Research

Christopher C Butler, Kathryn O'Brien, Timothy Pickles, Kerenza Hood, Mandy Wootton, Robin Howe, Cherry-Ann Waldron, Emma Thomas-Jones, William Hollingworth, Paul Little, Judith Van Der Voort, Jan Dudley, Kate Rumsby, Harriet Downing, Kim Harman and Alastair D Hay, on behalf of the DUTY study team

Childhood urinary tract infection in primary care:

a prospective observational study of prevalence, diagnosis, treatment, and recovery

Abstract

Background
The prevalence of targeted and serendipitous treatment for, and associated recovery from, urinary tract infection (UTI) in pre-school children is unknown.

Aim
To determine the frequency and suspicion of UTI in children who are acutely ill, along with details of antibiotic prescribing, its appropriateness, and whether that appropriateness impacted on symptom improvement and recovery.

Design and setting
Prospective observational cohort study in primary care sites in urban and rural areas in England and Wales.

Method
Systematic urine sampling from children aged <5years presenting in primary care with acute illness with culture in NHS laboratories.

Results
Of 6079 children's urine samples, 339 (5.6%) met laboratory criteria for UTI and 162 (47.9%) were prescribed antibiotics at the initial consultation. In total, 576/7101 (8.1%) children were suspected of having a UTI prior to urine sampling, including 107 of the 338 with a UTI (clinician sensitivity 31.7%). Children with a laboratory-diagnosed UTI were more likely to be prescribed antibiotics when UTI was clinically suspected than when it was not (86.0% versus 30.3%, *P*<0.001). Of 231 children with unsuspected UTI, 70 (30.3%) received serendipitous antibiotics (that is, antibiotics prescribed for a different reason). Overall, 176 (52.1%) children with confirmed UTI did not receive any initial antibiotic. Organism sensitivity to the prescribed antibiotic was higher when UTI was suspected than when treated serendipitously (77.1% versus 26.0%; *P*<0.001). Children with UTI prescribed appropriate antibiotics at the initial consultation improved a little sooner than those with a UTI who were not prescribed appropriate antibiotics initially (3.5 days versus 4.0 days; *P* = 0.005).

Conclusion
Over half of children with UTI on culture were not prescribed antibiotics at first presentation. Serendipitous UTI treatment was relatively common, but often inappropriate to the organism's sensitivity. Methods for improved targeting of antibiotic treatment in children who are acutely unwell are urgently needed.

Keywords
antibacterial agents; child; diagnosis; primary health care; urinary tract infections.

INTRODUCTION

Urinary tract infection (UTI) in young children often presents with non-specific symptoms and obtaining a urine sample from those who are acutely unwell is challenging.[1] Sampling rates are generally lower than recommended, and it has been estimated that up to half of children with UTI in primary care may not be diagnosed when first consulting.[2] A recent UK primary care study found that up to 80% of UTIs may be missed.[3] Primary care clinicians have been urged to lower their threshold for obtaining a urine sample for culture in children who are acutely unwell.[4]

A recent study emphasised the importance of prompt and empirical antibiotic treatment of childhood UTI.[5] When the threshold for prescribing antibiotics for children with non-specific symptoms is low, children with 'occult UTI' may be serendipitously treated for their UTI.[6] A small UK study found that children with UTI that had not been suspected by the GP had all received antibiotics (amoxicillin) for alternative infections.[7] In the 1990s, antibiotic prescriptions for children reduced by almost one-third in the UK, US, and many European countries.[8,9] This reduction then plateaued and, although prescribing levels may be increasing slightly, they remain much lower than in the 1990s.[8,9]

The problem of undiagnosed and untreated UTIs in children, therefore, may have become more common in light of the reduced prescribing of antibiotics in primary care to children who are acutely unwell. The proportion of children who have a UTI diagnosed on urine culture who are not suspected of having a UTI in the normal course of primary care has been unclear. A recent UK study of 1003 children who were acutely ill found the prevalence of UTI to be 5.9% (95% confidence interval [CI] = 4.3 to 8.0).[3] The small number of UTI cases in this study did not allow for accurate analyses of associations between clinical suspicion, treatment, and recovery.[3] As a result of that, the aim of the current study was to determine:

