antibiotic use. 10 Patients infected by these resistant pathogens often experience higher length of stay and poor clinical outcomes 10, 11 and require the use of broad-spectrum systemic antibiotics, such as carbapenems, potentially driving the emergence of pan-resistant strains. Both strategic and pharma-led pediatric clinical trials (CTs) focusing on the treatment of febrile UTIs due to resistant pathogens are now required. The US Food and Drug Administration (FDA 1998 and 2015) 12, 13 and the European Medicines Agency (EMA 2012) 14, 15 have provided guidance for conducting CTs in adults with complicated urinary tract infections. However, there is no guidance on the conduct of pediatric UTI trials.

This review aims to assess the variability in the study design of CTs addressing efficacy of antibiotics in children with febrile UTIs. The specific objectives were to systematically review (i) the extent to which UTI trials apply consistent definitions for participant selection or exclusion, (ii) the consistency of pediatric UTIs trials design with the FDA and EMA guidance for adults complicated UTIs trials 12-15 and with the American Academy of Pediatrics (AAP) and National Institute for Health and Care Excellence (NICE) clinical management guidelines, 16-19 and (iii) the items and timing used to evaluate the endpoints in UTIs CTs.

**Methods**

**Search strategy and selection criteria**

This systematic review was conducted according to the PRISMA guidelines. 20 We searched Medline, Embase and Cochrane central databases between January 1, 1990, and November 24, 2016, combining MeSH and free-text terms for: “urinary tract infections”, AND “therapeutics”, AND “clinical trials” in children (age range 0–18 years). We searched ClinicalTrials.gov from January 1, 1990, to November 24, 2016, with the above terms for ongoing, completed, and unpublished trials. The search was limited from 1990 onwards as we considered reporting to be incomplete in earlier trials (http://www.consort-statement.org/about-consort/history). No language restriction was initially applied. The full search strategy is available in the Supplemental Material (Supplemental Methods). We included randomized CTs reporting the efficacy of antibiotics or other type of antibacterial or anti-inflammatory agents in children presenting with acute febrile UTI. We excluded studies with the following criteria: i) exclusively focusing on the following clinical infection syndromes: uncomplicated UTI, cystitis, lower UTI, recurrent UTI, UTI due to inconsistent pathogens (as defined by FDA guidance; 13 e. g. viral, fungal, parasitic or sexually transmitted infections); ii) studies including exclusively patients with underlying conditions (e. g. major UT abnormalities, immunodeficiency, diabetes, spinal cord injury); and iii) those targeting only antibiotic prophylaxis, pharmacokinetics, safety or long-term endpoints, such as renal scarring, because of the absence of evidence of treatment’s efficacy on the resolution of infection. We included trials with different type of infections only if specific information (inclusion and exclusion criteria and endpoints) on “upper UTI” or “pyelonephritis” or “febrile UTI” or “complicated UTI” outcomes could be identified. Studies were only included if age-related information could be identified. We defined children as aged 0–18 years, including neonates. Two reviewers (RB and KV) independently extracted the following data according to pre-specified criteria: year of publication, country, language, study period, study design, study population, inclusion and exclusion criteria, and type and timing assessments of clinical, laboratory, microbiological and radiological endpoints. Disagreements were resolved in discussion with a third reviewer (JB).

**Quality score assessment**

To score the quality of trial reporting, we used the Consolidated Standards of Reporting Trials (CONSORT) Statement 2010 for reporting parallel-group randomised trials. 21 We calculated the proportion of items of the CONSORT 2010 checklist adequately reported for each study (Supplemental Table 1). We did not exclude any studies based on quality. We could not assess quality of trials identified through ClinicalTrials.gov because the full protocols were not accessible, nor for any published abstracts, where full texts were not available.

