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**Childhood UTI in primary care: Prospective observational study of prevalence, clinical and laboratory diagnosis, targeted and serendipitous treatment, and associated recovery**

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## **Abstract**

### **Background**

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

### **Design, setting and method**

Prospective observational cohort study with systematic urine sampling from children less than five years old presenting in primary care with acute illness, with urine cultured in NHS laboratories.

### **Results**

339 (5.6%) of 6079 children's urine samples met laboratory criteria for UTI, and 162 (48.0%) were prescribed antibiotics at the initial consultation. 576 (8.1%) 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 clinically suspected than when UTI was not suspected (86.0% vs. 30.3%;  $p < 0.001$ ). 70 of 231 (30.3%) children with unsuspected UTI received serendipitous antibiotics. 177 (52.3%) of 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% vs. 26.0%;  $p < 0.001$ ).

Children with UTI who were prescribed appropriate antibiotics at the initial consultation improved a little sooner than children with a UTI who were not prescribed appropriate antibiotics at the initial consultation (3.5 days vs. 4.0 days;  $p = 0.005$ ).

### **Conclusions**

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

### **Keywords (up to 6 MeSH headings)**

Primary Health Care, Urinary tract infections, Child, Anti-Bacterial Agents, Drug Resistance Microbial, Diagnosis

### **How this fits in**

#### **What was previously known?**

A previous study found that almost 6% of children presenting with an acute illness in primary care are found to have UTI on laboratory culture

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.

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**What this research adds**

Less than a third of children presenting with acute illness in primary care and meeting microbiological criteria for UTI are clinically suspected.

Over half of children with a UTI on laboratory culture received antibiotics 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 to those treated serendipitously.

Children with UTI who are prescribed an appropriate antibiotic at initial presentation improve a little more quickly than those who are not.

## **Introduction**

Urinary tract infection in young children often presents with non-specific symptoms and obtaining a urine sample from acutely unwell children 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 acutely unwell children.(4)

A recent study emphasized 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 children with UTI not 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, USA 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 may, therefore, have become more common in the light of reduced prescribing of antibiotics to acutely unwell children in primary care. 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 acutely ill children found the prevalence of UTI to be 5.9% (95% CI: 4.3%-8.0%).(3) However, the small number of UTI cases in this study did not allow for accurate analyses of associations between clinical suspicion, treatment and recovery.(3) We therefore set out to determine the frequency with which children with 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 and how this appropriateness was associated to 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 three months and five years, during April 2010 to April 2012. The DUTY study was implemented in four UK centres based in Cardiff, Bristol, Southampton and London. The full DUTY study protocol has been published.(10)

### ***Study sites***

Primary care sites comprised general practice (GP) surgeries, children's emergency departments (CEDs) and walk in centres (WICs). Primary care 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, and 326 (65.7%) agreed to participate. A total of 294 (90.2%) of these sites were trained in the DUTY study processes and 234 (79.6%) of these actively recruited at least one participant. The majority of sites were GP surgeries; with four CEDs and four WICs.

### ***Patients***

[Type text]

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

- they were not constitutionally unwell (e.g. 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;
- antibiotics had been taken within seven days.

### ***Clinical data collection***

A detailed outline of study procedures is presented in the DUTY study protocol.<sup>(10)</sup> In summary, parents were asked to provide consent for their child's participation following which clinicians recorded data using a standardised case report form (CRF) on eligibility, personal details, medical history, presenting symptoms, results of the clinical examination, empiric management including any antibiotics prescribed and the presumptive indication. The clinician was 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 we used the post-dipstick clinical suspicion but where this was not completed we used the pre-dipstick result.

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

At 14 days after the initial consultation, we aimed to contact all parents of children with a microbiological diagnosis of UTI 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 (diapers) whose parents did not think clean catch would be successful, Newcastle Nappy Pads were used. Nappy pads were inserted into the nappy (diaper) 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 write the time and date the sample was obtained. They 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. Since 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.