- the frequency with which children with

CC Butler, FRCGP, professor of primary care, Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford. **K O'Brien**, PhD, clinical lecturer, Cochrane Institute of Primary Care and Public Health; **T Pickles**, MSc, research associate in statistics; **K Hood**, PhD, director of clinical trials and professor of statistics; **C-A Waldron**, PhD, research associate; **E Thomas-Jones**, PhD, research fellow, South East Wales Trials Unit, Cardiff University, Cardiff. **M Wootton**, PhD, lead scientist; **R Howe**, FRCPath, consultant microbiologist, Specialist Antimicrobial Chemotherapy Unit; **J Van Der Voort**, FRCPCH, consultant paediatrician, Department of Paediatrics and Child Health, University Hospital of Wales, Cardiff. **W Hollingworth**, PhD, professor of health economics, School of Social and Community Medicine; **H Downing**, MPhil, clinical trials manager; **K Harman**, Dhealth, study manager; **AD Hay**, FRCGP, professor of primary care and NIHR research professor Centre for Academic Primary Care, University of Bristol, Bristol.

P Little, FRCGP, professor of primary care research, ; **K Rumsby**, MSc, clinical trails manager, Primary Care and Population Sciences Division, University of Southampton, Southampton.
J Dudley, PhD, consultant paediatric nephrologist, Bristol Royal Hospital for Children, Bristol.

Address for correspondence
Christopher C Butler, Nuffield Department of Primary Care Health Sciences, University of Oxford, New Radcliffe House, Radcliffe Observatory Quarter, Woodstock Road, Oxford OX2 6NW.
E-mail: christopher.butler@phc.ox.ac.uk

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How this fits in

A previous study on laboratory culture found that almost 6% of children presenting with an acute illness in primary care have a urinary tract infection (UTI). Antibiotic resistance in uropathogens cultured from urine samples routinely received by laboratories is rising. If antibiotic prescribing for children is to be reduced, there is concern that serendipitous UTI treatment could also be reduced, leading to worse outcomes. This study found that UTI is clinically suspected in fewer than a third of children presenting with acute illness in primary care and meeting microbiological criteria for UTI. More than half of children with UTI on urine culture did not receive any initial antibiotic at an initial consultation for an acute illness. Children with clinically-suspected UTI are more likely to receive an antibiotic to which the pathogen is sensitive compared with those treated serendipitously. In addition, children with UTI who are prescribed an appropriate antibiotic at initial presentation improve a little more quickly than those who are not.

acute illness in primary care had a UTI;

- whether those with a UTI were or were not suspected on clinical grounds;
- the frequency with which each of these groups were treated with appropriate antibiotics (those to which the infecting organism was sensitive); and
- how this appropriateness was associated with symptom improvement and overall recovery.

METHOD

The Diagnosis of Urinary Tract infection in Young children (DUTY) study was a multicentre, prospective, observational study that recruited children aged between 3 months and 5 years from April 2010 to April 2012. It was implemented in four UK centres based in Cardiff, Bristol, Southampton, and London. The full DUTY study protocol has been published elsewhere.[10]

Study sites

Primary care sites comprised GP surgeries, children's emergency departments, and walk-in centres. These sites were recruited by each of the four research study centres covering both urban and rural areas across England and Wales. A total of 496 sites expressed an interest in the study, with 326 (65.7%) agreeing to participate. A total of 294 (90.2%) of these sites were trained in the DUTY study processes and 234 (79.6%) of those actively recruited at least one participant. The majority of sites were GP surgeries; only four children's emergency departments and four walk-in centres participated in the study.

Patients

Children presenting to primary care with any acute illness episode of up to 28 days' duration — even if the responsible clinician was confident of the diagnosis (for example, a child with bronchiolitis) — were eligible to take part in the study. Children were excluded if:

- they were not constitutionally unwell (for example, acute conjunctivitis only);
- they were known to have a neurogenic or surgically reconstructed bladder;
- they were using a permanent or intermittent urinary catheter;
- the main presenting problem was trauma; or
- antibiotics had been taken within 7 days.

Clinical data collection

A detailed outline of study procedures is presented in the DUTY study protocol.[10] In summary, parents were asked to provide consent for their child's participation, after which clinicians recorded the following data using a standardised case report form:

- eligibility;
- personal details;
- medical history;
- presenting symptoms;
- results of the clinical examination; and
- empirical management, including any antibiotics prescribed and the presumptive indication.

