Improving the diagnosis and treatment of urinary tract infection in young children in primary care: results from the 'DUTY' prospective diagnostic cohort study

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ABSTRACT

Purpose Up to 50% of urinary tract infections (UTIs) in young children are missed in primary care. Urine culture is essential for diagnosis, but urine collection is often difficult. Our aim was to derive and internally validate a two-step clinical rule using (1) symptoms and signs to select children for urine collection; and (2) symptoms, signs and dipstick testing to guide antibiotic treatment.

Methods We recruited acutely unwell children <5 years from 233 primary care sites across England and Wales. Index tests were parent reported symptoms; clinician reported signs; urine dipstick results; and clinician opinion of UTI likelihood ('clinical diagnosis') prior to dipstick and culture. The reference standard was microbiologically confirmed UTI cultured from a clean catch urine sample. We calculated sensitivity, specificity and area under the receiver operator characteristic (AUROC) curve of coefficient-based (graded severity) and points-based (dichotomised) symptom/sign logistic regression models and internally validated the AUROC using bootstrapping.

Results 3036 children provided urines and culture results were available for 2740 (90%). Of these 60 (2.2%) were positive: 'clinical diagnosis' was 46.6% sensitive with AUROC of 0.77. Previous UTI, increasing pain/crying on passing urine, increasingly smelly urine, absence of severe cough, increasing clinician impression of severe illness, abdominal tenderness on examination and normal ear examination were associated with UTI. The validated coefficient (points) based model AUROCs were 0.87 (0.86), increasing to 0.90 (0.90) by adding dipstick nitrites, leucocytes and blood.

Conclusions A symptoms and signs based clinical rule is superior to clinician diagnosis and performs well for identifying young children for non-invasive urine sampling. Dipstick results add further diagnostic value for empiric antibiotic treatment.

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INTRODUCTION

The accurate and timely diagnosis of urinary tract infection (UTI) in children is important to alleviate short-term suffering[1] and prevent the possible long-term consequences such as renal scarring, impaired renal growth, recurrent pyelonephritis, impaired glomerular function, hypertension, end stage renal disease, and pre-eclampsia.[2 3 4] Guidelines universally recommend urine sampling for microbiological confirmation, by clean catch (preferred in Europe),[5] or catheterization or suprapubic aspiration (SPA) for unwell children where clean catch is not immediately available (preferred in the US[6] and Australia[7]).

There are three possible explanations why half of UTIs are not diagnosed at the earliest opportunity in UK primary care.[8] First, there is a paucity of primary care relevant evidence regarding which children should be suspected. Guidelines, which emphasise the importance of fever,[6 7 9] are largely informed by studies conducted in emergency departments.[10 11 12] Second, the symptoms and signs of UTI are often non-specific, especially in very young children. Finally, obtaining an uncontaminated sample can be challenging, time-consuming, and for invasive catheter and SPA sampling methods, painful,[13] frightening[14] and induce infection.[15]

We report a large, prospective cohort study designed to investigate the diagnostic features of UTI in young children presenting to primary care. Our aim was to develop and internally validate a two-step clinical rule: step 1 used symptoms and signs to select children for urine sampling and step 2 (once urine was obtained) used symptoms, signs and dipstick testing to guide empiric antibiotic treatment. 'Coefficient' and 'points' based clinical rules were developed for use with and without computer assistance.

METHODS

Design

'DUTY' was a multicenter, prospective, diagnostic cohort study recruiting children presenting to National Health Service (NHS) primary care sites. General Practitioners (GPs), nurses and children's emergency department (CED) doctors (from here on 'clinicians') working in primary care sites (GP clinics, CEDs and Walk-in Centres) are the clinicians who provide primary care for children. Primary care sites were recruited and trained by four UK centre hubs (Bristol, Cardiff, London and Southampton).

Participants

Children were eligible if presenting with any acute (<28 days) illness episode, where the illness was associated with: (a) at least one constitutional symptom or sign identified by the National Institute of Health and Clinical Excellence (NICE)[5] as a potential marker for UTI (fever, vomiting, lethargy/malaise, irritability, poor feeding and failure to thrive); and/or (b) at least one urinary symptom identified by NICE[5] as a potential marker of UTI (abdominal pain, jaundice (children <3 months only), hematuria, offensive urine, cloudy urine, loin pain, frequency, apparent pain on passing urine and changes to continence). As a result, constitutionally unwell children consulting with an apparently obvious cause for their symptoms (such as acute otitis media or bronchiolitis, without a urinary symptom) were included. Children were excluded if: constitutionally well (e.g. acute conjunctivitis only); neurogenic or surgically reconstructed bladder; permanent or intermittent urinary catheter; trauma as the main presenting problem; or antibiotics had been taken within seven days. Clinicians were asked to recruit consecutive eligible children and where this was not possible to log children's age and gender.

Index tests and urine collection

Following consent, 107 index tests (symptoms, signs and dipstick results, Web Table 1) were recorded on a standardised Case Report Form by qualified clinicians blind to the reference standard. Parent-reported items included the child's medical history and symptoms. Signs, from a full clinical examination, included clinicians' global illness severity impression (zero to ten) and abdominal tenderness. Before urine dipstick testing, clinicians recorded their rating of UTI likelihood ('clinical diagnosis').

Our preferred urine collection method was 'clean catch'. For toilet trained children, we used a sterile bowl that the parent could hold under the child or put in a potty. For other children, the parent cleaned the nappy area using water alone and sat the child on their knee with the bowl placed under their perineum. If it was not possible to obtain a sample at the site, the parent was given equipment and advice on taking the sample at home. Where clean catch was not feasible, we used NICE-recommended 'Newcastle Nappy Pads' (a sterile pad placed inside the diaper),[5] but because of differences in contamination rates and children's ages between clean catch and nappy pad samples, the current analysis focuses on clean catch samples.