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Urine samples were transported to NHS laboratories in the laboratories' usual sterile urine container and processed using their Standard Operating Procedures (SOPs). Bacterial growth was quantified (as  $<10^3$ ;  $10^3$  to  $10^5$ ; or  $>10^5$  CFU/mL), purity of growth determined (pure/predominant; mixed growth 2 species; mixed growth  $>2$  species), organism speciated for up to two species, and microscopy performed to determine the presence and count of white and red cells. Sensitivities to first line antimicrobials were recorded for pure/predominant cultures.

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

### ***Statistical analysis***

$\chi^2$  tests were used to examine associations between whether the UTI was suspected on clinical grounds and whether an antibiotic was prescribed at the initial consultation, and also whether organisms present were sensitive to the prescribed antibiotic. Survival analyses, in the form of Kaplan-Meier plots and Log Rank (Mantel-Cox)  $\chi^2$  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 but were not prescribed appropriate antibiotics at the initial consultation.

### **Results**

We recruited 7374 children in the first five years of life who were consulting with an acute illness in primary care. 211 were withdrawn or excluded leaving 7163 with data. Urine samples were obtained from 6390. 6242 urine samples were received and 6079 were cultured in local NHS laboratories (Figure 1).

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.

Considering all the children, irrespective of culture result, 576 out of 7101 (8.1%) were suspected on clinical grounds of having a UTI, and this suspicion was correct in 107 out of 397 (27.0%) cases where a sample had been cultured in the local NHS laboratories.

Figure 2 shows a summary of the clinical suspicion and antibiotic treatment of children subsequently found to have UTI. 107 (31.7%) were suspected of having a UTI. Of those with suspected UTI, 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%) were prescribed an antibiotic. There was a significant association between suspicion of UTI and higher levels of antibiotic prescribing ( $p<0.001$ ). 177 (52.3%) of children with confirmed UTI did not receive any initial antibiotic.

When UTI was suspected on clinical grounds and the organism in these urine samples was tested for the prescribed antibiotic, 54 out of 70 (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 the prescribed antibiotic, 13 out of 47 (27.7%) were

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sensitive to that antibiotic. In addition to the 47 cases where we have sensitivity tests for the prescribed antibiotic, there were 3 cases where the antibiotic given was erythromycin, which is not excreted in urine and therefore is ineffective for treatment of UTI. Thus, in total 13 (26.0%) of the 50 cases where susceptibility information was available were sensitive 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 was made amongst those suspected of UTI, the most commonly prescribed antibiotic was Trimethoprim in 48 out of 92 (52.2%) (Table 1). Amoxicillin was prescribed in 11 (12.0%) of children suspected of UTI. Where a prescription was made amongst those not suspected of UTI, the most commonly prescribed antibiotic was Amoxicillin in 46 out of 70 (65.7%). Trimethoprim was prescribed to 1 (1.4%) child not suspected of UTI. Nitrofurantoin was prescribed to only one child overall (who was suspected of UTI).

Overall the most commonly prescribed antibiotic in this cohort was Amoxicillin, prescribed in 57 children (35.2% of the 162 who were prescribed antibiotics) (Table 1). Amongst all samples tested, organism sensitivity to Amoxicillin was 29.4% (resistance 70.6%). Trimethoprim was prescribed to 49 and had an overall sensitivity of 83.7% (resistance 16.3%).

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 (3.5 days vs. 4.0 days;  $p = 0.005$ ) than those who were not prescribed appropriate antibiotics, or were not prescribed anything, at the initial consultation. (Table 2, Figure 2). Overall child recovery also occurred sooner in those prescribed an appropriate antibiotic at the initial consultation in comparison 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. (Table 2, Figure 3;  $p = 0.568$ ).

## **Discussion**

### ***Summary of main findings***

Less than a third of children presenting with acute illness in primary care and meeting microbiological criteria for UTI are 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 to those treated serendipitously, and children with UTI who are prescribed an appropriate antibiotic at initial presentation improve more quickly than those who are not. Over 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 (70.6%). An appropriate antibiotic (one to which the infecting organism was sensitive) was more likely to be prescribed when UTI was clinically suspected (77.1%) compared to an antibiotic prescribed for a different reason (serendipitous treatment; 26.0%) ( $p < 0.001$ ; Figure 2).