Clinicians were asked to record their view of the most likely diagnosis prior to urine sampling and dipstick testing, and then again after dipstick testing. Where available, the post-dipstick clinical suspicion was used; where this was not completed, the pre-dipstick result was used.

The children defined as having a microbiological diagnosis of UTI were subdivided according to whether or not the clinician had suspected a UTI prior to microbiological analysis.

At 14 days after the initial consultation, all parents of children with a microbiological diagnosis of UTI were to be contacted by telephone to ask them about the number of days to symptoms improvement and overall child recovery.

Obtaining urine samples

Urine samples were obtained by clean catch, where possible, for children who were toilet trained or for whom the parent was happy to attempt collection. For children still using nappies, whose parents did not think clean catch would be successful, Newcastle nappy pads were used. These pads were inserted into the nappy then removed as soon as the child urinated to reduce the risk of contamination. Once the nappy pad was removed, the urine was extracted with a syringe into a sterile container.

If it was not possible to obtain a sample before the child left the primary care site, the parent was given the necessary equipment, and advice, on taking the sample at home. They were given a labelled Sterilin® bottle into which to transfer the urine, and asked to record the time and date the sample was obtained. Parents were advised to store the sample in the fridge and return it to the primary care site as soon as possible, preferably within 24 hours.

Laboratory analysis

Urine samples were split into two fractions for microbiological analysis. As results might be needed for clinical management, the priority fraction was sent to the local NHS laboratory routinely used by the recruiting primary care site. Urine samples were transported to NHS laboratories in the laboratories' usual sterile urine container and processed using their standard operating procedures. As part of the analysis, the following steps were undertaken:

- bacterial growth was quantified — as $<10^3$, 10^3–10^5, or $>10^5$ colony-forming units per ml (CFU/ml);
- purity of growth was determined — pure/predominant, mixed-growth two species, mixed growth two or more species;
- organism was speciated for up to two species;
- microscopy was performed to determine the presence and count of white and red cells; and
- sensitivities to first-line antimicrobials were recorded for pure/predominant cultures.

Urine samples were considered positive for UTI if the NHS laboratory reported a pure or predominant uropathogen growth of $>10^5$ CFU/ml. For the purposes of the DUTY study, a uropathogen is defined as any *Enterobacteriaceae*.

Statistical analysis

The researchers used χ^2 tests to examine associations between the UTI being suspected on clinical grounds and an antibiotic being prescribed at the initial consultation, and also present organisms being sensitive to the prescribed antibiotic.

Survival analyses, in the form of Kaplan-Meier plots and log-rank (Mantel-Cox) χ^2 tests, were used to test the hypothesis that children who had a microbiological diagnosis of UTI and who were prescribed appropriate antibiotics at the initial consultation recovered faster than those with a UTI, who

Figure 1. Flowchart of study process.