**Statistical analysis**

We calculated the proportion of included studies that used each type of inclusion and exclusion criteria as well as clinical, laboratory, microbiological, and radiological endpoints. Categorical variables were compared by Chi-square test. We used two-tailed Mann-Whitney U tests for two independent samples to compare CONSORT scores for papers according to the year of publication (up to and including 2001, or after 2001 [publication of the first revision of the CONSORT statement]) to determine changes in reporting after the publication of the revised criteria. A p-value <0.05 was considered statistically significant. All statistical tests were performed with R statistical package 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

**Results**

**Study selection and description**

We identified 3,086 published studies and registered CTs. Forty studies were included in the final analysis (Figure 1). Of those, 35 trials were published between 1991 and 2016; 22-56 four were registered clinical trials (two recruiting and two were terminated) (ClinicalTrials.gov, numbers NCT01595529, NCT00724256, NCT01110408, NCT02497781) and one was a published abstract presented at an international congress 57 (Supplemental Table 1). Thirty-nine countries were represented; 24 studies were carried out in high-income countries 24, 26-30, 32-35, 37-43, 45-47, 49, 53 (NCT01595529, NCT00724256); 11 in middle or lower-income countries 22, 23, 25, 36, 44, 48, 50, 54-57 and five were conducted in all settings 31, 51, 52 (NCT01110408, NCT02497781), according to the 2016 World Bank Classification. 58 Of the 36 published papers, 31 (86%) were in English; 22-25, 27-33, 37-44, 46-51, 53-57 three (8%) in French; 26, 34, 35 one (3%) in Italian, 52 and one (3%) in Spanish. 45 Three studies described various infectious syndromes, but UTI-related inclusion and exclusion criteria, specified populations with a UTI, as well as relevant endpoints were clearly identifiable. 26, 31, 52

The median duration of the study periods was 25 months (interquartile range: 14 - 37 months), while eight studies (20%; 8/40) did not report the study periods. 22, 39, 46, 49, 51-53, 56 Six trials (15%) were double-blinded, 22, 25, 38, 55 (NCT01595529, NCT01110408) and three (8%) were single-blinded, 24 (NCT00724256, NCT02497781) while 14 (35%) were multicenter trials. 26, 28, 31, 33-35, 37, 41-43, 46, 47, 51, 52 Twelve (30%) 24, 25, 33, 37, 39, 41, 43, 46, 47, 49 (NCT01110408, NCT02497781) studies were sponsored by pharmaceutical company, while 12 (30%) 22, 28, 30, 32, 34, 35, 38, 42, 55, 56 (NCT01595529, NCT00724256) were investigator led. In 16 studies, information on funding source was not reported.

**Quality assessment of included studies**

Overall, the published studies reported on a median of 59% (range 31-94%) of CONSORT items (Supplemental Table 1,). Studies published prior (n=21) and after 2001 (n=14) showed no significant difference in the median percentage of CONSORT items reported (57% versus 69%, respectively; p=0.2).

Only 12 (30%) studies reported the estimated sample size in order to detect statistically significant difference between groups 22, 27-29, 32, 37, 41-43, 46, 47, 55 and the required number of patients at the end of the study was not reached in three CTs, mostly due to secondary consent withdrawal, inadequate follow-up or protocol violations. 28, 32, 43

**Included population**

A total of 4,896 children (4,381 (90%) with a febrile UTI and 515 (11%) with an afebrile UTI) were included in the 36 published studies. Six (15%) out of the 40 studies included a mixed population. 23, 31, 35, 37, 46, 49 The characteristics of the included patients are reported in Supplemental Table 2, highlighting a wide variability in diagnostic terms used. The exact age-range distribution of the studied population is available in the Supplemental Figure 1. Only three studies (8%) included neonates (<28 days). 26, 38, 52

**Patient inclusion criteria**

The inclusion criteria used in the 40 included studies are presented in Table 1.