Urine samples were tested at the site using Siemans/Bayer multistix 8SG dipsticks. Urine samples were split into two fractions for microbiological analysis. The priority fraction was sent to the site's usual laboratory. When at least 1ml was left, the remainder was sent using first class postal Safeboxes^{TM} in boric acid monovettes to the Public Health Wales Microbiology Specialist Antimicrobial Chemotherapy Unit in Cardiff (the "research laboratory").

Reference standard

The reference standard was determined at the research laboratory, which spiral plated (Don Whitley, United Kingdom (UK)) 50µL of urine onto chromogenic agar and standard blood agar. Quantitative total counts were recorded for up to six organisms and the presence of antimicrobial substances measured. Samples were processed by two staff members using a single, standardised procedure. As per UK guidelines,[16] our microbiological definition of UTI was either the 'pure' (single) or 'predominant' growth of a uropathogen (an *Enterobacteriaceae*) at $\geq 10^5$ Colony Forming Units (CFU)/mL. We defined 'predominant' growth as $\geq 10^5$ CFU/mL of a uropathogen with ≥ 3 $\log_{10}$ (1000-fold) difference between the growth of this and the next species. For comparison, we used the United States (US) definition[6] of a pure uropathogen growth >50,000 CFU/ml with ≥25 white blood cells/mm^3 on microscopy or leucocyte positive (threshold at nil/trace) on dipstick.

Sample size calculation

We assumed a candidate predictor prevalence of 10% and UTI prevalence of 2%.[17] With 80% power and a two-sided alpha of 5%, 3000 urine results were required to detect an odds ratio of 2.4 while 3100 results would give a clinical rule with 80% sensitivity a 95% CI width of 10%. We originally proposed to recruit 4000 children with a target of recovering urines from at least 3,100 (77.5%) for clinical rule derivation and a further 2000 children for external validation. However, we did not anticipate the need to stratify analyses by clean catch/diaper pad collection method. We therefore decided to use all available clean catch results to derive the models, with internal bootstrap validation instead of external validation.

Statistical analysis

We compared the age and gender of the children who were recruited with those children whose parents declined to participate. We used logistic regression to estimate associations of index tests with urine culture positivity. Where categorical variables had one category with very few observations, we examined the frequency of symptom and sign categories blind to association with urine culture results and merged the least frequent categories prior to analyses. P values were derived using likelihood ratio tests. For ordinal variables, both heterogeneity and trend p values were derived. Continuous variables were divided into quintiles and trend p values were derived using the median within categories. We examined plots of the log odds of culture positivity against the median within quintiles for evidence of non-linearity. We used two methods for dealing with missing data, including "don't know" responses. First, missing data were coded as the modal non-missing value. Second, we repeated multivariable analyses using the chained

equations approach to multiple imputation: estimates and Wald p values[18] based on 50 imputed datasets were derived using Rubin's rules.[19] A complete case analysis was not feasible due to the reduction in sample size.

Step 1 - symptoms and signs

We derived 'coefficient-based' models in two stages. First, we selected symptoms and signs with either trend or heterogeneity univariable p values <0.01. Second, we derived models from selected symptoms and signs using backwards stepwise selection and an exclusion criterion of heterogeneity p value >0.1. We investigated using more liberal p value thresholds of 0.1 and 0.2 at the first stage, and found no important diagnostic utility differences of the final models (results available on request).

We generated 'points-based' models (easy to calculate without a computer) by dichotomising parent-reported symptom variables to 'present/absent', except for cough which was dichotomised at 'severe/all other categories' and clinicians' global illness severity impression at ≥6 threshold. We removed other physical examination variables as these contributed least to the models. We derived the points by dividing each coefficient by the smallest coefficient in the model and rounding to the nearest integer.

We quantified diagnostic accuracy using the area under the receiver operating characteristic (AUROC) curve with 95% confidence interval. We internally validated coefficient-based models using the bootstrap procedure described by Steyerberg:[20] we calculated a validated AUROC and a calibration slope (shrinkage factor) by which we multiplied model coefficients in order to derive internally validated odds ratios. Because 'points-based' models have fixed coefficients such internal validation is not possible: instead we internally validated these models before rounding the coefficients. For each model, we selected linear predictor cut-points corresponding to a range of values for sensitivity, and then calculated the corresponding specificity, negative and positive predictive values, and proportion of children classified positive, with 95% confidence intervals. Model diagnostic parameters were compared against 'clinical diagnosis' of UTI (where clinicians considered UTI to be 'fairly' or 'very' certain). In a sensitivity analysis we fitted the coefficient models in data restricted to children under three years of age.

Since children presenting with 'fever of unknown origin' is a group of particular clinical interest, we investigated the presence of UTI among children identified as having fever without symptoms or signs suggestive of another source. We used three 'fever' variables (parent reported 'fever now or in the past 24 hours', parent reported 'fever at any time during this illness' and temperature ≥38°C on examination) combined with symptoms and signs regarded as evidence of a non-UTI illness (rash, diarrhoea, blocked/runny nose, cough, wheeze, shortness of breath, chest pain, earache, sore throat, oxygen saturation <94%, throat abnormality, ear abnormality, and chest abnormality).

Step 2 - symptoms, signs and dipstick testing

We used the model development processes described in step 1, extending the symptoms and signs models to include dipstick results, with the points-based model dipstick results dichotomised at the 'negative /positive' threshold. To assess the added value of dipsticks over symptoms and signs alone we first quantified the change in AUROC and second, used a simulation approach based on the step 1 points-based model together with multinomial logit models in which dipstick results were predicted by the dichotomised symptoms and signs as predictors. The simulation procedure: (i) sampled coefficient values from the multivariate normal distribution of the multinomial logit parameter estimates; (ii) randomly generated a set of dipstick results based on the sampled coefficients; and (iii) computed the corresponding probability of UTI based on the shrunken coefficients for the symptoms, signs and dipstick points-based model. For each combination of symptoms and signs we generated 10,000 samples and calculated the probability of UTI with and without the dipstick results and the change in probability of UTI after accounting for the dipstick results. One of the dipstick combinations was dropped since it was observed in only three individuals and led to numerical instability.