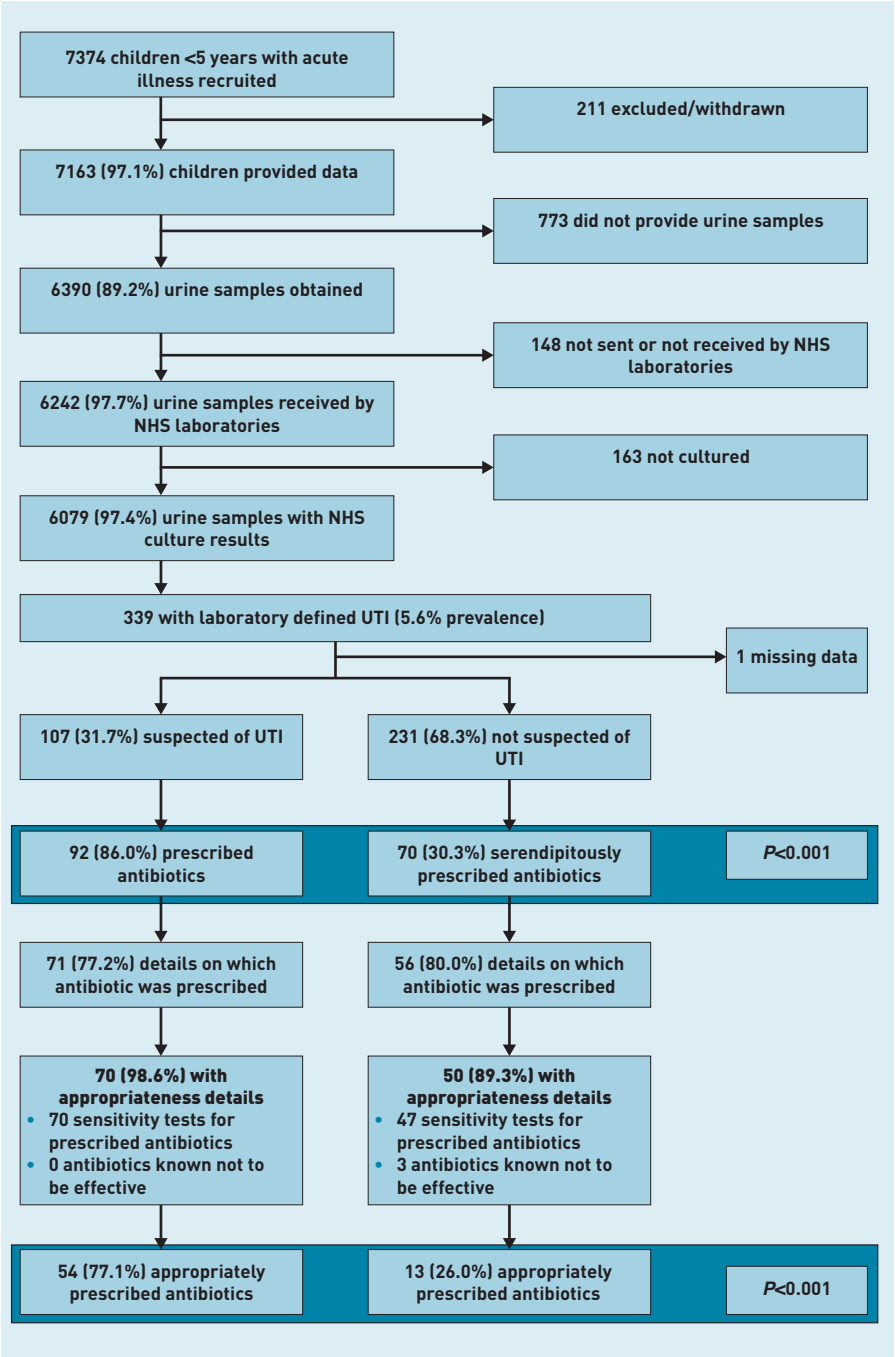


Table 1. Prescribed antibiotics and sensitivity in patients with a microbiological diagnosis of UTI

	UTI suspected, *n* = 107			UTI not suspected, *n* = 231		
	Antibiotic prescribed, *n* = 92[a]			Antibiotic prescribed, *n* = 70[b]		
Antibiotic	Prescribed, *n* (%)	Sensitivity to prescribed antibiotic tested, *n* (%)	Tested sensitive, *n* (%)	Prescribed, *n* (%)	Sensitivity to prescribed antibiotic tested, *n* (%)	Tested sensitive, *n* (%)
Amoxicillin	11 (15.5)	10 (90.9)	4 (40.0)	46 (82.1)	41 (89.1)	11 (26.8)
Cephalexin	8 (11.3)	8 (100.0)	7 (87.5)	0 (0.0)	—	—
Ceftriaxone	0 (0.0)	—	—	1 (1.8)	0 (0.0)	—
Co-amoxiclav	3 (4.2)	3 (100.0)	3 (100.0)	1 (1.8)	1 (100.0)	1 (100.0)
Erythromycin	0 (0.0)	—	—	3 (5.4)	0 (0.0)	—
Nitrofurantoin	1 (1.4)	1 (100.0)	0 (0.0)	0 (0.0)	—	—
Penicillin	0 (0.0)	—	—	4 (7.1)	4 (100.0)	0 (0.0)
Trimethoprim	48 (67.6)	48 (100.0)	40 (83.3)	1 (1.8)	1 (100.0)	1 (100.0)

Antibiotics were prescribed in 162 (47.9%) children with a laboratory confirmed UTI; with 176 (52.1%) not prescribed antibiotics at the initial consultation. [a]Details available for 71 prescriptions (data missing for 21 prescriptions). [b]Details available for 56 prescriptions (data missing for 14 prescriptions). UTI = urinary tract infection.

were not prescribed appropriate antibiotics at the initial consultation.