Microbiological and clinical criteria were the most commonly used as core inclusion criteria (Table 1). A positive urine culture was the most common inclusion criterion (37 studies, 93%). However, among the three studies that did not clearly mention it, one was a published abstract, 57 one was a registered CT (NCT00724256) and one described the results of urine culture during the follow-up period. 56 A minimal bacterial count was required in 32 (80%) studies, while the type and the number of distinct isolated pathogens were mandatory in 19 (48%) trials (Table 1). Among the 40 studies, the clean-catch midstream sample method was the most frequently used (n=24; 60%), while 12 (30%) studies did not specify the method. More than 80% of studies used a threshold of ≥ 100,000 CFU/ml for clean-catch midstream specimens or urine bags, but the thresholds were more variable for supra-pubic aspiration and bladder catheterization specimens (Supplemental Table 3). A wider variability was observed in the thresholds used to evaluate pyuria and bacteriuria. Although the cut-off of ≥ 5/mm3 leukocytes in centrifuged urine (and ≥ 10/mm3 in uncentrifuged urine) is considered necessary for diagnosis by the AAP, 16-18 EMA and FDA, only seven (18%) studies followed this guidance (Table 1). Only 25 (63%) studies provided the resistance pattern for the isolated pathogen, at least for the study drugs. 22-24, 28, 29, 32-35, 37, 39-44, 46-48, 50-55

Temperature was the most common clinical inclusion criterion (n=31; 78%). 23-28, 30, 32, 34-45, 47-55 (NCT01595529, NCT02497781) In the rest of the studies, 22, 29, 31, 33, 46, 56, 57 (NCT00724256) (NCT01110408) authors clearly defined the included population as cases of pyelonephritis, complicated UTIs or febrile UTIs, and recorded temperature at baseline or during outcome, implying that temperature was possibly assessed during inclusion in all of them. Other clinical findings, inflammatory markers, and imaging tests were less frequently used (Table 1). Remarkably, only two trials (5%) 24, 42 cited any reference 59-61 for the selection of their inclusion criteria.

**Patient exclusion criteria**

Exclusion criteria used in the 40 trials are reported in the Supplemental Table 4. Medical history of potential drug allergy and general or urinary tract-related underlying conditions were the most common exclusion criterion (n=28; 70% and n=32; 80%, respectively). 22, 24, 26-29, 31-34, 37-56 (NCT01595529, NCT00724256, NCT01110408, NCT02497781) The other main exclusion criteria were related to unacceptable concurrent/recent treatment (n=25; 63%), 23, 24, 26, 28, 31-33, 36-44, 46, 47, 50, 52, 54, 55 (NCT00724256, NCT01110408, NCT02497781) disease’s severity (n=21; 53%), 22, 24, 28, 33, 35, 37, 40-47, 52, 55, 56 (NCT01595529, NCT00724256, NCT01110408, NCT02497781) or microbiological findings (n=25; 63%). 23, 24, 26-29, 31-33, 35, 37, 39-41, 46, 48-52, 54-56 (NCT01595529, NCT02497781)

**Intervention**

All studies used antibiotic treatment in both intervention and control groups. Among parenteral antibiotics, broad-spectrum cephalosporins 24-28, 34, 36, 37, 42-45, 47, 54 (NCT01110408, NCT02497781) and aminoglycosides 23, 29, 32, 34, 39, 44, 45, 50, 52, 53 were the most commonly studied drugs. Similarly, oral third generation cephalosporins 27, 28, 31, 33-37, 41, 43, 44, 51, 54 (NCT01595529, NCT00724256) were widely used, followed by penicillins. 31, 35, 40, 42, 44, 46, 51

Nineteen (48%) trials attempted to compare different regimens for drug administration, with 15 comparing short versus long course therapy, 25, 27, 28, 30, 34, 37, 40, 42-44, 46, 49, 54 (NCT01595529, NCT00724256) and four comparing once daily versus three times daily dose for aminoglycoside administration. 29, 32, 50, 53 In contrast, 14 studies (35%) compared the efficacy of different antimicrobial drugs, 23-26, 31, 33, 35, 39, 41, 47, 51, 52 (NCT01110408, NCT02497781) with notably, six (15%) studies evaluated the efficacy of adjunct non-antimicrobial treatment (i.e. Vitamin A, Vitamin C, Vitamin E, Zinc, N-acetyl-cysteine, Methylprednisolone). 22, 38, 48, 55-57. The duration of treatment in each study is depicted on Figure 2.