Effects of replacing US with UK UTI definition

We calculated the prevalence and bias adjusted kappa statistic to assess agreement between UK and US UTI definitions[21] and used crude and adjusted odds ratios, and the AUROC to assess strength of association, and diagnostic utility, of index tests identified as diagnostic using the UK UTI definition.

RESULTS

Between April 2010 and April 2012, 516 staff (61 research nurses; 182 GPs; and 273 site nurses) recruited participants from 233 primary care sites (225 GP practices, four Walk-in centers and four CEDs) across England and Wales. Of 10138 children screened potentially eligible, 1276 (12.6%) declined participation, 1684 (16.6%) could not be recruited for other reasons and 15 (0.15%) withdrew (Web Figure 1). Urine was collected using clean catch from 3036 children, with reference standard (research laboratory) results available for 2740 (90%). Of these, 2561 (93%) were two years or older and 1473 (54%) female (Table 1). The most common working diagnoses were upper respiratory tract infection (28%), viral illness (15%), otitis media (10%) and gastroenteritis (3.6%).

Sixty (2.2%) children met the laboratory definition for UTI: 50 (83.3%) with *Escherichia coli*; 5 (8.3%) with *Proteus* species*;* 3 (5.0%) with *Klebsiella* species*;* 1 (1.7%) with *Morganella morganii* and 1 (1.7%) with *Citrobacter farmeri*. 2627 (96%) samples were provided within 24 hours of index test measurement. Urinary antimicrobial substances were found in 128 (4.5%) samples and in 4 (6.7%) of the UTI positive samples. A 'clinical diagnosis' of UTI prior to urine dipstick testing was made in 168 (6.1%) children, of whom 28 (16.7%) were UTI positive. 'Clinical diagnosis' achieved 46.6% sensitivity, 94.7% specificity and AUROC 0.77 (95% CI 0.71 to 0.83). Missing data and 'not known' responses were infrequent (Table 1).

Step 1 - symptoms and signs

The parent-reported index tests associated with UTI in crude (Table 1) and adjusted (Table 2) analyses were pain/crying while passing urine, smelly urine, previous UTI and absence of severe cough. For the first two, there was a graded association with increasing symptom severity. Clinician-reported index tests associated with UTI were increasing illness severity (graded association), abdominal tenderness and absence of ear abnormalities. None of the other index tests (Web Table 1) met our criteria for model inclusion, and there was no evidence of association for fever of unknown origin (Web Table 3) or prior illness duration (data not shown).

The multiple imputation-based AUROC for the coefficient-based step 1 model was 0.89 (95% CI 0.85 to 0.95, internally validated AUROC 0.88, Table 2, Figure 1). To achieve sensitivities of 70% (all children with linear predictor ≥-2.729) or 85% (linear predictor ≥-3.717) with the step 1 model would require urine sampling in 6.8% to 17.6% of children (Table 3, upper); with corresponding positive predictive values of 22.6% to 10.6% and specificities of 94.6% to 83.9%. While the points-based model had a similar AUROC 0.86 (95% CI 0.81 to 0.90, validated 0.85, Web Table 2) to the coefficient-based model, other diagnostic parameters were inferior: using an 85.0% sensitivity (≥3 point cut-off) only increased the post-test probability to 6.9%, with a lower specificity (74.4%) and higher (26.9%) urine collection rate (Web Table 4, upper). Using a ≥5 point cut-off ("any three of five" symptoms and signs) increased the post-test UTI

probability to 17.7%, with increased specificity (94.6%) and reduced urine collection rate (6.4%), but at the expense of reduced sensitivity (51.7%, Web Table 4 (upper) and Figure 2).

Urine samples were available for 88, 91 and 612 children <12, 12 to 23, and 24 to 35 months with laboratory confirmed UTI in 4, 2 and 16 of these children respectively (Table 1). The coefficient model performed well in children under 3 years, with similar estimated odds and AUROC (Web Table 5).

Step 2 - symptoms, signs and dipstick testing

Dipstick leukocytes, nitrites, and blood were strongly associated with UTI (Tables 1 and 2). The coefficient-based, multiple imputation model AUROC was 0.93 (95% CI 0.90 to 0.97, validated 0.90), an increase of 0.034 (p=0.009) when dipstick results were added to symptoms and signs (Table 2, Figure 1). If all children had a urine sample and dipstick test, the dipstick test results could maintain sensitivity at 80% while improving specificity from 88.3% to 93.8% and reducing the percentage of children treated with antibiotics from 13.2% to 7.8%, assuming immediate antibiotic use (Table 3). The points-based model AUROC was 0.90 (95% CI 0.85 to 0.95, validated 0.89), and increased (by 0.045, p=0.003) when dipstick results were added to symptoms and signs (Table 4).

Results of the simulation study showed a clear trend towards increased diagnostic value of dipstick results (change in probability of UTI) as the step 1 (symptoms and signs) based probability of UTI increased (Web Table 7). In children with a relatively low (<5%) step 1 probability of UTI (points score <5), the median absolute change in post-test UTI probability with dipstick results was 0.3%, and only exceeded 4% in 2.5% of simulations. In children with a higher (≥5%) step 1 UTI probability (points score ≥5), the dipstick results had a larger impact on the UTI probability (median post-test probability change 9.9%).

Serious adverse events

79 (1.1%) of the 7163 recruited children were hospitalized, three related to dipstick testing (two with UTI and one with diabetes).

Effects of replacing US with UK UTI definition

Data were available for all 2740 (100%) children, 35 (1.3%) of whom were UTI positive using the US UTI definition. We found good agreement (prevalence and bias adjusted kappa = 0.98), and crude and adjusted odds ratios were similar, comparing US and UK UTI definitions, showing the same graded associations, except for 'severe cough' (adjusted odds ratio 0.74 (0.23 to 2.37) US compared with 0.29 (0.09 to 0.97) UK, data available from the authors). Step 1 and step 2 diagnostic utilities were stable to the US definition, with validated AUROCs of 0.882 and 0.925 respectively.