[Type text]



Serendipitous treatment of UTI in young children is common, and the infecting organism is often resistant to such serendipitous treatment. Children with UTI and who were prescribed appropriate antibiotics at the initial consultation had their symptoms improve sooner ( $p=0.006$ ).

### ***Strengths and limitations***

This is the largest prospective observational study of UTI in acutely unwell children presenting to primary care with acute illness. We recruited large numbers and had 6079 urine samples analysed in one of 65 NHS laboratories. Laboratory culture results will include an unknown proportion of false positive and false negatives. Thus, not all children positive for a UTI on culture will be disadvantaged through not receiving initial antibiotic treatment.

For these analyses, we based our definition of UTI 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) We did not use methods such as suprapubic aspiration or catheterisation, 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 at the laboratory within two days of the sample being taken. Our findings are similar to the only other UK study in general practices with systematic urine sampling and using NHS laboratories.(3)

Since 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.

### ***Comparison with existing literature***

We have 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 acutely unwell children in primary care which found that GPs suspected UTI in 20% of those subsequently found to have UTI.(3)

### ***Implications for practice and research***

Improved recognition of UTI in children will lead to improved treatment and outcomes.(11) Recognition may be improved in the future through the use of a validated clinical algorithm quantifying the diagnostic relationship between symptoms, signs and dipstick testing and laboratory confirmed UTI, and 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 without a UTI.

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**Ethical approval**

Multi-centre ethical approval was granted by the South West Southmead Research Ethics Committee (previously Southmead Research Ethics Committee, then South West 4 REC), Ref #09/H0102/64.

**Competing interests**

None for all except for P. Little who is a member of the NIHR Journals Library Board and has provided consultancy work to Bayer Pharmaceuticals. All authors have completed the unified competing interest form at [www.icje.org/coi\\_disclosure.pdf](http://www.icje.org/coi_disclosure.pdf) (available on request from the corresponding author) and declare (1) no financial support for the submitted work from anyone other than their employer; (2) no financial relationships with commercial entities that might have an interest in the submitted work (3) no spouses, partners, or children with relationships with commercial entities that might have an interest in the submitted work; and (4) no non-financial interest that might be relevant to the submitted work.

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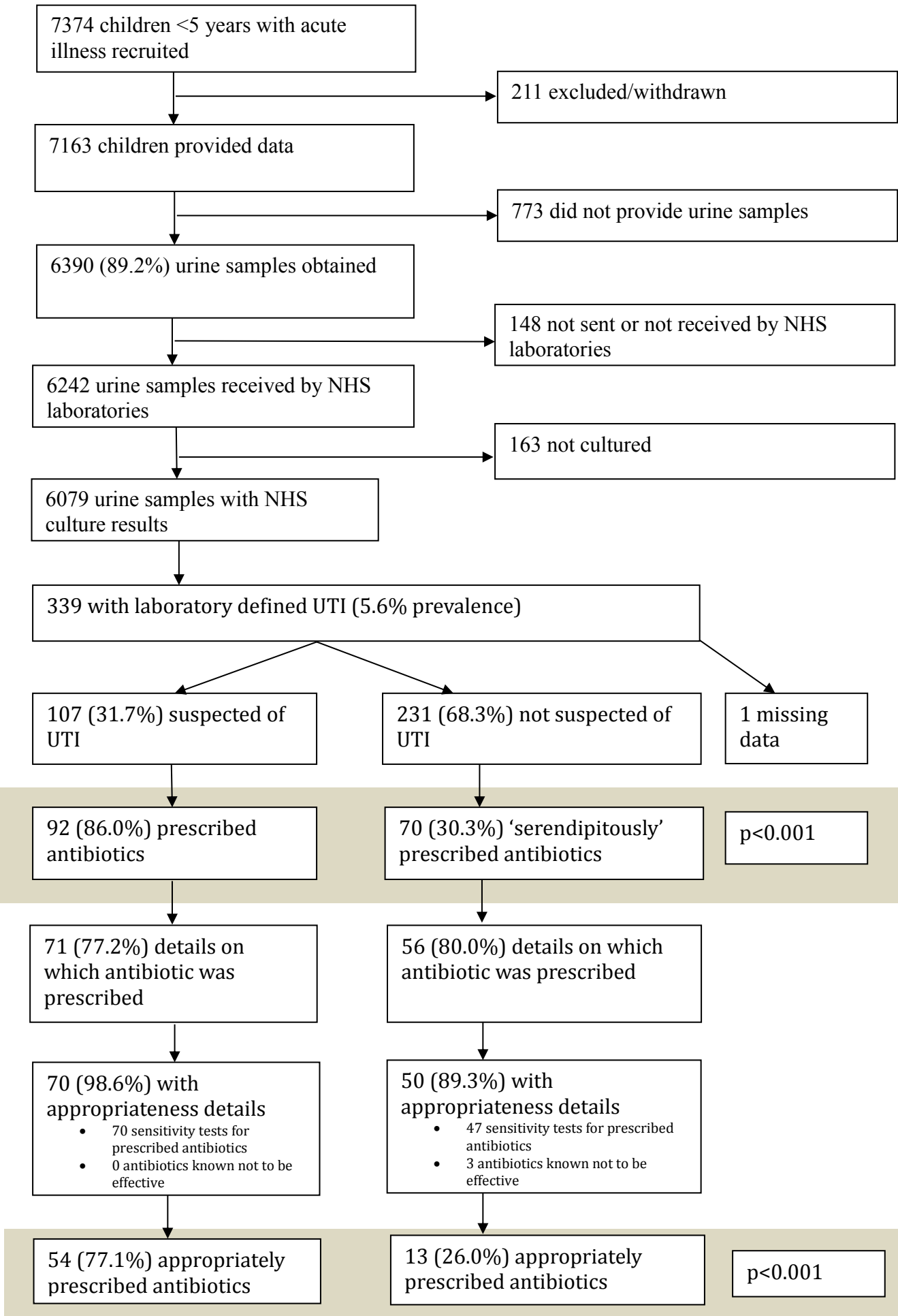
We would like to thank all the members of the DUTY study team; the study steering committee; the recruitment sites; laboratories and research networks; and most of all, the participating children and their families. CCB was supported in part by the National Institute for Social Care and Health Research funded Wales School of Primary Care Research.