**Endpoints**

The analysis of the proportion of studies assessing clinical, laboratory, microbiological, and radiological endpoints showed a wide variability between the studies (Table 2).

Clinical efficacy endpoints were evaluated in 35 studies. 22-26, 28-33, 35-45, 47, 48, 50-52, 54-57 (NCT01595529, NCT00724256, NCT01110408, NCT0249778) Fifteen studies (38%) 26-29, 33-36, 39, 41, 47, 50, 52 (NCT01110408, NCT02497781) defined clinical cure or improvement as the resolution or decrease in clinical signs and symptoms after starting treatment. Only 13 studies (33%) 24, 29-31, 33, 35-37, 39, 41, 47, 52 (NCT02497781) defined clinical failure as the persistence, increasing, recurrence or relapse (reappearance) of signs and symptoms after initiation of treatment, and/or the decision to add another or change the current antibiotic to an alternative one. Fever was the most commonly evaluated clinical sign (n=27; 68%), particularly the time to obtain defervescence after the beginning of the treatment. 22-33, 35, 37-39, 42, 43, 45, 47, 48, 50, 51, 55-57 (NCT01110408) Twelve studies (30%) 22, 23, 25, 30, 31, 35-37, 51, 55-57 recorded the evolution of symptoms and signs specifically related to the urinary tract (dysuria, flank pain-tenderness, urinary frequency, dribbling, urinary incontinence-intermittency, nocturia, enuresis) and 14 (35%) 24, 26, 28, 29, 32, 33, 38, 39, 42, 43, 45, 47, 48 (NCT01110408) of non-specific signs (vomiting, abdominal pain, clinical appearance, vital signs). Nine (23%) studies 40, 41, 44, 50, 52, 54 (NCT01595529, NCT00724256, NCT02497781) did not specify the signs/symptoms used to evaluate clinical outcomes.

Microbiological endpoints were assessed in 37 studies (93%), 22-27, 29-56 (NCT01595529, NCT01110408, NCT02497781) and urine culture was assessed in 36 (90%). 23-27, 29-56 (NCT01595529, NCT01110408, NCT02497781) Twenty-seven studies (68%) 23-27, 29-37, 39-41, 44, 46, 47, 49-53 (NCT01110408, NCT02497781) used microbiological endpoints to define cure, failure, recurrence, relapse or new infection. Microbiological cure was defined as the bacterial eradication during or after treatment. Failure was defined as the persistence of the causative pathogen despite treatment. Recurrence or relapse were defined as the growth of the same pathogen (same strain or isolate with the same sensitivity pattern), whereas isolation of a new bacterium or the same pathogen but with a changed antibiotic resistance pattern was generally considered to represent a new infection. In case of failure, antibiotic susceptibility testing of the isolated pathogens for the development of acquired resistance was evaluated in six (15%) studies. 35, 40, 41, 45, 46 (NCT01595529)

Laboratory and radiological endpoints were less commonly assessed (Table 2), usually to confirm cure or detect possible complications, respectively.

**Timing of endpoints**

The specific timing of endpoints assessment for each study is presented in Figure 2. To better analyze these results, we identified 4 timing periods: “on antibiotic-therapy” (OAT); “early follow-up” within the first week after the end of treatment (EOT); “mid-term follow-up” between 1 and 3 weeks after EOT; and “late follow-up” more than 3 weeks after EOT. The proportion of studies assessing clinical, laboratory, microbiological, and radiological endpoints at each timing period is reported in Supplemental Table 5.