DISCUSSION

Summary of findings

In a large cohort of young children presenting with acute illness to primary care, 2.2% of clean catch urine samples met the microbiological criteria for UTI. Based on data obtained from clean catch samples, we developed novel coefficient (for computer use) and points-based clinical rules to help clinicians identify children for urine sampling and antibiotic treatment with high diagnostic utility. For step 1, the coefficient-based rule was diagnostically superior to the points-based rule, which in turn, was superior to clinical diagnosis. For step 2, dipstick testing was diagnostically superior to symptoms and signs alone (both coefficient and points-based rules), and was not diagnostically useful in children with the lowest UTI probability, in whom step 1 would not result in urine collection.

Strengths and limitations

To our knowledge, this is the largest and most rigorous diagnostic accuracy study of UTI in children under five years in primary care. Participating children were similar to those invited but declining. We achieved high levels of data completeness across a large number of primary care sites and maintained blinding of recruiting staff to the reference standard. Index tests were measured according to routine clinical practice using standardised reporting forms and equipment, and nearly all were completed within 24 hours of urine sample retrieval, minimising disease progression bias. The low number of samples with antimicrobial substances minimises treatment paradox. Our reference standard was specific to common uropathogens, and excluded index tests. Two members of staff, blind to all index tests bar age, performed the microbiological cultures and interpreted results, using a standardised process in a single laboratory. Our broad eligibility criteria allowed us to identify previously unidentified clinical features useful for both increasing (smelly urine) and decreasing (absence of severe cough, normal ear examination) UTI probability, as well as demonstrate the absence of diagnostic utility of other features (such as fever, fever of unknown origin, vomiting, lethargy, irritability and poor feeding) widely believed[5 6] to be diagnostically useful. Our results are stable using the more conservative US definition of UTI.

The main limitation is the relatively small number of UTI diagnoses, especially in the youngest children, which impacted on three areas. First, we were not able to externally validate our rules. While external validation is desirable prior to clinical application, bootstrap validation takes account of model over-optimism. By analogy, it is reasonable for clinical practice to change on the basis of a single, well conducted randomised trial, though replication is desirable. That said, since we recruited from 'first-point-of-contact' primary care sites, we consider it necessary to evaluate the rule's performance prior to use in secondary care. Second, our rule development breached the widely quoted "10 events per candidate predictor". However, this rule of thumb has little theoretical or empirical justification: the consequences of variable selection are strongly dependent on the strength of association of candidate predictors with the outcome. Here, predictors of UTI are biologically plausible and associations substantial. Finally, children under two

years are under-represented in these analyses because of the difficulty of obtaining clean catch samples in this age group. However, we found our rule to be diagnostically accurate in children under three years and we know of no reason why the symptoms and signs identified in our study would not generalise to younger age groups. Our secondary care experience, and a recent report describing a bladder stimulation technique for infants,[22] suggest that when sufficient time, space and personnel are available, clean catch sampling is possible in most young children.

We mitigated the impact of false positive urine cultures (arising as a result of asymptomatic bacteriuria[23] or contamination) using three design features. First, children were only eligible if experiencing constitutional and/or urinary symptoms; second, the rule was developed only using clean catch samples; and third, we used a single research laboratory, which used methods superior to NHS laboratories to distinguish contaminated urine. Incorporation bias could have inflated the AUROC for step two using the US definition of UTI since dipstick leucocytes were used as both an index test and within reference standard definition.

Results in context with other studies

One systematic review of eight primary studies (7892 children),[24] and five primary studies[10 11 25 26 27] of a further 18,796 children (with only one[25] conducted in GP surgeries) have assessed UTI prevalence and the diagnostic value of clinical symptoms and signs in children <5 years.[28] These found similar UTI prevalence and showed abdominal pain, back pain, dysuria, frequency, and new-onset urinary incontinence were positively associated with UTI.[24] Stridor, audible wheeze, circumcision, temperature <39°C with a source, abnormal chest sounds, chest crackles, age under three years, not feeling hot, and rapid breathing were inversely associated with UTI. The largest study, which included 16,000 children presenting to the CED, derived a complex model based on 27 symptoms and signs, with an AUROC of 0.80 (95% CI 0.78 to 0.82).[26] The only previous study to recruit from GP surgeries found that younger age, urinary frequency and pain/crying on passing urine were associated with UTI, but had insufficient children with UTI to develop a clinical rule.[25] Previous investigation of malodorous urine has shown conflicting results,[27 29] but our study strongly supports its diagnostic value. Dipstick testing has been considered diagnostically unhelpful in young children.[5]

Clinical and research implications

In keeping with recently updated US guidelines,[6] our results support a more sophisticated 'risk-based' approach to the identification of children for investigation of UTI. Pain or crying while passing urine, smelly urine, previous UTI, absence of severe cough, abdominal tenderness, and absence of ear abnormalities can be used for deciding which children to urine sample (step 1) and dipstick results to improve specificity for antibiotic treatment (step 2). For both steps, increasing diagnostic sensitivity can be achieved by increasing urine sampling rates, which may not be feasible or affordable. The clinical rules can be used (Figure 2) by clinicians with a wide range of experience, and focus attention on predictive factors rather than those (such as fever) with poor diagnostic utility. Clinicians concerned about over-diagnosis and treatment could select

a higher specificity threshold, while higher sensitivity thresholds would reduce under-diagnosis. The rule should supplement not replace clinical judgement.

Further research is needed to distinguish pathogens from contamination and asymptomatic bacteriuria.[23] Given the expense of an external validation study, and the low rates of routine urine sampling (which render routine datasets unsuitable), we consider the most cost-effective future research strategy would be to assess the impact of the DUTY clinical rule on clinical behaviour and patient outcome in a randomised trial, and that the strongest design would integrate the presentation of the coefficient-based clinical rule within routine clinical care, probably via electronic medical records.

CONCLUSIONS

Our rule can be used to enhance current clinical practice in the identification of young children for non-invasive urine sampling in primary care. Fever should not be used to stratify UTI probability and dipstick testing can be used to improve specificity for empiric antibiotic treatment in this population.