RESULTS

An outline of the study process is given in Figure 1. A total of 7374 children aged <5 years, who consulted with an acute illness in primary care were recruited. Of these, 211 were withdrawn or excluded, leaving 7163 with data. Urine samples were obtained from 6390 and in total, 6242 urine samples were received by NHS laboratories for analysis and 6079 were cultured.

There were 339 (5.6% of 6079) children with urine culture meeting the definition of UTI in NHS laboratories. One of these 339 had to be removed from further analysis due to missing management and prescription data, leaving 338. Taking all of the children into consideration, irrespective of culture result, 576 out of 7101 (8.1%) were suspected on clinical grounds of having a UTI (62 did not provide this information); 107 (31.7%) of those with laboratory confirmed UTI were suspected of having UTI by clinicians.

Figure 1 shows a summary of the clinical suspicion and antibiotic treatment of children subsequently found to have UTI. UTI was suspected in 107 (31.7%) children, of whom, 92 (86.0%) were prescribed an antibiotic at the initial consultation. Where a UTI was not suspected on clinical grounds, 70 out of 231 (30.3%) children were prescribed an antibiotic. There was a significant association between suspicion of UTI and higher levels of antibiotic prescribing ($P<0.001$). Of the children with confirmed UTI, 176 (52.1%) did not receive any initial antibiotic.

Where UTI was suspected on clinical grounds and the organism in these urine samples was tested for sensitivity to the prescribed antibiotic ($n = 70$), 54 (77.1%) were sensitive to that antibiotic. Where a UTI was not suspected on clinical grounds and the organism in these urine samples was tested for sensitivity to the prescribed antibiotic ($n = 47$), 13 (27.7%) were sensitive to that antibiotic. In addition to those 47 cases for which sensitivity tests for the prescribed antibiotic were performed, there were three cases in which the antibiotic given was erythromycin, which is not excreted in urine and is ineffective for treatment of UTI. As such, of those 50 cases, 13 (26.0%) of those that included susceptibility information showed sensitivity to the antibiotic given.

Suspicion of UTI was significantly associated with appropriate antibiotic prescribing: 77.1% when suspected and 26.0% when not suspected ($P<0.001$). Where a prescription for antibiotics was given, data on which antibiotic was prescribed was missing in 35 (21.6%). Where a UTI was suspected, the most commonly prescribed antibiotic was trimethoprim (48/71 cases, 67.6%) (Table 1), and amoxicillin was prescribed in 11 (15.5%) children in whom UTI was suspected.

Where a prescription was made for those in whom UTI was not suspected, the most commonly prescribed antibiotic was amoxicillin; in 46 out of 56 (82.1%) prescriptions. Trimethoprim was prescribed to one (1.8%) child in whom UTI was not suspected. Nitrofurantoin and ceftriaxone were each only prescribed to one child.

Overall, the most commonly prescribed antibiotic was amoxicillin, which was

Table 2. Symptom improvement and recovery time,[a] by prescription or non-prescription of antibiotics

	Appropriate antibiotic prescribed at initial consultation (*n* = 67)			Did not prescribe/ appropriate antibiotic not prescribed at initial consultation (*n* = 229)			
Variable	*n*	Median	IQR	*n*	Median	IQR	*P*-value[b]
How many days since your child started the study was it until their symptoms improved?	40	3.5	2.0–5.0	114	4.0	3.0–7.0	0.005
How many days since your child started the study was it until they were entirely well and had returned to their normal activities for 2 consecutive days?	40	7.0	5.0–14.0	113	7.5	5.0–15.0[c]	0.568

[a]Recovery time according to the parental self-review at 14 days after the initial consultation. [b]From a log-rank (Mantel-Cox) χ^2 test. [c]15 days entered for those who did not recover within 14 days, so the value of 15 means some value >14. This analysis is on 296 out of the total of 338 children; the remaining 42 could not be assigned to one of these groups as there was neither information on the antibiotic prescribed, nor a sensitivity test available for the prescribed antibiotic . IQR = interquartile range.