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**Figure 1: Flow diagram, clinical suspicion and antibiotic treatment of children with UTI**



[Type text]

Table 1: Results of Sensitivity Tests for Prescribed Antibiotics in patients with a microbiological diagnosis of UTI

Antibiotic Prescribed	Clinician Suspects UTI (n = 107)						Clinician Does Not Suspect UTI (n= 231)					
	Clinician Prescribes Antibiotic (n= 92)*						Clinician Prescribes Antibiotic (n= 70)**					
	Prescribed?		Sensitivity tested to prescribed antibiotic?		Sensitive		Prescribed?		Sensitivity tested to prescribed antibiotic?		Sensitive	
	n	%	n	%	n	%	n	%	n	%	n	%
Amoxicillin	11	12.0	10	90.9	4	40.0	46	65.7	41	89.1	11	26.8
Cefalexin	8	8.7	8	100.0	7	87.5	0	0.0	Blacked out cells represent where no further information can be displayed			
Ceftriaxone	0	0.0	Blacked out cells represent where no further information can be displayed				1	1.4				
Co-amoxiclav	3	3.3	3	100.0	3	100.0	1	1.4	1	100.0	1	100.0
Erythromycin	0	0.0	Blacked out cells represent where no further information can be displayed				3	4.3	0	0.0	Blacked out cells represent where no further information can be displayed	
Nitrofurantoin	1	1.1	1	100.0	0	0.0	0	0.0	Blacked out cells represent where no further information can be displayed			
Penicillin	0	0.0	Blacked out cells represent where no further information can be displayed				4	5.7	4	100.0	0	0.0
Trimethoprim	48	52.2	48	100.0	40	83.3	1	1.4	1	100.0	1	100

Blacked out cells represent where no further information can be displayed

\*Details available for 71 prescriptions

\*\*Details available for 56 prescriptions

[Type text]

Table 2: Tests for differences between those prescribed appropriate antibiotics and not prescribed appropriate antibiotics or not prescribed at the initial consultation in terms of symptom improvement time and child recovery time (from the Parental Self-review at 2 weeks from the initial consultation)