ETHICAL APPROVAL AND THE ROLE OF THE FUNDER

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DATA SHARING STATEMENT

The full data set will be made available when all studies described within the protocol are complete and published. Application for the data to be released should be made in writing to Professor Alastair Hay (co-Chief Investigator) via the Freedom of Information Officer at the University of Bristol.

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COMPETING INTERESTS STATEMENT

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in

the previous three years; and no other relationships or activities that could appear to have influenced the submitted work.

AUTHOR CONTRIBUTIONS

ADH and CCB (co-chief investigators) were responsible for overall study design, management and data interpretation. ADH led the writing of, and approved, the final manuscript. CCB also made substantial contributions to writing and reviewed the final manuscript. JS was lead study statistician and made substantial contributions to overall study design, statistical analysis, writing and reviewed the final manuscript. KHo contributed to overall study design, data analysis, study management, contributed to and reviewed the final manuscript. PL contributed to study design, supervised recruitment, contributed to and reviewed the final manuscript. BD contributed to overall study and data collection instrument design, supervised recruitment, and contributed to and reviewed the final manuscript. WH was lead health economist and made substantial contributions to study design, data analysis, writing and reviewed the final manuscript. MW was responsible for microbiology data and contributed to study design, data analysis, and contributed to and reviewed the final manuscript. RH and AM were co-lead microbiologists and contributed to study design, data analysis, and contributed to and reviewed the final manuscript. ML conducted data analysis, clinical rule development, writing and reviewed the final manuscript. JB conducted economic analysis, writing and reviewed the final manuscript. TP contributed to the data management, statistical analysis, contributed to and reviewed the final manuscript. KB contributed to data analysis, contributed to and reviewed the final manuscript. KOB contributed to the overall study design, data interpretation, contributed to and commented on the final manuscript. C-AW contributed to study management, contributed to and reviewed the final manuscript. JD and JvdV provided specialist paediatric nephrology advice, contributed to study design, contributed to and reviewed the final manuscript. MF contributed to study design, contributed to and reviewed the final manuscript. HD and ET-J were co-lead study managers, contributed to and reviewed the final manuscript. KHa contributed to study management, contributed to writing and reviewed the final manuscript. CL contributed to data management, data analysis, contributed to and reviewed the final manuscript. KR contributed to study management, contributed to and reviewed the final manuscript. SD developed web-based data collection systems, contributed to and reviewed the final manuscript. PW contributed to study design, literature reviewing, writing and reviewed the final manuscript.

All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis

ADH is guarantor for the study and affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Table 1. Children's characteristics and crude odds ratio for associations with UTI.

Demographics and index tests*		N (%)[a]	UTI positive (%)[b]	Crude OR (95% CI)
Gender	Male	1267 (46.2%)	13 (1.0%)	1 (ref)
	Female	1473 (53.8%)	47 (3.2%)	3.18 (1.71,5.90)
Age of child	<6 months	34 (1.2%)	1 (2.9%)	1.13 (0.15,8.77)
	6 to <12 months	54 (2.0%)	3 (5.6%)	2.19 (0.62,7.77)
	1 to <2 years	91 (3.3%)	2 (2.2%)	0.84 (0.19,3.70)
	2 to <3 years	612 (22.3%)	16 (2.6%)	1 (ref)
	3 to <4 years	1073 (39.2%)	21 (2.0%)	0.74 (0.39,1.44)
	4 years plus	876 (32.0%)	17 (1.9%)	0.74 (0.37,1.47)
Clinician diagnosis prior to dipstick	Not UTI certain / v. certain	1149 (41.9%)	6 (0.5%)	0.28 (0.12,0.69)
	Not UTI fairly certain / uncertain	1417 (51.7%)	26 (1.8%)	1(ref)
	UTI fairly to very certain	168 (6.1%)	28 (16.7%)	10.75 (6.13,18.8)
	Missing	6 (0.2%)	0 (0.0%)	
Pain/crying when passing urine*	No problem	2234 (81.5%)	22 (1.0%)	1 (ref)
	Slight problem	182 (6.6%)	6 (3.3%)	2.97 (1.21,7.29)
	Moderate problem	128 (4.7%)	12 (9.4%)	9.01 (4.45,18.2)
	Severe problem	51 (1.9%)	15 (29.4%)	36.30 (17.81,74.0)
	Missing/not known	145 (5.3%)	5 (3.4%)	
Smelly urine*	No problem	2108 (76.9%)	20 (0.9%)	1 (ref)
	Slight problem	174 (6.4%)	10 (5.7%)	5.87 (2.76,12.5)
	Moderate problem	179 (6.5%)	16 (8.9%)	9.46 (4.93,18.2)
	Severe problem	51 (1.9%)	10 (19.6%)	23.5 (10.6,52.3)
	Missing/not known	228 (8.3%)	4 (1.8%)	
Cough*	No problem	773 (28.2%)	24 (3.1%)	1 (ref)
	Slight problem	556 (20.3%)	16 (2.9%)	0.93 (0.48,1.76)
	Moderate problem	829 (30.3%)	17 (2.1%)	0.66 (0.35,1.23)
	Severe problem	579 (21.1%)	3 (0.5%)	0.16 (0.05,0.54)
	Missing/not known	3 (0.1%)	0 (0.0%)	
Previous UTI*	No	2449 (89.4%)	43 (1.8%)	1 (ref)
	Yes	177 (6.5%)	12 (6.8%)	3.81 (1.99,7.31)
	Missing/not known	114 (4.2%)	5 (4.4%)	
Clinician global impression of illness severity (0-10)*	0-1	989 (36.1%)	14 (1.4%)	1 (ref)
	2	739 (27.0%)	14 (1.9%)	1.35 (0.64,2.85)
	3	531 (19.4%)	14 (2.6%)	1.89 (0.89,4.00)
	4-5	363 (13.2%)	12 (3.3%)	2.39 (1.09,5.21)
	6 or more	115 (4.2%)	6 (5.2%)	3.85 (1.45,10.21)
	missing	3 (0.1%)	0 (0.0%)	
Abdominal exam: any tenderness*	No	2237 (81.6%)	46 (2.1%)	1 (ref)
	Yes	63 (2.3%)	8 (12.7%)	7.34 (3.33,16.19)
	Missing	440 (16.1%)	6 (1.4%)	
Ear exam: any acute abnormality*	No	1783 (65.1%)	50 (2.8%)	1 (ref)
	Yes	635 (23.2%)	4 (0.6%)	0.23 (0.08,0.64)
	Missing	322 (11.8%)	6 (1.9%)	
Dipstick: leukocytes*	Negative	2272 (82.9%)	17 (0.7%)	1 (ref)
	Trace	154 (5.6%)	6 (3.9%)	5.40 (2.10,13.9)
	+	110 (4.0%)	2 (1.8%)	2.47 (0.56,10.8)
	++	148 (5.4%)	19 (12.8%)	19.61 (9.95,38.6)
	+++	48 (1.8%)	16 (33.3%)	66.6 (30.9,143.3)
	Missing	8 (0.3%)	0 (0.0%)	
Dipstick: nitrites*	Negative	2658 (97.0%)	35 (1.3%)	1 (ref)
	Positive	74 (2.7%)	25 (33.8%)	38.4 (21.4,68.9)
	Missing	8 (0.3%)	0 (0.0%)	
Dipstick: blood*	Negative	2297 (83.8%)	29 (1.3%)	1 (ref)
	Non-heme	246 (9.0%)	8 (3.3%)	2.64 (1.19,5.84)
	Heme trace	50 (1.8%)	6 (12.0%)	10.70 (4.23,27.08)
	Heme +	67 (2.4%)	4 (6.0%)	4.98 (1.70,14.60)