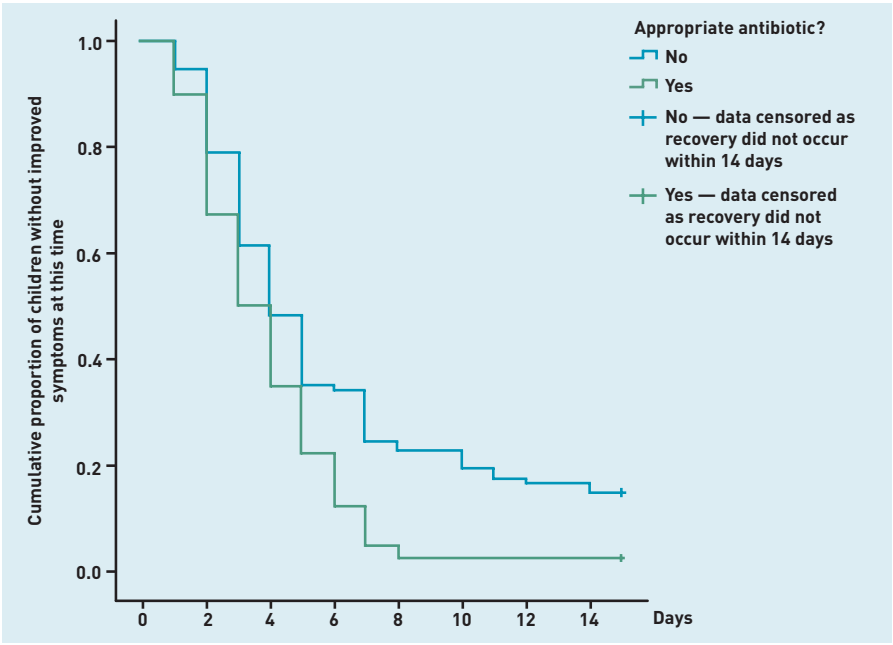


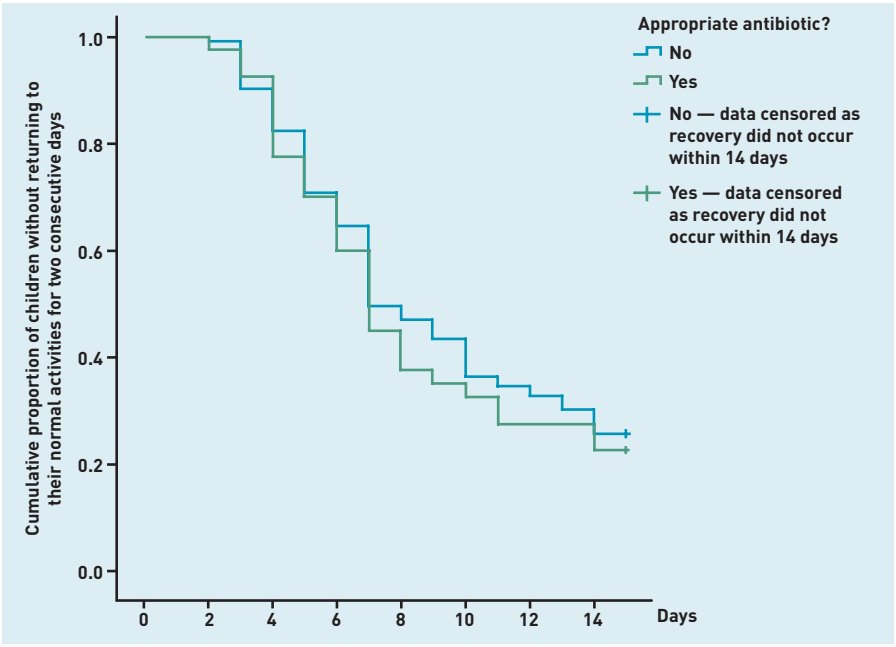
Figure 2. Days from initial consultation until symptoms improved, by prescription/ non-prescription of antibiotics.

prescribed in 57 children (44.9% of the 127 for which there were antibiotic data). Among all the samples tested, organism sensitivity to amoxicillin was 29.4% (resistance 70.6%, data not shown). Trimethoprim was prescribed to 49 children and had an overall sensitivity of 83.7% (resistance 16.3%, data not shown).

The associated outcomes show that the symptoms of children who had a microbiological diagnosis of UTI and who were prescribed appropriate antibiotics at the initial consultation, improved significantly sooner than those who were neither prescribed appropriate antibiotics, or prescribed anything, at the initial consultation (3.5 days versus 4.0 days; $P = 0.005$) (Table 2, Figure 2).