Variable	Clinician Prescribed Appropriate Antibiotic at the Initial Consultation (n = 67)			Clinician Did Not Prescribe Appropriate Antibiotic or Did Not Prescribe at the Initial Consultation (n = 229)			p-value*
	n	Med	IQR	n	Med	IQR	
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 two consecutive days?	40	7.0	5.0, 14.0	113	7.5	5.0, 15.0‡	0.568

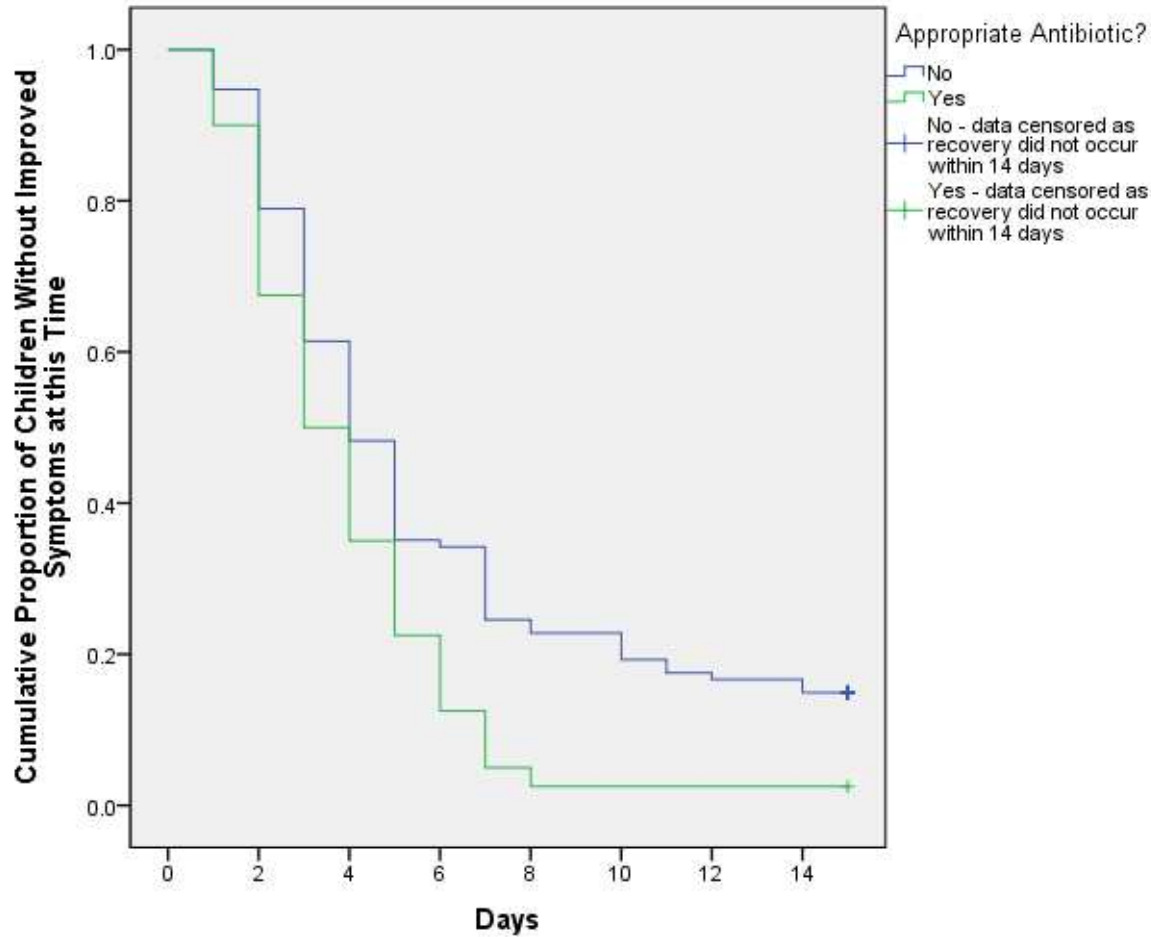
\*From a Log Rank (Mantel-Cox) Chi-Square test.

‡15 days entered for those who did not recover within 14 days. The value of 15 therefore means some value greater than 14.