Demographics and index tests*		N (%)[a]	UTI positive (%)[b]	Crude OR (95% CI)
	Heme ++ or +++	72 (2.6%)	13 (18.1%)	17.29 (8.56,34.94)
	Missing	8 (0.3%)	0 (0.0%)	

* Index tests independently associated with UTI in multivariable models. Missing values were assigned to the modal category for crude OR.

[a] All children column gives the percentage of observations within that category

[b] Children with UTI column gives the percentage of positives relative to the number of observations within that category

Table 2. Coefficient based models[a] for symptoms and signs; symptoms, signs and dipstick results; including results based on multiple imputation

Index tests	Symptom and sign model		Symptom, sign and dipstick model	
	Adjusted OR[a] (95 % CI)[b]	MI[c] adjusted OR[a] (95% CI)	Adjusted OR[a] (95 % CI)[b]	MI[c] adjusted OR[a] (95% CI)
Pain/crying when passing urine				
No problem	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Slight problem	1.56 (0.68,3.61)	1.73 (0.73,4.06)	1.01 (0.37,2.80)	1.16 (0.41,3.24)
Moderate problem	4.58 (2.27,9.25)	4.80 (2.30,10.04)	2.68 (1.16,6.18)	2.87 (1.21,6.82)
Severe problem	14.32 (6.81,30.11)	15.81 (7.37,33.89)	9.64 (3.92,23.69)	10.33 (4.11,25.96)
Smelly urine				
No problem	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Slight problem	4.08 (2.00,8.33)	4.28 (2.02,9.05)	2.97 (1.29,6.85)	3.16 (1.32,7.59)
Moderate problem	5.00 (2.64,9.48)	5.14 (2.60,10.19)	4.16 (2.02,8.57)	4.34 (2.00,9.39)
Severe problem	8.49 (3.74,19.26)	8.76 (3.76,20.41)	4.13 (1.51,11.31)	4.44 (1.57,12.54)
Previous UTI				
No	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Yes	2.71 (1.39,5.27)	2.66 (1.34,5.26)	2.39 (1.12,5.11)	2.36 (1.10,5.03)
Cough				
No problem	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Slight problem	1.28 (0.67,2.45)	1.32 (0.68,2.55)	1.27 (0.59,2.72)	1.30 (0.60,2.81)
Moderate problem	1.31 (0.69,2.48)	1.38 (0.72,2.68)	1.95 (0.95,4.00)	2.04 (0.98,4.22)
Severe problem	0.28 (0.08,0.93)	0.29 (0.09,0.97)	0.36 (0.09,1.48)	0.36 (0.09,1.51)
Clinician global impression of illness severity (0-10)				
0-1	1 (ref)	1 (ref)	1 (ref)	1 (ref)
2	1.97 (0.95,4.12)	1.98 (0.93,4.19)	2.14 (0.93,4.91)	2.13 (0.92,4.97)
3	2.66 (1.28,5.54)	2.72 (1.28,5.81)	2.65 (1.16,6.07)	2.63 (1.13,6.14)
4-5	3.57 (1.61,7.91)	3.87 (1.72,8.73)	2.96 (1.18,7.42)	3.24 (1.28,8.24)
6 or more	6.84 (2.52,18.56)	7.24 (2.59,20.25)	5.80 (1.81,18.60)	6.28 (1.92,20.61)
Abdominal exam: any tenderness				
No	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Yes	2.40 (1.03,5.61)	2.24 (0.95,5.25)	1.34 (0.40,4.45)	1.18 (0.35,3.94)
Ear exam: any acute abnormality				
No	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Yes	0.30 (0.11,0.83)	0.27 (0.10,0.74)	0.46 (0.18,1.22)	0.40 (0.15,1.09)
Dipstick: leukocytes				
Negative			1 (ref)	1 (ref)
Trace			1.81 (0.68,4.81)	1.78 (0.66,4.78)
+			0.70 (0.16,3.13)	0.66 (0.14,3.12)
++			5.27 (2.52,11.04)	5.19 (2.45,10.98)
+++			10.45 (4.11,26.53)	10.36 (3.94,27.26)
Dipstick: nitrites				
Negative			1 (ref)	1 (ref)
Positive			5.25 (2.56,10.77)	5.37 (2.58,11.19)
Dipstick: blood				
Negative			1 (ref)	1 (ref)
Non-heme			0.88 (0.36,2.17)	0.89 (0.35,2.21)
Heme trace			4.16 (1.34,12.85)	4.08 (1.28,13.05)
Heme +			2.65 (0.87,8.03)	2.84 (0.92,8.79)
Heme ++ or +++			1.71 (0.65,4.51)	1.74 (0.64,4.73)
Area under ROC curve (95% CI)[d]	0.892 (0.84,0.94)	0.899 (0.85,0.95)	0.926 (0.89,0.96)	0.933 (0.90,0.97)
Validated area under ROC curve [e]	0.871	0.876	0.904	0.903
Calibration slope[e]	0.865	0.871	0.832	0.832