The clinical 22-25, 28-33, 35, 37-39, 42-45, 47, 48, 50-52, 55-57 (NCT02497781) and laboratory efficacy 22, 33, 36, 40, 42, 43, 47 endpoints were more commonly assessed during OAT rather than within follow-up periods (p<0.01) (Supplemental Table 5). Microbiological efficacy endpoints were more frequently assessed within the “early follow-up” period (n=26; 70%), 23, 26, 30, 32-39, 41, 43-47, 49, 51-55 (NCT02497781, NCT01110408, NCT01595529) but were also assessed at all timing periods with a wide variability (Figure 2 and Supplemental Table 5). Of note, all 14 studies assessing radiological efficacy evaluated the endpoint within the “late follow-up” (p<0.0001). 27, 28, 30, 32, 37-40, 42, 43, 48, 54, 55 (NCT00724256)

**Consistency of timing of endpoints with FDA and EMA guidance**

Most of the trials were conducted before the FDA 2015 or EMA 2012 guidance was available. Many of them (n=21) 24-27, 29, 31, 33-37, 40, 42, 46, 47, 49-54 started recruiting before and some (n=18) 22, 23, 28, 30, 32, 38, 42-45, 48, 55-57 (NCT01110408, NCT01595529, NCT00724256, NCT02497781) after FDA 1998 guidance publication. 12 As older FDA guidance is no longer available (<https://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/default.htm>), we assessed compliance of the latter with the relevant guidance. After 1998, ten trials (56%) assessed consistently the concomitant clinical and microbiological OAT primary endpoints (Figure 2). 22, 23, 42-45, 48, 55, 56 (NCT02497781) However, only three (17%) 44 (NCT01110408, NCT02497781) and four (22%) 30, 44 (NCT01110408, NCT02497781) studies assessed consistently the test of cure (TOC) and the secondary endpoints, respectively (Figure 2). Finally, only three (17%) 44 (NCT01110408, NCT02497781) studies recruiting after 1998 assessed both primary and secondary endpoints in accordance to FDA 1998 guidance.

Currently, new guidance is published by FDA and EMA, 13-15 confirming the need for the simultaneous assessment of clinical and microbiological endpoints at specific timing periods (Figure 2 and Supplemental Table 5). Of note, only five (13%) 41, 44, 47 (NCT02497781, NCT01110408, NCT00724256) studies assessed the primary endpoints, and five (13%) 44, 47, 52, 54 (NCT02497781, NCT01110408, NCT00724256) studies assessed the secondary endpoints as suggested by the guidance whereas, no study assessed, consistently, both primary and secondary endpoints (Figure 2).

**Discussion**

To our knowledge, this is the largest systematic review focusing on the study design of randomized CTs on pediatric febrile UTIs. A wide variation in study design was identified, especially in microbiological inclusion criteria and endpoints.

UTI CTs demonstrated high heterogeneity in terms of urinalysis and urine culture interpretation when including patients. Different urine sampling methods, variable thresholds of pyuria in urinalysis and number of colonies in urine culture account for the wide variability observed. The selection of the most appropriate thresholds is a major challenge when assessing children for inclusion, with an active debate over the clinical diagnosis of childhood UTIs. 16-19, 62, 63 The high variability of the number of colonies according to different sampling methods can be partially explained by the multiple colonies thresholds used by the current available guidance 16, 19 that could have guided many trials. Despite the homogenous approach of adult 12-14 and pediatric guidance 16-18, 62 on pyuria, only 18% of pediatric CTs followed the proposed threshold, leading to extreme variability in this inclusion criterion. Although numerous, detailed pediatric guidelines on diagnosis and management of febrile UTIs 16-19, 62, 63 exist, along with the adult guidance of FDA and EMA on the conduct of CTs on complicated UTIs, no study appeared to reference these key design features. Lack of specific pediatric guidance and the variability between the pediatric UTIs guidelines, appears to have had a profound impact on the marked variability of case-definitions and studies design.