Note that this analysis is on 296 out of the total of 338. The remaining 42 could be assigned to one of these groups as there was either no information on the antibiotic prescribed, or there was not a sensitivity test available for the prescribed antibiotic (except in the case of an erythromycin prescription).

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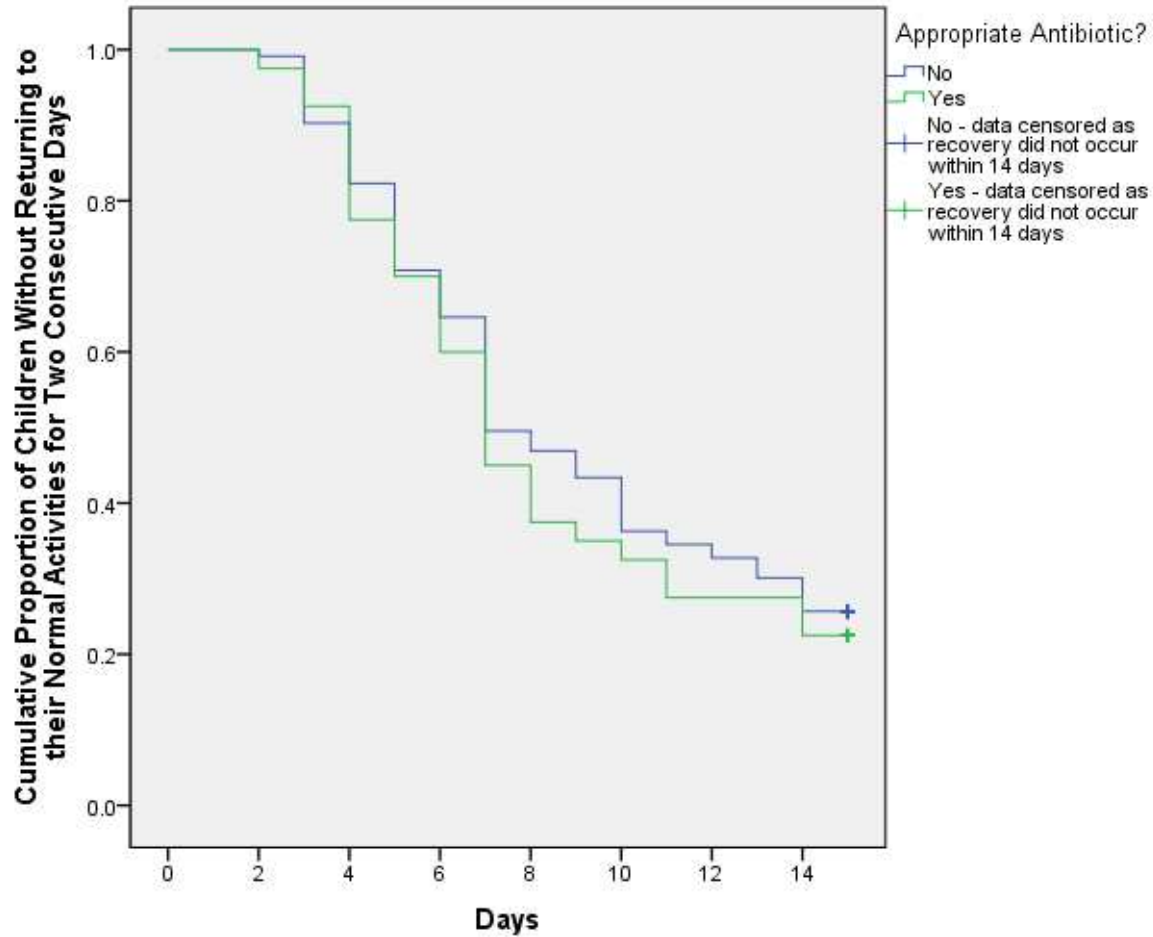
Figure 2: Survival Functions for those prescribed and not prescribed antibiotics at the initial consultation representing ‘How many days since your child started the study was it until their symptoms improved?’



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Figure 3: Survival Functions for those prescribed and not prescribed antibiotics at the initial consultation representing ‘How many days since your child started the study was it until they were entirely well and had returned to their normal activities for two consecutive days?’



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