[a] Odds ratios calculated using shrunken estimates from the bootstrap internal validation calibration slope; [b] Missing values coded to modal category; [c] MI: multiple imputation; [d] Calculated without internal validation. [e] Calculated from the bootstrap internal validation

Table 3. Diagnostic test characteristics (95% CI) of coefficient based models[a] for a range of sensitivity cutpoints, using symptoms and signs model (upper part of table for urine sampling and antibiotic treatment) and the symptoms, signs and dipstick model (lower part of table for antibiotic treatment).

Linear predictor cutpoint – shrunken coefficients (≥)[b]	Linear predictor cutpoint – unshrunken coefficients (≥)[b]	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Percentage of children clinical rule positive
Symptom and sign model						*Percentage urine sampled/antibiotic treated*[c]
-0.504	-0.195	20.0% (11.7%, 32.0%)	99.8% (99.5%, 99.9%)	66.7% (42.9%, 84.2%)	98.2% (97.7%, 98.7%)	0.7% (0.4%, 1.0%)
-1.092	-0.87	30.0% (19.8%, 2.7%)	99.5% (99.1%, 99.7%)	56.3% (39.0%, 72.1%)	98.4% (97.9%, 98.9%)	1.2% (0.8%, 1.6%)
-1.813	-1.698	40.0% (28.5%, 52.8%)	98.2% (97.6%, 98.6%)	32.9% (23.1%, 44.4%)	98.7% (98.1%, 99.0%)	2.7% (2.1%, 3.3%)
-2.059	-1.98	50.0% (37.6%, 62.4%)	97.5% (96.9%, 98.1%)	31.3% (22.8%, 41.2%)	98.9% (98.4%, 99.2%)	3.5% (2.9%, 4.3%)
-2.372	-2.34	60.0% (47.2%, 71.5%)	96.3% (95.5%, 97.0%)	26.7% (19.9%, 34.7%)	99.1% (98.6%, 99.4%)	4.9% (4.2%, 5.8%)
-2.729	-2.75	70.0% (57.3%, 80.2%)	94.6% (93.7%, 95.4%)	22.6% (17.1%, 29.1%)	99.3% (98.9%, 99.6%)	6.8% (5.9%, 7.8%)
-3.396	-3.515	80.0% (68.0%, 88.3%)	88.3% (87.0%, 89.4%)	13.3% (10.1%, 17.2%)	99.5% (99.1%, 99.7%)	13.2% (12.0%, 14.5%)
-3.717	-3.884	85.0% (73.6%, 92.0%)	83.9% (82.4%, 85.2%)	10.6% (8.1%, 13.6%)	99.6% (99.2%, 99.8%)	17.6% (16.2%, 19.1%)
-4.567	-4.86	93.3% (83.5%, 97.5%)	61.0% (59.1%, 62.8%)	5.1% (3.9%, 6.6%)	99.8% (99.4%, 99.9%)	40.2% (38.4%, 42.0%)
-5.299	-5.7	96.7% (87.6%, 99.2%)	37.8% (35.9%, 39.6%)	3.4% (2.6%, 4.3%)	99.8% (99.2%, 100.0%)	63.0% (61.2%, 64.8%)
-6.138	-6.664	100%	15.7% (14.4%, 17.1%)	2.6% (2.0%, 3.3%)	100%	84.6% (83.2%, 85.9%)
Symptom, sign and dipstick model						*Percentage antibiotic treated*[d]
0.801	1.43	20.0% (11.7%, 32.0%)	99.9% (99.7%, 100.0%)	85.7% (57.3%, 96.4%)	98.2% (97.7%, 98.7%)	0.5% (0.3%, 0.9%)
-0.122	0.321	40.0% (28.5%, 52.8%)	99.9% (99.7%, 100.0%)	88.9% (70.7%, 96.4%)	98.7% (98.2%, 99.0%)	1.0% (0.7%, 1.4%)
-1.346	-1.15	60.0% (47.2%, 71.5%)	99.3% (98.8%, 99.5%)	64.3% (51.0%, 75.7%)	99.1% (98.7%, 99.4%)	2.0% (1.6%, 2.6%)
-3.114	-3.275	80.0% (68.0%, 88.3%)	93.8% (92.9%, 94.7%)	22.5% (17.4%, 28.6%)	99.5% (99.2%, 99.7%)	7.8% (6.8%, 8.8%)
-3.700	-3.98	83.3% (71.7%, 90.8%)	88.3% (87.0%, 89.5%)	13.8% (10.6%, 17.7%)	99.6% (99.2%, 99.8%)	13.2% (12.0%, 14.6%)
-4.746	-5.237	96.7% (87.6%, 99.2%)	66.3% (64.5%, 68.1%)	6.0% (4.7%, 7.7%)	99.9% (99.6%, 100.0%)	35.0% (33.3%, 36.8%)
-5.235	-5.825	98.3% (89.1%, 99.8%)	53.1% (51.2%, 54.9%)	4.5% (3.5%, 5.7%)	99.9% (99.5%, 100.0%)	48.1% (46.2%, 49.9%)
-5.955	-6.69	100%	29.5% (27.8%, 31.2%)	3.1% (2.4%, 3.9%)	100%	71.2% (69.4%, 72.8%)

[a] Results based on models using multiple imputation to deal with missing values

[b] Derived from the coefficient based models using multiple imputation where the coefficients are listed within Web Table 5

[c] Percentage of children who would be at or above this threshold assuming that all children had a urine sample

[d] Percentage of children who would be at or above this threshold assuming that all children had a urine sample and dipstick test

For comparison, 'clinician diagnosis' sensitivity was 46.6% and specificity 94.7%

Figure 1. ROC curve for multiple imputation, coefficient-based models for clinician diagnosis (dashed line), symptoms and signs only (solid line) and symptoms, signs and dipstick (dotted line).