For assessment of efficacy, the most common clinical and microbiological endpoints used were similar to those recommended by FDA and EMA (clinical signs and urine culture). However, less than 25% of the pediatric trials reviewed assessed these endpoints at the recommended timings. Only 17% and 22% of the studies assessed TOC and secondary endpoints at the time proposed by FDA 1998, 12 respectively, while only three studies (14%) assessed all endpoints concordantly. Finally, none of the trials assessed all endpoints consistently with the newest available guidelines on conducting research. 13-15 These results highlight the difficulty for pediatricians to follow the existing adult guidance, which is potentially not suitable for children. Certain aspects of the available guidance of FDA and EMA do not seem to be directly applicable to children. For example, the microbiological cure defined by FDA and EMA guidance as a reduction to fewer than 10,000 CFU/ml and 1,000 CFU/ml, respectively, cannot be easily applied to children. Given that the former threshold is already considered for the diagnosis of a UTI either by trials included in this review or international pediatric guidelines, 17, 18, 62, 63 a different definition of cure would be needed for the pediatric population.

The heterogeneity observed in this study is similar to other systematic reviews on pediatric clinical trials on other infectious syndromes. 64, 65 The variability of assessing endpoints is concordant with the results of a recent systematic review that identified that more than a quarter of pediatric randomized clinical trials did not identify any primary outcome, and also that there was an inconsistency and heterogeneity of terms used to define the outcomes or the outcome measures. 66 Finally, the low median CONSORT statement reporting rate that we observed (59%, with only 7 studies reaching a score of 80% or higher) is concordant with those previously reported in review on pediatric randomized CTs. 64, 66, 67

**Limitations**

Although we excluded studies focusing only on patients with general or urinary tract-related underlying conditions, 50% included mixed populations with an underlying disease. Similarly, despite focusing on febrile UTIs, this review included six trials studying a subgroup of patients with afebrile UTIs, representing 11% of the entire population. These may have influenced the observed disparity of study designs, leading to a greater heterogeneity in terms of definitions and endpoints assessed. However, as those trials defined different cases consistently, we assumed that the impact was probably low.

**Conclusion**

International harmonization of pediatric UTI trial design, with the application of consistent criteria for inclusion and carefully selected primary and secondary endpoints are required. In Table 3 we have suggested potential new standardized criteria based on our interpretation of the FDA and EMA guidance and previous literature. The current literature on pediatric UTIs has already demonstrated the efficacy of a shorter antibiotic course 25, 27, 28, 30, 34, 37, 40, 42-44, 46, 49, 54, 60, 68-72 (NCT01595529, NCT00724256) and novel trial designs such as SCOUT (NCT01595529) aiming at improving treatment outcomes while reducing selection of resistance will be increasingly important. Future trials on the optimal systemic and oral treatment of childhood UTIs due to ESBL-producing *Enterobacteriaceae* in the resource poor setting are an urgent priority and harmonizing study designs would facilitate study comparisons.

**Ethical approval:** Not required.

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**Figures Legends**

**Figure 1. Diagram for study selection**

a, Excluded publication types were: reviews, meta-analyses, observational studies, case reports, not randomized trials, editorials, comments

b, Excluded populations were: cystitis, urinary tract abnormalities, and underlying disorders, inconsistent pathogen, mixed infections with no specific data on urinary tract infection

UTI, urinary tract infection

**Figure 2. Timing of assessment of clinical, laboratory, microbiological and radiological efficacy endpoints in pediatric trials on complicated urinary tract infections**

Horizontal full grey bars represented the treatment period duration; if it was variable, bars were partially-filled with grey dots; if it was not clearly specified, the beginning of treatment was arbitrarily represented by a star.

Vertical full black line (at day 0) represent the end of treatment.

Colored squares and horizontal bars represented the precise time or the range of the timing to assessing the clinical (blue), laboratory (red), microbiological (green) and radiological (yellow) efficacy endpoints, respectively. Colored strips were used in case of two types of endpoints were assessed during the same period. The number of each investigations was not specified. In cases where the timing of the endpoints was variable due to a variable treatment duration, bars were partially-filled with colored dots. Safety endpoints were not shown on the figure.