Overall, child recovery also occurred sooner in those prescribed an appropriate antibiotic at the initial consultation in comparison with to those who were not prescribed appropriate antibiotics, or were not prescribed anything, at the initial consultation, although the difference here was not shown to be statistically significant ($P = 0.568$; Table 2, Figure 3).

Figure 3. Days from initial consultation until full recovery, by prescription/non-prescription of antibiotics.



DISCUSSION

Summary

This study found that fewer than one-third of children presenting with acute illness in primary care and meeting microbiological criteria for UTI were clinically suspected as having a UTI. Children with clinically-suspected UTI are more likely to receive an antibiotic to which the pathogen is sensitive compared with those treated serendipitously, and children with UTI who are prescribed an appropriate antibiotic at initial presentation improve more quickly than those who are not. More than half of the children with a UTI on laboratory culture did not receive a prescription for an antibiotic when they first consulted for an acute illness.

The most commonly prescribed antibiotic was amoxicillin, to which there were high levels of resistance. An appropriate antibiotic was more likely to be prescribed when UTI was clinically suspected compared with an antibiotic prescribed serendipitously.

Serendipitous treatment of UTI in young children is relatively common, and the infecting organism is often resistant to such serendipitous treatment. Children with UTI, who were prescribed appropriate antibiotics at the initial consultation experienced symptom improvement sooner than those who were neither prescribed appropriate antibiotics, nor anything at all, at the initial consultation ($P = 0.006$).

Strengths and limitations

This is the largest prospective observational study of UTI in children who are acutely unwell presenting to primary care. Large numbers were recruited and each of the 6079 urine samples was analysed in one of 65 NHS laboratories. Laboratory culture results will include an unknown proportion of false positive and false negatives; as such, not all children who tested positive for a UTI on culture will be disadvantaged by not receiving initial antibiotic treatment.

For these analyses, the researchers' definition of UTI was based on culture results

only. However, to avoid including children with asymptomatic bacteriuria, children were only eligible if they were constitutionally unwell or had urinary symptoms.[4]

Urine samples were often difficult to obtain and the nappy-pad method was commonly used in younger children; this could have led to greater levels of contamination.[3] Methods such as suprapubic aspiration or catheterisation were not used, as these are not feasible for large numbers of children in primary care.[4]

Urine samples were transported to the NHS laboratory using routine procedures for collecting samples from primary care sites, and typically arrived within 2 days of the sample being taken. The findings of this study are similar to the only other UK study in general practices with systematic urine sampling using NHS laboratories.[3]

As clinicians knew they were participating in a study investigating UTI, and they received more urine dipstick information than would usually be available, they may have been more likely to suspect UTI than in routine clinical practice. This may have influenced the true detection of UTI in a positive manner, because GPs were more alert to the possibility.

Not all children with UTI were successfully followed up for clinical outcomes, and not all organisms were tested for sensitivity to the prescribed antibiotic. Organisms cultured in urine are not generally tested for sensitivity to antibiotics that are not commonly used for treating UTI.

Comparison with existing literature

This study found that only 31.7% of all those with UTI were suspected to have UTI on clinical grounds by GPs at the initial consultation. This is a higher clinical suspicion than a previous study of systematically sampled urine in children who were acutely unwell in primary care; in that study, it was found that GPs suspected UTI in 20% of those subsequently found to have UTI.[3]

Implications for research and practice

Improved recognition of UTI in children will lead to improved treatment and outcomes.[11] Heightened suspicion of UTI in acutely unwell children presenting to primary care is therefore indicated. Recognition may be improved in the future through the use of a validated clinical algorithm quantifying the diagnostic relationship between symptoms, signs, dipstick testing, and laboratory-confirmed UTI. This may increase the proportion of children with a UTI on culture who are prescribed an antibiotic at the first consultation, while avoiding antibiotics for children who do not have a UTI.

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Ethical approval

Multicentre ethical approval was granted by South West Southmead Research Ethics Committee (previously Southmead Research Ethics Committee, then South West 4 Research Ethics Committee), ref: 09/H0102/64.

Provenance

Freely submitted; externally peer reviewed.

Competing interests

Paul Little is a member of the National Institute for Health Research Journals Library Board and has provided consultancy work to Bayer Pharmaceuticals. All other authors have declared no competing interests.

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