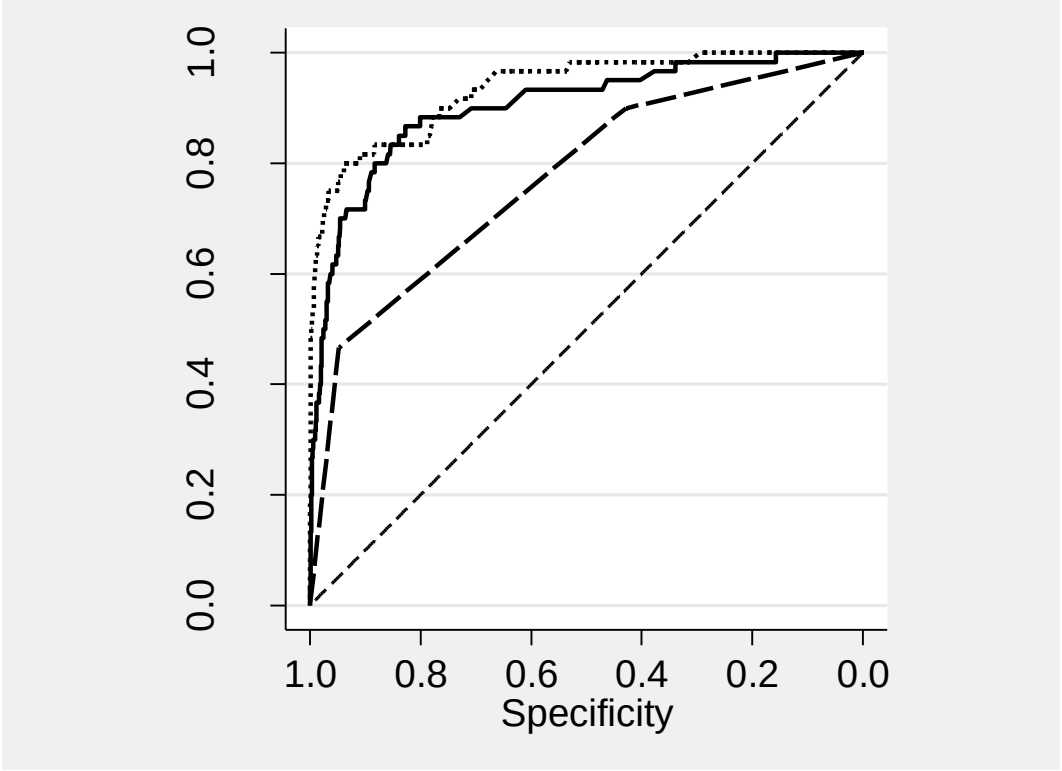

Figure 2. DUTY (Diagnosis of Urinary Tract infection in Young) Children Clean Catch Criteria

How to use the DUTY Clean Catch Urine Criteria

1. The *DUTY Clean Catch Urine Criteria* are for children in whom a clean catch sample is possible.
2. Urinary tract infection (UTI) was defined as $\geq 10^5$ Colony Forming Units (CFU)/mL of a single or predominant uropathogen cultured from a clean catch urine specimen
3. Table A: Use the symptoms and signs to decide if a clean catch urine should be collected/antibiotics given (≥5 points or can be operationalised as '*any three of the five*' symptoms and signs has been shown to be cost effective). Clinicians concerned about over-diagnosis and treatment can select a higher specificity (at least six points) threshold. Higher sensitivity thresholds (e.g. ≥3 points or ≥4 points) would reduce under-diagnosis, but these thresholds have not been shown to be cost effective.
4. It is not clear which of the following possible antibiotic treatment strategies is most cost effective: (i) immediate presumptive treatment of all sampled children; (ii) immediate dipstick guided treatment; or (iii) laboratory guided (delayed) treatment.
5. For children urine sampled at the ≥5 point threshold, the probability of UTI will be 18% (Web Table 3 (upper)). Although not demonstrably cost-effective, dipstick testing can raise or lower this probability (see Table B).
6. Table B: Refer to Web Table 3 (lower) for probability of UTI with total score
7. Consider advising all (urine and non-urine sampled) children's parents to seek medical advice if their child gets worse
8. The *DUTY Clean Catch Urine Criteria* are designed to supplement and not replace clinical judgement

Table A: Should I get a urine sample?

Clinical characteristic (present/absent)[a]	**POINTS[b]**
Symptoms and signs	***To guide urine collection***
Pain/crying passing urine[c]	2
Smelly urine[c]	2
Previous UTI[c]	1
Absence of severe cough[d]	2
Severe illness present[e]	2
	Collect clean catch urine if symptoms and signs points total ≥5 "any three of the five"

Table B. Should I give antibiotic treatment?

Clinical characteristic (present/absent)[a]	**POINTS**
Symptoms, signs and dipstick	***To guide antibiotic treatment***
Pain/crying passing urine[c]	*2*
Smelly urine[c]	*2*
Previous UTI[c]	*1*
Absence of severe cough[d]	*2*
Severe illness present[e]	*2*
Dipstick: Leukocytes positive	*2*
Dipstick: Nitrites positive	*3*
Dipstick: Blood positive	*1*

[a] Clinical characteristic wording as used in study Case Report Form and reported by parent/clinician unless stated otherwise

[b] Refer to Web Table 3 (upper) for probability of UTI with total score

[c] Parents were asked to report presence/absence

[d] Parents were asked to grade presence of cough as no problem, slight problem, moderate problem or severe problem

[e] Score of ≥6 on the clinician global illness severity scale with range 0 (child completely well) to 10 (child extremely unwell).

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